Advances in the molecular basis of non-insulin dependent diabetes mellitus: Indian Perspective

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Comments

A few decades ago Neel stated that the genetics of NIDDM was a "nightmare". More recently it has been described as a "headache". This underscores the frustration in understanding the genetics of a disease which undoubtedly has a strong genetic component in its etiopathogenesis. In the above article, Pearce and Aitman present a succint review of recent studies on the genetics of NIDDM. Over the decades, several genetic modes of inheritance have been proposed for NDDM—autosomal dominant, recessive and polygenic or multifactorial inheritance. A recent paper in Diabetologia from our group at Madras (McCarthy et al., 1994) in collaboration with Dr. Graham Hitman of the Royal London Hospital, provides information on the genetics of NIDDM in south Indian subjects. Using complex segregation analysis and sophisticated mathematical modelling it was shown that in south Indians segregation of NIDDM is not explained by simple modes of inheritance. The best fits were obtained with "multifactorial" models. The best supported model for segregation of NIDDM featured a diallelic gene accounting for approximately 35% of the variance in liability of diabetes. An identical study was published on Caucasians by another group in the U.K. in the same issue of Diabetologia (Cook et al, 1994). While their results showed that the segregation analysis of NIDDM in Caucasian pedigrees favoured a dominant model of inheritance their data was also in accord with a mixed model or polygenic inheritance.

It is most likely that a major gene plays a role in determining the glucose levels throughout the range of glucose intolerance. Several candidate genes further modify this risk to produce NIDDM. To date, over 250 candidate genes have been investigated in studies of the genetics of NIDDM patients. Positive association have been found both with genes involved in insulin secretion and insulin action and Pearce and Aitman have nicely reviewed the present status of various candidate genes studies. In the case of a rare subset of NIDDM known as Maturity Onset Diabetes of the Young (MODY) glucokinase mutations have been shown to account for over 50% of all MODY families. In the "common garden" or "every day" variety of NIDDM, the role of candidate genes is far from clear. In collaboration with Dr. Graham Hitman, we have studied various candidate genes in NIDDM. The results of these studies have recently been reviewed (Mohan et al, 1994). *Table-1* summarises the candidate gene associations in south Indian NIDDM.

Table 1: Summary of candidate gene studies in south Indian NIDDM

Positive association	Negative association
Insulin gene hvr	Amylin
Apolipoprotein D	Insulin Receptor
Glucocorticoid	HLA
Glucokinase	GLUT—4
Complement C4 B2	

The difficulties in "zeroing in" on candidate genes is related to the fact that environmental factors play an equally important (if not more important) role in the etiology of NIDDM. It is also possible that genetic and environmental factors are inter-dependent. What needs to be resolved is whether there is a major gene for NIDDM which can explain part of the genetic predisposition to the disease or whether NIDDM is truly a polygenic disease. It is hoped that with rapid developments in molecular biology techniques these issues will be resolved quite soon, thus relieving the "headache" of the geneticist.

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Cook JTE, Shields DC, Page RCL, Levy JC, Hattersley AT, Shaw JAG, Neil HAW, Wainscoat JS, Turner RC (1994) Segregation analysis of NIDDM in Caucasian families. *Diabetologia* **37**: 1231–1240

McCarthy MI, Hitman GA, Shields DC, Morton NE, Snehalatha C, Mohan V, Ramachandran A, Viswanathan M (1994) Family studies of non-insulin dependent diabetes mellitus in South Indians. *Diabetologia* **37**:1221–1230

Mohan V, Premalatha G, Viswanathan M, Hitman GA (1994) Genetics of NIDDM in South Indians. In: Proceedings of the *Third Novo Nordisk Update*, Madras, Kapur A (ed.) Health Care Communications, Bombay, 71–76