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A new patient with a clinical profile of CDG-IIf suffers in reality from a severe α-1 anti-trypsin inhibitor syndrome

In 2005, we discovered the first CDG-IIf with a genetic defect of the CMP-sialic acid transporter *SLC35A1*. He died at 37 months with severe megathrombocytopenia repeated hemorrhagies, neutropenia and complete lack of leukocyte sialyl-Le^{X}. This clinical profile was conducted to a second patient, but the cDNA profile was more complex. He had in addition a 10-fold increase of hyaluronic acid, plus abnormalities in plasma apolipoprotein C-III. The whole exome DNA sequencing did not show inactivating mutations of CDG-type-II, but two autosomal co-dominant missense mutations of *SERPINA1*. He was heterozygous for the paternal Z-allele and the maternal S-allele. Patients mutated in this gene are characterized as A1AT deficient. The Sequenom analysis demonstrated a disequilibrium expression in favor of the Z allele in fibroblasts. He had a SZ genotype, but appeared clinically and biologically as a severe homozygous ZZ deficient. Several organs: lung, liver, thymus, gut, skin or hematopoietic cells were affected and accumulation of degraded or aberrantly glycosylated proteins were observed in liver and fibroblasts. The extracellular matrix structure was altered, due to aberrant production of HA and large amounts of macrophage infiltration in all organs, since the tissues were not protected with enough protease inhibitor. Excess of active elastase not inhibited by the mutated A1AT destroyed the ECM elastin and destabilized connective tissue. In conclusion, what we thought to be a new CDG-IIf was in reality a patient with a severe alpha-1 antitrypsin deficiency (AADT) with a dysfunction in the glycan maturation and aberrant glycoprotein traffic.

Biography

Rosella Mollicone did his PhD at UPMC-Paris-VI. She worked with Rafael Oriol on his *FUT1-FUT2* genetic model. She completed her Post-doc with JB Lowe in Ann Arbor, USA. She has published more than 90 papers in international journals, has been an Editorial Board Member, Referee and Opponent for several PhD thesis. She is a full CNRS Research Director since 1997, responsible for the group of fucosyltransferases at INSERM U1197 (Villejuif, France). She works on CDG-type-II and in human ES and IPS cell glycan differentiation. She has received a price for a new human embryonic α3-fucosyltransferase.

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