RESPONSE TO COMMENT ON DUBOIS-LAFORGUE ET AL.

Diabetes, Associated Clinical Spectrum, Long-term Prognosis, and Genotype/Phenotype Correlations in 201 Adult Patients With Hepatocyte Nuclear Factor 1B (*HNF1B*) Molecular Defects. Diabetes Care 2017;40:1436–1443

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Diabetes Care 2018;41:e8–e9 | https://doi.org/10.2337/dci17-0048

We thank Clissold et al. (1) for their comments on our article (2) that demonstrated genotype/phenotype correlations in patients with *HNF1B* molecular defects. We reported that, compared with the patients with an *HNF1B* mutation, those with *HNF1B* whole-gene deletion due to the 17q12 deletion were leaner at diagnosis and might have a more severe diabetes phenotype. They also had a better renal prognosis as suggested by a higher estimated glomerular filtration rate (eGFR) at diabetes diagnosis and at follow-up, a less frequent need for renal replacement by dialysis or renal transplantation, and a more frequent normal function at follow-up (49% vs. 22%) (2). Clissold et al. (1) mentioned that previous studies showed similar results as regards renal function (3,4). Actually, in our article published in 2005 (5), which demonstrated that many patients with maturity-onset diabetes of the young 5 (MODY5) have an *HNF1B* deletion due to the 17q12 deletion, we already reported a higher eGFR in the 10 patients with the deletion compared with the 18 with a mutation (61 $\pm$ 31.6 vs. 40 $\pm$ 20.1 mL/min/1.73m^2, respectively). However, probably owing to the small size of the studied population, the difference did not reach statistical significance ($P = 0.08$). The two studies (3,4) quoted by Clissold et al. (1) showed that patients with *HNF1B* deletion had a higher eGFR than those with truncating mutations. In two of these three previous studies, the patients with *HNF1B* mutations were significantly older than those with an *HNF1B* deletion at the time of eGFR estimates. Since renal function deteriorates with time in patients with hepatocyte nuclear factor 1B (HNF1B)-related renal disease, this and other confounders may have played a role in the lower eGFR observed in the patients with *HNF1B* mutations. No multivariable analyses were performed in these three studies (3–5), and thus no firm conclusion could be drawn from these observations. Accordingly, until recently it was thought that no genotype/phenotype correlations were observed in patients with HNF1B-related renal disease. In our present study (2), owing to the large size of the population, logistic regression analyses were performed and allowed us to establish that, compared with mutations, *HNF1B* deletion was independently and strongly associated with a normal renal function at diabetes diagnosis (odds ratio 12.14, 95% CI 3.24–45.47, $P = 0.0002$) and at follow-up (odds ratio 3.54, 95% CI 1.52–8.21, $P = 0.0033$). As regards the putative explanations of these correlations, we acknowledge that the two nonexclusive suggested hypotheses, i.e., a dominant negative effect of some mutations worsening the renal phenotype, or the deletion of gene(s) other than *HNF1B* because of the large 17q12 deletion improving it, deserve further studies. Elucidating the mechanisms involved in this observation may have important implications for the pathophysiology of the HNF1B-related disease and also for other progressive renal diseases.

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

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