Hidden aberrant transcripts in TTC37 cause Trichohepatoenteric syndrome (THES)

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Inroduction: Trichohepatoenteric Syndrome is a rare, progressive, multisystemic and autosomal recessive enteropathy, caused by pathogenic variants in the *TTC37* or *SKIV2L* genes. THES is a congenital disease presenting with early-onset severe intractable diarrhea in born infants, characterized by facial dysmor-phism, growth failure, immune disorders, and early onset of severe liver cirrhosis in some patients [1–3]. Together with two copies of Ski8p, the proteins coded by these genes form the superkiller complex (SKIc) that functions as the cofactor of cytosolic exosome, responsible for degradation of aberrant mRNAs [4]. In this paper we present the first case of THES in Brazil caused by new pathogenic variants in the *TTC37* gene.

Results: Whole exome analysis was performed and revealed the variant p.Gln1411* in heterozygosis in the *TTC37* gene. This new variant was confirmed by Sanger sequencing in the patient and in her mother. Considering that THES is an autosomal recessive disease, we tried to find out the second variant responsible for the symptoms in the patient. A WGS was performed but no additional information regarding the second variant could be obtained. Therefore, we investigated *TTC37* gene expression in total RNA from white blood cells from the patient, his mother and his father. By using long range PCR with primers spanning almost the entire mRNA of *TTC37* (5201 bp), two aberrant transcripts were detected, lacking 4.932 and 4.766 bp, from exons 3 to 43 at different regions (NM_014639.4:r215_r4995del and NM_014639.4:r217_r5163del). The aberrant transcripts were also shown to be expressed in the RNA from the father (Figure 1A-C).

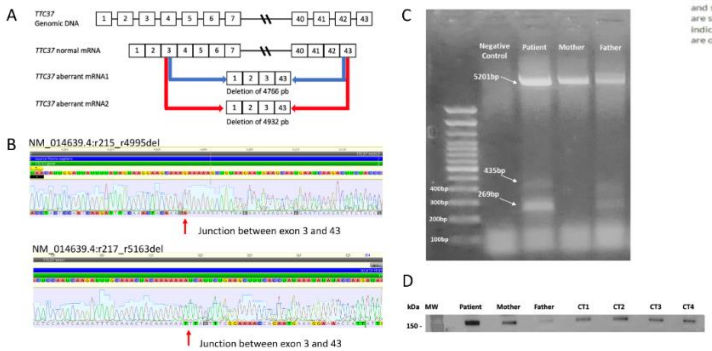

FIGURE 1 | (A) *TTC37* gene molecular structure showing the exons (boxes) and introns (lines) and the spliced regions in the aberrant transcripts. (B) The sequences show the breakpoint of the deletions (red arrow) observed in one allele of the patient in the mRNA of the *TTC37*. (C) Aberrant transcripts carried by the patient and the father. (D) Immunoblotting analysis of TTC37 protein in the serum. [Colour figure can be viewed at wileyonlinelibrary.com]

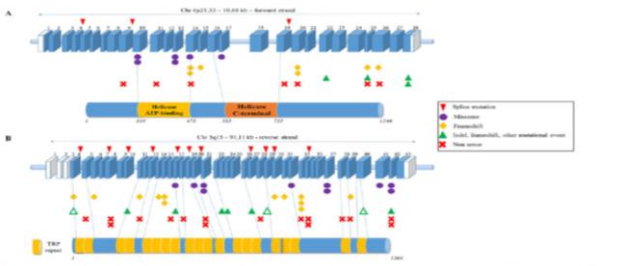

FIGURE 3 *SKIV2L* and *TTC37* mutation spectrum, molecular analysis. **A**: Schematic representation (not to scale) of human *SKIV2L* gene locus and structure. Exons are represented as boxes, introns as tubes. Exon numbering is indicated, noncolored boxes are untranslated regions. Below are shown both localization and type of mutation. Lower panel is the schematic representation of corresponding protein, with functional domains indicated. Numbers correspond to amino acids. **B**: Same representation for human *TTC37* gene and protein. Note that the TRP domains of *TTC37* are only predictions from the yeast homolog

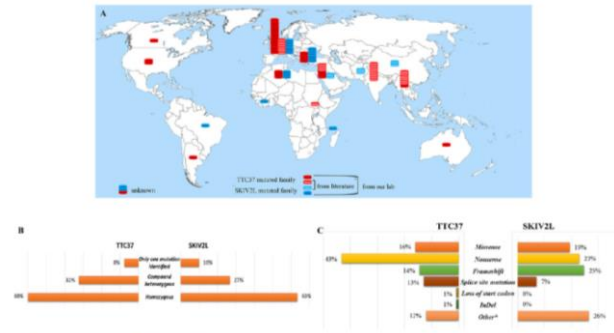

FIGURE 2 *SKIV2L* and *TTC37* mutation spectrum, global analysis. **A**: Geographical distribution of mutations around the world by gene. Light color, previously reported mutations. Plain color, French cohort. **B**: Mutational status of patients by gene. **C**: Types of mutations by gene

Conclusion: In THES, the clinical diagnosis is challenging. Our findings suggest that although the patient has one pathogenic exonic variant (p.Gln1411*) from the maternal allele, she carries also an aberrant splicing transcript of paternal origin, which probably leads to the production of a normal protein, which is secreted to the circulation in higher amounts than normal. Therefore, these variants together appear to be sufficient for the appearance of clinical manifestations, but with less severity in relation to pathogenic variants in homozygous or compound heterozygous individuals

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