Observations

Maturity onset diabetes of the young (MODY) and early onset Type II diabetes are not caused by loss of imprinting at the transient neonatal diabetes (TNDM) locus

To the Editor: Maturity onset diabetes of the young (MODY) is an unusual cause of diabetes that usually develops before the age of 25, is not insulin dependent and is inherited as an autosomal dominant trait [1]. Mutations in five genes have now been identified leading to MODY; hepatic nuclear factor (HNF)-4α (MODY1), glucokinase (MODY 2), HNF-1α (MODY 3), insulin promoter factor-1 (MODY 4) and HNF-1β (MODY 5) [1, 2, 3]. Mutations in the transcription factors NEUROD 1 and Islet brain 1 have also been proposed as causing early onset Type II (non-insulin-dependent) diabetes mellitus [4, 5]. In a considerable proportion of MODY families (about 20%) the aetiological genes have not been defined [6]. The definition of the genes in these families will give new insights into critical pathways in the beta cell.

Transient neonatal diabetes mellitus (TNDM) is a rare condition that presents with significant intra-uterine growth retardation in infants born at term who develop hyperglycaemia usually within the first week of life. The condition then goes into remission only to relapse in at least 60% of cases usually in adolescence (median age 14 years). The relapse is characterised by non-ketotic hyperglycaemia with no evidence of autoimmune aetiology and characteristically minimal requirement for either exogenous insulin therapy or oral hypoglycaemic agents [7].

The first anomaly described in TNDM was uniparental isodisomy of chromosome 6 (UPD 6) in which two haplo-identical copies of paternal chromosome 6 are inherited from the father with no contribution from the mother. The second basis for TNDM is an unbalanced duplication, either micro or submicroscopic, of paternal chromosome 6 in the region *6q24* (long-arm chromosome 6). With this anomaly children inherit a small extra quantity of paternal chromosome 6 making them liable to neonatal diabetes. Only if this duplication comes from the father does inheritance result in diabetes suggesting that the gene(s) is imprinted. The third anomaly is a methylation defect at a locus within chromosome *6q24* that in normal subjects is hemizygously methylated, a state characteristic of imprinted genes [8]. We have shown that TNDM patients with paternal UPD 6 do not have methylation at this locus; moreover, four patients with no other identifiable genetic lesion have a methylation pattern identical to UPD 6 patients. Two members of a family in our TNDM cohort carried a paternal unbalanced duplication of *6q24* with no history of neonatal diabetes but later onset gestational or early onset Type II diabetes (aged 25 years). This study set out to examine whether imprinting defects within the TNDM locus might be associated with MODY or early onset Type II diabetes. We therefore examined the TNDM locus in patients with young onset diabetes in whom a mutation in the MODY genes had not been identified.

The 83 subjects were selected from the Diabetes UK MODY collection held in Exeter. All patients had young onset (< 40 years) diabetes and were not insulin dependent. Patients with a mutation in the known MODY genes had been identified and were excluded. Forty-eight patients conformed to conventional criteria for MODY (autosomal dominant diabetes with at least one member diagnosed before the age of 25). The remaining 35 did not reach MODY criteria because they were diagnosed after reaching 25 years of age ($n = 24$) or did not have a family history ($n = 11$). Samples were tested as in previous experiments studying the genetic basis of TNDM: UPD6 was investigated by using polymorphic markers along chromosome 6, unbalanced duplication was assayed using fluorescent quantitative polymerase chain reaction (PCR), methylation status was analysed by DNA digestion with *Hpa* II and *Msp* I before amplification by PCR using primers spanning CCGG sites [8].

None of the cases analysed showed any of the genetic re-arrangements seen in TNDM. We therefore conclude that genetic re-arrangements causing TNDM are not a common cause of undefined MODY or young onset Type II diabetes.

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