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CORRESPONDENCE

Response to Riccardi et al.

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Exome sequencing and other next-generation sequencing technologies have made it possible to acquire genomic sequencing data individuals who are likely to have a monogenic disorder. However, finding the causative variant out of more than 100,000 exonic variants identified can be a challenging task.[1] Genome sequencing will yield even an order of magnitude more variants out of which the pathogenic one must be selected.[2] For Down syndrome and fragile X syndrome, the variants are found quite easily as these neurodevelopmental disorders are relatively common.[3] However, for the remainder of individuals with a neurodevelopmental disorder, the identification of the causal variants can be a tour de force as variants in more than 2,000 genes can cause the disorder.[4]

Riccardi et al.[5] describe four individuals with intellectual disability (ID) and a variant in *MED12*. They all have de novo missense variants in *MED12* and display a phenotype similar to the variable one described by Polla et al.[1] The authors suggest that milder ID and syndactyly are more frequent than previously thought in female individuals. Mild ID and syndactyly were reported in three of the four patients. Only one of the ten patients described by Polla et al.[1] had mild ID and in two patients syndactyly was noticed. Although this is important, the number of female patients added to the total number of patients is limited as there are now a total of 15 females with missense de novo variants in *MED12* described. However, I agree with the authors that mild ID and syndactyly are part of the spectrum of *MED12*-related disorders, which can range from severe syndromic ID, including absent speech, hearing loss, nystagmus, and syndactyly, to individuals with mild nonsyndromic ID or maybe even no ID at all, but with other symptoms, such as a thin corpus callosum.

However, even with the identical recurrent de novo p.Arg1138Trp variant, the phenotype can differ among individuals.[2] One of the individuals had strabismus, nystagmus, patent ductus arteriosus, and lambdoid synostosis, whereas the other had hyperopia, a large fontanel, a prominent forehead, bitemporal narrowing, and small, dysplastic, low set, posteriorly rotated ears with an auricular tag on the left side. We suspect that this is caused by differential X-inactivation patterns and/or stochastic events specifically addressing the head area and the brain during critical stages of development. It is unfortunate that we can only test for X-inactivation in blood, saliva, and fibroblasts of affected individuals, and not in neuronal tissues.

So, a pathogenicity test is needed that can prove that these *MED12* variants can be causative. As variants in more than 2,000 genes can cause ID,[4] without additional evidence a missense *MED12* variant cannot be unambiguously called pathogenic. We propose an male isogenic neuronal cell line model in which we can introduce the missense variants by a techniques such as CRISPR-Cas. Since MED12 influences the expression of other genes, we expect to find a specific subset of genes that are differentially expressed in patients. The discovery of such patterns would help in future diagnostics and determine the causality of the *MED12* variants. I therefore strongly support the idea of submitting all potentially pathogenic variants in known genes to variant databases and gene matching platforms to establish the phenotypic spectrum and for further causality testing.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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