

Sequence of *MKRN3* and *DLK1* genes in cases with familial central precocious puberty

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BACKGROUND:

- Approximately one-third of the central precocious puberty (CPP) cases have familial transitions. Although more than 30 genes related to puberty have been reported to date, only a few (*KISS1*, *KISS1R*, *MKRN3*, *DLK1* and *PROKR2*) were associated with CPP.
- This study aims to reveal the associated sequence variants of *MKRN3* and *DLK1* genes in cases with familial CPP and their etiology.

MATERIAL/METHOD:

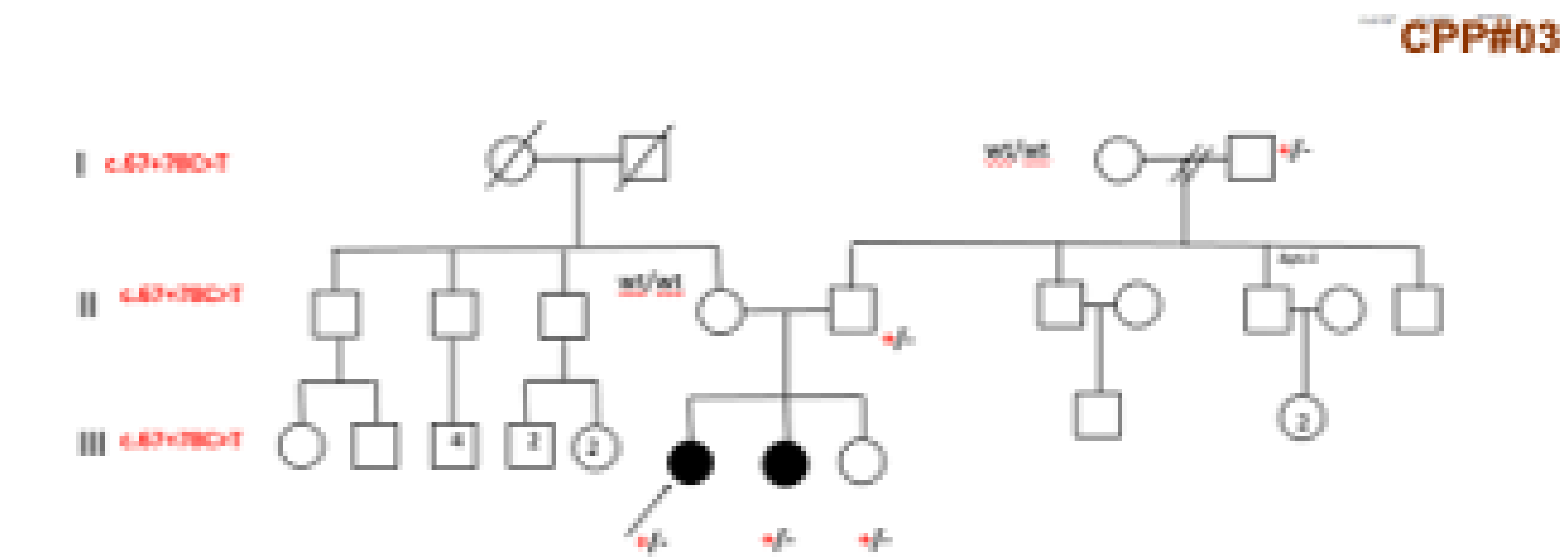
This study includes 18 cases (16F, 2M) from different families, whose past medical history, physical examination, laboratory and follow-up records were evaluated. SDS calculation was performed according to national standards; bone-age (BA) was assessed by Greulich-Pyle-method, and predicted adult height (PAH) was calculated according to Bayley-Pinneau-method. Family pedigrees were drawn for each case, and informed consents from all families were obtained before genetic testing. Sanger sequencing was performed in regions coding *MKRN3* (NM_005664.3) and *DLK1* (NM_003836.6). Segregation analyses were performed in families with pathogenic variants.

RESULTS:

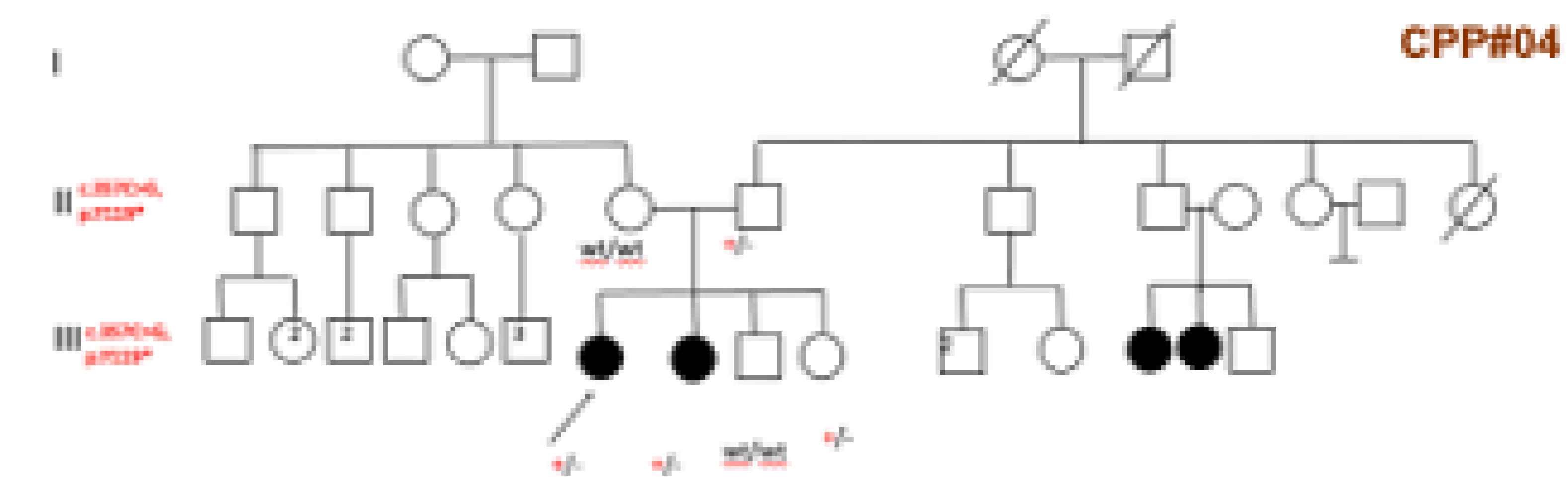
- The mean onset of pubertal age was 7.3 years (6.38-7.58) in females; 6.7 and 8.8 years in two males.
- The mean birth weight SDS was -0.6 (-1.3-0.9). At presentation, height and body mass index SDS were 0.3 (-1.2-2.6) and -0.5 (-1.1-3.2) respectively.
- The mean BA was 8.8 years (7.8-10.5), and chronological age-BA difference was 3 years (1.6-4.9). Mean PAH was 156.7cm (-0.78 SDS) (147-171.6) in females; 167.9 and 181.7cm in males. The mean target height SDS was -0.7 (-2.18 and -0.1) in females; -0.7 and 0.32 in males.
- Cranial-pituitary MRI of all cases was normal. Fifteen cases received GnRHa. The initial age of treatment was 8.9 years (7.2-9.8) in females; 6.8 and 9.7-years in males. GnRHa was discontinued at age of 11.2 years (10.8-12.6) in females; 10.2 and 12.8 years in males.
- Two different novel heterozygous variants in the *DLK1* gene in two different families and a pathogenic variant in the *MKRN3* gene in one case were detected in genetic analyses.
- The first variant of *DLK1* gene was c.357C>G(p.Tyr119Ter) in exon 4, and the second variant was c.67+78C>T in intron1 (Figure 1).
- Segregation-analyses of these families had shown a paternal origin for these variants.
- The heterozygous variant in *MKRN3* gene was c.982C>T(p.Arg328Cys, which is also paternally derived (Figure 1).

CONCLUSIONS:

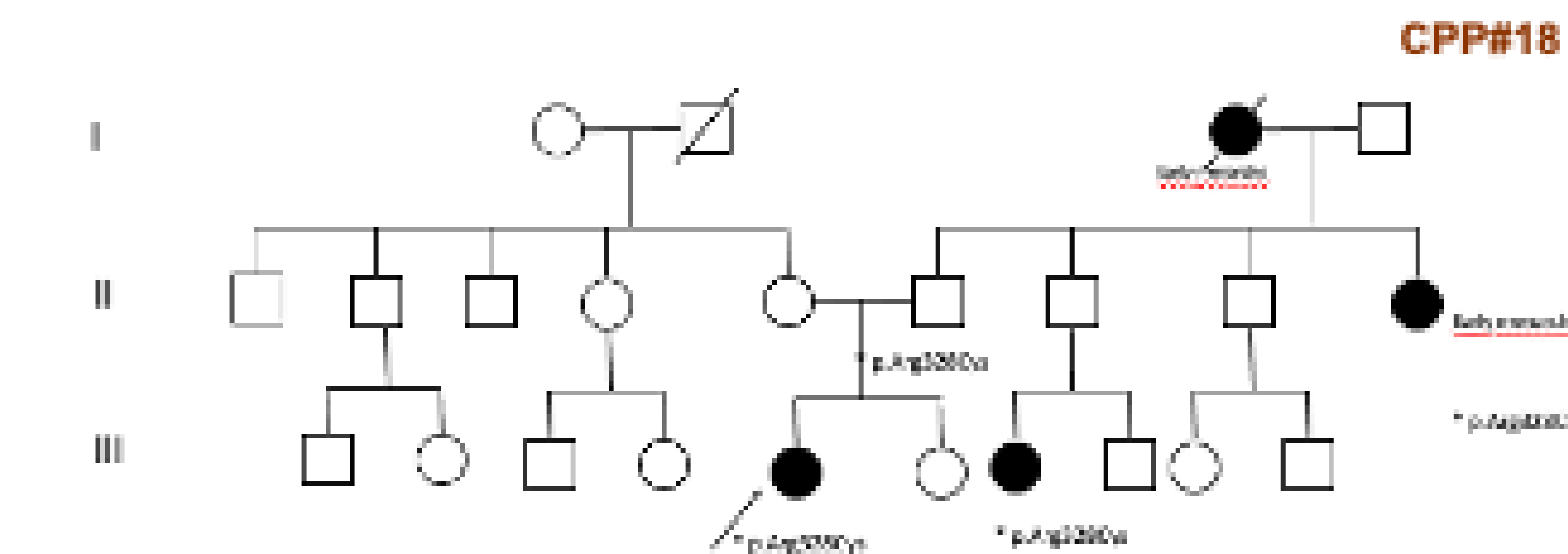
- Although more frequent in literature, mutation in *MKRN3* gene was detected only in one case in our study.
- Two-variants in the *DLK1* gene were found to be compatible with the paternal imprinted gene model.
- In-silico analysis predicted that the first would lead to clipping error and the second to protein truncation. Transcription level study was planned for the clipping region change in the intronic region.
- We suggest that performing WES analysis in cases without pathogenic variant may help to explain the new genes and their relationships in familial CPP.



DLK1; IVS1; III NOVEL; MUT TASTER; disease causing;
NM_003836.6: c.67+78C>T; g.1509C>T; CCGTGCCCCGCAYGCCCGTCTCG



DLK1; EX4; NOVEL; MUT TASTER; disease causing;
NM_003836.6: c.357C>G; NP_003827.3: p.Y119*; p.Tyr119*; TGCCCCCGGGTASTCGGG
AAAGGA



*EX1; CM1512773; rs1264639964; Disease causing mutation; Central precocious puberty; Highest population MAF: <0.01; NM_005664.3: c.982C>T; NP_005655.1: p.R328C; p.Arg328Cys; T=0.00000 (1/251494, GnomAD_exome); chr15:23566764; Simon (2016) Eur J Endocrinol 174: 1 PubMed: 26431553; CCCCCAATGACCGC(C/T)GCTTTGGCATTCTT

Figure 1: Pedigree of patients with pathogenic variants.