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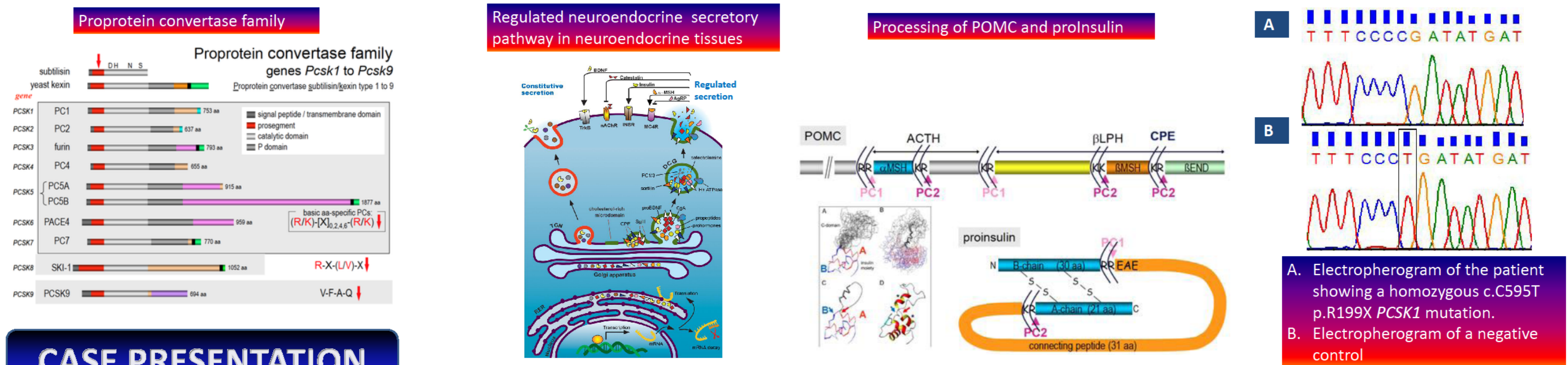
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BACKGROUND

Proprotein convertase 1/3 (*PCSK1*) is a neuroendocrine convertase that belongs to a family of subtilisin-like serine endoproteases that process large precursor proteins into mature bioactive products. Other members of this family include furin, which acts within the constitutive secretory pathway, and Proprotein Convertase 2 (*PCSK2*), which, like PC1, is involved in tissue-specific processing of prohormones and neuropeptides precursors within the regulated neuroendocrine secretory pathway. PC1 and PC2 are therefore implicated in the process of a subset of inactive prohormones into biologically active hormones, including pro-opiomelanocortin (POMC), prothyrotrophin releasing hormone (TRH), proinsulin, proglucagon, and progonadotrophin releasing hormone (GnRH). PC1 is expressed in endocrine cells in the gut, in the arcuate and paraventricular nuclei of the hypothalamus, and in β cells of the pancreas.

Congenital deficiency of *PCSK1* is a very rare autosomal-recessive syndrome causing malabsorptive diarrhea contrasting with hyperphagia, severe early-onset obesity and hypopituitarism (Jackson RS 1997, Farooqi 2007, Martin 2013).

We described here a new case of congenital *PCSK1* deficiency in a 6 years old Turkish boy.

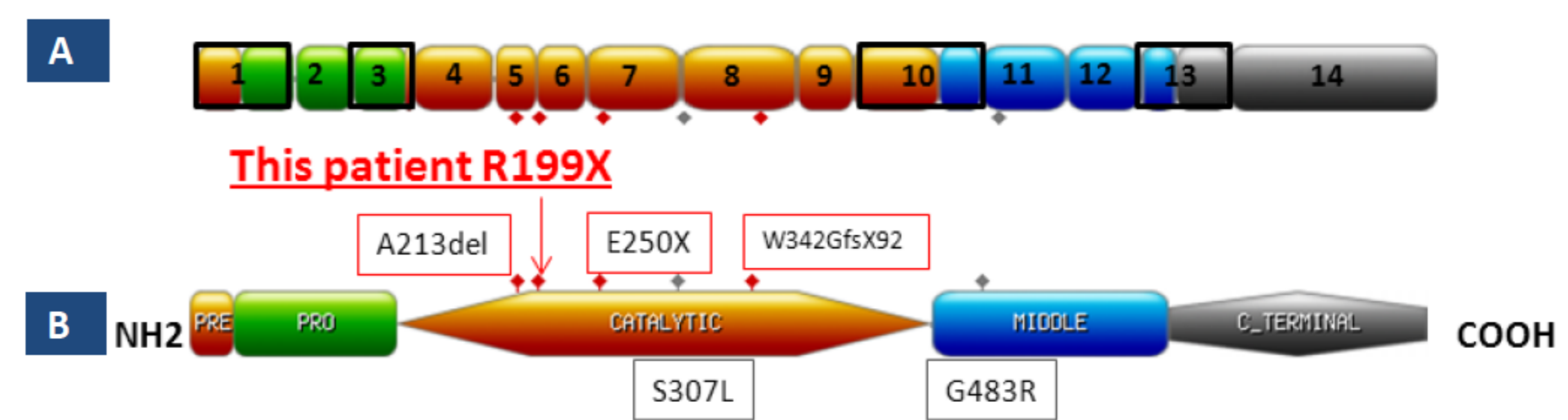
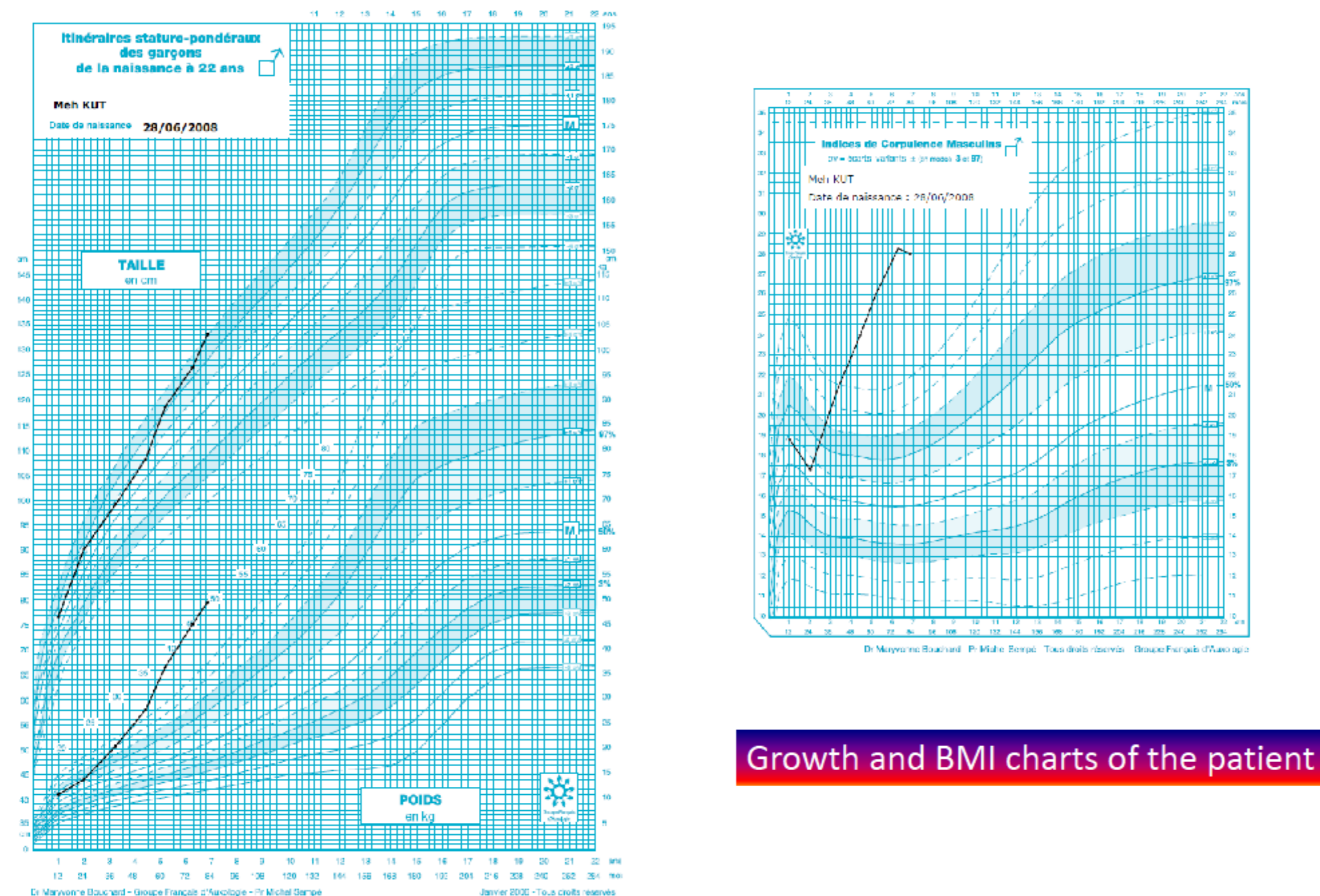


CASE PRESENTATION

The male proband was born in 2008 at 41 weeks of amenorrhea from consanguineous parents of Turkish origin, after an uneventful pregnancy. His two sisters were both healthy. He presented macrosomia at birth (Wt 4580g, Ht 55cm). His parents are first cousins. Moderate dysmorphic features were noticed: macroglossia, bilateral clinodactyly of 4th and 5th toes, frontal bossing, mid-face hypoplasia, depressed nasal bridge and micropenis. He developed severe malabsorptive diarrhea with pancreatic exocrine insufficiency and recurrent hypoglycaemia immediately after birth. Nocturnal parenteral nutrition was necessary during 3 years. Endocrine investigations confirmed isolated growth hormone deficiency at age 2 months (Low IGF1 levels, between 6 and 31 ng/ml, low IGFBP3 levels, under 600 ng/ml, and low GH peak during glucagon test 10,1 mUI/L). Multiple pituitary hormone deficiency was diagnosed by the age of 3, including diabetes insipidus, mild central hypothyroidism and hypocortisolism. Central hypogonadism was also strongly suspected. Pituitary MRI was normal. He developed severe early-onset obesity and eating disorders with a BMI of 28 kg/m² at 6 ½ yrs (see growth charts). Parental adherence to hormonal substitution was erratic.

In view of the combination of chronic diarrhea, rapid weight gain and hypopituitarism, the possibility of *PCSK1* deficiency was assumed. Fasting plasma insulin was normal (2.7 μ U/mL; N 5-25) but proinsulin was very increased (between 300 and 1255 pmol/l; N 3.3-28).

As conventional Sanger sequencing of *PCSK1* was not provided, we performed whole exome sequencing. We found an homozygous stop gain in the exon 5 of *PCSK1* (c.C595T; p.R199X; isoform NM_000439, cf figure). Considering the precocity of the stop codon, non sense mediated decay is likely. Thus complete loss of function is expected, as already described mutations.



Exonic (A) and protein structure (B) of *PCSK1* with previously reported mutations (nonsense in red, missense in grey). Of note, an intronic splice mutation leading to premature stop codon and a whole gene deletion have also been reported. Loss of function has been demonstrated for both missense mutations.

CONCLUSION

We described a rare case of neonatal malabsorptive diarrhea associated with panhypopituitarism and severe obesity caused by a new homozygous mutation in *PCSK1*, resulting in a complete *PCSK1* loss of function.

REFERENCES

1. Jackson RS, et al. Nat Genet 1997; 16:303-306.
2. Farooqi IS, et al. J Clin Endocrinol Metab 2007; 92:3369-3373.
3. Martin MG, et al. Gastroenterology 2013;145:138-148.

