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Editorial - Late Breaking Chromosomes

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Expanded Phenotypic Spectrum or Multiple Syndromes?

From time to time patients with a spectrum of phenotypes that do not clearly fit into a known syndrome are encountered. Then clinical geneticists have to decide whether this particular patient has a syndrome with an expanded phenotypic spectrum or something entirely different. As a matter of routine, chromosomal microarrays are performed [Miller et al., 2010]. The outcome of this test may be a chromosomal deletion or may be unremarkable, which then prompts whole-exome or even whole-genome sequencing, or, if a chromosomal deletion encompasses several OMIM genes, one has to consider a contiguous gene syndrome. For this, the genes affected by the deletion should be gene dosage sensitive, i.e., loss of one allele will provoke a clinical phenotype by a dominant mechanism. Such cases of contiguous gene syndromes are frequently seen in pediatric genetics. In addition, patients with a combination of a chromosomal deletion and an autosomal recessive disorder have been reported [Flipsen-ten Berg et al., 2007]. This constellation arises when a deletion of a segment of one chromosome coincides with a recessive mutation in a gene on the other, intact chromosome. This mechanism, known as "unmasking" of recessive mutations, has been reported for at least 23 cases [Poot and Haaf, 2015].

Whole-exome sequencing has uncovered a third molecular mechanism of double disorders [Posey et al., 2017]. In this class of disorders pathogenic variants were found at 2 or more chromosomal loci. The variants may be both autosomal dominant, either arising after a de novo mutation or being inherited from affected parents, or a combination of recessive and dominant variants. In the latter constellation both parents are unaffected and the child has inherited 2 recessive variants, while the second variant resulted from a de novo mutation. This situation is clearly distinct for digenic inheritance, in which pathogenic variants at distinct loci have been transmitted by 2 unaffected parents. Phenotypically double disorders may appear as overlapping or expanded syndromes, or as 2 completely distinct syndromes altogether. The first situation arises when the pathogenic variants occur in 2 genes that encode proteins participating in a single biochemical pathway or being part of a protein complex. Two completely distinct syndromes occur when the encoded, mutant proteins are not functionally related.

Dual diagnoses were found in 4.9% of referrals investigated by whole-genome sequencing [Posey et al., 2017]. In those cases, some 67% of variants arose de novo in autosomal dominant disease genes and 52% were in X-linked disease genes. In 45% of patients with 2 monoallelic variants both were de novo, while pathogenic copy number variations were found in 12% of cases with multiple diagnoses. For autosomal recessive and complex disorders parental consanguinity was found in roughly half of the families, albeit that again in half of those cases a de novo variant has arisen. In the literature, familial consanguinity has often been reported with complex, in particular neurodevelopmental, disorders with a significant contribution of de novo variants [Lupski et al., 2011; Karaca et al., 2015; McKenna et al., 2018].

Recently, *Molecular Syndromology* has published a case report on a consanguineous family with 2 children with autism spectrum disorder and skeletal abnormalities in which 3 candidate homozygous variants were identified [Farajzadeh Valilou et al., 2020]. An article in the cur-

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rent issue describes a patient with a 15.7-Mb contiguous deletion of region 13q22q31.3, containing among others the *MIR17HG* gene, and a hemizygous variant of the *COL4A5* gene [Demir et al., 2022]. The *MIR17HG* gene has been associated with autosomal dominant Feingold syndrome type 2. The variant in the *COL4A5* gene, which is "unmasked" by the hemizygous deletion, is thought to be responsible for the hematuria and proteinuria of the patient. The latter phenotypes are consistent with autosomal recessive Alport syndrome. In a second article in this issue, a patient with co-occurring Wilson disease and atypical galactosemia is described [Doğulu et al., 2022]. Upon targeted sequencing of a panel of 450 genes for inherited metabolic diseases, a homozygous c.2293G>A (p.Asp765Asn) variant in the *ATP7B* gene was found. Based on this finding the observed hepatosplenomegaly of the patient was attributed to Wilson disease. Yet, the patient also presented with a cataract and borderline mental capacity, as well as cognitive and speech retardation. The latter probably relates to a homozygous c.1018G>T (p.Glu340Ter) variant of the *GALT* gene. Thus, this patient is an example of a dual disorder with genomic variants at 2 distinct loci.

These reports represent a growing number of patients with a broad phenotypic spectrum that turns out to include more than one separate syndrome. In these cases the underlying genomic variants have been uncovered with genome-wide screening methods such as chromosomal arrays and whole-exome or whole-genome sequencing. *Molecular Syndromology* welcomes in particular such case reports combining in-depth, structured phenotyping with elucidation of multiple genomic variants by genome-wide methods [Farajzadeh Valilou et al., 2020; Demir et al., 2022; Doğulu et al., 2022].

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