3EME JEUDI DE GENETIQUE CLINIQUE - AFGC

Institut *IMAGINE* – Hôpital Necker, Paris

Jeudi 17 juin 2021

« Best of 2021 ! »

Coordination Estelle Colin et Mélanie Fradin

Matinée : 10h-13h

- 10h : **Dr Salima El Chehadeh (Strasbourg). Syndrome d'Ehlers Danlos parodontal, la cohorte française, description phénotypique et focus sur l'atteinte vasculaire.**

- 10h15 : **Dr Caroline Racine (Dijon). 10 ans de données de la filière Anddi-rares via la base de données de la BNDMR : une ressource unique pour faciliter la recherche et l'épidémiologie dans les anomalies du développement en France.**

Introduction: In France, the Ministry of Health launched a comprehensive program for rare diseases (RD) including an epidemiological program as well as the establishment of expert centers for RD clinical care. Since 2007, most of the developmental disorders Rare Diseases centers have filled patients' data into the BNDMR (Banque National de Données Maladies Rares), the national data repository for all rare diseases, through a web portal. This portal allowed the collation of descriptive demographic, clinical data, and the chronology of medical follow-up of patients seen within each center. We address the interests and difficulties of such national data collection ten years after its implementation. Materials and methods: Since 2007, clinicians and researchers have reported the "Minimum Dataset (MDS)" for each patient who came to their expert centers. We retrospectively analyzed administrative and demographic data, care organization and diagnoses. Results: Over 10 years, 228,243 RD patients have visited an expert center. Thus,167,361 were patients affected by a rare disease (median age 11 years, 54% children, 46% adults) with a balanced sex ratio and 60,882 were unaffected relatives (median age 37 years). The majority of patients (87%) were seen no more than once a year, and 52% of visits were for a diagnostic procedure. Among the 2869 recorded rare disorders, 1907 (66.5%) were recorded in less than 10 patients, 802 (28%) in 10 to 100 patients, 149 (5.2%) in 100 to 1,000, and 11 (0.4%) in >1,000. Overall, 45.6% of patients had no diagnosis and 6.7% an uncertain diagnosis. Children are mainly referred by their pediatrician (n=55755; 46%) and adults by a medical specialist (n=14053; 34%). Given the geographical coverage of the centers, patients have a median distance to travel of 25.1 km (IQR= 6.3km –64.2km). Discussion: BNDMR provides an unprecedented support for epidemiological, clinical, and therapeutic studies in the field of rare diseases. Researchers can consider the national scope of BNDMR data, but also focus on specific diseases or patient subgroups. This endeavor represents a major collective effort among the French RD experts to gather such a large-scale data collection into the BNDMR and it provides tremendous potential to improve RD patient's care.

- 10h30 : **Auriane Cospain (Rennes). Holoprosencéphalie et agénésie du pancréas, un variant récurrent dans *CNOT1.***

Présentation d'un cas fœtal d'holoprosencéphalie, pour lequel l'examen fœtopathologie a révélé une agénésie complète du pancréas. Le séquençage de l'exome à mis en évidence un variant dans le gène CNOT1. Ce variant, c.1603C>T (p.Arg535Cys), déjà décrit dans la littérature est associé de façon récurrente à ce même phénotype. Nous proposons une collaboration dans l'optique de créer une cohorte.

- 10h45 **: Dr Evan Gouy (Lyon) : Conception pédagogique d'un Massive Open Online Course (MOOC) en médecine génomique. Expérience du MOOC BiG - Bioinformatique pour la génétique médicale (session 1).**

- 11h00 : **Dr Domitille Laur (Robert Debré). Description de cinq nouveaux patients avec une encéphalopathie GLYT1 et variants pathogènes bialléliques du gène SLC6A9. De la forme fœtale à la survie à long terme.** Appel à collaboration

- 11h15 : **Pr Dominique Bonneau* / Dr Alban Ziegler (Angers). Bi-allelic variants in *IPO8* cause a connective tissue disorder associated with cardiovascular defects, skeletal abnormalities, and immune dysregulation.**

Dysregulated transforming growth factor TGF-β signaling underlies the pathogenesis of genetic disorders affecting the connective tissue such as Loeys-Dietz syndrome. Here, we report 12 individuals with bi-allelic loss-of-function variants in IPO8 who presented with a syndromic association characterized by cardio-vascular anomalies, joint hyperlaxity, and various degree of dysmorphic features and developmental delay as well as immune dysregulation; the individuals were from nine unrelated families. Importin 8 belongs to the karyopherin family of nuclear transport receptors and was previously shown to mediate TGF-β-dependent SMADs trafficking to the nucleus in vitro. The important in vivo role of IPO8 in pSMAD nuclear translocation was demonstrated by CRISPR/Cas9-mediated inactivation in zebrafish. Consistent with IPO8's role in BMP/TGF-β signaling, ipo8-/- zebrafish presented mild to severe dorso-ventral patterning defects during early embryonic development. Moreover, ipo8-/- zebrafish displayed severe cardiovascular and skeletal defects that mirrored the human phenotype. Our work thus provides evidence that IPO8 plays a critical and non-redundant role in TGF-β signaling during development and reinforces the existing link between TGF-β signaling and connective tissue defects. (Am J Hum Genet. 2021 Jun 3;108(6):1126-1137).

- 11h30 : **Pr Florence Petit (Lille). La délétion de sites CTCF au locus *SHH* modifie les interactions enhancer-promoteur et conduit à l'achéiropodie**.

L'achéiropodie, malformation congénitale à type de membres tronqués, est associée à des délétions homozygotes autour de la ZRS, un enhancer régulant l'expression de SHH au cours du développement des membres. Le mécanisme moléculaire à l'origine de la dérégulation de SHH dans cette pathologie était inconnu jusqu'alors. Par séquençage génome entier chez un patient présentant une achéiropodie, nous avons identifié une délétion de 12 kb contenant 3 sites de fixation au facteur CTCF. L'étude en 4C-seq et FISH-3D met en évidence une altération des interactions chromatiniennes au locus ZRS-SHH, conduisant à une dérégulation de SHH au cours du développement du membre. Ces résultats montrent que l'altération de motifs CTCF peut être responsable de maladies mendéliennes par altération des interactions enhancer-promoteur. (Travail collaboratif publié Nat Commun. 2021 Apr 16;12(1):2282).

- 11h45 : **Dr Médéric Jeanne (Tours). Missense variants in *DPYSL5* cause a neurodevelopmental disorder with corpus callosum agenesis and cerebellar abnormalities**.

The collapsin response mediator protein (CRMP) family proteins are intracellular mediators of neurotrophic factors regulating neurite structure/spine formation and are essential for dendrite patterning and directional axonal pathfinding during brain developmental processes. Among this family, CRMP5/DPYSL5 plays a significant role in neuronal migration, axonal guidance, dendrite outgrowth, and synapse formation by interacting with microtubules. Here, we report the identification of missense mutations in DPYSL5 in nine individuals with brain malformations, including corpus callosum agenesis and/or posterior fossa abnormalities, associated with variable degrees of intellectual disability. A recurrent de novo p.Glu41Lys variant was found in eight unrelated patients, and a p.Gly47Arg variant was identified in one individual from the first family reported with Ritscher-Schinzel syndrome. Functional analyses of the two missense mutations revealed impaired dendritic outgrowth processes in young developing hippocampal primary neuronal cultures. We further demonstrated that these mutations, both located in the same loop on the surface of DPYSL5 monomers and oligomers, reduced the interaction of DPYSL5 with neuronal cytoskeleton-associated proteins MAP2 and βIII-tubulin. Our findings collectively indicate that the p.Glu41Lys and p.Gly47Arg variants impair DPYSL5 function on dendritic outgrowth regulation by preventing the formation of the ternary complex with MAP2 and βIII-tubulin, ultimately leading to abnormal brain development. This study adds DPYSL5 to the list of genes implicated in brain malformation and in neurodevelopmental disorders. (Am J Hum Genet. 2021 May 6;108(5):951-961).

- 12h00 : **Meghane Durizot (Trousseau). Large variabilité d'expression intra et inter-familiale de variants pathogènes du gène *BMP4* dans deux familles.** Appel à collaboration.

- 12h15 : **Dr Aurore Garde (Dijon). *SRSF1* haploinsufficiency is responsible for a new syndromic form of developmental delay associating facial features, intellectual disability, with or without cardiac and skeletal malformations.**

SRSF1 (also known as ASF/SF2) is an evolutionary highly conserved non-snRNP protein that belongs to the SR (serine/arginine rich domain) family. It contains two RNA Recognition Motif domains (RRMs) capable of recognizing messenger RNA, and it represents an important regulator of constitutive and alternative splicing. Somatic overexpression of SRSF1 had been highlighted in several human tumors, including breast cancer. However, the effects of pathogenic germline variants of SRSF1 have never been described before. In this work, through international data sharing, we gathered 15 patients (8 females and 7 males) carrying germline SRSF1 variants including 2 frameshift, 3 nonsense, and 6 missense variants. One patient carried a microdeletion of the region 17q22 including *SRSF1*. Variants occurred mostly de novo, however in one family two siblings have the same variant suggesting germinal mosaicism in one parent. In another case the familial segregation was incomplete. Principal features of patients were developmental delay, intellectual disability, hypotonia, behavioral disorders, skeletal and cardiac anomalies. In order to test the functional readout of missense variants, we exploited a previously established *in vivo SRSF1* splicing assay in Drosophila in which eye-specific overexpression of SF2, the Drosophila ortholog of SRSF1 (72% similarity, 63% identity), induced a severe developmental eye phenotype due to missplicing of key genes involved in normal eye development. We found that overexpression of human SRSF1 recapitulated this phenotype while splicing-deficient form of SRSF1 lost this capacity, showing that SRSF1 and SF2 are functional homologs. Next, we used this functional assay to test the potential loss-of-function nature of 2/6 human variants in SRSF1 (i.e. p.(G40V) and p.(V160M) which are both located within the RNA recognition motifs. Since both variants lost their ability to disturb normal eye development upon overexpression we classified them as splicing-deficient loss-of-function SRSF1 variants. SF2 deficient fly lines have now been generated and are ready for phenotypic characterization and rescue experiments with clinical mutations. Finally, transcriptome sequencing from Drosophila and patient-derived samples will allow us to explore splicing defects associated with the *SRSF1* mutation spectrum. These results suggested that loss-of-function *SRSF1* variants were responsible of a new neurodevelopmental disorder.

- 12h30 : **Dr Clara Houdayer (Angers). Further delineation of the clinical phenotype of individuals with ARID2 pathogenic variants: a report of 12 new cases and literature review.**

ARID2 (AT-rich interaction domain 2) is a newly described disease-causing gene encoding a protein belonging to BAF complexes, an ATP-dependent chromatin remodeling complex which regulates DNA accessibility at the nucleosome and facilitates DNA transcription, replication and repair. ARID2 acts as a tumor suppressor and has also been involved in intellectual disabilities related to BAFopathies. To date, 22 individuals have been reported with *ARID2* pathogenic variants or deletion. They share clinical features including intellectual disability, hypotonia, behavioral problems, short stature, and dysmorphic features. In order to further delineate the ARID2 phenotypical spectrum, we report a cohort of twelve additional unrelated individuals harboring *ARID2* pathogenic variants or deletion, and we compare their features with those previously described. The clinical characteristics of individuals from this series appear to be more moderate than those previously reported. In particular, they have milder or even absent intellectual disability and fewer growth abnormalities. Behavioral problems, anxiety and attention-deficit hyperactivity disorder appear to be common features of this condition.

- 12h45 : **Dr Roseline Caumes (Lille). Apport des données apportées par le site GENIDA pour la prise en charge des patients porteurs de mutations *MED13L*.**

The GenIDA (Genetically determined Intellectual Disabilities and Autism Spectrum Disorders) International Project is an online cohort study. The main objective is to gather information on the natural history, medical complications, behavioral disorders, and responses to pharmacological treatments in patients affected with intellectual disabilities (ID) and/or autism spectrum disorder (ASD) of genetic origin. GenIDA is a website dedicated to Patients, Families, and healthcare professionals. Since 2014, the project has included 526 disease-causing genes and regrouped patients from more than 40 countries. Clinical forms are available in 5 different languages (English, French, Dutch, German and Portuguese.) It is a radically new approach for medical studies, as the data are self-reported by patients or families.

MED13L syndrome, due to *MED13L* deletion or heterozygous variation, has been described in approximately 80 patients in scientific reports. Patients presented moderate to severe intellectual disability, dysmorphic features, hypotonia, and

inconsistently congenital cardiac defects. Since MED13L syndrome count for one of the most commonly identified genetic cause of ID, the cohort of MED13L-syndrome patients corresponds to the fifth largest cohort in the GenIDA database, with 55 registered families.
MED13L Cohort data in GenIDA confirmed the global developmental delay, highlighting it as the main difficulty, and confirming previous scientific reports. The distinctive feature of this approach lies in the focus on everyday difficulties and can help the clinicians to improve the follow-up of rare genetic disorders, allowing personalized healthcare approaches.

Après-midi : 14h00-16h00

- 14h : **Pr David Geneviève (Montpellier). Geneticist against the machine : challenge distinction Clinique entre KS1 et KS2.**

- 14h 20 : **Dr Colombine Meunier (IPG - Belgique). Le DPNI comme test de dépistage de première ligne, l'expérience belge.**

- 14h 40 : **Adeline Perrot (Oxford). Questions éthiques autour du DPNI**

- 15h10 : **Dr Pascale Kleinfinger (CH Pontoise, Cerba, ACLF) / Dr Nicolas Chatron (HC Lyon, ACLF). DPNI, extension aux syndromes microdélétionels et autre anomalies cytogénétiques**.

- 15h30 : **Pr David Genevièvre (AFGC). Questions posées par le DPNI, discussion.**