No evidence for diabetes-associated mutations of PEK/EIF2AK3 gene in French patients with early-onset Type II diabetes

To the Editor: The Wolcott-Rallison syndrome (WRS, OMIM No. 226980) is a rare, autosomal recessive disorder characterized by permanent neonatal or early infancy diabetes and at a later age by multiple epiphyseal dysplasia, osteoporosis, growth retardation and frequent multisystemic manifestations [1]. Whereas it is not likely to have an auto-immune aetiology, insulin is required from the onset of diabetes. Pancreatic beta-cell destruction associated with WRS suggests that the biological process involved might be relevant to other forms of non-auto-immune diabetes, and particularly to young-onset forms of Type II (non-insulin dependent) diabetes mellitus like MODY. On the basis of two consanguineous families of different ethnic origins, a study recently mapped WRS locus to a region of less than 3 cM on chromosome 2p12 [2]. They explored the gene encoding the eukaryotic translation initiation factor 2-α kinase 3 (EIF2AK3), which is located in this region. *EIF2AK3* was considered a candidate gene because of its high expression in pancreatic islets. In each of the families, they identified in a homozygous state two distinct mutations (Ins345 fs/K345Stop and R587Q) segregating with the disease.

Of note, phosphorylation of eukaryotic translation initiation factor-2α (eIF-2α) is one of the key steps where protein synthesis is regulated in response to changes in environmental conditions. The eIF-2α phosphorylation is carried out by distinct eIF-2α kinases [3]. The pancreatic eIF2-α kinase (PEK) was shown to regulate protein synthesis both in vitro and in vivo [4]. Northern blot analysis showed that PEK mRNA was expressed in all human tissues, with the highest expression in the pancreas and placenta. However, PEK protein was only detected in pancreatic δ cells [5], contrasting with the specific reduction of pancreatic beta cells found in WRS. A targeted mutation of the mouse *EIF2AK3* gene abolished the eIF2-α phosphorylation in response to accumulation of malfolded proteins in the endoplasmic reticulum, resulting in abnormally increased protein synthesis and increased endoplasmic reticulum stress [6]. Therefore, it is proposed that PEK functions maintain the integrity of beta cells as well as regulate protein translation in response to glucose signaling.

These data lead us to screen by direct sequencing the 17 exons of the *EIF2AK3* gene in a cohort of 30 unrelated probands with early onset Type II diabetes (average age at onset of diabetes: 21.6 ± 7.7). Of the subjects, 8 presented an overweight (BMI of 29.4 to 32.4 kg/m^2), 11 subjects, were treated with insulin therapy and 12 with oral hypoglycaemic agents. These subjects were selected from MODY-like families in the French population, most of whom had at least two members diagnosed with diabetes before 25 years of age and at least two generations of affected members with no bilineal inheritance or at least one member diagnosed at an age younger than 25 plus at least three affected generations. Typical clinical features of Type II diabetes were present in these families. All the probands were previously screened negative for mutations in glucokinase (*GCK*) and HNF1α (*TCF1*), which are the two most prevalent MODY 2 and 3 genes in France [7, and unpublished data]. The screening of *EIF2AK3* gene was carried out in probands, with one non-obese non-diabetic white person as the control subject. The 17 exons of the gene and the intron-exon boundaries were sequenced on PCR-amplified genomic DNA as described previously [2]. Our analysis confirmed the 9 common polymorphisms previously identified in exons and flanking intronic regions and no mutation was observed. Alltogether 8 different haplotype combinations out of the 11 already reported were seen in the 30 unrelated subjects. The early-onset Type II diabetes probands selected for mutation screening covered a range of heterogeneous clinical phenotypes associated with Type II diabetes, different in age at onset (from very early diabetes, with age at onset ≤ 15 years, to young adulthood), in severity of diabetes and in association or not with insulin resistance or with obesity.

In conclusion, we didn't detect any mutation of PEK *EIF2AK3* gene responsible for glucose intolerance or overt diabetes in early onset Type II diabetes in the French population, suggesting that this gene is not likely to play a major part in monogenic forms of diabetes. Little is known, however, about the biochemical and molecular bases involving PEK activity into translational control at the level of pancreatic islets and how it is related to normal pancreatic function. Still, other genes involved in this pathway might contribute to the genetic risk of Type II diabetes, especially in the early onset sub-types.

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