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Clinical and Genetic Characteristics of Splicing Variant in CYP27A1 in an Iranian Family with Cerebrotendinous xanthomatosis

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ABSTRACT

Background: CTX is a rare congenital lipid-storage disorder, leading to a progressive multisystem disease. CTX with autosomal recessive inheritance is caused by a defect in the *CYP27A1* gene. Chronic diarrhea, tendon xanthomas, neurologic impairment, and bilateral cataracts are common symptoms of the disease. **Methods:** Three affected siblings with an initial diagnosis of non-syndromic intellectual disability were recruited for further molecular investigations. To identify the possible genetic cause(s), WES was performed on the proband. Sanger sequencing was applied to confirm the final variant. The clinical and molecular genetic features of the three siblings from the new CTX family and other patients with the same mutations, as previously reported, were analyzed. The *CYP27A1* gene was also studied for the number of pathogenic variants and their location. **Results:** We found a homozygous splicing mutation, NM_000784: exon6: c.1184+1G>A, in *CYP27A1* gene, which was confirmed by Sanger sequencing. Among the detected pathogenic variants, the splice site mutation had the highest prevalence, and the mutations were mostly found in exon 4. **Conclusion:** This study is the first to report the c.1184+1G>A mutation in Iran. Our findings highlight the other feature of the disease, which is the lack of relationship between phenotype and genotype. Due to nonspecific symptoms and delay in diagnosis, CYP27A1 genetic analysis should be the definitive method for CTX diagnosis. ***DOI: 10.29252/ibj.25.2.132***

Keywords: Cerebrotendinous xanthomatosis, *CYP27A1*, Intellectual disability, *Iran*, Whole exome sequencing

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INTRODUCTION

Cerebrotendinous xanthomatosis is a rare autosomal recessive lipid storage disease caused by a defect in *CYP27A1* gene, encoding the mitochondrial cytochrome P450 sterol 27-hydroxylase enzyme[1]. As a result of this deficiency, certain metabolites, such as cholesterol and cholestanol, accumulate in various tissues, particularly eye lenses and muscle tendons, as well as in the central nervous system[2,3]. CTX has neurologic and systemic presentations[4-6], and its clinical symptoms include

List of Abbreviations:
CADD, Combined Annotation Dependent Depletion; **CTX,** Cerebrotendinous xanthomatosis; **ExAC,** Exome Aggregation Consortium; **GERP,** Genomic Evolutionary Rate Profiling; **WES,** whole exome sequencing