Am. J. Hum. Genet. 46:1017–1023, 1990

Assignment of the Locus for Waardenburg Syndrome Type I to Human Chromosome 2q37 and Possible Homology to the Splotch Mouse

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Summary

We have demonstrated close linkage between the locus for the autosomal dominant Waardenburg syndrome type I and the placental alkaline phosphatase locus on chromosome 2q37. In five families the peak lod score was 4.76 at a recombination fraction of .023. In the mouse the Splotch locus maps to near the homologous position. Splotch mice have white spotting and hearing defects, suggesting that Splotch may be the murine homologue of Waardenburg syndrome type I.

Introduction

Waardenburg syndrome type I (WS1; McKusick 19350) is characterized by dystopia canthorum (lateral displacement of the inner canthi), pigmentary disturbances (heterochromia irides, white skin patches, white frontal blaze, and premature greying of the hair), and sensorineural deafness. The inheritance is autosomal dominant with variable expression and incomplete penetrance. Manifestations vary widely even within families. Dystopia canthorum is the most consistent feature, and Arias et al. (1975) claim penetrance is .98–.99 when dystopia is carefully assessed. The incidence is said to be 1–2 $\times$ 10^{-5} (Arias and Mota 1978).

As a part of a study of Waardenburg syndrome, we have been attempting to map the WS1 locus by linkage analysis. Members of families segregating Waardenburg syndrome have been studied clinically and audiologically and have been typed for a number of genetic markers. Initial studies used available highly informative markers, as well as markers from candidate chromosomal regions suggested by possible mouse homologues of Waardenburg syndrome. These data, combined with previously published linkage studies, enabled us to exclude the WS1 locus from approximately 23% of the human genome. Recently Ishikiriyama et al. (1989) described a Japanese child with a de novo inversion of 2q35–q37 who had many features of Waardenburg syndrome (dystopia, heterochromia irides, deafness, and a white "watchstrap" skin patch) despite having no family history of the disease. We therefore analyzed our families with a probe, ALP-1, which maps to 2q37, and we obtained good evidence of close linkage.

Received December 1, 1989; revision received February 1, 1990.

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0002-9297/90/4606-0002$02.00

Material and Methods

Families with at least 3 generations of affected individuals in an autosomal dominant pattern of inheritance were recruited from the northwest of England. Blood samples were taken with informed consent. All affected people had dystopia canthorum, diagnosed both clinically and by the use of biometric indices (Arias 1971; Arias and Mota 1978). In each instance there were other diagnostic signs present, such as high nasal root, sensorineural hearing loss, heterochromia irides, hypoplastic blue eyes, white forelock, and early greying or hypo- or hyperpigmented skin patches. Figure 1 shows the pedigrees, and table 1 shows the clinical features of affected people in the five families segregating Waardenburg syndrome type I which were informative for ALP-1 polymorphisms.

DNA extraction from blood, digestion with restric-

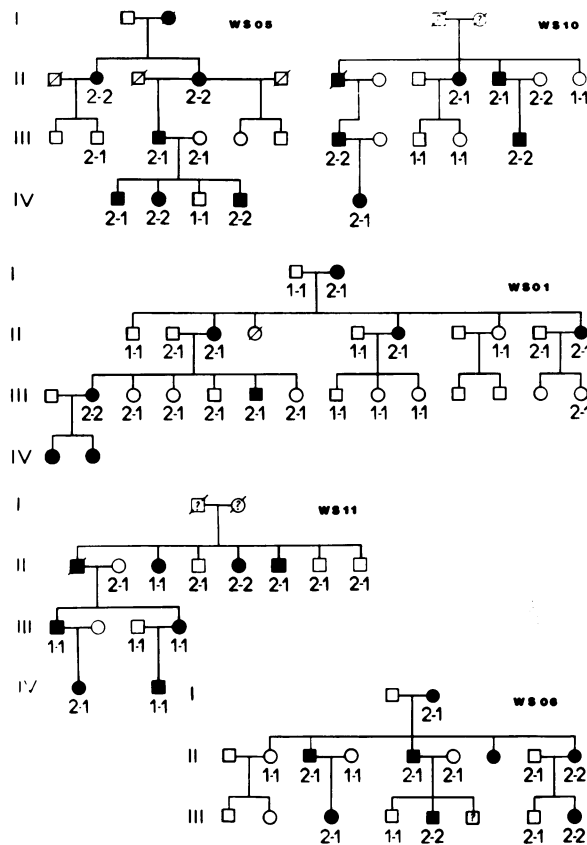

Figure 1 Five families segregating WS1 and ALPP and showing genotypes for the ALP-1/*Rsa*I polymorphism.

tion enzymes, agarose gel electrophoresis, Southern transfer to Hybond-N membranes, and hybridization to radiolabeled probes were carried out by standard methods (Maniatis et al. 1982). Probes were labeled by random hexanucleotide priming (Feinberg and Vogelstein 1983). ABO and HLA types were determined by conventional serology. The probes used are summarized in table 2. ALP-1 is a 1.1-kb *Eco*RI-*Apa*I fragment of the cDNA of the placental alkaline phosphatase gene (locus symbol ALPP), isolated from a lambda-gt10 cDNA library of the cell line HEp-2 (Martin et al. 1987*b*). It has been mapped to 2q37 with somatic cell hybrids and by in situ hybridization (Martin et al. 1987*a*). ALP-1 detects both a frequent polymorphism with *Rsa*I and a rarer one with *Taq*I (Martin et al. 1987*a*). Locations and further details of all the other probes are given elsewhere by Kidd et al. (1989).

Lod scores were calculated using the MLINK program (Lathrop and Lalouel 1984), version 5.03, in conjunction with the LINKSYS data-handling package of

Table 1

Clinical Signs in Affected People in the Five Families Shown in Figure 1

Family and Individual (sex)	Feature[a]							
	DysC	HNR	SN	HetI	HypE	WF/EG	Skin	Eyb
WS.01:								
I_2 (F)	+	+	+	+	−	+	−	+
II_3 (F)	+	+	+	−	+	+	+	−
II_6 (F)	+	+	−	+	−	−	−	+
II_{10} (F)	+	+	+	−	+	+	+	+
III_2 (F)	+	+	±	−	+	+	−	+
III_6 (M)	+	+	+	−	+	+	+	+
IV_1 (F)	+	+	+	+	−	−	−	−
IV_2 (F)	+	+	−	−	−	+	−	+
WS.05:								
II_2 (F)	+	+	+	−	+	+	+	+
II_4 (F)	+	+	+	−	−	+	−	−
III_3 (M)	+	+	+	−	−	−	−	−
IV_1 (M)	+	+	+	−	+	−	+	+
IV_2 (F)	+	+	+	−	+	+	−	−
IV_4 (M)	+	+	+	−	−	+	−	−
WS.06:								
I_2 (F)	+	+	−	−	−	+	−	+
II_3 (M)	+	+	−	−	−	+	−	+
II_5 (M)	+	+	−	−	−	+	+	+
II_9 (F)	+	+	−	−	−	+	−	+
III_3 (F)	+	+	−	−	−	−	+	+
III_5 (M)	+	+	+	−	+	−	−	+
III_8 (F)	+	+	−	−	−	+	−	+
WS.10:								
II_1 (M)	+	+	−	?	?	−	?	+
II_4 (F)	+	+	±	−	−	+	−	−
II_5 (M)	+	+	+	−	−	+	−	−
III_1 (M)	+	+	±	+	−	−	−	+
III_5 (M)	+	+	+	+	−	+	−	+
IV_1 (F)	+	+	+	−	−	−	−	+
WS.11:								
II_1 (M)	+	+	−	−	−	−	?	−
II_3 (F)	+	+	+	+	−	+	−	−
II_5 (F)	+	+	+	+	−	−	−	−
II_6 (M)	+	+	+	+	−	+	−	+
III_1 (M)	+	+	+	−	−	+	−	+
III_4 (F)	+	+	+	−	−	+	−	±
IV_1 (F)	+	+	±	−	−	−	−	±
IV_2 (M)	+	+	+	−	−	−	−	±

[a] DysC = dystopia canthorum; HNR = high nasal root; SN = sensorineural hearing loss; HetI = heterochromia irides; HypE = hypoplastic blue eyes; WF/EG = white forelock and early greying; Skin = hypo- or hyperpigmented skin patches; Eyb = bushy confluent eyebrows. + = sign present; − = sign absent; ± = sign ambivalent.

Attwood and Bryant (1988). The gene frequency and penetrance of WS1 were taken as 5×10^{-5} and .95, respectively, for all analyses. To guard against the slight risk of false-positive diagnosis within a family, the

Table 2

Data for Exclusion Map of WSI Shown in Figure 2

Locus	Probe	Position	Lod Score at Recombination Fraction of .0	.05	.10	.20	.30	.40
RH[a]		1p36.2-p34	−2.78	−1.32	−.84	−.38	−.15	−.04
D1S7	lambdaMS1	1p35-p33	−10.13	−2.98	−1.36	.03	.46	.40
PGM1[a]		1p22.1	−1.36	−.55	−.32	−.15	−.08	−.05
ACP1 (AcPh)[a]...		2p25	−2.53	−1.26	−.81	−.36	−.14	−.04
APOB (Ag)[a]		2p24-p23	−3.31	−.96	−.50	−.11	.03	.05
D4S10	G8	4p16.3	−5.92	−3.46	−2.30	−1.05	−.42	−.10
D4S125	pYNZ32	4p16.3	−5.92	−4.41	−3.11	−1.52	−.67	−.20
GC[a]		4q12-q13	.20	.24	.26	.24	.18	.10
INP10.........	IP-10	4q21	−5.06	−2.14	−1.28	−.60	−.40	−.28
GYPA (MNS)[a] ..		4q28-q31	−2.97	−1.52	−1.04	−.54	−.26	−.08
D5S43	lambdaMS8	5q35-qter	−9.62	−5.61	−3.85	−1.98	−1.00	−.42
HLA-A,B		6p21.3	−5.56	−2.49	−1.28	−.17	.18	.16
HLA[a]		6p21.3	−4.07	−2.31	−1.63	−.91	−.48	−.20
D7S21	lambdaMS31	7pter-q22	−12.16	−6.56	−4.23	−1.89	−.78	−.27
MET	pmetH, pmetD	7q31	−1.95	−.88	−.35	.15	.30	.24
D7S22	lambdag3	7q36-qter	−13.05	−9.04	−6.74	−3.71	−1.89	−.73
ABO		9q34	−6.75	−2.01	−.96	−.07	.19	.16
ABO[b]		9q34	−25.17	−10.97	−6.55	−2.08	−.23	.28
PRB1-4........	pPRP-1	12p13.2	−5.74	−2.00	−1.24	−.53	−.20	−.04
D12S4	p9F11	12cen-q14	−1.98	−1.10	−.72	−.33	−.13	−.03
D12S17	pYNH15	12q	−inf.	−2.45	−1.54	−.69	−.27	−.06
D12S8	p7G11	12q14-qter	−4.13	−1.97	−1.15	−.38	−.07	.03
D12S7	pDL32B	12q14-q24.1	−2.69	−.97	−.45	−.05	.04	.02
D12S11	lambdaMS43	12q24.3-qter	−.06	−.04	−.03	−.01	.00	.01
IGHG1[a]		14q32.33	−5.51	−3.08	−2.14	−1.13	−.57	−.21
D16S85	3'HVR	16p13.3	−3.88	−2.10	−1.03	−.11	.12	.09
HP[a]...........		16q22.1	−.09	−.14	−.18	−.19	−.13	−.06
ADA[a]		20q13-qter	−3.16	−1.10	−.71	−.32	−.12	−.03

[a] Lod scores recalculated from data of Simpson et al. (1974).
[b] Lod scores recalculated from data of Arias and Mota (1978).

homozygous normal genotype was assigned a penetrance of .01 rather than 0. Exclusion mapping was performed using the EXCLUDE program of Edwards (1987).

Results

A. Exclusion Mapping

Table 2 shows negative linkage results from analysis of our families. Also included are data reported by Simpson et al. (1974) and Arias and Mota (1978). Lod scores from these papers have been recalculated from the published raw data. Differences between the scores in table 2 and those originally reported are mostly small and attributable to our use of incomplete penetrance, except for PGM1, ACP1, ABO1, and IGHG. The discrepant scores (at 10% recombination; our value first) are PGM1 −.32 (.062), ACP1 −.81 (−.367), ABO −6.55 (−8.06), and IGHG1 −2.14 (−1.59). Figure 2 shows the exclusion map generated from the combined data. As a rough guide to the exclusions achieved, the white (excluded) segments total 23% of the measured length of the figures.

B. Linkage to the Placental Alkaline Phosphatase Locus

Five families were informative for WS1 and the *Rsa*I polymorphism of ALP-1. Two other WS1 families were uninformative for either the *Rsa*I or *Taq*I polymorphisms detected by this probe. Table 3 lists the lod scores of ALPP in the five informative families. The peak lod score is 4.767 at recombination fraction .023 (or 4.96 at recombination fraction .033 if Waardenburg syn-

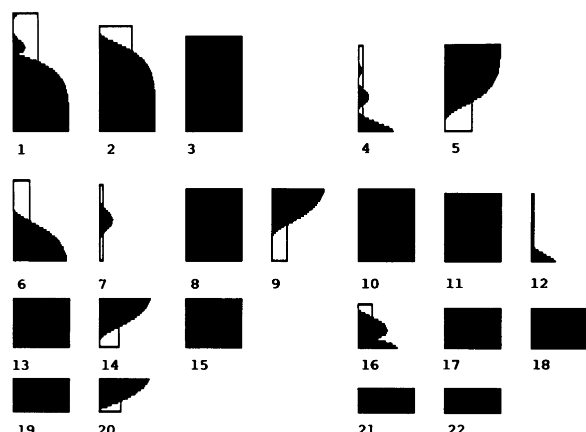

Figure 2 Exclusion mapping of WS1, by using all data in table 2. White areas are excluded; the length of the black bars indicates the likelihood that WS1 is located at that position.

drome is assumed to be fully penetrant with no phenocopies). There is only one likely recombinant, individual II_5 in pedigree WS.11.

Discussion

Mapping of WS1 Locus and Possible Homology to Splotch

We report lod scores with 29 markers, including those from previous workers. When many markers are studied, the likelihood of a false-positive result is increased, and therefore the threshold of significance used should be higher than the conventional lod score of 3.0. A suitable threshold for random markers might be estimated by multiplying the probability by the number of markers tried, which for this study gives a value of 3.0+ log(29) = 4.46. In fact, ALP-1 is not a random marker. There are two reasons for picking distal 2q as a candidate region: (1) the patient reported by Ishikiriyama et al. (1989) who had apparent de novo Waardenburg syndrome together with an inversion of 2q35-q37 and (2) the possible homology to the Splotch mouse. Thus the prior probability of linkage is higher than with a random probe, and the risk of a false-positive assignment is correspondingly lower. Our lod score of 4.76 therefore makes the assignment of WS1 to 2q37 highly probable. However, this should still be confirmed in other families.

The homology between human chromosome 2q and the proximal part of mouse chromosome 1 rests on the gene assignments summarized in table 4. Another possible homology is between Engrailed-1 genes (human EN1 and mouse En-1; Logan et al. 1989). The comparative maps are shown and discussed by Searle et al. (1989). The mouse alkaline phosphatase gene Akp-3 lies at the distal end of this conserved group. In man, two alkaline phosphatase genes—those for the intestinal enzyme (ALPI) and the placental enzyme (ALPP)—are located on the distal long arm of chromosome 2. They show 89.5% identity at the nucleotide level (Henthorn et al. 1987). Which one of these human genes corresponds to the mouse Akp-3 gene is not clear. The probe we used, ALP-1, is derived from the placental gene. O'Connell et al. (1989) have published a map of 20 markers on chromosome 2, a map that forms a continuous linkage group of 306 cM in males (529 cM in females) but that does not include any of the alkaline phosphatase genes.

Table 3

Linkage of WS1 and ALPP in the Five Families Shown in Figure 1

Family	Lod Score at Recombination Fraction of .00	.05	.10	.20	.30	.40
WS.01	2.26	2.06	1.86	1.42	.93	.42
WS.05	.96	.88	.80	.62	.44	.23
WS.06	1.15	1.00	.84	.53	.24	.05
WS.10	1.45	1.28	1.10	.73	.36	.09
WS.11	−1.26	−.55	−.33	−.14	−.05	−.01
Total	4.56	4.68	4.27	3.16	1.91	.77

NOTE.—The peak lod score is $\hat{Z}$ = 4.767 at $\hat{\theta}$ = .023.

The Splotch locus in the mouse maps 4 cM proximal to Akp-3 and 3 cM distal to the fibronectin gene Fn-1 (Searle et al. 1989). Splotch homozygotes have severe malformation of the inner ear as well as lethal neural tube defects (Silvers 1979). Splotch heterozygotes have white spotting on the belly and occasionally on the feet, back, and tail (Silvers 1979). It is not clear what, if any, hearing defect is present in the heterozygote. The Splotch mutation has arisen independently at least five times, including a milder allelic variant (Splotch delayed; Silvers 1979) and a severe form (Splotch retarded), which has a cytogenetically visible deletion.

Deafness with White Spotting

WS1 is one of a number of human conditions in which pigmentary disturbances are associated with deafness. Two other types of Waardenburg syndrome have been recognized (McKusick 1988). Waardenburg syndrome type II (WS2; McKusick 19351) was described by Arias (1971) as a separate entity without dystopia cantho-

Table 4

Homologous Loci on the Long Arm of Human Chromosome 2 and the Proximal Part of Mouse Chromosome 1

Gene	Human	Mouse	Reference
Glutaminase	GLS	Gls	Mock et al. 1989
Fibronectin	FN	Fn-1	Skow et al. 1987
Myosin light chain	MYL1	Mylf	Cohen-Haguenauer et al. 1988
Villin	VIL1	Vil	Rousseau-Merck et al. 1988
Isocitrate dehydrogenase	IDH1	Idh-1	Searle et al. 1989
Acetylcholine receptor, gamma subunit	CHRNG	Acrg	Cohen-Haguenauer et al. 1987
Acetylcholine receptor, delta subunit	CHRND	Acrd	Beeson et al. 1989
Crystallin gamma chain	CRYG1	Cryg-1	Lubsen et al. 1987
Inhibin alpha	INHA	Inha	Barton et al. 1989
Cytotoxic T lymphocyte-associated protein 4	CTLA4	Ctla-4	Dariavach et al. 1989

rum and was claimed to be 20–25 times more common than WS1. This distinction was supported by Hageman and Delleman (1977), who also suggested a higher incidence of deafness in Waardenburg syndrome type 2. However, without dystopia the distinction from other dominant deafness is not simple. Waardenburg syndrome type III or Klein-Waardenburg syndrome (WS3; McKusick 14882) denotes the facial and ocular features of Waardenburg syndrome accompanied by hypoplasia of the upper limbs. Few cases have been described (Goodman et al. 1982). Piebald trait (PBT; McKusick 17280) is an autosomal dominant condition with white forelock and patchy skin depigmentation. Heterochromia irides is sometimes present, and some patients are deaf (Comings and Odland 1966; Reed et al. 1967).

A similar association of deafness and white spotting is known in several mammals, especially mice: Steel and Bock (1983) distinguished several types of inner-ear pathology in deaf mice. In mutants associated with white spotting, Reissner's membrane is collapsed and the organ of Corti is damaged. The hearing defects in Waardenburg syndrome are generally of this type, known in man as the Scheibe type and in animals as the cochleo-saccular type (Fisch 1959; Nemansky and Hageman 1975). The primary pathology is a failure of melanocytes to migrate from the neural crest during embryogenesis. Melanocytes are absent from the white areas of skin (rather than present but nonfunctional, as in albinos). In the inner ear melanocyte-like cells form the intermediate layer of the stria vascularis in the cochlea and have been shown to be absent in the deaf W^v (viable dominant spotting) mouse mutant (Steel and Barkway 1989).

The Splotch mouse has often been included in a different class of deaf mutants, the morphogenetic group (Steel and Bock 1983). These have structural malformations of the labyrinths and correspond to the Michel or Mondini-Alexander malformations in man (Ormerod 1960). Splotch, with white spotting in the heterozygote but inner-ear malformations in the homozygote, has features of both the morphogenetic and cochleo-saccular groups of mutants. Splotch homozygotes also have lethal neural tube defects (Silvers 1979). According to Deol (1966), the neural tube helps induce normal embryonic development of the otic capsule. Thus gross failures of the neural tube may produce morphogenetic abnormalities, while subtler failures of the neural crest can produce cochleo-saccular defects and white spotting. Probably the distinction between morphogenetic and cochleo-saccular mutants is not fundamental.

The Question of Linkage between WS1 and ABO Blood Group

There is a widespread impression that probable linkage has been demonstrated between Waardenburg syndrome and the ABO blood group locus. This stems from the work of Simpson et al. (1974) and Arias et al. (1975). Simpson et al. (1974) studied 16 blood groups and protein polymorphisms in a single 4-generation family with WS1. The lod scores are summarized in table 2; only ABO gave a positive result, reported as 1.10 at 0 recombination. Arias et al. (1975) analyzed ABO versus WS1 in three new families together with Simpson's family and obtained a peak lod of 1.60 at 20% recombination. A later reanalysis of these four families, sup-

plemented by new data, gave a peak lod of only 0.36 at 40% recombination (Arias and Mota 1978). Thus, despite the widespread impression to the contrary, previously available data did not support linkage of WS1 and ABO, and results in our families are negative (table 2).

Implications and Future Work

To minimize the risk of heterogeneity, we confined our initial analysis to families showing the most specific sign of WS1: dystopia canthorum. Now it will be important to test families with supposed Waardenburg syndrome type 2 and other variants, to see whether these forms might be allelic.

If the suggested homology of WS1 to Splotch is correct, then WS1 homozygotes might be severely, maybe lethally, malformed. We are unaware of any well-confirmed reports of Waardenburg syndrome homozygotes. A presumed homozygote for piebald trait (Hulten et al. 1987) lacked all pigment and was deaf and severely retarded. David and Warrin (1972) described a couple who both had Waardenburg syndrome; one child, also described by Amer and El-Shazly (1974), had notably severe pigmentary disturbances which led Fraser (1976) to suggest she might be homozygous, but she had no malformations. Since assortative marriage is common among deaf people, it might be prudent for genetic counselors to keep this possible risk in mind.

We may hope that, with a translocation breakpoint and a possible animal model, cloning the WS1 gene will be less formidably difficult than cloning the cystic fibrosis gene. The target region can be narrowed by further family studies. Then we need to isolate far more probes from the target region in order to construct a long-range map. If the breakpoint in the Japanese patient could be located on the map, it should lie within or extremely close to the WS1 gene. As a gene controlling some aspect of cell recognition, its function could be of general interest.

Acknowledgments

We are grateful to Karen Steel for helpful discussions about mouse mutants; to Rob Elles, Roger Mountford, and Irene Smeaton for assistance in the laboratory; to John Trowsdale for the ALP-1 probe; and to many other colleagues for the probes listed in table 2. John Attwood, John Edwards, and Jurg Ott supplied the LINKSYS, EXCLUDE, and MLINK computer programs. This work was supported by grants from the UK Northwestern Regional Health Authority and the Hearing Research Trust.

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