SP015

COMPOUND HETEROZYGOUS MUTATIONS IN AMNIONLESS CAUSE IMERSLUND-GRÄSBECK SYNDROME IN TWO HALF-SISTERS

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Background

Imerslund-Gräsbeck Syndrome (IGS) is a rare autosomal recessive disease characterised by intestinal vitamin B12 malabsorption. Clinical features include megaloblastic anemia, recurrent infections, failure to thrive, and mild proteinuria. Recessive mutations in cubilin (*CUBN*) and in amnionless (*AMN)* have been shown to cause IGS. To date, there are only about 300 cases described worldwide with only 41 different mutations found in *CUBN* and 30 different in the *AMN* gene.

Methods

We collected pedigree structure (Figure 1), clinical data (Table 1) and DNA samples from 2 half-sisters with IGS. Molecular diagnostics was performed by direct Sanger sequencing of all 62 exons of the *CUBN* gene and 12 exons of the *AMN* gene. Because of lack of parental DNA, cloning and sequencing of multiple plasmid clones was performed to assess the allele of identified mutations.

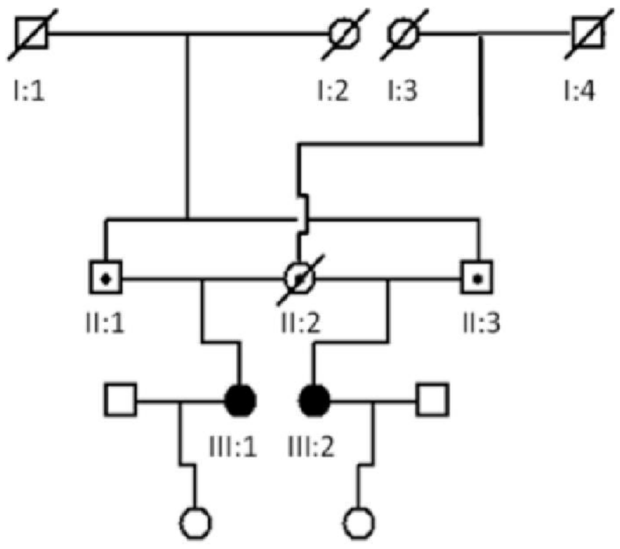

FIGURE 1
A. Pedigree diagram. Circles represent females, squares represent males. Shaded equals affected status, dots equals presumed carrier status.

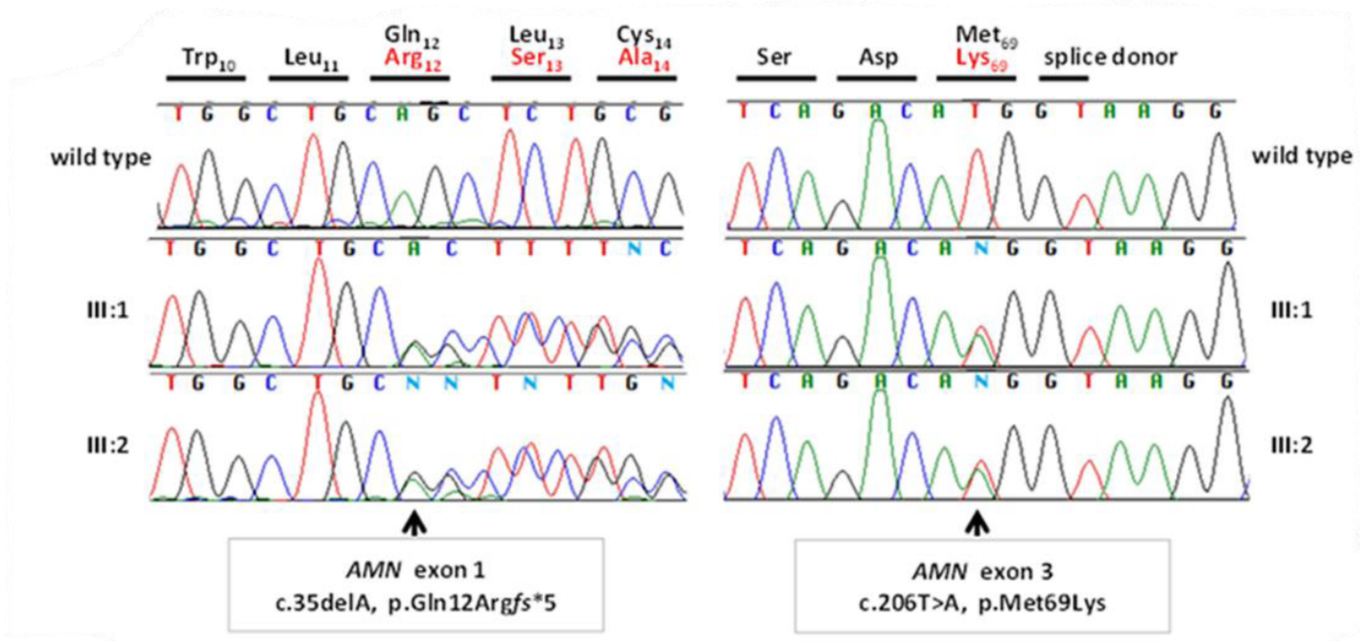

FIGURE 2
Chromatograms of 2 novel compound heterozygous mutations in the gene *AMN* (Genbank NM_030943.3), encoding for the protein amnionless, identified in 2 half-sisters (III-1 and III-2) with Imerslund-Gräsbeck syndrome.

Table 1: Clinical features of two half-sisters with Imerslund-Gräsbeck syndrome

ID	Age at diagnosis [years]	Vitamin B12 deficient	B12 level on treatment [ng/L]	Serum Creatinine [µmol/L]	Urinary protein/ creatinine ratio [mg/mmol]	Total Vitamin D level (nmol/L)	24 h urine protein [g/24 h]	Neurological symptoms
III:1	2	Yes	405	64 (stable)	50-90	73	0.6-0.7	No
III:2	3	Yes	743	62 (stable)	66-71	76	0.65	No

Results

Genetic characterization revealed 2 novel compound heterozygous *AMN* mutations in both half-sisters with IGS (Figure 2). *Trans*-configuration of the mutations was confirmed.

Conclusions

We identified novel compound heterozygous mutations in *AMN* in a Caucasian family, extending the spectrum of known mutations for IGS.

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