COMMENT ON COLCLOUGH ET AL. AND SAINT-MARTIN ET AL.

Syndromic Monogenic Diabetes Genes Should Be Tested in Patients With a Clinical Suspicion of Maturity-Onset Diabetes of the Young. Diabetes 2022;71:530–537, and Gene Panel Sequencing of Patients With Monogenic Diabetes Brings to Light Genes Typically Associated With Syndromic Presentations. Diabetes 2022;71:578–584

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Diabetes 2022;71:e9–e10 | https://doi.org/10.2337/db22-0305

We read with keen interest the articles by Colclough et al. (1) and Saint-Martin et al. (2), which came to a common conclusion of supporting the inclusion of syndromic genes in monogenic diabetes test panels regardless of clinical features documented at case presentation. Our ongoing study on monogenic diabetes, in a multiethnic Asian population, includes testing for m.3243A>G using TaqMan allelic discrimination assay and *HNF1B* variants using 16-gene-panel next-generation sequencing and multiplex ligation–dependent probe amplification for *HNF1A*, *HNF4A*, *GCK*, and *HNF1B* (3,4). Key criteria for consideration of genetic testing are onset age ≤35 years, negative GAD antibody, absence of diabetic ketoacidosis, and BMI <32.5 kg/m^2. To date, we observed that among patients who carry a deleterious variant for monogenic diabetes, m.3243A>G (16.3%) and *HNF1B* (4.7%) variants were the fourth and fifth most common subtypes, trailing *HNF1A* (27.9%), *HNF4A* (25.6%), and *GCK* (16.3%).

Among the seven patients with the m.3243A>G variant, only one patient had hearing impairment, a characteristic feature of maternally inherited diabetes and deafness. Most of them (six out of seven) had a family history of diabetes in two or more generations. However, the history of only one of the patients suggests maternal transmission. We also observed that affected family members did not report any extrapancreatic features documented under family history. For this particular patient, retrospective review of medical records revealed frequent gastrointestinal disturbances, a possible clinical manifestation of maternally inherited diabetes and deafness that was not associated with it upon case presentation. In addition, as part of our family cascade screening, we recruited both the brother and mother of another proband with the m.3243A>G variant who did not report any extrapancreatic feature. Both family members were also found to carry the m.3243A>G variant, but only the proband's mother reported bilateral sensorineural hearing loss, 11 years after diabetes diagnosis. Therefore, phenotypic heterogeneity in mitochondrial diabetes is extensive and exists even among first-degree relatives, likely secondary to known tissue heteroplasmy. As for both patients with *HNF1B* variants, whole-gene deletions had been detected. Retrospective clinical evaluations and review of medical records revealed extrapancreatic features that were either not detected or not associated with *HNF1B* monogenic diabetes upon case presentation (5). This resulted in a diagnostic delay of 26 and 10 years, respectively. If presence of extrapancreatic features was a prerequisite for genetic testing, then these cases, which account for ∼20% of all our true monogenic diabetes cases, would have been missed.

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In summary, our observations of syndromic monogenic diabetes (m.3243A>G and *HNF1B*) in our local multiethnic Asian population, scarcely reported in the literature, are concordant with the authors' conclusion that variable expressivity in phenotype and lack of data collection and association impede early accurate diagnoses. While increasing the awareness and appropriate training of health care professionals in data collection, documentation, and association may partially mitigate the diagnostic challenge, the extensive phenotypic heterogeneity inherent to syndromic diabetes will likely remain a problem in the clinics. Therefore, we fully support the inclusion of syndromic monogenic diabetes genes, particularly m.3243A>G and *HNF1B*, in gene panels regardless of clinical manifestations.

Acknowledgments. The authors thank the patients for their participation and doctors for their referrals, without which this study would not have been possible.

Funding. Our research is funded by Alexandra Health Pte. Ltd. Science Translational and Applied Research grants STAR17201, STAR18107, STAR19111, STAR19204, STAR20106, STAR21106, and STAR21203.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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