Genetics in Medicine

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CORRESPONDENCE

Response to Gao et al.

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Maintaining clinical diagnoses is critical to dissect horizontal pleiotropy.

We appreciate Gao et al.'s interest in our work. Reciprocally, we must emphasize that their own work in clinical and mouse genetics has been essential to better understand the consequences of *ATP6V1B2* pathogenic variants. In their correspondence, they suggest to consider the diagnosis of dominant deafness and onychodystrophy (DDOD) syndrome rather than deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures (DOORS) syndrome in all individuals with the recurrent truncating pathogenic variant in *ATP6V1B2* (NM_001693.4:c.1516C>T, p.Arg506*), even in presence of intellectual disability or epilepsy, to simplify the diagnostic nomenclature.[1]

Although we strongly agree with the importance of integrating the genotype into the final diagnosis, we do not consider that genotypic information should inevitably lead to a reclassification of a prior clinical diagnosis. The first descriptions of both DDOD and DOORS syndrome were made long before their genetic bases were identified and were then solely based on clinical features. Still today, a clinical diagnosis is usually made before molecular analyses are performed, although we may eventually transition to a "genotype-first" clinical approach in the medium to long term.[2] Accordingly, an individual with all clinical features of DOORS syndrome is currently likely to receive this diagnosis, independently of the genotype.

In the cohort that we reported, four individuals with the recurrent *ATP6V1B2* pathogenic variant had all five main characteristics of DOORS syndrome, namely deafness, onychodystrophy, osteodystrophy, intellectual disability, and epilepsy. Seizure onset was in the first year of life for three of them, while the remaining one had his first seizure at the age of 52.[3] Of note, the individual with DOORS syndrome recently reported by Zadori et al.[4] was included in our cohort (individual 9)[5] since we performed the genetic analyses in this patient. When considering the five characteristic features of DOORS syndrome and the onset of seizures in early life as diagnostic criteria, 3/9 individuals would still have received a diagnosis of DOORS syndrome in a pediatric clinical genetic evaluation. This illustrates that even strict clinical criteria (stricter than the criteria used for recruitment in our DOORS syndrome study initiated in 2010) could not always discriminate DOORS syndrome caused by *TBC1D24* pathogenic variants from DOORS syndrome caused by an *ATP6V1B2* pathogenic variant.

As Gao et al. rightly point out, it is not excluded that a certain proportion of individuals reported with DDOD in childhood could develop epilepsy later in their life, or that intellectual disability could have been missed at an early age. It would be of the greatest interest to ensure follow-up of these individuals to report new clinical findings, if applicable. Should they develop such symptoms, it would reinforce the difficulty to distinguish DDOD from DOORS syndrome.

There are numerous examples of phenotypic heterogeneity, where pathogenic variants in the same gene are associated with distinct phenotypes. For example, individuals with pathogenic variants in *TBC1D24* do not always have all five features of the DOORS acronym; they rather can have any combination of those features. Some have only deafness, and some do not have intellectual disability, and they are thus not diagnosed with having DOORS syndrome.[6] It is less frequent in clinical genetics for a specific pathogenic variant to be associated with different Mendelian conditions, a phenomenon often referred to as horizontal pleiotropy.[7] Phenotypic heterogeneity and horizontal pleiotropy are thus both observed in individuals with *ATP6V1B2* pathogenic variants, as several conditions are now associated with such pathogenic variants, i.e., Zimmerman–Laband syndrome type 2, DDOD syndrome, and DOORS syndrome, and there are even reported individuals without sufficient criteria to receive either of these clinical diagnoses.

As stated in our article, TBC1D24 was previously shown to interact with V-ATPase subunits.[8] More recently, the molecular roles of NCOA7, a member of the TLDc protein family like TBC1D24, was studied by Castroflorio et al. They generated a knockout mouse model and showed that *Ncoa7* regulates V-ATPase formation and function in the brain.[9] This further supports the existence of interactions between ATP6V1B2 and proteins of the TLDc family. Interactions specifically between ATP6V1B2 and TBC1D24 could in part explain the similarities in the phenotypes caused by pathogenic variants in those genes.

DDOD and DOORS syndromes clinically overlap, and their underlying pathophysiology probably involves a common molecular function. We therefore propose to maintain the diagnosis as determined based on clinical features, but to specify the causal gene once genotypic information is available. Following the principles of McKusick in the *Mendelian Inheritance in Man*, we think a condition should be ideally named in a medically informative and meaningful way.[10] Sometimes what is the most useful is to use acronyms of the clinical features present in the patients, other times it is using a gene name, or an eponym that people will remember better than gene names; it depends on each condition. As an example, individuals could be diagnosed as having DOORS syndrome caused by an *ATP6V1B2* pathogenic variant or DOORS syndrome caused by *TBC1D24* pathogenic variants. Maintaining clinical diagnoses is indeed critical to define horizontal pleiotropy and eventually dissect the molecular pathophysiology of Mendelian disorders.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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