Genetics in Medicine

CORRESPONDENCE

Correspondence on "DOORS syndrome and a recurrent truncating *ATP6V1B2* variant" by Beauregard-Lacroix et al.

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We read with great interest the article by Beauregard-Lacroix et al. entitled "DOORS syndrome and a recurrent truncating ATP6V1B2 variant",[1] in which the same truncating variant c.1516C>T (p.Arg506*) in *ATP6V1B2* were identified in nine patients with deafness, onychodystrophy, osteodystrophy, and mental retardation (DOORS) syndrome and in two families with dominant deafness–onychodystrophy (DDOD) syndrome.

We appreciated Beauregard-Lacroix et al.'s study and believe that their findings are crucial to expand the disease phenotype associated with *ATP6V1B2* c.1516C>T (p.Arg506*). In the past, the same variant was reported to cause DDOD syndrome.[2] Through this correspondence, we intend to discuss about the diagnosis of DOORS syndrome in nine patients belonging to eight unrelated families. It seems important to question whether these patients with *ATP6V1B2* c.1516C>T (p.Arg506*) should be diagnosed with DDOD syndrome. In addition, is the clinical diagnosis of DOORS syndrome justified in these cases? In the present cohort, nine patients were clinically diagnosed with DOORS syndrome based on the clinical diagnostic criteria (≥3 of the 5 main clinical features). The authors also mentioned that all previously reported patients with DOORS syndrome had an autosomal recessive inheritance, while *ATP6V1B2* c.1516C>T (p.Arg506*) was associated with an autosomal dominant inheritance. We raise the question on the reclassification of the phenotypic expression based on the genotypic findings by summarizing the clinical features of DDOD/DOORS cases with genetically identified causes (Supplementary Table 1).

PHENOTYPE OF PATIENTS WITH THE CLINICAL DIAGNOSIS OF DDOD SYNDROME AND *ATP6V1B2* C.1516C>T (P.ARG506*)

ATP6V1B2 c.1516C>T (p.Arg506*) has been reported as the only pathogenic variant in patients with DDOD syndrome by several previous studies.[2–4] DDOD syndrome is an autosomal dominant disorder, and the main clinical features of this syndrome include deafness and onychodystrophy,[3] which overlap with the core features of DOORS syndrome. Although the main differentiating clinical features between DDOD and DOORS are seizures and developmental delay/intellectual disability, these features are not specific for DOORS syndrome as they have also been observed in some patients diagnosed with the DDOD syndrome. For example, unsatisfactory speech rehabilitation has been reported in a patient with DDOD syndrome 7 years after cochlear implantation, although the implanted cochlea worked well and the hearing loss achieved effective compensation, which indicates possible learning and memory problems in DDOD patients.[3] In another family with DDOD syndrome, the mother (age: 21 years) was diagnosed with mild intellectual disorder, as assessed by the Hastgawa Dementia Scale, with a score of 29 (normal value = N31), while her 17-month-old son presented with a mental age of 9 months according to the results of the Denver Developmental Screening test.[3] Regarding the seizures, in one patient with the clinical diagnosis of the DDOD syndrome and *ATP6V1B2* c.1516C>T (p.Arg506*) reported by Beauregard-Lacroix et al., seizures were observed at the age of 36 years. We proposed that, in DDOD patients, the pre-existing central nervous system disorders can be easily neglected at an early age. Although the number of adult patients with the DDOD syndrome at present is extremely small to determine whether they will develop seizures later in the life, the above evidence as well as the phenotypic outcomes from the *Atp6v1b2* c.1516C>T knockin mouse model[4] support the fact that seizures and developmental delay/intellectual disability could present in the DDOD patients.

PHENOTYPES IN PATIENTS WITH THE CLINICAL DIAGNOSIS OF DOORS AND *TBC1D24* PATHOGENIC VARIANTS

DOORS syndrome has been documented as autosomal recessive disorder. Biallelic variants in *TBC1D24* account for 50% of all cases with strictly defined DOORS syndrome (composed of all five features making the DOORS acronym).[5] Considering the fact that the clinical features of DOORS syndrome overlap with other syndromes, including DDOD syndrome, Coffin–Siris syndrome, and inherited glycosylphosphatidylinositol deficiencies, the cohort was clinically diagnosed with DOORS, which may include some individuals with disorders that overlap with, but are different from, the DOORS syndrome, as also mentioned by Campeau et al.[6] Notably, the clinical phenotypes of the cohort of individuals with clinically diagnosed DOORS syndrome and the *TBC1D24* biallelic variants is highly homogeneous considering that all five main features were present in each patient. In addition, seizures in *TBC1D24*-associated DOORS syndrome usually start in the first year of life,[5] which is different from the late-onset seizures in patients with *ATP6V1B2* c.1516C>T (p.Arg506*)–associated disorders. We hence considered adding the five main characteristics of DOORS as criteria for the diagnosis.[6] In addition, we have discussed the recommendations of defining seizures observed in the early life as one of the DOORS diagnostic criteria.

PHENOTYPES IN PATIENTS WITH THE CLINICAL DIAGNOSIS OF DOORS PATIENTS AND *ATP6V1B2* C.1516C>T (P.ARG506*)

In Beauregard-Lacroix et al.'s cohorts, nine individuals were clinically diagnosed with DOORS syndrome and heterozygous *ATP6V1B2* c.1516C>T (p.Arg506*). Seizures and developmental delay/intellectual disability were absent in some patients of this cohort. For instance, four of the nine cases did not show seizures, while another three showed late-onset first seizures at the age range of 39–52 years, while two cases did not present with any developmental delay and/or intellectual disability. All nine patients displayed some identical phenotypes, including deafness and onychodystrophy, which is in accordance with the diagnosis of DDOD syndrome. Notably, DOORS syndrome was documented as autosomal recessive disorder, although the inheritance was autosomal dominant in nine cases.

Recently, Zadori et al. also reported a Caucasian male patient with heterozygous *ATP6V1B2* c.1516C>T (p.Arg506*) who died at the age of 72 years. Although the patient presented with all clinical features of DOORS syndrome, the patient's first-time seizure age was 52 years and the inheritance was autosomal dominant.[7]

In summary, we suggest that, in the cohorts with *ATP6V1B2* c.1516C>T (p.Arg506*), the diagnosis of DDOD syndrome should be considered. Whether the already reported DDOD patients develop seizures and intellectual disability later in life needs to be carefully followed up. As it is difficult for clinicians to discriminate between these two disorders based on the symptoms alone, especially during the early childhood phase, we suggest the integration of genetic-based diagnosis into the existing clinical criteria for a clear distinction. These efforts are based on the general desire to simplify the overall diagnostic criteria.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41436-021-01167-0.

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