Linkage studies in a pedigree with Van der Woude syndrome

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SUMMARY A kindred segregating for Van der Woude syndrome (VWS) through five generations is described. Biochemical and serological phenotypes at 36 polymorphic marker loci have been determined, of which 27 were informative for linkage analysis to the VWS gene (LIPED 36 computer programme). Lod scores are reported and show exclusion of close linkage for most of the marker loci. Only *VWS:Duffy (Fy)* resulted in uniformly positive lod scores ($\theta=0.0$, $z(\theta)=1.31$).

Van der Woude syndrome (VWS) is a rare genetic malformation syndrome characterised by one or more of three primary manifestations: (1) bilateral lower lip pits, (2) cleft lip with or without cleft palate, or (3) isolated cleft palate. It is inherited as an autosomal dominant trait with 70 to 80% penetrance suggested by early studies,¹⁻² although Janku *et al*³ have reported a higher penetrance of about 97%. The lower penetrance reported in earlier papers on this syndrome is most probably due to incomplete ascertainment, that is, non-recognition of patients with 'microforms', and true penetrance is probably close to 100%. The chromosomal location of the VWS gene is not known. Three pedigrees have been analysed for linkage relations so far,⁴⁻⁶ but only the data of Eastman *et al*⁵ were reported in detail. No evidence of close linkage was found between the VWS gene and any segregating marker locus in these studies. We had the opportunity to study another large pedigree with Van der Woude syndrome and report here the results of linkage analysis using 36 marker loci.

Subjects and methods

This family came to our attention when an affected member (IV.7, figure) requested genetic counselling. All living members reside in rather isolated conditions in the southern part of the Black Forest. They are in touch with one another and know their ancestry well. All those interviewed knew the

'family mark' and were remarkably accurate in their description of pits and clefts, although they could rarely give information about missing teeth (hypodontia). The pedigree, spanning five generations, comprises a total of 116 members and has been presented in full by Hudek.⁷ Only 19 of the living members and four spouses were cooperative and they were examined for the presence of VWS

FIGURE Pedigree of family.

TABLE Linkage relations of the VWS gene.

Locus (chromosome assignment)	Sex	Lod scores at recombination fraction (θ)				
		0.05	0.1	0.2	0.3	0.4
<i>Rh</i> (1p36.2→p34)	M	-2.16	-1.33	-0.58	-0.23	-0.05
	F	-1.74	-1.16	-0.61	-0.31	-0.12
	Sum*	-2.70	-1.65	-0.67	-0.28	-0.11
<i>PGM1</i> (1p22.1)	M	-1.39	-0.86	-0.39	-0.16	-0.04
	F	-0.98	-0.66	-0.37	-0.18	-0.07
	Sum*	-3.26	-2.08	-1.76	-0.87	-0.15
<i>Fy</i> (1p21→q23)	M	+0.13	+0.10	+0.06	+0.03	+0.01
	F	+1.08	+0.98	+0.78	+0.56	+0.30
	Sum*	+1.08	+1.12	+0.98	+0.72	+0.38
<i>ACPI</i> (2p25 or 2p23)	M	-0.16	-0.12	-0.06	-0.03	-0.01
	F	-1.19	-0.88	-0.49	-0.26	-0.10
	Sum*	-0.94	-0.70	-0.35	-0.18	-0.07
<i>JK</i> (2)	M	+0.07	+0.05	+0.03	+0.01	0.00
	F	-0.46	-0.32	-0.15	-0.06	-0.01
	Sum*	-0.07	-0.05	+0.01	+0.02	+0.01
<i>TF</i> (3q21→q26.1)	M	-0.05	-0.04	-0.02	-0.01	0.00
	F	-1.18	-0.80	-0.38	-0.16	-0.04
	Sum	-1.23	-0.84	-0.40	-0.17	-0.04
<i>GC</i> (4q12→q13)	M	-1.49	-0.94	-0.43	-0.18	-0.04
	F	-2.67	-1.79	-0.90	-0.42	-0.14
	Sum	-4.16	-2.73	-1.33	-0.60	-0.18
<i>MNS</i> (4q28→q31)	M	-0.09	-0.07	-0.04	-0.02	0.00
	F	-0.46	-0.20	0.00	+0.05	+0.05
	Sum*	-2.87	-1.43	-0.67	-0.27	-0.06
<i>ME2</i> (6p)	F	-1.72	-1.14	-0.59	-0.30	-0.11
<i>HLA</i> (6p21.3)	M	-2.06	-1.24	-0.52	-0.20	-0.04
	F	-1.30	-0.76	-0.18	+0.06	+0.10
	Sum	-3.36	-2.00	-0.70	-0.14	+0.06
<i>BF</i> (6p21.3)	M	-2.07	-1.25	-0.53	-0.20	-0.05
<i>GLO</i> (6p21.31→p21.1)	M	-0.15	-0.11	-0.06	-0.03	-0.01
<i>PGM3</i> (6q12)	F	-0.70	-0.43	-0.19	-0.07	-0.02

TABLE (continued)

Locus (chromosome assignment)	Sex	Lod scores at recombination fraction (θ)				
		0.05	0.1	0.2	0.3	0.4
<i>PLG</i> (6q25→qter)	F	-1.65	-1.07	-0.48	-0.19	-0.04
<i>ABO</i> (9q34)	M	-0.03	+0.15	+0.20	+0.13	+0.04
	F	-0.29	-0.25	-0.17	-0.11	-0.05
	Sum*	-0.77	-0.29	+0.07	+0.09	+0.02
<i>ESD</i> (13q14.1)	M	-0.21	-0.16	-0.08	-0.03	-0.01
<i>PI</i> (14q32.1)	M	-1.23	-0.72	-0.30	-0.11	-0.03
<i>Gm</i> (14q32.3)	M	-1.40	-0.85	-0.36	-0.14	-0.03
	F	-2.13	-1.50	-0.80	-0.40	-0.15
	Sum	-3.53	-2.35	-1.16	-0.54	-0.18
<i>HP</i> (16q22.1)	M	-0.65	-0.39	-0.16	-0.06	-0.01
	F	-1.13	-0.71	-0.25	-0.04	+0.04
	Sum*	-1.26	-0.69	-0.12	+0.08	+0.11
<i>LU</i> (19)	M	-1.45	-0.91	-0.42	-0.17	-0.04
<i>C3</i> (19p13)	M	-0.19	-0.14	-0.08	-0.03	-0.01
<i>ADA</i> (20q13.2→qter)	M	-1.32	-0.79	-0.33	-0.12	-0.03
<i>PI</i> (22)	M	-0.30	-0.19	-0.08	-0.03	-0.01
	F	+0.02	+0.01	+0.01	+0.01	0.00
	Sum*	-0.07	-0.29	-0.12	-0.03	-0.01
<i>C6</i>	M	-0.72	-0.44	-0.19	-0.08	-0.02
	F	-0.08	-0.07	-0.05	-0.04	-0.02
	Sum	-0.80	-0.51	-0.24	-0.12	-0.04
<i>CDA</i>	F	-2.17	-1.38	-0.67	-0.35	-0.16
<i>FI3B</i>	M	-0.27	-0.04	+0.09	+0.08	+0.03
	F	+0.20	+0.18	+0.14	+0.10	+0.05
	Sum	-0.07	+0.14	+0.23	+0.18	+0.08
<i>GPT</i>	M	-2.05	-1.24	-0.52	-0.20	-0.04
	F	-1.40	-0.84	-0.31	-0.07	+0.02
	Sum	-2.45	-2.08	-0.83	-0.27	-0.02

* Including the data of Eastman *et al.*⁵

stigmata. Blood samples were analysed for a total of 36 marker loci, of which 27 were informative for linkage studies (table). *KEL*, *CO*, *Km*, *AHCY*, *AK*, *AMY2*, *GALT*, *GOT1*, and *PGD* were not informative. Linkage studies were performed using the LIPED 3 computer programme of Ott⁸; a penetrance of 97% was used for the analysis.

Results and discussion

The part of the pedigree analysed is shown in the figure, together with the relevant clinical data. Fourteen of the 19 family members investigated had symptoms of Van der Woude syndrome, six males and eight females. Ten of them had lip pits and the

other four had some evidence of cleft lip or palate. Another five subjects not seen by us were reported to have lip pits or other manifestations (II.1, III.1, III.4, IV.1, and V.2).

The lod scores at standard recombination fractions are given for each locus analysed in the table, along with the scores of Eastman *et al.*⁵ Uniformly negative lod scores were obtained with *ACPI*, *ADA*, *BF*, *C3*, *C6*, *CDA*, *ESD*, *GC*, *GLO*, *Gm*, *GPT*, *HLA*, *LU*, *ME2*, *MNS*, *PGM1*, *PGM3*, *PI*, *PLG*, *Rh*, and *TF*. Inconclusive but largely negative lod scores were obtained with *ABO*, *FI3B*, *JK*, *HP*, and *PI*. Only the *VWS:Fy* relation resulted in uniformly positive lod scores: $\hat{\theta}=0.0$, $z(\hat{\theta})=1.31$. After combining our data with those of Eastman *et*

al,⁵ however, a peak lod score at $\hat{\theta}=0.09$, $z(\hat{\theta})=1.13$ for VWS:Fy was calculated. Further studies are being undertaken to verify the possible Duffy linkage.

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