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Probable Genetic Linkage between Autosomal Dominant Retinitis Pigmentosa (*RP*) and Amylase (AMY_2): Evidence of an *RP* Locus on Chromosome 1

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Retinitis pigmentosa (RP) is a group of retinal dystrophies with similar clinical manifestations which shows three forms of inheritance: X-linked, autosomal dominant, and autosomal recessive. The autosomal dominant form of inheritance occurs in 3%–15% of the cases [1, 2]. Sporadic cases of RP have been reported, and atypical RP occurs as a component in at least one rare syndrome [1].

Gene linkage studies in which several families are pooled have been reported for both the autosomal dominant [2] and X-linked [3–5] forms of the disease; none of these studies detected a linkage. In the present study, we examined a large pedigree with the typical autosomal dominant form of retinitis pigmentosa. The results indicate a close linkage to the serum amylase locus, AMY_2, which is on chromosome 1.

METHODS

The general clinical features of retinitis pigmentosa which occur in this family include nightblindness appearing in the late teens or early twenties, followed by severe visual difficulties in the mid-thirties or early forties, and total blindness by the late forties to early sixties. In addition, posterior subcapsular cataracts are a consistent finding. Recent generations have shown an earlier progression of symptoms, a finding not uncommon in diseases with a late onset.

Individuals were categorized on the basis of past medical history with confirmation by direct ophthalmoscopy. A few members of the family had thorough examinations, including visual fields, electroretinograms, and fundus photographs which documented the disease in those members. Specific clinical details will be presented elsewhere (J. R. Heckenlively, in preparation).

Red blood cell and serum gene markers were analyzed by standard techniques [6–11]. Serum

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amylase was determined using the method of Merritt et al. [12]. In addition, secretor status was recorded as indicated by the Lewis antigen typing [7]. Ability to taste phenylthiocarbamide was determined by use of the standard threshold solution for Caucasians [13].

Lod scores, as defined by Morton [14, 15], were computed using a modified version of the LIPED computer program developed by Ott [16, 17]. The pedigree (fig. 1) was divided into two sections for analysis. The left branch, referred to as B in table 1, contains 49 individuals of whom 36 were examined for gene markers. The right branch, denoted C in table 1, contains 30 individuals of whom 18 were studied. An additional 10 individuals constitute the pedigree denoted A. The relationship of A to B and C could not be specified, and it was analyzed independently. When there was any doubt concerning the diagnosis, the status of unknown was used during the analysis. Correction for age of onset was not undertaken in these studies since only one individual in the youngest generation remained doubtful.

RESULTS

The lod scores for the two branches of the large pedigree are given in table 1 for the *RP* locus and the markers on chromosome no. 1. The lod score z with serum amylase is 3.9023 at a recombination fraction θ of .01. This is highly significant and well above the level of $z = 3.0$ suggested by Morton [14] for the acceptance of linkage. Linkage could be excluded at values of $\theta = .05$ or less for *RP* and PGM_1. The lod scores are less than the value $z = -2.0$ which was suggested by Morton [14] for the exclusion of linkage.

A summary of lod scores for the *RP* locus and 23 additional autosomal loci is given in table 2. Linkage with $\theta < .2$ can be excluded for ACP_1, $\theta < .1$ for *ABO* and *MNSs*, $\theta < .05$ for *GPT* and *Hp*, and $\theta < .01$ for *Lu*, *ADA*, *Gc*, *Pi*, and *Se*.

Lod scores were also computed among the marker loci on chromosome no. 1. The results of these analyses are presented in table 3.

DISCUSSION

Retinitis pigmentosa occurs as both an autosomal and X-linked trait. The large pedigree in this study demonstrates male-to-male transmission of RP, and it is clear that the disorder is the result of an autosomal dominant allele.

The lod scores for serum amylase (AMY_2) and *RP* are statistically significant. There were no recombinants and seven nonrecombinants in cases where recombination could be clearly discerned. The most likely estimate of recombination between these two loci is $\theta \leq .01$; male and female recombination frequencies being equal. AMY_2 has been located on chromosome no. 1 [18]. The lod scores between *RP* and other loci on chromosome no. 1 do not achieve statistical significance. The scores indicate, however, that *RP* may be relatively close to Duffy (*Fy*) with the maximum lod score, $z = 1.23$ at $\theta = .01$, and may be relatively further from *Rh*, $z = 2.4989$ at $\theta = .1$, and PGM_1, $z = 0.4175$ at $\theta = .3$

The most likely order of loci on chromosome no. 1 has been suggested as *Fy*, centromere, AMY_2, PGM_1, *Rh*, and *6PGD* [19]. The results from this family for linkage with *RP* indicate, instead, an order of AMY_2, *Rh*, and PGM_1. The scores for *Fy*, as shown in table 3, result in the same order. The data within this pedigree are consistent, and some other reported studies also differ from the suggested order [19]. It is not surprising that AMY_2 and *RP* give the same results since there are no crossovers between the two loci. The consistent nature of the results among the other loci support

TABLE 1

LOD SCORES FOR RETINITIS PIGMENTOSA AND LOCI ON CHROMOSOME NO. 1 (RECOMBINATION FRACTION θ)

Loci	Family RP01	.01	.05	.10	.20	.30	.40
AMY_2	B	1.76	1.61	1.41	0.98	0.53	0.15
	C	2.14	1.97	1.75	1.29	0.82	0.38
Total	...	3.90	3.58	3.16	2.27	1.35	0.53
Rh	B	1.51	2.06	2.08	1.69	1.10	0.50
	C	−0.29	0.28	0.42	0.40	0.28	0.15
Total	−	1.22	2.34	2.50	2.09	1.38	0.65
Fy	B	0.47	0.40	0.32	0.18	0.09	0.03
	C	0.65	0.57	0.47	0.29	0.15	0.05
Total	...	1.12	0.97	0.79	0.47	0.24	0.08
PGM_1	B	−4.51	−1.88	−0.88	−0.11	0.15	0.16
	C	−1.62	−0.36	0.06	0.29	0.27	0.15
Total	...	−6.13	−2.24	−0.82	0.18	0.42	0.31
6PGD	B	0.04	0.03	0.03	0.01	0.01	0.00
	C	0.06	0.05	0.04	0.03	0.01	0.00
Total	...	0.10	0.08	0.07	0.04	0.02	0.00

NOTE.—Family RP01 is presented in figure 1; B refers to the left branch and C refers to right branch.

TABLE 2

TOTAL LOD SCORES FOR RETINITIS PIGMENTOSA AND 23 ADDITIONAL LOCI (RECOMBINATION FRACTION θ)

Locus	.01	.05	.1	.2	.3	.4
ABO	−9.16	−4.46	−2.46	−0.81	−0.18	0.02
MN	−2.73	−1.28	−0.66	−0.16	0.00	0.03
Ss	−8.00	−4.00	−2.41	−1.04	−0.43	−0.12
Lu	−3.99	−1.51	−0.57	0.17	0.32	0.21
Kell	0.06	0.05	0.04	0.02	0.01	0.00
Kp	−0.47	−0.43	−0.38	−0.30	−0.20	−0.09
JK	−0.29	−0.16	−0.08	−0.02	−0.01	−0.01
P	−0.48	0.16	0.37	0.44	0.35	0.20
AK	0.09	0.08	0.06	0.04	0.02	0.01
ADA	−2.12	−0.86	−0.39	−0.00	0.14	0.13
PGM_2	0.02	0.02	0.01	0.01	0.00	0.00
ACP_1	−18.47	−9.63	−6.05	−2.87	−1.32	−0.45
GALT	0.19	0.17	0.14	0.11	0.07	0.04
GPT	−5.44	−2.72	−1.56	−0.51	−0.08	0.05
EsD	0.04	0.45	0.58	0.58	0.45	0.26
Hp	−7.07	−3.08	−1.53	0.30	0.12	0.17
Tf	0.01	0.01	0.01	0.00	0.00	0.00
Gc	−2.75	−0.15	0.73	1.07	0.77	0.31
Pi	−3.85	−1.84	−1.06	−0.39	−0.11	0.00
E_1	1.22	1.14	1.04	0.83	0.59	0.32
PTC	−1.52	−0.82	−0.55	−0.31	−0.18	−0.08
Se	−3.18	−1.69	−1.01	−0.41	−0.16	−0.04

TABLE 3

TOTAL LOD SCORES FOR LOCI ON CHROMOSOME NO. 1
(RECOMBINATION FRACTION θ)

Loci	.01	.05	.1	.2	.3	.4
AMY_2 and *Fy*	0.42	0.36	0.28	0.16	0.07	0.02
AMY_2 and *Rh*	−0.89	−0.17	0.13	0.22	0.12	0.02
AMY_2 and PGM_1	−0.68	−0.49	−0.32	−0.12	−0.03	−0.01
Fy and *Rh*	0.07	0.05	0.04	0.02	0.01	0.00
Fy and PGM_1	0.08	0.07	0.05	0.03	0.01	0.00
Rh and PGM_1	−1.81	0.03	0.59	0.78	0.59	0.30

the hypothesis that the locus for *RP* is on chromosome no. 1. It is clear that even the large studies do not completely agree on the order of the loci on no. 1 [20], and it is not unreasonable that the sampling from this single family produces results different from the suggested order, although, given the confidence interval of the estimates, our results are not incompatible with the suggested order for no. 1.

The data for this linkage are restricted to a single pedigree where the *RP* allele is apparently in coupling with the AMY_2^A allele. The hypothesis of association for these two alleles cannot be tested with the data, but there is no a priori reason to suggest a cause and effect relationship. The findings are compatible with the positive lod scores reported by Hussels-Maumenee et al. [2] for *RP* and *Fy*. Their study did not analyze serum amylase.

The consistent pattern among the gene markers on chromosome no. 1 and the level of statistical significance of the lod score for *RP* and AMY_2 suggest that the *RP* locus is on the no. 1 chromosome close to the AMY_2 locus. This is the ninth autosomal dominant disorder mapped to a specific chromosome. Since the relative position of the centromere is not known, the *RP* locus cannot be assigned to a specific chromosome arm. It remains to be seen if other families with the autosomal dominant variety will map to the same area, but a tight linkage with AMY_2 should make it possible to test for genetic heterogeneity in relatively small families. Confirmation of the close linkage would also make it possible to predict relatively accurately those individuals at risk prior to onset of symptoms. Examinations of these individuals may lead to a better understanding of the disease process, and the information available from the linkage may eventually be applied in prenatal detection of affected individuals.

SUMMARY

A linkage analysis is reported for three branches of a single family segregating for autosomal dominant retinitis pigmentosa. A statistically significant lod score of 3.9 is obtained for the RP locus and AMY_2 at a recombination frequency of 1%. This linkage indicates that the *RP* locus is on the no. 1 chromosome since the AMY_2 locus has been placed on the short arm of 1. Lod scores are reported for four other loci on chromosome 1; none of these achieve statistical significance. Analyses are reported for

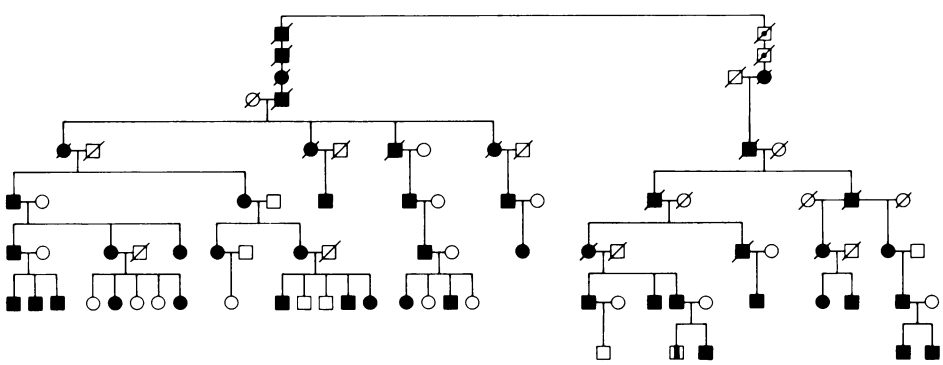

FIG. 1.—This is UCLA research pedigree RP01. □ = unaffected; ■ = affected; ⊡ = individuals presumed to have had the trait; ◧ = individuals whose status is currently unknown.

23 additional autosomal markers and close linkage with *RP* can be excluded for a number of these.

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REFERENCES

1. McKusick VA: *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. Baltimore, Johns Hopkins Univ. Press, 1975
2. Hussels-Maumenee I, Pierce ER, Bias WB, Schleutermann DA: Linkage studies of typical retinitis pigmentosa and common markers. *Am J Hum Genet* 27:505–508, 1975
3. Hussels IE: Une famille atteinte de rétinopathie pigmentaire liée au sexe, de maladie de Parkinson et d'autres troubles neuropsychiatriques. *J Genet Hum* 16:106–155, 1967
4. Warburg M, Simonsen SE: Sex-linked recessive retinitis pigmentosa: a preliminary study of the carriers. *Acta Ophthalmol (Kbh)* 46:494–499, 1968
5. Grutzner P, Sanger R, Spivey BE: Linkage studies in X-linked retinitis pigmentosa. *Humangenetik* 14:155–158, 1972
6. Chen SH, Giblett ER, Anderson JE, Fossum BLG: Genetics of glutamic-pyruvic transaminase: its inheritance, common and rare variants, population distribution and differences in catalytic activity. *Ann Hum Genet* 35:401–409, 1972
7. Giblett ER: *Genetic Markers in Human Blood*. Philadelphia, Davis, 1969
8. Hopkinson DA Mestriner MA, Cortner J, Harris H: Esterase D: a new human polymorphism. *Ann Hum Genet* 37:119–137, 1973
9. Issitt PD, Issitt CH: *Applied Blood Group Serology*, 2d ed. Oxnard, Calif., Becton-Dickinson, 1975
10. Kuhnl P, Nowicki L, Spielmann W: Untersuchen zum polymorphismus der Galaktose-1-Phosphate-Uridyltransferase (E.C.2.7.7.12) mittels agarose electrophorese. *Humangenetik* 24:227–230, 1974
11. Spencer N, Hopkinson DA, Harris H: Adenonsine deaminase polymorphism in man. *Ann Hum Genet* 32:9–14, 1968
12. Merritt AD, Rivas ML, Bixler D, Newell R: Salivary and pancreatic amylase electrophoretic and genetic studies. *Am J Hum Genet* 25:510–522, 1973
13. Crandall BF, Spence MA: Linkage relations of the phenylthiocarbamide locus (PTC). *Hum Hered* 24:247–252, 1974
14. Morton NE: The detection and estimation of linkage between the genes for elliptocytosis and the Rh blood type. *Am J Hum Genet* 8:80–96, 1956
15. Morton NE: Further scoring types in sequential linkage tests, with a critical review of autosomal and partial sex linkage in man. *Am J Hum Genet* 9:55–57, 1957
16. Ott J: Estimation of the recombination fraction in human pedigrees: efficient computation of the likelihood for human linkage studies. *Am J Hum Genet* 26:588–597, 1974
17. Ott J: A computer program for linkage analysis of general human pedigrees. *Am J Hum Genet* 28:528–529, 1976
18. Merritt AD, Lovrien EW, Rivas ML, Conneally PM: Human amylase loci: genetic linkage with the Duffy blood locus and assignment to linkage group I. *Am J Hum Genet* 25:523–528, 1973
19. Hamerton JK, Bodmer W, Cook PJL, McAlpine PJ, Rivas M: Report of the committee on the genetic constitution of chromosomes 1 and 2. *Baltimore Conference (1975): Third International Conference on Human Gene Mapping, Birth Defects: Orig Art Ser* 12(7), New York, The National Foundation, 1976, pp 7–23

20. MEYERS DA, CONNEALLY PM, LOVRIEN EW, MAGENIS RE, MERRITT AD, NORTON JA, PALMER CG, RIVAS ML, WANG L, YU PL: Linkage group I: the simultaneous estimation of recombination and interference. *Baltimore Conference (1975): Third International Conference on Human Gene Mapping, Birth Defects: Orig Art Ser* 12(7), New York, The National Foundation, 1976, p 335–339

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