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Genetic heterogeneity in Gaucher disease

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SUMMARY Considerable clinical variability occurs in adult Gaucher disease type I and three main subtypes may be delineated: a very mild form, a severe form, and a moderate form which itself presents various clinical manifestations. A study based on 25 families from our clinic and a review of published reports showed that when both parents were heterozygous and more than one child was affected with Gaucher disease type I, there was always intrafamilial similarity concerning the three subtypes. In families where one parent and at least one child were affected, variability in the clinical subtype of Gaucher disease type I might occur among the affected members of the family. We propose that the three different clinical subtypes of this disease reflect the genetic heterogeneity of two alleles, G_1^a and G_1^b, and the three corresponding genotypes represent the three different subtypes of the disease.

Gaucher disease occurs in three distinct forms classified according to the degree of neurological involvement: type I non-neuronopathic, adult type; type II acute neuronopathic, infantile type; and type III chronic neuronopathic, juvenile type.[1] These three types are considered to be caused by three different mutations at the β-glucocerebrosidase locus which are most probably allelic.[1] Type I is the most common of the three and we shall be concerned with this only.

Gaucher disease type I shows considerable clinical variability and has been divided into three clinical subtypes[2]: (1) a severe form which begins early in childhood leading to severe clinical complications; (2) a mild, almost asymptomatic form which is sometimes detected accidently and is not accompanied by apparent clinical symptoms; and (3) an 'intermediate' form which is diagnosed in late childhood or later. In the third subtype various organs are affected with different degrees of severity and the clinical manifestations of these patients vary according to the affected organs. Gaucher disease type I is relatively frequent among Ashkenazi Jews, but has been reported to occur in all ethnic groups.[1] Genetic heterogeneity of type I has been demonstrated in various ethnic groups by differences in the kinetic behaviour of the residual β-glucocerebrosidase.[3]

Because of the clinical variability of type I it is difficult to give genetic counselling regarding the prognosis and the severity of the disease in future children. We have analysed families with two or more patients with the disease in order to find out if genetic heterogeneity could explain the clinical variability of type I.

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Patients and methods

We included families with members with Gaucher disease, in whom at least two generations were examined. Twenty-five families with at least one type I patient were tested for β-glucocerebrosidase activity in leucocyte homogenates as previously described.[4] They represent most of the families with type I patients who were examined and followed up in the paediatric haematological clinic at the Beilinson Hospital. Since these Gaucher disease patients were diagnosed in a paediatric clinic, they do not represent the relative frequency of the different clinical subtypes of type I in Israel.

Additionally we reviewed available published reports of families in whom more than one member was affected with Gaucher disease type I. Few such families could be used since in earlier reports the enzymatic determinations were not always performed, and in most of the recent publications few clinical details were given. Furthermore, in most reports the parents were not examined. Therefore, the overall analysis could be performed on only 34 reported families.[5–30]

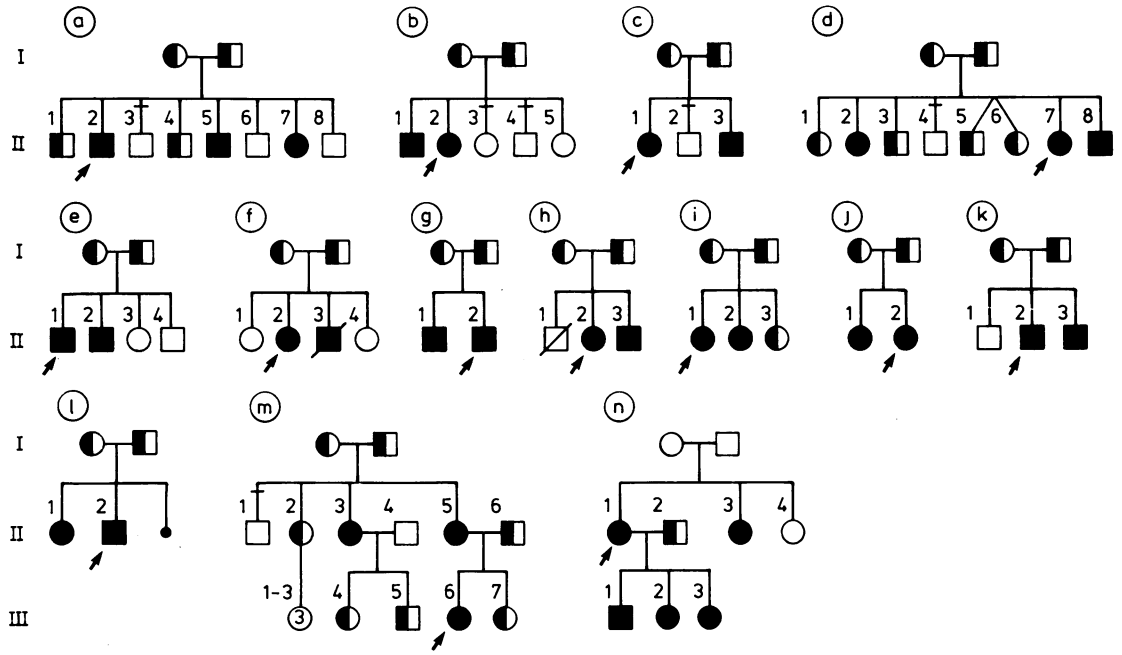

FIGURE *Pedigrees of the families examined by the authors in which more than one patient had Gaucher disease type I. The affected patients appear as black symbols and heterozygotes as half black symbols and were classified by enzymatic determinations. Persons in whom enzymatic determinations were in the normal range appear with a horizontal bar over the symbol.*

Results and discussion

The activity in leucocyte homogenates of β-glucocerebrosidase in parents and children was determined in 25 families. Enzyme activity was in the heterozygote range in both parents in 23 of these families, while in the other two families one parent had very low enzyme activity and was clinically affected with Gaucher disease type I, and the other parent was a carrier (table 1).

Among the 23 families in which both parents were carriers, in 10 only one child was affected, in 11 families two children were affected, and in two families three children were affected (table 1, families a to m in the figure and appendix). In the 13 families in whom more than one child was affected, the clinical presentation as classified by subtypes was the same within each sibship (table 1).

In two families (m and n) one of the parents was affected with type I disease. In family n all affected members had a mild disease, while in family m the daughter (III.6) had a 'severe' form and her mother (II.5) had a 'mild' disease.

A similar pattern was observed in families described in the published reports. The combined results of these and of the patients from our clinic are summarised in table 2. In probands whose parents were healthy carriers, the affected sib had a similar subtype of the disease. Only in the family described by Choy and Bouillon[9] did the children show clinical variability, but the parents in this study were not examined. In families with one affected parent and the other a carrier, clinical variability was observed. The variability in Gaucher disease subtypes was either between the affected parent and the children or among the children.

TABLE 1 *Twenty-five families with one or more patients with Gaucher disease examined by the authors.*

	No of families	*Clinical manifestations within families*
Both parents heterozygotes		
One child affected	10	—
Two children affected	11	Similar
Three children affected	2	Similar
One parent affected, one heterozygote		
One child affected	1	Different
Three children affected	1	Similar

TABLE 2 *Manifestations of Gaucher disease in affected members of 49 families with two or more patients from published reports (34 families) and examined by the authors (15 families).*

	Clinical manifestation within families	
	Similar	*Different*
Both parents 'healthy'	32 (20*)	1 (1*)
One or both parents with disease	3 (1*)	12 (10*)
One parent affected, asymptomatic	0	7 (6*)
Both parents affected, asymptomatic	0	2 (2*)
One parent affected, symptomatic	3 (1*)	3 (2*)

*Classification of Gaucher disease by clinical or pathological criteria only.

Hypothesis

Based on the data presented above, our hypothesis is that the clinical variability of Gaucher disease type I stems from genetic heterogeneity, that is, different mutations at the β-glucocerebrosidase locus. According to this hypothesis there are at least two different allelic mutations causing Gaucher disease type I, G_I^a and G_I^b, and each of the three genotypes represents a different phenotype: $G_I^a G_I^a$, a severe form; $G_I^b G_I^b$, a moderate form; and $G_I^a G_I^b$, a mild form.

The overall observations from our clinic together with those from published reports clearly showed that intrafamilial variability was observed only in families where at least one parent was affected with one of the forms of type I disease. This is compatible with the proposed hypothesis. When both parents were heterozygotes, as demonstrated by enzymatic examinations, each could have contributed only one Gaucher disease allele and the presentation in affected children was always within the same clinical subgroup. In some of these families, clinical differences were observed within sibships, yet all the affected children belonged to the same subgroup. In families where one parent was affected with type I, children affected with type I had either the same subtype as the parent or differed from the parent. In families where one parent had the mild form, affected children presented with one of the three subtypes. The mild subtype must therefore be a compound heterozygote $G_I^a G_I^b$ which may explain the possibility of having the three subtypes in the offspring.

This hypothesis can be confirmed by the demonstration of biochemical or molecular differences in the different subtypes of Gaucher disease type I. Klibansky *et al*[4] studied the kinetics of the residual enzyme in leucocytes of patients with the different subtypes of type I disease. The residual β-glucocerebrosidase activity and apparent Km were similar in all patients studied, yet a significant difference in heat inactivation was observed in patients who were severely affected as compared to the other forms. In the same study, members of family m were examined. The mother (II.5), who was mildly affected, has a residual activity of β-glucocerebrosidase similar to that of her severely affected daughter (III.6), but the heat inactivation profile of the enzyme was significantly different between the two. These observations are compatible with our hypothesis.

The relation between the genetic heterogeneity of Gaucher disease type I and the clinical variability is important, since it may allow the prediction of the clinical course of the disease within families. Further studies are needed to elucidate the molecular basis of the mutations causing Gaucher disease type I.

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APPENDIX *Clinical data on patients from 15 families examined by the authors (see figure).*

Family and patient	*Sex*	*Age at diagnosis (y)*	*Presenting symptoms*	*Last examinations*			*Other*
				Age (y)	*Enlarged spleen/liver*	*Bone disease*	
aII.2	M	4½	Hepatosplenomegaly	9	−/++	+	Partial splenectomy (9 years)
II.5	M	3	Family study, hepatosplenomegaly	4	++/++		
II.7	F	Birth	Family study				Not examined after diagnosis
bII.2	F	3	Hepatosplenomegaly	5	++/++		
II.1	M	7	Family study, hepatosplenomegaly	13	++/++	+	
cII.1	F	17	Mild thrombocytopenia	19	+/−		Mild thrombocytopenia
II.3	M	18	Family study	18	+/−		Mild thrombocytopenia
dII.7	F	6	Hepatosplenomegaly	11	+/+		No symptoms, constant mild hepatosplenomegaly
II.2	F	10	Family study	15	+/−		
II.8	M	5	Family study	10	−/−		
eII.1	M	1½	Hepatosplenomegaly	18	+++/++		
II.2	M	1½	Hepatosplenomegaly	15	−/++	+	Splenectomy (14 years)
fII.2	M	8	Hepatosplenomegaly	13	++/++	+	
II.3	M	1	Family study	3	+/+		Died, fulminant sepsis
gII.2	M	½	Hepatosplenomegaly	10	−/++	+	Partial splenectomy (10 years)
II.1	M	3	Family study	12	+++/+		
hII.2	M	19	Mild thrombocytopenia	29	−/−		Mild thrombocytopenia
II.3	M	13	Mild thrombocytopenia	23	−/−		Mild thrombocytopenia
iII.1	F	9	Hepatosplenomegaly	13	++/++	+	
II.2	F	3	Family study, hepatosplenomegaly	5	++/++		
jII.2	F	13	Hepatosplenomegaly	17	+/+		Mild thrombocytopenia
II.1	F	23	Family study	23	+/−		
kII.2	M	4	Splenomegaly	26	−/++		Splenectomy (13 years)
II.3	M	4	Splenomegaly	23	−/++		Splenectomy (7 years)
lII.2	M	3	Hepatosplenomegaly	3	+/+		
II.1	F	6	Hepatosplenomegaly	6	+/+		
mIII.6	F	1	Hepatosplenomegaly	17	−/++		Splenectomy (5 years)
II.5	F	32	Family study	48	+/−		Asymptomatic
II.3	F	40	Family study	56	+/−		Asymptomatic
nII.1	F	29	Thrombocytopenia	33	+/−		Very mild thrombocytopenia
II.3	F	?	Family study	?	−/−		'Very mild disease'
III.1	M	4	Family study	7	−/−		Asymptomatic
III.2	F	2	Family study	5	−/−		Asymptomatic
III.3	F	Birth	Family study	2	−/−		Asymptomatic