Title: Decoding the Undiagnosed: Syndrome Discovery in the Era of Collaborative Genomics

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A substantial proportion of patients with suspected genetic disorders remain undiagnosed despite the widespread implementation of genome-wide sequencing. These unresolved cases often represent the frontier of rare disease discovery. In the era of collaborative genomics, international data sharing and interdisciplinary research have become critical to transforming such cases into newly characterized syndromes.

Our team has initiated or contributed to five recent international studies that have led to the identification of previously unrecognized syndromes and the elucidation of novel disease mechanisms, exemplifying this paradigm. These include: (i) the delineation of a previously unrecognized cohesinopathy through integrated analysis of prenatal and postnatal phenotypes; (ii) the identification of a novel autosomal dominant neurodevelopmental disorder using matchmaking platforms and functional validation in model organisms; (iii) the characterization of a new neurodevelopmental condition based on a multicenter cohort of over 50 patients, complemented by transcriptomic profiling and organoid modeling; (iv) the investigation of a rare disorder linked to defective autophagy, supported by both cellular and *in vivo* studies; and (v) the definition of a new microduplication syndrome through collaborative copy number variations mapping and analysis of three-dimensional chromatin architecture.

These cases illustrate how federated clinical and genomic efforts enable the discovery and mechanistic understanding of previously undiagnosed conditions. Together, they underscore the transformative impact of coordinated international research in advancing rare disease diagnostics, and reflect a broader shift in medical genetics toward global, network-based approaches to syndrome discovery.

SPEAKER BIOSKETCH – Dr. Guillaume Jouret (MD)

(Maximum one page – please include your ORCID ID)

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CURRENT AND PAST POSITIONS:

Dr Guillaume Jouret is a medical doctor specialised in medical genetics. He is currently Head of the Clinical Genetics Service a. i. at the National Center of Genetics, Laboratoire National de Santé (LNS), Luxembourg. On the clinical front, he provides consultations for patients suffering from genetic diseases and hereditary predisposition syndromes. His medical work is combined with his involvement in European collaborative translational research projects, and the organisation, as principal investigator, of international clinical research studies that have contributed to the discovery and characterisation of several new syndromes.

EDUCATION:

Dr Guillaume Jouret pursued a dual academic path in medicine and science at several French universities. He began his medical training at the La Timone campus in Marseille, where he ranked 34th out of 2,974 candidates in the national PCEM1 examination. He completed his specialisation in medical genetics within the university hospitals of Reims, Strasbourg, and Université Paris-Saclay, acquiring broad clinical and academic expertise in the field.

AWARDS AND HONORS:

In 2019, he was awarded the Early Career Award by the European Society of Human Genetics for Best Clinical Research Poster at the European Human Genetics Conference in Gothenburg, Sweden—selected as the top clinical research presentation among over 3,000 submissions.

OTHER RELEVANT PROFESSIONAL ACTIVITIES AND ACCOMPLISHMENTS:

His medical practice is integrated with his participation in European collaborative translational research initiatives, and he conducts international clinical research as a principal investigator. These clinical studies have led to the identification and description of several novel genetic disorders. He also contributes to the teaching of medical genetics at the University of Luxembourg.