European Joint Programme on Rare Diseases
(EJP RD)

Call for Proposals 2022

"Development of new analytic tools and pathways to accelerate diagnosis and facilitate diagnostic monitoring of rare diseases"

Abstract book
Proposals invited to submit a Full proposal

Content

PROPOSAL NO. 13: SMART-INS

Systems Multiomics Approach for pRecision diagnosTics of Idiopathic Nephrotic Syndrome

Medical domain: Nephrology/Urology

Type of study:

- Prognostic markers/biomarkers investigations for early diagnosis and monitoring;
- Development of pathway models to enable diagnosis, especially for newly discovered diseases that may share underlying molecular mechanisms with already known diseases.

New proposal

Abstract

Idiopathic nephrotic syndrome (INS) is a group of rare glomerulopathies of unclear etiology, characterized by severe proteinuria, oedema and extensive podocyte injury. INS is currently treated with corticosteroids and immunosuppressants, which cause severe side effects. Many patients manifest treatment resistance or dependence, conferring a high risk of progression to end-stage renal failure. INS often recurs after transplantation, causing premature graft loss, presumably due to one or more circulating permeability factor(s), still unidentified. At present there are no specific diagnostic biomarkers or predictive of post-transplant recurrence, seriously hampering novel drug development and treatment strategies.

Our consortium brings together a unique combination of clinical and research experts in INS, global analysis technologies and cutting-edge models. This project aims to apply our latest findings and technological developments to unveil reliable biomarker profiles of post-transplant recurrence, allowing a better stratification for precise intervention. Our aims are: (i) to search for new relevant biomarkers by untargeted multiomics on a retrospective cohort; (ii) to validate the potential of the new candidate signatures on a prospective cohort and that of a newly developed podocyte morphometry test; (iii) to develop pre-clinical INS models and endpoints that could either constitute biomarkers and/or contribute to biomarker validation. The proposed program will provide new tools for precision medicine, contributing to improved treatment and disease monitoring.

PROPOSAL NO. 16: COMPRARE

Towards the most accurate diagnosis and monitoring of Complement-mediated rare kidney diseases

Medical domain: Nephrology/Urology

Type of study:

- Prognostic markers/biomarkers investigations for early diagnosis and monitoring;
- Functional strategies to globally stratify variants of unknown significance (VUS) for clinical use; setting up of (in vitro) systems to distinguish between VUS and pathogenic variants (e.g. confirming disruption of splicing for deep intronic variants, loss of protein function, and gain of toxic protein function);
- Development of pathway models to enable diagnosis, especially for newly discovered diseases that may share underlying molecular mechanisms with already known diseases.

New proposal

Abstract

Two rare complement-mediated kidney diseases are atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy (C3G). These diseases lead to end-stage kidney failure and tend to recur after transplantation. In both conditions an overactive complement system initiates and drives the disease. The complement system consists of mainly plasma proteins that protect us (the host) from pathogens such as bacteria, while it activates the immune system against these pathogens. If the complement system is overactive it can damage the host's own cells. Genetic defects encoding for complement proteins and/or circulating auto-antibodies lead to this overactivity. To timely diagnose as well as to differentiate these diseases from other kidney diseases that have overlapping symptoms is difficult. Timely diagnosis is essential in order to initiate appropriate therapy. For both diseases complement inhibitory drugs are the main choice. In aHUS eculizumab can control disease activity leading to drastically improved kidney function eliminating the need for renal replacement therapy. Relapses can still occur and there is a need for optimized monitoring and treatment schedules. For C3G various complement inhibitory drugs targeting different levels of the complement pathway are in phase 3 trials. After the correct diagnosis is made an appropriate drug is chosen. This consortium of leading scientists and clinicians, working in this field, aims to improve and define new analytic tools to diagnose and characterize these diseases thereby affecting time to diagnosis and choice of treatment.

PROPOSAL NO. 33: UPS-NDDIAG

Development of diagnostic solutions for neurodevelopmental disorders caused by ubiquitin-proteasome system dysfunction

Medical domain: Neurology

Type of study:

- Phenotype-driven diagnosis: integration across different ontologies, integration of shared pathways, digital phenotyping, development of artificial intelligence approaches/applications to extract health related data in aid of diagnosis;
- Prognostic markers/biomarkers investigations for early diagnosis and monitoring;
- Functional strategies to globally stratify variants of unknown significance (VUS) for clinical use; setting up of (in vitro) systems to distinguish between VUS and pathogenic variants (e.g. confirming disruption of splicing for deep intronic variants, loss of protein function, and gain of toxic protein function);
- Development of pathway models to enable diagnosis, especially for newly discovered diseases that may share underlying molecular mechanisms with already known diseases.

New proposal

Abstract

Neurodevelopmental disorders (NDDs) are a major public health problem worldwide, affecting more than 3% of children. These past years, an increasing number of variants in genes encoding proteins of the ubiquitin-proteasome system (UPS) has been identified in patients with NDD. The UPS is a major protein degradation pathway, which is essential to neuronal development and function. Yet, there are still no reliable biological markers or cell/animal models that can be used for diagnostic purposes in patients with such disorders. We have conceived the UPS-NDDiag project to address this shortcoming. Our main objective is to develop tools and a method likely to help diagnose this group of rare diseases. Thanks to an international collaborative effort, we collected and stored, in a dedicated biobank, biological samples of 67 patients with UPS-NDD, and we gathered related photos and clinical information that will be managed in a patient registry hosted by GestaltMatcher. Using simultaneously blood T cells, induced pluripotent stem cell (iPSC)-derived neuronal cell models and animal models, we will search for biological markers, molecular or epigenetic signatures, and morphological and phenotypic features specific to UPS-NDDs, thus relying on our promising preliminary data that suggested overlapping pathophysiological mechanisms across UPS-NDDs. In parallel, we will keep including additional patients whose samples will be used to assess the diagnostic value of highlighted biomarkers, signatures and cell features.

PROPOSAL NO. 39: BACHB STUDY

BiomArker for Congenital Heart Block Study

Medical domain: Cardiology/Vascular Diseases

Type of study:

- Prognostic markers/biomarkers investigations for early diagnosis and monitoring;

New proposal

Abstract

Congenital heart block (CHB) is a disorder that affects baby hearts at 16 weeks of pregnancy in mothers with lupus or Sjøgren's syndrome (although the mother may be unaware). In CHB, heart conduction cells cannot properly transmit electrical signals. This results in a slow heart rate, heart failure and sometimes death, even before birth. Autoimmunity is caused by antibodies (Abs) in the blood that attack certain proteins in your own body. In the mother the antibodies target proteins called Ro, and these Abs are almost always present when the baby has CHB. However, of mothers with anti-Ro antibodies, only 2% have a baby with CHB, suggesting a more specific Ab is yet to be found. Finding these specific CHB Abs will allow a clinical test to identify which pregnancies will be affected.

We invented a way to find the mother's Abs and the baby's heart proteins that are targeted. We use normal heart cells, either from fetal hearts or from stem cells that have been turned into heart conduction cells, to find these Abs. We spread out the cells' proteins based on weight and acidity and identify which ones the mother's Abs are targeting. At the time of birth, thirty different Abs against the heart are present, but by looking earlier to 16 weeks in pregnancy, we found only four that predict CHB development, including a protein that is concentrated on the outside of the hearts conducting cells. In this project, we will identify which antibodies appear first, and whether they accurately predict disease using a larger sample of biobanked samples and prospective samples of pregnancies at risk.

PROPOSAL NO. 43: PLANET

Inherited thrombocytopenia: Functional screen of variants of unknown significance

Medical domain: Haematology/Immunology
Type of study:

- Functional strategies to globally stratify variants of unknown significance (VUS) for clinical use; setting up of (in vitro) systems to distinguish between VUS and pathogenic variants (e.g. confirming disruption of splicing for deep intronic variants, loss of protein function, and gain of toxic protein function);

New proposal

Abstract

Our project provides a novel technological platform to investigate platelet pathogenesis and to identify to validate genes and variants of unknown significance (VUS) for Inherited platelet disorders. Around 3 million people worldwide are affected by an inherited bleeding or platelet disorder. Whole exome and genome sequencing (WES/WGS) have been implemented to facilitate diagnostic and gene discovery processes. However, the newly discovered genes and variants require further functional studies to prove they are the cause of the disorders. To dissect the role of these new genes and variants, we propose to exploit an advanced technology method to mimic the 3D structure and composition of the bone marrow, using silk biomaterials,from B. mori cocoons, where human hematopoietic progenitor cells from patients or induced pluripotent stemcells (iPSC) can be grown and differentiated toward the megakaryocyte lineage. The iPSCs will be generated using the CRISPR/Cas9 technology based on the homologous recombination. We plan to exploit our 3D bioreactor to assess the process of megakaryopoiesis and platelet production using modified iPSCs for disease modeling to develop a tool for investigating the impact of VUS on platelet production. These disease models will be compared with the findings obtained culturing cells derived from the peripheral blood of patients carrying the same variants. This will validate the proposed system as an innovative tool to directly establish the pathogenic role of novel variants identified with WES/WGS in patients with Inherited platelet disorders.

PROPOSAL NO. 45: IMAGINER

Optical imaging as a diagnostic tool for monitoring brain function in X-linked rare disorders: from preclinical models to patients

Medical domain: Neurology

Type of study:

- Prognostic markers/biomarkers investigations for early diagnosis and monitoring;

New proposal

Abstract

Fragile X syndrome (FXS) and Creatine Transporter Deficiency (CTD) are the two most common causes of X-linked intellectual disability. Despite their etiological heterogeneity, FXS and CTD share common clinical traits and pathological substrates. There is no cure for these disorders and the efficacy study of potential treatments is hindered by the scarcity of unbiased, quantitative biomarkers for monitoring brain function. Since a disruption of brain energy metabolism is a major disease mechanism linking FXS and CTD, and oxygen consumption represents a sensitive proxy of brain function, the objective of this project is to exploit optical imaging techniques to devise a non-invasive biomarker for FXS and CTD. We will use imaging of intrinsic optical signals (IOS) in animal models and functional near-infrared spectroscopy (fNIRS) in patients. The study of the visual phenotype is a paradigmatic model to evaluate cortical processing in different neurodevelopmental disorders and we plan to assess visual evoked responses. More specifically, we will: 1. test whether IOS can discriminate between mutants and controls in animal models of FXS and CTD; 2. investigate cellular, extracellular and molecular mechanisms underlying altered IOS; 3. assess whether fNIRS represents a non-invasive tool to facilitate diagnostic monitoring in patients. This analytic biomarker will (i) optimize preclinical studies and the follow-up of patients; (ii) provide a reliable protocol to longitudinally monitor, in combination with behavioral testing, the efficacy of potential therapeutic strategies.

PROPOSAL NO. 49: PROGEROMICS

Identification of biomarkers to monitor the progression of Hutchinson-Gilford progeria syndrome

Medical domain: Cardiology/Vascular Diseases

Type of study:

- Prognostic markers/biomarkers investigations for early diagnosis and monitoring;

New proposal

Abstract

Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare genetic disease (prevalence 1 person in 18 million) caused by the expression of a mutant protein called progerin. Children with HGPS age prematurely and inevitably die at an average age of 14.5 years. Starting at 1-2 years, patients gradually develop growth failure and problems in multiple organs, and die mainly from complications of severe atherosclerosis (myocardial infarction, heart failure or stroke). Genetic testing isavailable to confirm diagnosis once HGPS symptoms are manifest; however, there is no cure for this fataldisease and there is a lack of biomarkers for monitoring disease progression from early stages to more advanced stages with clinical symptoms. ProgerOmics is a transnational 3-year program that aims to identify new biomarkers for monitoring HGPS progression. Five research groups with ample and complimentary expertise in HGPS research, high-throughput omics, and bioinformatics will join forces to thoroughly characterize multiple alterations caused by progerin in plasma, peripheral blood mononuclear cells (PBMCs), and aorta from progeroid mice. Integration of phenotypic and multi-omics data using bioinformatics and artificial intelligence tools will allow the identification of robust biomarkers of disease progression, which will be tested in a pilot study with plasma and PBMCs from HGPS patients. The social relevance of ProgerOmics isguaranteed by the participation of 3 HGPS patient associations, which will help to disseminate results andpromote patient engagement.

PROPOSAL NO. 58: PREDICT

Towards a PREcise DIagnosis in Ciliopathies

Medical domain: Others
Type of study:

- Phenotype-driven diagnosis: integration across different ontologies, integration of shared pathways, digital phenotyping, development of artificial intelligence approaches/applications to extract health related data in aid of diagnosis;
- Prognostic markers/biomarkers investigations for early diagnosis and monitoring;
- Methodologies for solving cases that are currently difficult to analyze due to different underlying mechanisms (e.g. mosaicism, genomic (non-coding) alterations, gene regulation, complex inheritance), including new genomics / functional genomics technologies, multi-omics, mathematics, biostatistics, bioinformatics and artificial intelligence approaches;

New proposal

Abstract

Ciliopathies are rare Mendelian disorders caused by dysfunction of primary cilia, cellular organelles crucial for signal transduction during development and cell function. Clinically, ciliopathies present with recurrent sets of symptoms, involving multiple organ systems. Substantial phenotypic variability and overlap between ciliopathy disorders make predicting the precise outcome for a given patient particularly difficult, especially for progressive features. As for most syndromic disorders, current ciliopathy diagnoses remain frustratingly imprecise, typically including a broad range of possible end-organ involvements with varying onset and severity, which represent dramatically different outcomes for patients. This project aims at providing a precise diagnosis to enable tailored surveillance and treatment. We will combine detailed patient clinical data with comprehensive genetic information and extensive publicly available data and use artificial intelligence to generate predictive models for specific endorgan involvement. Predictions will be tested in vitro using simple cellular assays and more complex induced pluripotent stem cell (iPSC)-derived organoid models and in vivo using zebrafish models, circumventing the limitation of poor statistical power inherent to rare disorders through functional assays. Cellular assays will further serve as diagnostic tools for accurate classification of ciliopathies, using high-content imaging and transcriptional signatures. PREDICT will pave the way towards a precise diagnosis and tailored diagnostic monitoring for ciliopathies.

PROPOSAL NO. 84: EURONET- NF

European Network for improved molecular diagnostics of the Neurofibromatoses-schwannomatoses and related disorders

Medical domain: Others
Type of study:

- Methodologies for solving cases that are currently difficult to analyze due to different underlying mechanisms (e.g. mosaicism, genomic (non-coding) alterations, gene regulation, complex inheritance), including new genomics / functional genomics technologies, multi-omics, mathematics, biostatistics, bioinformatics and artificial intelligence approaches;
- Functional strategies to globally stratify variants of unknown significance (VUS) for clinical use; setting up of (in vitro) systems to distinguish between VUS and pathogenic variants (e.g. confirming disruption of splicing for deep intronic variants, loss of protein function, and gain of toxic protein function);

New proposal

Abstract

Neurofibromatoses (NFs) comprise three rare disorders NF1, NF2 and non-NF2 schwannomatosis. Equally, Legius syndrome and Constitutional Mismatch Repair Deficiency are rare diseases and both are alternative diagnoses of suspected NF1. The majority of these five syndromes are complex, potentially affecting almost every organ system and associated with a high tumor risk that requires adequate surveillance and management. Therefore, an early genetic diagnosis is essential for individual patient's care and to better define the global policy and strategy of patient's care. However, we are daily confronted with complex genetic diagnostic challenges. Currently used techniques can miss the pathogenic, i.e. disease-causing, variant in the. In addition, for many variants we identify it is not clear whether they are disease causing. Moreover, certain lab procedures are expensive and highly specialized. We aim to develop and share new sensitive high throughput techniques on DNA, RNA and protein level and bioinformatic tools that can be globally used in the genetic diagnosis of NFs and related disorders. Although we realize not all patients can be finally diagnosed, we expect to improve the genetic diagnosis of the majority of unsolved cases. For a specific subset of negative patients new potential candidate genes will be searched for. In conclusion, improved genetic diagnostics of NFs and related disorders by novel, sensitive and specific assays will open new perspectives for the patient with translation to better treatment and follow-up and family planning.

PROPOSAL NO. 94: SMART-RET

Single-molecule multi-omics, artificial intelligence and retinal organoids to accelerate noncoding variant interpretation in autosomal dominant inherited retinal diseases

Medical domain: Ophthalmology
Type of study:

- Phenotype-driven diagnosis: integration across different ontologies, integration of shared pathways, digital phenotyping, development of artificial intelligence approaches/applications to extract health related data in aid of diagnosis;
- Methodologies for solving cases that are currently difficult to analyze due to different underlying mechanisms (e.g. mosaicism, genomic (non-coding) alterations, gene regulation, complex inheritance), including new genomics / functional genomics technologies, multi-omics, mathematics, biostatistics, bioinformatics and artificial intelligence approaches;
- Functional strategies to globally stratify variants of unknown significance (VUS) for clinical use; setting up of (in vitro) systems to distinguish between VUS and pathogenic variants (e.g. confirming disruption of splicing for deep intronic variants, loss of protein function, and gain of toxic protein function);
- Development of pathway models to enable diagnosis, especially for newly discovered diseases that may share underlying molecular mechanisms with already known diseases.

Proposal asking for an extension of a previously funded E-Rare project Solve-RET

Abstract

Inherited retinal diseases (IRD) represent a major cause of blindness affecting 350,000 people in Europe. Significant advances in the genomic underpinnings of IRD have culminated in novel therapies for IRD. Despite this progress important challenges related to the diagnosis, mechanisms and therapy development remain for autosomal dominant IRD (adIRD), which represent 25%–40% of IRD. We demonstrated an emerging role for complex structural variants (SVs) and defects in noncoding regions such as noncoding RNAs and cis-regulatory elements in adIRD. It is our main goal to establish a novel pathway to tackle SV and noncoding variant identification and interpretation in adIRD using single-molecule multi-omics, artificial intelligence (AI) and retinal organoids (ROs). Specifically, we will generate retinal precursor cells for undiagnosed adIRD cases. We will establish a single-molecule multi-omics framework including long-read genome and transcriptome sequencing and optical genome mapping. We will perform AIbased reanalysis of genome-phenome data. We will establish the 3D genome architecture of human retina and assess the impact of SVs on the 3D genome. We will advance noncoding variant interpretation by establishing a regulatory retinal database and by using single-cell CRISPR enhancer screens and single-cell omics in patient-derived ROs. Finally, we will transfer research findings to the clinic through ERN-EYE and patient advocacy organizations. Our multidisciplinary expertise, track record and European network offer a unique opportunity to accelerate diagnosis of unsolved adIRD.

PROPOSAL NO. 102: CMT-MODS

A transcriptomic approach to the identification of disease modifiers and biomarkers in Charcot-Marie-Tooth 1A (CMT1A)

Medical domain: Neurology
Type of study:

- Phenotype-driven diagnosis: integration across different ontologies, integration of shared pathways, digital phenotyping, development of artificial intelligence approaches/applications to extract health related data in aid of diagnosis;
- Prognostic markers/biomarkers investigations for early diagnosis and monitoring;

Resubmission from EJP RD JTC2019 CMT-MODs

Abstract

The most common form of inherited neuropathy is Charcot-Marie-Tooth disease type 1A (CMT1A), caused by a duplication of the PMP22 gene. CMT1A patients develop symptoms in early childhood with variable progression and there is no therapy. Therapy must start in childhood, before peripheral nerves die. However, we lack easily obtainable biomarkers in early disease stages. In peripheral nerves from young CMT1A rats, we found changes in gene regulation that predicted the clinical disease severity later in adulthood, and gene expression from blood samples in young CMT1A rats were strong predictors of the future disease course. In blood samples from adult CMT1A patients, changes in gene expression also correlated with disease severity, demonstrating that findings can be "translated" from CMT rats to patients. In CMT-MODs, we will perform a molecular analysis in nerves of young CMT1A rats in order to identify novel early markers of disease severity. In parallel, we will assess a large cohort of CMT1A children aged 6-18 years applying 5 novel clinical outcome measures and MRI over 1,5 years. Blood samples will be taken and gene expression of the most promising candidates, which we originally identified in CMT rats, will be measured. This unprecedented assessment of CMT patients and animal models at early disease stages will allow CMT-MODs to establish biomarkers that may serve as a standard readout for disease severity and predict the disease course. Our patient organizations emphasize that these novel diagnostic measures are urgently needed for clinical trials in CMT children.

PROPOSAL NO. 123: GENOMIT

GENOMIT: A multi-omics approach for diagnostics and monitoring of mitochondrial disorders

Medical domain: Metabolic Diseases

Type of study:

- Prognostic markers/biomarkers investigations for early diagnosis and monitoring;
- Methodologies for solving cases that are currently difficult to analyze due to different underlying mechanisms (e.g. mosaicism, genomic (non-coding) alterations, gene regulation, complex inheritance), including new genomics / functional genomics technologies, multi-omics, mathematics, biostatistics, bioinformatics and artificial intelligence approaches;
- Functional strategies to globally stratify variants of unknown significance (VUS) for clinical use; setting up of (in vitro) systems to distinguish between VUS and pathogenic variants (e.g. confirming disruption of splicing for deep intronic variants, loss of protein function, and gain of toxic protein function);
- Development of pathway models to enable diagnosis, especially for newly discovered diseases that may share underlying molecular mechanisms with already known diseases.

Proposal asking for an extension of a previously funded E-Rare project GENOMIT

Abstract

Mitochondrial disorders (MD) are a genetically diverse group of individually rare, but severe human diseases for which no causal treatments are available. The GENOMIT consortium assembles the national networks from Germany, Austria, Italy, UK, Spain and Japan and the centre for MDs in France, collectively following > 8,000 patients with about 500 novel cases annually. GENOMIT acts in close collaboration with the international patient organization to improve the diagnosis and care of MD patients.

GENOMIT will i) develop novel diagnostic strategies empowered by technologies and data sciences, ii) establish MD-specific metabolic and epi-signatures and correlate them with MD progression, iii) extend functional studies on novel variants, genes and pathways involved in the pathophysiology of MD.

GENOMIT partners are established national hubs for molecular diagnosis and state-of-the-art care for patients with mitochondrial disease. This global collaboration led to a global registry and the largest collection of multi-omics data pertaining to MDs worldwide. We incorporate groups with unique expertise for biochemical and genetic diagnostics, the clinical management of MD and computational scientists who have developed multi-omics databases and statistical models for diagnostics. GENOMIT translates biochemical and genetic research to patient care by establishing an integrated multi-omics pipeline to increase the diagnostic yield, by implementing a large-scale screening for discovery and validation of MD biomarkers, and will be an invaluable resource for clinical trials.

PROPOSAL NO. 134: RESOLVE 15Q

Resolving complex outcomes in 15q13.3 copy number variants using emerging diagnostic and biomarker tools

Medical domain: Psychiatry/Psychology

Type of study:

- Methodologies for solving cases that are currently difficult to analyze due to different underlying mechanisms (e.g. mosaicism, genomic (non-coding) alterations, gene regulation, complex inheritance), including new genomics / functional genomics technologies, multi-omics, mathematics, biostatistics, bioinformatics and artificial intelligence approaches;

New proposal

Abstract

Genetic changes affecting the copy number of chromosome 15q13.3 have been linked to a group of rare conditions including developmental delay, intellectual disability, autism spectrum disorder, epilepsy, schizophrenia, and others. The critical region contains approximately 10 genes. There are no treatments that reverse or cure the impairments experienced by individuals. Further, not each person harboring a 15q13.3 copy number change will manifest disease, and the severity and clinical diagnosis is difficult to predict. This represents a significant challenge in determining the health outcomes and counseling of families. To improve diagnostic approaches, we are using a multifaceted approach with an international team of clinicians and scientists. Our work identified that human brain EEG recordings and network analysis can discern a 15q13.3 signature, while genomics and functional studies reveal that 2 key genes in the 15q13.3 region, OTUD7A and CHRNA7, may drive the neurological syndrome. Our team will use long-range sequencing to resolve the complete genetic details of the 15q13.3 CNV region, as well as clinical examination and brain network analysis to improve diagnostic tools. We will also utilize 15q13.3 and individual gene mouse models, and patient stem cellderived 3D brain organoids, to identify disease pathogenesis and clinical biomarkers. The outcome of our 15q13.3 CNV project will be a better understanding of the biological basis of disease, diagnostic tools to predict disease severity, and information to help clinicians in the management of affected individuals.

PROPOSAL NO. 139: ODINO

Optimization of the diagnostic approach for inborn errors of immunity leading to hyper-inflammation

Medical domain: Haematology/Immunology
Type of study:

- Phenotype-driven diagnosis: integration across different ontologies, integration of shared pathways, digital phenotyping, development of artificial intelligence approaches/applications to extract health related data in aid of diagnosis;
- Methodologies for solving cases that are currently difficult to analyze due to different underlying mechanisms (e.g. mosaicism, genomic (non-coding) alterations, gene regulation, complex inheritance), including new genomics / functional genomics technologies, multi-omics, mathematics, biostatistics, bioinformatics and artificial intelligence approaches;
- Functional strategies to globally stratify variants of unknown significance (VUS) for clinical use; setting up of (in vitro) systems to distinguish between VUS and pathogenic variants (e.g. confirming disruption of splicing for deep intronic variants, loss of protein function, and gain of toxic protein function);

New proposal

Abstract

The inborn errors of immunity (IEI) are a group of more than 500 conditions leading to an alteration of the immune response, namely increased susceptibility to infection (primary immunodeficiencies) or over-activation of the inflammatory response (autoinflammatory diseases, SAID). Aim: to improve the diagnostic approach to IEI, using SAID as proof of concept. In particular, we will focus on three critical aspects: i) exponential growth of the number of genes and clinical phenotypes; ii) lack of information on the actual pathogenic impact of different variants of unknown significance (VUS) found in the diagnostic work-up; iii) correct explanation and interpretation of the intrafamilial phenotypic variability for a proper genetic counselling. Workplan: i)validation and optimization of the current bioinformatics tools currently available for the interpretation of genotype-phenotype correlations; ii) elaboration of high-throughput functional assays for the systematic evaluation of the actual pathogenic impact of VUS in an homogeneous group of genes associated with SAID; iii) application of novel genetic and biostatistics methodologies (SNP array with polygenic risk score, single cell RNA seq, methylome and miRNome studies) to unravel the intrafamilial phenotypic heterogeneity in SAID; The whole project will be focused on the integration of in-silico and in-vitro approaches with reallife data coming from a large international registry (Eurofever) and from an online repository of all the variants associated with SAID-related genes (Infevers).

PROPOSAL NO. 157: EPIEURONET

Epigenome diagnostics: Genome-wide DNA methylation profiling to speed up diagnosis and optimize care of patients with rare diseases

Medical domain: Others

Type of study:

- Prognostic markers/biomarkers investigations for early diagnosis and monitoring;
- Methodologies for solving cases that are currently difficult to analyze due to different underlying mechanisms (e.g. mosaicism, genomic (non-coding) alterations, gene regulation, complex inheritance), including new genomics / functional genomics technologies, multi-omics, mathematics, biostatistics, bioinformatics and artificial intelligence approaches;
- Functional strategies to globally stratify variants of unknown significance (VUS) for clinical use; setting up of (in vitro) systems to distinguish between VUS and pathogenic variants (e.g. confirming disruption of splicing for deep intronic variants, loss of protein function, and gain of toxic protein function);

New proposal

Abstract

The use of genomic sequencing in clinical practice has significantly improved the diagnostic yield in patients with rare diseases (RDs). Nevertheless, ~50% of them remains without diagnosis. Recently, genome-wide DNA methylation (DNAm) array analysis has allowed to identify unique signatures (i.e., episignatures) for an increasing number of RDs, allowing to reach the diagnosis in patients in whom genetic testing is not informative. The partners and collaborators of this consortium have significantly contributed to this achievement by discovering the majority of these episignatures and developing data-analysis tools.

While previous work has demonstrated the value of genome-wide DNAm profiling as a tool to reach diagnosis and classify ambiguous genomic findings, further work is required to broaden its use in the clinical setting. Overall goal of EpiEuroNet is to generate new data and tools allowing an immediate and direct use of this new technology in the clinical practice to speed up diagnosis and offer proper counseling and personalized care. Through the implementation of a dedicated database, we plan to refine known episignatures to increase their specificity, sensitivity and robustness, and discover new disease/gene/variant-specific episignatures. Research will also be directed to test their sensitivity in the classification of postzygotic variation and explore the use of this technology in the diagnosis of rare complex traits, non-genetic RDs and prenatally. Finally, guidelines for the use of DNAm profiling in the diagnostic and research settings will be generated.

PROPOSAL NO. 165: PREDYT

PREdictive biomarkers in DYsTonia: defining the paradigm of monogenic dystonia to implement the diagnosis and prognosis of undiagnosed forms

Medical domain: Neurology
Type of study:

- Phenotype-driven diagnosis: integration across different ontologies, integration of shared pathways, digital phenotyping, development of artificial intelligence approaches/applications to extract health related data in aid of diagnosis;
- Prognostic markers/biomarkers investigations for early diagnosis and monitoring;
- Methodologies for solving cases that are currently difficult to analyze due to different underlying mechanisms (e.g. mosaicism, genomic (non-coding) alterations, gene regulation, complex inheritance), including new genomics / functional genomics technologies, multi-omics, mathematics, biostatistics, bioinformatics and artificial intelligence approaches;
- Functional strategies to globally stratify variants of unknown significance (VUS) for clinical use; setting up of (in vitro) systems to distinguish between VUS and pathogenic variants (e.g. confirming disruption of splicing for deep intronic variants, loss of protein function, and gain of toxic protein function);
- Development of pathway models to enable diagnosis, especially for newly discovered diseases that may share underlying molecular mechanisms with already known diseases.

New proposal

Abstract

Dystonias encompass a heterogenous group of rare hyperkinetic movement disorders. Leveraging the advance in genetic technology, researchers have been able to elucidate the genetic cause of various monogenic forms of dystonia, revealing different pathogenic mechanisms. However, in most cases the genetic diagnosis fails, hindering the understanding of the pathogenesis, and therefore an idea of prognosis and targeted therapeutic approaches. Based on our previous data, we hypothesize that undiagnosed forms can be stratified into distinct categories that reflect mechanisms in common with the monogenic forms.

To test this hypothesis, we will integrate complementary datasets using graph-based statistical and explainable artificial intelligence approaches. Specifically, by applying these analyses to a combination of OMICS and deep phenotyping data, we aim to i) increase the diagnostic yield in dystonias, either detecting previously unrecognized etiological gene variants or identifying less penetrant disease-predisposing alleles ii) transfer prioritized gene variants into 3-D human-based models to validate the underlying mechanisms iii) identify prognostic markers based on the molecularly resolved cases, which can be used to predict the course of undiagnosed patients. To these ends, we will employ clinical cohorts, large collections of samples and patient induced pluripotent stem cell 3D models that recreate dystonia features at cellular and functional level.

This multidisciplinary approach encompasses multiple areas of expertise, gathered at a transnational level by the consortium.

PROPOSAL NO. 169: EUREKA

Bonding molecular genotyping and phenotyping to outcome measures in AL amyloidosis: A EUropean REgistry and sample sharing networK to promote the diagnosis and management of light chain Amyloidosis

Medical domain: Haematology/Immunology
Type of study:

- Phenotype-driven diagnosis: integration across different ontologies, integration of shared pathways, digital phenotyping, development of artificial intelligence approaches/applications to extract health related data in aid of diagnosis;
- Prognostic markers/biomarkers investigations for early diagnosis and monitoring;

New proposal

Abstract

Immunoglobulin light chain (AL) amyloidosis is caused by antibody fragments, light chains (LCs), produced by antibody-producing plasma cells (PCs). Amyloid LCs target vital organs and form typical deposits. Therapy is based on anti-PC drugs, aiming at reducing LC production, improving organ function and extending survival. Members of our consortium substantially contributed to setting up current staging systems and response criteria. However, previous studies were limited by small size, retrospective design, patient selection, lack of molecular data, and analysis approach.

We will create a single registry collecting all new cases of AL amyloidosis evaluated at 4 referral Centers across Europe or at their satellite sites, linked to a cross-border biobank and sample sharing network for molecular/phenotypic profiling of pathogenic PCs and LCs. A fifth site will support the consortium with big data analysis and artificial intelligence. We aim at 1) defining the impact of molecular profiling on disease phenotype to promote early diagnosis and guide therapeutic choices; 2) describing real-world presentation (including subjects who are usually excluded from clinical trials), access to treatments, and outcome (including quality of life); 3) defining the role of standard and new tools for assessing minimal residual disease after treatment.

Besides deepening our current understanding of the biology of AL amyloidosis, the data produced within this study will be instrumental in promoting early diagnosis, personalizing individual patient management and in the design of clinical trials.

PROPOSAL NO. 172: SYMFORD

Systems Medicine Federated for Rare Diseases

Medical domain: Neurology
Type of study:

- Phenotype-driven diagnosis: integration across different ontologies, integration of shared pathways, digital phenotyping, development of artificial intelligence approaches/applications to extract health related data in aid of diagnosis;
- Methodologies for solving cases that are currently difficult to analyze due to different underlying mechanisms (e.g. mosaicism, genomic (non-coding) alterations, gene regulation, complex inheritance), including new genomics / functional genomics technologies, multi-omics, mathematics, biostatistics, bioinformatics and artificial intelligence approaches;
- Development of pathway models to enable diagnosis, especially for newly discovered diseases that may share underlying molecular mechanisms with already known diseases.

New proposal

Abstract

Genomics studies have delivered important insights into genetic causes of rare diseases. However, we have arrived at a bottleneck, where better methods and more data is needed to unravel diseases due to complex genetic interactions. Currently, genomics data is distributed over countless repositories world-wide, preventing the collaborative use of Artificial Intelligence (AI) for gaining insights from genomics data. To unravel mechanisms underlying rare diseases, we need (i) mechanisms combining existing genomic datasets without moving them across jurisdictional boundaries and (ii) AI methods go beyond the impact of individual genetic variants and exploit mechanism-based diagnosis. Federated database and AI tools build on technology that allows them to securely access genomics data without centralization and in compliance with privacy regulation. However, existing federated databases for rare diseases do not optimally support AI techniques or systems medicine tools that leverage prior knowledge for extracting shared molecular mechanisms. With SyMFoRD, we aim to unravel complex genetic causes of rare diseases by building a federated genomics platform hosting the largest cohort of neurodevelopmental diseases (>5000 patients and > 13,000 relatives) to date. SyMFoRD will employ novel AI methods and privacy-preserving patient matching techniques that benefit and demonstrate the value of the federated setup. Finally, our clinical experts will follow up on our results by investigating the role of potential disease pathways in independent data collected in a large population cohort.