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Case report

Heterozygous c.1730G > C (p.Trp577Ser) Variation in a Case with Familial Hypercholesterolemia

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SUMMARY

Introduction: FH is an autosomal dominant disease of lipid metabolism. Hypercholesterolemia, xanthomas, and death from early coronary artery disease (CAD) are common in this disease due to a mutation in the *LDLR, Apo-B100* or *PCSK9* genes.
Case report: A 4-year-old male patient with a very rare heterozygous c.1730G > C (p.Trp577Ser) variation in exon 12 of the low-density lipoprotein receptor (*LDLR*) gene that causes familial hypercholesterolemia (FH) was reported. As in this case, the heterozygous form may not show any symptoms in the first decade. This variation is region specific. Therefore, region-specific diagnostic criteria should be developed.
Conclusion: We aimed to contribute to the literature on the development of diagnostic criteria by discussing the patient's condition with the clinical results.

Keywords: **familial hypercholesterolemia, case report, *LDLR* gene, xanthomas**

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INTRODUCTION

A decrease in LDL catabolism in FH causes an increase in LDL concentration in plasma (1). This leads to childhood death due to early coronary artery disease (2). Early diagnosis is very important in the treatment of the disease, however, the heterozygous form is asymptomatic in the first decade (3). The aim of this paper was to contribute to the literature by discussing the case of a four-year-old male patient who presented to Malatya Training and Research Hospital Medical Genetics Clinic with the complaint of growth retardation and diagnosis of familial hypercholesterolemia.

CASE REPORT

In the physical examination of our 4-year-old patient with heterozygous c.1730G > C (p.Trp577Ser) variation, xanthoma was not detected and there were no symptoms other than high cholesterol levels. Due to high cholesterol levels in some of their close relatives, it was decided to perform genetic analysis. Although clinical features, family history and laboratory findings are important in the diagnosis of the disease, molecular genetic analysis is required to make a definitive diagnosis.

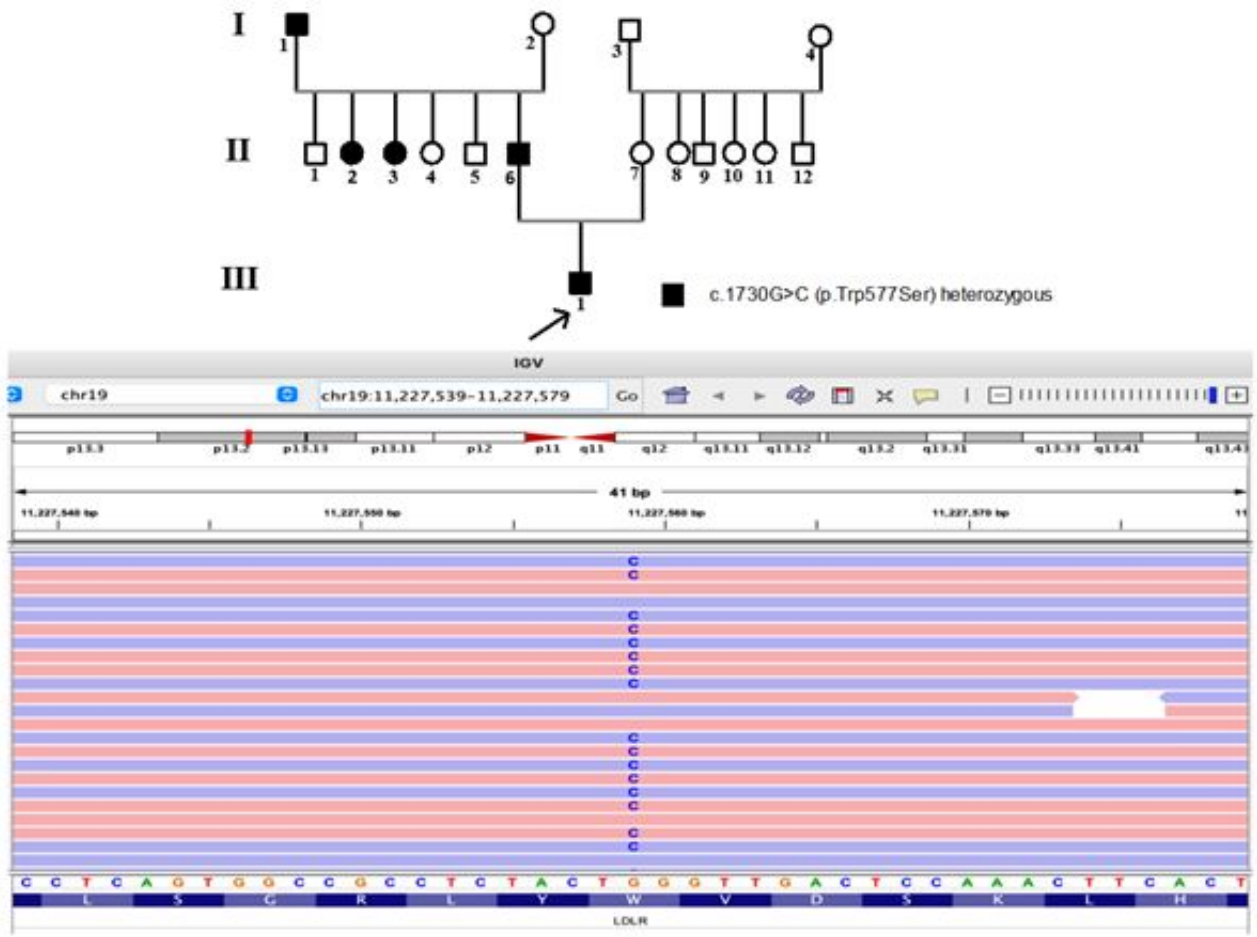
The patient presented with the complaint of growth retardation; his body weight was 13.5 kg (5 – 10 p), height was 98.5 cm (10 – 25 p), and head circumference was 50 cm (25 – 50 p). Heart peak beat was 92/min and blood pressure was 130/80 mmHg. Although he had no growth retardation, his height and weight were close to the lower limits of normal. There was no mental retardation. Cardiac echo result was normal and no additional dysmorphic findings were detected. Biochemical analysis revealed high total cholesterol and LDL levels. It was decided to conduct a genetic analysis for the patient who was found to have high cholesterol levels in his father, two aunts and his grandfather. As a result of the analysis, a pathogenic heterozygous c.1730G > C (p.Trp577Ser) variation on the 12th exon of the *LDLR* gene was detected. Family pedigree and sequencing traces of the patient showing the presence of the pathogenic heterozygous mutation 1730G > C (p.Trp577Ser) in the exon 12 of *LDLR* gene were given in Figure 1. Sequencing was done using the next-generation sequencing method (4).

The entire exome dataset including Genome

Table 1: *The entire exome dataset including Genome Aggregation Database (gnomAD), conservation score (GERP), predictions of pathogenicity based on ACMG recommendations*

GENE	*LDLR*
Transcript ID	NM_000527.4
dbSNP	rs138947766
Variant	c.1730G > C (p.Trp577Ser)
Variant location	Exon 12
Variant type	Missense
MutationTaster	Disease-causing
PROVEAN	Damaging
SIFT	Damaging
gnomAD (exomes)	f = 0.00000795
ClinVar	Likely pathogenic, pathogenic
Conservation	Conserved
DANN score	0.9885
GERP score	NR: 5.48; RS: 5.48
ACMG classification	Pathogenic
ACMG pathogenicity criteria	PM1, PM2, PM5,PP2, PP3, PP5

ACMG: The American College of Medical Genetics and Genomics



Aggregation Database (gnomAD), conservation score (GERP), predictions of pathogenicity based on The American College of Medical Genetics and Genomics (ACMG) recommendations was given in Table 1.

DISCUSSION

In Turkey, there is a limited number of studies conducted with a limited number of cases on the status of mutations in the *LDLR*, *Apo-B100* and *PCSK9* genes, which are involved in the etiology of the disease (5, 6). Therefore, common mutations in our country are not known exactly. In two studies conducted in Turkey, the most common mutations in the exons 4, 9 and 12 region of *LDLR* gene were reported. These studies show that the *LDLR* mutations in Turkey is very heterogeneous, with different distribution (5, 6). The c.1730G > C (p.Trp577Ser) variation detected in our patient, carrying on the 12th exon of the *LDLR* gene, is one of the pathogenic variations seen in familial hypercholesterolemia cases.

When the studies conducted around the world were evaluated, it was seen that the *LDLR* gene contains different types of variations mutations (7). *Apo-B100* gene or *PCSK9* mutations were detected in some of the patients followed up with the diagnosis of FH. Therefore, it is recommended to evaluate these genes in cases where no mutation can be detected in the *LDLR* gene (8 - 10).

In another study conducted on *LDLR* gene in 39 FH patients from Turkey, 21 of them (53.8%) presented to hospitals because of other complaints, and laboratory results indicated hyperlipidemia. In the other 18 (46.2%) cases, the disease was recognized due to the history of hyperlipidemia and/or early coronary artery disease in their mother, father or siblings (11). Our patient presented to the hospital due to another cause such as growth retardation, but we suspected FH because of high cholesterol level of family history. Although clinical and laboratory findings indicate the presence of *LDLR* gene mutations in most of the patients followed up with FH, more than 1100 mutations were detected in the rele-

vant region (7). This situation generally leads to the failure of mutation screening studies performed in patients diagnosed with FH (12). For this reason, screening in risky patients is not applied in our country because it will be very costly and will not provide significant benefit. Some diagnostic criteria have been developed for the early diagnosis of FH cases in the world. The most widely used of these are Simone-Broome criteria and Dutch Lipid Clinic Network criteria (13). These criteria are to classify the cases with high LDL-C based on physical examination, laboratory findings and family history data. A study conducted in Canada aimed to determine the criteria specific to this population and positive results were reported (14). Due to the large number and diversity of mutations in the relevant gene region and the fact that these mutations are population-specific, it may be useful to determine country-specific criteria for faster diagnosis of FH.

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Heterozigotna c.1730G > C (p.Trp577Ser) varijacija u slučaju bolesnika sa porodičnom hiperholesterolemijom

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S A Ž E T A K

Uvod. Porodična hiperholesterolemija je autozomno dominantna bolest metabolizma masti. Hiperholesterolemija, ksantomi i smrt zbog rane koronarne arterijske bolesti često se beleže kod ovog oboljenja, zbog mutacije na genima *LDLR, Apo-B100* or *PCSK9*.
Metode. U radu je opisan četvorogodišnji bolesnik sa veoma retkom heterozigotnom varijacijom c.1730G > C (p.Trp577Ser) u egzonu 12 gena lipoproteinskog receptora male gustine, koji uzrokuje porodičnu hiperholesterolemiju. Kao i u ovom slučaju, heterozigotna forma ne mora da bude praćena simptomima u prvoj dekadi. Ova varijacija je specifična za određenu regiju i u skladu sa tim treba izraditi odgovarajuće dijagnostičke kriterijume.
Zaključak. Cilj ovog rada bio je doprinos literaturi o razvoju dijagnostičkih kriterijuma, prikazivanjem stanja našeg bolesnika i kliničkih rezultata.

Ključne reči: **porodična hiperholesterolomija, prikaz slučaja, gen *LDLR*, ksantomi**