

Letters in Response to Published Articles

Misinterpretation of ATP2C1 gene mutations

Sir,

I have carefully read the manuscript of Tian *et al.*, where the authors reported several mutations of the human ATP2C1 gene, six of which they claim to have been identified for the first time.^[1] However, two of them have been reported previously.

Tian *et al.* reported as new “the aberrant splice mutation c.621 (-1A>G) in exon 3 of the ATP2C1 gene from the patient FHHD-3”.^[1] However, the authors did not indicate any gene to properly address the reported mutation making proper localization of the reported mutation along the ATP2C1 gene difficult. Nevertheless, the coding region surrounding the mutation as reported in Figure 1e of Tian *et al.*^[1] (TCT AAT AAG CTG ATC T; underlined is the mutated site), overlaps with the intron 2/exon 3 region of the ATP2C1 gene as reported previously by Sudbrak *et al.* [Table 1].^[1,2] Moreover, in a previous report, Fairclough *et al.* described a mutation (patient NC12, mutation 118 [-1G>A], aberrant splicing in intron 2) that is identical to that reported to be new by Tian *et al.* (patient FHHD-3, mutation 621 [-1A>G] aberrant splicing in exon 3).^[1,3]

In addition, two further mistakes may also be noticed in Tian *et al.*'s paper.^[1] First, the mutation reported by Tian *et al.* would be a single nucleotide substitution A>G on the last nucleotide of intron 2 and not of exon 3 as reported by Tian *et al.*^[1] [see also Table 1 in Fairclough *et al.*].^[3] Second, the adenine at position-1 of the splice site of intron 2/exon 3 is present in the mutated sequence of the ATP2C1 gene, whereas guanine is in the original position and not vice versa as reported by Tian *et al.*^[1-3] Thus, the mutation reported in the ATP2C1 gene in patient FHHD-3 is not new and has not been correctly reported (neither for corresponding nucleotide position [118, and not 621] nor nucleotide replacement [G>A and not A>G, is the correct mutation]).

Further analysis of the manuscript indicated some more inconsistencies. Tian *et al.* referring to the patient SHHD-5 described a new missense c. 666T>C in exon 3, generating a glycine in the place of arginine [R66G].^[1] However, while glycine is coded by four codons (GGT, GGC, GGA, and GGG), the arginine is coded by six codons (CGT, CGC, CGA, CGG, AGA, and AGG). Therefore, what has been reported by Tian *et al.* may not be correct.^[1] Besides, according to the reported mutation, if thymine was replaced with cytosine in the unique codon encoding for an arginine containing a thymine (CGT), one generates CGC which is still coding for an arginine. However, something interesting comes up if the correct reading frame of the ATP2C1 is considered [see Table 1 in Sudbrak *et al.*].^[2] The surrounding sequence of the ATP2C1 gene where the mutation c. 666T>C in patient SHHD-5 occurs [Figure 1g in Tian *et al.*], presents the reading codon frame CAT AGG CGA GCC TTT (encoding for His-Arg-Arg-Ala-Phe, respectively; underlined is the mutation site).^[1] First, the codon CGA, where the mutation is located, is codon 55 and not codon 66, as reported by Tian *et al.* (for the correct coding sequence, relative frame and corresponding amino acid sequence, see <http://www.ncbi.nlm.nih.gov/nuccore/AF181120>).^[1] Second, in the mutation c. 666T>C, cytosine was replaced with thymine (and not 666T>C - which would have meant that thymine was replaced with a cytosine), which would generate a TGA codon which is a STOP codon. The codon CGA could be mutated encoding for a glycine replacing thymine with cytosine. Furthermore, this mutation has been previously described.^[4] Interestingly, the same team of authors of the manuscript reported this mutation in exon 13 instead of exon 3 (patient FHHD-8, c. 163C>T), indicating it as “recurrent” [Table 1].^[1,5]

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Conflicts of interest

There are no conflicts of interest.

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