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LETTER TO EDITOR

Long-term Pseudo-Hypertriglyceridemia due to Novel GK Splice Variant c.894+2T>C

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Introduction

We here report on a case of a 46-year-old male under evaluation for persistent long-term (for more than 20 years) Hypertriglyceridemia (HTG) submitted to us for a genomic study based on an exome analysis of a mixed dyslipidemia, with Hypercholesterolemia (HC) and HTG (in multiple serum determinations, in recent years on Abbott Alinity Chemistry Analyzers), with unequal response to treatment (with statins for HC, and fibrates for HTG), with a progressive decrease in cholesterol values (now at almost optimal values of LDL cholesterol, around 125 mg/dL) while with no effect on TGs measurements (commonly around 600 mg/dL).

A clinical exome analysis, with reagents and equipments from Agilent (for SureSelect Human All Exon V8; https://www.agilent.com) and Illumina (https://emea.illumina.com), and software from Agilent, illumina and Genoox (https://franklin.genoox.com), was undertaken searching for gene mutations of different types (sequence variants as well as exon deletions and duplications) in the entire gene coding sequences (including short intronic sequences closed to coding exons). Such a complete analysis did not lead to identification of relevant findings in genes associated to Familial HC (FHC), including three genes responsible for a majority (~90%) of cases, LDLR (60%–80%), APOB (1%–5%) and PCSK9 (up to 3%). Neither in genes occasionally implicated in FHC, most notably LDLRAP1, CYP27A1, APOE, ABCG5, ABCG8, LPL, USF1, SORT1, STAP1, LIPA and PNPLA5 [1–3]. Accordingly, an involvement of as yet unidentified genes cannot be ruled out, nor a case of polygenic origin, which after some speculations would be responsible for up to ~40% of FHC cases without an identified one-gene Mendelian linkage.

Further, a survey of genes implicated in Familial HTG (FHTG) neither yielded relevant findings. FHTG is a dyslipidemia with proposed monogenic linkage in severe cases to the genes LPL, APOC2, APOA5, LMF1, GPHBP1 and GP1. And with a multigene (polygenic) association in mild-moderate cases to LPL, APOC2, GCKR, APOB, LMF1, GPHBP1, CREBH, APOE and...
less relevant variants of other genes [4]. However, a consideration of many other candidate genes, associated to HTG, as proposed by HPO database (https://hpo.jax.org/app/browse/term/HP:0002155), led to identification of variant c.894+2T>C of GK gene (Figure 1) considered relevant.

GK (Glycerol Kinase) is a gene of locus Xp21.2 that catalyzes the phosphorylation of glycerol to glycerol-3-phosphate, necessary for triglyceride production. It is implicated by X-Linked Recessive inheritance (XLR) in the Glycerol Kinase Deficiency (GKD), a disorder characterized by elevated plasma and urine glycerol levels and variable neurometabolic manifestations. It can occur as a contiguous gene deletion syndrome (from Xp21.2–Xp21.3) with congenital adrenal hypoplasia and Duchenne muscular dystrophy, in ‘complex’ forms, the severity depending on the size of the deletion (number of missing genes). In cases of exclusive GK involvement is detected only as hyperglycerolemia, as observed in our patient, with recent results of very high glycerol blood content (3,922 μmol/L; measured with a spectrophotometric assay, with reference range of 20–250 μmol/L). It becomes now clear that the high glycerol content has been the reason for the repeatedly erroneous determinations of TGs in serum, as well as in urine (37,742 mg/dL) that was tested as a proof of false determinations because TGs are never found in urine [5]. Besides, and according to a NMR spectroscopy assay (Liposcale), our patient has normal TGs values in serum, of 84 mg/dL (<150 mg/dL).

The identified GK variant, c.894+2T>C, of intron 12 (in reference sequence NM_001205019.2), is found in hemizygosis (in all the single sequences of the patient’s X chromosome, as shown in Fig. 1). Although we are not aware of its occurrence before, neither in patients nor in healthy individuals, it is considered relevant, by altered mRNA splicing, as similar mutations in these locations, so that according to ACMG (American College of Medical Genetics and Genomics) criteria it could be considered as a likely pathogenic mutation, as proposed by knowledge bases Franklin (https://franklin.genoox.com/clinical-db/variant/snp/chrx-30725717-T-C) and VarSome (https://varsome.com/variant/hg19/NM_001205019:c.894+2T>C).

Thus, and in conclusion, the valuable genomic analysis of HTG based on NGS has facilitated the finding of novel variant c.894+2T>C of GK gene, responsible for the pseudo-HTG of our patient, a rare case of hyperglycerolemia due to GKD that – as it has been repeatedly described– in adulthood is often asymptomatic [6–8] and does not require pharmacological treatment, therefore avoiding the use of fibrates, although a diet at more frequent intervals and rich in complex carbohydrates might be advisable [8]. The genomic study has on the other
hand not allowed us to establish a gene linkage for the HC, apparently well managed with statins which nevertheless might be related to the slight transaminase elevations noted in the patient.

References


