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To the Editor:

We read with great interest the article "Predicted Protein Structure Variations Indicate The Clinical Presentation of *CYP4V2*-Related Bietti Crystalline Dystrophy" by Chan et al.[1] In the study, the authors analyzed the relationship between different *CYP4V2* variants and disease severity in 21 patients with Bietti crystalline dystrophy (BCD) from 19 unrelated families.

The study is interesting as it establishes protein structure predictions of *CYP4V2* variants using protein structure modeling, which is novel.[1] Several studies using retinal imaging to predict visual acuity in BCD have demonstrated a good correlation between the best-corrected visual acuity with preservation of the ellipsoid zone[2] and choriocapillaris.[3] These image-predicting parameters could explain different visual function in patients with identical variants or stages of BCD. In addition, these image parameters could be used to evaluate the treatment outcome after gene therapy, even if the visual acuity decreases to a level that fails to provide a statistically significant difference.

It is not surprising that *CYP4V2* truncating variants are deleterious and have higher severity scores as shown in Table 1.[1] As mentioned by the authors, since the c.237G>T and c.367A>G variants were relatively far from the CYP4V2 ligand binding site, the severity scores were 1.[1] In fact, these two variants should be classified as a "variant of unknown significance (VUS)" instead of "likely pathogenic" in Table 1,[1] according to current ACMG classification guidelines.[4] In ClinVar, both variants (Variation IDs: 39,259 and 39,264) were submitted from several groups as benign or VUS except one by GeneReviews as pathogenic, which cited an article by Li et al,[5] which listed a case with these two variants in Table 2. However, although the patient's ethnicity is unclear, the predicted effect of these two variants was listed as "Unknown" in the same table by the original authors.[5] Furthermore, the overall minor allele frequency of variant c.237G>T (p.Glu79Asp) is 0.0002475 in the general population and 0.003508 among East Asians in the gnomAD database.[6] It is predicted to be tolerated by 16 of 19 functional annotation algorithms for

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nonsynonymous single-nucleotide variants in the human genome.[7–10] Regarding variant c.367A>G (p.Met123Val), the overall minor allele frequency is 0.0007425 in the general population and 0.008520 among East Asians in the gnomAD database.[6] It is predicted to be tolerated by 16 of 18 functional annotation algorithms for nonsynonymous single-nucleotide variants in the human genome.[7–10] Since these two variants have not been functionally characterized, their biological significance remains unknown.

Although the authors did not mention whether phase determination was conducted in patients with compound heterozygous variants to differentiate between paternal and maternal variant inheritance,[11] we assume that all these cases were *in trans* compound heterozygous variants. Regarding Figure 4 (Patient 18),[1] we noted that the fundus autofluorescence images differ from previously reported patient cases.[12] The area encompassed by the hyper-AF ring in the macula[1] contrasts previous literature, where lobular hypo-AF patches are typically observed and associated with retinal pigment epithelial atrophy and BCD (Fig. 10.3).[12] While this may be a novel phenotype of the *CYP4V2* gene, the pathogenicity of these variants must be carefully defined. Given that Table 2 indicates that patient 18 has the same variants (c.237G>T and c.367A>G) as patients 19 and 21,[1] including the retinal images of these two patients would be helpful in elucidating the possibility of unique AF features in patients with BCD with these two variants. In addition, it is unclear whether patients 18, 19, and 21 are related because they share the same variants. Although currently classified as a VUS, identifying multiple variant cases from unrelated families could raise the pathogenicity classification.[13] Depending on the relationship between patients 18, 19, and 21, the potential impact on the ACMG classification of c.237G>T and c.367A>G may vary. Therefore, demonstrating family linkages and providing clinical retinal images of patients 19 and 21 are critical in this study for current and future research.

Figure 7 provides new insights into the relationship between severity score and visual score.[1] Since the follow-up time for each individual patient was not specified, we assume that the data points plotted for each severity score are from different patients at different ages rather than a longitudinal follow-up (>10 years) for an individual patient, which may be problematic as combining separate patient progression rates may be a nonrepresentative of the overall progression rate. Considering BCD is a progressive disease that varies between each age, stage, and patients with same variants, the “fixed” scores of protein structure and genetic variants have limited correlation with patients’ visual function at different stages and ages. It would be helpful to conduct a long-term longitudinal follow-up (>10 years) on each patient to determine the comprehensive relationship between severity scores and visual deterioration.

In summary, the authors have presented a unique set of *CYP4V2* disease-causing variants. Because of limited information in this study and evidence from past literature, both the c.237G>T and c.367A>G variants should be classified as a “variant of unknown significance (VUS)” instead of “likely pathogenic” in Table 1,[1] according to current ACMG classification guidelines. We hope our perspectives are helpful and aid in advancing their investigation.

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