



The N309K Pro-Protein Convertase Type 1 (PCSK1) Gene Mutation Causes Lack of Spontaneous Puberty and Primary Amenorrhea

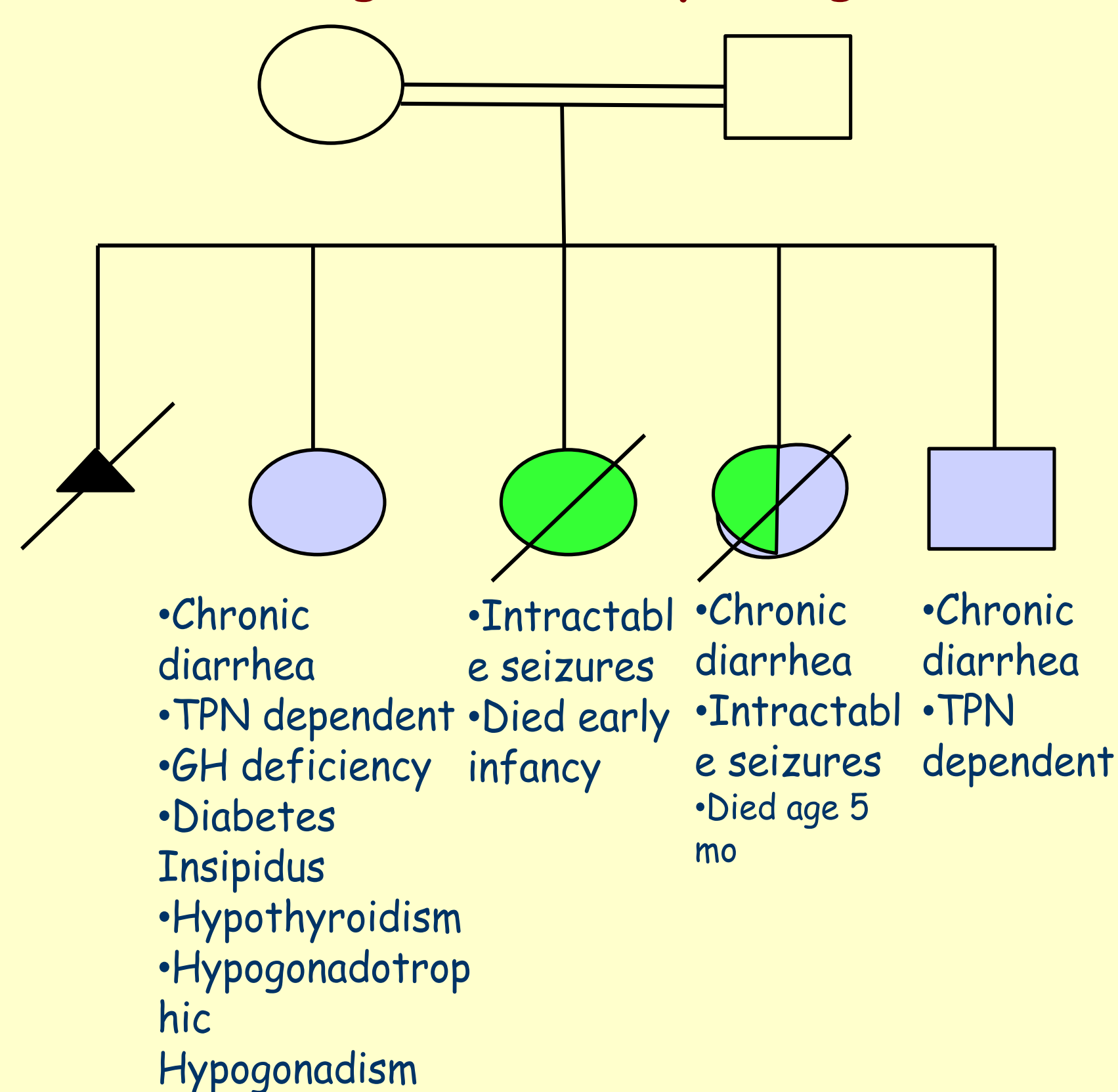
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Background

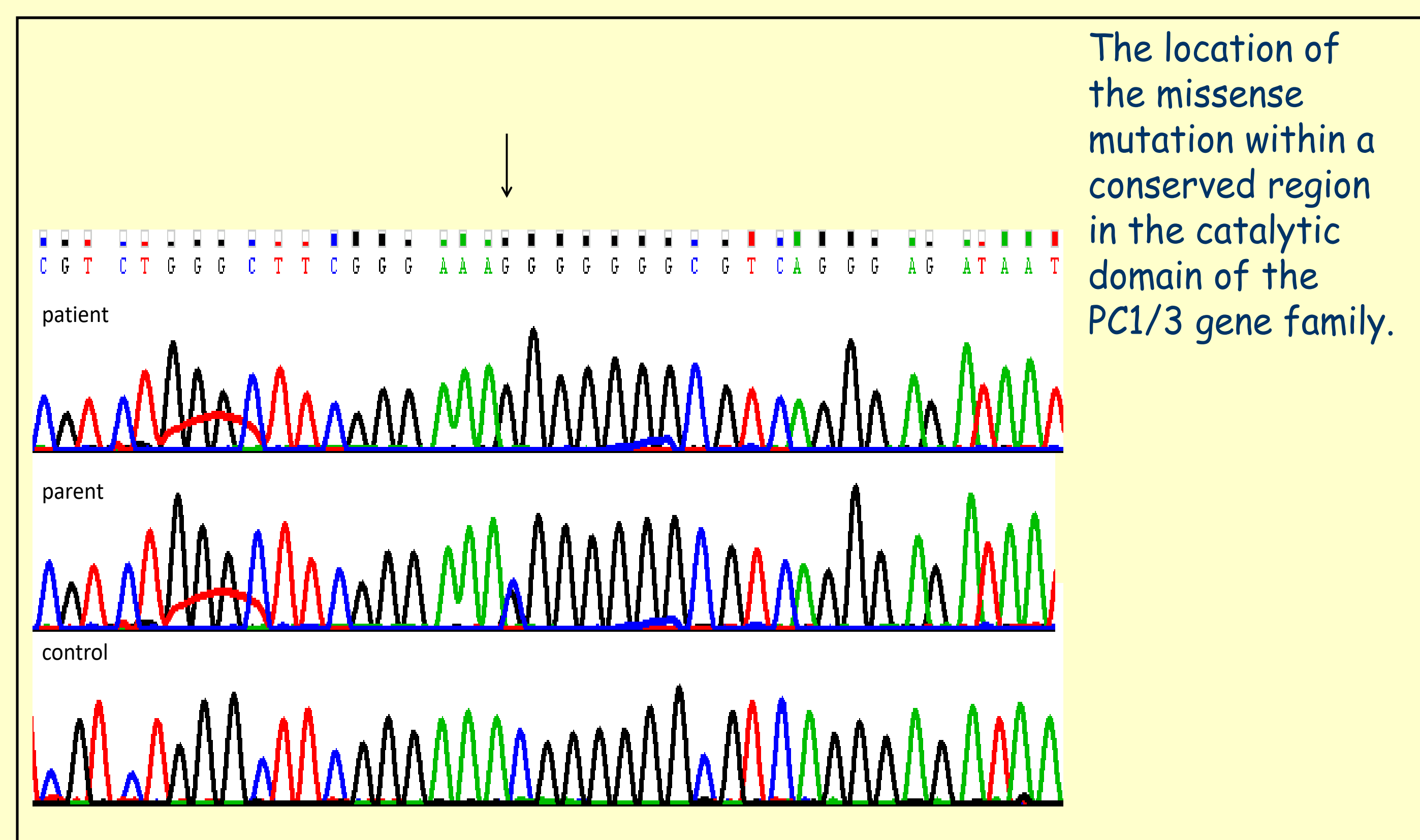
PCSK1/3 gene mutations are known as a cause for congenital diarrhea and various endocrinopathies. Hypogonadotrophic hypogonadism and aberrant pubertal development due to PCSK1 dysfunction was not characterized yet. This study aimed to characterize the pubertal development in a family reported to carry the novel N309K mutation in the PCSK1 gene.

Figure 1: Family Pedigree



Pedigree showing intractable diarrhea (blue) and seizures (green) and other clinical phenotypes. "/" - Deceased, "=" - consanguineous parents.

Figure 2: Sanger sequencing validation of the N309K variant



Methods and Results

We Identified 2 siblings who presented with severe congenital diarrhea followed by overweight, and endocrinopathies during early childhood to have a novel homozygous N309K PCSK1 gene mutation.

The female developed mal-absorptive diarrhea in the first week of life and kept on parenteral nutrition until the age of 5 years. She was diagnosed with mild central hypothyroidism at the age of 2 years following persistent low FT4 levels (7-9 pmol/l) and non increasing TSH levels between 2-3mIU/ml. She was started on thyroid replacement therapy. Poor growth rate with low GH response in 2 stimulation tests (only 3.5-6.5 ng/ml) at the age 3-4 years led us to initiate GH treatment for a total of 9 years reaching a final height of 163 cm at the age of 13.5 with BA 15 years .

She also had self limited episodes of DI which were treated shortly with intranasal desmopressin. At age of 6 years she became severely obese with Body mass index (BMI) -21.6 despite GH treatment and adequate thyroid replacement.

She started to have pubertal development at the age of 12years. But no menarche occurred by the age of 13 years.

She underwent lab tests which showed baseline LH=0.33 IU/L FSH= 1.4Iu/L Estradiol less than 70 pg/ml.

LHRH test revealed no adequate elevation of Gonadotropins.

Table 1 : LHRH Test showing no Gonadotropin elevation upon stimulation

| Time in minutes | LH IU/L | FSH IU/L |
|-----------------|---------|----------|
| Zero | <0.2 | 0.96 |
| 20 | 0.99 | 2 |
| 40 | 1.1 | 2.39 |
| 60 | 1.2 | 2.5 |

•The patient was started on Hormone replacement therapy for puberty initiation at age 14 years at Tanner stage I-II Initial Dose was 0.25 mg of Estradiol (*Estrofem*) daily for 3 months with gradual increase in Estrofem dosage up to 2mg daily with addition of medroxyprogesterone resulting in full pubertal development and regular periods .

Conclusions

PCSK1 gene mutations with PC1/3 deficiency is a very rare genetic disorder causing congenital Diarrhea and multiple endocrinopathies. Little is reported and understood about the exact mechanism of delayed/absent puberty in PCSK1 patients . Inactivating mutations in the genes encoding the human kisspeptin receptor result in pubertal failure. A.K Topaloglu et al .Inactivating *KISS1* Mutation and Hypogonadotrophic Hypogonadism. N Engl J Med 2012; 366: 629-635.

Literature supports that that PC1/3 might be involved in processing Kisspeptin precursors and by this path impair GnRH synthesis in PCSK1 mutations . Martin et al. Gastroenterology. 2013 July; 145 (1): 138-148.

This case illustrates the crucial role of the prohormone convertase 1/3 PCSK in enabling normal pubertal development in females. The novel homozygous N309K mutation causes severe obesity associated with hypogonadotrophic hypogonadism and primary amenorrhea that fully respond to hormonal replacement therapy.

The authors have nothing to disclose .