Genetics inMedicine | CORRESPONDENCE

High-frequency low-penetrance copy-number variant classification: should we revise the existing guidelines?

Chromosomal microarray analysis is a first-tier clinical diagnostic test utilized in individuals with neurodevelopmental disabilities or congenital anomalies, as well as in pregnancies with major fetal sonographic malformations. In addition, recently microarray testing came into use in pregnancies with normal ultrasound, able to detect clinically significant findings about 1% of such cases.

A crucial issue in microarray testing is the consistency of the terminology defining the clinical significance of copy-number variants (CNVs) throughout the medical community. In 2011, the American College of Medical Genetics and Genomics (ACMG) introduced its later widely accepted classification,[1] wherein variants are assigned to three groups: pathogenic, variants of uncertain clinical significance (VOUS), and benign. VOUS are further subdivided into likely pathogenic; likely benign; and uncertain clinical significance, no subclassification (NOS). Recently updated ACMG guidelines formulated a quantitative scoring framework, still using the five-tier categorization system.[2] European guidelines support this classification, assigning CNVs to five classes: benign (class 1), likely benign (class 2), uncertain clinical relevance (class 3), likely pathogenic (class 4), and pathogenic (class 5).

Most CNVs can be clearly classified in one of the five categories. However, a rather common subgroup of CNVs with low-penetrant susceptibility loci for neurodevelopmental disorders (such as intellectual disability, autism, epilepsy, psychiatric and behavioral disorders) does not clearly fit into any category. Examples of the common low-penetrant variants, reported in over 1/1000 cases in normal population,[3] include proximal 1q21.1 duplication, 15q11.2 deletion, 15q13.3 duplication, and 16p13.11 duplication (Supplementary Table 1). Low penetrance is commonly estimated to be 5–10%, and the risk for clinically significant manifestations of such genomic variants is difficult or even impossible to precisely predict. Penetrance might be influenced by numerous factors, including family history, inheritance, additional medical problems, the presence of additional CNVs, and ethnic background. In addition, following the establishment of national biobanks, which made it possible to analyze the medical outcomes of middle- and older-aged CNV carriers, many of these variants were found to exert profound health effects (including increased risk of diabetes, hypertension, obesity, and renal failure) in carriers who had largely escaped neurodevelopmental morbidity.[3]

The manner of classification of common low-penetrant variants has raised considerable controversy among laboratories. Some centers classify such findings as purely pathogenic, leaving the interpretation of the clinical significance and the explanation of variable expressivity and low penetrance to the genetic counseling session. However, such annotation might mislead patients to believe that the finding unequivocally leads to neurodevelopmental disorders, causing unnecessary anxiety and even unjustified pregnancy termination. In addition, in many clinical cases of complicated phenotypes involving intellectual disability, dysmorphism, and congenital malformations, the detection of a CNV may not explain the phenotype, and further genetic testing should be recommended to search for a single gene–related disorder.

Other laboratories classify low-penetrant variants as VOUS, whether likely pathogenic, likely benign, or NOS. This lack of uniformity in the classification poses a considerable challenge during genetic counseling and confuses patients' perception of the pathogenicity, especially when the variant is annotated in different ways in the same family.

One possible solution to overcome the described issues is the establishment of a new, separate category of CNVs called high-frequency low-penetrant variants (HFLP). This classification is designated to include all variants with a penetrance below 10% and a frequency of over 0.1% in a healthy population. By highlighting the commonness and the low pathogenicity of such findings, this definition has an advantage over previously proposed descriptions such as "risk variant" or "susceptibility loci." This uniform categorization can be expected to facilitate the interpretation of appropriate CNVs by the laboratory, assist the genetic counselors, and enhance patients' understanding of pathogenicity.

Management of HFLP findings is also controversial, differing among laboratories and countries. One approach is to report only a limited number of such variants. For example, in Belgium, HFLP findings are reported only when they are associated with structural malformations (for which ultrasound follow-up is warranted) or if the risk of a severe phenotype is sufficiently high.[4] Recently, a uniform consent form for prenatal microarray testing was introduced in Israel, including a list of four HFLP CNVs, with an option not to be informed of such findings. An additional option is uniform nonreporting, without preliminary counseling of the patients regarding the possibility of such findings. This possibility might not be suitable for the contemporary setting, as many patients today demand to be informed of all possible findings, and not doing so could have medicolegal implications.

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A better understanding of specific HFLP penetrance values in different populations can be achieved by establishing local CNV databases for affected individuals and control populations. This is also true for single-nucleotide variations identified by next-generation sequencing, including coding as well as noncoding regions. One of the important advantages of such databases is that they allow for better estimation of the penetrance of recurrent CNVs in specific populations. For example, incomplete penetrance of congenital scoliosis in patients with proximal 16p11.2 microdeletions encompassing the *TBX6* gene was recently explained by the concomitant presence of a common haplotype in the second *TBX6* gene allele, in accordance with the two-hit hypothesis. Another example of the two-hit hypothesis is the higher burden of additional rare CNVs in patients with 22q11.2 deletion and intellectual disability compared with normal carriers.

In summary, we propose the introduction of a new, separate category of known low-penetrant susceptibility loci for neurodevelopmental disorders, defined as HFLP CNVs, into the current classification of variants. In the contemporary era of increasing genome-wide genetic testing, we believe this category is important not only to describe the results obtained by microarray technology, but also to categorize variants revealed by exome and genome sequencing.

SUPPLEMENTARY INFORMATION

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DISCLOSURE

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