RESPONSE TO COMMENT ON MISRA ET AL.

Homozygous Hypomorphic *HNF1A* Alleles Are a Novel Cause of Young-Onset Diabetes and Result in Sulfonylurea-Sensitive Diabetes. Diabetes Care 2020;43:909–912

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We thank Wu et al. (1) for their correspondence. We agree, low levels of high-sensitivity C-reactive protein (hs-CRP) are characteristic of heterozygous loss-of-function mutations affecting *HNF1A* (2). Wu et al. query the interpretation of the heterozygous p.A251T variant being pathogenic on the basis of the father's "'higher" hs-CRP level; however, this comment is factually incorrect. Our data support that p.A251T is *not* maturity-onset diabetes of the young (MODY)-causing in the heterozygous state, as evidenced by the hs-CRP level in the heterozygous father who does not have diabetes and, notably, by the lack of response to sulfonylurea therapy and higher BMI in the heterozygous mother, who does have diabetes. We quite agree, and have acknowledged in the article, that there are likely to be other drivers of dysglycemia in the proband's parents. This very point illustrates the complexity of interpreting alleles that are not fully penetrant and require additional environmental and/or genetic contributions for disease manifestation.

Wu et al. next query whether a novel MODY-causing gene could account for the observed phenotype, as we undertook targeted next-generation sequencing of known diabetes-related genes and not whole genome/exome sequencing. We are satisfied that in vitro and in vivo studies show that the pathology lies in the *HNF1A* gene, particularly given the observed sulfonylurea sensitivity in the proband. We caution against using whole genome/exome approaches for novel gene discovery in isolated kindreds; this approach has limited power to detect novel genes and is best used when studying extreme phenotypes in multiple affected kindreds. We finally note that whole exome sequencing of MODY cohorts has yielded only cases with mutations in known MODY genes and has not resulted in compelling new gene discoveries (3,4).

We agree the probability of the identical twin brothers and two siblings all inheriting homozygous copies of A251T is 0.016. We must, however, offset these odds against the unusual context of four siblings (two genetically identical) developing early-onset insulin-treated diabetes, with retained endogenous C-peptide. If we consider other potential diagnoses, be it heterozygous mutations in unknown genes or type 1 or type 2 diabetes, the odds of all four siblings presenting identically remains low. We therefore conclude that recessive inheritance in all four siblings is most likely and emphasize that the chance of each future child is independent of the outcome in previous children, i.e., always 25%.

Finally, we agree that diagnosis BMI is more representative of diabetes phenotype than BMI post-diagnosis. However, we would caution against using BMI at diagnosis to support diabetes classification, as with rising population BMI and ethnic differences (5), adequately sensitive and specific cut-offs are unlikely.

In summary, our study expands the allelic spectrum of observed *HNF1A* variants. We show that hypomorphic alleles may have variable penetrance in the heterozygous state. However, the same hypomorphic variant inherited in the homozygous state is fully penetrant with an HNF1A-MODY phenotype. We conclude that the best way to define pathogenicity of *HNF1A* variants is through a multimodal approach that carefully collates genetic, clinical, biochemical, and functional data.

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