Mitochondrial DNA defects in diabetes mellitus

Dear Sir,

The hypothesis that mitochondrial DNA might play a role in the pathogenesis of diabetes is not new. However, the recent outline of the possible mechanisms involved is useful [1].

In 1991 we demonstrated a strong maternal effect in the transmission of Type 2 (non-insulin-dependent) diabetes mellitus [2]. Thus, of patients with Type 2 diabetes and an affected parent, 75% had affected mothers as opposed to the 50% which would be predicted by Mendelian genetics. This finding has been confirmed by other groups [3, 4]. Some workers have suggested this maternal transmission may be related to the role of the intra-uterine environment in the development of the disease [5].

The possibility that mitochondrial gene defects inherited along the maternal line could explain the observed maternal transmission was discussed in our original paper and in greater length in a recent thesis [6]. These findings, together with those cited by Gerbitz [1], have prompted us to search for mitochondrial mutations in Type 2 diabetes. To date we are aware of three families with Type 2 diabetes in which the disease segregates with a specific mitochondrial DNA mutation. One of these families has recently been reported on by another group [7] and is probably the same pedigree previously reported as carrying a BstN1 polymorphism [8] and cited by Gerbitz [1].

I would take issue with the use of the term 'evolution' by Gerbitz [1] to describe de novo mutations in the mitochondrial DNA, since there is no evidence that such random mutations lead to any beneficial effect in mammalian cells.

Any discussion on the role of mitochondrial mutations in diabetes also needs to take into account the phenomenon of heteroplasmy whereby individuals possessing a mitochondrial mutation will have differing numbers of normal and mutated mitochondria in different cells of the body [9]. In diabetes, the beta cell, liver or muscle may play an important part in primary disease pathogenesis. The finding of mitochondrial DNA mutations by employing polymerase chain reaction (PCR) techniques in peripheral blood may not accurately reflect the number of mutated mitochondria in the tissue of most interest to the diabetologist.

Finally, I think it important to mention that not all mitochondrial diseases will show maternal transmission since mitochondrial gene expression is controlled by nuclear-DNA-coded proteins [10]. A defect of nuclear DNA can therefore produce defective mitochondrial function. Thus, the reported excess of paternal transmission in Type 1 diabetes does not rule out the possibility of a mitochondrial defect in the disease.

Despite the concluding paragraph of Gerbitz [1], I would suggest that current evidence points to mitochondrial defects being potentially more important in Type 2 than Type 1 (insulin-dependent) diabetes.

Yours sincerely,

J. C. Alcolado

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Dr. J. C. Alcolado
Department of Medicine
Prince Charles Hospital
Gurnos Road
Merthyr Tydfil
Wales
UK

Response from the author

Dear Sir,

The predominantly maternal transmission of Type 2 (non-insulin-dependent) diabetes has been known for a long time [1]; evidence that mutations of the mtDNA could account for this phenomenon is new. Several publications also on this topic have recently appeared [2–4] which confirm my hypothetical question. Hopefully, the Type 2 diabetic families with specific mtDNA mutations mentioned by Dr. Alcolado will be published in the near future. Deletions, duplications and defined mtDNA point mutations are not only found in families with maternally inherited diabetes, but also in pedigree members suffering from both mitochondrial encephalomyopathy and diabetes [5–11] (Table 1). In none of the respective cases described so far is diabetes the only symptom; there is always an association with neurological symptoms (deafness, ataxia, etc.) usually not combined with diabetes. Thus, it seems likely that those forms of diabetes which have been described as being associated with mtDNA defects do not belong to the classic idiopathic Type 1 (insulin-dependent) or Type 2 diabetes. They may represent subclassi-

Table 1. See text

Ref.	Diabetes type	Single case	Familial cases	mtDNA mutation	Heteroplasmy
2	IDDM		x	deletion	x
6	IDDM	x		deletion	x
7	IDDM	x		deletion	x
8	IDDM	x		del. + duplication	x
9	IDDM	mother-child	x	duplication	x
3	NIDDM		x	tRNA Leu-nt 3243	x
4	IDDM/NIDDM		x	tRNA Leu-nt 3243	x
5	IDDM/NIDDM		x	tRNA Leu-nt 3243	x
10	IDDM		x	tRNA Leu-nt 3243	x
11	IDDM	x in a pedigree		tRNA Leu-nt 3260	x