Non-Association of Friedreich's Ataxia and HLA Based on Five Families

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SUMMARY: *HLA-A, B, and C typing was carried out on five families with classical Friedreich's Ataxia (F.A.). Segregation patterns in a total of 16 offspring, 10 with the disease and 6 without, indicated no association between F.A. and HLA.*

RÉSUMÉ: *L'étude des HLA-A, B et C a été faite chez 5 familles souffrant d'ataxie de Freidreich classique. L'étude de la ségrégation chez 16 enfants, 10 atteints et 6 non atteints, n'indique aucune association entre l'ataxie de Friedreich et les groupes HLA.*

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Friedreich's ataxia, one of the heredo-familiar spino-cerebellar diseases, is a progressive degenerative disorder always inherited as an autosomal recessive. Its onset is usually before puberty and never after the age of 20 (Geoffrey et al., 1976).

The highly polymorphic HLA-A and -B antigenic specificities encoded on chromosome 6 are exceptionally useful for linkage studies within this region. The possibility of finding a genetic marker which could identify susceptible individuals at an early age within a family led to studies on the segregation of HLA in families with autosomal dominant forms of hereditary ataxia in the first instance. Thus, Yakura et al. (1974) showed that in a family with Marie's ataxia the three affected children had inherited the same haplotype from the father, whereas the two unaffected siblings inherited the other paternal haplotype. Information on an extended family with olivopontocerebellar atrophy led Jackson et al. (1971) to suggest that on the basis of linkage estimations (lod scores), there was a strong association between disease susceptibility and HLA. Since olivopontocerebellar atrophy occurs after the age of 20, their study was based only on patients and not on unaffected family members. However, Wastiaux et al. (1977) in another autosomal dominant form of spino-cerebellar atrophy (possibly olivo-pontocerebellar atrophy - type 1), found no evidence for linkage with HLA.

Niese et al. (1977) reported on an association between Friedreich's ataxia and HLA-Bw35, Cw4, and Dw1 in 9 patients, although it appears from their abstract that some of the patients were siblings.

We have tissue typed both healthy and affected members of five families in which the classical features of Friedreich's ataxia have appeared. All the healthy children have passed the age at which their affected siblings first showed signs of the disease. They are thus unlikely to develop the disease in the future, as age of onset is consistent within each family.

In three of the families, the segregation of HLA and Friedreich's ataxia is clearly independent (Table 1). In family 1, all four of the offspring have acquired the disease; two are HLA identical (a, d) and share one haplotype with one of their siblings (a, c), and the second haplotype with the other (b, d). In family 3, only one of the three HLA identical siblings has the disease and in family 5 the patient is HLA identical to her non-affected sibling. It is interesting to note that if only families "2" (all three HLA identical siblings have the disease) and "4" (the patient is only haplo-identical to the two healthy siblings) were considered, there would appear to be evidence for an association between HLA and this particular disease.

The disease presents a relatively homogenous picture in all five families, which suggests a common disease entity; our data indicates that the autosomal recessive disease susceptibility gene for classical Friedreich's ataxia is not linked to HLA.

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TABLE I

HLA-A, -B and -C Antigens in Five Families with Friedreich's Ataxia

Families		Sex	Disease state	Age	HLA haplotypes	
1	Father		—		Aw32-B14/A25-Bw44-Cw5	a/b
	Mother		—		A2-B15-Cw3/A3-B15-Cw3	c/d
Sib. 1	A.J.	F	F.A.		Aw32-B14/A3-B15-Cw3	a/d
Sib. 2	J.J.	F	F.A.		Aw32-B14/A3-B15-Cw3	a/d
Sib. 3	R.J.	F	F.A.		Aw32-B14/A2-B15-Cw3	a/c
Sib. 4	R.J.	M	F.A.		A25-Bw44-Cw5/A3-B15-Cw3	b/d
2	Father		—		A2-Bw50/X-B15-Cw3	a/b
	Mother		—		A1-B14/Aw24-B7	c/d
Sib. 1	H.B.	F	F.A.	17	A2-Bw50/Aw24-B7	a/d
Sib. 2	T.B.	F	F.A.	16	A2-Bw50/Aw24-B7	a/d
Sib. 3	R.B.	M	F.A.	9	A2-Bw50/Aw24-B7	a/d
Sib. 4	M.B.	M	—	12	A2-Bw50/A1-B14	a/c
3	Father				A29-B7/A26-Bw44	a/b
	Mother				A1-B17/A11-B27-Cw2	c/d
Sib. 1	M.D.	M	F.A.	15	A26-Bw44/A11-B27-Cw2	b/d
Sib. 2	A.D.	F	—	13	A26-Bw44/A11-B27-Cw2	b/d
Sib. 3	T.D.	M	—	17	A26-Bw44/A11-B27-Cw2	b/d
4	Father				A2-B17/Aw24-Bw44-Cw2	a/b
	Mother				A1-B8/Aw32-B40-Cw3	c/d
Sib. 1	R.H.	F	F.A.	19	Aw24-Bw44*/A1-B8-*Cw2	b/c
Sib. 2	H.H.	M	—	24	A2-B17/Aw32-B40-Cw3	a/d
Sib. 3	R.H.	F	—	26	A2-B17/Aw32-B40-Cw3	a/d
5	Father				A1-B8/A3-Bw40-Cw3	a/b
	Mother				A26-Bw35-Cw4/A11-B5	c/d
Sib. 1	M.B.	M	F.A.	19	A3-Bw40-Cw3/A26-Bw35-Cw4	b/c
Sib. 2	S.B.	F	—	25	A3-Bw40-Cw3/A26-Bw35-Cw4	b/c

* deduced

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