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RESEARCH LETTER

Macrosomia and neonatal hypoglycaemia in RW pedigree subjects with a mutation (Q268X) in the gene encoding hepatocyte nuclear factor 4α (*HNF4A*)

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To the Editor: In a recent publication, Pearson et al. [1] reported on a previously unrecognised feature of the natural history of the type 1 form of maturity onset diabetes of the young (MODY1), which is caused by mutations in the gene encoding hepatocyte nuclear factor 4α (*HNF4A*). In a comparison of 54 mutation carriers (from 15 European pedigrees and with 12 different mutations) with their unaffected family members, they found a significant increase in median birthweight (790 g) with a 56% prevalence of macrosomia compared with 13% in family members without mutations. Macrosomia was inherited from either mother or father (64 and 46% of total cases, respectively). Transient neonatal hypoglycaemia was reported in eight of 54 neonates, three of whom had documented hyperinsulinaemia as infants. Similar observations were made in a mouse model with a beta cell-specific *Hnf4a* deletion [1].

Since only 50–60% of neonates had macrosomia [1], phenotypic heterogeneity resulting from the study of subjects with 12 different mutations was considered possible, as has been reported for plasma apolipoprotein concentrations in MODY1 pedigrees with different mutations [2]. Our aim was to compare the findings in the European cohort with the prevalence of macrosomia and neonatal hypoglycaemia in a single, large six-generation MODY1 pedigree with a Q268X mutation: the RW pedigree from Michigan. This pedigree has been followed prospectively by one of us (S. S. Fajans) since 1958 [3–7].

Birthweight and genotype were available for 34 mutation carriers and 52 family members without the mutation. Birthweight and history of neonatal hypoglycaemia were obtained by parental recall, supported by data in baby books for some. Informed consent was obtained from all participants and the study was approved by the Institutional Review Board of The University of Michigan. Birthweight was increased by a median of 751 g (mean of 704 g) in mutation carriers as compared with family members without the mutation ($p<0.0001$). As in the report by Pearson et al., macrosomia was defined as a birthweight exceeding 4,000 g, but we used actual birthweights rather than birthweights corrected for sex and gestational age. Among neonates, macrosomia occurred in 59% (20/34) of mutation carriers compared with 8% (4/52) of those without a mutation ($p<0.0001$). The prevalence of macrosomia was 68% (13/19) if the mutation was inherited from the mother ($p=0.0001$) and 47% (7/15) if inherited from the father ($p<0.01$). The high prevalence of macrosomia in the offspring of fathers with the mutation excludes an effect mediated by maternal hypoglycaemia. In the 52 neonates without the mutation, the rates were 9% (3/32) for offspring of an affected mother and 5% (1/20) for an affected father. There was no extreme macrosomia (birthweight exceeding 5,000 g). As several macrosomic neonates were delivered

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7–30 days before term, correction for gestational age would have caused an increase in median and mean birthweight.

There were only two instances of neonatal hypoglycaemia in the RW pedigree. In one (born in 1995), the hypoglycaemia was attributed to carnitine palmitoyl transferase deficiency. This male carrier had a plasma glucose concentration of 0.6 mmol/l at birth and received glucose intravenously for several days, with resulting plasma glucose levels of 1.7–2.2 mmol/l. He had a birthweight of 4,101 g; higher than expected for an infant with this deficiency alone. Although enzyme activity measurements were not available, high plasma carnitine concentrations (total, free and esterified) 3 months after birth provide evidence for this enzyme deficiency. Retrospectively, it is most likely that the neonatal hypoglycaemia was primarily due to the presence of the *HNF4A* mutation. The infant's father, a mutation carrier, has diabetes and his mother had a normal OGTT and no family history of diabetes. The second infant with neonatal hypoglycaemia (born in 1975) had a birthweight of 4,338 g and needed glucose intravenously for 5 days. Diabetes was diagnosed at age 9 following an OGTT that revealed hypoinsulinaemia. He received sulfonylurea therapy at 10 years of age, and has been treated with insulin since age 14. His brother, also a mutation carrier, had a birthweight of 4,026 g. Impaired glucose tolerance was observed at age 10, with remission at age 23 with strenuous physical activity. Their father, a mutation carrier, had asymptomatic diabetes diagnosed at age 11, and from age 30 has been treated with insulin for severe insulin-deficient diabetes with extremely low plasma C-peptide concentrations. Their mother had a normal OGTT and no family history of diabetes.

The findings with regard to increased birthweight, prevalence of macrosomia and occurrence of transient neonatal hypoglycaemia in the RW pedigree, interpreted as a manifestation of fetal and neonatal hyperinsulinaemia, closely resemble those in the group of 15 smaller European pedigrees with 12 different mutations. Phenotypic heterogeneity introduced by different mutations can therefore be ruled out as an explanation for the 50–60% prevalence of macrosomia. The variability in the clinical expression of this trait remains to be explained. Our results establish this novel phenotype of *HNF4A* mutation carriers beyond doubt. They strongly support the conclusion of Pearson et al. that the natural history of MODY1 includes hyperinsulinaemia in fetal and neonatal life, progressing to insulin-deficient diabetes in later years, and add some new perspectives. The pathogenesis and the exact timing of this switch in beta cell function have not been elucidated as yet. We have observed a hypoinsulinaemic response to ingested glucose during the OGTT in normoglycaemic as well as diabetic subjects of the RW pedigree from age 7 upwards. A male carrier had a birthweight of 4,338 g and a normal OGTT at age 3 with a low normal insulin response to glucose (peak insulin 7 pmol/l, utilising a glucose load of 1.75 g/kg body weight).

An increase in birthweight, macrosomia, and neonatal hypoglycaemia was not found in neonates of MODY3 families who have a mutation in the *HNF1A* gene (also known as *TCF1*) [1]. Such individuals also have a hypoinsulinaemic response to glucose [8]. It will be important to ascertain which genes are regulated by *HNF4A* but not *HNF1A* and whose altered expression in carriers leads to increased beta cell activity and hyperinsulinaemia in fetal and neonatal life, followed by possible accelerated apoptosis in later life.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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