

Distribution of Type II Diabetes in Nuclear Families

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Type II diabetes has a substantial genetic component, but the mode of inheritance and the molecular basis of this inheritance are uncertain. This study documents the familial distribution of the disease in the parents and siblings of a consecutive series of type II diabetic subjects. We studied 66 first-degree relatives of 20 white subjects with type II diabetes and both parents alive. They were tested with a continuous infusion of glucose ($5 \text{ mg} \cdot \text{kg IBW}^{-1} \cdot \text{min}^{-1}$) ($n = 49$) or FPG and hemoglobin A1c ($n = 17$). Seven probands had neither parent affected with diabetes or IGT, 10 had one parent affected (6 with diabetes and 4 with IGT), and 3 had both parents affected. The probands with affected and those with unaffected parents were phenotypically similar. These findings indicate that a sizable subgroup of type II diabetic subjects may have neither parent affected with a demonstrable abnormality of glucose tolerance. The assumption of autosomal dominance with complete penetrance is not supported, although it remains possible that a dominant gene of low penetrance may play a role in some pedigrees. Polygenic inheritance would appear likely, and genetic heterogeneity may occur. The inheritance of diabetic traits from phenotypically normal parents needs to be considered in the analysis of genetic linkage with type II diabetes. *Diabetes* 42:106–12, 1993

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Type II diabetes, non-insulin-dependent diabetes mellitus; BMI, body mass index; WHO, World Health Organization; MODY, maturity-onset diabetes of the young; IBW, ideal body weight; IGT, impaired glucose tolerance; FPG, fasting plasma glucose; CV, coefficient of variation; GTT, glucose tolerance test.

Type II diabetes is a common metabolic disorder with considerable morbidity and mortality. Despite evidence for a substantial genetic component, the mode of inheritance and the molecular basis of this inheritance remain unknown.

Because monozygotic twins share genes and, in most cases, early environment, concordance is suggestive of genetic determination, whereas discordance is strongly suggestive of environmental effects. Barnett et al. (1) documented 91% concordance for type II diabetes in monozygotic twin pairs. The Barnett study was more likely to ascertain concordant twins because the authors were selecting twins with diabetes; each member of a twin pair could be a proband, and testing of a nondiabetic cotwin is likely to have taken place once one member of a twin pair had been diagnosed. Newman et al. (2) excluded this bias by investigating male monozygotic twin pairs recruited without regard to the diabetic status of either twin. The Newman study confirmed marked concordance for type II diabetes (58%) at the initial examination, and only 1 of 15 originally discordant twin pairs remained discordant at a second examination 10 yr later. These studies suggest a strong genetic predisposition to type II diabetes, but the lack of complete concordance and variation in age of onset between twins suggests input from environmental influences.

Although the monozygotic twin studies point to a large genetic contribution to type II diabetes, they do not discriminate between monogenic and polygenic inheritance. In three populations where diabetes is common, bimodality of glucose tolerance has been demonstrated (3–5). Bimodality of itself, however, does not signify a single gene effect. An alternative explanation is that the transition from normality to disease is rapid rather than gradual, possibly from the deleterious effects of hyperglycemia (6). Bimodality has not been described in the

white population (7) but has been reported in the first-degree relatives of white, type II diabetic subjects (8).

Kobberling and Tillil (9) documented the family histories of 311 subjects with type II diabetes. They performed an age correction according to the modified Stromgren method to calculate the frequency of diabetes among first-degree relatives. The calculated ultimate prevalences for the siblings and children of type II diabetic subjects were 37.9 and 32.2%, respectively. Because of incomplete penetrance, these figures have been interpreted as being consistent with dominant inheritance. The prevalence for the parents of type II diabetic subjects was 20.8%, a lower prevalence than is consistent with a dominant model of inheritance with constant penetrance.

That segregation analysis is a necessary prerequisite for more sophisticated genetic studies seems obvious, but such data have not been reported since the differentiation of type I and type II diabetes (10–14). Family studies are difficult in type II diabetes. Physiological assessment of all family members is essential because of the prevalence of subclinical disease. The late age of onset and the differential mortality of affected subjects result in a paucity of complete nuclear families. The major difficulty is simply that in most cases one or both parents of a subject with type II diabetes are deceased, while their children are not yet old enough to express the disease.

The clinical subtype, MODY, is characterized by the presentation of diabetes in early adult life and by pedigree structures suggestive of simple autosomal dominant transmission (15). A WHO study group in 1985 stated that "evidence is accumulating to suggest that type II diabetes susceptibility also may be conferred by a dominant gene (16)." Linkage studies with candidate genes for type II diabetes have been analyzed assuming autosomal dominant inheritance, with age-dependent penetrance for subjects >60 yr of age reaching a maximum of 0.8 in the putative heterozygote and 0.95 in the putative homozygote (17,18). The assumption of autosomal dominance implies that at least one parent of a subject with type II diabetes will demonstrate clinical diabetes or subclinical glucose intolerance.

This study describes the distribution of type II diabetes in the nuclear families of a consecutive series of type II diabetic subjects who have been ascertained without regard to family history of the disorder. A low prevalence of type II diabetes has been found in the parents, with the occurrence of type II diabetic probands with neither parent affected with diabetes or glucose intolerance. We will discuss the implications of these findings for the likely mode of inheritance of type II diabetes and for the application of genetic linkage analysis.

RESEARCH DESIGN AND METHODS

The Central Oxford Research and Ethics Committee approved the protocol for this study. All subjects gave their informed consent. We questioned 417 white, type II diabetic subjects about the availability of living parents for participation in the study. Twenty subjects who had

both parents alive and available for study were ascertained consecutively without regard to family history of the disease. Fifteen were men, and five were women. They were 40 ± 5 yr of age (mean \pm SD). None had ketonuria >1.5 mM (Ketostix, Ames) at presentation; all were treated by diet or tablets for at least 3 mo and were islet cell antibody negative. Their BMI was 30 ± 5 kg/m², and the FPG was 8.2 ± 2.4 mM on therapy. Paternity was confirmed by DNA fingerprinting (19). Table 1 gives details of the probands.

The probands, their siblings, and both parents were studied with a continuous infusion of glucose (CIGMA) test (20). This consisted of a continuous intravenous infusion of 5 mg glucose \cdot kg IBW⁻¹ \cdot min⁻¹ for 60 min. IBW was taken from the Metropolitan Life Insurance tables for a medium frame (21). The achieved plasma glucose value is the mean of the 50-, 55-, and 60-min samples. IGT was defined as an FPG or achieved plasma glucose level >2 SD above the mean normal value for the subject's age and obesity, as determined in comparison with a population of 104 normal subjects (age range 21–76 yr, IBW range 86–158%).

Type II diabetes was diagnosed according to the WHO criterion of FPG >7.8 mM. A formal study of the reproducibility of the CIGMA test in 30 subjects (13 nondiabetic subjects, 11 diet-treated type II diabetic subjects, and 6 subjects with IGT) gave a CV of 5% (21a). In 17 of the elderly parents glucose tolerance testing was not possible and FPG and HbA_{1c} were obtained instead. Glucose tolerance status was determined solely by the plasma glucose levels in view of the known unreliability of glycated hemoglobin for diagnosing IGT or diabetes (22). Affected status was defined as including both IGT and type II diabetes.

Plasma glucose was measured with a hexokinase method using a Cobas MIRA centrifugal analyzer. Islet cell antibodies were assessed by an indirect immunofluorescence technique. HbA_{1c} was measured with ion-exchange high-performance liquid chromatography using the Bio-Rad DIAMAT (Richmond, CA). The normal range (\pm 2 SD) in a population of nondiabetic subjects aged 73 ± 6 yr was 4.8–6.8%.

Except where otherwise stated, the data are presented as means \pm SD. Comparisons between groups were made with the Mann-Whitney U test.

RESULTS

Seven diabetic probands had neither parent affected with type II diabetes or IGT, 10 had one parent affected (6 type II diabetes, 4 IGT), and 3 had both parents affected (2 IGT/IGT, 1 type II diabetes/diabetes). The probands with one or more affected parents and those with unaffected parents had similar age at diagnosis (39 ± 5 and 42 ± 5 yr) and obesity (30 ± 3 , 29 ± 8 kg/m²).

The affected and unaffected parents were of similar age (73 ± 6 , 73 ± 8 yr) and obesity (26 ± 5 , 26 ± 6 kg/m²). Tables 2 and 3 show the clinical details of the parents. Unsuspected type II diabetes was diagnosed in the father of proband 15. Although the father of proband

TABLE 1
Clinical characteristics of the type II diabetic probands

Case no.	Affected parents (n)	Age at diagnosis (yr)	Duration (yr)	BMI (kg/m ²)	Sex	Presentation	Initial treatment	Duration on initial treatment (yr)	Current treatment	FPG on treatment (mM)	Complications
1		37	6	25	Female	Symptoms	OHA	6	OHA	6.2	Nil
2		44	8	30	Male	Incidental	Diet	8	Diet	9.5	Nil
3		43	5	46	Female	Incidental	Diet	1	Insulin	10.7	Nil
4		40	3	34	Male	Incidental	OHA	3	OHA	6.1	Nil
5		44	3	24	Male	Symptoms	OHA	3	OHA	9.3	Nil
6		34	2	21	Male	Symptoms	Diet	2	Diet	14.1	Retinopathy
7		50	7	28	Female	Incidental	OHA	7	OHA	7.7	Nil
8	1	37	8	33	Male	Incidental	Diet	4	OHA	7.6	Nil
9	1	43	3	28	Male	Incidental	OHA	3	OHA	8.9	Nil
10	1	36	5	33	Male	Incidental	Diet	4	OHA	13.2	Retinopathy
11	1	45	7	29	Male	Symptoms	Diet	1.5	OHA	7.7	Retinopathy
12	1	33	11	26	Male	Symptoms	OHA	0.8	Insulin	10.3	Nil
13	1	43	2	27	Male	Incidental	Diet	2	Diet	5.5	Retinopathy
14	1	42	2	30	Male	Symptoms	OHA	2	OHA	6.0	Nil
15	1	35	1.5	29	Male	Symptoms	OHA	0.7	Insulin	7.6	Nil
16	1	30	16	28	Male	Symptoms	OHA	2	Insulin	6.8	Impotence, retinopathy
17	1	36	18	26	Female	Infection	OHA	18	OHA	6.5	Nil
18	2	37	1	34	Female	Symptoms	OHA	3	Insulin	6.3	Nil
19	2	40	2	29	Male	Incidental	Diet	2	Diet	8.1	Nil
20	2	49	5	34	Male	Symptoms	OHA	5	OHA	6.3	Impotence

OHA, oral hypoglycemic agents. Symptoms are thirst, polyuria, and lethargy.

12 had normal glucose tolerance when studied, he had been diagnosed with diabetes at age 68 and had received oral hypoglycemic therapy for 8.5 yr. A below-knee amputation 6 mo before the date of testing was followed by the loss of 23 kg of weight and the cessation of the requirement for oral therapy.

Seven of the 33 siblings of the type II diabetic subjects were unavailable for study, and none was known to have type II diabetes. Of the 26 siblings studied, 3 were known to have type II diabetes, and 9 were found to have IGT on testing. No new cases of type II diabetes were diagnosed in the siblings. In the 7 pedigrees with neither parent affected, 3 of 10 (30%) siblings were affected, one with diabetes and two with IGT. In the 10 pedigrees with one affected parent, 6 of 13 (46%) siblings were affected, 2 with diabetes and 4 with IGT. In the 3 pedigrees with 2 affected parents, each of the 3 siblings available for testing had IGT.

In the 10 pedigrees with 1 affected parent, 9 of 10 times the affected parent was the father. Given the 1.5:1 prevalence of men to women in new-onset type II diabetic patients in the UK (23), this pattern is of borderline statistical significance ($P = 0.048$ using a binomial distribution).

In the 20 nuclear families, 5 probands had no affected first-degree relatives (parents or siblings), 6 had only glucose-intolerant first-degree relatives, and 9 had 1 or more first-degree relatives with type II diabetes. The family trees of the 20 probands are shown in Fig. 1.

DISCUSSION

The identification of a gene (or genes) contributing to susceptibility to type II diabetes would have profound implications on its prevention and management. Linkage

analysis in pedigrees is a powerful tool for examining the role of candidate genes in the etiology of inherited diseases (24). The analysis of complex disorders such as type II diabetes, however, presents methodological difficulties not encountered with fully penetrant Mendelian conditions. The mode of inheritance must be specified for the likelihood calculations generally used, and the results at least partly depend on the assumptions of the model.

In this study, 7 of 20 type II diabetic probands have neither parent affected with diabetes or IGT. These findings indicate that the assumption of autosomal dominant inheritance with complete penetrance is not applicable.

The probands with unaffected parents were phenotypically similar to the 13 probands with one or more affected parents. The 30% prevalence of affection in the siblings of the probands with unaffected parents makes an inherited trait possible in these families, although shared environmental influences also may be relevant.

Affected status was defined as including subjects both with IGT and type II diabetes. The white population has a continuous distribution of blood glucose values (7), and subjects with IGT have an increased risk of both macrovascular disease (16) and progression to type II diabetes (25–28). If a stricter criterion of affected status had been applied to the data, a higher proportion of the type II diabetic probands would have had unaffected parents.

In 90% of the pedigrees with one affected parent, it was the father who had type II diabetes or IGT. This raises the question of imprinting (29), but in other type II diabetic families, an excess of maternal affection has been described (30).

Type II diabetes probands were 30–50 yr of age at presentation of the disease. Because the criterion for

TABLE 2
Clinical characteristics of the parents of the 7 probands with unaffected parents

Proband No.	Parent's sex	Age (yr)	Affection status	BMI (kg/m ²)	FPG (mM)	Achieved plasma glucose (mM)	HbA _{1c} (%)	FPG Z (SD)	Achieved plasma glucose Z (SD)
1	Male	67	Normal	19	5.0		5.0	0.2	
	Female	64	Normal	26	5.0	8.6	6.2	0.3	-0.1
2	Male	76	Normal	25	5.8		6.5	1.9	
	Female	73	Normal	24	4.5		6.0	-1.0	
3	Male	75	Normal	35	5.3	9.0	6.0	0.7	0.6
	Female	68	Normal	27	5.1	9.6	5.7	0.4	0.9
4	Male	68	Normal	21	4.8	9.1	5.6	-0.1	-0.1
	Female	69	Normal	27	5.0	8.9	6.2	0.3	0.1
5	Male	75	Normal	32	5.0		5.3	0.1	
	Female	72	Normal	25	4.9		3.8	0.0	
6	Male	62	Normal	25	4.7		6.0	-0.3	
	Female	60	Normal	21	4.6		6.3	-0.4	
7	Male	92	Normal	15	3.5		6.1	-3.6	
	Female	91	Normal	25	4.3		6.3	-1.9	

Z, deviation of the plasma glucose in SDs from the age- and obesity-predicted value for a nondiabetic individual; OHA, oral hypoglycemic agents. IGT defined as a fasting or an achieved plasma glucose two SDs above the mean of an age- and body-weight-matched normal population.

selecting subjects was availability of living parents, the study had a selection bias toward subjects with an earlier age of onset. Three of 11 probands who had the disease at or before 40 yr of age had neither parent affected, 6 had one parent affected, and 2 had both parents affected. This compares with the data of O'Rahilly et al. (31)

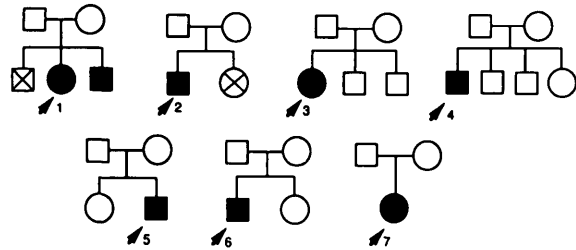
who reported 92% affection in the 23 available parents of 13 type II diabetic subjects who were in this age-group at presentation. An increased chance of finding diabetes in the relatives was possible in that study, because six probands were ascertained through an affected family member.

TABLE 3
Clinical features of the parents of the 13 probands with affected parent(s)

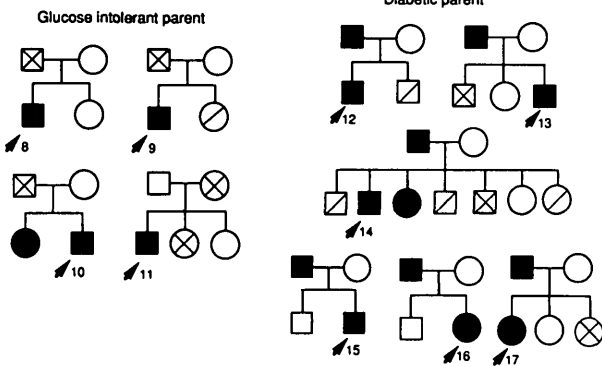
Proband No.	Parent's sex	Age (yr)	BMI (kg/m ²)	Duration of known diabetes (yr)	Current treatment	FPG (mM)	Achieved plasma glucose (mM)	HbA _{1c} (%)	FPG Z (SD)	Achieved plasma glucose Z (SD)	Affection status
8	Male	76	15			6.8		6.3	4.0		IGT
	Female	67	40			4.9		5.5	0.0		Normal
9	Male	79	29			6.2	11.7	6.7	2.6	2.9	IGT
	Female	76	30			5.2		5.9	0.5		Normal
10	Male	77	29			6.7	9.8	6.2	3.7	0.9	IGT
	Female	69	20			4.7	9.8	6.5	-0.4	0.6	Normal
11	Male	73	22			4.7	9.5	6.5	-0.5	0.3	Normal
	Female	72	25			6.0	9.0	6.8	2.3	0.1	IGT
12	Male	77	21	9	Diet	5.3	9.8	4.8	0.7	0.5	Diabetes
	Female	80	22			5.1	9.3	5.6	0.1	0.0	Normal
13	Male	73	20	15	OHA	7.7	12.3	6.7	6.1	3.2	Diabetes
	Female	71	22			5.3	10.4	5.5	0.9	1.4	Normal
14	Male	74	24	5	Diet	6.0		5.8	2.3		Diabetes
	Female	71	25			4.8	7.2	5.2	-0.3	-1.7	Normal
15	Male	65	27	0		19.3	21.1	11.5	31.7	13.0	Diabetes
	Female	66	40			5.4	8.0	5.1	1.3	0.3	Normal
16	Male	82	28	0.7	Diet	12.0	15.8	8.6	15.3	7.1	Diabetes
	Female	80	27			5.0	9.2	6.1	0.0	0.3	Normal
17	Male	81	20	49	Diet	7.5		7.8	5.4		Diabetes
	Female	77	26			5.2		6.0	0.6		Normal
18	Male	65	28			5.8	9.5	6.1	2.1	0.9	IGT
	Female	64	36			7.2	10.7	5.8	5.3	2.8	IGT
19	Male	72	21			6.3	11.9	6.7	2.9	2.8	IGT
	Female	61	31			6.6	11.2	6.0	4.0	3.0	IGT
20	Male	78	28	2	OHA	6.6		7.4	3.6		Diabetes
	Female	77	32	20	Insulin	10.4		8.0	11.9		Diabetes

OHA, oral hypoglycemic agents.

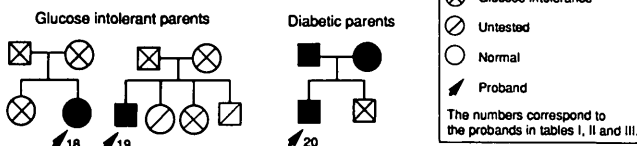
1. Neither parent affected



2. One parent affected



3. Both parents affected



● Type 2 diabetic subject
 ⊗ Glucose intolerance
 ○ Untested
 ○ Normal
 ↙ Proband

The numbers correspond to the probands in tables I, II and III.

FIG. 1. Family trees of the 20 consecutive type II diabetic subjects with living parents.

The increased mortality of diabetic parents would introduce a selection bias in favor of probands with unaffected parents. What remains unclear is whether this low prevalence of affection in the parents applies to the general type II diabetic population. The accumulation of further families will permit validation of this finding but will not remove this potential source of bias.

The pattern of inheritance in these 20 families would be consistent with an autosomal recessive or polygenic mode of inheritance and with a dominant gene with incomplete penetrance. The reported prevalence of type II diabetes in the offspring of white, conjugal diabetic parents makes a single recessive gene a less likely model of inheritance for the usual form of type II diabetes (32–35). These data were collected before the distinction between type I and type II diabetes was fully recognized. Although the majority of the parents had maturity-onset diabetes, this possible source of heterogeneity makes the results difficult to interpret. Cooke et al. (32) found a prevalence of known diabetes in the offspring of conjugal diabetic parents of 4.4%. Kahn et al. (33) performed GTTs and found a 41–62% prevalence of abnormal glucose tolerance, depending on the age and weight of the offspring. Tattersall and Fajans (34), by using oral GTTs, assessed the cumulative risk of abnormal glucose tolerance or diabetes by the age of 60 in the

offspring of conjugal diabetic parents to be ~60%. On the basis of a 10-yr follow-up of the 700 offspring of 205 conjugal diabetic parents, Ganda and Soeldner (35) have estimated that by age 85, 33% of the offspring will have diabetes, and >50% will demonstrate an abnormality of glucose tolerance on repeated testing. Although each of these studies has limitations, they demonstrate that not all the offspring of conjugal diabetic couples develop diabetes. These results do not support the assumption of autosomal recessivity.

An oligogenic model, with a few genetic mutations being major determinants, or a polygenic model in which many mutations can contribute, would seem more likely for the inheritance of type II diabetes. Some patients with distinct clinical syndromes associated with extreme insulin resistance are compound heterozygotes for different mutant alleles that impair insulin-receptor function by different mechanisms (36). The parents who were heterozygous carriers demonstrated less severe insulin resistance. In a similar manner, type II diabetes may be attributable to combinations of mutations in one or more genes. Differentiation of these models from monogenic inheritance with incomplete penetrance would be difficult even with the segregation analysis of a large number of pedigrees. Type II diabetes is likely to be heterogeneous, and the data do not exclude the possibility that a dominant gene of low penetrance could play a crucial role in some pedigrees, in combination with other genetic or environmental factors.

A limiting factor in the analysis of genetic linkage with type II diabetes has been the requirement of specifying a genetic model. Numerous programs have been developed, such as COMBIN (37), which perform combined segregation and linkage analysis in a given data set. An alternative approach is that of Cox et al. (38), who performed the likelihood calculations for linkage analysis with several different assumptions for the mode of inheritance.

Other robust methods for linkage analysis are available, although they are less statistically powerful than classical linkage analysis. The affected sib-pair approach (39) does not require assumptions about the mode of inheritance, but the collection of a suitably large number of type II diabetic sib-pairs with living parents is difficult. By the time two siblings have developed type II diabetes, at least one of the parents usually has died, and if early onset probands are selected, the analysis may be complicated by having two affected parents. In the absence of parental information, the statistical power of this method is substantially reduced. The affected-pedigree-member method of Weeks and Lange (40) does not require either the specification of a genetic model or parental information because the calculations are based on identity-by-state comparisons. As expected, however, statistical power is less than standard linkage analysis. Because of autosomal-dominant transmission and penetrance at a young age, pedigrees with MODY may provide a more useful model for genetic linkage and the identification of diabetogenic genes (15). Bell et al. (41) reported linkage of the adenosine deaminase locus with MODY in one large pedigree, but linkage

with this locus has not been found with other MODY pedigrees (42). Linkage between the glucokinase gene locus on chromosome 7p and diabetes has been reported in French pedigrees and a British pedigree with MODY (43,44), and glucokinase mutations have been identified (45,46). The relevance of this susceptibility gene for MODY to the more usual form of type II diabetes needs to be determined.

Because genetic heterogeneity would appear likely in type II diabetes, the direct search for mutations in candidate genes may prove to be a valuable approach. Mutations can be detected using the polymerase chain reaction (47) with electrophoresis for single-strand conformation polymorphisms (48) or with a denaturing gradient (49), followed by direct DNA sequencing (36). These techniques can be applied to individual patients or specific cohorts, and do not depend on the availability of large pedigrees or on information concerning the mode of inheritance.

The identification of a subgroup of type II diabetic patients with neither parent affected suggests that traits inducing diabetes may be inherited from unaffected parents. The genetic analysis of type II diabetes needs to deal with the potential complexities of polygenicity and genetic heterogeneity.

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