EDITORIAL

Adoption of a "Pathogenic, Predisposing, Risk and Benign" classification of DNA variants for precision medicine – a step forward

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Precision medicine is often at odds with *medical genetics* in classifying gene mutations that have high impact on protein expression or function but do not "cause" disease.

The Case of Chronic Pancreatitis

The classification of *SPINK1* and *CTRC* variants (e.g., *SPINK1* p.N34S and *CTRC* p.G60G) is important because they clearly increase the risk of recurrent acute and chronic pancreatitis by decreasing protection from prematurely activated trypsin in the pancreas.[1-4] These common variants do not "cause" pancreatitis by strict medical genetic definition, but by disrupting protective mechanisms within a complex system and thus facilitating disease development. In short, many medical geneticists and genetic counselors struggle to understand a patient's precision medicine report because the term "pathogenic" is applied by complex disease modelers to describe the effect of a variant on a gene, not based on a criterion of being "disease-causing." This does not fit the script!

One Term with Two Meanings

Classic Mendelian genetics is based on the premise that genetic diseases result from severe mutations in a single gene, leading to rare autosomal dominant, autosomal recessive, or X-linked traits that run in families. Thus, genetic variants are classified as "pathogenic" or "benign," with uncertain classifications of "likely" and "variant of unknown significance."[5] In contrast, precision medicine for common complex disorders is more mechanism-based, utilizing disease modeling and other approaches to predict pathogenic responses of specific specialized cells and systems to injury or stress (i.e., engineering-based rather than case-control based on syndromic phenotype).[6, 7] However, the expanding field of precision medicine must work with medical genetics in defining terms that describe variants affecting the mechanisms of non-Mendelian disorders that make up the majority of non-infectious chronic diseases that represent 90% of US healthcare expenses (CDC stats).

Geneticists have recognized the conundrum of limited insights using Mendelian genetics to understand complex diseases that are linked to hundreds of "risk" variants found in genome-wide association studies (GWAS) that are not disease-causing.[8] The realization that rare, high-effect "pathogenic" variants and common low-effect "risk" variants cannot explain the apparent genetic impact of these diseases was termed "missing heritability."[8] One approach has been to combine the GWAS results into polygenic risk scores (PRS), as described in this issue of SMART-MD JPM by Greer and DeFrancesco-Oranburg (Link to paper).[9] However, "risk" variants typically have minimal independent risk—unlike *SPINK1* and *CTRC* variants that have high risk—only under specific conditions! If these "conditions" exist, then they are "pathogenic." If not, then they are benign.

The point is that there are problems in using the term "pathogenic" in precision medicine (referring to the effect of a variant on a gene) because it causes confusion in medical genetics (referring to the variant's ability to cause a disease). A new classifying category is needed.

SPINK1 as a Case Example for New Terminology

Wang et al.[10] recently proposed a solution to the current pathogenic variant conundrum by proposing to expand the terminology for genetic variants along a spectrum:

(1) **pathogenic** (retaining Medical Genetics meaning)

(2) **predisposing** (new term)

(3) **risk** (as used in PRS)

(4) **benign** (used in contrast to "pathogenic" but may be "predisposing" in some circumstances and context)

This framework bridges the gap between binary classifications and the nuanced reality of variant effects, paving the way for more accurate risk assessment in clinical practice. The new classifier still has limitations, as the effect of the genetic variants are still defined by diseases

The Example of Celiac Disease

A prime example is celiac disease (CeD), where common variants in human leukocyte antigen (HLA) genes are required but not sufficient to cause the condition.[11] In addition, exposure to an environmental factor is required (i.e., gluten), along with a pro-inflammatory trigger (e.g., an episode of viral enteritis). [12] However, framing CeD in a Mendelian genetics framework greatly limits the understanding of the genetics of CeD.

In this issue, Prof. Eamonn Quigley (link to paper) highlights the current problem of a "genetic gap" in CeD. [13] First, he points out that specific HLA-DQA1 / HLA-DQB1 gene variants are necessary but not sufficient to "cause" CeD. These variants are not "pathogenic" but not benign either. Rather, they are "predisposing" to CeD but also "predisposing" to type 1 diabetes, thyroiditis, and other disorders. Second, he points out the "genetic gap" in CeD, where genetics are implicated but not well defined. Although GWAS studies have identified >40 additional "risk" variants, there are no models to make sense of the complexity using case-control approaches. He also notes the limitations of current genetic approaches to CeD, where utility is limited to excluding CeD in patients with symptoms that overlap CeD using genetics.

Thus, precision medicine is needed!

Call to Action

The need for adoption of a new classifier for genetic variants in relation to complex diseases is highlighted in this issue of SMART-MD JPM (Quigley) [13] and previous articles (Waqar) [4]. We recommend that the major professional societies consider integrating the new "predisposing" classifier proposed by Wang et al. into future guidelines. Furthermore, the term "benign variant" must be better defined to distinguish "not disease-causing" from "not affecting the expression or function of a gene product."

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