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Letter to the Editor

Pathogenicity of C-terminal mutations in *CDKL5*

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To the editor

It was with great interest that we read the report by Martínez et al. [1] entitled "*CDKL5* in different atypical Rett syndrome variants: Description of the first eight patients from Spain", and in particular of a late C-terminal missense mutation in *CDKL5*.

The mutation described, p.Pro976Leu (c.2927C>T) was identified in a female patient with Rett syndrome (RTT) with regression of late onset. The patient had very mild symptoms in comparison with the others in the report and most strikingly, had never had any seizure episodes. This is in contrast to the general description of patients with *CDKL5* mutations [2–4], characterized by early-onset seizures, usually difficult to control. The mutation in this patient was de novo and X-chromosome inactivation (XCI) in the patient's lymphocytes showed a random pattern of inactivation.

We propose that the effect of this missense mutation is minimal due to its position along the *CDKL5* gene. Recently, we reported an alternate *CDKL5* protein isoform, which differs from the recognized isoform at the C-terminal end at exon 18 (GenBank reference sequence NM_003159.1: c.2713) onwards [5]. The C-terminus of the newly-identified isoform is encoded by an alternatively-spliced exon 18, which extends into intron 18 by at least 170 bases. The presence of an in-frame termination codon in this sequence means that translation beyond exon 18 does not occur in this isoform.

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As the missense mutation p.Pro976Leu is located on exon 20, the mutation would only affect the previously-recognized isoform (GenBank reference sequences NM_001037343 and NM_003159). Expression analysis in different human tissues indicates that the initially recognized isoform is the minor isoform [5], and most abundantly expressed in testis. In contrast, the newly-identified isoform is expressed in all tissues, highest in parts of the brain, and is likely to be of greater physiological importance.

To the best of our knowledge, only three other C-terminal *CDKL5* variations in exons 19, 20 or 21 have been reported in patients with RTT or a related disorder. One of these is also a missense variation, p.Val999Met (c.2995G>A), reported as a polymorphism by Intusoma et al. [6] and has a heterozygosity of 0.118 (NCBI dbSNP, rs35693326). The other two variations are nonsense mutations, p.Arg952X and p.Arg970X. The latter mutation (p.Arg970X, c.2908C>T) was reported in a female patient with a Rett-like phenotype, and late-onset seizures at 17 mo [7]. Parental screening was limited only to the mother, and XCI studies were not carried out.

The other nonsense mutation p.Arg952X (c.2854C>T) was identified in a female with severe mental retardation without RTT features, and seizures starting from 11 mo [6]. Familial screening found the same mutation in the grandmother, mother and half-sister of the patient. A difference in phenotypes could not be attributed to skewed XCI. Furthermore, population screening revealed an allele frequency of 0.8%, suggesting that although rare, the truncating variation is not likely to be pathogenic.

In all, the existing data indicate that C-terminal mutations in *CDKL5* should be interpreted with care.

Although the role of the initially recognized isoform in disease pathogenesis should not be completely ruled out, mutations affecting only this isoform may have little or no effect in later development. Truncating mutations in this region should not be assumed to be pathogenic and *in vitro* expression of missense mutations, in particular, may be required to determine the functional consequences (if any). In the absence of *in vitro* functional studies, protein substitution programs may be of some use to predict whether the purported amino acid changes may be tolerated, but such interpretations should still be considered as tentative.

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