Abstracts

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P1

RD-Connect: data sharing and analysis for rare disease research within the integrated platform and through GA4GH Beacon and Matchmaker Exchange

Beltran S[1,2], Piscia D[1,2], Laurie S[1,2], Protasio J[1,2], Cañada A[3,14], Fernández JM[3,14], Kaliyaperumal R[6], Lair S[7], Sernadela P[8], Girdea M[9], Thompson R[10], Lochmüller H[10], Badowska D[10], Straub V[10], Roos M[6], 't Hoen PAC[6], Valencia A[3,14], Salgado D[4,5], Béroud

[1]Centro Nacional de Anà¡lisis Genàmico (CNAG-CRG), Center for Genomic Regulation, Barcelona Institute of Science and Technology (BIST), Barcelona, Spain; [2]Universitat Pompeu Fabra (UPF), Barcelona, Spain; [3]Centro Nacional de Investigaciones Oncológicas (CNIO) , Madrid, Spain; [4]Aix-Marseille Université, Marseille, France; [5]Inserm, UMR_S 910, Marseille, France; [6]Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands; [7]Interactive Biosoftware, Rouen, France [8]DETI/IEETA, University of Aveiro, Portugal; [9]Centre for Computational Medicine, Hospital for Sick Children and University of Toronto, Toronto, ON, Canada; [10]John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine, MRC Centre for Neuromuscular Diseases, Newcastle University, UK; [11]Centre for Comparative Genomics, Murdoch University, Perth, Western Australia; [12]APHM, Hôpital TIMONE Enfants, Laboratoire de Génétique Moléculaire, Marseille, France; [14]Instituto Nacional de Bioinformática (INB), Spain

Presenting author: Dorota Badowska
Contact: dorota.badowska@ncl.ac.uk

RD-Connect is a platform for rare disease research bringing together multiple omics data types (genomics, proteomics, transcriptomics) with biosample and clinical information at individual-patient, family or whole-cohort level. It provides both a centralized data repository and a user-friendly online analysis system. Whole-genome, exome or gene panel data are deposited at the European Genome-phenome Archive for long-term storage, then processed by RD-Connect's standardised analysis and annotation pipeline to make data from different sequencing providers comparable. Clinical information is recorded in PhenoTips, simplifying clinical data entry using the Human Phenotype Ontology. Results are made available to authorised users through the highly configurable platform (platform.rd-connect.eu) which enables filtering and prioritization of variants using common genomic location, effect, pathogenicity and population frequency annotations, enabling users to do their primary genomic analysis of their own patients online and compare with other submitted cohorts. The platform enables data sharing at various levels. At the most basic (â€œdoes this variant exist in this cohort?â€•) is the Global Alliance Beacon (www.beacon-network.org). At the next â€“ finding patients in different databases with matching phenotype and candidate variant in the same gene â€“ it is further developing Matchmaker Exchange (www.matchmakerexchange.org), allowing users of different systems to exchange information to find confirmatory cases. Finally, since patients have been consented for data sharing, authorized users can access datasets from other centres for further study. The platform is open to any rare disease and already includes hundreds of datasets from partner projects such as NeurOmics (www.rd-neuromics.eu) and BBMRI-LPC (www.bbmri-lpc.org). RD-Connect is free and open for contributions: platform@rd-connect.eu.

P2 Agreement Model between Telethon Network of Genetic Biobanks and Patient Organisations

Baldo C[1], Casareto L[2], Renieri A[3], Merla G[4], Garavaglia B[5], Goldwurm S[6], Pegoraro E[7], Moggio M[8], Mora M[9], Politano L[10], Sangiorgi L[11], Wang CM[12], Monaco L[12], Filocamo M[2,13]

[1]SC Laboratorio di Genetica Umana, EO Ospedali Galliera, Genova, Italy; [2]Coordination Hub of Telethon Network of Genetic Biobanks c/o Istituto G. Gaslini, Genova, Italy; [3]Medical Genetics, University of Siena and Genetica Medica, Azienda Ospedaliera Universitaria Senese, Siena, Italy; [4]Medical Genetics Unit, IRCCS Casa Sollievo della Sofferenza, S. Giovanni Rotondo (FG), Italy; [5]UOC Neurogenetica Molecolare, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy; [6]Parkinson Institute, ASST Centro Specialistico Ortopedico Traumatologico G. Pini-CTO, Milano, Italy; [7]Università di Padova, Azienda Ospedaliera Universitaria, Padova, Italy; [8]Neuromuscular and Rare Diseases Unit, Dino Ferrari Centre, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milano, Italy; [9]Laboratorio di Biologia Cellulare, UO Malattie Neuromuscolari e Neuroimmunologia, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy; [10]Cardiomiologia e Genetica Medica, Dipartimento di Medicina Sperimentale, Università degli Studi della Campania "Luigi Vanvitelli" ed Azienda Ospedaliera Universitaria "Luigi Vanvitelli" Napoli, Italy; [11]SSD Genetica Medica e Malattie Rare Ortopediche Istituto Ortopedico Rizzoli, Bologna, Italy; [12]Fondazione Telethon, Milano, Italy; [13]UOSD Centro di Diagnostica Genetica e Biochimica delle Malattie Metaboliche, Istituto G. Gaslini, Genova, Italy

Presenting author: Chiara Baldo
Contact: chiara.baldo@galliera.it

One of the main aims of the Telethon Network of Genetic Biobanks (TNGB) has always been to promote biobanks' services within Patient Organisations (POs) to foster their active participation. Thanks to this interaction, the POs' interest in TNGB services has enormously increased leading to the formalisation of a working partnership via a written agreement to define terms and tasks of the parties. The agreement template describes purposes, roles and responsibilities and includes as annexes the parties' charters and TNGB forms - i.e. informed consent, sample submission and Material Transfer Agreement forms -which are mutually accepted.

Concerning parties' roles and responsibilities, the PO undertakes to (i) identify a representative who keeps associated families and referring clinicians informed of the Biobank's activities and policies; (ii) promote the recruitment of patients and relatives; and (iii) organise sample shipment to the appointed Biobank, which, in its role, undertakes to (i) provide biobanking service according to TNGB policies and SOPs; (ii) publish the sample collection on the TNGB online catalogue; and (iii) keep the PO's representative informed of the sample workflow and availability of potential findings resulting from the distribution service.

Presently, 14 agreements have been formalised and 2,457 samples have been biobanked and 791 distributed, resulting in 3 original scientific papers.

To the best of our knowledge, this type of agreement is unique worldwide within rare diseases, and represents an innovative tool which not only facilitates the collection and the centralisation of rare disease samples, ensuring participants' rights, but also can be useful to foster the integration of rare disease resources, such as registries/clinical databases and biobanks.

This experience may serve as a model of collaboration between disease-oriented Biobanks and Patient Organisations, based on mutual respect and effective collaboration, which are essential prerequisites to share objectives and maximise efforts to support research on rare diseases.

P3

The RD-Connect/EuroBioBank biobank network: an opportunity for rare disease biobanks in Europe and beyond

Benvenuti S[1], Wang M[1], Mora M2, van Enckevort D[3], Müller H[4], Reihs R[4], Merino-Martinez R[5], Monaco L[1]

[1]Fondazione Telethon, Milan, Italy; [2]Neuromuscular Diseases and Neuroimmunology Unit, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy; [3]Genomics Coordination Centre, UMC Groningen, Groningen, Netherlands; [4]Medical University Graz, Graz, Austria; [5]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet , Stockholm, Sweden

Presenting author: Stefano Benvenuti
Contact: sbenvenuti@telethon.it

The RD-Connect biobank area is home to EuroBioBank, the first RD biobank network in Europe established in 2001, which has evolved into the RD-Connect/EuroBioBank.

New RD biobanks are invited to join RD-Connect/EuroBioBank; this will multiply the biobank impact on the RD scientific community by increasing the visibility of the biobank and the chances of scientific collaborations and by linking biological samples to correlated clinical and omics data within the RD-Connect platform.

Through a dedicated web interface called ID-Cards (catalogue.rd-connect.eu) any RD biobank can submit its membership application by completing a self-assessment questionnaire on its biobanking activities, which is reviewed by a panel of experts aimed at ensuring that minimum quality standards are met. The Panel covers expertise on biobanking operations, quality, IT infrastructure capability and ethical, legal and social issues (ELSI). All approved biobanks will adhere to the EuroBioBank Charter/RD-Connect Code of Practice and become members of the RD-Connect/EuroBioBank network. RD-Connect biobanks can get access and contribute to the biobanking standard operating procedures developed by EuroBioBank and to the full services for biobanks provided via the RD-Connect platform:

1) The RD-Connect/EuroBioBank ID-Cards directory;

2) The RD-Connect on-line sample catalogue accessible via web to any researcher looking for RD biological samples;

3) The Negotiator to manage sample requests by researchers who identified interesting samples in the RD-Connect catalogue service under development in collaboration with BBMRI-ERIC.

Finally, for the whole duration of the RD-Connect project, all biobanks can count on the technical support by the RD-Connect IT service to load their data into the on-line catalogue and possibly to deploy ad-hoc APIs to allow the automatic synchronization of their own local databases with the RD-Connect sample catalogue.

Core EuroBioBank members are currently in the process of uploading their data on more than 148,000 biological samples representing more than 950 rare diseases; this figure is expected to increase rapidly as soon as new biobanks will join the network.

P4 **Knowledgebase and mini-expert platform for the diagnosis of inborn errors of metabolism (IEMbase.org)**

Blau N[1], Lee J[2], Wasserman W[2,3], Hoffmann G[1], van Karnebeek C[2]

[1]Dietmar-Hopp-Metabolic Center, University Children's Hospital, Heidelberg, Germany; [2]Centre for Molecular Medicine and Therapeutics; Child and Family Research Institute, Vancouver, BC, Canada; [3]Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada

Presenting author: Nenad Blau
Contact: nenad.blau@med.uni-heidelberg.de

Purpose: Recognizing individuals with inherited diseases can be difficult as signs and symptoms often overlap those of common medical conditions. Focusing on inborn errors of metabolism (IEMs), we present a method that brings the knowledge of highly specialized experts to professionals involved in early diagnoses. We introduce IEMbase, an online expert-curated IEM knowledgebase combined with a prototype diagnosis support (mini-expert) system.

Methods: Disease-characterizing profiles of specific biochemical markers and clinical symptoms were extracted from an expert-compiled IEM database. A mini-expert system algorithm was developed using cosine similarity and semantic similarity. The system was evaluated using 190 retrospective cases with established diagnoses, collected from 15 different metabolic centers.

Results: IEMbase provides 560 well-defined IEM profiles and matches a user-provided phenotypic profile to a list of candidate diagnoses/genes. The mini-expert system matched 62% of the retrospective cases to the exact diagnosis and 86% of the cases to a correct diagnosis within the top five candidates. The use of biochemical features in IEM annotations resulted in 41% more exact phenotype matches than clinical features alone.

Conclusion: IEMbase offers a central IEM knowledge repository and a model for many genetic diagnostic centers and clinical communities seeking support in the diagnosis of IEMs.

P5

Myotubular and Centronuclear Myopathy Patient Registry: Accelerating the pace of research and treatment

Bullivant J[1], Napier K[2], Radochonski M[2], Render L[2], Hunter A[2], Spring M[3], Lennox A[3], Bellgard M[2], Lochmüller H[1]

[1]John Walton Muscular Dystrophy Research Centre, Newcastle University, UK; [2]Centre for Comparative Genomics, Murdoch University, Australia; [3]Myotubular Trust

Presenting author: Jo Bullivant
Contact: joanne.bullivant@ncl.ac.uk

Background:

The Myotubular and Centronuclear Myopathy (MTM and CNM) Patient Registry (www.mtmcnmregistry.org) is an important tool to facilitate and accelerate clinical research through identification of information and participants. This international disease-specific registry was developed by the Myotubular Trust in 2013 after consultation with the research community. In 2015 they awarded a grant to Newcastle University to continue the work as part of the TREAT-NMD Alliance.

Aims:

- Help identify patients for clinical trials
- Support research projects by providing specific data
- Encourage further research due to the existence and availability of data
- Provide information on living with and managing the conditions to develop standards of care
- Support communication links with the patient community

Methods:

MTM or CNM patients enter data by creating a password-protected account on an online portal, allowing them to update their data at any time. Registration of female carriers of X-linked myotubular myopathy (XLMTM) and deceased patients is also welcomed. The registry dataset includes demographic, clinical, genetic, phenotypic and familial information.

Results:

There are over 170 people registered from 26 different countries; the majority being patients diagnosed with XLMTM. The age of people registered ranges from 0 to 80 years old, with the greatest numbers between 0 and 9 years old. The majority of registered patients use a wheelchair, and over half required ventilation at birth. Approximately half of the female carriers registered have experienced difficulty running or walking, and a third have experienced difficulty swallowing. 40% of deceased patients registered died before the age of 12 months, with 74% dying before the age of 6 years old.

Conclusion:

Patient registries are invaluable tools in the field of rare diseases. The MTM and CNM Registry has the potential not only to accelerate clinical trials but to assist in all areas of research including in the identification of outcome measures, in increasing understanding of phenotype-genotype correlation and in improving standards of care.

P6 The RD-Connect Central Authentication Service: components and deployment.

Capella S[1,2], Fernàndez JM, Cañada A, Piscia D, Protasio J, Beltran S, Valencia A

[1]Spanish National Cancer Research Institute (CNIO), Madrid, Spain; [2]Spanish National Bioinformatics Institute (INB), Spain; [3]Centro Nacional de Análisis Genómico (CNAG-CRG), Center for Genomic Regulation, Barcelona, Spain

Presenting author: Salvador Capella
Contact: scapella@cnio.es

The RD-Connect platform connects and integrates sensible data, rare disease developments and knowledge, like medical records from several registries, sample metadata from biobanks, experiments databases, pipeline analysis databases and clinical bioinformatics tools. All these resources have their own web platforms, and most of them have some kind of access control mechanism in order to restrict the access to sensible information. These control mechanisms are managed independently, so a common infrastructure which allows creating a web of trust among them is mandatory in order to use them in RD-Connect platform. The RD-Connect Central Authentication Service (CAS) has been setup and deployed to play this role, providing a single sign-on facility trusted by all these distributed resources. Moreover, we are working to integrate the ELIXIR AAI (Authentication and Authorization Infrastructure) as part of a coordinated effort in the context of the ELIXIR-EXCELERATE project. ELIXIR AAI will facilitate the access to additional data and service resources making possible further analyses in a transparent manner for users, as long as they have the appropriate permissions.

P7 **Bring Your Own Data workshop a joint effort to promote and support FAIR RD-Registries**

Carta C[6], Roos M[1], Jansen M[2], van Enckevort D[3], Wilkinson MD[4], Kaliyaperumal R[1], Cornet R[5], Torreri P[6], da Silva Santos LOB [2,7], Kodra Y[6], Taruscio D[6]

[1]Leiden University Medical Center, Leiden, The Netherlands; [2]Dutch Techcentre for Life Sciences/ELIXIR-NL, Utrecht, The Netherlands; [3]University of Groningen, University Medical Center Groningen, The Netherlands; [4]Universidad Politécnica de Madrid, Spain; [5]Academic Medical Center, University of Amsterdam, The Netherlands; [6]National Centre for Rare Diseases, Istituto Superiore di Sanità , Rome, Italy; [7]Vrije Universiteit, Amsterdam, The Netherlands

Presenting author: Claudio Carta
Contact: claudio.carta@iss.it

The EC and patient organizations encourage rare disease (RD) registries as key instruments for research. There is a push for RD registries to interoperate internationally, and optimize the usability of their data. To promote registries becoming Findable, Accessible, Interoperable, and Reusable (FAIR) for humans and computers, the National Centre for Rare Diseases of Istituto Superiore di Sanità in Rome (CNMR-ISS), DTL/ELIXIR-NL and RD-Connect have organized "Bring Your Own Data" workshops (BYODs) for registry managers since 2014: hands-on learning experiences that introduce "FAIRification" protocols and demonstrate question-answering across dispersed registries. We developed a reusable roadmap for the organisation of BYODs encompassing (i) a preparatory phase with two webinars, (ii) the BYOD, (iii) a follow-up phase to bolster outcomes. BYODs emphasize interdisciplinary knowledge exchange. In two days, BYOD participants experience how preparing data for linking at the source facilitates complex inquiry. A third day involves exploration of distinct FAIR data sources. New for this BYOD was a focus on the role of registry managers. Selfâ€“sketching the "FAIRification" workflow clarified the process, including authorization issues, for managers without an IT-background. Outcomes included identifying skills required in a "FAIRification" team, and how managers can bring those skills together. In conclusion, BYODs have proven an excellent starting-point for FAIR adoption. The interest of registry managers is growing, and they responded positively to the adoption of the FAIR principles. We offer help to accommodate these ideas in new grants or in the 2017 RD data linkage plan. We also initiated collaborations with registry software providers to lower the "FAIRification" effort via their tools. We wish to stimulate the organization of FAIR expert networks, such as in Italy, and the next BYOD (Rome, end of September 2017) welcomes the active involvement of the Italian node of ELIXIR. Successful BYODs depend on all participants and FAIR experts whom we thank for their excellent contribution. CC, MR, and MJ equally contributed to the work.

P8 Overcoming Friction between Biobanks' Legal Requirements and the Pre-Existing Situation: The ECLT and TNGB Experience

Tomasi M[1,2], Filocamo M[3,15], Baldo C[4], Goldwurm S[5], Renieri A[6], Pegoraro E[7], Moggio M[8], Mora M[9], Merla G[10], Politano L[11], Garavaglia B[12], Sangiorgi L[13], Wang CM[14], Casareto L[15], Santosuosso A[2,16]

[1]Free University of Bozen-Bolzano, Italy; [2]Interdepartmental Research Center, European Centre for Law, Science and New Technologies, University of Pavia, Italy; [3]UOSD Centro di Diagnostica Genetica e Biochimica delle Malattie Metaboliche, IRCCS Istituto G. Gaslini, Genova, Italy; [4]SC Laboratorio di Genetica Umana, EO Ospedali Galliera, Genova, Italy; [5]Parkinson Institute, ASST Centro Specialistico Ortopedico Traumatologico G. Pini-CTO, Milano, Italy; [6]Medical Genetics, University of Siena and Genetica Medica, Azienda Ospedaliera Universitaria Senese, Siena; [7]Università di Padova, Azienda Ospedaliera Universitaria, Padova, Italy; [8]Neuromuscular and Rare Diseases Unit, Dino Ferrari Centre, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milano, Italy; [9]Laboratorio di Biologia Cellulare, U.O. Malattie Neuromuscolari e Neuroimmunologia, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy; [10]Medical Genetics Unit, IRCCS Casa Sollievo della Sofferenza, S. Giovanni Rotondo (FG), Italy; [11]Cardiomiologia e Genetica Medica, Dipartimento di Medicina Sperimentale, Università degli Studi della Campania "Luigi Vanvitelli" e Azienda Ospedaliera Universitaria "Luigi Vanvitellia", Napoli, Italy; [12]UOC Neurogenetica Molecolare, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy; [13]SSD Genetica Medica e Malattie Rare Ortopediche Istituto Ortopedico Rizzoli, Bologna, Italy; [14]Fondazione Telethon, Milano, Italy; [15]Coordination Hub of Telethon Network of Genetic Biobanks c/o IRCCS Istituto G. Gaslini, Genova, Italy; [16]Court of Appeal of Milan, Milano, Italy

Presenting author: Lorena Casareto
Contact: lcasareto@telethon.it

Biobanks have existed for decades. Although their origin dates back in time, the attention of law and policy makers for this reality arose much more recently. This circumstance created a situation in which frictions between legal requirements and the existing situation might happen.

In order to face these issues, the Telethon Network of Genetic Biobanks (TNGB) started a collaboration with the European Centre for Law Science and New Technologies of the University of Pavia (ECLT) in order to: i) map the situation of samples and data collected before the introduction of specific regulations; ii) identify ethical and legal critical points of the practice of the Network biobanks; iii) improve the process of seeking informed consent.

To this end, biobank directors underwent single interviews, through a relevant questionnaire, by which ECLT legal experts gathered information useful to outline the situation of samples and data collected in regard to the existing regulations.

The survey results allowed to start a discussion with ELSI experts to revise the TNGB informed consent model. This proved to be very necessary in order to align the rules governing the TNGB with the strictness of the Italian regulation, partly due to its unfamiliarity with the operational reality of research biobanks. The new consent form and the underlying informational process are now tailored to ensure, as much as possible, a balance between the constitutional interest of the freedom of scientific research and the protection of self-determination of people taking part in it.

P9

Material Transfer Agreement: A Fundamental Tool for International Exchange of Biological Material

Casareto L[1], Baldo C[2], Goldwurm S[3], Renieri A[4], Pegoraro E[5], Moggio M[6], Mora M[7], Merla G[8], Politano L[9], Garavaglia B[10], Sangiorgi L[11], Benvenuti S[12], Merico A[13], Filocamo M[1,14]

[1]Coordination Hub of Telethon Network of Genetic Biobanks c/o IRCCS Istituto G. Gaslini, Genova, Italy; [2]SC Laboratorio di Genetica Umana, EO Ospedali Galliera, Genova, Italy; [3]Parkinson Institute, ASST Centro Specialistico Ortopedico Traumatologico G. Pini-CTO, Milano, Italy; [4]Medical Genetics, University of Siena and Genetica Medica, Azienda Ospedaliera Universitaria Senese, Siena, Italy; [5]Università di Padova, Azienda Ospedaliera Universitaria, Padova, Italy; [6]Neuromuscular and Rare Diseases Unit, Dino Ferrari Centre, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milano, Italy; [7]Laboratorio di Biologia Cellulare, UO Malattie Neuromuscolari e Neuroimmunologia, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy; [8]Medical Genetics Unit, IRCCS Casa Sollievo della Sofferenza, S. Giovanni Rotondo (FG), Italy; [9]Cardiomiologia e Genetica Medica, Dipartimento di Medicina Sperimentale, Università degli Studi della Campania "Luigi Vanvitelli", ed Azienda Ospedaliera Universitaria "Luigi Vanvitelli" Napoli, Italy; [10]UOC Neurogenetica Molecolare, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy; [11]SSD Genetica Medica e Malattie Rare Ortopediche, Istituto Ortopedico Rizzoli, Bologna, Italy; [12]Business Development Office, Fondazione Telethon, Milano, Italy; [13]Fondazione Telethon, Milano, Italy; [14]UOSD Centro di Diagnostica Genetica e Biochimica delle Malattie Metaboliche, IRCCS Istituto G. Gaslini, Genova, Italy

Presenting author: Lorena Casareto
Contact: lcasareto@telethon.it

The exchange of samples between biobanks (BBs) and researchers is a common, and much needed, practice. Material Transfer Agreements (MTAs) are written legal contracts between the provider and the recipient of samples and linked data, setting out the condition of transfer and use. The MTA, signed by the Legal Representative of the involved institutions, ensures traceability of samples and data and accountability of the BB and its users.

The Telethon Network of Genetic Biobanks (TNGB) processes about 5000 sample/1yr (200 requests) and has always been careful to appropriately manage such type of transfer. TNGB, with the support of the Telethon Technology Transfer Office, has worked to draft an exhaustive MTA template, applicable to both non-profit and for-profit organisations. The MTA has been build to define the rights, obligations and restrictions for both the recipient and provider with respect to the samples and minimum dataset exchanged with them. This process has required effort in finding the right balance to meet needs of any type of entity that might be involved. Briefly, the MTA ensures: (i) use of samples only for the research purpose specified in the request form; (ii) destruction or return of residual samples after use or, alternatively, submission of a new request; (iii) prohibition to transfer samples to third parties without BB written permission; (iv) prohibition of any activity aimed at identifying patients; (v) mandatory return of research results relevant to the health of patients to the BBs; (vi) proper BB citation and acknowledgment in any publication resulting from samples use. TNGB, being aware of the important contribution of for-profit entities in developing treatments for rare diseases, has also focused on the policies to be implemented with them. Among these, a devoted recovery cost list for sample access has been defined to avoid unreasonable requests of such precious rare samples and acknowledge their relevance and the efforts of the BB in collecting and preserving them. In conclusion, to protect patientsâ€™ rights, TNGB can relies on a comprehensive MTA which regulates sample and minimum dataset exchange with the scientific community.

P10 **European Reference Network for rare Neuromuscular Diseases: EURO-NMD**

Evangelista T, Leary R, Lochmüller H, Bushby K, EURO-NMD Network

John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, UK

Presenting author: Teresinha Evangelista
Contact: teresinha.evangelista@ncl.ac.uk

EURO-NMD is a European Reference Network for the thematic grouping of rare neuromuscular diseases (NMDs), a broad group of related disorders that represent a major cause of mortality and lifelong disability in children and adults. NMDs are caused by acquired or genetic defects of motorneurons, peripheral nerves, neuromuscular junctions or skeletal muscle, resulting in muscle weakness and wasting, swallowing and breathing difficulties, and cardiac failure. NMDs are difficult to recognize, and patients experience long delays in diagnosis. No curative treatments yet exist for any NMD and their rarity and diversity pose specific challenges for healthcare and research, and for the development and marketing of therapies.

NMDs collectively affect an estimated 500,000 EU citizens and result in significant costs for families and the healthcare system. EURO-NMD unites 61 of Europe's leading NMD clinical and research centres in 14 Member States and includes highly active patient organizations. More than 100,000 NMD patients are seen annually by the ERN. The network addresses harmonizing and implementing standards for clinical and diagnostic best practice, improving equity of care provision across Member States, decreasing time to diagnosis, increasing cost efficiency through better care pathways, access to specialist training and education, application of eHealth services, development and application of care guidelines, facilitating translational and clinical research, harmonising data and samples for research reuse, and sharing of high-quality data.

EURO-NMD partners will form the backbone for national implementation of best practice NMD care and will form trusted partnerships with payers, national health systems and RD national plans. Ultimately, EURO-NMD will improve health outcomes in NMD patients across Europe, provide new opportunities for translational research, and reduce the burden of these chronic disabling conditions for families and healthcare systems in Europe.

P11 Comparative (epi)genomics focused on rare diseases

Fernàndez JM[1], Carrillo E[1], Topf A[2], Azuma Y[2] Evangelista T[2], Capella-Gutierrez S[2,3], 't Hoen PAC[4], Lochmüller H[2], Valencia A[5,3,1]

[1]Structural and Computational Biology Programme, CNIO (Centro Nacional de Investigaciones Oncológicas), Madrid, Spain; [2]The John Walton Muscular Dystrophy Research Centre, MRC Centre for Neuromuscular Diseases, Institute of Genetic Medicine, Newcastle University, Central Parkway, Newcastle upon Tyne, NE1 3BZ, UK; [3]INB (Spanish National Bioinformatics Institute), ELIXIR ES; [4]Leiden University Medical Center, Building 2, Room S-04-036, Einthovenweg 20, 2333 ZC Leiden, Netherlands; [5]Life Sciences Department, BSC (Barcelona Supercomputing Center), Barcelona, Spain

Presenting author: Jose Fernandez
Contact: jmfernandez@cnio.es

The impact of large and complex (epi)genomic datasets on clinical applications and rare diseases in particular, is limited by the lack of accessible tools able to represent the complex information in an intuitive and comprehensive manner.

The EPICO comparative (epi)genomics system was created as a general cyber-infrastructure to facilitate the creation of project specific analysis systems for comparative genomic analysis. A first implementation of EPICO was successfully carried out with the creation of the BLUEPRINT data analysis portal (http://blueprint-data.bsc.es). This portal allows users without specific training in bioinformatics, to visualize and compare epigenomic and transcriptomic data of 62 hematopoietic cell types from more than 500 samples. The portal allows users to select samples from a defined classification (ontology) to answers queries about the organization of specific genomic regions providing summary statistics and comparative analysis.

We present here a new implementation of the EPICO cyber-infrastructure for the analysis of data in the RD-Connect ecosystem. This new implementation will allow the direct comparison of genomic features (obtained from project specific genome browser tracks, for example) of patient data selected by the users by their phenotypic/symptoms characteristics (from the Human Phenotype Ontology annotations), while taking into possible familial relationships. A typical operation with the new system will be to select a set of cases from a cohort with a different response to a drug and to detect and visualise regions with differential SNVs and differential expression, while keeping in the information display the familial links between cases.

The potential of the system will be demonstrated with an initial use case of CMS (congenital myasthenic syndrome), composed by 20 cases analyzed in collaboration with Hanns Lochmüller's team from The John Walton Muscular Dystrophy Research Centre.

P12 Japan's integrative data-sharing platform for rare and intractable diseases

Furusawa Y[1], Izumi K[1], Matsuda F[2], Yamano Y[3], Asano Y[4], Matsubara Y[5], Nishino I[6], Matsumoto N[7], Takano A[8]

[1]The Japan Agency for Medical Research and Development http://www.amed.go.jp/en/; [2]Kyoto University; [3]St. Marianna University School of Medicine; [4]Osaka University; [5]National Center for Child Health and Development; [6]National Center for Neurology and Phychiatry; [7]Yokohama City University; 8IBM Japan

Presenting author: Yoshihiko Furusawa
Contact: yoshihiko-furusawa@amed.go.jp

Japan has a long history of rare and intractable diseases research. Building upon this over-40-year legacy and close collaboration with the Ministry of Health, Labour and Welfare of Japan (MHLW), the Japan Agency for Medical Research and Development (AMED) has been committed to supporting research projects in this area since 2015 as one of the nine major key prioritized fields1. The approximately 200 awarded projects at present under the Rare/Intractable Disease Project of Japan demonstrate our entire scope ranging from basic research to clinical trials, genomic studies, and to those contributing to the development of registries and biorepositories in this specific field.

Among long-desired research infrastructure has there been a platform enabling data sharing, data integration, and secondary use under a predetermined policy. Every piece of data obtained by individual projects is indispensable for current and future research; and especially in rare diseases this need must be met to address the scarcity of patient populations. For this reason, AMED launched a Nan-Byo (literally "difficult" + "illness") platform project in February 2017.

The Nan-Byo platform will collect, integrate, and promote the secondary use of research data from MHLW- and AMED-funded projects. Made available will be data generated from clinical, genomic and other omics studies, in addition to data stored in existing and future biorepositories. The platform will also be harnessed by a prototype of an artificial intelligence-assisted diagnosis system, the core technology of which consists of genomic analysis for the detection of causative genes and image analysis for diagnosis.

Collaboration is essential for the effective use of the Nan-Byo platform. At present a couple of Japanese initiatives are underway to supplement the larger picture of Nan-Byo research. In the near future, however, communication and collaboration with an even broader pool of stakeholders must be strengthened; within our scope are patient advocacy groups as well as international counterparts developing similar platforms for rare diseases research.

P13 **HIPBI-RD: Harmonising phenomics information for a better interoperability in the rare disease field**

Hanauer M[1], Olry A[1], Lanneau V[1], Lourghi H[1], Koehler S[2], Groza T[5], Rodwell C[1], Maiella S[1], Jupp S[4], Robinson PN[6], Brudno M[3], Parkinson H[4,] Rath A[1]

[1]INSERM, US14 - Orphanet, Paris, France; [2]Institute for Medical Genetics and Human Genetics, Charité Universitätsmedizin Berlin, Germany; [3]The Hospital for Sick Children, Toronto, Canada; [4]European Bioinformatics Institute, European Molecular Biology Laboratory (EMBL-EBI), Hinxton, United Kingdom; [5]Garvan Institute of Medical Research, Darlinghurst, Sydney, Australia; [6]The Jackson Laboratory , USA

Presenting author: Marc Hanauer
Contact: marc.hanauer@inserm.fr

HIPBI-RD project builds on 3 resources largely adopted by the rare disease (RD) community: Orphanet, its ontology ORDO (the Orphanet Rare Disease Ontology), HPO (Human Phenotype Ontology) as well as PhenoTips and PhenomeCentral. Our project aims to provide the community with an integrated, RD-specific bioinformatics ecosystem to harmonise the way phenomics information is stored in databases and patient files worldwide, and thereby contribute to interoperability.

The project aims to:

1. Create an ontological resource allowing semantic interoperability in a computable, re-usable way.

2. Enrich RD knowledge via automated concept recognition in the literature, enabling experts to manually validate the output of the concept recognition process.

3. Enrich RD knowledge via crowdsourcing and enable experts to manually validate crowdsourced annotations.

4. Provide improved algorithms for phenotype-driven rare disease differential diagnostics.

Currently, 41.6% of Orphanet disorder entities are annotated with relevant HPO terms together with information on frequency of occurrence of these phenotypic features. Two new tools are new online:

- Phenotate (www.phenotate.org) a tool allowing users to annotate ORDO nosological entities with HPO terms.

- Phenomizer-Orphanet: a clinical diagnostic support tool enabling users to suggest a differential diagnosis by entering phenotypes using HPO controlled vocabulary .

This emerging HIPBI-RD ecosystem contributes to the interpretation of variants identified through exome /full genome sequencing by harmonising the way phenotypic information is collected, thus improving diagnostics and delineation of RD. HIPBI-RD's ultimate goal is to provide a resource that will contribute to bridging genome-scale biology and a disease-centered view on human pathobiology.

P14 RD-ACTION support for European Reference Networks

Hedley V[1], Johnson M[2], Bottarelli V[2], Bushby K[1]

[1]John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine, University of Newcastle, Newcastle upon Tyne NE1 3BZ, UK; [2] EURORDIS-Rare Diseases Europe, Plateforme Maladies Rares, 96, rue Didot, 75014 Paris, France

Presenting author: Victoria Hedley
Contact: victoria.hedley@ncl.ac.uk

RD-Action ('Data and Policies for Rare Diseases') continues the foundational work of the EUCERD Joint Action, in supporting the conceptualisation and implementation of European Reference Networks (ERNs). The Policy WP, led from Newcastle by Kate Bushby, agreed to focus much of its activities on the topic of ERNs, working to address specific issues such as how ERNs will: leverage eHealth solutions; share and re-use data; interact with patient registries; develop best practice guidelines; interact with Industry, regulatory bodies etc.; and conduct research. RD-ACTION supported the rare disease and specialised care field in organising itself into 24 compressive, robust ERNs. EURORDIS partners ensured meaningful, active patient involvement in each Network via the concept of ePAGs (European Patient Advisory Groups). Once the Networks were in place, the goal of the RD-ACTION Policy WP workplan is to continue to provide support to the rare disease community in conceptualising, implementing and evolving robust ERNs capable of meeting the needs and expectations of people living and working with conditions requiring a specific concentration of expertise. As the 1st ERNs are established and evolve, shared consensus guidance is important to support the Networks but also to ensure a baseline compatibility and interoperability (at various levels) between the ERNs. This poster demonstrates some of the key successes of RD-ACTION to-date, and illustrates the workshops planned in the coming year to support the Networks in addressing some of their common policy-related challenges.

P15 **Network analysis of mdx multi-omics data reveal a disease-related signature in blood**

Hette K[1], Tsonaka R[3], Charrout M[1], Veth O[1], Seyer A[2], Mina E[1], 't Hoen PAC[1], Aartsma-Rus A[1], Spitali P[1]

[1]Department of Human and Clinical Genetics, Leiden University Medical Centre, Leiden, The Netherlands; [2]Profilomic, 31 rue d'Aguesseau, 92100 Boulogne Billancourt, France; [3]Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands

Presenting author: Kristina Hettne
Contact: k.m.hettne@lumc.nl

Duchenne muscular dystrophy is an X-linked recessive fatal disease characterized by muscle degradation. Patients are unable to produce dystrophin, an important structural protein in muscle. This study was performed on dystrophin-deficient mouse models (mdx) to study the effects of dystrophin deficiency in detail, and to enable testing of novel treatments. The main goal of this study was to find biomarkers for disease severity by comparing the blood metabolome, lipidome and transcriptome of the mdx with the more severe mdx/utrn+/- model. Additional goals were to identify biomarkers for disease progression in mice and to find biomarkers in blood that reflect specific aspects of disease in muscle. The metabolome and lipidome of 5 time points' plasma samples from mice were measured using LC-MS. Similarly, the blood transcriptome was measured using paired-end 125bp Illumina sequencing. Muscle tissue was collected at the last time point and sequenced. Network analysis using the Weighted Gene Co-expression Analysis (WGCNA) package in R was performed per time point for each -omic dataset to establish groups of molecules (modules) that share a similar co-expression pattern (genes) and a similar concentration pattern (metabolites and lipids). Euretos was used for module annotation. No significant modules between the WT vs mdx or mdx vs mdx/utrn+/- groups could be found in the transcriptome. The metabolomics data revealed significant modules in week 6, 12 and 18 between the WT vs mdx/utrn+/+, WT vs mdx/utrn+/ and mdx/utrn+/+ vs mdx/utrn+/- groups. In the lipidomics data four significant modules were found in week 12 between the WT vs mdx groups. To compare changes in the transcriptome between dystrophic blood and muscle tissue WGCNA results were compared at the last time point, revealing 8 significant module pairs. By retrieving the top 5 most interconnected module genes, we found through Euretos that the Aldoa gene (blood) had a connection with the Pck1 gene (muscle) through the gluconeogenesis pathway. Future work includes integration of the different -omics sets through cross-correlation of module eigengenes and investigation of annotation overlap using Euretos.

P16

Boosting genotype-phenotype and translational research on rare diseases by establishing Findable, Accessible, Interoperable and Reusable data resources through data linking technologies

Jacobsen A[4], van Enckevort D[1], Carta C[2], Thompson R[3], 5 Szabo T[5], Thompson M[4], Ehrhart F[6,7], Kaliyaperumal R[4], Sernadela P[8], Reihs R[9], da Silva Santos LOB[10,11], Wilkinson MD[12], Müller H[9], Oliviera JL[8], Evelo C[6,7], Taruscio D[2], 't Hoen PA

[1]University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [2]National Centre for Rare Diseases, Istituto Superiore di Sanità , Rome, Italy; [3]Newcastle University, Newcastle upon Tyne, The United Kingdom; [4]Leiden University Medical Center, Leiden, The Netherlands; [5]Murdoch University, Murdoch, Australia; [6]Department of Bioinformatics, Maastricht University, The Netherlands; [7]Rett Expertise Centre - GKC, Maastricht University Medical Center, The Netherlands; [8]Universidade de Aveiro, Aveiro, Portugal; [9]Medical University of Graz, Austria; [10]Dutch Techcentre for Life Sciences, Utrecht, The Netherlands; [11]Vrije Universiteit, Amsterdam, The Netherlands; [12]Universidad Politécnica de Madrid, Spain

Presenting author: Annika Jacobsen
Contact: a.jacobsen@lumc.nl

Genotype-phenotype and translational research on rare diseases (RDs) depends on combining data from biobanks, knowledge-bases, patient registries, and "omics" sources. RD data are sparse, often "sensitive" and distributed across countries and institutes. Currently, RD researchers spend a lot of time getting access to different datasets and reconciling data ambiguities. An infrastructure where data are readily accessible and harmonized would boost RD research. However, with 5000-7000 RDs, the scale and ethical and legal bottlenecks make a central data warehouse impossible to maintain.

We present a "rare disease data linkage service plan" that applies the principles of Findable, Accessible, Interoperable, and Reusable (FAIR) data for humans and computers at the source to create a decentralised infrastructure. RD stakeholders, infrastructure experts (i.e. from ELIXIR and BBMRI), projects such as RD-Connect, ELIXIR-EXCELERATE, and patient organisations support the plan. The plan brings together an international interdisciplinary collaboration and co-investment of RD stakeholders, FAIR data experts and software engineers. They support RD data managers in the data "FAIRification"• process and services that reduce the effort to combine data for computational analysis.

The initial step of the plan is to make Duchenne Muscular Dystrophy (DMD) patient registries FAIR using specific ontologies such as Human Phenotype Ontology and the Orphanet Rare Disease Ontology. Ontological models will be built in order to answer specific cross-resource questions by DMD researchers. The software and ontological models that are used for the DMD use case are shared with the community to be reused for similar cases, thus stimulating convergence within the RD domain. We acknowledge the generous support from RD stakeholders, RD-Connect, ELIXIR, ELIXIR-EXCELERATE, BBMRI-NL, ODEX4All and FAIR-dICT.

P17 ePGA: a platform for PharmacoGenomics variant exploration and validation.

Kanterakis A[1], Lakiotaki K[1], Kartsaki E[1], Katsila T[2], Patrinos G[2], Potamias G[1]

[1]Institute of Computer Science, Foundation for Research and Technology - Hellas (FORTH), Heraklion, Crete, Greece; [2]Department of Pharmacy, School of Health Sciences, University of Patras, Patras, Greece

Presenting author: Alexandros Kanterakis
Contact: kantale@ics.forth.gr

Today there is a plethora of Locus Specific Mutation Databases (LSMDs) that provide invaluable information regarding the genotype - phenotype interaction for certain genetic variants.

A class of LSMDs focus on variants with PharmacoGenomics (PGx) interest.

These variants have a proven relationship to the efficacy and metabolizing status of a wide set of administered drugs for various diseases.

The proper exploitation of this knowledge in a healthcare system or clinical setting can improve the choice of therapeutic targets and avoid potential adverse reactions.

Pharmacogenomics is in the first line of clinical genetics since is promises to deliver directly applicable health guidelines tailored to an individual's genetic profile.

In this work we present ePGA (electronic PharmacoGenomic Assistant) which is mainly an LSMD for known PGx variants.

The primary source of information is other similar LSMDs (like PharmGKB) on top of which we have applied very stringent quality control methods to verify and additional annotate the listed variants.

ePGA offers a simple, intuitive and very fast interface for variant / drug / disease browsing.

This interface has been extended to include haplotype information.

All variants include information for the purpose of verifying their existence in a sequenced or genotyped sample.

It also offers an online haplotype matching algorithm.

Finally it offers an API and an interface where ORCID authenticated researchers can submit novel PGx information.

This information is further analyzed and after quality control is inserted in ePGA along with proper attribution to the original submitter.

P18 Body weight of Japanese DMD boys comparing with normal growth charts

Kimura E[3], Takanoha-Homma S[1], Takeuchi F[2,3], Yonemoto N[3,4], Nakamura H[3]

[1]Department of Nutrition Management, National Center of Neurology and Psychiatry, Japan; [2]The John Walton Muscular Dystrophy Research Centre, Newcastle University, UK; [3]Translational Medical Centre, National Center of Neurology and Psychiatry, Japan; [4]Department of Biostatistics, Kyoto University School of Public Health, Japan

Presenting author: En Kimura
Contact: enkimura@ncnp.go.jp

Purpose: Body weight of DMD patient is an important indicator. We present data analysis of individual body weight in the Remudy DMD/BMD database to clarify the age-specific body weight of DMD patients.

Methods: The study was a cross-sectional study. We analyzed the body-weight data in a national dystrophinopathy registry in Japan, Remudy, from July 2009 to June 2012.

Results: There were 615 individual body weight data in the Remudy database, excluded 174, then classified by age, the neonatal group (0-5 years): 90, the child and adolescence group (5.1-17.9 years): 369, and the over 18 group: 156. The weight-aged curves showed body weight of patients were quite varied, especially, over 15 years of their age. Tenth percentiles and median weights from DMD patients were lower than the standard weights in all ages.

Discussion: We presented real body weight data in the present-day Japan comparing normal boys, based on the accuracy of diagnosis of DMD, with evaluation of a series of data from newborn to adult DMD patients, including the body weight data of the patients between 0 and 5 years of age.

Conclusion: We presented baseline body-weight of DMD boys from broad age-ranged registry database, as a fundamental data for nutrition assessment and management.

P19 **Strategy to support and improve quality of rare diseases registries**

Posada-de-la-Paz M[1], Lopez E[1], Ahmed F[2], Coi A[3,4], Santoro M[3,4], Bianchi F[3,4], Weinbach J[5], Landais P[6], Rubinstein YR[7], Torreri P[8], Gainotti S[9], Carta C[8], Ambrosini A[10], Bros-Facer V[11], Renault D[11], von Gizycki R[11], Van Meel M[11], Popa V[11], Lemonnier L[11], Taruscio D[8]

[1]Institute of Rare Diseases Research, ISCIII, SpainRDR and CIBERER, Madrid, Spain; [2]Professor FRCPCH SamsonGemmell Chair of Child Health, Consultant in Paediatric Endocrinology Royal Hospital for Children, Glasgow School of Medicine, University of Glasgow United Kingdom; [3]Institute of Clinical Physiology, National Research Council, Pisa, Italy; [4]Fondazione Toscana Gabriele Monasterio (FTGM), Pisa, Italy; [5]RaDiCo, The French National Programme on Rare Disease Cohorts. National Institute of Health and Medical Research, UMR S933, Paris, France. www.radico.fr; [6]EA2415 Clinical Research Institute, Montpellier University and RaDiCo, INSERM UMRS 933, Hopital Trousseau, Paris; [7]Special Volunteer to the National Information Center of Health Services Research & Health Care Technology, National Library of Medicine/ National Institute of Health, USA French National Institute of Health and Medical Research, Paris France; [8]National Centre for Rare Diseases, Istituto Superiore di Sanità , Rome, Italy; [9]Bioethics Unit, Office of the President, Istituto Superiore di Sanità, Rome, Italy; [10]Fondazione Telethon, Milan, Italy; [11]Member of the Patient Advisory Council of RD-Connect coordinated by EURORDIS-Rare Diseases Europe

Presenting author: Yllka Kodra
yllka.kodra@iss.it

In the field of rare diseases, registries are powerful instrument to develop clinical research, to facilitate the planning of appropriate clinical trials, to improve patient care and support healthcare planning. Patient registries will constitute also key infrastructure systems to support the forthcoming activities of European Reference Networks (ERNs) on Rare Diseases. In fact, according to the Directive 2011/24/EU, one main aim of ERNs is to “reinforce research (and), epidemiological surveillance like registries”. A rapid proliferation of rare diseases registries has occurred during the last years and significant variability exists in their structure, aims, data content and governance. There is an urgent need for a strategy that supports their quality. In response to these heterogeneities, in the framework of the RD-Connect project and thanks also to our experience based on the EPIRARE project, a group of experts, including members of Patients Organisations, is collaborating to create guidance on the minimum requirements and standards of a high quality registry. The output of the working group will be the development of recommendations, methodological tools and standard operating procedures to define a quality registry complying with a list of quality indicators. Those indicators should provide description and evaluation of all aspects related to the registry activities, from inclusion of new cases to the dissemination of the final data analysis reports. These tools will be useful instruments in helping registry curators and owners for their self-quality assessment. Training programs, such as the International Summer School on Rare Diseases Registries, organised yearly by National Centre for Rare Diseases (Istituto Superiore di Sanità), will be a good place to empower the existing and the new registry operators on the importance of registry data quality.

P20 Integration of the Spanish Undiagnosed Rare Diseases Program (SpainUDP) with local, national and international resources on rare diseases

López E[1], Bermejo E[1], Martínez-Delgado B[2], Gómez-Mariano G[2], Javier Alonso F[2], Monzún S[3], Cuesta I[3], Alonso V[1], Posada M[1]

[1]Institute of Rare Diseases Research, IIER-ISCIII & Centre for Biomedical Network Research on Rare Diseases, CIBERER (Madrid, Spain); [2]Institute of Rare Diseases Research, IIER-ISCIII (Madrid, Spain); [3]Bioinformatics Unit, ISCIII (Madrid, Spain)

Presenting author: Estrella López
Contact: elopez@isciii.es

SpainUDP aims to offer a multidisciplinary approach to those patients who have long sought a diagnosis without any success. This complex approach requires the establishment of a series of relationships between this Program and diverse RD resources at the local, national and international level.

In a first phase of the protocol, undiagnosed cases are sent to SpainUDP through patient organizations and hospitals. Clinical information is stored in the Spanish National RD Registry and biosamples in the Spanish National RD Biobank. Both resources are interoperable by means of a centralized data-management system, which allows that clinical data is linked to biosamples data at the national level. Also, they are connected to the RD-Connect platform through the ID-Card Catalogue, an international directory of RD registries and biobanks, and the Sample Catalogue, useful to share individual biosamples data at the international level.

In a second step, WES experiments are carried out in the Human Genetics laboratories of the IIER. Raw genomic data from sequencing experiments is realigned and reprocessed through a standard pipeline and held in the central RD-Connect database. On the other hand, phenotypic terms are extracted from the clinical documents stored in the Registry, mapped to HPO terms and uploaded into PhenoTips (PT), an open source software tool used for collecting phenotypic information which is linked to genetic information stored in the genomics RD-Connect platform. Also, the system allows to push data from PT to Phenome Central (PC), a central repository that facilitates the matching of cases with similar clinical and genotypic profiles within larger international networks, such as the UDNI.

RD-Connect, PC and UDNI are participating in the Matchmaker Exchange (MME), a federated platform that enables to communicate specific case details to find cases with similar profiles. Since SpainUDP is contributing with its undiagnosed cases to these three international initiatives, it is indirectly linked to the remaining projects that belong to MME. Thus, it allows a comparison of patient data from SpainUDP across multiple projects submitting data to the MME platform

P21 **Prioritising Participation - rare disease patient views of taking part in genome sequencing research**

McCormack P

Newcastle University

Presenting author: Pauline McCormack
Contact: pauline.mccormack@ncl.ac.uk

A workshop was organised help identify and prioritise critical issues for social and ethical research around genome sequencing, by consulting representatives of rare disease groups in the UK. The workshop was attended by 14 patient advocates and used Open Space methodology which encouraged self-organisation and allowed workshop participants to decide the agenda and direction for the day. The day was divided into 2 sessions.

The first session asked explored: what are your views on getting involved with genome sequencing? Participants noted that in order to become involved in genome sequencing research they would ask what the immediate benefits might be for them, their family and the wider community. They would need to be convinced that there was a purpose to participation and that the project would deliver on its objectives and participation should not be too onerous. Expectations need to be managed, including providing outlines of: timescale and different stages of process; risks, safety and privacy; and feedback. Negative examples were provided of people who had joined genome sequencing research projects more than 12 months ago, and had not yet received any results, recontact or feedback.

The second session asked: what are your views on receiving results from genome sequencing? Workshop participants would want an answer to questions under the theme of â€˜what does this meanâ€™? This would include answers to practical, personal questions around the significance of results, treatments and prognosis. They would want chances to discuss wider impact, for the future, for the rest of their family, and how to deal/cope with unwelcome outcomes. If a diagnosis is given, they would want to be guided as to the next steps and be made aware of outside support in the form of patient organisations. Parents receiving results about children would want information about the long term prognosis. If no diagnosis is available, participants would expect to be guided through the next steps - including being assured that there were next steps. Clinicians delivering results should be appropriately trained and sensitive to the impact of a diagnosis/non diagnosis on families.

P22 Federation Framework for Biobank Data Sharing

Merino, R[1], van Enckevort D[2], Chiuhui M[3], Monaco L[3]

[1]Karolinska Institute; [2]UMCG; [3]Fondazione Telethon

Presenting author: Roxana Merino
Contact: roxana.martinez@ki.se

We have developed a generic software framework for making available data from different and heterogeneous data sources. The software components of the federation are: (1) Mapper: a web service to map local data to a pre-established standard, (2) local file repository monitoring for each member of the federation, (3) centralised data indexing, visualisation and querying. The framework uses open-sources software based on ElasticSearch and in-house developed software for the mapping and software modules integration. The use case is the RD-Connect biobank network and the standard for the federation is a data model based on MIABIS standard.

P23 **Identification of common disease signatures in blood and brain tissue following a novel systems approach for Huntington's Disease biomarker discovery**

Mina E, Toonen L, van Roon-Mom W, Hettne K, 't Hoen PAC, Mons B, Roos M

Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands

Presenting author: Eleni Mina
Contact: e.mina@lumc.nl

Huntington's disease (HD) is a devastating brain disorder with no effective treatment or cure available. The scarcity of brain tissue makes it hard to study changes in the brain and impossible to perform longitudinal studies. However, peripheral pathology in HD suggests that it is possible to study the disease using peripheral tissue to monitor for disease progression or efficacy of novel therapies. In our previous study we showed that indeed HD blood exhibits changes that are similar to brain at a functional level, but not necessarily at the level of individual genes. We were able to identify two disease signatures in HD that are common between blood and brain: immune response and spinocerebellar ataxias.

Our methodology uses a unique approach to characterize functional similarities encompassing a weighted gene coexpression network analysis and exhaustive literature-based functional analysis. Methods that compare only gene expression and gene overlap are much more limited when comparing heterogeneous tissues.

In order to further validate our results and demonstrate their utility as biomarkers for therapeutic efficacy, we will apply the same methodology to discover disease signatures in data obtained from the YAC128 mouse model (blood and brain). In addition, to test if these signatures can be used as peripheral biomarkers of the disease in a clinical trial, we will apply our methodology to the same mouse model treated with antisense oligonucleotides (ASO). The disease mouse signatures will be used as a monitoring tool to determine whether those signatures respond to the ASO treatment.

Our approach is very promising not only for HD but also for other brain disorders that are in need of biomarkers from more accessible tissues. With this project we will also obtain information about the degree of similarity between the disease signal in humans and mouse models. This will be beneficial for past and future studies that use mouse models to investigate HD and will help to focus on that particular part of the signal that is shared with humans. Our approach will open new gateways towards biomarker discovery in a more robust and less time-consuming manner.

P24

Clinical Innovation Network

New strategy to improve the environment of the clinical development

Nakamura H[1], Takeda S[2]

[1]Translational Medical Center, National Center of Neurology and Psychiatry, Japan; [2]National Institute of Neuroscience, National Center of Neurology and Psychiatry, Japan

Presenting author: Harumasa Nakamura
Contact: hnakamura@ncnp.go.jp

Real-world evidence is derived from Real-world data (RWD), and can inform drug/device development, research on outcomes and health care systems, safety surveillance, well-controlled effectiveness studies, and patient care. Clinical Innovation Network (CIN) is a new strategy supported by Ministry of Health, Labour and Welfare Japan to improve the environment of the clinical development that enables efficient clinical trial by utilizing patient registry that is a primary key source of RWD. Usefulness of patient registry in clinical trial/research in the clinical development can be broadly outlined as follows; market research, survey on the feasibility of clinical trial, creation of protocol, recruiting patients to clinical trial, establishing control group in non randomized control study, post-marketing survey and safety measures. To promote this, it is required to establish a network of the related institutions and to form the clinical study consortium in cooperation with the industry and academia, as well as regulatory agency. The following issues were considered as common problems regardless of the individual disease area. 1) Gathering Information about existing patient registries, analysis and listing in the form that is easy to use for pharmaceutical companies and others, 2) Ethical issues and how to handle personal information, 3) Standardization of registry items and information technology system, 4) How to use and apply patients registry data to clinical trial/clinical research. In addition, infrastructure of the central support to provide the function of "One-Stop"service is demanded by pharmaceutical companies. Since 2016, The Japan Agency for Medical Research and Development (AMED), Japanese research funding agency, has engaged in research for CIN activity, and many studies on CIN has just began.

P25 **SCALEUS: Semantic Web Services Integration for Rare Diseases Research**

Sernadela P, Oliveira JL

University of Aveiro

Presenting author: Pedro Sernadela
Contact: sernadela@ua.pt

Rare diseases studies are normally rare, heterogeneous, and distributed over different research centres and clinical labs. To enable an easy access and improved identification of potential treatments, relevant data needs to be processed and combined from a wide range of data warehouses, typically non-interoperable. In this way, rare disease research requires efficient and extensible systems for data integration and distributed access that easy to deploy, configure and use. To facilitate this transition, we have developed Scaleus, an open source semantic web migration tool that can be deployed on top of traditional rare diseases repositories, to bring knowledge, inference rules, and query federation to the existent data. This web-based platform offers, in a single package, straightforward data integration and semantic web services that help developers and researchers in the creation process of new semantically enhanced information systems. A Scaleus-based demonstrator that supports cross-resource queries over traditional rare disease resources, including biobanks (biological sample data), patient registries, genomic data and public repositories of biological relations is available at http://bioinformatics.ua.pt/rd-connect-demo/.

P26 Genetic Profiling Of Rare Haematological Malignancies

Stojiljkovic M, Tosic N, Pavlovic S

Institute for Molecular Genetics and Genetic Engineering University of Belgrade, Belgrade, Serbia

Presenting author: Maja Stojiljkovic
Contact: maja.stojiljkovic@imgge.bg.ac.rs

Introduction: Rare hematological malignancies are a heterogeneous group of the disease. Malignant transformation of a hematopoietic stem cell is a result of gradual accumulation of mutations in a number of genes involved in basic cellular processes. One of the main goals in the study of hematological malignancies is the definition of genetic markers crucial for the development of the disease. In our study we applied amplicon based next generation sequencing (NGS) approach, using TruSeq Amplicon Cancer Panel (TSCAP) for 48 cancer-related genes (Illumina, Inc). We analyzed DNA samples from 19 patients with primary diffuse large B-cell lymphoma of central nervous system (DLBCL CNS), as well as DNA samples from 20 childhood acute myeloid leukemia (cAML) and 20 adult acute myeloid leukemia (aAML) patients.

Results: In primary DLBCL CNS patients, we identified a total of 920 variants in the coding regions (median per patient 43). Most of protein-changing mutations were detected in 8 genes: CTNNB1, PIK3CA, PTEN, ATM, KRAS, PTPN11, TP53, and JAK3. Our findings strongly suggested that the TP53 and ATM genes were involved in the molecular pathophysiology of primary DLBCL CNS. Mutations in the PTEN and SMO genes could affect survival of the patients. In cAML and aAML patients, we identified a total of 412 variants in the coding regions (median per patient 3 in both groups). The prevalence of the most frequent single gene AML associated mutations differed in cAML and aAML patient cohorts. Protein-changing variants were found in tyrosine kinase genes or genes encoding tyrosine kinase associated proteins (JAK3, ABL1, GNAQ, and EGFR) in cAML, while among aAML, the prevalence is directed towards variants in the methylation and histone modifying genes (IDH1, IDH2, and SMARCB1).

Conclusions: Our results showed that AML contains small number of genetic alterations, contrary to other hematological malignancies like lymphoma. Application of NGS technology resulted in the information about genetic profile of each patient. Individual genetic profiling leads to highly specific personalized therapy of hematological malignancies.

P27 **MOLGENIS 3.x updates: patient registries, DNA/RNA processing, FAIRification tools and great pathogenicity classification**

Swertz M[1], van der Velde J[1], van Enckevort D[1], van Gijn M[2], Sinke R[1], Sikkema B[1], van den Akker P[1], MOLGENIS open source development team

[1]University of Groningen, University Medical Center Groningen, Genomics Coordination Center & Dept of Genetics, Groningen, the Netherlands; [2]University Medical Center Utrecht, Department of Medical Genetics, Utrecht, the Netherlands.

Contact: m.a.swertz@gmail.com, joeriv@gmail.com, d.j.van.enckevort@umcg.nl

Presenting author: Morris Swertz
Contact: m.a.swertz@gmail.com

We here report major updates to the MOLGENIS flexible open source software suite for scientific data, highlighting applications in the rare disease domain.

We are in particular excited about Gene-Aware Variant INterpretation (GAVIN, http://molgenis.org/gavin), a new method that accurately classifies variants in disease genes for clinical diagnostic purposes. In a benchmark on 18 clinical gene sets, we achieve a sensitivity of 91.4% and a specificity of 76.9%. This accuracy is unmatched by 12 best existing tools (van der Velde et al, Genome biology 2017).

In addition we have upgraded MOLGENIS core such that any data can now be loaded and queried. In particular useful you can now change data structure online. This is now used for all kinds of omics and phenotype research including RD-connect sample catalogue (see other poster) and BBMRI-ERIC Directory of biobank collections. And in particular relevant for rare disease patient registries and biobanks, we have updated MOLGENIS patient registry suite (e.g. http://deb-central.org and http://chd7.org).

Subsequently, we have dramatically improved MOLGENIS system for data harmonization and "FAIRification" (Pang et al, Bioinformatics 2017). The result is MOLGENIS/connect (www.molgenis.org/connect), a system to find, match and pool data from different data sources. The system automatically shortlists relevant source attributes from thousands of candidates using ontology-based query expansion to overcome variations in terminology. Then it also generates algorithms that transform source attributes to a common target DataSchema, representing a vast reduction in the human effort and expertise needed to pool data.

Finally, we upgraded our DNA and RNA analysis pipelines to latest state of the art, which includes GAVIN, and is used for routine DNA diagnostics of the UMCG (get started at https://molgenis.gitbooks.io/molgenis-pipelines/). This includes GAVIN which allowed UMCG diagnostics department to reduce variants needing interpretation by hand in half without missing anything compared to human curation. All software is available as open source at http://molgenis.org.

P28 Deep learning in Rare Diseases: the road to biomedical knowledge integration

Valencia A[1,3], Cirillo D, Capella-Gutierrez S, Topf A[4], Azuma Y[4], Evangelista T[4], Peter-Bram 't Hoen PAC[6], Lochmüller H[4]

[1]Barcelona Supercomputing Center (BSC), Barcelona, Spain; [2]Spanish National Cancer Research Institute (CNIO), Madrid, Spain; [3]Spanish National Bioinformatics Institute (INB), Spain; [4]The John Walton Muscular Dystrophy Research Centre. MRC Centre for Neuromuscular Diseases. Newcastle University, Newcastle upon Tyne, UK; [5]Center for Human and Clinical Genetics. Leiden University Medical Center (LUMC). Leiden, The Netherlands.

Presenting author: Alfonso Valencia
Contact: alfonso.valencia@bsc.es

Deep learning (DL) is a class of machine-learning techniques that makes use of multiple layers of non-linear data transformations to automatically discover features needed for detection and classification. In the context of Biomedicine, the increased amount of available computation and data has brought DL at the forefront of artificial intelligence applications for healthcare and research due to its ability at discovering intricate structures in high-dimensional data.

A special class of DL methods are Recurrent Neural Networks (RNNs), a powerful system for tasks that involve sequential inputs. RNNs process a sequence, element by element, maintaining the information on the dependencies of all the past elements in the sequence. RNN have obtained remarkable results in machine translation.

Clinical data, comprising disease-associated phenotypes (or symptoms) as well as molecular and functional annotations, are commonly represented in the form of ontologies, whose dependencies can be converted to sequential orderings through topological sorting algorithms. This sequential representation permits the application of encoder-decoder RNNs to facilitate the interconversion and integration of different ontologies. In this way, patient-specific clinical symptoms can be automatically translated into patient-specific molecular annotations, and the other way around, while keeping the coherence of the information and adding significance scores. The development of DL methods that are able to integrate and unify biomedical knowledge without losing dependencies and relations of its graph representation will constitute a major advance in the application of artificial intelligence to Biomedicine.

As a first test case of this new DL methodology will be study the possible molecular causes of the differential drug response in a cohort of patients with Congenital Myasthenic Syndrome (CMS) disease in collaboration with Hanns Lochmüller's team from The John Walton Muscular Dystrophy Research Centre.

P29 **RD-Connect Sample Catalogue**

van Enckevort D[1], Reihs R[2], Merino Martinez R[3], Wang M[4], Slofstra M[1], van der Geest M[1]*, Bijlsma M[1], The MOLGENIS development team, Cox D[5], Thompson R[5], Lopez Martin E[6], Posada M[6], Casareto L[4], Mora M[7], Vella J[8], Benvenuti S[4], Müller H[2], Monaco L[4]+, Swertz M[1]+

[1]University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [2]Medical University of Graz, Graz, Austria; [3]Karolinska Institutet, Stockholm, Sweden; [4]Fondazione Telethon, Milano, Italy; [5]Newcastle University, Newcastle, UK; [6]Instituto de Salud Carlos III, Madrid, Spain; [7]Instituto Neurologico Carlo Besta, Milano, Italy, [8]University of Malta, Msida, Malta.

*Until July 2016. +Contributed equally

Presenting author: David van Enckevort
Contact: david.van.enckevort@umcg.nl

The RD-connect sample catalogue is the central repository with information on the availability of rare disease samples. As such it will play a crucial role in the ability of researchers to find relevant samples for their research. As such it should include the information from all biobanks in RD-Connect and the associated projects. We are collaborating with BBMRI-ERIC "Directory" to enable future growth to include all European rare disease biobanks.

The catalogue is build using the MOLGENIS framework, a flexible open source web application for scientific data (http://www.molgenis.org). In the last year we have been working on developing the catalogue into a production version to be deployed in the platform and the integration of data from the different biobanks. To facilitate biobanks in publishing their samples, either by hand or via an automated pipeline, we offer several tools for data ingest, such as manual data entry, batch upload through Excel (piloted with NCL, ISCIII, UCL, Malta), and a REST API (piloted with TNGB). In addition, we included tools for data integration and harmonisation such as the mapping service and biobank connect which eases the conversion between local sample registers and the RD-connect standard.

Future developments will focus on lowering the barrier for biobanks to contribute their sample data by improving the tooling within MOLGENIS based on the lessons learned, extending the FAIR implementation of the catalogue as part of the RD-Connect Linked Data plan and implementing support for additional federative approaches as piloted by Karolinska Institutet.

P30 The Malta BioBank / BBMRI.mt

Vella J, Borg J, Grech L, Soler D, Scerri C, Felice A

Presenting author: Joanna Vella
Contact: joanna.vella@um.edu.mt

The Malta BioBank forms part of the new inter-faculty Centre of Molecular Medicine and BioBanking at the University of Malta. It hosts the Maltese National Node (BBMRI.mt) in BBMRI-ERIC. It is a founding partner in EuroBioBank and RD-Connect and holds an online catalogue of samples. It is also an associate partner in EuRenOmics. BBMRI.mt is strategically positioned to engage neighbouring Mediterranean countries in biobanking.

The Population Bank holds a reference Maltese exome which could be used as an epidemiological tool. A research co-operative is being developed whereby research partners share ownership of the projects.

BBMRI.mt participated in the 2016 BBMRI-LPC whole exome sequencing call with two collaborative research projects focused on mitochondrial disorders and undiagnosed neuropathies.

Further studies of a large number of samples from the biobank revealed ones that had the haematological phenotype of Î² thalassaemia yet without a Î² globin gene mutation though with mutations in the transcription factor KLF1 and now known as a pseudo-Î²-thalassaemia.

The Malta BioBank partnered with the National Alliance for Rare Diseases Support - Malta and is very active in public outreach on rare diseases. A high level workshop "Integrating Research and Healthcare for Rare Diseases: a structured cooperation with high community added value" and a conference on "Development and Access of Medicines for Rare Diseases" were organised in parallel to the Informal meeting of EU Health Ministers in Malta as part of the Presidency agenda of the Council of the EU.

P31 Quality of whole exome sequences in RD-Connect

Whalley J[1,2], Trotta JR[1,2], Laurie S[1,2], Matalonga Borrel L[1,2], Gut M[1,2], Beltran S[1,2], Gut I[1,2], on behalf of RD-Connect

[1]CNAG-CRG, Centre for Genomic Regulation (CRG), Barcelona Institute of Science and Technology (BIST), Barcelona, Spain; [2]Universitat Pompeu Fabra (UPF), Barcelona, Spain

Presenting author: Justin Whalley
Contact: justin.whalley@cnag.crg.eu

RD-Connect has over 1700 whole exome sequences, from several sequencing centres using different exome capture kits under varying protocols. To assess the quality of these diverse whole exome sequences, we assembled a limited set of non-redundant measures. The quality control measures, calculated for each sample on the target regions sequenced, take into account several features of coverage, as well as looking into discrepancies between paired reads. For each quality control measure we defined a threshold and assigned a star for each quality control measure a sample passed. This star rating provides researchers within RD-Connect, at a glance, a summary of the sequencing quality of the samples they are interested in.

The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement No. 305444 (RD-Connect) and funding from ELIXIR-EXCELERATE (EC321 H2020 #676559).

P32 Using the tranSMART data exploration tool to define renal disease mechanisms

Ascani H, Steck B, Kincaid C, Patterson R, Dull R, Gates C, Nair V, Eichinger F, Ju W, Kretzler M

Applied Systems Biology Core, Internal Medicine/Bioinformatics, University of Michigan Medical Center, Ann Arbor, MI, USA.

Presenting author: Heather Ascani
Contact: ascanihk@umich.edu

A significant challenge in collaborative science and research is designing an “informational commons” - a virtual space for researchers to share and explore large-scale datasets. To address this challenge, the University of Michigan supports and utilizes tranSMART, a software tool that simplifies data exploration and uniform meta-analysis across multiple cohorts, diseases and datasets.

The tranSMART platform is an open-source translational medicine platform, originally developed by Johnson and Johnson. It allows user-specified exploration of cohort-study datasets along the entire genotype-to-phenotype continuum. The tranSMART platform enables users to upload per-patient data of multiple data types. Users can explore the data by performing a variety of analyses, generating hypotheses and developing ancillary research questions to share with other fellow researchers. To date, we have established three separate tranSMART instances and curated data for over 1,800 patients. Across the three instances, users will find prospective clinical phenotypes, histological descriptors, environmental exposures, genotypic information and gene and protein expression profiles.

Transcriptomic data of human renal disease can provide critical information to identify de novo molecular pathways associated with kidney disease. tranSMART empowers researchers who, perhaps, don't have statistics or bioinformatics knowledge to employ sophisticated systems-biology tools to extract key information and to generate hypotheses for further experimental investigations.

The University of Michigan continues to support tranSMART, facilitating access to human kidney-disease clinical and gene-expression data for the renal research community. tranSMART empowers geographically-distributed research networks to jointly advance research, contributing to the diagnosis, prognosis, intervention, and ultimately the improvement of patient care.

P33 Binding capacity of podocin dimers in view of their pathogenicity

Balogh E[1], Miká A[1], L'Auné G, Arrondel C[3], Schay G[4], Antignac C[5], Mollet G[6], Tory K[7]

[1]MTA-SE Lendület Nephrogenetic Laboratory, Budapest, Hungary; and 1st Department of Pediatrics, Semmelweis University, Budapest, Hungary; [2]MTA-SE Lendület Nephrogenetic Laboratory, Budapest, Hungary; [3]Institut National de la Santé et de la Recherche Médicale (INSERM) Unité Mixte de Recherche (UMR) 1163, Laboratory of Hereditary Kidney Diseases, Paris, France; and Paris Descartes University-Sorbonne Paris Cité, Imagine Institute, Paris, France; [4]Department of Biophysics and Radiation Biology, Semmelweis University , Tűzoltó utca 37-47, Budapest H-1094, Hungary; [5]Assistance Publique-Hôpitaux de Paris, Department of Genetics, Necker Hospital, Paris, France; Inserm UMR 1163, Laboratory of Hereditary Kidney Diseases, Paris, France; and Paris Descartes University - Sorbonne Paris Cité, Imagine Institute, Paris, France; [6]Institut National de la Santé et de la Recherche Médicale (INSERM) Unité Mixte de Recherche (UMR) 1163, Laboratory of Hereditary Kidney Diseases, Paris, France; and Paris Descartes University -Sorbonne Paris Cité, Imagine Institute, Paris, France; [7]MTA-SE Lendulet Nephrogenetic Laboratory, Budapest, Hungary; and 1st Department of Pediatrics, Semmelweis University, Budapest

Presenting author: Eszter Balogh
Contact: baloghesztermail@gmail.com

NPHS2, encoding podocin, is the most frequently mutated gene in steroid-resistant nephrotic syndrome. We recently showed that the pathogenicity of its frequent R229Q variant depends on the trans-associated mutation, as it is only pathogenic with some mutations. Based on molecular modeling, we predicted that the pathogenic associations form abnormal heterodimers.

We aimed to determine the binding capacity of pathogenic and non-pathogenic podocin variants with different levels of truncation.

Podocin variants (wt, R229Q, R286Tfs*17, A317Lfs*31, F344* and F344Lfs*4) were transiently expressed in HEK293 cells, extracted by immunoprecipitation, eluted by competitive peptide elution and stained by either Alexa 488 and 555 maleimides. Differently stained podocin variants were mixed two by two and FRET was measured by fluorescence lifetime spectrometer. All measurements were repeated three times.

We found the heterodimerization of both R229Q and wt podocin to be highly dependent on the C-terminal truncation of the interacting podocin: while the R286Tfs*17 podocin - lacking all three C-terminal helical regions - had no significant effect on fluorescence lifetime, A317Lfs*31, F344* and F344Lfs*4 all significantly reduced that of both wt and R229Q podocin, A317Lfs* the most efficiently. The amino acid changes encoded by the frameshift sequence of the F344Lfs*4 podocin exerted a different effect on its dimerization with the wt and R229Q podocin by increasing the fluorescence lifetime of the former and decreasing the latter. Nevertheless, we found no clear-cut difference in the binding capacity of the pathogenic and the non-pathogenic dimers: that of R229Q-F344Lfs*4 was comparable to that of several non-pathogenic dimers.

In conclusion, as the R286Tfs* does not form dimers, the dimerization capacity of podocin is determined exclusively by its C-terminal part. As the R286Tfs*17 podocin is localized to the plasma membrane, the dimerization of podocin is not necessary for the membrane-targeting. Though C-terminal dimerization plays a key role in determining the pathogenicity of R229Q podocin, it cannot be simply explained by an altered binding capacity.

P34 A Monogenic Cause in Half Cases of Autosomal Dominant FSGS

Boyer O[1], Gribouval O[1], Tâte MJ[1], Servais A[3], Bole C[4], Nitschke P[5], Schaefer F[6], Antignac C[1,7]

[1]Inserm U1163, Imagine Institute, Paris Descartes University; [2]Pediatric Nephrology, Necker Hospital; [3]Adult Nephrology & Transplantation, Necker Hospital; [4]Genomic Core Facility, Imagine Institute; [5]Bioinformatics Core Facility, Paris Descartes University, Paris, France; [6]Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, University of Heidelberg, Heidelberg, Germany; [7]Genetic Department, Necker Hospital, Paris, France

Presenting author: Olivia Boyer
Contact: olivia.boyer@aphp.fr

The advent of next generation sequencing (NGS) has tremendously facilitated the genetic diagnosis in hereditary FSGS, and podocyte gene panels are increasingly used as the first step of genetic analyzes in familial cases.

We aimed to determine the causative gene mutations through Sanger sequencing and NGS in a large worldwide cohort of 140 families (253 patients) with FSGS starting during childhood or adulthood and an apparent autosomal dominant (AD) inheritance. Monogenic cause was identified in 66 families (47%). The mutation rate did not differ according to the size of pedigrees or the number of affected generations. The segregation was verified when several DNA samples were available. The most prevalent gene mutations were the following: INF2 (20/66 families, 30%), COL4A3-5 (17/66, 26%), and WT1 (11/66, 17%). ACTN4 and TRPC6 mutations were detected in only 1 and 5 families (1.5% and 7.5%) respectively. An X-linked transmission was also possible in the 8 families with COL4A5 mutations and at least one affected relative had microscopic hematuria in 5/8, but no deafness was reported. Interestingly, we identified WT1 mutations in families with late-onset FSGS diagnosed at a median age of 19 years and no Wilma's tumor, including 3 pedigrees with fertile males who transmitted the mutation. Among the 59 different mutations identified, 30 were published pathogenic mutations (51%), 6 were novel truncating mutations (10%), 12 were novel missense variants in functional domains of the protein (20%) and 12 were predicted damaging missense variants (20%).

We conclude that 1) a high mutation rate is observed in families with AD-FSGS 2) isolated FSGS could result from mutations in collagen and developmental podocyte genes that should be included in all NGS diagnosis approaches to FSGS 3) a third of mutations are only probably pathogenic requiring further segregation/functional studies. This highlights the complexity of mutational analysis in identifying the true and nothing but the true pathogenic mutations in hereditary FSGS.

P35

A Heterozygous de novo Mutation in SLC41A1 Causes Hypomagnesemia and Renal Magnesium Wasting

de Baaij J[1], Arjona FJ[1], Schlingmann KP[2], Burtey S[3], Thomassen M[1], van der Wijst J[1], Knoers NVAM[4], Bindels RJM[1], Konrad M[2], Hoenderop JGJ[1]

[1]Department of Physiology, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, The Netherlands; [2]Department of General Pediatrics, University Hospital Münster, Münster, Germany; [3]Aix Marseille Université, INSERM, Vascular Research Center of Marseille, Marseille, France; [4]Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands

Presenting author: Jeroen de Baaij
Contact: jeroen.debaaij@radboudumc.nl

Over the last decades, the identification of hereditary hypomagnesemia-causing genes has increased our understanding of the mechanisms underlying renal magnesium (Mg2+) reabsorption. In the kidney, urinary Mg2+ excretion is determined in the distal convoluted tubule, as no Mg2+ is reabsorbed beyond this segment. In the distal convoluted tubule, the epithelial Mg2+ channel transient receptor potential melastatin type 6 (TRPM6) mediates active Mg2+ reabsorption from the pro-urine into the cell. However, to date the molecular identity of the proteins facilitating Mg2+ extrusion from the cell towards the blood remains elusive.

In this study, a three-year-old girl was identified with tetanic convulsions caused by severe hypomagnesemia and hypocalcemia. A Mg2+-loading test showed urinary Mg2+ wasting, demonstrating a renal origin of the disease. Whole exome sequencing identified a heterozygous de novo p.Ile98Phe mutation in the SLC41A1 gene. 25Mg2+ transport assays in human embryonic kidney 293 cells overexpressing SLC41A1 demonstrated that this transporter mediates cellular Mg2+ extrusion. To examine the pathogenicity of the mutation, a slc41a1 zebrafish knockdown model was generated using two separate morpholino approaches. Slc41a1 knockdown resulted in a 20% reduction of the total magnesium content. Overexpression of SLC41A1 in slc41a1-knockdown zebrafish restored the total magnesium content. Conversely, total magnesium levels were not normalized in slc41a1-knockdown zebrafish overexpressing the patient's SLC41A1 mutant. Co-expression of wild-type and mutant SLC41A1 in zebrafish disturbed the Mg2+ balance, demonstrating that mutant SLC41A1 has a dominant negative effect over wild-type SLC41A1.

In conclusion, a heterozygous de novo mutation in SLC41A1 causes hypomagnesemia and renal Mg2+ wasting. These findings demonstrate the essential role of SLC41A1 in renal Mg2+ handling and maintenance of body Mg2+ balance. Based on our experiments, we propose that SLC41A1 may facilitate basolateral Mg2+ extrusion in the distal convoluted tubule.

P36 A zebrafish ctns mutant showing glomerular and tubular dysfunction: A new animal model for cystinosis

Elmonem M, Khalil R, Khodaparast L, Khodaparast L, Arcolino FO, Morgan J, Pastore A, Tylzanowski P, Ny A, Lowe M, de Witte PA, Baelde HJ, van den Heuvel LP, Levtchenko E

Department of Pathology, Leiden University Medical Centre, the Netherlands; Department of Cellular and Molecular Medicine, Switch Laboratory, VIB, University Hospitals Leuven, KU Leuven, Belgium; Department of Cellular and Molecular Medicine, Switch Laboratory, VIB, University Hospitals Leuven, KU Leuven, Belgium; Department of Pediatric Nephrology & Growth and Regeneration, University Hospitals Leuven, KU Leuven, Belgium; Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom; Laboratory of Proteomics and Metabolomics, Children's Hospital and Research Institute "Bambino GesÃ¹" IRCCS, Rome, Italy; Department of Development and Regeneration, Laboratory for Developmental and Stem Cell Biology, Skeletal Biology and Engineering Research Centre, University of Leuven, Leuven, Belgium; Laboratory for Molecular Bio-discovery, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium; Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom; Laboratory for Molecular Bio-discovery, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium; Department of Pathology, Leiden University Medical Centre, the Netherlands; Department of Pediatric Nephrology & Growth and Regeneration, University Hospitals Leuven, KU Leuven, Belgium; Department of Pediatric Nephrology & Growth and Regeneration, University Hospitals Leuven, KU Leuven, Belgium;

Presenting author: Mohamed Elmonem
mohamed.ibrahim@kuleuven.be

Cystinosin is a lysosomal membrane protein acting as a one way transporter of the amino acid cystine from the lysosomal compartment and into the cytoplasm. Pathogenic mutations of the human CTNS gene lead to defective cystinosin function, intralysosomal cystine accumulation and the development of cystinosis. In humans, kidneys are initially affected with generalized proximal tubular dysfunction (renal Fanconi syndrome), then the disease rapidly affects glomeruli and progresses towards end stage renal failure and multiple organ dysfunction. Animal models of cystinosis are limited, with only a Ctns knock-out mouse reported, showing cystine accumulation and late signs of tubular dysfunction but lacking the glomerular phenotype. We established and characterized a mutant zebrafish model with a homozygous nonsense mutation (c.706C>T; p.Q236X) in exon 8 of ctns. Cystinotic mutant larvae showed cystine accumulation, delayed development, and signs of pronephric glomerular and tubular dysfunction mimicking the early phenotype of human cystinosis patients. Furthermore, cystinotic larvae showed a significantly increased rate of apoptosis that could be partially ameliorated with cysteamine, the human cystine depleting therapy. Our data demonstrate that, ctns gene is essential for zebrafish pronephric podocyte and proximal tubular function and that the ctns-mutant can be used for studying the disease pathogenic mechanisms and for testing new therapeutic agents for cystinosis.

P37 Genetic findings in Adults with Sporadic Steroid-Resistant Nephrotic Syndrome

Servais A[2], Boyer O[1,3], Tête MJ[1], Bole C[4], Nitschke P[5], Schaefer F[6], Antignac C[1,7]

[1]Inserm U1163, Imagine Institute, Paris Descartes University; [2]Adult Nephrology & Transplantation, Necker Hospital; [3]Pediatric Nephrology, Necker Hospital; [4]Genomic Core Facility, Imagine Institute; [5]Bioinformatics Core Facility, Paris Descartes University, Paris, France; [6]Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, University of Heidelberg, Heidelberg, Germany; [7]Genetic Department, Necker Hospital, Paris, France

Presenting author: Olivier Gribouval
Contact: olivier.gribouval@inserm.fr

In recent years, proposals for genetic screening paradigms in Steroid-Resistant Nephrotic Syndrome (SRNS) preferentially addressed congenital, infantile onset and familial cases. Sporadic SRNS/FSGS adult patients are used to be only tested for the NPHS2 nonneutral p.R229Q polymorphism. To uncover the distribution of disease-causing gene mutations in an adult sporadic FSGS/SRNS population, we used a NGS panel in a cohort of adult patients.

We selected adult patients (age at onset of proteinuria above 18 years), with non syndromic biopsy proven FSGS and/or SRNS, without known family history. We used strict clinical criteria including no response to glucocorticoids but also to cyclosporine and no relapse after renal transplantation. We applied a NGS panel covering 37 genes to 132 adult patients.

Mean age at onset of proteinuria was 30.4 (18.1-84.0) years. Among the 132 patients who were tested, sixteen (12.1%) presented with mutation (13/132, 9.8%) or variant of unknown significance (3/132, 2.3%) in known monogenic steroid-resistant nephrotic syndrome genes and fourteen (10.6%) with APOL1 high risk allele. We identified 10 novel mutations including mutations in PAX2, INF2, NPHS2, MYO1E, and CD2AP genes. Collagen mutations represented 43.7% of all mutations. Mean age at onset of proteinuria was lower in the group with mutation than in patients with no mutation or APOL1 risk variant (25.9Â±8.2 vs 31.0Â±11.8, p=0.03). Mutations in non collagen genes were all found in patients younger than 30 years of age, whereas mutations in collagen genes were also identified in older patients until 50 years of age. Patients with mutation presented with lower eGFR at diagnosis (43.6Â±31.8 vs 87.4Â± 34.8 ml/min/1.73mÂ², p=0.006), reflecting a more severe disease. Age at ESRD was higher in patients with mutation in collagen genes than in patients with mutation in other genes (47.5Â±1.6 vs 24.8Â±3.6 years, p=0.02).

We identified a mutation or a variant of unknown significance in known monogenic SRNS genes in 12.1% of patients and APOL1 high risk allele in 10.6%. Collagen mutations causing Alport Disease were the more frequent mutations identified.

P38 Simultaneous sequencing of 37 genes identifies causative mutations in 70% of children with renal tubulopathies

Iancu D[4], Ashton E[1], Legrand A[2], Benoit V[3], Roncelin I[2], Venisse A[2], Zennaro MC[2], Jeunemaitre X[2], van 't Hoff WG[5], Walsh SB[4], Rotthier A[6], Del Favero J[6], Devuyst O[7], Schafer F[8], Jenkins L[1], Kleta R[4,5], Dohan K[3,9], Vargas Poussou R[2], Bockenhauer D[4,5]

[1]North East Thames Regional Genetics Service Laboratories, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; 2Département de Génétique, Hôpital Européen Georges Pompidou, Paris, France; [3]Center of Human Genetics, Institut de Pathologie et Génétique, Gosselies, Belgium; [4]Centre for Nephrology, University College London Institute of Child Health, London, UK; [5]Department of Pediatric Nephrology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; [6]Multiplicom N.V., Niel, Belgium; [7]University of Zurich, Institute of Physiology, Zurich Center for Integrative Human Physiology (ZIHP), Mechanisms of Inherited Kidney Disorders Group, Zurich, Switzerland; [8]Department of Paediatric Nephrology, Heidelberg University Medical Center, Heidelberg, Germany; [9]Division of Nephrology,Â Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium

Presenting author: Daniela Iancu
Contact: d.iancu@ucl.ac.uk

Background: The clinical diagnosis of inherited renal tubulopathies can be challenging, as they are rare kidney diseases with phenotypic variability. Yet establishing a definitive diagnosis is important for clinical management. Advances in sequencing technologies enable the simultaneous testing of multiple genes, greatly facilitating the establishment of a molecular diagnosis.

Methods: DNA samples from children with a clinical diagnosis of a renal tubulopathy were amplified with 9 multiplex PCR reactions producing 571 amplicons to cover 37 genes associated with tubulopathies, followed by massively parallel sequencing and bioinformatics interpretation. Identified mutations were confirmed by Sanger sequencing.

Results: We assessed 410 children from 384 families. A total of 269 unique mutations were identified in 26 genes, of which 113 have not been previously described. These provided a genetic diagnosis in 287 (70%) of the overall cohort or 261 (68%) of the 384 index patients. Genetic testing changed the clinical diagnosis in 22 children.

Conclusions: Genetic testing has a high diagnostic yield in children with a clinical diagnosis of a renal tubulopathy, consistent with a predominantly genetic etiology in known disease genes. Genetic testing can help establish a definitive diagnosis in the majority of patients and in this way informs prognosis and management and enables genetic counselling.

P39 **Targeted exome sequencing of a cohort of 204 patients identifies PBX1 as a novel gene involved in monogenic CAKUT**

Jeanpierre C[3], Heidet L[1], Moriniere V[2], Henry C[3], De Tomasi L[3], Reilly ML[3], Humbert C[3], Alibeu O[4], Fourrage C[5], Tores F[5], Jeanpierre M[6], Pietrement C[7], Gaillard D[7], Gonzales M[8], Novo R[9], Schaefer E[10], Roume J[11], Martinovic J[12], Malan V[13], Salomon R[1,3], Saunier S[3], Antignac C[2,3], Jeanpierre C[3]

[1]Pediatric Nephrology Department, Reference Center MARHEA, Necker Hospital, Paris, France; [2]Genetic Department, Necker Hospital, Paris; [3]Inserm UMR1163, Imagine Institute, Paris Descartes University, Paris, [4]Genomic platform, Imagine Institute, Paris; [5]Bioinformatic platform, Paris Descartes University, Paris; [6]Département de Génétique, Hôpital Cochin, Paris, France; [7]Pediatric Nephrology and Genetic Departments, CHU Reims, France; [8]Genetic Department, Hôpital Trousseau, Paris; [9]Pediatric Nephrology Department, CHU Lille, France; [10]Genetic Department, CHU Strasbourg, France; [11]Genetic Department, CHI Poissy, France; [12]Unit of Fetal Pathology, Antoine Béclère Hospital, Clamart, France; [13]Cytogenetic Department, Necker Hospital, Paris

Presenting author: Cecile Jeanpierre
Contact: cecile.jeanpierre@inserm.fr

CAKUT (Congenital Anomalies of the Kidney and Urinary Tract) are major causes of chronic kidney disease in children. They are phenotypically and genetically heterogeneous diseases. Monogenic causes of CAKUT have been identified, with more than 50 genes reported as mutated, mostly in syndromic forms. Most of the mutations are heterozygous, with autosomal dominant inheritance and variable expressivity. The most frequently mutated genes are HNF1B, PAX2, EYA1 and SIX1, all encoding transcription factors. Many of the other genes are mutated in only few patients and their implication is sometimes elusive.

To improve molecular diagnosis and identify new causative genes, we developed a targeted exome sequencing strategy focusing on 330 genes, either involved in CAKUT or being candidates (genes whose knock-out in mouse lead to CAKUT, genes involved in cellular processes/signaling pathways relevant for kidney development), in a cohort of 204 unrelated CAKUT cases, 45% of which were severe fetal cases.

This approach allowed us to identify heterozygous loss-of-function mutations/deletions in PBX1, a gene reported to play a crucial role in kidney development in the mouse, in 5 cases with syndromic (4 patients) or isolated (1 fetus) renal hypodysplasia. We showed that all the mutations (including a nonsense, a frameshift and a splice mutation and 2 large deletions encompassing PBX1 and additional genes) occurred de novo. PBX1 is thus a novel gene involved in monogenic CAKUT in humans.

This targeted exome sequencing strategy also proved to be efficient and cost-effective to identify pathogenic mutations and copy number variations in known CAKUT genes. Indeed, we identified heterozygous mutations/deletions in HNF1B (9 cases), PAX2 (9 cases), EYA1 (5 cases), GATA3 (3 cases), ANOS1 (2 cases) and CHD7 (1 cases), and biallelic mutations in KIF14 (2 fetuses with renal hypodysplasia and microcephaly), thus providing a genetic diagnosis in 15% of the cohort. The rate of deletion (removing one or several exons) was quite high (47%).

Our results also led us to call into question the role of some variations in SOX17 and DSTYK recently reported as pathogenic in CAKUT.

P40 Metabolic phenotyping: a novel technology giving improved understanding in renal medicine

*Boulangé CL[1], *Kaluarachchi M[1], Holmes E[1,2], Lindon JC[1,2]

[1]Metabometrix Ltd, Sir Alexander Fleming Building, Prince Consort Road, London, UK; [2]Computational Systems Medicine, Division of Surgery & Cancer, Imperial College, London, UK

Presenting author: Manuja Kaluarachchi
Contact:

Background: Metabolic phenotyping of biofluids and tissues characterises changes in small molecule metabolites due to genetic differences, environment and disease or drug perturbations. NMR spectroscopy and mass spectrometry provide sensitive and reproducible detection of hundreds to thousands of metabolites. Here we report biomarkers of disease activity, prognosis and treatment responses that have been discovered by way of metabolic screening in different body fluids within and across conventional diagnostic categories including steroid resistant nephropathies (SRNS), membranous nephropathies (MN), tubulopathies, complement disorders and congenital anomalies of the kidney (CAKUT).

Methods: Samples from cohorts affiliated with WPs 2, 3, 4 or 6 of the Eurenomics consortium were made available for metabolic phenotyping. Uni-(UVA) and Multi-(MVA) variate statistical modelling was used to elucidate class differences and to determine the spectroscopic discriminators.

Results: MVA showed discrimination due to genetic differences in SRNS patients carrying the NPHS2 and WT1 genotype in the PODONET cohort. N-phenylacetyl-L-glutamine was higher in the WT1 group. UVA is on-going to discover metabolites associated to end points determined by the collaborating center.

Urine metabolic features associated with urine uromodulin (UMOD) concentration were investigated using UVA. Metabolites including acetone, allantoin and acetylcarnitine were positively correlated with UMOD concentration. Murine urine samples will be analysed to investigate the metabolic effect of UMOD knock-outs.

Metabolic phenotyping of amniotic fluid from the CAKUT cohort has shown that metabolites such as lysine, glucose and tyrosine discriminate samples from children with normal renal function at 2 years of age and those with severely altered renal function. The same approach will be applied to a second sub-set of samples for validation.

Conclusions: The results herein indicate that metabolic profiling by way of 1H NMR and UPLC-MS provides a way forward for discovery and validation of biomarkers of disease activity, prognosis and treatment responses and helps towards the wider aims of the Eurenomics consortium.

P41 **Transcriptome-based network analysis reveals renal celltype-specific dysregulation of hypoxia-associated transcripts**

Lindenmeyer M[6], Shved N[1], Warsow G[2], Eichinger F[3], Hoogewijs D[4], Brandt S[5], Wild P[5], Kretzler M[3], Cohen C[6]

[1]Institute of Physiology and Division of Nephrology, University of Zurich, Switzerland; [2]Department of Anatomy and Cell Biology, Universitätsmedizin Greifswald, Germany, Division of Theoretical Bioinformatics (B080), DKFZ, Heidelberg, Germany; [3]Department of Medicine, University of Michigan, Ann Arbor, Michigan, USA; [4]Department of Medicine / Physiology, University of Fribourg, Switzerland; Institute of Physiology, University of Zurich, Switzerland; [5]Institute of Pathology, University Hospital Zurich, Switzerland; 6Ludwig-Maximilians-Universitaet Muenchen

Presenting author: Maja Lindenmeyer
Contact: maja.lindenmeyer@med.uni-muenchen.de

Accumulating evidence suggests that dysregulation of hypoxia-regulated transcriptional mechanisms is involved in development of chronic kidney diseases (CKD). As hypoxia has been associated with fibrosis the question arises which relevance hypoxia-induced transcription factors (HIFs) have in the dysregulation of hypoxia-associated gene products in different renal cells, which additional regulatory mechanisms might contribute to disease progression. Genome-wide expression profiles of more than 200 renal biopsies from patients with different CKD stages revealed significant correlation of several HIF-target genes with eGFR in glomeruli and tubulointerstitium. These correlations were positive and negative and in part compartment-specific. Microarrays of proximal tubular cells and podocytes with stable HIF1Î± and/or HIF2Î± suppression displayed cell type-specific HIF1/HIF2-dependencies as well as dysregulation of several pathways. WGCNA analysis identified gene sets (modules) that were highly coregulated within the modules. Characterization of the modules revealed common as well as cell group- and condition-specific pathways, GO-Terms and transcription factors. Gene expression analysis of the hypoxia-interconnected pathways in patients with different CKD stages revealed an increased dysregulation with loss of renal function. In conclusion, our data clearly point to a compartment- and cell type-specific dysregulation of hypoxia-associated gene transcripts and might help to obtain an improved understanding of renal effects of hypoxia, HIF dysregulation and transcriptional program response in CKD.

P42 **Identification of regulatory networks connecting genes with common biological functions in CAKUT (Congenital Anomalies of the Kidney and Urinary Tract)**

Lindenmeyer M[4], Renkema K[1], Grote K[2], Kretzler M[3], Cohen C[4], Knoers N[1], Werner T[2]

[1]Universitair Medisch Centrum Utrecht; [2]GENOMATIX - Genomatix Software GmbH; [3]University of Michigan; [4]Ludwig-Maximilians-Universitaet Muenchen

Presenting author: Maja Lindenmeyer
Contact: maja.lindenmeyer@med.uni-muenchen.de

CAKUT is the leading cause of ESRD in children. Analysis of 453 CAKUT-patients for the coding exons of a recently designed a panel of 208 genes by next generation sequencing, showed that the contribution of previously implicated genes to CAKUT risk was significantly smaller than expected, and that the disease might be more complex than previously assumed (Nicolaou et al Kidney Int 2015). The aim of the present study was to elucidate the functional context within the panel genes and identify new potential CAKUT-asscociated genes by integrated transcription factor (TF)-gene interactions and regulatory network analysis. The following strategy was applied: first the genes were sub-grouped for regulatory analysis and the respective promoter sequences extracted. Next, a promoter context analysis of TFBSs (Multiple Organized Regulatory Elements (MORE)-cassettes) was performed followed by scanning of all human promoters for the identified MORE-cassettes. Finally, a biological context analysis was carried out including analysis of regulation in disease. We used the standard integrated analysis package Genomatix Software Suite as well as the newly established EURenOmics database. We identified a total of 39 CAKUT-associated MORE-cassettes. Analysis of these MORE-cassettes in all human promoters resulted in 1866 genes containing at least one CAKUT-associated MORE-cassette. 48 promoters of the initial 208 CAKUT panel genes harboured at least one MORE-cassette representing the core CAKUT-associated regulatory network. Pathway-analysis of the 208 CAKUT-genes identified 42 significantly enriched canonical pathways, including BMP2, Wnt, and ERK signalling. Comparison of all pathway genes with the 1866 MORE-genes resulted in 128 genes with CAKUT-associated MORE-cassettes including 25 known CAKUT-genes. In summary, our TF-gene networking approach, which combines different lines of evidence, such as knowledge-based methods (GO-Terms, pathways), experimental data (CAKUT genes) and genomics-based sequence analysis (promoters, MORE-cassettes) allowed us to identify regulatory networks within the CAKUT panel genes, and also identification of potential, novel candidate genes.

P43 Genomic imbalances in children with chronic kidney disease

Lipsak Ziekiewic B[1], Koczkowska M[1], Wühl E[2], Wong C[3], Bayazit AK[4], Duzova A[5], Canpolat N[6], Sözeri B[7], Bulut IK[7], Azukaitis K[8], Niemirska[9], Anarat A[4], Ranchin B[10], Shroff R[11], Melk A[12], Querfeld U[13], Franz Schaefer F[2] for the ESCAPE and 4C Study Consortia

[1]Department of Biology and Medical Genetics, Medical University of Gdańsk, Poland; [2]Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, University of Heidelberg, Heidelberg, Germany; [3]Department of Pediatrics, Division of Nephrology, University of New Mexico Children's Hospital, Albuquerque, USA; [4]Department of Pediatric Nephrology, Cukurova University, Adana, Turkey; [5]Department of Pediatric Nephrology, Hacettepe University Faculty of Medicine, Ankara, Turkey; [6]Department of Pediatrics, Division of Pediatric Nephrology, Istanbul University Cerrahpaşa Faculty of Medicine, Istanbul, Turkey; [7]Department of Pediatric Nephrology, Ege University Medical Faculty, Izmir, Turkey; [8]Vilnius University Children`s Hospital, Vilnius, Lithuania; [9]Department of Nephrology, Kidney Transplantation and Arterial Hypertension, The Children's Memorial Health Institute, Warsaw, Poland; [10]Service de Pédiatrie and Inserm U820, Centre de Référence des Maladies Rénales Rares, Hôpital Femme-Mère-Enfant & Université de Lyon, France; [11]Renal Unit, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom; [12]Pediatric Kidney, Liver and Metabolic Disease, MHH Children´s Hospital, Hannover, Germany; [13]Pediatric Nephrology Charité, University Children's Hospital Berlin, Berlin, Germany

Presenting author: Beata LipskaZietkiewic
Contact: b.lipska@gumed.edu.pl

Chromosomal microarrays are routinely utilized for genetic testing of developmental delay/intellectual disability, autism spectrum disorders or multiple congenital anomalies. Here, we studied the prevalence of DNA copy number variations (CNVs) in a large cohort of European and Turkish children presenting with chronic kidney disease.

986 consecutive patients enrolled in the ESCAPE and 4C studies were genotyped at âˆ¼2.4 million SNP markers using the Illumina Infinium 2.5M microarray. Data was interpreted in accordance to ACMG Practice Guidelines using the Nexus Copy Number software. Filtering criteria included the size of imbalance, overlap with known benign CNVs, gene content, and verification against Decipher and ISCA databases.

890 (90.3%) samples were eventually eligible to detailed genotype-phenotype correlations, of these 74 (8.3%) were classified as having a definite pathogenic genomic aberration and another 11 as having a likely pathogenic CNV. In addition, 34 patients were found to have a heterozygous variant in a known AR gene associated with a hereditary kidney disorder. Definite diagnoses were made in 4.7% of individuals with CAKUT, 2.8% of patients with a glomerulopathy and 27.9% of those with a tubulointerstitial disorder.

The most frequent imbalances were chromosome 2q13 homozygous deletions of the NPHP1 region (n=37), 1q21.1 deletions including the CHD1L gene (n=7), rearrangements at 22q11.2 (n=7) and 17q12 deletions encompassing the HNF1B locus (n=6). Small, including single gene, rearrangements were reported for 56 genes including CTNS, PKD1, TSC2, ROBO2, NOTCH2 and TFAP2A loci.

Clinical diagnosis was revised in 10 CAKUT cases (HNF1ÃŸ nephropathy (n=5); nephronophthisis (n=5)) and in one clinical suspicion of Bardel-Biedl syndrome (nephronophthisis). The detection of a genomic imbalance allowed for reverse phenotyping in most cases, resulting in clinical interventions such as evaluation for extra-renal involvement and implementation of multidisciplinary care.

Genomic imbalances account for a significant portion of children with CKD and their diagnosis has important implications for genetic counselling and clinical management.

P44 Analysis of two novel Umod KI models of autosomal dominant tubulointerstitial kidney disease

Olinger E[1], Schiano G[1], Takata T[1], Debaix H[1], Dahan K[2], Rampoldi L[3], Devuyst O[1]

[1]Institute of Physiology, University of Zurich, Zurich, Switzerland; [2]Institute of Pathology and Genetics, Gosselies, Belgium; [3]San Raffaele Scientific Institute, Milan, Italy

Presenting author: Eric Olinger
Contact: eric.olinger@uzh.ch

Uromodulin (UMOD), the most abundant urinary protein, is mainly expressed in the TAL. Mutations in UMOD cause autosomal dominant tubulointerstitial kidney disease (ADTKD-UMOD) characterized by ER-retention of misfolded UMOD with interstitial fibrosis and renal failure. Molecular mechanisms of disease and possible genotype-phenotype correlations are unknown.

We recruited 148 ADTKD families with available clinical data. Among them, 50 families (33.8%) harbor a mutation in UMOD affecting a cysteine bridge in half of the cases. We created 2 knock-in (KI) mouse lines with representative mutations in Umod by substituting a cysteine (p.C170Y) or an arginine (p.R185S). UmodR186S/+ mice show impaired renal function starting from 1 month of age with concomitant retention of premature UMOD in the kidney and develop polyuria/polydipsia at 2 months. UMOD accumulates in the ER where it selectively induces the overexpression of ER stress-associated effectors, on both mRNA and protein levels. Major fibrotic changes were observed in UmodR186S/+ kidneys starting from 4 months. Surprisingly, UmodC171Y/+ mice up to 6 months of age have normal renal function and display accumulation of membrane-bound UMOD. We did not observe ER stress nor fibrosis in UmodC171Y/+ kidneys. ER retention of UMOD in UmodC171Y/C171Y TALs suggests a gene dosage effect, at least regarding UMOD processing. Finally, we investigated active ER stress pathways in the kidneys of Umod KI mice. We detected the selective activation of one branch of the Unfolded Protein Response (UPR) pathway, on both transcriptional and protein levels. We also observed a strong increase of Lipocalin-2 (LCN-2/NGAL) in the urine of Umod KI mice. The urinary levels of LCN-2 can potentially act as a biomarker of disease progression.

The patient registry and the KI models are critical tools to investigate the pathophysiology of ADTKD. Comparative analysis of disease models with different disease severity will help to link the defective UMOD processing with the mechanisms of kidney damage and to validate urinary biomarkers.

P45 **Development of an Automated High Content Screening Platform to Identify Cystic Kidney Disease-Modifying Substances in Zebrafish**

Pandey G[1], Westhoff JH[1], Schaefer F[1], Gehrig J[2]

[1]Department of Pediatrics, University Children's Hospital, University of Heidelberg, Heidelberg, Germany; [2]ACQUIFER is a division of DITABIS, Digital Biomedical Imaging Systems AG, Pforzheim,Germany

Presenting author: Gunjan Pandey
Contact: gunjan.pandey@med.uni-heidelberg.de

Due to various experimental advantages and genetic similarity to humans, zebrafish embryo has been well established for whole organism screening applications. Consequently, large scale chemical screening increasingly employs zebrafish in drug discovery studies. However, to fully exploit the potential of this model, novel automation technologies are needed that overcome common challenges such as generation of low resolution data or automated phenotypic scoring. The goal of this project is to establish a high content screening pipeline which will automate high resolution imaging and compound-induced phenotype classification for identification of cyst-modifying substances in zebrafish model for human cystic kidney disease. To this extent, morpholino-based (MO) knockdown of intraflagellar transport (ift) 172 gene is used to induce large glomerular cysts in GFP-expressing pronephrons of transgenic Tg(wt1b::EGFP) zebrafish line. Embryos are exposed to approve drug library compounds until 72 hours post fertilization. They are dorsally oriented in microtiter plates using 3D printed orientation tools and imaged using robotic microscopy. A Smart Imaging module is used to automatically detect the region of interest, i.e. pronephric kidney, and subsequently zooming in to capture details at higher magnification. The images are further quantified by running through a series of scripted modules developed using freely available programming interfaces: ImageJ and Python. Using this pipeline, experimental parameters including dose response curve of ift 172 MO for knock-down conditions and validation of the model system using the control compound rapamycin have been optimized. In addition to that, time lapse experiments to characterize cyst formation during development and standardization of compound treatment procedures have been performed. The automated pipeline efficiently acquires, scores and quantifies cysts. Ultimately, this in-vivo large scale study will lead to identification of compounds that might be considered for treatment of human cystic kidney diseases. The developed pipeline will serve as a unique platform for automatic categorization of cyst-modifying compounds.

P46 Proteomic Characterisation of a Novel Gene FAM20A and its Involvement in Calcium Homeostasis

Patel V[2], Wheeler J[1], Klootwijk R[2], Himmerkus N[5], Bleich M[6], Bockenhauer D[3], Kleta R[4]

[1]Laboratory of Molecular Structure; National Institute for Biological Standards and Control, Hertfordshire, UK; [2]Centre for Nephrology, University College London, London, UK, [3]Centre for Nephrology, University College London, London, UK; [4]Centre for Nephrology, University College London, London, UK; [5]Physiology, University of Kiel, Kiel, Germany; [6]Physiology, University of Kiel, Kiel, Germany

Presenting author: Vaksha Patel
Contact: vaksha.patel@ucl.ac.uk

Background: FAM20A is the causative gene of Amelogenesis Imperfecta (AI) in combination with Nephrocalcinosis (NC). It is characterized by defects in the dental enamel and calcium deposits within the kidneys respectively. Unlike most cases of NC where hypercalciuria is its instrumental cause, patients with AINC have normocalciuria, suggesting a novel underlying mechanism in the handling of calcium within the kidneys. This investigation has used quantitative proteomics to decipher this atypical mechanism.

Methods: Tandem mass tags (TMT) technology has been employed to identify differentially expressed proteins in Fam20a -/- kidneys.

Results: Bioinformatic analyses revealed six key proteins (Apolipoprotein E, Calbindin D28, Coronin-1A, Fibrinogen gamma chain, Lysosome-associated membrane glycoprotein 2 and Calbindin-D9k) associated with calcium regulation. These are found to be significantly compromised in Fam20a-/-. Functional gene ontology (GO) enrichment analysis points towards a dysregulation of metabolic processes in mitochondria in these mice.

Conclusion: This is the first study to provide a reference proteome map pertinent to AINC and the outcome of the bioinformatic analyses offers not only a list of potential candidates for the diagnosis and therapy of this disorder but provides new insights into mechanisms of calcium homeostasis and biomineralisation.

P47 **Comparison of six methods for isolation of urinary microvesicles for miRNA profiling in proteinuria.**

Rood I[1], Laufer T[2], van den Brand J[1], Saiz A[2], Schroers H[2], van der Vlag J[1], Wetzels JFM[1], Deegens JKJ[1]

[1]Department of Nephrology, Radboud University Medical Center, Nijmegen, The Netherlands; [2]Hummingbird Diagnostics GmbH, Heidelberg, Germany.

Presenting author: Ilse Rood
Contact: ilse.rood@radboudumc.nl

Background: Urinary extracellular vesicles (uEVs) are a promising source for biomarker discovery, including miRNAs (small noncoding single stranded RNAs, which regulate gene expression). UEVs can be isolated by different techniques. In healthy subjects, an exosome precipitation protocol (exoquick) yielded the highest quantities of miRNA in uEVs. The optimal isolation method of uEVs for miRNA profiling in patients with proteinuria is unknown.

Methods: Urine samples were collected from 10 patients with proteinuria >2g/day. UEVs were isolated by six different protocols: exoquick(B), exoRNeasy(C), exoquick after DTT treatment and additional 17.000g centrifugation step(D), exoRNeasy after DTT treatment and additional 17.000g centrifugation step(E), ultracentrifugation (UC)(F), and UC followed by size exclusion chromatography(G). The miRNA-profiles were compared with the profile of cell-free urine supernatant after 3,000g centrifugation for 10 minutes(A). Expression profiles of all miRBase release v20 human miRNAs using HBDxâ's custom Agilent SurePrintG3 Human miRNA (8x60K) microarrays were determined.

Results: UEV precipitation protocols (B and D) resulted in a too low yield of miRNAs for further profiling. The heatmap and PCA showed a clear differential clustering of protocol F in one group and protocols A, C, and E in a second group. Additional DTT treatment did not result in a different miRNA-profile or yield between method C and E.

Overall, 69 miRNAs were significantly enriched by protocol F compared to protocols A and C, whereas protocol C significantly enriched 28 miRNAs compared to protocols A and F. Respectively 61% and 84% of these significantly enriched miRNAs specifically target genes associated with a hereditary kidney disease.

Conclusions: Different miRNAs are enriched following uEV isolation by ultracentrifugation or ExoRNeasy. Ultracentrifugation appears to be superior to exoRNeasy for miRNA-profiling of uEV in proteinuric samples, however the latter method is easier to perform and less expensive. Preferably, both methods are used as complimentary techniques in biomarker discovery studies for miRNA-profiling of uEV in proteinuric samples.

P48 Whole-genome sequencing for CAKUT in an island population

Said-Conti V, Zammit E, Felice AE

University of Malta

Presenting author: Valerie Said Conti
Contact: valerie.said@gov.mt

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are the primary cause of kidney failure in children. Several studies point to a genetic mutation as the underlying cause and in recent years a number of genes have been implicated with various modes of inheritance although in most cases the disease-causing mutation remains to be discovered. This research was intended to uncover the genetics of CAKUT in children of Maltese origin using whole-genome sequencing (WGS).

Methods: 84 samples of blood from paediatric patients with CAKUT and their families were collected with written informed consent, processed and stored at the Malta BioBank. WGS was used to analyse ten samples of unrelated patients. Phenotypes included vesico-ureteric reflux, ureterocele, posterior urethral valves, duplex kidneys, and renal dysplasia. The coding regions of 96 genes implicated in non-syndromic CAKUT and known to play a role in kidney development, including HNF1B, PAX2, ROBO2, EYA1, RET and BMP4 are being studied at present using R, Ensembl, PolyPhen-2 and SIFT. Synonymous variants were excluded.

Results: This research has been instrumental in establishing a collection of renal rare disease blood samples at the BioBank. Ten WGS datasets are being explored.

Conclusion: CAKUT is a rare disease and an international collaboration will yield better results. Data from the Maltese registry will further contribute to this research with the aim to better elucidate the genetic background of CAKUT and direct early identification and treatment of patients who are at risk of progressing to kidney failure.

P49 **Analysis of gene function in embryonic kidney organoid model**

Skovorodkin I[1], Saarela U[1], Rak-Raszewska A[2], Tarakanchikova Y[2], Vainio SJ[2]

[1]University of Oulu, Faculty of Biochemistry and Molecular Medicine, Oulu, Finland; [2]University of Oulu, Department of Optoelectronics and measurement techniques, Oulu, Finland

Presenting author: Ilya Skovorodkin
Contact: ilya.skovorodkin@oulu.fi

Mammalian embryonic kidneys and renal organoids can be cultured ex vivo to study different aspects of early nephrogenesis and applied as a model to analyse the origin of different congenital diseases (CACUT for example).In our laboratory we have earlier developed an experimental system where embryonic kidney cells can be dissociated, sorted (to exclude or add specific cell populations), genetically modified and reaggregated to form renal organoids. We will present recent data concerning optimisation of imaging methods to analyse the process of nephrogenesis in renal organoids and comparison of several methods of genetical transformation of primary embryonic kidney cells.

P50 **HaploForge: A Comprehensive Pedigree Drawing and Haplotype Visualisation Web Application**

Tekman M[1], Mozere M[1], Medlar A[2], Kleta R1, Stanescu H[1]

[1]Division of Medicine, University College London, UK; [2]Institute of Biotechnology, University of Helsinki, Finland

Presenting author: Mehmet Tekman
Contact: m.tekman@ucl.ac.uk

Motivation: Haplotype reconstruction is an important tool for understanding the aetiology of human disease. Haplotyping infers the most likely phase of observed genotypes conditional on constraints imposed by the genotypes of other pedigree members. The results of haplotype reconstruction, when visualised appropriately, show which alleles are identical by descent despite the presence of untyped individuals. When used in concert with linkage analysis, haplotyping can help delineate a locus of interest and provide a succinct explanation for the transmission of the trait locus. Unfortunately, the design choices made by existing haplotype visualisation programs do not scale to large numbers of markers. Indeed, following haplotypes from generation to generation requires excessive scrolling back and forth. In addition, the most widely-used program for haplotype visualisation produces inconsistent recombination artefacts for the X chromosome.

Results: To resolve these issues, we developed HaploForge, a novel web application for haplotype visualisation and pedigree drawing. HaploForge takes advantage of HTML5 to be fast, portable and avoid the need for local installation. It can accurately visualise autosomal and X-linked haplotypes from both outbred and consanguineous pedigrees. Haplotypes are coloured based on identity by descent using a novel A* search algorithm and we provide a flexible viewing mode to aid visual inspection. HaploForge can currently process haplotype reconstruction output from Allegro, GeneHunter, Merlin and Simwalk.

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P51 Computational Modelling of Early Nephrogenesis

Tikka P, Schaefer F

University Hospital of Heidelberg

Presenting author: Pauli Tikka
Contact: pauli.tikka@med.uni-heidelberg.de

Mammalian kidney development is a highly complex process involving migration, condensation, differentiation and proliferation of renal progrenitor cells containing various steps. The aim of this study is to develop two mechanistic models explaining: 1) the collective migration of committed mesenchymal cells towards formation of the pretubular aggregrates (PTA), and 2) condensation of PTA to renal vesicle (RV). The hypothesis is that a combination of random spontaneous motility and directed movement following mechanochemical signals leads to early PTA construction and subsequent nephron patterning. The principal method is the computational analysis of the nephron progenitor cell movements using the CompuCell3D software, which uses cellular Potts mathematical formulations in 2D or 3D to describe tissue dynamics, assuming the experimentally demonstrated Wnt9b and β-catenin diffusion spaces as the chemotactic driving force. Recently, time lapse microscopy studies of ex vivo organ cultures of tagged renal precursor cells have been performed which provide a basis for computational modelling of the complex, swarm like behaviour of cells in the metanephric mesenchyme capping the ureteric tips (Zubkov et al. 2015, Lawson et al. 2016, and Combes et al. 2016). The studies are expected to generate two robust models. Namely, the mechanisms driving the migration of committed mesenchymal cells, nephron progenitor cells toward the PTA stage, NPC (Model 1), and secondly the aggregation of tubules to vesicle (Model 2).

P52 **The von Hippel-Lindau gene is required to maintain renal proximal tubule and glomerulus integrity during zebrafish development**

van Rooijen E[1,2], van de Hoek G[3,4], Logister I[1,2], Knoers NV[4], van Eeden F[2], Schulte-Merker S[2], Giles RH[1,3]

[1]Dept. Medical Oncology, University Medical Center, Utrecht, The Netherlands; [2]Hubrecht Institute, Utrecht, The Netherlands; [3]Dept. Nephrology and Hypertension, University Medical Center, Utrecht, The Netherlands; [4]Dept. Genetics, University Medical Center, Utrecht, The Netherlands

Presenting author: Glenn van de Hoek
Contact: g.vandehoek@umcutrecht.nl

Background: The von Hippel-Lindau (VHL) gene is an important factor for instigating renal clear cell carcinoma, however its role in renal development is less understood. We previously described a zebrafish model lacking the orthologue of human VHL to recapitulate human VHL disease phenotypes, such as polycythemia, disturbed angiogenesis, and vascular retinopathies.

Methods: To better understand the role of VHL in kidney development, we used histopathological and functional assays to investigate the pronephros in our zebrafish model.

Results: Here, we report that loss of vhl in zebrafish embryos results in severe pronephric abnormalities. In vhl mutants the glomerulus is enlarged, the Bowman space is widened and dilated cxcr4a-positive capillary loops are observed. While wild-type siblings exhibit a single layer of cuboidal cells comprising the proximal tubule, vhl mutant tubular cells are irregular with a grape-like or alveolar appearance. Ultrastructural analysis revealed mutant cells which accumulate excessive amounts of vesicles that are variable in size and electron density. Glomerular filtration in vhl-/- proximal tubule cells was not impaired. VEGF receptor inhibition revealed that neovascularization of the vhl-/- proximal tubule does not obviously contribute to the aberrant cell morphology. Using an endocytic fluorescent marker AM1-43, we observe a vesicle accumulation and altered dynamics which we can recapitulate in human cells lacking VHL.

Conclusions: Our data indicate that vhl is required to maintain pronephric tubule and glomerulus integrity during zebrafish development.

P53 **Zebrafish modeling of genetic variants identified in CAKUT patients**

van de Hoek G[1,2], van Eerde AM[2], Bongers EMHF[3], Renkema K[2], Giles RH[1], Knoers NV[2]

[1]Dept. of Nephrology and Hypertension, University Medical Center, Utrecht, The Netherlands; [2]Dept. of Genetics, University Medical Center, Utrecht, The Netherlands; [3]Dept. of Human Genetics, Radboud university medical center, Nijmegen, The Netherlands

Presenting author: Glenn van de Hoek
Contact: g.vandehoek@umcutrecht.nl

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) constitute the principal cause of end-stage renal disease in children. The genetic architecture behind CAKUT is complex. Recently, we have identified a large amount of genetic variants in CAKUT patients. However, besides in silico predictions, we have no proof to their pathogenic effects. To determine the effects of these variants on kidney development, we use the zebrafish as a model system. Zebrafish larvae quickly develop a functional renal system with conserved genetic developmental factors, which makes them suitable for kidney developmental studies.

Methods: Via the CRISPR/Cas9 genetic engineering technique, we have generated multiple mutant zebrafish lines for candidate genes implicated in renal disease, including retinitis pigmentosa GTPase regulator (RPGR) and cysteine rich transmembrane BMP regulator 1 (CRIM1). RPGR was found mutated in two families with CAKUT, with kidney dysplasia and obstructive mega-ureter respectively. A de novo CRIM1 variant was found in a patient with CAKUT. Fluorescent transgenic zebrafish lines were used to facilitate imaging of the early zebrafish kidney including a pronephros-specific pax2.1:gfp line that shows expression in early renal progenitor cells, as in later pronephric tubular structures. Standard histopathological and functional assays will be used to investigate the larvae for cyst formation (indicative of renal failure) and overall pronephros morphology.

Results: Currently, we are screening for mutant founders to use for phenotypic analysis. Conclusion: Through modelling in a vertebrate model of genetic variants that we have identified in CAKUT patients we aim to generate new insights into the molecular mechanisms underlying CAKUT.

P54 **Anti-PLA2R antibodies as a biomarker in the treatment of membranous nephropathy**

Van De Logt A, Wetzels JFM
Radboud UMC, Nijmegen, Netherlands

Presenting author: Anne Els van de Logt
Contact: anne-els.vandelogt@radboudumc.nl

Background: Antibodies against PLA2R are present in 70-80 % of patient with primary membranous nephropathy (MN). The introduction of a qualitative immunofluorescence test (IFT) allowed easy detection in routine clinical care, and established anti-PLA2R antibodies (aPLA2R) as an accurate diagnostic biomarker. More recently, a quantitative ELISA assay was developed. It was shown that measurement of aPLA2R levels might allow prediction of prognosis and treatment response: rituximab therapy was not very effective in patient with high aPLA2R levels. In our center patients with MN are treated with cyclophoshamide (CP) and prednisone. Treatment duration is guided by disappearance of aPLA2R using IFT. In this study, we examined if quantitative measurement of aPLA2R at the start of therapy using the ELISA test predicted the response to CP.

Methods: CP-therapy (combined with steroids) was started in patients with aPLA2R positive MN and high risk of progression. aPLA2R were repeatedly monitored (IFT test) at 8, 16, and 24 weeks after start of treatment. If antibodies became negative, CP was stopped and prednisone was tapered. Otherwise, therapy was continued after 24 weeks with MMF and prednisone. In the stored baseline samples of these patients aPLA2R were measured with ELISA (Euroimmunâ). '

Results: We studied 30 patients (19 males), mean age 56 Â± 13 years, median serum creatinine level 115 Âµmol/l (97-141) and median protein creatinine ratio 8.7 g/10 mmol (6.2-12.8) . All patients tested positive with ELISA. When grouped in tertiles of aPLA2R, there were no differences in baseline characteristics. In patients in the highest tertile the disappearance of aPLA2R was slower and as a consequence more prolonged immunosuppression was given. At the end of follow-up there were no differences in remission rate. Relapse rate was numerically lower in this group, however this might be related to the longer duration of therapy.

Conclusions: Patients with higher levels of aPLA2R often need more prolonged immunosuppressive therapy with cyclophosphamide. However, with the use of anti-PLA2R as a biomarker of treatment response, clinical outcome is comparable.

Table: Characteristics and outcome of patients in tertiles of aPLA2R

aPLA2R titer	Lowest Tertile	Middle Tertile	Highest Tertile	P value
Male/Female	7/3	5/5	7/3	ns
ElISA titer RU/ml (range)	15-67	86-134	136-776	0.000
Follow-up from start of therapy (months)	11.8 (2.8-25.9)	11.0 (5.4-29.8)	14.1 (3.4-20.4)	ns
IFT aPLA2R negative after 8 weeks (n)	8	8	2	0.024
Remission (n)	6	9	7	ns
Relapse (n)	3	4	0	ns

P55 Safety of Rituximab compared to Steroids and Cyclophosphamide for Idiopathic Membranous Nephropathy

van den Brand J[1], Ruggenenti P[2,3], Chianca A[3], Hofstra JM[1], Perna A[3], Ruggiero B[3], Wetzels JFM[1], Remuzzi G[2,3]

[1]Department of Nephrology, Radboud University Medical Center, Nijmegen, The Netherlands; [2]Unit of Nephrology, Azienda Socio Sanitaria Territoriale (ASST) Ospedale Papa Giovanni XXIII, Bergamo, Italy; [3]IRCCS - Istituto di Ricerche Farmacologiche Mario Negri, Clinical Research Center for Rare Diseases "Aldo e Cele Daccò" Ranica, Bergamo, Italy

Presenting author: Jan van den Brand
Contact: Jan.vandenbrand@radboudumc.nl

Guidelines recommend steroid plus cyclical cyclophosphamide (ST-CP) therapy for patients with Idiopathic Membranous Nephropathy (IMN) at high risk of progression to end stage kidney disease. Rituximab (RTX) may be a safer alternative. In this retrospective, observational cohort study we compared time to any adverse event (primary outcome), serious or non-serious events, partial and complete remission of the nephrotic syndrome, and a composite of doubling of serum creatinine, end stage kidney disease, or death, between 100 RTX treated and 103 patients who received daily ST-CP. Patients were monitored with standardized protocols. We adjusted for baseline characteristics by Cox regression. Over a median follow-up period of 40 months there were significantly less adverse events (51 vs 175, p<0.001), both serious (11 vs 48, p<0.001) and non-serious (40 vs 127, p<0.0001), in the RTX than in the ST-CP group. Cumulative incidence of any first (35.5% vs 69.0%, p<0.001), serious (16.4% vs 30.2%, p=0.002), or non-serious (23.6% vs 60.8%, p<0.001) event was significantly lower with RTX. Adjusted Hazard Ratios between RTX and ST-CP groups were 0.27 (95% Confidence Interval: 0.16 to 0.44) for any adverse event, 0.36 (0.17 to 0.78) for serious, and 0.23 (0.14 to 0.41) for non-serious adverse events. Although the cumulative incidence of partial remission was lower in the RTX group, rates of complete remission and the composite renal endpoint were not significantly different between groups. Because of its superior safety profile, we suggest that rituximab might replace steroids and cyclophosphamide as first-line immunosuppressive therapy in IMN patients with nephrotic syndrome.

P56 Reversible Nephroprotective Action of RAS Blockade in Mice Carrying R140Q Podocin Mutation

Wlodkowski T[1], Tabatabaeifar M[1], Mollet G[2], Antignac C[2], Schaefer F[1]

[1]Pediatric Nephrology Division, Heidelberg University, Germany; [2]Inserm U1163-Imagine Institute, Paris Descartes University, France

Presenting author: Tanja Wlodkowski
Contact: tanja.wlodkowski@med.uni-heidelberg.de

NPHS2 mutations cause hereditary nephrotic syndrome and progressive renal failure.We established an inducible knock-in mouse model carrying R140Q, the analogue of the most common human mutation R138Q.These mice develop focal-segmental glomerulosclerosis with nephrotic syndrome and progressive renal failure.In our previous studies, we demonstrated significant nephroprotection by RAS blockade in this podocin nephropathy model.Here we investigated the effect of discontinuing drug administration on the disease progression.

In C57BL/6 mice with Nphs2Flox/R140Q/Cre+ genotype, hemizygosity for mutant podocin was induced by tamoxifen injection.Animals received combined high-dose ACE inhibition and AT1 receptor blockade (ramipril+candesartan 10 mg/kg each) or remained untreated.Treatment was started either prophylactically (P) at time of induction or with a 4-wk delay (D).The withdrawal group (W) was treated prophylactically for 4 wks and thereafter the drug administration discontinued for another 4 wks.Animals were either sacrificed after 5 wks or 9 wks.

Induction of R140Q-podocin hemizygosity caused massive proteinuria peaking at 5 wks, followed by a gradual decrease as progressive renal failure developed.While in the P animals proteinuria remained constantly low (13% of U animals at wk 5, $p<0.001$), upon withdrawal of the drug the antiproteinuric effect vanished.Proteinuria increased progressively and reached a peak at week 8. In the D group, proteinuria sharply decreased upon RAS blockade (37% of U animals at wk 6, $p<0.001$).P as well as D group animals showed a higher number of podocytes per glomerulus and lower glomerulosclerosis index (P 1.04 vs U 1.59, $p<0.001$; D 1.91 vs U 2.39, $p<0.01$). Furthermore, no difference was observed for the histopathological lesions in W group animals compared to U animals. Moreover, improved biochemical parameters observed in P and D animals were lost in W group animals. Interestingly, whereas the wild-type podocin mRNA was decreased in all groups, R140Q mutant podocin mRNA was only preserved in P and D animals.

In mice carrying the most common human podocin mutation, RAS blockade attenuates proteinuria, podocyte loss, glomerulosclerosis and delays renal failure.Treatment is more effective when applied prophylactically than when started in established nephropathy. Discontinuing drug administration abolishes the nephroprotective effect of RAS blockade.

P57 **Reversing mdx cardiomyocyte hypertrophy in vitro**

Carr S[1], Ritso M[1], Krebs S[2], Graf A[2], Laval S[1], Blum H[2], Roos A[1], Lorenz K[3], Lochmüller H[1]

[1]John Walton Muscular Dystrophy Research Centre, International Centre for Life, Newcastle University; [2]LAFUGA Genomics, Genzentrum, Universität München (LMU), Feodor-Lynen-Strasse 25, 81377 München, Germany; [3]Institut für Pharmakologie und Toxikologie - Universität Würzburg, Versbacher Str. 9, 97078 Würzburg, Germany

Presenting author: Stephanie Carr
Contact: S.carr2@ncl.ac.uk

Several therapies to treat Duchenne Muscular Dystrophy (DMD) are under development; unfortunately many lack efficacy in the heart. In addition, there is increasing need to treat dystrophin-deficient cardiomyopathy due to extending patient life expectancy resulting in a prevalence of cardiac symptoms. Despite the primary genetic defect being identical in skeletal and cardiac muscle, the symptoms and severity differ suggesting the involvement of secondary organ-specific pathways that are yet to be fully understood. We have developed an in vitro model of cardiomyocyte hypertrophy using cardiomyocytes isolated from mdx (mouse model of DMD) hearts. Using this model, we have been able to utilise various therapeutic approaches to lessen the phenotype. This model could be a fast, efficient way to screen new and existing pharmaceutical and gene-based approaches for therapeutic efficacy. Additionally, by employing transcriptomic and proteomic approaches, this model can be used elucidate the secondary organ-specific pathways involved. Transcriptomic analysis of cardiomyocytes revealed dysregulation of genes involved in pathways such as angiogenesis, fibrosis and calcium regulation.

P58 CAG expansion influences the autophagosome-lysosome fusion events in HD patients-derived iPS cells

Conforti P, Vitiello G, Cattaneo E

Department of Biosciences and Centre for Stem Cell Research, University of Milan, Milan, Italy and Istituto Nazionale di Genetica Molecolare "Romeo ed Enrica Invernizzi" Milan, Italy

Presenting author: Paola Conforti
Contact: paola.conforti@unimi.it

Autophagy is an essential cellular pathway for degrading damaged organelles and toxic/aggregated proteins. Defects in autophagy have been implicated in several neurodegenerative diseases including Huntington Disease (HD), a disorder caused by the unstable expansion of CAG repeats in the Huntingtin gene (HTT). Autophagy is required for clearance of HTT aggregates, but the presence of mutant HTT carrying expanded polyQ tract (mHTT) interferes with the process.

Here, we reported the presence of HTT aggregates in the cytoplasm of proliferating HD-iPSCs reprogrammed from corresponding fibroblasts carrying different CAG expansions, formally 60, 109 and 180 repeats. The same cells show impairment in the autophagic process with accumulation of both LC3-II punctae and p62/SQSTM1 bodies measured by biochemical and immunocytochemical assays. Subsequently, we used different compounds to modulate autophagy in order to identify which is/are the step/s compromised by the mutation. We found a dysregulation in the autophagosome-lysosome fusion event in proliferating pluripotent HD-iPSCs compared to control lines.

All data collected demonstrated that the impairment of the autophagy process is due to a defect at the level of autophagosome-lysosome fusion. Given the potential role of HTT in regulating autophagy, further work would be required to identify therapeutic targets that could restore HTT function and normalize the autophagosome-lysosome fusion alteration by using this HD-iPS platform.

P59 **Personalized next-generation sequencing to genetically characterize 92 Spanish patients presenting with heterogeneous rare neurological diseases.**

Corral M[1], Segarra A[1], Ispierto L[2], Martínez-Piñeiro A[3], Vilas D[2], Almendrote-Muñoz M[3], Gardenyes J[5], Ramos-Fransi A[3], Marín R[7], Patiño A[6], Volpini V[5], Casquero P[4], Coll J[3], Alvarez R[2], Sánchez I[1], Matilla-Dueñas A[1]

[1]Functional and Translational Neurogenetics Unit, Department of Neurosciences, Germans Trias i Pujol Research Institute -IGTP, Can Ruti Campus, Badalona, Spain; [2]Neurodegeneration Unit, Department of Neurosciences, University Hospital Germans Trias i Pujol (HUGTiP), Can Ruti Campus, Badalona, Spain; [3]Neuromuscular Unit, Department of Neurosciences, University Hospital Germans Trias i Pujol (HUGTiP), Can Ruti Campus, Badalona, Spain; [4]Neurology Service, Hospital Mateu Orfila, Maá³, Menorca, Spain; [5]Bellvitge Biomedical Research Institute, IDIBELL, Hospitalet de Llobregat, Spain; [6]Clinical Genetics Unit, CIMA, Clá-nica Universidad de Navarra, Pamplona, Navarra, Spain; [7]Medical Genetics Service, University Hospital Puerta del Mar, Cá¡diz, Spain

Presenting author: Marc Corral
Contact: mcorral@igtp.cat

The most common undiagnosed disorders involve a neurologic phenotype. The aim of this study was to implement a personalized comprehensive approach to next-generation sequencing (NGS) by combining potent algorithms with thorough clinical phenotype evaluation to identify the genetic causes of heterogeneous rare neurological diseases.

Ninety-two patients with rare undiagnosed neurological disorders referred from 5 Reference Hospitals in Spain were included. WES/WGS or a custom-made multigene panel including 326 neurological genes were sequenced with HiSeq. Identified variants were annotated with Ensembl and analyzed with coding and non-coding pathogenic prediction tools. Variants were filtered using in-house algorithms adapted for each clinical case and validated by sequencing and familiar segregation. Two ataxia pedigrees were included in wide-genome linkage studies with Infinium Human Omni5, 2-point and multipoint genetic linkage using MERLIN 1.1.2, MLINK and LINKMAP.

Using our custom multigene panel or NGS with genetic linkage, we unequivocally diagnosed 45% of our cohort of undiagnosed patients: 28/48 presented with ataxia, 5/16 with spastic paraplegia, 2/4 with myopathy, 2/4 with polyneuropathy, 1/3 with muscular dystrophy, 2/2 with myotonia, and 1/1 with myasthenia gravis. A total of 55 causative mutations were identified: 31 novel and 24 previously reported. Remarkably, by NGS and genetic linkage studies we identified 2 novel ataxia genes: SCA37 on 1p32 and SCA44 (pending assignation) on 7q21.2, and 1 novel gene associated with dominant polyneuropathy on 18q21.

In conclusion, this study demonstrates the feasibility of a comprehensive approach involving thorough clinical phenotype evaluation and personalized next-generation sequencing to maximize clinical benefit by uncovering the underlying genetic defects associated with undiagnosed rare neurological diseases.
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P60 **Mutations in the Popeye domain-containing genes POPDC1 and POPDC2 cause severe heart rhythm disorders with LGMD or isolated cardiac phenotype**

Ferlini A[1], Rinné S[2], Schindler R[3], Ortiz-Bonnin B[2], Stallmeyer B[4], Schindler RFR[3], Gualandi F[1], Rapezzi C[5], Arbustini E[6], Selvatici R[1], Schulze-Bahr E[4], Brand T[3], Decher N[2]

[1]Unit of Medical Genetics, Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [2]Institute for Physiology and Pathophysiology, Vegetative Physiology, Philipps-University of Marburg, Marburg, Germany; [3]Heart Science Centre, National Heart and Lung Institute, Imperial College, Hill End Road, Harefield UB9 6JH, United Kingdom; [4]Institute for Genetics of Heart Diseases (IfGH), Department of Cardiovascular Medicine, University Hospital Münster, Münster, Germany; [5]Unit of Cardiology, Policlinico S. Orsola Bologna; [6]Policlinico S. Matteo, Pavia, Italy; [7]Dubowitz Neuromuscular Centre, Developmental Neuroscience Programme, University College of London, Institute of Child Health, London, United Kingdom.

Presenting author: Alessandra Ferlini
Contact: fla@unife.it

We recently described POPDC1 mutation causing atrio-ventricular block and muscular dystrophy (Schindler RF, et al. J Clin Invest. 2016;126:239-253) highlighted that POPDC proteins may play a key role for atrio-ventricular conduction and muscle function.

The Popeye domain containing (POPDC) gene family encodes proteins with three transmembrane domains which are predominantly expressed in the heart and skeletal muscle. POPDCs proteins interact with the K2P potassium channel TREK-1 enhancing its current amplitude and were recently identified as novel cAMP binding proteins involved in cardiac pacemaking (Froese A, et al. J Clin Invest. 2012;122:1119-1130).

Using whole exome sequencing of German twins with a third degree atrio-ventricular block and another, unrelated dominant Italian family with atrio-ventricular block, we identified a heterozygous non-sense mutation in the POPDC2 gene which is predicted to introduce a premature stop codon at position 188 (POPDC2W188*), deleting parts of its putative cAMP binding-domain. In addition to atrio-ventrucular block, the Italian patients (mother and son both carrying the mutation) do also have high CK and mild muscle weakness. Using several functional studies we demonstrated that POPDC2W188* reduces current amplitudes of the cardiac sodium channel SCN5A in a cAMP-dependent manner, albeit with a reduced efficiency. We propose that POPDC2 loss-of-function mutations cause atrio-ventricular block, mechanistically characterized by reduced potassium currents and increased SCN5A conductance. POPDC genes are therefore new playing figures acting both in the heart conduction system and in muscle membrane excitability regulation. They might be candidate for a variety of rare diseases with cardiomuscular phenotypes.

P61 **Huntington's disease blood and brain show a common gene expression pattern and share an immune signature with Alzheimer's disease**

Flower MHensman Moss DJ[1], Lo KK[2], Miller JRC1, van Ommen GB[3], 't Hoen PAC[3], Stone TC[4], Guinee A[5], Langbehn DR[6], Jones L[4], Plagnol V[2], van Roon-Mom WM[3], Holmans P*[4], Tabrizi SJ*[1]

[1]Department of Neurodegenerative Disease, University College London Institute of Neurology, London, WC1B 5EH, UK; [2]University College London Genetics Institute, University College London, London, WC1E 6BT, UK; [3]Department of Human Genetics, Leiden University Medical Center, Leiden, Postzone S-4-P, The Netherlands; [4]MRC Centre for Neuropsychiatric Genetics and Genomics, School of Medicine; [5]Cardiff University, CF24 4HQ, UK Faculty of Education, University of Cambridge, CB2 8PQ, Cambridge UK; [6]Departments of Psychiatry and Biostatistics, University of Iowa, IA 52242, USA

Presenting author: Michael Flower
Contact: michael.flower.14@ucl.ac.uk

There is widespread transcriptional dysregulation in Huntington's disease (HD) brain, but analysis is inevitably limited by advanced disease and postmortem changes. However, mutant HTT is ubiquitously expressed and acts systemically, meaning blood, which is readily available and contains cells that are dysfunctional in HD, could act as a surrogate for brain tissue. We conducted an RNA-Seq transcriptomic analysis using whole blood from two HD cohorts, and performed gene set enrichment analysis using public databases and weighted correlation network analysis modules from HD and control brain datasets. We identified dysregulated gene sets in blood that replicated in the independent cohorts, correlated with disease severity, corresponded to the most significantly dysregulated modules in the HD caudate, the most prominently affected brain region, and significantly overlapped with the transcriptional signature of HD myeloid cells. High-throughput sequencing technologies and use of gene sets likely surmounted the limitations of previously inconsistent HD blood expression studies. Our results suggest transcription is disrupted in peripheral cells in HD through mechanisms that parallel those in brain. Immune upregulation in HD overlapped with Alzheimerâ€™s disease, suggesting a common pathogenic mechanism involving macrophage phagocytosis and microglial synaptic pruning, and raises the potential for shared therapeutic approaches.

P62 **DNA repair pathways as a common genetic mechanism modulating the age at onset in polyglutamine diseases**

Bettencourt C[¥1,2], Hensman Moss DJ[¥3], Flower M[¥3], Wiethoff S[¥1,4], Brice A[5,6], Goizet C[7,8], Stevanin G[5,9], Koutsis G[10], Karadima G[10], Panas M[10], Yescas-Gómez P[11], García-Velázquez LE[11], Alonso-Vilatela ME[11], Lima M[12,13,14], Raposo M[12,13,14], Traynor B[15], Sweeney M[16], Wood N[1], Giunti P[1,17], Durr A[5,6] for the French SPATAX network, Holmans P[18], Houlden H[1,16], Tabrizi SJ[§3], Jones L[§18]

[¥]These authors contributed equally to this work; [§]These authors supervised this work

[1]Department of Molecular Neuroscience, Institute of Neurology, University College London, London WC1N 3BG, UK; [2]Department of Clinical and Experimental Epilepsy, Institute of Neurology, University College London, London WC1N 3BG, UK; [3]Department of Neurodegenerative Disease, Institute of Neurology, University College London, London WC1N 3BG, UK; [4]Center for Neurology and Hertie Institute for Clinical Brain Research, Eberhard-Karls-University, Tübingen, Germany; [5]Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, UPMC University Paris 06 UMR S 1127, Institut du Cerveau et de la Moelle épinière (ICM), Paris, France; [6]APHP, Department of Genetics, University Hospital Pitié-Salpêtrière, 75013 Paris, France; [7]Univ. Bordeaux, Laboratoire Maladies Rares: Génétique et Métabolisme, INSERM1211, Bordeaux, France; [8]CHU Pellegrin, Service de Génétique Médicale, F-33000, Bordeaux, France; [9]Ecole Pratique des Hautes Etudes, 75014 Paris, France; [10]Neurogenetics Unit, 1st Department of Neurology, University of Athens Medical School, Eginition Hospital, 115 28 Athens, Greece; [11]Neurogenetics Department. National Institute of Neurology and Neurosurgery, "Manuel Velasco Suárez", Mexico City CP14269, Mexico; [12]Department of Biology, University of the Azores, 9500-321 Ponta Delgada, Portugal; [13]Instituto de Investigação e Inovação em Saúde, Universidade do Porto, 4150-180 Porto, Portugal; [14]Institute for Molecular and Cell Biology (IBMC), University of Porto, 4150-180 Porto, Portugal; [15]Laboratory of Neurogenetics, National Institute of Aging, NIH, Bethesda, MD 20892, USA; [16]Neurogenetics Unit, National Hospital for Neurology and Neurosurgery, University College London Hospitals, London WC1N 3BG, UK; [17]Ataxia Center, Institute of Neurology, University College London, London WC1N 3BG, UK; [18]MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff CF24 4HQ, UK

Presenting author: Davina J Hensman Moss & Michael Flower
Contact: d.hensman@ucl.ac.uk / michael.flower.14@ucl.ac.uk

Background: Over 30 human diseases are caused by expansion of unstable microsatellite sequences. Nine of these are caused by expanded CAG tracts encoding polyglutamines in different genes. This subgroup of diseases, usually referred to as the polyglutamine diseases which include Huntington's disease (HD), several spinocerebellar ataxias (SCAs), and spinal and bulbar muscular atrophy, are amongst the commonest hereditary neurodegenerative diseases. Longer CAG repeat tracts are associated with earlier ages at onset (AAO), but this does not account for all the variance, suggesting the existence of additional modifying factors. DNA repair pathways have been recently associated with the HD motor AAO in a recent HD GWAS.

Aims: To confirm the association between HD motor AAO and DNA repair pathways; and to investigate whether these modifying effects of variants in DNA repair genes can be extended to other polyglutamine diseases.

Methods: We collected an independent cohort of 1462 subjects with HD and polyglutamine SCAs, and genotyped SNPs selected from the most significant hits in the HD study.

Results: In an overall analysis of DNA repair pathway, we found the most significant association with AAO when grouping all polyglutamine diseases (HD+SCAs, p=1.43x10-5). Significant associations were also found for HD (p=0.00194), all SCAs (p=0.00107), SCA2 (p=0.0035), and SCA6 (p=0.00162). Testing individual SNPs, we found significant associations for rs3512 in FAN1 with HD+SCAs (p=1.52x10-5) and all SCAs (p=2.22x10-4), and rs1805323 in PMS2 with HD+SCAs (p=3.14x10-5). All these associations follow the same direction as in the HD GWAS.

Conclusions: We show that DNA repair genes significantly modify the AAO not only in HD, but also in polyglutamine SCAs. This suggests a common pathogenic mechanism for these diseases, which could operate through the observed somatic expansion of repeats. Manipulation of DNA repair pathways may offer novel therapeutic opportunities in multiple diseases.

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P63

Identification of genetic variants associated with Huntington's disease progression: a genome-wide association study

Hensman Moss DJ[*1], Pardiñas AF[*2], Langbehn D[3], Lo K[4], Leavitt BR[5], Roos R[6], Durr A[7], Mead S[8], Holmans P[2], Jones L[§2], Tabrizi SJ[§1] and the REGISTRY and the TRACK-HD investigators

[*] These authors contributed equally to this work; [§] These authors contributed equally to this work

[1]UCL Huntington's Disease Centre, UCL Institute of Neurology, Dept. of Neurodegenerative Disease, London, UK; [2]MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK; [3]University of Iowa Carver College of Medicine, Dept. of Psychiatry and Biostatistics, Iowa, USA; [4]UCL Genetics Institute, Div. of Biosciences, London, UK; [5]Centre for Molecular Medicine and Therapeutics, Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada; [6]Department of Neurology, Leiden University Medical Centre, Leiden, Netherlands; [7]ICM and APHP Department of Genetics, Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, UPMC Univ Paris 06 UMR S 1127, Pitié- Salpêtrière University Hospital, Paris, France; [8]MRC Prion Unit, UCL Institute of Neurology, London, UK

Presenting author: Davina J Hensman Moss
Contact: d.hensman@ucl.ac.uk

Background: Huntington's disease (HD) is a fatal inherited neurodegenerative disease, caused by a CAG repeat expansion in HTT. Age at onset (AAO) has been used as a quantitative phenotype in genetic analysis looking for HD modifiers, but is hard to define and not always available. Therefore here we aimed to generate a novel measure of disease progression, and identify genetic markers associated with this progression measure.

Methods: We generated a progression score based on principal component analysis of prospectively acquired longitudinal changes in motor, behavioural, cognitive and imaging measures in the TRACK-HD cohort of HD gene mutation carriers (data collected 2008 – 2011). We generated a parallel progression score using 1773 previously genotyped subjects from the REGISTRY study of HD mutation carriers (data collected 2003 – 2013). 216 subjects from TRACK-HD were genotyped. Association analyses was performed using GCTA, gene-wide analysis using MAGMA and meta-analysis using METAL.

Findings: Longitudinal motor, cognitive and imaging scores were correlated with each other in TRACK-HD subjects, justifying a single, cross-domain measure as a unified progression measure in both studies. The TRACK-HD and REGISTRY progression measures were correlated with each other (r=0·674), and with AAO (r=0·315, r=0.234 respectively). A meta-analysis of progression in TRACK-HD and REGISTRY gave a genome-wide significant signal (p=1.12x10-10) on chromosome 5 spanning 3 genes, MSH3, DHFR and MTRNR2L2. The lead SNP in TRACK-HD (rs557874766) is genome-wide significant in the meta-analysis (p=1.58x10-8), and encodes an amino acid change (Pro67Ala) in MSH3. In TRACK-HD, each copy of the minor allele at this SNP is associated with a 0.4 (95% CI=0.16,0.66) units per year reduction in the rate of change of the Unified Huntington's Disease Rating Scale (UHDRS) Total Motor Score, and 0.12 (95% CI=0.06,0.18) units per year in the rate of change of UHDRS Total Functional Capacity. The associations remained significant after adjusting for AAO.

Interpretation: The multi-domain progression measure in TRACK-HD is associated with a functional variant that is genome-wide significant in a meta-analysis. The strong association in only 216 subjects implies that the progression measure is a sensitive reflection of disease burden, that the effect size at this locus is large, or both. As knock out of Msh3 reduces somatic expansion in HD mouse models, this highlights somatic expansion as a potential pathogenic modulator, informing therapeutic development in this untreatable disease.

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“Integrated European –omics research project for diagnosis and therapy in rare neuromuscular and neurodegenerative diseases (NEUROMICS)”; CHDI Foundation; the Medical Research Council UK, the Brain Research Trust, the Guarantors of Brain.

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The launch of the European Reference Network for Rare Neurological Diseases: new prospects for quality care and research in Europe

Graessner H

Centre for Rare Diseases, University of Tübingen

Presenting author: Holm Graessner
Contact: holm.graessner@med.uni-tuebingen.de

Background and Aims: Imagine if the best specialists from across Europe could join their efforts to tackle rare medical conditions that require highly specialised healthcare and a concentration of knowledge and resources. That's the purpose of the European Reference Networks (ERNs) and it's becoming a reality. In 2016 the European Commission has issued a call for the formation of ERNs for rare diseases.

Methods: The European Reference Network for Rare Neurological Diseases (ERN-RND) has been formed in response to the call and is a network of 32 Healthcare Providers from 13 EU member states. ERN-RDN builds on existing expert centres and mature networks dedicated to RND as well as established rare disease infrastructures such as Orphanet, EURORDIS and RD-Connect.

Results: The European Reference Network for Rare Neurological Diseases is one of the very first ERNs that have officially been approved by the Board of Member States on 15 December 2016.

Conclusion: As a consequence of the official approval, ERN-RND will begin to operate in the first quarter of 2017. The network is in a very good position to achieve its strategic objectives of the first five year period. These are: 1. To increase the overall percentage of RND patients with a final diagnosis; 2. To improve care of RND patients; 3. To develop, share and implement care pathways and guidelines ; 4. To create, develop and enhance RND training, education and capacity building measures; 5. To develop a comprehensive and data based European RND cohort to better understand these conditions and help developing and testing treatments.

P65

Identification of putative disease-causing mutations in patients with ataxia or paraplegia using disease specific gene panels

Harmuth F[1], Schulze M[2], Kootz B[1], Sturm M[1], Synofzik M[3], Schüle-Freyer R[3], Lohmann E[3,4], Riess O[1], Schoels L[3], Bauer P[1,5]

[1]Institute of Medical Genetics and Applied Genomics, Eberhard-Karls-University, Tübingen, Germany; [2]CeGaT GmbH, Tübingen, Germany; [3]Department of Neurology and Hertie Institute for Clinical Brain Research, German Center of Neurodegenerative Diseases, Eberhard-Karls-University, Tübingen, Germany; [4]Department of Neurology, Medical School, Istanbul University; [5]Centogene AG, Rostock, Germany

Presenting author: Florian Harmuth
Contact: florian.harmuth@med.uni-tuebingen.de

Neurodegenerative diseases with ataxia or paraplegia are highly heterogeneous (>150 genes) and show autosomal dominant, recessive and X-linked forms of inheritance. Work package five aimed to identify putative disease-causing mutations in cohorts of 100 patients per disease group using two custom-made disease specific gene panels.

In order to achieve this objective we established disease specific gene panels (HaloPlex, Agilent) with 202 target genes for ataxia and 136 genes for paraplegia. The target region of 679kb (ataxia)/ 391kb (paraplegia) was sequenced on a MiSeq (Illumina) with 2x 150bp paired-end runs. The read sequences were analyzed by an in-house bioinformatics pipeline.

Currently, index patients from 160 families (ataxia: 100/ paraplegia: 60) have been sequenced. HaloPlex disease panel approach achieved a high efficiency: median target region coverage â‰¥20 reads: >96% (ataxia)/ >98% (paraplegia); median depth: 218 (ataxia)/ 440 (paraplegia). Mapping the reads to the human genome (hg19) followed by annotation to different databases resulted in large lists of variants per sample (ataxia: 204-490/ paraplegia: 133â€“259) which were further filtered for rareness (in-house database, ExAC, Kaviar) and for functional relevance (ns, indel). This led to a reduced number of 1-51 (ataxia)/ 0-18 (paraplegia) variants per patient. Several rare, disease-causing and potentially causative mutations were found in different genes (ataxia: SACS, CACNA1A, SPG7/ paraplegia: SPG11, KIF1C, IFIH1). Panel sequencing elucidated the molecular basis in 19 ataxia (18%) and 21 paraplegia families (39%) respectively. For both disease groups, potentially disease causing variants of yet uncertain significance could be identified in another 23%/ 26% of cases.

Disease specific panel sequencing is a sensitive, robust and cost-efficient method to rapidly identify putative causative mutations. Within the NeurOmics project, for most interesting patients in whom no disease-causing mutations could be detected by panel sequencing, whole exome or genome sequencing will further elevate the clearance rate. For the latter approach, data mining and analyzing is still an ongoing task.

P66 Induced pluripotent stem cell-derived disease model of Hereditary Spastic Paraplegia SPG5

Hauser S[1], Hoeflinger P[1,4], Theurer Y[1], Rattay TW[2], Bjoerkhem I[3], Schüle R[2], Schoels L[1,2]

[1]German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany; [2]Hertie Institute for Clinical Brain Research, Department of Neurodegenerative Diseases, Tübingen, Germany; [3]Division of Clinical Chemistry, Karolinska University Hospital, Huddinge, Karolinska Institutet, Stockholm, Sweden; [4]Graduate Training Centre of Neuroscience, Tübingen, Germany

Presenting author: Stefan Hauser
Contact: stefan.hauser@dzne.de

Hereditary spastic paraplegia (HSP) refers to a group of rare monogenetic disorders, which are characterized by a progressive axonal degeneration of corticospinal motor neurons, leading to spasticity and weakness of the lower limb.

Spastic paraplegia gene 5 (SPG5) is an autosomal recessive subtype of HSP caused by mutations in CYP7B1, encoding the cytochrome P-450 oxysterol 7-Î±-hydroxylase, essential for the liver-specific alternative pathway in bile acid synthesis. In SPG5, a decreased enzyme activity leads to an accumulation of oxysterol substrates (e.g. 27-hydroxycholesterol) in plasma and cerebrospinal fluid (CSF) of patients.

Research on molecular pathogenesis of HSP is limited by restricted access to primary neurons and hepatocytes from patients. In order to circumvent this obstacle we reprogrammed primary fibroblasts of five SPG5-patients and two age-matched controls using non-integrative episomal plasmids and characterized genetic integrity and pluripotency of the generated induced pluripotent stem cells (iPSC). The disease-specific iPSCs provide an unlimited cell source for any somatic cell type. We established the differentiation into iPSC-derived neurons and hepatocyte-like cells, providing us with an in vitro human cell model.

In cultures of motor neuron-like cells (NSC-34) and iPSC-derived neurons a neurotoxic effect of accumulating oxysterols could be demonstrated, supporting the hypothesis that substrates of CYP7B1 lead to progressive axonal degeneration. After validating the disease model, it will be further used to elucidate the disease mechanism in SPG5 thereby studying lipidomic changes with special focus on oxysterols and other cellular mechanisms influenced by accumulation of oxysterols. Ultimately, this cell model can be used as a platform for a compound screening. These studies will improve our insight in the pathogenesis of SPG5 and will help to develop new therapeutic approaches for HSP treatment.

P67 **Targeted Gene Panel Sequencing with Expanded Gene Profile Enables High Diagnostic Yield in Motor Neuron Disorders**

Karakaya M[1], Storbeck M[1], Strathmann E[1], Altmüller J[1,2], Schrank B[3], Yis U[4], Kalafatcilar I[4], Wunderlich G[5], Nürnberg P[2], Heller R[1], Wirth B[1]

[1]Institute of Human Genetics, Center for Molecular Medicine Cologne, and Institute of Genetics, University of Cologne, Cologne, Germany; [2]Cologne Center for Genomics, University of Cologne, Germany; [3]Department of Neurology, DKD HELIOS Kliniken, Wiesbaden, Germany; [4]Dokuz Eylül University, Department of Pediatric Neurology, Izmir, Turkey; [5]Department of Neurology, University Hospital of Cologne, Cologne, Germany

Presenting author: Mert Karakaya
Contact: mert.karakaya@uk-koeln.de

Motor neuron disorders (MND) such as spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS), hereditary motor neuropathies (HMN) or hereditary spastic paraplegia(HSP) represent a heterogeneous group of neuromuscular disorders (NMD) often with overlapping phenotypes. More than 120 genes have been identified to cause MNDs. A targeted NGS method covering only genes of a certain phenotype often results in a low diagnostic yield due to the significant overlap between MNDs and other NMDs. Our first diagnostic approach to identify disease causing variants in a cohort of 36 Lower Motor Neuron Disease (LMND) patients was carried out with a 65 LMND-associated gene panel. Ion AmpliSeq technology was used for target enrichment, and samples were sequenced on Ion PGM System. Later, the broader panel (NMD Panel) was developed, and the 1st version of NMD panel included 443 genes, known to be involved in MND, CMS and myopathies. A 2nd version included additional newly discovered NMD genes. Moreover regions not optimally covered in the 1st version were boosted. For target enrichment and library preparation, SureSelect technology was utilized. The samples were sequenced on an Illumina Hiseq4000 platform, and bioinformatically analyzed using the Varbank pipeline. The panel restricted to 65 LMND-associated genes yielded a diagnostic success rate of 14%. 40% of undiagnosed cases could be identified via WES/WGS with variants in known NMD genes that were not included in LMND panel. Moreover, 38% of the cases were found to have mutations in related myopathies. Instead, the expanded NMD panel provided a genetic diagnosis in 13 of 30 LMND cases (43%).The mean read depth and the percentage of coverage have risen dramatically after the improvements in the 2nd version. 98.8% of all HGMD-reported mutations in the 446 genes were represented with sufficient coverage. The diagnostic yield applying a broader panel represents a significant improvement compared to LMND panel with 65 genes. The results of the NMD panel demonstrate the efficiency of panel sequencing as the first tier in the diagnosis of MNDs.

P68 **Functional analysis of Bicaudal D2, a highly conserved motor adaptor, involved in autosomal dominant SMA, lower extremity-predominant 2 (SMALED2)**

Martinez L[1,3], Gabriel E[3], Donohoe C[4], Hölker I[1,2,3], Wason A[3], Storbeck M[1,2,3], Uhlirova M[4], Gopalakrishnan J[3], Wirth B[1,2,3]

[1]Institute of Human Genetics, University of Cologne, 50931 Cologne, Germany; [2]Institute for Genetics, University of Cologne, 50674 Cologne, Germany; [3]Center for Molecular Medicine, University of Cologne, 50931 Cologne, Germany; 4Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, 50931 Cologne, Germany

Presenting author: Lilian Martinez
Contact: lilian.martinez-carrera@uk-koeln.de

Heterozygous variants in BICD2 are causative of autosomal dominant spinal muscular atrophy, lower extremity-predominant 2 (SMALED2). BICD2 is ubiquitously expressed, functions as motor protein adaptor and regulates microtubule transport. To study the pathogenic consequences of SMALED2-associated BICD2 mutations, we have performed functional analysis in fibroblast cells derived from individuals with SMALED2, interaction studies, lentiviral transduction of motor neurons, and generated an in vivo SMALED2 Drosophila model. We show that fibroblasts derived from SMALED2 individuals - independently of BICD2 mutation- exhibit long and stable microtubules. Motor neurons overexpressing BICD2 mutations, develop axonal aberrations such as collateral branching and overgrowth. Furthermore, in vivo analysis of BICD2 mutant Drosophila reveal impaired locomotion with reduced NMJ size. Thus, we have identified a common mechanism of BICD2 mutations affecting microtubule array in motor neurons leading to increase axonal branching and alteration on NMJ development.

P69 **Identification and functional characterization of CHP1, a novel causative gene of human autosomal recessive ataxia**

Mendoza Ferreira N[1], Coutelier M[2,3], Janzen E[1], Hosseinibarkooie S[1], Löhr H[4], Schneider S[1], Milbradt J[1], Riessland M[5], Pichlo C[6], Torres-Benito L[1], Singleton A[7], Zuchner[8], Brice A[3], Leber I[3], Durr A[3], Hammerschmidt M[4], Stevanin G[2], Wirth B[1]

[1]Institute for Human Genetics, University of Cologne. Institute of Human Genetics, University of Cologne. Centre for Molecular Medicine, University of Cologne. Cologne, Germany; [2]Laboratoire de Neurogénétique, Ecole Pratique des Hautes Etudes. Paris, France; [3]Institut du Cerveau et de la Moelle épinière, Hôpital de la Pitié-Salpêtrière. Paris, France; [4]Institute for Zoology, Developmental Biology, University of Cologne. Cologne, Germany; [5]Laboratory of Molecular and Cellular Neuroscience, The Rockefeller University, New York, USA; [6]Institute of Biochemistry, University of Cologne. Cologne, Germany; [7]Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA; [8]John P. Hussman Institute for Human Genomics, University of Miami, Miller School of Medicine, Miami, USA.

Presenting author: Natalia Mendoza
Contact: natalia.mendoza-ferreira@uk-koeln.de

Autosomal recessive cerebellar ataxias (ARCAs) are a heterogeneous group of neurodegenerative disorders characterized by incoordination, poor balance and postural tremor. Several clinical types of ARCAs are currently recognized, with variable phenotypes involving both the central and peripheral nervous systems and other non-neurological signs. The advent of whole exome sequencing (WES) has significantly expanded the number of genes linked to ARCAs, nevertheless 50% of the patients still remain with an unresolved etiology.

In this study we describe a consanguineous family with two siblings presenting with an undiagnosed neuropathy, cerebellar vermis atrophy, intellectual disability and slow ocular saccades. WES combined with genome-wide linkage analysis led to the identification of a homozygous 3-bp deletion in the CHP1 gene (Calcineurin-like EF-hand protein 1). Focused screening for CHP1 variants in an ARCA cohort (N=319) did not yield any additional variant, thus confirming the extreme scarcity of CHP1 mutations. CHP1 plays a crucial role in axonal ion homeostasis and pHi regulation, by controlling the maturation and membrane localization of NHE1; a major Na+/H+ exchanger implicated in ataxia-deafness syndromic cases. Chp1 knockdown mice present reduced axonal NHE1 localization and exhibit ataxia.

Time-course expression analysis, subcellular fractionation and size exclusion chromatography experiments proved that mutant CHP1 is misfolded and prone to form aggregates, leading to diminished levels of soluble protein and decreased NHE1 targeting to the membrane. To validate in vivo the pathogenic effect of the CHP1 mutation, we downregulated chp1 expression in zebrafish using antisense morpholinos (MO). Injected MO larvae exhibited irregular swimming behavior, motor axon abnormalities and cerebellar defects, which were ameliorated by co-injection with WT, but not mutant, human CHP1 mRNA.

Taken together, our results validate CHP1 as a novel ataxia causative gene in human, further expanding the spectrum of ARCAs-associated loci, and corroborate the crucial axonal-pHi regulation role of NHE1 in the pathogenesis of these disorders.

P70 **The success of Whole exome sequencing analysis in Neuromuscular Diseases patients: the UNIFE experience within Neuromics project**

Neri M[1], Scotton C[1], Selvatici R[1], Gualandi F[1], Wirth B[2], Schols L[3], Klockgether T[4], Lochmuller H[5], Muntoni F[6], D'Amico A[7], Bertini E[7], Pane M[8], Mercuri E[8], Ferlini A[1,6]

[1]Unit of Medical Genetics, Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [2]Institute of Human Genetics, Institute for Genetics and Center for Molecular Medicine of The University of Cologne Cologne, Germany; [3]Department of Diagnostic and Interventional Neuroradiology, University Hospital Tübingen, Tübingen, Germany; [4]Department of Neurology, University of Bonn, and German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; [5]John Walton Centre for Muscular Dystrophy Research, MRC Centre for Neuromuscular Diseases, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK; [6]Dubowitz Neuromuscular Centre, University College London, Institute of Child Health, London, UK; [7]Unit of Neuromuscular and Neurodegenerative Diseases, Department of Neurosciences, Bambino Gesù Childrens Hospital, Rome, Italy; [8]Paediatric Neurology Unit, Catholic University, Rome, Italy

Presenting author: Marcella Neri
Contact: nremcl@unife.it

The heterogeneous genetic landscape of NMDs raises challenges regarding the definition of a molecular diagnosis, now becoming mandatory for the inclusion in emerging therapeutic trials. To improve the diagnostic definition in our NMDs patients we used a Next Generation Sequencing approach: clinical gene panel analysis for the screening of known genes, WES (whole exome sequencing) and WGS (whole genome sequencing) analysis aimed at the identification of novel causative genes.

WES analysis was performed in 6 "families of four" and 2 "trios": 3 of them with congenital myopathy/dystrophy, 1 with spastic paraplegia, 2 with ataxia, 1 with Myofibrillar Myopathy, and 1 with AV block and LGMD.

We identified 3 mutations in known genes (RYR1, ISPD and STIM1) and 2 novel causative genes POPDC1 and MSTO1, functionally validated. In the remaining 3 families, 2 candidate genes SARS2 and MMP8 were identified however not similar phenotypes were observed within the project making difficult the variation clinical validation.

The WES in the last family identified a compound heterozygosis in the CPSF3L gene and transcript analysis is ongoing.

WES analysis unraveled the genetic cause in 5 out of 8 families corresponding to more than 60% of families studied.

P71 Clinical Gene Panel In Unife Patients, Orphans Of Genetic Diagnosis

Neri M[1], Selvatici R[1], Scotton C[1], Storbeck M[2], Vezyroglou K[2], Heller R[2], Tugnoli V[3], Bigoni S[1], Timmerman V[4], Wirth B[2], De Grandis D[5], Gualandi F[1], Ferlini A[1]

[1]Unit of Medical Genetics, Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [2]Institute of Human Genetics, University Hospital of Cologne, Cologne, Germany; [3]Department of Neuroscience and Rehabilitation, Division of Neurology, University Hospital of Ferrara, Ferrara, Italy; [4]VIB - Department of Molecular Genetics Peripheral Neuropathy Group, University of Antwerpen, Belgium; [5]UILDM- Verona, Italy

Presenting author: Marcella Neri
Contact: nremcl@unife.it

We studied for diagnostic purpose 6 families orphan of genetic definition: one with hereditary neuropathy, four with hereditary ataxia and one with recurrence of arthrogriposis. With a clinical gene-panel approach we were able to identify the causative mutation in known genes in 3 out of 5 families. Two brothers with a distal axonal motor neuropathy and a focal autonomic dysfunction were studied using an in-house-designed lower motor neuron diseases gene panel. This analysis allowed us to identify a hemizygous missense mutation (p.A991D) in the X-linked ATP7A gene , present in both the affected brothers. ATP7A missense mutations have been reported in two families with X-linked dHMN (SMAX3). The phenotype we describe in our family is novel since includes autonomic dysfunction. All the four families with recurrence of cerebellar ataxia showed autosomal dominant mode of inheritance. In the affected patients molecular analysis of the SCA expansion genes and of the SCA15 gene resulted negative. NGS analysis of a targeted genes panel for SCA was carried in one affected member of each family. In the first family the analysis identified an heterozygous missense mutation in AFG3L2 gene (p.Met666Val); the variation has been published to cause AD SCA28. In our family the progression of the disease is very slow but there is an anticipation of the onset in the proband (at 35 years) compared to the mother (at 70 years) despite the identified mutation is not a trinucleotide expansion. In the second family the proband started experiencing progressive ataxia since childhood associated to dysarthria and cerebellar signs; the disease is slowly progressive. The mother was affected since childhood as well and died aged 50.

The analysis identified a missense mutation in KCNC3 gene (Arg423His) known to be causative of SCA13.In the remaining two families and in the family with recurrence of arthrogryposis the analysis did not identify mutations in known causative genes; a clinical redefinition of the phenotype has been requested in the patients with ataxia in order to address any further analysis. Whole genome sequencing is ongoing in the arthrogryposis family.

P72 WES Analysis Identified MSTO1 As Novel Disease Gene In Patients With Congenital Onset Of Muscle Disorder And Cerebellar Ataxia

Nasca A[1], Scotton C[2], Zaharieva I[3], Selvatici R[2], Neri M[2], Magnusson OT[4], Gal A[5], Kiriko G[5], Weaver D[5], Rossi R[2], Armaroli A[2], Pane M[6], Cecconi A[7], Sewry C[3], Phadke R[3] Feng L[3], Donati A[8], Mercuri E[6], Zeviani M[9], Muntoni F[3], Ghezzi D[1], Ferlini A[2,3]

[1]Molecular Neurogenetics Unit, Foundation IRCCS Neurological Institute Besta, Milan, Italy; [2]Medical Genetics Unit, Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [3]UCL Great Ormond Street Institute of Child Health, London UK; [4]deCODE Genetics, Reykjavik, Iceland; [5]MitoCare Center for Mitochondrial Imaging Research and Diagnostics, Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA, USA; [6]Neuropsichiatry Unit, Catholic University, Policlinico Gemelli, Rome, Italy; [7]Pediatrics Medical Genetics, Hospital S. Maria Annunziata, Florence, Italy; [8]Unit of Metabolic and Muscular Diseases, Meyer Children Hospital, Florence, Italy; [9]Mitochondrial Biology Unit - MRC, Cambridge, UK

Presenting author: Marcella Neri
Contact: nremcl@unife.it

Using WES we identified two independent families with 3 patients affected by a multisystemic condition characterised by growth and motor delay, early onset muscle weakness, cerebellar hypotrophy and ataxia, dystrophic features on muscle biopsy and raised CK. The two affected siblings from Family 1 carried compound heterozygous MSTO1 mutations c.1033C>T (p.R345C) and c.1128C>A (p.F376L) and the affected case from Family 2 was compound heterozygous for c.971C>T (p.T324I) and c.966+1G>A.

Human MSTO1 is a poorly studied protein; it has been suggested to encode a mitochondrial protein regulating morphology and distribution of mitochondria. As for other mutations affecting genes involved in mitochondrial dynamics, no biochemical defects typical of mitochondrial disorders were reported. We performed studies in fibroblasts from the patients from Family 1which revealed that MSTO1 protein levels were strongly reduced; moreover the mitochondrial network was fragmented and the fusion events among mitochondria were decreased, confirming the deleterious effect of the identified variants and the role of MSTO1 in modulating mitochondrial dynamics. We also found that MSTO1 is mainly a cytosolic protein. These findings indicate recessive mutations in MSTO1 as a new cause for inherited neuromuscular disorders with multisystem features.

P73 Characterisation of MYO9A as a pre-synaptic CMS gene

O'Connor E[1], Cordts I[2], Mueller J[1], Topf A[1], Phan V[2], Roos A[1], Lochmüller H[1]

[1]John Walton Muscular Dystrophy Research Centre, Newcastle University, Institute of Genetic Medicine, Newcastle-upon-Tyne, NE1 3BZ; 2Leibniz-Institute for Analytical Science ISAS, Dortmund, Germany

Presenting author: Emily O'Connor
Contact: e.a.oconnor@ncl.ac.uk

Background:

Congenital myasthenic syndromes (CMS) are a group of rare, inherited disorders characterised by compromised function of the NMJ. CMS usually manifests in childhood with fatigable weakness of limb, ocular and bulbar muscles depending on the underlying genetic defect. We identified mutations in MYO9A as causative for CMS but the precise pathomechanism remained to be characterised.

Aims:

To unravel the pathophysiology underlying CMS caused by mutations in MYO9A. We hypothesised that defects in MYO9A affect the neuronal cytoskeleton, and thus lead to impaired vesicular transport and protein secretion.

Method:

NSC-34 cells (mouse motor neuron-derived cell-line), depleted for MYO9A, were used to assess the effect of reduced MYO9A expression on the cytoskeleton using immunofluorescent and immunoblotting techniques. Vesicular transport was analysed using three main assays; a secretome study to observe effects on secreted proteins from NSC-34 cells, a surface-biotinylation assay to assess the abundance of plasma-membrane proteins and a recycling assay to look at receptor recycling processes. In addition, an unbiased approach utilising label-free comparative proteomic profiling of wild-type and MYO9A-depleted NSC-34 cells was performed to identify key players of the pathophysiology.

Results:

Disruption of the cytoskeleton has been identified in cells depleted for MYO9A, with an upregulation of actin and a downregulation of other structural proteins. Accordingly, defects in receptor recycling and regular transport of proteins to the cell surface were also observed in cells depleted for MYO9A. Proteomic data support a role for defective vesicular transport in NSC-34 cells and identified affected proteins which are also involved in the manifestation of further neuromuscular disorders.

Conclusion:

Our combined data allow new insights into the pathophysiology of CMS and show that loss of MYO9A affects the neuronal cytoskeleton, and leads to impaired transport, vesicular recycling and secretion of proteins. Hence, altered protein transport leads to this CMS phenotype by affecting important NMJ proteins, as well as the structure of the nerve terminal.

P74 Genetic characteristics of sporadic adult onset degenerative ataxia

Paap B[3], Harmuth F[1] , Klockgether T[2, 3], Bauer P[1]

[1]Institute of Medical Genetics and Applied Genomics, University of Tübingen, Tübingen, Germany; [2]Department of Neurology, University Hospital of Bonn, Bonn, Germany; [3]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

Presenting author: Brigitte Paap
Contact: brigitte.paap@dzne.de

Introduction: Sporadic ataxia with adult onset is often caused by multiple system atrophy of cerebellar type (MSA-C). However, many patients do not fulfil MSA-C criteria and are designated as sporadic adult onset ataxia of unknown aetiology (SAOA). Here, we present genetic data on a large cohort of patients with sporadic degenerative ataxia of adult-onset.

Methods: In the SPORTAX registry we enrolled patients with (1) progressive ataxia, (2) onset > 40 years, and (3) informative and negative family history from 14 European referral centres. In all participants, acquired causes of ataxia were excluded, and genetic tests for common repeat mutations were negative. Further, we determined in all probands whether MSA-c criteria were met. Participants were followed longitudinally. Participants who did not fulfil MSA-C criteria and a disease duration of > 10 years were designated as SAOA/non-MSA. Participants who did not fulfil MSA-c criteria with a disease duration < 10 years were designated probable SAOA.

DNA samples were screened for mutations using a high-coverage ataxia-specific gene panel in combination with next generation sequencing (NGS).

Results: The analysis was performed on 249 subjects enrolled between April 1, 2010 and March 18, 2016. 83 subjects met diagnostic criteria of clinically probable MSA-C at baseline and another 12 during follow-up. 48 participants who did not fulfil MSA-C criteria and had a disease duration of > 10 years were designated as SAOA/non-MSA.

In 196 subjects DNA analysis was performed. Variants of definitive or probable pathogenicity were found in 10% of the tested subjects. Another 8% carry variants, we regard as interesting, but could not relate to any status of pathogenicity yet. In all others no genetic cause could be determined.

Interpretation: Screening for causative mutations with a gene panel approach yielded a genetic diagnosis in 10% of the cohort.

P75 **The Identification of a Potential Novel Disease Causing Gene, MYH13 using Whole Exome Sequencing**

Porter A[1], Topf A[1], Roos A[1], McMacken G[1], Harris E[1], Mcarthur D[2], van den Berg P[3], Straub V[1], Lochmüller H[1]

[1]The John Walton Muscular Dystrophy Research Center, Newcastle University; [2]The Analytic and Translational Genetics Unit, Massachusetts General Hospital

Presenting author: Anna Porter
Contact: anna.porter@nuth.ac.uk

Introduction: Limb Girdle Muscular Dystrophies (LGMD) are characterised by weakness of the pelvic and shoulder girdle musculature. LGMDs are a highly heterogeneous group of neuromuscular diseases (NMD) both clinically and genetically. There are approximately 300 monogenetic causes of NMD, however approximately 50% of patients do not have a genetic diagnosis.

Aim: In this study we aim to analyse whole exome sequencing (WES) data for disease causing variants in a genetically undiagnosed patient, presenting with clinical symptoms of LGMD.

Results: We identified rare variants in MYH13, a myosin heavy chain, not previously reported in the literature as disease causing. Additionally, we have identified a second patient with a clinical diagnosis of NMD and rare variants in MYH13.

Conclusions: Genetic diagnoses are vital for patients and clinicians to make informed decisions about future care and family planning. This study demonstrates the stages involved in making a genetic diagnosis and the identification of potential novel disease causing variants.

P76

Absence of BiP Co-chaperone DNAJC3 Associated with Diabetes Mellitus and Multisystem Neurodegeneration Increases Mitochondrial Respiratory Dysfunction Resulting from Cholesterol-Overload induced ER Stress.

Roos A[1], Jennings M[1], Synofzik M[2], Hathazi D[3], Horvath R[1]

[1]John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicince, Newcastle University, Newcastle, UK; [2]Department of Neurodegeneration, Hertie Institute for Clinical Brain Research (HIH), University of Tübingen, Tübingen, Germany; [3]Leibniz-Institute for Analytical Science -ISAS-, Dortmund, Germany

Presenting author: Andreas Roos
Contact: andreas.roos@ncl.ac.uk

Background: Endoplasmic reticulum stress and unfolded protein response (UPR) have been previously associated with both diabetes mellitus and various forms of neurodegenerative disease, as well as cellular mitochondrial homeostasis. Recently, mutations in DNAJC3 encoding for an ER-resident co-chaperone have been identified in two families (inherited chaperonopathy). Patients displayed diabetes mellitus and widespread degeneration of the central and peripheral nervous system.

Aims: To unravel pathophysiology of DNAJC3-caused phenotype by making use of patient-derived fibroblasts via combined proteomics and cell biological studies.

Methods: Primary fibroblasts were cultured from DNAJC3 patients and healthy controls, under ER-stress conditions inducted by cholesterol with ACAT inhibitor treatment and under un-stressed conditions. Global proteome profiling was carried out to identify proteins affected by loss of functional DNAJC3 and moreover mitochondrial stress tests were performed using Seahorse assay to determine oxygen consumption rate. In addition, western blots were performed for DNAJC3 and mitochondrial respiratory complexes.

Results: Proteomic findings revealed alterations in mitochondrial proteins suggesting inability of DNAJC3 mutants to resolve ER stress leads to dysregulation of mitochondria. DNAJC3 mutant cell lines show major disruption of the respiratory chain following ER-stress treatment, particularly the maximal rate of respiration. In contrast, control cell lines show little effect from ER-stress treatment. Minimal alterations in non-mitochondrial respiration revealed that this effect is not caused by cell death.

Conclusions: Findings suggest that the inability of cells lacking DNAJC3 to resolve ER stress induced by cholesterol-overload leads to significant disturbances in mitochondrial regulation and function. This provides evidence that dysfunction in the UPR can cause widespread mitochondrial dysfunction associated with cell death, potentially an important mechanism in the pathophysiology of the DNAJC3-chaperonopathy.

P77 **Whole Genome Sequencing in Neuromuscular Diseases: the UNIFE experience within the Neuromics project.**

Selvatici R, Neri M, Scotton C, Falzarano MS, Armaroli A, Rossi R, Gualandi F, Fini S, Ferlini A

Unit of Medical Genetics, Department of Medical Sciences, University of Ferrara, Ferrara, Italy

Presenting author: Rita Selvatici
Contact: svr@unife.it

In order to identify novel candidate genes involved in complex neuromuscular phenotypes, we provided patients to DeCode to perform whole genome sequencing (WGS) in:

i) 3 patients respectively with : ataxia complicated by spastic paraparesis, ataxia and dystonia, Duchenne-like phenotype. We analyzed the trios in all.

ii) 2 families of four, respectively with recurrence in siblings of congenital arthrogryposis and of spastic paraparesis plus ataxia and neuropathy.

iii) a sibling pair with limb girdle muscular dystrophy (LGMD).

The analysis unraveled the genetic cause of the LGMD: a compound heterozygosis in the CAPN3 gene was identified and validated in both the affected.

In the female with a Duchenne-like muscular dystrophy, WGS analysis identified a compound heterozygosis for two missense mutations in the PLEC gene inherited one from each parent. This gene is knwon to be associated with a peculiar forms of autosomal recessive LGMD.

In the patient with ataxia complicated by spastic paraparesis , WGS analysis identified two missense mutations in SPG7 and KIF5A genes not previously described and predicted to be pathogenetic. Segregation analysis in the family showed that the variations were respectively inherited one from the mother and one from the father; both parents are clinically asymptomatic. Therefore we can speculate that the disease is due to the compound heterozygosis identified.

In the family with ataxia and dystonia the analysis identified variations in few candidate genes; the variations have been filtered according to the inheritance of the disease, the class of pathogenicity and their functions. All the identified variation will be validated.

In the family with congenital arthrogryposis a panel of known disease genes resulted negative and the WGS analysis is still ongoing.

P78 Multi-omic analysis of serum allows identification of biomarkers for Duchenne muscular dystrophy

Spitali P, Hettne K, Tsonaka R, Sabir E, Seyer A, Lourbakos A, Koeks Z, Roos A, Picillo E, Ergoli M, Hemerik J, Goeman J, Straub V, Piscos Domingos J, Muntoni F, Al-Khalili-Szigyarto A, Teunissen CE, Lochmüller H, Politano L, Niks E, Aartsma-Rus A

Presenting author: Pietro Spitali
Contact: p.spitali@lumc.nl

Background: Duchenne muscular dystrophy (DMD) is a lethal neuromuscular disease affecting 1 in 5000 newborn males. It is caused by mutation in the DMD gene causing lack of dystrophin. As disease progresses muscle mass is substituted by fibro-adipose tissue leading to reduced patients motility and death. Muscle biopsies are the major source of information for pathophysiologic studies and for interventional proof of concept and dose finding studies.

Objectives: The objective of this study was to identify serum based biomarkers in order to non-invasively describe the characteristic pathophysiological signature and disease progression. Furthermore we intended to provide a list of biomarker candidates that could be used to monitor the efficacy of therapies aiming to correct the different aspects of the disease.

Methods: Aptamer based proteomics and mass spectrometry based metabolomics and lipidomics analyses were performed. The study includes case control comparisons and longitudinal analysis of cases.

Results: The obtained data show that the investigation of serum samples enables to observe multiple of the pathophysiological features which characterise DMD. Several proteins (259) and metabolites (9) and only a few (2) lipids were able to discriminate between cases and controls and some were also good discriminants for other forms of muscular dystrophy such ad LGMDs and DM1. Longitudinal analysis enabled to identify over 400 proteins which are affected over time in DMD patients. The profile of these proteins resembles the loss of muscle mass and increase in fat composition of muscle groups. Integration of the different -omic datasets enables to highlight which of the affected molecular pathways could be targeted by the drugs currently in clinical development.

Conclusion: Multi-omic analysis of serum enables to study the pathophysiology of DMD and to track the progression of the pathological pathways over time, providing an unbiased tool to monitor patients' condition and early response to therapy.

P79 **By which mechanism is the human protective modifier PLS3 upregulated in SMA asymptomatic individuals?**

Strathmann EA[1], Storbeck M[1], Hosseinibarkooie S[1], Come J[2], Altmüller J[1], Karakaya M[1], Magnússon Ó[3], Nothnagel M[4], Martinat C[2], Wirth B[1]

[1]Institute of Human Genetics, Center for Molecular Medicine Cologne, University of Cologne, Cologne, Germany; [2]Institut National de la Santé et de la Recherche Médicale (INSERM) - I-STEM, France; [3]deCode Genetics, Reykjavik, Iceland; [4]Cologne Center for Genomics, University of Cologne, Cologne, Germany

Presenting author: Eike Strathmann
Contact: eike.strathmann@uk-koeln.de

Spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by mutations or deletion of the gene survival of motor neuron 1 (SMN1). Affected individuals show characteristic disease features including loss of alpha motor neurons in the anterior horns of the spinal cord and muscle wasting. The severity of SMA is influenced by the copy number of the nearly identical gene SMN2. However, fully asymptomatic SMN1 deleted individuals were identified that carry the same number of SMN2 copies as their SMA affected siblings. Plastin 3 (PLS3), an actin-binding and -bundling protein was identified as a protective modifier that is able to rescue axonal growth defects and motor neuron function in asymptomatic individuals and SMA mice overexpressing PLS3. We identified seven PLS3-discordant families with increased PLS3 expression in Epstein-Barr virus (EBV) transformed lymphoblastoid (LB) cells. Similar high PLS3 expression was found in motor neurons derived from iPSCs of asymptomatic but not SMA-affected siblings. Instead, fibroblasts of the same individuals did not show any difference in PLS3 expression. We generated transcriptome and whole-genome data of iPSCs-derived motor neurons. Moreover, RNA sequencing from LBs and fibroblasts of the same individuals will be carried out. We will analyse the genetic variation and differential gene expression in our data sets.

There is some evidence that the SMA rescuing effect of PLS3 is gender-specific since all the asymptomatic individuals are women and PLS3 is an X-linked gene. One of our hypotheses is that the overexpression of PLS3 is caused by escape from X-inactivation. The macrosatellite DXZ4, which is essential for the X-inactivation is located next to PLS3. In males and the active X-chromosome in women, DXZ4 features heterochromatic epigenetic features, while it is euchromatic on the inactivated X-chromosome. Based on the variable repeat number of DXZ4 (50 â€“ 100 repeats of a 3-kb repeat monomer) and the location next to each other, it was suggested that DXZ4 could modulate the transcription of PLS3 in women. We will analyse the repeat number of DXZ4 using genome combing analysis.

P80 **A knock-in / knock-out mouse model for small heat shock protein hspb8 mimicking distal hereditary motor neuropathy and myofibrillar myopathy**

Bouhy D[1], Katona I[2], Juneja M[1], Haidar M[1], Holmgren A[1], De Winter V[1], Irobi J[1], Weis J[2], Timmerman V[1]

[1]Peripheral Neuropathy Research Group, Institute Born Bunge, VIB, University of Antwerp, Antwerp, Belgium; [2]Institute of Neuropathology, University Hospital, RWTH Aachen University, Aachen, Germany

Presenting author: Vincent Timmerman
Contact: vincent.timmerman@uantwerpen.be

Patients with distal hereditary motor neuropathy (dHMN) develop progressive motor impairments, weakness and atrophy of distal limb muscles. Since our first description of the K141N missense mutation in the small heat shock protein HSPB8, a number of additional dHMN patients and families have been reported. Interestingly, most mutations target the same amino acid residue (K141E, K141M, K141N, K141T) in the highly conserved Î±-crystallin domain of the HSPB8 protein. The spectrum of diseases caused by mutations in the HSPB8 gene was recently expanded to distal myopathy. HSPB8 is ubiquitously expressed, but is upregulated in motor neurons and muscles of transgenic SOD1 mutant mice modelling amyotrophic lateral sclerosis (ALS). The HSPB8 is a chaperone that participates in clearing misfolded poly-Q containing proteins such as mutant huntingtin and ataxin-3 involved in respectively Huntington's disease and spino-cerebellar ataxia. HSPB8 directly interacts with the co-chaperone BAG3 and their role in chaperone-assisted selective autophagy (CASA) is well described. To delineate the molecular deficits and functional consequences of HSPB8 mutations we generated a knock-in (KI) mouse model for the K141N missense mutation mimicking the neuropathy phenotype. We observed that homozygous mutant mice (HspB8K141N/K141N) develop a progressive axonopathy, with decreased compound motor action potential amplitudes, and loss of large and medium myelinated axons. This results in locomotor deficits with an impaired performance at the rotarod test. At the ultrastructural level, mice accumulate mutant HspB8 protein and display degenerative patterns similar to dHMN patients with the K141N mutation. Interestingly, these animals also develop a progressive myofibrillar myopathy as observed in some rare patients with HSPB8 mutations. Additionally, our model allowed us to generate HspB8 knock-out (KO) mice using the same targeting vector. Strikingly, the homozygous HspB8-KO animals (HspB8-/-) do not show any sign of axonopathy and display a much milder myopathy than the HspB8-KI animals.

P81 **NeurOmics: congenital muscular dystrophies and congenital myopathies gene identification**

Zaharieva I[1] Sarkozy A[1,2], Oates EC[3,4], Manzur A[1,2], Munot P[1,2], Morgan JE[1,5], Feng L[1], Sewry CA[1,6], Phadke R[1], Muntoni F[1,2,5]

[1]Dubowitz Neuromuscular Centre, UCL Great Ormond Street Institute of Child Health, UK; [2]Great Ormond Street Hospital, London, UK; [3]Institute for Neuroscience and Muscle Research, The Children's Hospital at Westmead, Australia; [4]Discipline of Paediatrics and Child Health, Faculty of Medicine, The University of Sydney, Australia; [5]MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, WC1N 3BG, UK; [6]Wolfson Centre for Inherited Neuromuscular Diseases RJAH Orthopaedic Hospital, Oswestry, UK

Presenting author: Irina Zaharieva
Contact: i.zaharieva@ucl.ac.uk

To identify novel congenital muscular dystrophy (CMD) and congenital myopathy (CMY) genes we applied whole exome sequencing (WES) or whole genome sequencing (WGS) to 106 CMD/CMY patients and their unaffected relatives. In 25% of the patients, mutations in known neuromuscular genes were detected. In a further 25%, novel candidate genes or known neuromuscular genes but associated with a new phenotype were identified. For example, we demonstrated a novel molecular pathomechanism in CMY due to recessive mutations in SCN4A. In vitro work showed that the SCN4A mutations in the CMY cases resulted in fully non-functional channels unable to conduct Na+ currents or in channels with significantly reduced Na+ flux.

WES also facilitated the detection of CACNA1S and STAC3 as causative for CMY. Both genes encode proteins essential for excitation-contraction coupling (EC). Recessive CACNA1S (Cav1.1) mutations were detected in a CMY patient analysed as part of NeurOmics. In parallel, WES in an international cohort revealed recessive or dominant Cav1.1 mutations in 11 CMY patients. Both type of mutations led to similar pathological changes of altered Ca2+ homeostasis and reduced EC coupling. A homozygous p.Trp284Ser STAC3 mutation was detected in 16 CMY patients from African/Middle Eastern/South American descendant. Recently an African/Caribbean patient, compound heterozygous for the p.Trp284Ser and a novel splice site change (c.997-1G>T) was identified. In vitro studies showed reduced peak Ca2+ response elicited by the RyR1 agonist 4-CMC and reduced peak Ca2+ in response to KCl induced depolarization.

The identification of these genes led to their incorporation in diagnostic gene panels and the research findings had direct impact on improving the diagnostic rates in CMD/CMY patients.

Work supported by NeurOmics also led to the detection of 6 novel candidate CMD/CMY genes (SRPK3, MYL1 and others) that are currently being functionally characterised.

In the remaining 50% of the analysed CMD/CMY cases, data analysis failed to detect disease causing variants emphasising the need for further work to reveal the genetic cause in such cases.

A FAIR RDRF: Findable, Accessible, Interoperable, and Reusable rare disease registry data

Tamas Szabo[1], David van Enckevort[2], Marco Roos[3], Lee Render[1], David Salgado[4,5], Sergi Beltran[6,7], Christophe Beroud[4,5,8], Ivo Gut[6,7], Hanns Lochmüller[9], Adam Hunter[1], Matthew Bellgard[1]

[1] Centre for Comparative Genomics, Murdoch University, Murdoch, Australia
[2] BBMRI-NL, Department of Genetics, Genomics Coordination Center, University Medical Center Groningen, University of Groningen , Groningen, the Netherlands
[3] Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands
[4] Aix-Marseille Université, Marseille, France
[5] Inserm, UMR_S 910, Marseille, France
[6] Centro Nacional de Análisis Genómico (CNAG-CRG), Center for Genomic Regulation, Barcelona Institute of Science and Technology (BIST), Barcelona, Spain
[7] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[8] APHM, Hôpital TIMONE Enfants , Laboratoire de Génétique Moléculaire, Marseille, France
[9] MRC Centre for Neuromuscular Diseases, Newcastle University, UK

Abstract

Rare disease registries are important for a number of reasons. They empower rare disease patient communities, become a focus for personalized and therapeutic interventions and interaction with orphan drug development, support public health and clinical research, facilitate service planning by analyses and reporting of relevant data, enable research by providing de-identified data to researchers, promote and disseminate new knowledge to inform best clinical practice and care, and identify and recruit volunteers for clinical trials.

The Rare Disease Registry Framework (RDRF) is a secure, open-source, web-based patient-centric registry framework that connects health stakeholders and patient advocates within rare disease communities and has been deployed for a number of rare diseases (Bellgard 2014 - https://muccg.github.io/rdrf/). A fundamental RDRF design decision allows registries to be defined dynamically - meaning new registries can be constructed without the need for bespoke software development. This philosophy extends to all parts of RDRF including demographics definitions, customisable patient consent, data elements definitions, structure of forms/sections presented to users. RDRF is able to scale across the many thousands of rare diseases. The FAIR Guiding Principles have been developed to support discovery through quality data management (Wilkinson, 2016). FAIR stands for data that is Findable, Accessible, Interoperable, and Reusable. In this presentation, we provide an overview of an implementation of a FAIR RDRF.

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