Genetics inMedicine | CORRESPONDENCE

Response to Maya et al.

We thank Maya et al.[1] for their correspondence. The recently published American College of Medical Genetics and Genomics (ACMG)/Clinical Genome Resource (ClinGen) technical standards for the interpretation and reporting of constitutional copy-number variants[2] (CNVs) serve as an initial template for guiding genetics professionals in the classification of constitutional CNVs. It is expected that these technical standards will evolve over time as we learn more about genomic variation and can better articulate how to standardize methods for interpretation. Maya et al.[1] raise an important point regarding reporting CNVs that have reduced penetrance and are not rare in the population. The ACMG/ClinGen group considered this issue while developing the new technical standards and will elaborate further here.

We agree that different approaches to categorizing CNVs associated with reduced penetrance and/or variable expressivity (such as proximal 1q21.1 duplications, 15q11.2 deletions, 15q13.3 duplications, etc.) have historically contributed to classification discrepancies between clinical laboratories. A telling example is the presence in ClinVar of 27 duplications involving the 15q13.3 (breakpoint 4 to breakpoint 5) region, including both the *CHRNA7* and *OTUD7A* genes. These duplications, while similar in genomic content, have clinical classifications ranging from pathogenic to benign. While other factors could contribute to such discrepancies (such as when a CNV was last evaluated, e.g., one pathogenic variant was last evaluated in 2010, and may no longer reflect the laboratory's current assessment of that variant), the fact that CNVs in these regions are associated with variable phenotypes and are frequently observed in apparently unaffected parents likely also plays a role. Reduced penetrance alleles create an apparent discrepancy between the pathogenic nature of a variant and the clinical relevance to the patient being studied, and as such we have recommended a deliberate uncoupling of these concepts in the updated guidance.[2]

This issue is not unique to CNVs. There are many examples of Mendelian disease genes in which sequence variants do not always lead to overt clinical presentations. Examples include the c.1100delC (p.Thr367fs) variant in *CHEK2* (associated with an approximate two- to threefold increased risk of breast cancer over that of the general population[3,4]), and the c.3920T>A (p.Ile1307Lys) variant in *APC* (associated with an approximate twofold increased risk of colon cancer over that of the general population among Ashkenazi Jewish individuals[5]). The latter has been reported in ClinVar by 20 different single-star submitters, with classifications of likely pathogenic, uncertain significance, likely benign, and "risk factor" (https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000000822.7).

ClinGen,[6] recognizing the need for consensus in professional practices for the assessment and classification of these challenging variants, formed the ClinGen Low Penetrance/Risk Allele Working Group (https://clinicalgenome.org/working-groups/low-penetrance-risk-allele-working-group/). As one of its first mandates, the group conducted a Delphi survey in 2019 to assess preferences within the clinical genomics community regarding the terminology used to describe low-penetrance variants on a clinical report. A description of the conclusions from that survey is available on the ClinGen website (https://clinicalgenome.org/site/assets/files/4531/clingenrisk_terminology_recomendations-final-02_18_20.pdf) and will be prepared for formal publication at a later date. As a result, the ClinGen Low Penetrance/Risk Allele Working Group has proposed using the descriptor "low penetrance" in addition to the primary variant classification term (e.g., pathogenic) when sufficient quantitative penetrance estimates are available, and the additional descriptor "reduced penetrance" when quantitative penetrance estimates are not available. For example, using this schema, a duplication of the 22q11.21 recurrent region (breakpoints A–D), associated with an estimate of 21% penetrance for neurodevelopmental disorders,[7] could be classified as "pathogenic, low penetrance." Using this same schema, pathogenic variants in the *SMARCE1* gene, which has been more recently associated with spinal and cranial clear cell meningiomas and possible sex-biased penetrance,[8] could be classified as "pathogenic, reduced penetrance," as there are no clear estimates yet of penetrance for this particular disorder. In either scenario, the classification of the variant should be accompanied by a clear statement of anticipated clinical relevance for the reported patient. The working group is now exploring whether the current standards/guidelines used for assessing Mendelian variant pathogenicity[2,9] can be adapted for the evaluation of low-penetrance variants.

We agree with Maya et al.[1] that consistent terminology is needed to reduce both the incidence of interlaboratory discrepancies and potential confusion among clinicians and patients. Ideally, such terminology will be applicable to both copy-number and sequence variants; with increasing ability to reliably call both types of variants from the same platform, we as a community should work toward aligning both our assessment practices and terminology. The definition put forth by Maya et al.[1] identifies "high-frequency low penetrant" variants as "variants with penetrance below 10% and a frequency over 0.1% in a healthy population." This suggestion is practical in the context of recurrent CNVs, where frequency is typically over the 0.1% threshold and penetrance estimates (most frequently in the context

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of neurodevelopmental disorders) are readily available. However, such a term and definition may not be broadly applicable in situations where rare variants are known to be associated with low penetrance. For example, the c.5096G>A (p.Arg1699Gln) variant in *BRCA1* is known to be associated with a lower lifetime risk of breast and ovarian cancer compared with other pathogenic *BRCA1* variants,[10] but the maximum allele frequency in gnomAD is 0.00005 in the European (non-Finnish) population (https://gnomad.broadinstitute.org/variant/17-41215947-C-T). The proposed term may also be difficult to apply to situations where specific estimates of penetrance are unavailable.

We fully recognize the difficulty in developing terminology and definitions for variant interpretation and classification that are applicable in all situations; for this reason, the ClinGen Low Penetrance/Risk Allele Working Group opted to put forth, as a first iteration, intentionally generic terminology recommendations. The working group intends to continue to investigate the scenarios in which different disease communities (e.g., hereditary cancer, cardiovascular disorders, hearing loss, blood disorders, neurodevelopmental disorders) need to describe low-penetrance variants and how they are using the recommended terms. Members of the ACMG/ClinGen Constitutional CNV Technical Standards Committee will continue to participate in these efforts and assess how current and future proposals in terms of the classification and assessments of low-penetrance variants may be best applied to classification of constitutional CNVs. We thank Maya et al.[1] for raising this issue and welcome continued dialogue, suggestions, and feedback.

DISCLOSURE

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