Genetics of NIDDM

M. Alan Permutt, MD

This brief review discusses the current level of understanding of the role of genetic defects in the etiology of non-insulin-dependent diabetes mellitus (NIDDM) and the use of molecular-genetic methods for this study. Evidence for genetic susceptibility is strong, and defects in both insulin production and action are suspect. With restriction-fragment–length polymorphisms and genomic sequencing, various candidate loci are being evaluated. Evidence that multiple genes are involved is only circumstantial. If NIDDM is genetically heterogeneous and also influenced by environmental components, population associations and linkage analyses in families may not be as easily interpreted as for diseases involving single major gene defects. *Diabetes Care* 13 (Suppl. 4): 1150–53, 1990

The purpose of this review is to provide a concise discussion of the current level of understanding of the role of genetic defects in the etiology of non-insulin-dependent diabetes mellitus (NIDDM) and to introduce the molecular-genetic methods used to define these defects. This subject has recently been reviewed (1), and in-depth discussions of the role of the insulin (2,3) and insulin-receptor (4,5) genes in NIDDM are available.

EVIDENCE FOR GENETIC SUSCEPTIBILITY

The tendency for diabetes to occur in family members has been known for a long time. The role of environmental factors in precipitating diabetes is also well established, and the familial tendency for diabetes could conceivably be due to similar patterns of obesity, diet, or perhaps lack of physical exercise that occur in the same family members (for review, see ref. 6). In the last few years, however, a considerable amount of evidence has accumulated that the familial aggregation of diabetes is due to an inherited defect in genes that predispose to diabetes. Although obesity remains the major risk factor for diabetes in the adult population, it appears that the relative risk for diabetes may be a function of the underlying background genetic susceptibility of an individual. These genes may convey susceptibility or perhaps resistance to diabetes, and many different genes may be involved.

What is the evidence that differences in genetic susceptibility exist in NIDDM? Important studies of concordance in monozygotic versus dizygotic twins have shown repeatedly that the concordance is greater in identical twins (7–9). The concordance in identical twins is >90% for NIDDM, whereas it is ~50% for insulin-dependent diabetes (IDDM). Furthermore, there seems to be no difference in degree of obesity or frequency of twins living apart in concordant and discordant identical twins. Further evidence for genetic factors predisposing to susceptibility include the observation of marked differences in prevalence of NIDDM in different ethnic groups living in the same geographical area. Zimmet (6) has observed that the diabetes prevalence in Japanese is only 1%, in Whites 2–3%, and in Blacks 4–6%. The highest prevalence (35%) of diabetes in the United States occurs in Pima Indians. Life-style, as discussed in Zim-

From the Metabolism Division, Washington University School of Medicine, St. Louis, Missouri.

Address correspondence and reprint requests to M. Alan Permutt, MD, Metabolism Division, Washington University School of Medicine, 660 South Euclid, Box 8127, St. Louis, MO 63110.

met's review, has been noted to have an important effect on the prevalence of diabetes, as evidenced in rural and urban Polynesians of Western Samoa, having 3.6 vs. 10% diabetes prevalence, respectively. Nevertheless, within a given urban environment and for equal degrees of obesity, it is clear that diabetes is far more prevalent in certain ethnic groups. Interestingly, evidence for genetic factors has been underscored by the fact that, in groups in which diabetes prevalence is high (Pima Indians, Australian Aborigines, Mexican Americans, and American Blacks), the prevalence of diabetes appears to be diminishing proportional to the degree of genetic admixture (10).

Before the genes involved in NIDDM can be identified, the clinical problem must be defined. NIDDM is characterized by a chronic metabolic state of insulin deficiency that has been shown by numerous investigations to be due to impaired insulin production and action. Both defects are somewhat reversed with therapy (11). Whether insulin production or action is the primary inherited defect is unclear, but evidence in experimental animals suggests that defects in insulin production can lead to defects in insulin action and vice versa (45,46). Furthermore, there are potentially many different steps involved in both insulin production and action, and current evidence favors heterogeneity of the etiology of NIDDM. Thus, NIDDM is viewed as a common phenotype, typically occurring in an obese adult with hyperglycemia as a manifestation of insulin lack without ketosis, but the genotypes (genetic susceptibility) in different individuals are probably diverse. In summary, the clinical picture of NIDDM is relatively consistent, but little is known about the genetic defect or defects.

CHOOSING SUITABLE GROUPS OF PATIENTS FOR STUDY

Through the use of modern recombinant DNA technology, many human genes are now available to evaluate the genes involved in NIDDM. For this type of analysis, the genes in populations of nondiabetic and diabetic individuals or in nondiabetic and diabetic members within a family can be studied. If diabetes is heterogeneous, then it would be preferable to study populations or families with discrete types of diabetes, but this goal is complicated by obscurities in the clinical classification. For example, in one form of NIDDM called maturity-onset diabetes of the young (MODY), a mild NIDDM occurs in young adults, often without obesity (12). A familial tendency for MODY is very strong, and often vertical transmission through several generations has been noted, suggesting a major gene defect inherited in an autosomal-dominant fashion. Recently, however, other investigators have noted that a number of lean young adults develop NIDDM, and they have an extraordinarily high frequency of both parents having diabetes (13). The investigators suggested that this is a different disorder than MODY and call it early-onset NIDDM, perhaps induced to an early onset by the presence of genes inherited from both diabetic parents. Another confusing clinical syndrome described by the same authors is the so-called late-onset IDDM. Here, they described eight young adults who developed NIDDM between the ages of 25 and 40 yr, and the only feature that distinguished this group from the other two groups was the presence of islet cell antibodies, a characteristic feature of IDDM.

CANDIDATE GENES THAT MAY PREDISPOSE INDIVIDUALS TO NIDDM

Cloning the human insulin gene through recombinant DNA technology in 1979 allowed investigators to study the role of the insulin gene in human diabetes (14–16). It was natural to suspect that defects at this locus might be involved, because almost all NIDDM individuals are characterized by insulin deficiency, either relative or absolute. Whereas insulin-gene structural defects might be anticipated to be rare, defects in the regulatory regions for glucose stimulation of insulin synthesis and secretion might be anticipated. Restriction-fragment–length polymorphisms (RFLPs) occur frequently in the human genome, and several were defined at the insulin locus (2,3,17). These RFLPs are either single-site polymorphisms or a variable number of tandem repeats. The extent of polymorphisms is so great at the insulin gene that heterozygosity is >90% when studied with various polymorphic enzymes. In addition, polymorphisms at nearby loci have also been used to identify insulin genes in diabetic and nondiabetic individuals (18–20). In studies of the frequency of polymorphisms at this locus in NIDDM, early studies suggested the positive association of a larger 5′-flanking region insulin gene. The early studies were in mixed racial groups, and later studies in Whites, American Blacks, Pima Indians, Nauruans, Japanese, and Punjabi Sikhs have shown a convincing lack of association of the insulin gene with NIDDM (2, 3,17,21–29).

Whereas positive associations are often suggestive, negative associations do not rule out possible involvement of the insulin gene. Linkage analysis in families is always a more powerful type of analysis. Here, the insulin genes are identified in the mother and father, and the sharing of the same genes by diabetic offspring is evaluated. Several White families with MODY and a few White, American Black, and Punjabi Sikh families with NIDDM have been studied, and all have shown a lack of linkage of diabetes to the insulin locus (30–32). Thus, although insulin-gene mutations may be responsible for contributing to the genetic susceptibility of diabetes in a few individuals, it is unlikely that insulin-gene defects play a major role in NIDDM.

Another likely candidate for inherited defects predisposing to diabetes is the human insulin-receptor gene. Several investigators have defined RFLPs specific for the α- and β-subunits of the 5000–base-pair receptor cDNA

(33–36). We have evaluated four RFLPs at the insulin-receptor locus in a large population of American Black NIDDM subjects divided into lean and obese groups and young-onset versus older-onset groups, reasoning that these would represent different subtypes of diabetes. Whereas neither age of onset nor obesity was important, there appeared to be no significant difference in the frequency of RFLPs in the NIDDM group compared with that in a nondiabetic Black group (4). Both associations and lack of associations have been reported for RFLPs and NIDDM at the insulin-receptor locus (33–40). Whether this locus will provide a genetic marker for NIDDM in American Blacks can only be determined by studies in Black families.

Another likely candidate for inherited defects predisposing to NIDDM is the glucose-transporter (GT) gene. The erythrocyte GT gene has been cloned and sequenced (40), and RFLPs have been identified (41–43). There is a suggestion that this GT gene may be different in diabetic and nondiabetic individuals (41), although no difference has been found in American Blacks (42) or Orientals (43). More recently, several GT genes with separate chromosomal locations have been identified (44). Whether GT genes are a genetic marker for NIDDM remains to be determined.

Finally, how would identification of genetic markers for diabetes benefit mankind? I like to think that the current state of knowledge of diabetes is equivalent to the knowledge of fever 300 years ago. All that was known then was that someone either had a fever or not, with no idea of what caused the fever and certainly no idea of how to treat it. Over the last 300 years, many different reasons have been found for fever, and many different ways have been found to treat it. Certain forms of treatment are appropriate for one type of fever but totally inappropriate for another. Once the many different causes of diabetes are defined, a more precise definition of the type of diabetes and more appropriate therapy may be forthcoming. The ultimate goal of the study of the genes involved in diabetes susceptibility is to identify individuals at risk and perhaps through genetic surgery to remove the risk before onset of diabetes. Expression of human insulin genes in transgenic mice has already been accomplished, so this seemingly far-fetched goal in humans may be reached sooner than anticipated.

REFERENCES

1. Permutt MA: The use of DNA polymorphisms for genetic analysis of non-insulin dependent diabetes mellitus. In *The Genetics of Diabetes*. Tait BD, Harrison LC, Eds. London, Saunders. In press
2. Permutt MA: The insulin gene and its regulation. In *Insulin Secretion: Molecular and Cellular Biology of Diabetes Mellitus*. Draznin B, Melmed S, LeRoith D, Eds. New York, Liss, 1988, p. 12–23
3. Permutt MA, Elbein SC: Insulin gene in diabetes: analysis through RFLP. *Diabetes Care* 13:364–74, 1990
4. Permutt MA, McGill J, Elbein SC, Province M, Lillioja S: Insulin receptor gene polymorphisms (RFLPs) in American Blacks and Pima Indians: assessment of the use of RFLPs in evaluating a candidate locus for NIDDM. In *Genes and Gene Products in the Development of Diabetes Mellitus. Basic and Clinical Aspects, Oslo, Norway, July 3–5, 1989*. Nerup J, Mandrup-Poulsen T, Hökfelt B, Eds. Amsterdam, Excerpta Med., 1990, p. 249–62
5. Seino S, Seino M, Bell GI: Human insulin-receptor gene. *Diabetes* 39:129–33, 1990
6. Zimmet P: Type 2 (non-insulin-dependent) diabetes: an epidemiological overview. *Diabetologia* 22:399–411, 1982
7. Rotter JI, Rimoin DL: The genetics of diabetes. *Hosp Pract* 22:79, 1987
8. Barnett AH, Eff C, Leslie RDG, Pyke DA: Diabetes in identical twins: a study in 200 pairs. *Diabetologia* 20:87–93, 1981
9. Newman B, Selby JV, King ML, Siemenda C, Fabsitz R, Friedman GD: Concordance for type 2 (non-insulin-dependent) diabetes mellitus in male twins. *Diabetologia* 30:763–69, 1987
10. Chakraborty R, Ferrell RE, Stern MP, Haffner SM, Hazuda HP, Rosenthal M: Relationship of prevalence of non-insulin-dependent diabetes mellitus to Amerindian admixture in the Mexican Americans of San Antonio, Texas. *Genet Epidemiol* 3:435–54, 1986
11. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG: The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. *Diabetes* 34:222–34, 1985
12. Fajans SS: Maturity-onset diabetes of the young (MODY). *Diabetes Metab Rev* 5:579–606, 1989
13. O'Rahilly S, Turner RC: Early-onset type 2 diabetes vs maturity-onset diabetes of youth: evidence for the existence of two discrete diabetic syndromes. *Diabetic Med* 5:3, 1988
14. Bell GI, Swain WF, Pictet R, Cordell B, Goodman HM, Rutter WJ: Nucleotide sequence of a cDNA clone encoding human preproinsulin. *Nature* (Lond) 282:525–27, 1979
15. Ullrich A, Dull TJ, Gray A: Genetic variation in the human insulin gene. *Science* 200:612–15, 1980
16. Bell GI, Pictet R, Rutter WJ, Cordell B, Tischer E, Goodman HM: Sequence of the human insulin gene. *Nature* (Lond) 284:26–32, 1980
17. Elbein SC, Permutt MA: The role of the insulin in diabetes: use of restriction fragment length polymorphisms in diagnosis. In *Molecular Biology of Islets of Langerhans*. Okamoto H, Ed. Cambridge, UK, Cambridge Univ. Press, 1990, p. 251–61
18. Zabel BU, Kronenberg HM, Bell GI, Shows TB: Chromosome mapping of genes on the short arm of human chromosome 11: parathyroid hormone gene is at 11;15 together with the genes for insulin, c-Harvey-*ras 1*, and B-hemoglobin. *Cytogenet Cell Genet* 39:200–205, 1985
19. Bell GI, Gerhard DS, Fong NM, Sanchez-Pescador R, Rall LB: Isolation of the human insulin-like growth factor genes: insulin-like growth factor II and insulin genes are contiguous. *Proc Natl Acad Sci USA* 82:6450–54, 1985
20. O'Malley KI, Rotwein P: Human tyrosine hydroxylase and insulin genes are continuous on chromosome 11. *Nucleic Acids Res* 16:4437–46, 1988
21. Bell GI, Karam JH, Rutter WJ: Polymorphic DNA region adjacent to the 5′ end of the human insulin gene. *Proc Natl Acad Sci USA* 78:5759–63, 1981

22. Rotwein PS, Chirgwin J, Province M, Knowler WC, Pettitt DJ, Cordell B, Goodman HM, Permutt MA: Polymorphism in the 5′ flanking region of the human insulin gene: a genetic marker for non-insulin-dependent diabetes. *N Engl J Med* 308:65–71, 1983
23. Elbein S, Rotwein P, Permutt MA, Bell GI, Sanz N, Karam JH: Lack of association of the polymorphic locus in the 5′-flanking region of the human insulin gene and diabetes in American Blacks. *Diabetes* 34:433–39, 1985
24. Bell GI, Horita S, Karam JH: A polymorphic locus near the human insulin gene is associated with insulin-dependent diabetes mellitus. *Diabetes* 33:176–83, 1984
25. Knowler WC, Pettitt DJ, Vasquez B, Rotwein PS, Andreone TL, Permutt MA: Polymorphism in the 5′ flanking region of the human insulin gene: relationships with non-insulin-dependent diabetes mellitus, glucose and insulin concentrations, and diabetes treatment in the Pima Indians. *J Clin Invest* 74:2129–35, 1984
26. Serjeantson SW, Owerbach D, Zimmet P, Nerup J, Thoma K: Genetics of diabetes in Nauru: effects of foreign admixture, HLA antigens and the insulin-gene-linked polymorphisms. *Diabetologia* 25:13–17, 1983
27. Haneda M, Kobayashi M, Maegawa H, Shigeta Y: Low frequency of the large insertion in the human insulin gene in Japanese. *Diabetes* 35:115–18, 1986
28. Aoyama N, Nakamura T, Doi K, Baba S, Takahashi R, Siguyama T: Low frequency of 5′-flanking insertion of human insulin gene in Japanese non-insulin-dependent diabetic subjects. *Diabetes Care* 9:365–69, 1986
29. Takeda J, Seino Y, Fukumoto H, Koh G, Otsuka A, Ikeda M, Kuno S, Yawata M, Moridera K, Morita T: The polymorphism linked to the human insulin gene: its lack of association with either IDDM or NIDDM in Japanese. *Acta Endocrinol* 113:268–71, 1986
30. Andreone T, Fajans S, Rotwein P, Skolnick M, Permutt MA: Insulin gene analysis in a family with maturity-onset diabetes of the young. *Diabetes* 34:108–14, 1985
31. Elbein SC, Corsetti L, Goldgar D, Skolnick M, Permutt MA: Insulin gene in familial NIDDM: lack of linkage in Utah Mormon pedigrees. *Diabetes* 37:569–76, 1988
32. Elbein SC, Ward WK, Beard JC, Permutt MA: Familial NIDDM: molecular-genetic analysis and assessment of insulin action and pancreatic β-cell function. *Diabetes* 37:377–82, 1987
33. Elbein SC, Corsetti L, Ullrich A, Permutt MA: Multiple restriction fragment length polymorphisms at the insulin receptor locus: a highly informative marker for linkage analysis. *Proc Natl Acad Sci USA* 83:5223–27, 1986
34. Oelbaum RS, Li S, Baroni MG, Galton DJ: Insulin receptor gene polymorphisms in Caucasian and Japanese type 2 (non-insulin-dependent) diabetic patients (Abstract). *Diabetologia* 31:528A, 1988
35. McClain DA, Henry RR, Ullrich A, Olefsky JM: Restriction-fragment–length polymorphism in insulin-receptor gene and insulin resistance in NIDDM. *Diabetes* 37:1071–75, 1988
36. Takeda J, Seino Y, Yoshimasa Y, Fukumoto H, Koh G, Kuzuya H, Imura H, Seino S: Restriction fragment length polymorphisms (RFLP) of the human insulin receptor gene in Japanese: its possible usefulness as a genetic marker. *Diabetologia* 29:667–69, 1986
37. Xiang K-S, Cox NJ, Sanz N, Huang P, Karam JH, Bell GI: Insulin-receptor and apolipoprotein genes contribute to development of NIDDM in Chinese Americans. *Diabetes* 38:17–23, 1989
38. Elbein SC, Borecki I, Corsetti L, Fajans SS, Hansen AT, Nerup J, Province M, Permutt MA: Linkage analysis of the human insulin receptor gene and maturity onset diabetes of the young. *Diabetologia* 30:641–47, 1987
39. O'Rahilly S, Trembath RC, Patel P, Galton DJ, Turner RC, Wainscoat JS: Linkage analysis of the human insulin-receptor gene in type-2 (non-insulin-dependent) diabetic families and a family with maturity onset diabetes of the young. *Diabetologia* 31:792–97, 1988
40. Mueckler M, Caruso C, Baldwin SA, Panico M, Blench I, Morris HR, Allard WF, Lienhard GE, Lodish HF: Sequence and structure of a human glucose transporter. *Science* 229:941–45, 1985
41. Li SR, Baroni MG, Oelbaum RS, Stock J, Galton DJ: Association of genetic variant of the glucose transporter with non-insulin-dependent diabetes mellitus. *Lancet* 10:368–70, 1988
42. Kaku K, Matsutani A, Mueckler M, Permutt MA: Polymorphisms of HepG2/erythrocyte glucose-transporter gene: linkage relationships and implications for genetic analysis of NIDDM. *Diabetes* 39:49–56, 1990
43. Cox NJ, Xiang K-S, Bell GI, Karam JH: Glucose transporter gene and non-insulin-dependent diabetes. *Lancet* 10:793–94, 1988
44. Mueckler M: Family of glucose-transporter genes: implications for glucose homeostasis and diabetes. *Diabetes* 39:6–11, 1990
45. Orland MJ, Chyn R, Permutt MA: Modulation of proinsulin messenger RNA after partial pancreatectomy in rats: relationship to glucose homeostasis. *J Clin Invest* 75:2047–55, 1985
46. Orland MJ, Permutt MA: Genetic susceptibility to diabetes in inbred strains of mice: measurements of proinsulin mRNAs and response to dexamethasone. *Diabetologia* 30:934–39, 1987