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CORRESPONDENCE

Correspondence on "De novo variants in *MED12* cause X-linked syndromic neurodevelopmental disorders in 18 females" by Polla et al.

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One of the current main challenges of clinical genetics is the interpretation of massive amounts of genetic data obtained by now widely available technologies such as genome or exome sequencing or large gene panels. In certain cases, variants are detected but not returned to the prescribing clinician if the phenotype previously associated with the identified gene does not correspond to the patient's presentation. Indeed, according to the ClinGen Sequence Variant Interpretation Recommendations for de novo criteria (PS2/PM6) (https://clinicalgenome.org/site/assets/files/3461/svi_proposal_for_de_novo_criteria_v1_0.pdf), a higher number of points are awarded to de novo variants if the phenotype is highly specific for a given gene, while de novo evidence is not used for variant classification if the phenotype is not consistent with the gene. Comprehensive phenotypic descriptions of patients with variants in recently described and relatively uncharacterized genes are therefore critically needed. Polla et al.[1] gathered an international cohort of 11 female patients with de novo missense variants in the *MED12* gene (Xq13.1), allowing the description of a new homogeneous neurodevelopmental phenotype, partially overlapping with the phenotype previously reported in male patients. We now describe four additional female patients that carry de novo missense variants in *MED12* (NM_005120.3) and present a similar phenotype to that outlined by Polla et al. (Supplementary Table S1). The following variants were identified by exome or large gene panel sequencing: c.1547G>A (p.Arg516His), c.2669T>A (p.Ile890Asn), c.3412C>T (p.Arg1138Trp), and c.3935T>C (p.Leu1312Ser). These variants clustered around the missense variants that have been previously described in female patients with the *MED12*-related phenotype.[1,2] All four variants were absent from population databases. One of these variants, p.Arg1138Trp, has been identified in two unrelated female patients by Polla et al. There was a likely pathogenic ClinVar entry for another variant, p.Arg516His, with no clinical information available for this case. All four variants were predicted to be deleterious by the majority of in silico pathogenicity prediction tools. The birth weight of our patients was within the normal range. All four patients had an intellectual disability, though it was severe only in one case. Severe speech difficulties were highlighted in the series described by Polla et al., which was consistent with findings in our series. Three patients had delayed speech and language development, while one patient developed no speech. Behavioral abnormalities, such as attention deficit and difficulties in social interactions, were present in all four patients. All patients had nonspecific facial features that included posteriorly rotated ears (2/4), thin lips (2/4), epicanthus (2/4), high or large forehead (2/4), as well as hypertelorism (1/4), anteverted nares (1/4) and thin eyebrows (1/4). One patient presented preauricular pits and tags, as has been previously described in female patients with Hardikar syndrome carrying loss-of-function variants in *MED12*.[3] Dental anomalies were observed in two patients and included small widely spaced teeth with a supernumerary incisor in one case and large incisors in another case. Syndactyly was present in three of four patients, including bilateral syndactyly of toes II–III (2/4), bilateral syndactyly of toes IV–V (2/4), as well as unilateral syndactyly of fingers III–IV (1/4) and minimal bilateral syndactyly of fingers III–IV (1/4). Conductive hearing loss was observed in two patients. Ophthalmological anomalies were present in three individuals, with two of them presenting hypermetropia with astigmatism and strabismus, and one showing a lacrimal duct atresia and stellate iris patterns. Two patients had chronic constipation, one of whom also presented an anteriorly placed anus. Tetralogy of Fallot was present in one patient. Magnetic resonance imaging (MRI) was performed in all four patients and was abnormal in one patient, showing a delay in myelinization, enlarged ventricular system, and white matter anomalies. Angiomas were observed in two patients. Consistent with findings by Polla et al., one patient in our series had a skin pigmentation anomaly. X-inactivation analysis was performed on blood lymphocytes from three patients and was found skewed, ranging from 84% to 100%, in concordance with the study by Polla et al. In one of these patients, 100% skewing was observed in both blood and buccal cells.

While a number of different phenotypic elements described by Polla et al. were present in our series, we found that one of the most prominent features was syndactyly (3/4 patients). In the study by Polla et al., syndactyly was more frequent in female patients with loss-of-function variants (5/7) than in patients with missense variants (2/11). Our findings suggest that syndactyly is a key element of *MED12*-related phenotype in females associated with both loss-of-function and missense variants. Another difference between the Polla et al. study and our series was the proportion of patients with severe intellectual disability (8/11 in Polla et al. and 1/4 in this study). Thus, our cases with milder forms of intellectual disability extend the phenotypic spectrum of the *MED12*-related disorder, showing that there can be a greater variability in intellectual impairment.

At the time of diagnosis, all centers reported difficulties in classifying the identified *MED12* missense variants in the absence of a clearly defined *MED12*-related phenotype in females. Even though our laboratories routinely submit variants in novel genes to GeneMatcher, *MED12* variants were not submitted since pathogenic variants in this gene have been previously reported in hemizygous males, while found only in a minority of carrier females with nonsyndromic intellectual disabilities.[4] The study of Polla et al. illustrates how sharing cases with atypical phenotypic presentations via variant databases and gene matching platforms can define novel syndromes with different phenotypic presentations and/or modes of inheritance for a given gene.

In conclusion, we report four female patients with de novo missense variants in *MED12* presenting a phenotype similar to that described by Polla et al. We thus expand the mutational spectrum of *MED12* by reporting three novel pathogenic variants and further define the recurrent p.Arg1138Trp variant as a potential mutational hotspot. Based on the phenotype of our patients, we also suggest that syndactyly and milder intellectual disability can be more frequent than previously thought in female patients with

de novo missense variants in *MED12*. Finally, we stress the importance of submitting cases with atypical phenotypes to variant databases and gene matching platforms, even if the gene has been previously described, to uncover novel phenotypic constellations.

DATA AVAILABILITY

The authors confirm that all data underlying the findings are fully available without restriction by request. All relevant data are within the paper and its Supporting Information files. All four *MED12* variants were submitted to LOVD-MED12 database (https://databases.lovd.nl/shared/genes/MED12).

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"Novel missense variants in MED12 *expand the mutational spectrum of* MED12*-related syndrome in females" Riccardi et al.*
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ETHICS STATEMENT

The data on *MED12* variants do not include any identifying information. These data correspond to retrospective analysis that does not require ethics committee approval at our institution. The appropriate consent was collected from each patient.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41436-021-01208-8.

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