Succinate Dehydrogenase Gene Variants and Their Role in Cowden Syndrome

To the Editor: The TCA Cycle Gene Mutation Database includes the succinate dehydrogenase (SDH) genes and was established to catalog the pathogenic mutations of these genes, which are primarily associated with the tumors paraganglioma (MIM 168000) and pheochromocytoma (MIM 171300). Recently, the database curators have received expressions of interest in certain SDH mutations from patients with Cowden Syndrome (CD [MIM 158350]) and clinicians involved in the treatment of the syndrome, stimulated by a report from Ni et al.1

This paper described germline mutations and variants in the SDHB (MIM 185470) and SDHD (MIM 602690) genes in Cowden and Cowden-like (MIM 612359) syndromes. Ni et al. screened 375 PTEN (MIM 601728) mutation-negative patients and selected cases for further analysis on the basis of increased expression of manganese superoxide dismutase (MnSOD), reasoning that this is a relevant indicator of mitochondrial dysfunction. Within this subset of 74 patients, they found ten individuals with mutations in SDHB or SDHD. Using a functional approach to address the question of the pathogenicity of these variants, they demonstrated that these variants show variable but generally increased activation of p-Akt and p-MAPK. In addition, three of the five variants showed increased levels of reactive oxygen species (ROS). They were not, however, able to present any genetic data showing the loss of the wild-type allele in tumors.

A functional screening approach to SDH variants is welcome, because very few reports of SDH-related mutations show additional experimental data supporting the pathogenic or benign function of newly reported variants. The patients with SDH variants also showed a striking spectrum of tumors, with a significantly different incidence compared to a PTEN-positive cohort.

Although generally clear, this paper left several important points unresolved. Was the quantification of functional data based on comparisons to the 18 controls (Results section) or the 700 controls (mentioned in the Discussion)? And how were these 18 selected from the 700? Because the entire control cohort of 700 was sequenced for SDHB, SDHC (MIM 602413), and SDHD, were the remaining 301 Cowden Syndrome patients also sequenced? And if so, what was the result of this analysis?

The data presented by Ni et al. suggested that these variants have a genuine functional role. However, the levels of p-MAPK and p-Akt activation in carriers of accepted pathogenic variants of the SDH genes or in PTEN mutation carriers were not provided for comparison. Over 700 normal controls did not show increases in MnSOD, p-MAPK, or p-Akt, which may indicate that the increases in p-MAPK or p-Akt are related to MnSOD levels, the selection criterion for inclusion in this analysis.

Although most of the variants reported by Ni et al. were already known, none are currently thought to be causative in paraganglioma or pheochromocytoma, despite being found in patients. These variants are common. Four out of five have a reported frequency greater than 1% in the Single Nucleotide Polymorphism database (dbSNP) (Table 1), and four out of five are predicted to be benign by in silico analysis, using current versions of Polyphen and SIFT (Polyphen-2 and SIFT BLink).2,3 In the routine clinical genetic analysis of rare syndromes, common variants are generally considered to be benign under the assumption that, because no evolutionary selective pressure is operative against a variant, it cannot be deleterious. So should we now reconsider this paradigm and reassess these variants in paraganglioma/pheochromocytoma syndrome? Or could these variants represent a new class that predisposes exclusively to Cowden Syndrome?

Ni and colleagues stressed the fact that although these variants are common in certain Western populations, they are rare in their control population of Northern European descent. This raises the question of the frequency of Cowden and Cowden-like syndromes in certain European populations. Although Cowden syndrome has a reported prevalence of 1 in 200,000 or less,4 components of the syndrome may be underdiagnosed. The frequency of some of these SDH variants exceeds 1 in 20 in certain populations, and even assuming that these variants show reduced penetrance, it is puzzling that Cowden-related disease is not more frequently recognized.

Can the variants themselves provide clues to their specific Cowden-related function? Three of the variants are located in the mitochondrial transit peptide sequence, which is generally poorly conserved, varies between 20 and 60 amino acids in length, and is most clearly characterized by a positive net charge of +3 to +6, indicating considerable flexibility in the exact amino acid composition.5 The remaining SDHB variant, c.487T>C, p.Ser163-Pro, is located in a poorly conserved region of exon 5,6 with few other missense variants, indicating that this region plays no vital role in protein structure or function.

The only rare variant identified in this study, SDHD c.433C>A, p.His145Asn, is located at the border of the third transmembrane domain and thus resembles the well-known pathogenic variant c.274G>T, p.Asp92Tyr, and several other missense variants, which are located at the borders of transmembrane domains. However, Polyphen analysis indicates that the asparagine (Asn) residue is a benign variant, and SIFT analysis indicates that this is the most tolerated of possible amino acid changes at this position (0.46), little different to a synonymous variant.
Although these variants clearly fail to comply with standard criteria for suspected pathogenic SDH mutations, could they be playing a subtle role in mitochondrial protein targeting or have a mild effect on protein function, thereby explaining the lack of bona fide pathogenic mutations in this analysis of Cowden patients? Although the data of Ni et al. suggest that these variants may affect downstream molecules of the PTEN pathway, further research should focus on the exact effect of these variants on SDH protein targeting and the stability or turnover of the SDH complex before definitive conclusions can be drawn on the pathogenicity of these variants. The TCA Cycle Gene Mutation Database currently lists these variants as nonpathogenic, but additional experimental evidence could lead to a reconsideration of this status.

The study by Ni et al. presents a cohort of Cowden syndrome-related patients with a striking frequency of SDHB and SDHD gene variants and suggests that their results have important implications for patient care and genetic counseling. Although the data presented are intriguing and represent a platform for further exploration of the possible functional role of these variants, the independent confirmation of this report is imperative before any general recommendations can be made. In light of the high frequency of these variants in many populations, the adequate comprehension of their clinical significance and thus appropriate counseling will be very challenging.

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Web Resources
The URL for data presented herein is as follows:

References

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