A Kindred with Familial Cold Urticaria : Linkage Analysis

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Summary. Familial cold urticaria is an autosomal dominant hereditary disease of which seven pedigrees have been published, six from the USA and the present one from Holland. Onset is shortly after birth. The patients develop skin symptoms sometimes accompanied by fever, chills, joint symptoms, and oedema, approximately one half to three hours after generalized exposure to cold.

In this paper the linkage data from the Dutch family are described; three generations containing 11 affected persons were studied in relation to 31 markers. While the data are inconclusive, they are presented here from the point of view of eventual accumulation when other families are studied in the same way.

Familial cold urticaria (FCU) is a rare autosomal dominant disease of which six pedigrees have been published from the USA (Kile and Rusk, 1940; Urbach, Hermann, and Gottlieb, 1941; Witherpoon *et al.*, 1948; Rodin, 1951; Tindall, Beeker, and Rosse, 1969; Derbes and Coleman, 1972). In addition, a brief case report from France (Castelain, 1971) mentioning dominant transmission through three generations is available. Onset is shortly after birth. The symptoms occur on generalized exposure to cold air after an interval of one half to several hours. The skin lesions begin on the exposed skin and consist of erythematous macules and plaques, urticarial lesions, and sometimes petechiae. After severe or prolonged exposure the skin lesions are accompanied by chills, fever, cushion-like oedema of the extremities, and joint complaints. The symptoms may last for up to 48 hours and are incapacitating in some cases. The only abnormal laboratory finding is a leucocytosis which precedes and accompanies the cold reaction. The symptoms tend to diminish with advancing age.

The disease is easily differentiated from acquired contact cold urticaria which is less rare, occurs

sporadically, and is characterized by symptoms like those seen during histamine release.

Recently the clinical findings in a kindred with FCU have been reported from the Netherlands (Doeglas, 1973 and 1974). In this family linkage studies were performed and these results are presented here. This is the first family with FCU in which linkage studies have been done.

Fig. 1

Material and Methods

Fig. 1 shows part of a larger pedigree. The complete pedigree covers more than 150 years and contains 108 descendants of a couple who were born in 1824. The family lives in the north-eastern part of the Netherlands, in a rural area between the city of Groningen and the German border. Some members have moved to a nearby province. The family data were obtained from local

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TABLE
PHENOTYPE DISTRIBUTION

	Sex	CU	Serum Types						Red Cell Enzymes			
			Gm ²	Inv ³	Gc	Hp	C'3	E ₁ ⁴	AcP	AK	GPT	PGM ₁
III.7	M	+	aa	++	1-1	2-1	S	U	BA	1	1	1
III.8	F	-	aa	--	2-1	2-1	FS	U	B	1	2-1	1
IV.11	M	-	aa	++	1-1	2-1	S	U	B	1	1	1
IV.13	F	+	aa	++	1-1	2-2	S	U	B	1	2-1	1
IV.15	F	+	aa	++	1-1	2-1	FS	U	BA	1	1	1
IV.16†	M	-	aa	--	2-2	1-1	S	U	B	1	2-1	2
IV.17	F	-	aa	--	1-1	1-1	S	U	BA	1	2-1	1
IV.19	F	+	aa	++	2-1	2-1	S	U	B	1	1	1
IV.20†	M	-	ab	++	2-1	2-2	S	U	BA	1	2-1	2-1
IV.21	F	+	aa	++	1-1	2-2	S	U	BA	1	2-1	1
IV.22†	M	-	aa	++	1-1	2-2	FS	I	BA	2-1	1	1
V.29	F	+	aa	--	2-1	1-1	FS	U	B	1	1	2-1
V.30	F	+	aa	++	2-1	2-1	S	U	B	1	1	2-1
V.31	M	+	aa	++	2-1	1-1	FS	U	B	1	1	2-1
V.32	F	+	aa	++	2-1	2-1	S	U	B	1	1	2-1
V.35	F	+	ab	++	1-1	2-1	S	U	BA	1	1	1
V.36	M	-	aa	++	2-1	2-1	S	U	A	1	1	1
V.37	F	-	aa	++	1-1	2-2	FS	I	BA	1	2-1	1
V.38	F	+	aa	--	1-1	2-2	FS	U	BA	2-1	1	1

¹ Tf, E₂, ADA, PGD, P, Lu, K, and chromosomes No. 1, 3, 4, 9, 15, 16 were invariable in this pedigree.

² aa = Gm(a-x-f+n+g-b+); ab = Gm(a+x+f+n+g+b+).

³ ++ = Inv(1+a+); -- = Inv(1-a-).

⁴ E₁ = pseudocholinesterase; U = usual; I = intermediate.

⁵ C = C-banding: presence (+) or absence (-) of C-band in one or the other or both of the No. 3 chromosomes.

⁶ A = chromosome No. 13 without a detectable marker on it; C is No. 13 with fluorescent short arms; S is No. 13 with a fluorescent satellite.

⁷ S = Satellite: presence (+) or absence (-) of a fluorescent satellite on the corresponding chromosome.

⁸ c = variant of c.

† Related by marriage only.

registry offices, which in the Netherlands contain data from 1810 onwards. The complete kindred has been presented in another publication (Doeglas, 1974) but only one branch (XC) of the family is of relevance to the present discussion as it includes living affected members. This point was established by investigation of the entire kindred mostly by home visits but relying on mail and telephone contact in a few cases.

At each contact the family history was cross checked with special attention to details about deceased members. Of all members of branch XC, blood was drawn for linkage studies (5 ml clotted blood, 5 ml in EDTA solu-

tion, and 5 ml in acid citrate dextran solution). The tubes were transferred to laboratories in Amsterdam and Leiden within 12 hours. The techniques used for the determination of the different markers are as described in the literature (Giblett, 1969; Pearson, Gerards, and van der Linde, 1973).

Branch XC (Fig. 1)

All affected living members occur in branch XC of the larger kindred of Doeglas (1974) of which the senior member is still alive (III.7). His older sister had severe

TABLE II
LOD SCORES FOR COLD URTICARIA LOCUS AND MARKER SYSTEMS
(COMPOSITE)

Marker System	No. of Children Scored	Recombination Fraction					
		0-00	0-05	0-10	0-20	0-30	0-40
Inv	11	-∞	-1.517	-0.758	-0.165	-0.023	+0.043
Hp	9	-∞	-1.630	-0.866	-0.264	-0.057	-0.004
C'3	4	-∞	-1.442	-0.887	-0.388	-0.152	-0.036
Gc	1	+0.301	+0.279	+0.255	+0.204	+0.146	+0.079
AcP	11	-∞	-4.907	-3.219	-1.667	-0.888	-0.409
GPT	2	+0.602	+0.558	+0.511	+0.408	+0.292	+0.158
ABO	4	-∞	-0.163	+0.066	+0.214	+0.216	+0.140
MNS	8	-∞	-2.884	-1.774	-0.776	-0.304	-0.072
Rh	12	-∞	-0.790	-0.096	+0.368	+0.421	+0.280
Fy	6	-0.297	-0.178	-0.110	-0.044	-0.014	-0.003
Chromosome No. 3	6	-∞	-3.442	-2.285	-1.184	-0.596	-0.230
No. 13	9	-∞	-3.885	-2.474	-1.174	-0.525	-0.168
No. 22	8	-∞	-3.185	-2.071	-1.050	-0.531	-0.212

I
IN BRANCH XC¹

Red Cell Antigens				Marker Chromosomes				
ABO	MNS	Rh	Fy	No. 3 ⁵ C	No. 13 ⁶ A-C-S	No. 14 ⁷ S	No. 21 ⁷ S	No. 22 ⁷ S
O	NNS -	CcDee	a+	+/+	SA	-/-	-/-	+/ -
A ₁	MMS +	CcDEe	a+	-/-	CA	-/-	-/-	-/-
O	MNS +	CcDee	a+	+/ -	AA	-/-	-/-	+/ -
A ₁	MNS -	CcDee	a+	+/ -	SA	-/-	-/-	+/ -
A ₁	MNS +	CcDEe	a+	+/ -	CA	-/-	-/-	+/ -
O	NNS -	Ccdee	a+	+/ +	CA	-/-	-/-	+/ -
A ₁	MNS +	CcDEe	a+	+/ -	CS	-/-	-/-	+/ -
O	MNS -	CcDee	a+	+/ -	AA	-/-	-/-	+/ -
O	MMS +	ccdee	a-	+/ -	AA	+/ -	+/ -	-/-
O	MNS +	CCDee	a+	+/ -	CS	-/-	-/-	-/-
O	MMS +	ccDEe	a+	+/ -	CA	-/-	-/-	+/ -
O	NNS -	CCDee	a+	+/ -	CA	-/-	-/-	+/ -
A ₁	NNS -	CCDee	a+	+/ -	CC	-/-	-/-	+/ -
O	MNS +	CcDee	a+	+/ -	CA	-/-	-/-	+/ -
O	MNS +	CcDEe	a-	+/ +	CA	-/-	-/-	-/-
O	MNS +	ccdee	a+	+/ -	AA	+/ -	+/ -	-/-
O	MNS +	CcDee	a+	+/ +	AA	+/ -	+/ -	+/ -
O	MNS +	CcDEe	a-	+/ -	CS	-/-	-/-	+/ -
O	MNS +	CcDee	a+	+/ +	SA	-/-	-/-	-/-

symptoms during life, but her only son and his offspring are free of the disease.

The father of III.7 was affected and was apparently the first case, thus possibly representing a new mutation although this cannot be regarded as established because of the circumstantial nature of evidence collected about generations too remote in time. Apart from III.7 and his affected sister, there were two other sibs who survived infancy; neither of them showed the disease.

Fig. 1 shows 11 cases of familial cold urticaria ranging from slight to severely incapacitating, among 19 individuals. Their case histories have been described extensively elsewhere (Doeglas 1974). There is autosomal dominant inheritance of the trait in this family.

Linkage Analysis

All the members of branch XC were investigated for the following 31 genetic markers in order to perform linkage analysis between each of the loci or chromosomal regions for these markers and the cold urticaria (CU) locus: ABO, MNS, P, Lu, Rh, K, Fy (blood groups); Gc, Gm, Inv, Hp, Tf, C₃, E₁, E₂ (serum groups); AcP, ADA, AK, PGD, PGM₁, GPT (red cell enzymes); and polymorphic chromosomes 1, 3, 4, 9, 13, 14, 15, 16, 21, and 22. The phenotypic distribution of the variable markers in this pedigree are shown in Table I. Lod scores calculated (Morton, 1955; Maynard-Smith, Penrose, and Smith, 1961) for the linkage of the cold urticaria

locus with these different marker systems are presented in Table II.

The data suggest that the loci for Inv, Hp, C₃, AcP, MNS, and Fy are probably not within measurable distance from the CU locus. More information is needed to define the linkage relationships between the CU locus and the loci for Rh and ABO, respectively. Based on the present material a linkage between the CU locus and the loci for red cell glutamic pyruvic transaminase (GPT) and Gc serum group respectively cannot be excluded. Polymorphisms of chromosomes 3, 13, and 22 were informative for linkage and it appears that a close linkage can be excluded between each of their C-banding and/or satellite regions and the CU locus.

All the basic data collected during the present investigations are included in this paper, in order to facilitate a comparative and combined treatment with similar data to be collected in future from other families.

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