New mutation of the *ATP6V0A2* gene in an autosomal recessive cutis laxa type 2 patient

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CONTEXT:

Subtypes of autosomal recessive cutis laxa (ARCL) are rare inherited diseases presenting with wrinkling skin and systemic involvements including dysmorphism, microcephaly, joint abnormalities, large fontanels and psychomotor retardation. Mutations in *fibulin* gene have been involved in a few cases of ARCL-I. Very recently, consanguineous ARCL-II patients sharing mutations in the gene encoding the α2 subunit of V-type H^+ ATPase (*ATP6V0A2*) have been reported. We present here the first French ARCL-II patient harboring a new mutation in *ATP6V0A2*.

PATIENT:

The girl from apparently non consanguineous parents presented at birth intraventricular communication, axial hypotonia and large fontanels in addition to major hypotrophy. She developed psychomotor retardation and anterior fontanel remained large until 8 year-old. At the age of twelve years, she presented microcephaly, low length and body weight and cutis laxa, joint laxity, nasal voice and strabismus were also noted, leading to glycosylation defects screening.

METHODS:

→ Two dimensional gel electrophoresis (2-DE)
- IEF followed by SDS-PAGE and Western-blot
- *N*-glycoproteins: Tranferrin
- *O*-glycoproteins: apoC-III: core1 mucin-type *O*-glycosylation

→ Mass spectrometry (MALDI-TOF)
- *N*- and *O*-glycans released from serum glycoproteins
- PNGase F digestion for *N*-glycans
- reductive β-elimination for *O*-glycans
-derivatization by permethylation

→ *ATP6V0A2* DNA sequencing

RESULTS:

Two-dimensional electrophoresis showed abnormalities in serum transferrin (increased % of hyposialylated isoforms indicated by red arrows; Fig.1) and apoC-III (increased % of apoC-III_1 i.e. the monosialylated isoform; Fig. 2), while MALDI-TOF mass spectrometry corroborated sialylation defects and further revealed hypogalactosylation of *N*-linked glycans (Fig. 3). Western-blotting of COG subunits showed no abnormality but brefeldin A induced a significant delay in the vesicular Golgi trafficking of patient's cells (not shown). Lastly, DNA sequencing of *ATP6V0A2* showed in this patient an homozygous G deletion leading to a stop codon (Fig.4) and which was retrieved at the heterozygous state in the parents.

Figure 1: 2-DE of transferrin

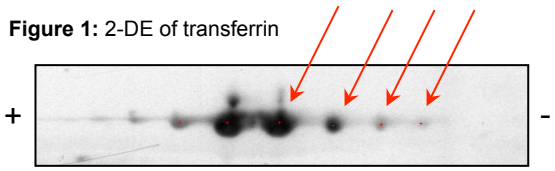


Figure 2: 2-DE of apoC-III

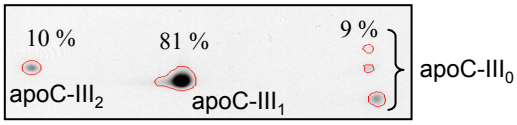


Figure 3: MALDI-TOF of serum *N*- and *O*-glycans

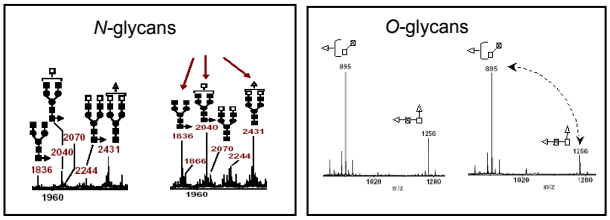
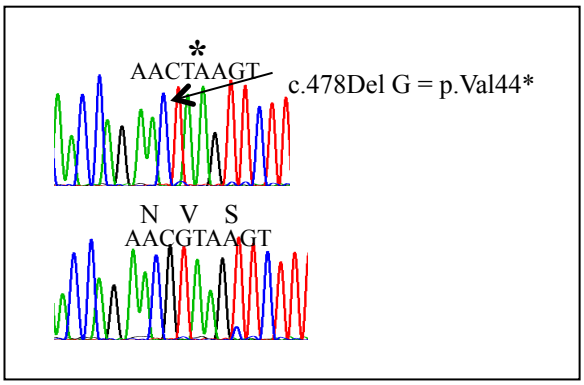


Figure 4: *ATP6V0A2* DNA sequencing



CONCLUSION:

Glycoproteomic tools and typical clinical findings allowed us to diagnose a novel case of ARCL-II-associated CDG sharing one original homozygous *ATP6V0A2* mutation.