Genetics of plasma paroxonase activity

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SUMMARY Complex segregation analysis of plasma paroxonase activity gives evidence for a major locus with incomplete dominance ($d = 0.70$) causing high activity plus a background of multifactorial inheritance (heritability = 0.09).

The arylesterase paroxonase (EC 3.1.1.2) exhibits a genetic polymorphism with autosomal recessive inheritance of low paroxonase activity in plasma.¹⁻⁴ Although the distribution of plasma paroxonase activity shows bimodality³ or even trimodality² the different subgroups are overlapping. This could result from methodological errors in the analysis or from other random environmental effects. However, it is also of interest to search for residual family resemblance owing to incomplete dominance and polygenes.

This paper describes a reanalysis of 40 British families described by Playfer *et al*³ using complex segregation analysis.^{5,6}

Materials and methods

The 40 nuclear families and methods of analysis of paroxonase activity have been described in detail before³ and are also given in the appendix. For the genetic analysis the actual activity measurements were used instead of grouping the activities into high and low (or high, medium, and low) which decreases the power to discriminate between different hypotheses.

Complex segregation analysis of a quantitative trait depends upon normality assumptions and in particular skewness may simulate a major gene.⁷ Before entering segregation analysis the skewness was removed using the power transform $y = rp^{-1}[(xr^{-1}+1)^p - 1]$ where x is the standardised (to mean zero and variance one) paroxonase activity and r is a scale parameter introduced to insure that every $(xr^{-1}+1)$ is positive in the sample. It was taken equal to 6 here. The standardised paroxonase activity without skewness is y . The parameter p is estimated

by maximum likelihood using the computer programme SKUMIX⁸ and was estimated to 0.1128.

Complex segregation analysis was performed under the mixed model,^{5,6} where segregation at a major locus, an additive multifactorial transmissible component, with generational differences and a random environmental component contribute independently to phenotype expression of a continuous trait. The model involves seven parameters: U , mean liability; V , variance of liability; H , the childhood multifactorial heritability; HZ , the adult multifactorial heritability; q , gene frequency of the major locus; t , displacement owing to the major locus (measured in standard deviation units); and d , degree of dominance at the major locus (position of the heterozygous mean relative to the means of the two homozygous classes). Estimates of the parameters of the model are obtained by maximising the probability density of the observed phenotypes of the children conditional upon the phenotypes of the parents using the computer program POINTER.⁶ Since ascertainment was through the parents selection was taken as complete.

Results

No significant sex difference for paroxonase activity was noted. There was significant evidence ($\chi^2_3 = 51.77$, $p < 0.001$) for commingling of two distributions, which suggests a major locus but is neither necessary nor sufficient for the existence of a major gene.

Likelihoods and estimates of the parameters under different sub-hypotheses of the mixed model are given in the table. There was no significant evidence for generational differences for multifactorial heritability ($\chi^2_1 = 273.16 - 272.88 = 0.28$) and Z was therefore set to one in the remaining analysis. The evidence for a major locus is strong ($\chi^2_3 = 273.16 -$

TABLE Tests of hypotheses and estimates for the mixed model (values within parentheses correspond to non-iterated parameters).

Hypothesis	$-2\ln L + C$	H	Z	q	$t/\sqrt{V}$	d
q = 0, Z = 1 No major locus, no intergenerational differences for multifactorial heritability	273.16	0.942	(1)	(0)	(0)	(0)
q = 0 No major locus	272.88	0.748	1.219	(0)	(0)	(0)
H = 0 Generalised single locus	237.49	(0)	(1)	0.266	2.42	0.691
d = 0 Recessive major locus	261.80	0.210	(1)	0.676	1.66	(0)
d = 0.5 Additive major locus	241.19	0.101	(1)	0.326	2.76	(0.5)
d = 1 Dominant major locus	232.14	0.109	(1)	0.218	1.82	(1)
General model	217.83	0.092	(1)	0.338	2.36	0.705

217.83 = 55.33, $p < 0.001$). The best fit is with $d = 0.705$, that is, intermediate between an additive model ($d = 0.5$) and a model with complete dominance ($d = 1$) causing high paroxonase activity. There is significant evidence ($\chi^2_1 = 237.49 - 217.83 = 19.66$, $p < 0.001$) for a small polygenic component ($H = 0.092$).

Since segregation analysis gave support for a major locus using a p value for one distribution, the data were reanalysed using $p = -0.984$ obtained from SKUMIX assuming two distributions. This analysis would give more reliable estimates of the major locus parameters. However, the difference was minimal and the results of the second segregation analysis are therefore not given.

Discussion

There is good evidence that a major gene is involved in the regulation of plasma paroxonase activity. The characterisation of this gene has, however, been difficult.²⁻⁴ This is not surprising since the methods used have been inefficient. Dichotomising or trichotomising quantitative data only decreases the possibilities of making meaningful genetic analyses. Elaborate statistical analysis of a frequency distribution to show bi- or trimodality² is not likely to give further insight into the genetics of a particular trait, since the presence of several modes is not sufficient evidence for a major gene. Today, only segregation analysis under the mixed model^{5,6} can incorporate and test for complications like incomplete dominance and multifactorial heritability.

For plasma paroxonase activity the major gene has an effect in the heterozygote ($d = 0.705$). In addition, there is a background of multifactorial

inheritance, with heritability 0.094, but with no evidence of an intergenerational difference. The estimate of the gene frequency, 0.338, is similar to the value estimated from the same data using a dichotomy, 0.2966.³

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References

- 1 Geldmacher-v Mallinckrodt M, Lindorf HH, Petenyi M, Flügel M, Fischer T, Hiller T. Genetisch determinierter Polymorphismus der menschlichen Serum-Paraoxonase (EC 3.1.1.2). *Humangenetik* 1973;17:331.
- 2 Geldmacher-v Mallinckrodt M, Hommel G, Dumbach J. On the genetics of the human serum paroxonase (EC 3.1.1.2). *Hum Genet* 1979;50:313-26.
- 3 Playfer JR, Eze LC, Bullen MF, Evans DAP. Genetic polymorphism and interethnic variability of plasma paroxonase activity. *J Med Genet* 1976;13:337-42.
- 4 Eiberg H, Mohr J. Genetics of paroxonase. *Ann Hum Genet* 1981;45:323-30.
- 5 Morton NE, MacLean CJ. Analysis of family resemblance. III. Complex segregation of quantitative traits. *Am J Hum Genet* 1974;26:489-503.
- 6 Lalouel JM, Morton NE. Complex segregation analysis with pointers. *Hum Hered* 1981;31:312-21.
- 7 MacLean CJ, Morton NE, Lew R. Analysis of family resemblance. IV. Operational characteristics of segregation analysis. *Am J Hum Genet* 1975;27:365-84.
- 8 MacLean CJ, Morton NE, Elston RC, Yee S. Skewness in commingled distributions. *Biometrics* 1976; 32:695-9.

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APPENDIX *Paroxonase activities in 40 British families. Values for female offspring are underlined.*

Family No	Father	Mother	Offspring				
1	884	945	851	1101	<u>261</u>		
2	1089	608	631	<u>1002</u>			
3	1098	782	279	<u>1055</u>	<u>1229</u>	557	<u>996</u>
4	610	1047	1189	398			
5	854	999	1014	<u>1277</u>	<u>1277</u>	336	
6	1083	806	438	<u>1098</u>			
7	740	744	<u>325</u>	737			
8	857	795	694	853			
9	736	889	<u>860</u>	704			
10	1252	1227	<u>1267</u>	1348			
11	661	665	<u>1149</u>	731	768	1036	<u>675</u>
12	274	399	473	477			888
13	536	535	<u>511</u>	154			
14	362	204	<u>358</u>	<u>368</u>	365		
15	276	180	<u>253</u>	228			
16	474	316	492	294			
17	1500	422	980	<u>1256</u>	<u>1161</u>		
18	855	532	249	962			
19	956	204	183	845	<u>989</u>	802	<u>191</u>
20	723	315	220	746			
21	1282	414	<u>897</u>	802			
22	868	394	<u>1090</u>	328			
23	817	317	<u>295</u>	795	266		
24	1087	467	<u>945</u>	792	365		
25	914	327	540	<u>558</u>			
26	1139	367	799	<u>754</u>			
27	733	466	977	793	368		
28	790	315	723	425	<u>425</u>		
29	1484	532	<u>988</u>	<u>1102</u>			
30	1047	319	<u>1028</u>	852	<u>1091</u>		
31	1028	358	<u>399</u>	976	<u>932</u>		
32	217	982	<u>951</u>	325	<u>367</u>		
33	470	785	<u>502</u>	<u>621</u>			
34	412	1142	379	<u>365</u>	415		
35	292	992	974	<u>277</u>	<u>919</u>		
36	354	1054	<u>1010</u>	945			
37	301	1009	254				
38	499	793	422	1340			
39	389	1307	<u>514</u>	657	350	646	
40	353	881	<u>1120</u>	<u>1252</u>			