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Glomus tumours and genomic imprinting: influence of inheritance along the paternal or maternal line

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Glomus tumours and genomic imprinting: influence of inheritance along the paternal or maternal line

Two new families with glomus tumours and two additions to earlier publications are presented. The pattern of inheritance is autosomal dominant. Familial glomus tumours are inherited almost exclusively via the paternal line, a finding inconsistent with autosomal dominant transmission. This can be explained by genomic imprinting. The maternally derived gene is inactivated during female oogenesis and can be reactivated only during spermatogenesis. Two different loci have been assigned, one to a 5 cM region of chromosome 11q13.1 and one to 11q22.3-q23.3. Genomic imprinting has already been found for the distal locus and here we demonstrate that the proximal locus is subject to genomic imprinting too. Genomic imprinting has considerable implications for genetic counselling in families with glomus tumours. In addition to this the sex ratio among affected offspring appears to be influenced by the paternal or maternal origin of the gene of the transmitting father.

Keywords *glomus tumours non-chromaffin chemodectoma paraganglioma genomic imprinting sex ratio*

Introduction

Glomus tumours are neoplasms that arise from the paraganglionic chemoreceptor cells. The main locations are the glomus caroticum, glomus vagale and the glomus jugulotympanicum. Multifocal presentation is seen in 60% of affected individuals in a large family.[1] The autosomal dominant pattern of inheritance for glomus tumours was recognized for the first time in 1949 by Bartels.[2]

In 1975, Van Baars drew attention to the high frequency of paternal transmission and the lack of affected children among the offspring of affected mothers.[3] This finding is inconsistent with autosomal dominant transmission. Recently, this phenomenon was attributed to genomic imprinting of the underlying genes. The maternally derived gene is inactivated during female oogenesis and can be reactivated only during spermatogenesis. Non-affected fathers who inherited the gene from their mother transmit the disorder to their offspring.[4]

The underlying molecular mechanism has not yet been found. By independent linkage studies the disorder has been assigned to two separate loci on chromosome 11, one on 11q13.1 between the anonymous DNA marker D11S956 and PYGM and another locus at 11q22.3-q23.3. The pattern of inheritance of glomus tumours in linked families, proved to be consistent with genomic imprinting of the responsible gene.[4,5,6,7]

Besides genomic imprinting, another influence on the occurrence of glomus tumours is a strong imbalance in the sex ratio, e.g. among 26 affected individuals 20 were males versus six females in one large family.[1] At the University Hospital Nijmegen, by contrast, the total population of patients who underwent surgery or radiotherapy for a glomus tumour comprised more women than men.[1] In this study, we report two

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families with linkage to 11q22.3-q23.3, an extension of a previously described family with linkage to 11q13.1 and one family in which linkage analysis has not yet been performed. Genomic imprinting could be demonstrated in all patients despite the different loci for gene linkage. These newly identified families with glomus tumours, together with data reported in the literature on fully investigated pedigrees were reviewed to determine the sex ratio of affected and non-affected offspring and to differentiate them according to inheritance along the paternal or maternal line.

Patients and methods

A literature search was made for reports on families with glomus tumours. The following inclusion criteria were used: the presence of glomus tumours had been confirmed histologically or radiologically; the family described was at least two generations and complete with regard to the sex of the family members; the pedigree showed clearly whether or not the father was affected and whether a non-affected father had inherited the disorder from his mother.

An analysis was made of the sex ratio of affected and non-affected siblings in all the fully-documented pedigrees found in the literature.

Transmission via an affected father (Table 1) has been described frequently, whereas pedigrees with transmission via a non-affected parent who received the predisposition from the mother, a characteristic of genomic imprinting of glomus tumours, have been described (Table 2) less frequently. Besides reports from the literature a new family was investigated in our department (see pedigree 1 in Fig. 1) with transmission via the affected father; linkage-analysis has not yet been completed. Several patients with glomus tumours and genomic imprinting were also investigated (Figs 2, 3 and 4). Pedigree 4 is an extension of the large Dutch family previously reported on by Van Baars *et al.*[8] and pedigree 2 is an extension of a pedigree of a family that was not described in full in a previous publication.[9] The non-affected fathers (Nos 1 and 2 in Fig. 2; No. 1 in Fig. 4) with affected daughters were examined for the presence of glomus tumours using MRI. In addition, MRI examinations were performed on two clinically non-affected brothers (Nos 3 and 4 in Fig. 2) and on one clinically non-affected brother (No. 5 in Fig. 2) of the affected sisters in one family.

Results

Figures 1 and 3 show two new pedigrees with glomus tumours. Figures 2 and 4 show the inheritance pattern which denotes genomic imprinting for glomus tumours. According to the pedigree, three non-affected fathers with affected children (Nos 1 and 2 in Fig. 2; No. 1 in Fig. 4) who varied in age between 64 and 78 yr, had inherited the predisposition for

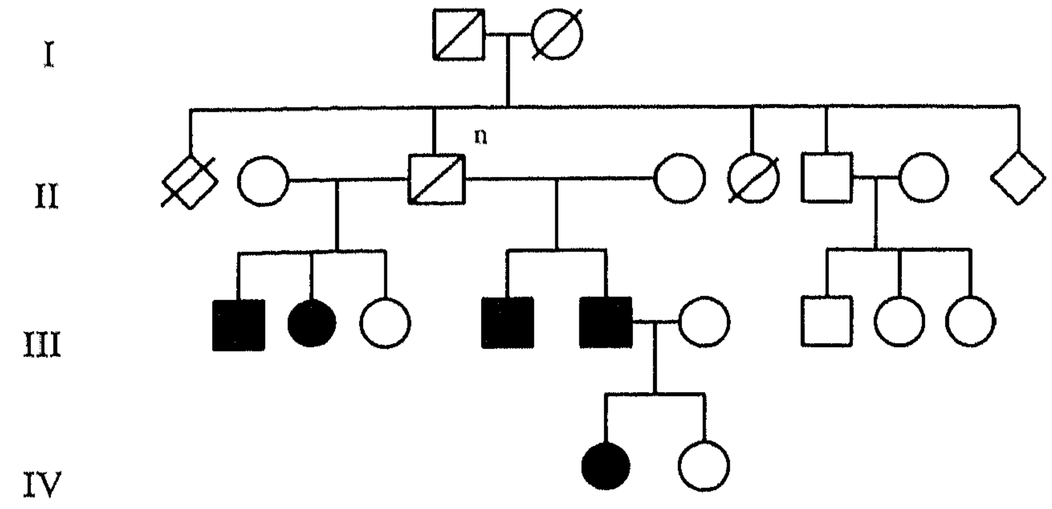

Figure 1. Pedigree 1, gene linkage analysis not yet performed. □ = unaffected male; ○ = unaffected female; ■ = affected male; ● = affected female; ⊘ = deceased male; ∅ = deceased female; + = investigated genetically; $\square^r$ and $\bigcirc^r$ = investigated radiologically; ⊞ and ⊕ = genetically proven carrier; $\square^n$ and $\bigcirc^n$ = not fully investigated.

glomus tumours from their mother. MRI of the head and neck region of the three fathers showed that they were non-affected, which supports the notion of genomic imprinting.

Together with other pedigrees from the literature two groups were constructed. Table 1 shows the number of affected and non-affected children from selected siblings with inheritance via an affected father, or via a father who according to the pedigree had inherited the predisposition from his father (group 1). Table 2 shows the number of affected and non-affected children for siblings with genomic imprinting (group 2). There seemed to be a trend regarding the penetrance per sex between the two groups (Fig. 5).

The overall sex ratio (M : F = 261 : 196) deviated significantly ($P = 0.0014$, binominal distribution) from a 1 : 1 ratio; the chance for the offspring to be male was $P > 0.53$ (i.e. 5% level of significance in a binomial distribution with $n = 457$). A similar observation was made about the sex ratio in the affected offspring of affected fathers (M : F = 180 : 137); the chance for an affected offspring to be male was $P > 0.52$. The proportions of affected males differed significantly between sons of affected fathers and sons of unaffected fathers ($\chi^2 = 5.61$, $P = 0.018$); penetrance among the former was not significantly below 100%, whereas that among the latter was

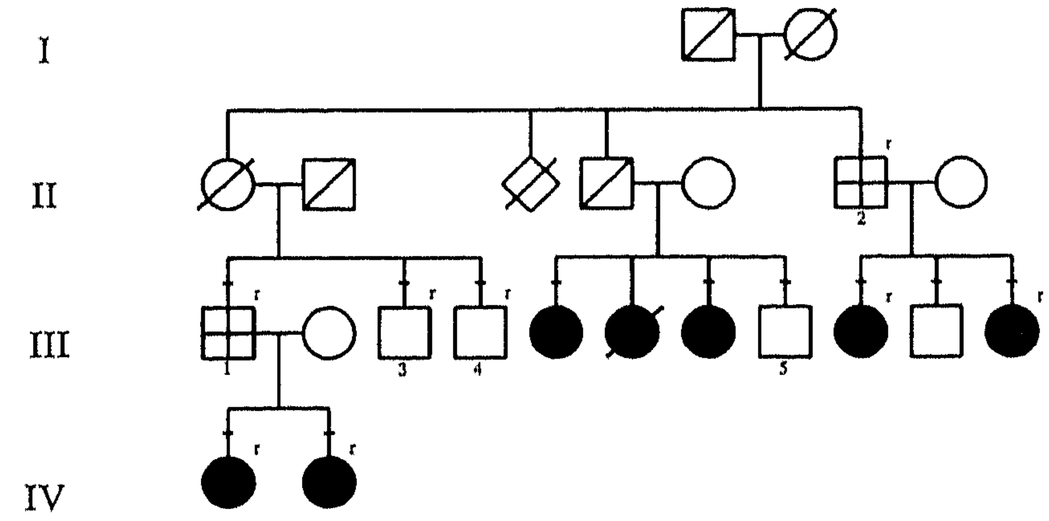

Figure 2. Pedigree 2, gene linkage to 11q22.3–q23.3. For symbols, see Figure 1.

Table 1. The offspring of fathers who inherited the trait from their father divided according to sex and clinical status (group 1)

First author; year of publication	Number of fathers	Sons affected	Sons not affected	Daughters affected	Daughters not affected
Bartels; 1949[2]	2	2	3	3	4
Sprong; 1949[13]	1	4	1	5	1
Desai; 1961[14]	2	3	6	0	5
Conley; 1963[15]	1	1	0	0	0
Kroll; 1964[16]	1	1	4	2	2
Del Fante; 1967[17]	1	2	0	0	0
Ribet; 1969[18]	2	4	3	2	1
Wilson; 1970[19]	4	5	1	3	0
Sugarbaker; 1971[20]	3	2	1	0	4
Chedid; 1974[21]	4	2	2	1	5
Kahn; 1976[22]	1	0	0	2	1
Rose; 1979[23]	1	2	0	0	0
van Baars; 1980, pedigree[1] 160806	2	6	2	0	2
van Baars; 1980, pedigree[1] 160808	3	3	6	1	7
van Baars; 1980, pedigree[1] 161207	3	2	3	0	4
Pereira; 1980[24]	4	8	8	1	1
Veldman; 1980[25]	4	6	12	4	8
van Asperen de Boer 1981[26], pedigree A	7	6	14	2	9
van Asperen de Boer 1981[26], pedigree B	2	2	1	0	5
Barbin; 1981[27]	1	0	0	3	0
Coia; 1981[28]	4	4	4	4	11
Parry; 1982, pedigree 5[29]	3	4	1	1	0
Parry; 1982, pedigree 6[29]	1	0	1	2	0
Parry; 1982, pedigree 7[29]	1	1	0	0	0
Miccoli; 1986[30]	2	0	3	2	4
van der Mey; 1989, pedigree A[4]	2	0	2	1	3
van der Mey; 1989 pedigree B[4]	4	4	4	1	3
van de Mey; 1989, pedigree C[4]	3	1	4	1	3
Barnes; 1990[31]	2	1	0	2	0
Shedd; 1990[32]	1	1	0	1	0
van Gils; 1992[33]	4	5	4	2	2
Present study; pedigree 1	1	0	0	1	1
Present study; pedigree 3	5	0	5	1	1
Present study; pedigree 4	2	1	2	1	3
Total	84	83	97	49	88

$P = 0.00016$; penetrance was below 78% with 95% probability.

Although penetrance among affected females was significantly below 100% only in the group of daughters of affected fathers ($P = 0.00055$; penetrance was below 86% with 95% probability), the proportion of affected females was not significantly different between daughters of affected fathers and daughters of unaffected fathers (χ^2 test).

Discussion

After it had been demonstrated that genomic imprinting occurs in families with gene linkage to 11q22.3-q23.3, it was recently demonstrated that genomic imprinting also occurs in the largest Dutch family with glomus tumours with gene linkage to a 5 cM region of chromosome 11q13.1.[5] This observation is based on careful examination of the pedigree, clinical

Table 2. The offspring of fathers who inherited the trait from their mother divided according to sex and clinical status (group 2)

First author; year of publication	Number of fathers	Sons affected	Sons not affected	Daughters affected	Daughters not affected
Lewison; 1950[34]	3	4	1	1	1
Desai; 1961[14]	2	2	3	0	0
Pratt; 1973[35]	3	1	7	6	4
van Baars; 1980[1], pedigree 161207	1	3	3	1	5
van Asperen de Boer; 1981[26], pedigree B	1	1	5	0	5
van der Mey; 1989[4], pedigree A	3	1	15	3	1
van der Mey; 1989[4], pedigree B	2	3	2	2	3
van der Mey; 1989[4], pedigree C	2	3	6	0	7
van Gils; 1992[33]	4	4	9	3	0
Present study; pedigree 4	2	4	2	6	4
Present study; pedigree 2	3	0	2	7	0
Total	26	26	55	29	30

examination and MRI of a non-affected father (No. 1 in Fig. 4) of an affected daughter, who had inherited the disorder from her paternal grandmother. The phenomenon of genomic imprinting could be confirmed in the same manner in pedigree 2 of a family with gene linkage to 11q22.3-q23.3. Van Baars *et al.*[3] noted previously that the sex ratio among the patients with glomus tumours who were treated at the University Hospital Nijmegen consisted of more women than men, whereas the large Dutch family they studied consisted of more affected men than women (20 : 6).

The phenomenon of genomic imprinting is intriguing and raises the question as to what extent it might influence the sex ratio among affected or non-affected offspring. For retinoblastoma, another imprinted disease, the sex ratio seems to be influenced by the sex of the transmitting parent.[10] A sufficient number of well-documented pedigrees have been published in the literature to shed some light on the answer to this question. We assumed that different study methods had been applied to the families examined during the past few decades and that this would have influenced the penetrance observed in these pedigrees.

Our present findings indicate that the sex of the transmitting grandparent may be an influence on the sex ratio.

Earlier studies have shown that the penetrance of glomus tumours increases with increasing age. Van Baars demonstrated that the penetrance in the family with gene linkage to chromosome 11q13.1 was 100% at about the age of 50 yr.[1] The introduction of less invasive investigation techniques such as MRI in comparison with previous subtraction angiography, has meant that clinical testing is much less demanding on the patient. Therefore, family members who are at increased risk of a glomus tumour on the basis of their position in the pedigree will come forward more readily for clinical examination. Being able to predict carriership of autosomal dominant inherited glomus tumours in the future, will increase our ability to detect glomus tumours at an earlier age. In this way the age at which glomus tumours are diagnosed in such families will decrease further, while the natural behaviour of the tumour will remain the same over the generations.

In this analysis of the sex ratio among affected and non-affected offspring of siblings in whom the gene may or may not have been subject to genomic imprinting, we did not distinguish between the families with gene linkage to 11q13.1 or to 11q22.3-q23.2, because these data were only available for a few of the families described in the literature. The sex ratio among affected and non-affected children of affected fathers (Table 1) shows that about as many sons were affected as would be expected, bearing in mind not yet full penetrance because it is age-dependent and also influenced by the examination technique applied. Intriguingly, penetrance was significantly lower among sons of unaffected fathers ($<78\%$) and perhaps also ($<86\%$) among daughters of affected fathers.

There was significant over-representation of affected males, particularly those who had an affected father, provided that the proportion of men in the relevant population was below 0.52 or 0.53 among men and women with an age distribution similar to that of the present offspring. In other diseases, the sex of the transmitting parent has been mentioned as a possible influencing factor for differences in phenotype, age of onset and severity.[11] Owing to the fact that the active gene is also transmitted to the offspring by the father, it appears that the gender of the transmitting grandparent or the mechanism of imprinting itself plays an important role.

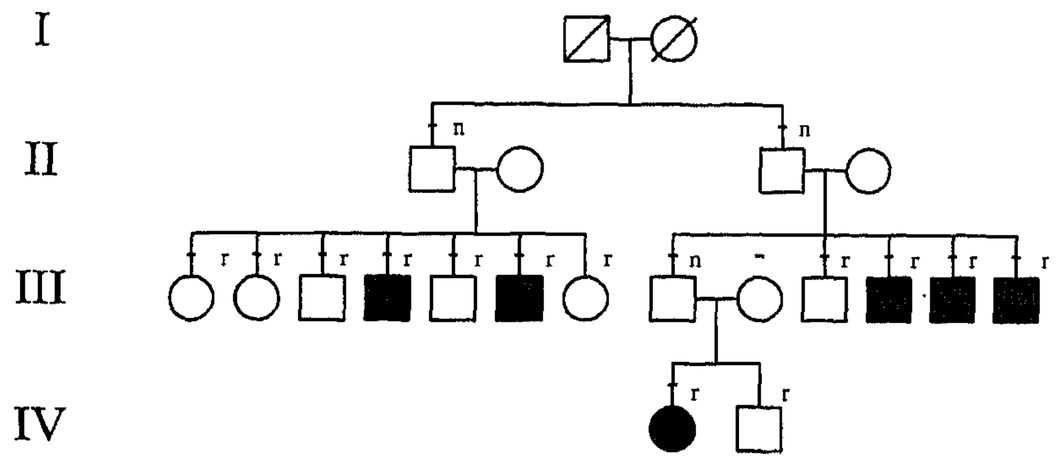

Figure 3. Pedigree 3, gene linkage to 11q22.3–q23.3. For symbols, see Figure 1.

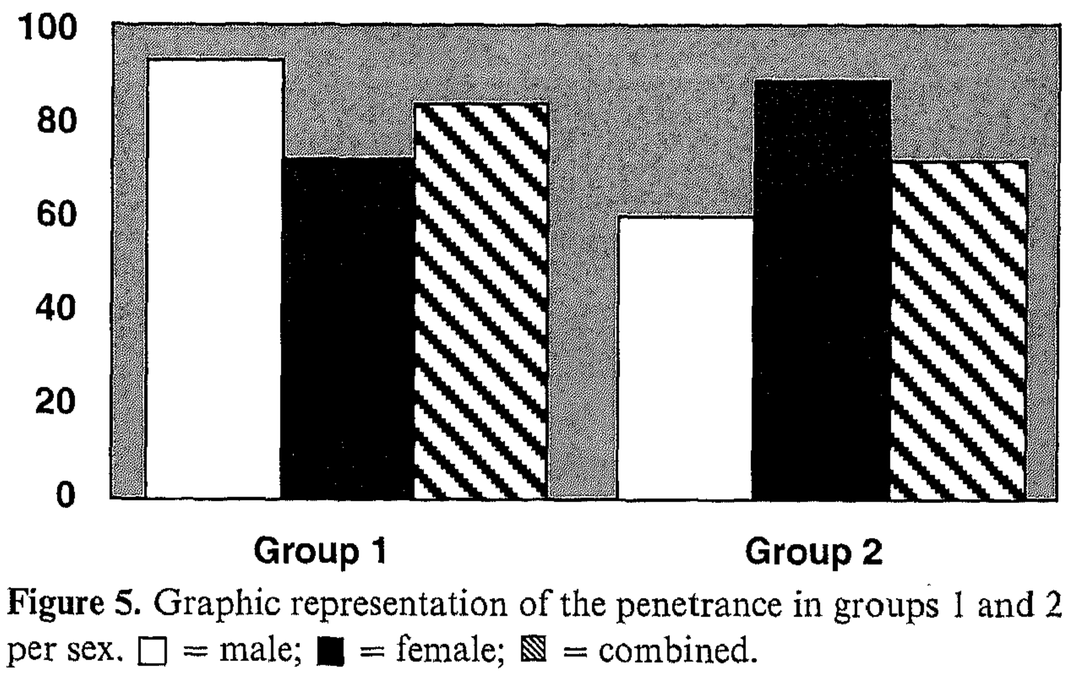

Figure 5. Graphic representation of the penetrance in groups 1 and 2 per sex. □ = male; ■ = female; ▨ = combined.

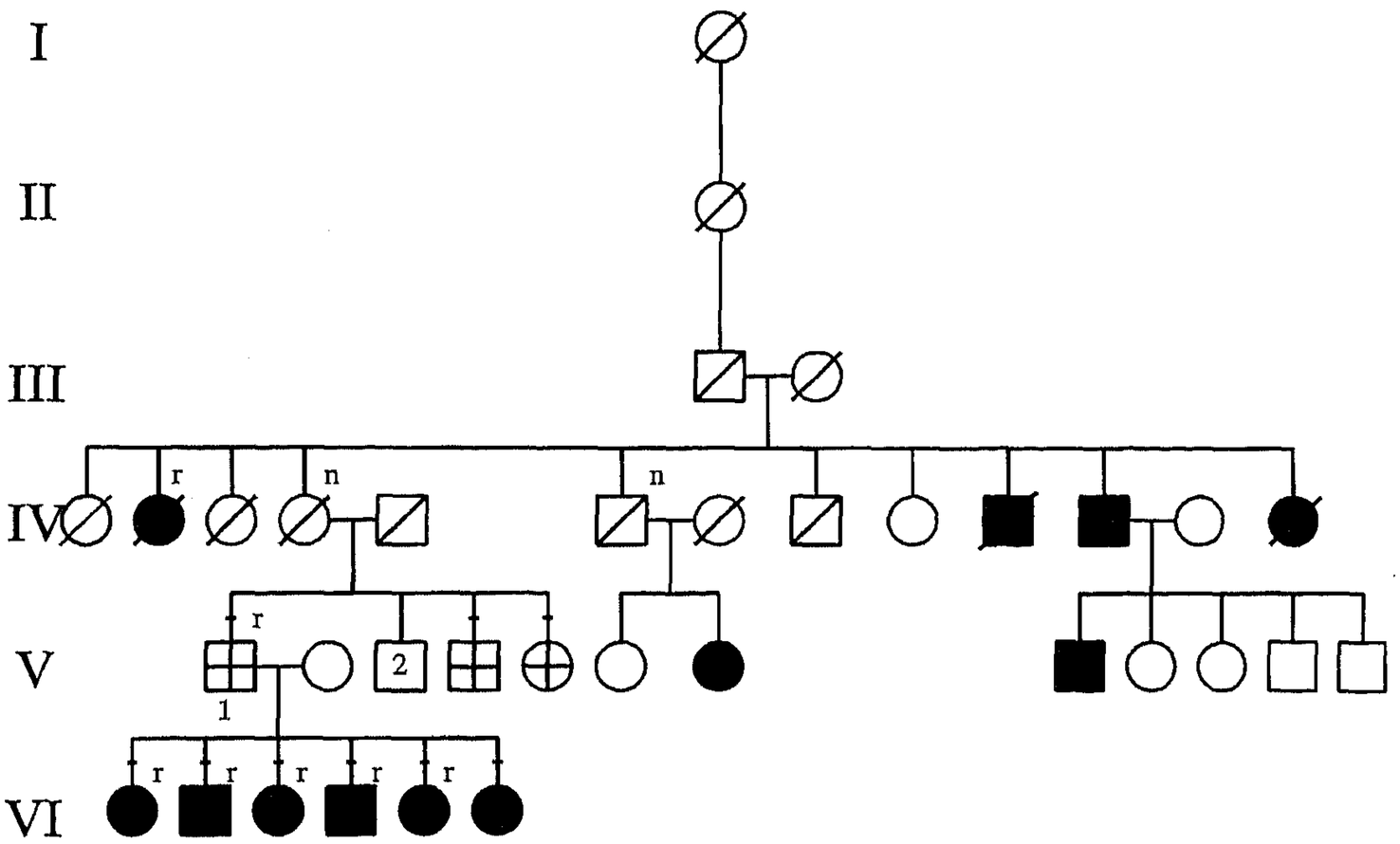

Figure 4. Pedigree 4, gene linkage to 11q13.1. For symbols, see Figure 1.

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