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

Rhian L. Clissold,[1] Lorna W. Harries,[1] Sian Ellard,[1] Coralie Bingham,[1,2] and Andrew T. Hattersley[1]

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We read with interest the large and impressive study by Dubois-Laforgue et al. (1) describing the phenotype, long-term follow-up, and genotype/phenotype correlations in 201 adults with hepatocyte nuclear factor 1B (HNF1B)-associated disease. They report that patients with an *HNF1B* mutation have a worse renal prognosis than those with a 17q12 deletion, as they had a higher frequency of chronic kidney disease stages 3–4/end-stage renal disease and a lower median estimated glomerular filtration rate (eGFR) at follow-up (42.5 vs. 75 mL/min/1.73 m^2, respectively; $P = 0.008$). The article did not comment on the fact that similar results have previously been found in two smaller studies (2,3). Heidet et al. (2) identified *HNF1B* molecular defects in 75 of 377 patients with a variety of renal phenotypes; they found that the proportion of participants with renal impairment was higher in those with a truncating mutation than in those with a deletion ($P = 0.01$). We recently described (3) the neurodevelopmental phenotype of 38 patients with HNF1B-associated renal disease; the median eGFR was 42.6 mL/min/1.73 m^2 (interquartile range 31–60) in those with an *HNF1B* mutation ($n = 18$) compared with 81.4 (56–91) in those with a 17q12 deletion ($P = 0.002$). The mutation and deletion groups in this small series were similarly matched in terms of age, and 17 of 18 intragenic mutations described were truncating. Therefore, the overall findings from the work by Dubois-Laforgue et al. and these two earlier articles suggest that the 17q12 deletion results in better renal function than *HNF1B* intragenic mutations that cause loss of function.

This result is unexpected because haploinsufficiency is accepted as the underlying disease mechanism in HNF1B-associated disease. Both *HNF1B* deletion and truncating mutations would be expected to cause complete loss of a single allele. One hypothesis suggested by Dubois-Laforgue et al. (1) is that some intragenic *HNF1B* mutations may exert a dominant negative effect that results in a more severe phenotype. Although truncating mutations anywhere other than the terminal exon usually cause transcript degradation via the nonsense-mediated decay pathway (4), previous work has shown that there is a considerable variation in the degree of nonsense-mediated decay that is seen with different *HNF1B* mutations (5). This could fit with a potential dominant negative effect. Another hypothesis involves the protective effect of one of the other genes lost in the 17q12 deletion. Further functional studies to explore some of these ideas will be important. In summary, the unexpected finding of a worse renal prognosis in individuals with an *HNF1B* mutation confirms the results from two smaller studies, but the mechanism underlying this observation remains unexplained.

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[1]*University of Exeter Medical School, Exeter, U.K.*
[2]*Exeter Kidney Unit, Royal Devon and Exeter National Health Service Foundation Trust, Exeter, U.K.*

Corresponding author: Rhian L. Clissold, rhian.clissold@nhs.net.