Bimodal expressivity in dominant retinitis pigmentosa genetically linked to chromosome 19q

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Abstract

A clinical, psychophysical, and electrophysiologic study was undertaken of two autosomal dominant retinitis pigmentosa pedigrees with a genetic mutation assigned to chromosome 19q by linkage analysis. Members with the abnormal haplotype were either symptomatic with adolescent onset nyctalopia, restricted visual fields, and non-detectable electroretinographic responses by 30 years of age, or asymptomatic with normal fundus appearance and minimal or no psychophysical or electroretinographic abnormalities. There was no correlation in the severity in parents and their offspring. Pedigree analysis suggested that although the offspring of parents with the genetic mutation were at 50% risk of having the genetic defect, the risk of being symptomatic during a working lifetime was only 31%. Such bimodal phenotypic expressivity in these particular pedigrees may be explained by a second, allelic genetic influence and may be a phenomenon unique to this genetic locus. Genetic counselling in families expressing this phenotype can only be based on haplotype analysis since clinical investigations, even in the most elderly, would not preclude the presence of the mutant gene.

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Epidemiological studies of retinitis pigmentosa consistently report a frequency of one in 5000 of the general population suggesting that there are approximately 100 000 retinitis pigmentosa sufferers in Europe and a similar number in the USA.[1] A family history of retinitis pigmentosa can be demonstrated in approximately 50% of new cases, and all three mendelian inheritance patterns occur. Autosomal dominant inheritance accounts for approximately 17-25% of all cases[1-3] and the condition has been found to be genetically heterogeneous. Over 60 different mutations in the rhodopsin gene on chromosome 3q[4] and 18 peripherin/RDS gene mutations[5] have been found in different autosomal dominant retinitis pigmentosa pedigrees. Five other loci for dominant retinitis pigmentosa genes have been identified on chromosomes 7p,[6] 7q,[7] 8cen,[8] 17p,[9] and 19q[10] by genetic linkage analysis.

In addition to the genetic diversity seen in autosomal dominant retinitis pigmentosa, phenotypic variability is also well established. Differences in clinical presentation have been reported between different families. Differences between members of the same family, variable expressivity, is also a common characteristic of autosomal dominant disease.[11] Here we report an extended clinical, psychophysical, and electrophysiological study of two families expressing a retinitis pigmentosa phenotype genetically linked to chromosome 19q.[10] Haplotype data have now allowed sound genetic diagnosis, making it possible to compare accurately the severity of disease in patients with that in their offspring. This has led to the identification of a large number of asymptomatic individuals carrying the disease gene suggesting an unusual polarity of phenotype in that those with the disease gene seem either to be severely afflicted or are asymptomatic with little psychophysical or electroretinographic abnormality, a phenotype unlike that reported in other retinitis pigmentosa genotypes.

Patients and methods

Some clinical details on these unrelated families have been reported previously (family 3 and 4 respectively).[12] The former originates in south Wales and the latter from northeast England. Further clinical studies and linkage analysis have allowed the identification of eight symptomatic and eight disease haplotype carriers not included in the previous report. Autosomal dominant inheritance is evident with symptomatic individuals in each generation and male to male transmission. Asymptomatic patients were assigned as having the causative genetic mutation if they had the same haplotype as symptomatic individuals within a 20 centimorgan region of chromosome 19q. Family members with this haplotype have a >98% probability of carrying the disease mutation.[10] Thirty individuals were identified as having the abnormal gene and enrolled into the study. In family '3' this included five symptomatic individuals and four asymptomatic individuals with the disease haplotype. One of these asymptomatic patients, an obligate carrier, had a symptomatic child. In family '4', 13 symptomatic patients and eight asymptomatic individuals with the disease haplotype were examined (including three obligate carriers).

An extensive ophthalmic history was recorded including details of visual acuity loss and age of onset of nyctalopia. Full ophthalmic examination was undertaken which included assessment of visual acuity, examination of the anterior segment and fundus. To assess whether or not a systemic abnormality might segregate with ocular disease, a detailed general medical history and a brief physical examination were undertaken.

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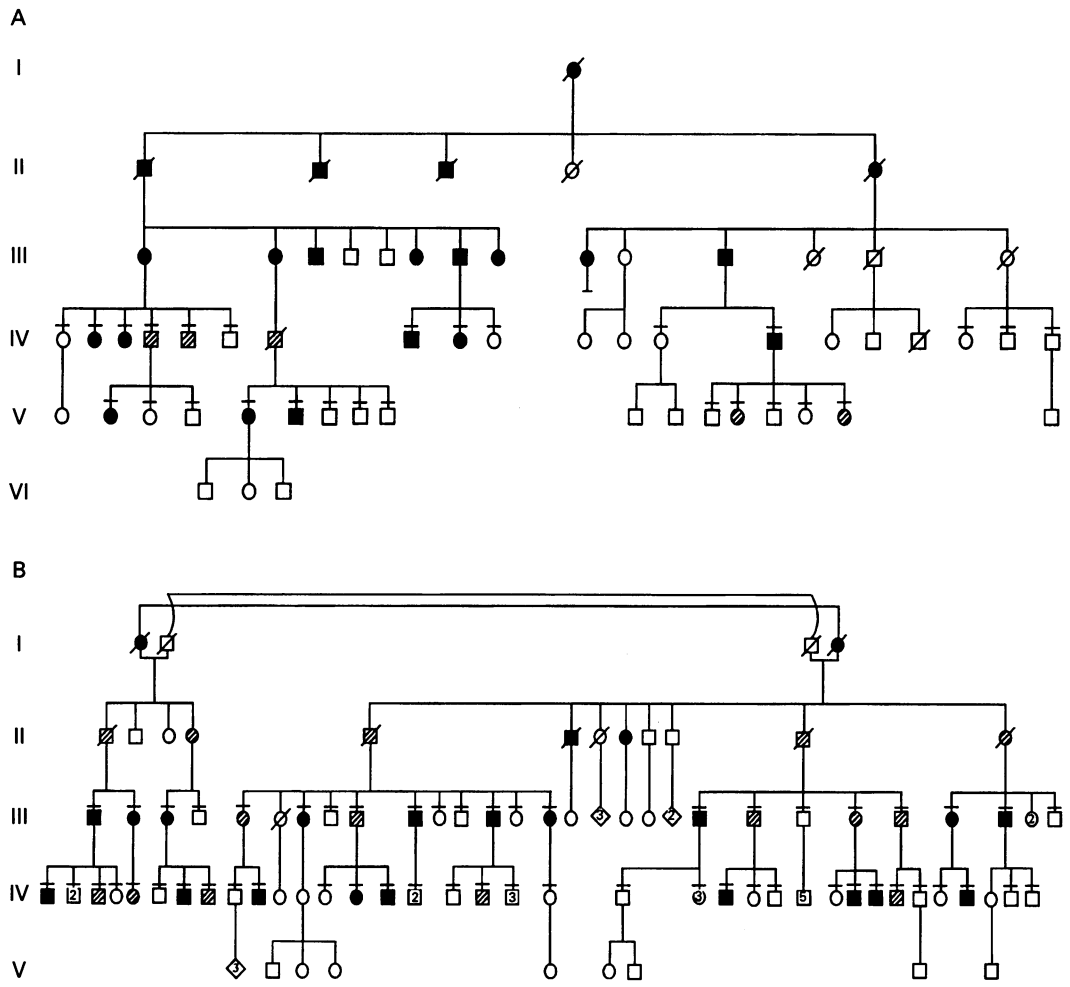

Figure 1 Pedigrees for families 3 (A) and 4 (B). ■ Symptomatic male, ○ unaffected female, ◍ disease-haplotype carrier. Bar above symbol identifies patients who underwent DNA examination.

For psychophysical studies pupils were dilated with 1% cyclopentolate hydrochloride and 2·5% phenylephrine hydrochloride, and subjects dark adapted for 40 minutes. Dark adapted static perimetry was undertaken using a modified Humphrey automated perimeter (Allergan Humphrey, San Leandro, CA, USA).[13–15] Cone and rod sensitivities were assessed using a standard Humphrey 30-2 program with the background illumination turned off. Size 5 red and blue test stimuli were used. In each case the eye with the better visual acuity was tested. For dark adaptometry, prebleach thresholds were then determined at selected positions. Patients were exposed to bright white light for 2 minutes sufficient to bleach 95% of rhodopsin (7·5 log scotopic Tröland-second delivered over 45 seconds). Recovery of sensitivity with time was assessed with size 5 blue test stimuli.[16–18]

Selected subjects underwent electrophysiological investigation using a 'short-protocol' adapted from that recommended by the International Standard for Clinical Ophthalmology.[19 20] Dark adapted electroretinography including blue flash ('run 7' to elicit rod isolated responses), red flash ('run 18', cone dominated responses), white flash ('run 20', mixed photoreceptor responses) and 30 Hz flicker ('run 31' cone isolated) responses were recorded. Electro-oculography was performed as previously described.[21]

The study was approved by the local ethics committee and informed consent was obtained from each subject enrolled into the study.

Results

Revised pedigrees are presented in Figures 1A and 1B. Linkage studies in both families identified seven individuals as recombinant over the entire 19q linked region. This prompted a reappraisal of their clinical status which had previously been based on ophthalmic history only. These examinations resulted in redesignation of disease status of two subjects in pedigree 3 (3-III-14 and 3-IV-20 as phenotypically normal) and five in pedigree 4 (4-III-7, 4-IV-1, and 4-IV-15 as phenotypically abnormal, 4-IV-25 and 4-IV-46 as normal). This and the identification of nine extra asymptomatic disease haplotype carriers accounts for differences from previously published family trees, more accurately reflecting segregation of the disease.[12] Because information was based on historical data in some generations, segregation of disease status was examined in generations III–V only in pedigree 3 and II–IV only in pedigree 4. This identified 57 symptomatic plus disease haplotype carriers and 63 unaffected individuals born to symptomatic or disease haplotype carrier parents. Approximately half (48%) of at risk individuals had inherited the disease

Table 1 Clinical details of 30 symptomatic and disease haplotype carrier patients

Patient	Age (years)	Genetic status	Nyctalopia age at onset (years)	Visual acuity		Lens opacities	Fundal examination
				Right	Left		
3-IV-2	62	s	6	6/60	6/60	PSC	MA, PEA, BS 360°
3-IV-15	61	s	10	6/36	6/36	PSC	MA, PEA, BS 360°
3-V-2	24	s	11	6/9	6/9	None	PEA, BS, BS 360°
3-V-5	57	s	15	6/9	6/12	PSC	PEA, BS 360°
3-V-6	52	s	9	6/24	6/36	None	PEA, BS 360°
4-III-1	61	s	8	6/60	6/60	PSC, CO	PEA, BS 360°
4-III-2	50	s	9	6/18	6/12	PSC	PEA, BS 360°
4-III-3	54	s	18	6/18	6/9	PSC	MO, PEA, BS 360°
4-III-13	60	s	10	6/60	6/60	PSC	MO, PEA, BS 360°
4-III-15	52	s	5	6/9	6/9	PSC	PEA, BS 360°
4-III-29	48	s	4	<3/60	<3/60	PSC	MA, PEA, BS 360°
4-IV-1	26	s	No	<3/60*	6/6	None	ONH, PEA, BS 360°
4-IV-8	25	s	5	6/12	6/12	PSC	MO, BS 360°
4-IV-11	45	s	5	6/18	6/9	PSC	PEA, BS 360°
4-IV-29	25	s	8	6/6	6/6	None	PEA, BS 360°
4-IV-38	33	s	13	6/12	6/9	None	MO, PEA, BS 360°
4-IV-39	30	s	10	6/9	6/9	None	PEA, BS 360°
4-IV-43	28	s	15	6/9	6/5	None	MO, BS 360°
3-IV-5	57	d	No	6/6	6/9	None	Normal
3-IV-6	55	d	No	6/6	6/6	None	Normal
3-V-13	33	d	No	6/6	6/6	None	Normal
3-V-16	24	d	No	6/5	6/5	None	Normal
4-III-5	75	d	No	6/9	6/9	CO	Normal
4-III-25	49	d	No	6/5	6/6	None	Normal
4-III-27	57	d	No	6/6	6/6	None	Normal
4-III-28	55	d	No	6/9	6/9	CO	Normal
4-IV-6	28	d	No	6/6	6/6	None	Normal
4-IV-9	26	d	No	6/9	6/6	None	Normal
4-IV-20	30	d	No	6/6	6/6	None	Normal
4-IV-40	26	d	No	6/6	6/6	None	Normal

3=Pedigree fig 1A, 4=pedigree Fig 1B. s=Symptomatic, d=disease haplotype carrier. PSC=posterior subcapsular lens opacities, CO=cortical lens opacities, PEA=retinal pigment epithelial atrophy, BS=bone spicule retinal pigmentation, MO=macular oedema, MA=macular atrophy, *=reduced acuity owing to optic nerve head hypoplasia (ONH) urelated to retinitis pigmentosa.

haplotype but only 37 (31%) were symptomatic.

Seventeen symptomatic patients had eight (47%) symptomatic and nine (53%) disease haplotype carrier children. This compared with 12 asymptomatic disease haplotype carrier patients who had 19 (76%) symptomatic and six (24%) disease haplotype carrier children. The difference between the percentages of symptomatic children born to symptomatic and asymptomatic disease haplotype carrier parents was not statistically significant ($\chi^2=3{\cdot}7$, $p=0{\cdot}05$). Of the 27 symptomatic individuals whose parents were also included in generations III–V of pedigree 3 and II–IV of pedigree 4, 17 had a male parent carrying the disease gene and 10 a female parent. Of 15 asymptomatic disease haplotype carriers with parents included in these generations 10 had a male parent carrying the disease gene and five a female parent. Therefore the sex of the parent carrying the disease gene did not seem to influence the likelihood that a child with the disease gene would be symptomatic.

Table 2 Dark adapted static sensitivities. Loss relative to lower normal limit

Patient	Genetic status	Dark adapted sensitivity loss (dB)					
		Blue stimulus			Red stimulus		
		3°	9°	27°	3°	9°	27°
3-IV-15	s	28	31	31	22	26	26
3-V-2	s	6	31	31	7	26	26
3-V-5	s	27	31	31	15	26	26
3-V-6	s	28	31	31	26	26	26
4-III-15	s	31	31	31	16	26	26
4-IV-11	s	15	31	31	4	22	26
4-IV-29	s	4	10	31	6	22	26
4-IV-38	s	23	31	31	13	26	26
3-IV-5	d	2	1	0	0	0	0
3-IV-6	d	0	0	0	0	0	0
3-V-13	d	0	0	0	0	0	0
3-V-16	d	0	0	0	0	0	0
4-III-5	d	2	1	2	0	0	0
4-III-25	d	2	1	1	0	0	0
4-III-27	d	6	5	2	2	0	1
4-III-28	d	0	0	0	0	0	0
4-IV-40	d	2	0	0	0	0	0

Normal sensitivity ranges, blue=31–50 dB, red=26–37 dB.
s=Symptomatic, d=disease-haplotype carrier.

The results of clinical examinations are presented in Table 1. No individual identified as a disease haplotype carrier reported nightblindness in contrast with all symptomatic individuals, who reported nyctalopia by their mid teens. Typical fundus features of extensive peripheral retinal degeneration were seen in even the youngest examined symptomatic patient (24 years) with macular atrophy, oedema, and secondary cataract formation in older symptomatic individuals. Normal visual acuities and fundus examinations were recorded for even the oldest asymptomatic disease haplotype carrier (75 years). No systemic abnormality was identified as segregating with eye disease.

All symptomatic individuals assessed (24–61 years of age) had elevated dark adapted threshold sensitivities for the whole 30° field tested with matching areas of rod and cone functional deficit (Table 2). Relative preservation of a central island of vision was evident in younger symptomatic individuals extending to approximately 9° around fixation. In middle age this island was <3°. In contrast, minimal threshold elevations were detected in the central 30° of asymptomatic disease haplotype carriers (within 7 dB of the normal limit). Abnormal dark adaptometry results were obtained from all symptomatic patients tested with elevation of prebleach thresholds and elevated final thresholds (Table 3). Prebleach threshold elevation above 50 dB precluded dark adaptometry in symptomatic individuals over 52 years of age. All symptomless disease haplotype carrier individuals gave responses within 5 dB of normal mean values.

Electroretinographic responses were not detectable (that is, <5 mV) in symptomatic individuals over 30 years of age. Significantly reduced electro-oculographic responses and ERG changes indicative of a severe rod-cone type photoreceptor deficit were seen in all younger symptomatic individuals (Table 4). Minor abnormalities in scotopic responses (within 34 mV of the lower normal limit with normal implicit times) were also evident in two asymptomatic disease haplotype carrier patients (4-V-16, 24 years and 4-IV-5, 57 years). Dramatic differences were therefore seen in the results of field analysis and electrical responses of the youngest symptomatic patients in comparison with those from even the oldest disease haplotype carriers. These differences were not attributable to age.

Discussion

Matching areas of both rod and cone functional loss classify the phenotype seen in these families as R type (regional, type II), which contrasts with the widespread reduction in rod sensitivity with relative sparing of cone function seen in D type (diffuse, type I) disease.[22 23] Some rhodopsin mutations appear to cause D type

Table 3 Dark adaptometry

Patient		Genetic status	Dark adapted rod prebleach threshold, elevation (dB)	Time to cone/rod break (minutes)	Time to prebleach threshold (minutes)	Dark adaption curve profile
Normal			0	9–11	30–45	
3-V-2	x	s	20	7	>45	Elevated final threshold
	y		30	12	>45	relative to prebleach value
4-IV-29	x	s	22	6	>45	Elevated final threshold
	y		40	13	>45	relative to prebleach value
4-III-25	x	d	8	9	35	Normal
	y		9	9	35	
4-III-5	x	d	10	12	40	Normal
	y		10	12	40	
4-III-27	x	d	10	6	42	Normal
	y		15	6	42	
4-III-28	x	d	9	9	37	Normal
	y		9	9	37	

s=Symptomatic, d=disease-haplotype carrier, x=visual field locus (3,3), y=visual field locus (9,9).

functional loss,[24–26] and others an R type loss associated with an altitudinal distribution of visual field deficit unlike that seen here.[18 27–34] Regional functional loss has also been described with peripherin/RDS mutations although severity was consistently related to age.[35] Detailed phenotype descriptions for pedigrees linked to 7q, 8cen, and 17p are as yet unpublished. A phenotype with variable expression and an R type pattern of deficit has been described for the dominant retinitis pigmentosa pedigree linked to chromosome 7p.[12] However, a graded disease severity has been reported with mild, moderate, and severely affected individuals. By extending the clinical study on the two families, the present study has identified a large number of haplotype carriers who on clinical examination and intensive investigation are essentially normal. This establishes the phenotype, R type functional deficit with bimodal expressivity, as a real phenomenon in two large families that may be a unique feature of the 19q locus, and allows analysis of segregation of disease in the pedigrees.

To explain this unusual phenotypic expression, another influence in addition to the underlying causative mutation mapping to 19q is most probably operating. This is unlikely to be environmental since such an effect would be expected to be dose dependent, and produce a graded rather than the 'all or nothing' phenotype seen here. In addition, despite extensive research, environmental factors such as ambient lighting have not been proved to have a large influence on disease severity in retinitis pigmentosa.[3 36] A number of genetic mechanisms have been associated with variable expression of disease phenotype. Anticipation describes disease severity related to increasing trinucleotide repeat expansion as seen in fragile X syndrome[37] and myotonic dystrophy.[38] Imprinting is often the basis for a phenotype influenced by sex of the carrier parent.[39] Incomplete penetrance in certain retinoblastoma pedigrees has been attributed to mutations in gene promoter sequence[40] or 'mild' germline mutations which reduce but do not eliminate tumour suppression protein function.[41] Anticipation, with severity related to position in a pedigree was not seen in this study, and the sex of the disease gene carrying parent did not influence the likelihood of a disease gene carrier being symptomatic. Also, the mechanism seen in retinoblastoma would not explain the bimodal expressivity seen in this study since incomplete penetrance of the retinoblastoma phenotype is usually associated with a relatively severe 'second hit' null mutation in somatic cells.[41] Such somatic cell mutations could not explain the panretinal disease seen in retinitis pigmentosa.

Digenic inheritance describes the association of germline mutations in different genes that result together in phenotype expression but cause minimal or no function deficit when inherited individually.[42] In retinitis pigmentosa cases associated with digenic inheritance, the gene products (peripherin/RDS and ROM1) are structural proteins known to interrelate functionally at a cellular level. Such a mechanism may imply that disease status in a particular individual linked to gene mutation at the 19q locus would be determined by the presence of a second gene expressing a functionally related protein. This suggests that the 19q mutation and another modulating gene may encode related structural proteins, ion transport channel subunits, or related membrane bound proteins. The protein products of these two mutations may also possibly be enzyme subunits. Mutations of enzyme coding genes conventionally result in recessive

Table 4 Electrodiagnostic results

			Electroretinography									
			Run 7 b wave		Run 18 b wave		Run 20 a wave		Run 20 b wave		Run 31	
Patient	Age (years)	EOG %	amp	imp	amp	imp	amp	imp	amp	imp	amp	imp
3-V-2 (s)	24		0	–	15	50	30	30	20	50	10	40
4-IV-1 (s)	26	100/110	0	–	30	50	30	30	30	50	5	42
4-IV-29 (s)	25	137/135	0	–	10	46	7	30	18	50	10	47
4-IV-43 (s)	28	100/100	0	–	16	42	6	20	18	48	10	32
3-IV-5 (d)	57	195/210	45	120	60	50	50	30	220	50	35	31
3-V-13 (d)	33		120	100	60	42	120	15	280	45	30	30
3-V-16 (d)	24	141/161	55	95	60	48	41	25	220	51	25	35
4-III-25 (d)	25	370/335	140	90	120	46	80	23	270	45	25	30
4-III-27 (d)	57	200/218	160	100	200	44	60	22	260	44	35	30
4-IV-9 (d)	26		80	106	40	20	41	25	200	40	20	32
Normal mean			199	100	153	47	132	22	384	45	43	29
Normal limits		160 to 400	79	126	59	57	41	25	208	49	10	32

EOG=electro-oculogram. Electroretinogram run 7 (rod isolated), run 18 (cone dominant), run 20 (mixed photoreceptor), and run 31 (cone photoreceptor) correspond to a 'short protocol' regimen.[19] amp=Wave amplitude, imp=implicit time. Normal limits for electroretinographic responses refer to the normal mean −2 SD for wave amplitudes and the normal mean +2 SD for implicit times. s=Symptomatic, d=disease haplotype carrier.

disease, but this well established dogma is not incontrovertible since a mutation in the β subunit of the enzyme phosphodiesterase has been associated with a dominant congenital stationary nightblindness.[43] The large number of symptomatic individuals from symptomless disease haplotype carriers would suggest that the second proposed mutation, derived from the unrelated spouse, may be common in the general population. Since in itself this second mutation is not associated with disease it could be described as a gene polymorphism. However, it would be expected that if digenic inheritance explained the disease segregation in this study, then symptomatic individuals would be significantly more likely to have symptomatic children than disease haplotype carriers. This was not the case in these families since only 50% of children carrying the disease gene derived from symptomatic individuals were themselves symptomatic compared with 76% of children with the disease gene derived from a disease haplotype carrier parent. This finding may be explained if the second genetic influence in these families was in fact allelic to the 19q mutation. Such allelic mutations, modifying disease expression have been identified in *Drosophila* where the phenomenon is termed intragenic complementation.[44] Also, an allelic, symptomless polymorphism of the spectrin gene, common in the population, has been implicated as modulating the severity of symptoms in humans with a primary spectrin mutation causing hereditary haemolytic anaemia.[45] This hypothesis will easily be testable once the 19q mutant gene is isolated.

Despite intensive work on cDNA libraries in many laboratories, to date no research worker has identified a retina specific gene on chromosome 19. However, techniques used to generate tissue specific libraries usually identify genes that give rise to larger amounts of protein. the 19q gene product, although important to cell function, may not be a large contributor to the protein content of retinal cells.[46] Alternatively, the gene of interest may not be retina specific. Although no systemic disease was identified, the function of the defective gene may be compensated for in other tissues in a way not possible in the retina.

In the past genetic counselling of such families has been difficult since clinical examination and extensive investigation would not exclude the presence of the abnormal gene even in late life. Although, as expected, roughly 50% of at risk individuals had the disease haplotype the overall risk of being significantly visually handicapped during a working lifetime was only 31%. In addition, 'minimal' disease in a parent did not imply an increased likelihood of 'minimal' disease in offspring. In these families accurate counselling is therefore dependent upon molecular genetic haplotype analysis.

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