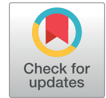

RESPONSE TO COMMENT ON COLCLOUGH ET AL. AND SAINT-MARTIN ET AL.

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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We thank Drs. Lim and Ang (1) for their positive comments on our article (2). We welcome their addition to the evidence base for systematic testing of all nonsyndromic and syndromic monogenic diabetes genes in patients with a clinical suspicion of maturity-onset diabetes of the young. Their data further support the strategy of testing all known genes rather than using gene selection based on clinical phenotype. This is essential to avoid missing cases of monogenic diabetes. The authors also confirm our findings that deafness is variably penetrant in families with m.3243A>G-related diabetes, whereas the renal phenotype is more likely to be present but either unreported or subclinical/undiagnosed in patients with diabetes and an *HNF1B* mutation.

Most patients in our cohort were of European ancestry, and it is therefore important and encouraging that the authors have replicated our findings in a multiethnic Asian population. In our other previous study by Patel et al. (3), we also demonstrated the importance of comprehensive testing that includes recessive syndromic diabetes genes in populations with higher rates of consanguinity and therefore higher prevalence of recessively inherited genetic disease. Genetic tests for monogenic diabetes offered by most commercial testing laboratories are focused on maturity-onset diabetes of the young, testing only dominantly inherited genes, and will therefore miss diagnoses (3).

We note that the authors used separate test methodologies for detecting the m.3243A>G mitochondrial gene mutation (TaqMan genotyping) and for copy number variants (CNVs) in nuclear genes (multiplex ligation–dependent probe assay). Our targeted next-generation sequencing (NGS) assay uses a custom capture library that includes an RNA bait for the m.3243A>G locus. The assay achieves a very high depth of coverage due to the large number of mitochondrial DNA (mtDNA) templates being sequenced and provides a highly accurate estimate of heteroplasmy level, down to 1%. The customizable nature of the library allows for the addition of other mtDNA variants associated with diabetes, thereby increasing diagnostic yield. We use the Mutect2 somatic variant caller (included in the GATK toolkit) to improve detection of mtDNA variants with low heteroplasmy levels (4). Our bioinformatics pipeline uses another tool, called SavvyCNV, to detect germline CNVs. This tool detects CNVs by looking at read depth over targeted regions and genome-wide using off-target reads. It uses a statistical model to assess differences in read depth from normal copy number. The tool is highly accurate and sensitive, and the off-target approach enables detection of very large deletions and chromosomal aneuploidies in patients with monogenic diabetes (5). The tool will detect CNVs in all the nuclear genes in the NGS panel compared

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with the limited number of genes analyzed by commercial multiplex ligation–dependent probe assays. SavvyCNV is freely available at https://github.com/rdemolgen/SavvySuite.

We therefore recommend that laboratories include m.3243A>G in their NGS panels and adopt CNV calling tools like SavvyCNV into their bioinformatics pipelines. This will reduce costs, free up staff, improve reporting times, and increase diagnostic yield.

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

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