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EDITORIAL

# Dual genetic diagnoses - underappreciated "double trouble"

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For a long time, the view on medical genetics was dominated by a prototype clinical genetic constellation, in which all affected members of a family were expected to share a pathogenic genotype for a certain gene, whereas this genotype would not be present in any of the unaffected family members. This simplistic understanding has meanwhile been extended to the more general concept of "genetic risk." We now fully appreciate that there is a continuum of genetic disease causations that includes Mendelian variants with high effects, rare variants with moderate effects, and common variants with small effects.

A completely unrelated recent expansion of the "single gene - single disorder" paradigm has apparently received much less attention: the phenomenon of dual genetic diagnoses (DGD). In patients with DGD, pathogenic genotypes for two genes are present, and each of these two genotypes would be disease-causing when occurring in isolation. Initial reports of DGD were about rare monogenic disorders in patients with common aneuploidies [1]. The availability of exome sequencing (ES) as a genome-wide screening tool subsequently resulted in numerous case reports on the combined occurrence of two classical monogenic disorders [2]. Side-findings from the first large-scale ES studies suggested that DGD may account for a significant fraction of patients [3,4]. However, surprisingly few studies have focused on DGD exclusively. Posey et al. [5], by performing a retrospective evaluation of >7,000 ES-analyzed cases, identified DGD in 1.4% of all patients and in 4.9% of genetically diagnosed patients. Two other publications involving large patient series presented similar figures and provided evidence for DGD to be particularly frequent in consanguineous families [6,7]. Notably, these three studies considered only pathogenic and likely pathogenic variants. Taking also variants of uncertain significance into account, the true prevalence of DGD can be expected to even be higher.

The obvious significance of DGD has direct practical implications. From a scientific point of view, case reports that claim "broadening" or "extension" of the phenotype for a single-gene disorder should be viewed with caution. In an extreme scenario, the clinical recognition of a "novel syndrome" may turn out to represent DGD for two known disorders, as nicely exemplified by the case of Fitzsimmons syndrome [8]. Even more important than the impact on the scientific literature are the implications of DGD for affected patients and for their families. In the era of precision medicine, treatment decisions and proper counseling rely on knowing the full extent of the genetic causalities for the observed symptoms.

How can professionals in the field of medical genetics contribute to ensure that instances of DGD are not missed? Physicians should describe all clinical features they observe, avoiding any bias potentially imposed by their experience with overtly similar patients. Regarding the genetic testing strategy, comprehensive approaches such as exome sequencing or genome sequencing should be preferred over arrays or gene panels. Geneticists should have appropriate pipelines for the identification of DGD in place. This means that the evaluation of genetic variants will not stop after a single diagnosis has been reached. Finally, there is a need for increasing awareness for the phenomenon. The Editorial Board of Journal of Biochemical and Clinical Genetics, therefore, welcomes submissions that describe DGD cases or case series.

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