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X-Linked Recessive Panhypopituitarism Associated with a Regional Duplication in Xq25-q26

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Summary

We present a linkage analysis and a clinical update on a previously reported family with X-linked recessive panhypopituitarism, now in its fourth generation. Affected members exhibit variable degrees of hypopituitarism and mental retardation. The markers DXS737 and DXS1187 in the q25-q26 region of the X chromosome showed evidence for linkage with a peak LOD score (Z_{max}) of 4.12 at zero recombination fraction ($\theta_{max} = 0$). An apparent extra copy of the marker DXS102, observed in the region of the disease gene in affected males and heterozygous carrier females, suggests that a segment including this marker is duplicated. The gene causing this disorder appears to code for a dosage-sensitive protein central to development of the pituitary.

Introduction

Hereditary pituitary dwarfism is a genetically heterogeneous group of conditions including congenital absence of the pituitary, autosomal and X-linked recessive panhypopituitary (XPH) dwarfism, isolated growth hormone (GH) deficiency (types I and II), Laron type of dwarfism, and peripheral unresponsiveness to GH, which is seen in African Pygmies (Rimoin 1971). We have investigated a family with XPH, inherited as a recessive trait, with affected males suffering from variable degrees of hypopituitarism (Phelan et al. 1971). Some affected males have died during the 1st d of life and exhibited postmortem findings of hypoadrenalism, presumably due to hypopituitarism. Others have variable combinations of hypothyroidism, delayed pubertal development, and short stature due to GH deficiency. All surviving patients exhibit mild to moderate mental retardation (table 1). We report regional localization of the gene causing this disorder to a segment located between the markers DXS425 and DXS998 on the long arm of the X chromosome. The region showing linkage is apparently duplicated in patients and carrier females.

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Subjects, Material, and Methods

Subjects and Psychological Assessment

This study concerns a previously reported Australian family with XPH (Phelan et al. 1971). Tests used for assessments were the Stanford Binet fourth edition (individuals III:3 and III:9), the Wechsler Intelligence Scale for children (individual IV:5), and the Wechsler Pre-School and Primary Scale of Intelligence (individual IV:1).

Southern Blot Analysis

Total genomic DNA was prepared from peripheral blood collected from 19 family members. Ten-microgram aliquots of the genomic DNA samples were restriction digested and subjected to electrophoresis through 0.9% agarose gels and were analyzed by Southern blot hybridization (Southern 1975) using nylon membranes (Hybond-N, Amersham). The X chromosome–specific probe DXS255 (table 2) was radiolabeled by random-primed synthesis with an oligolabeling kit (Pharmacia Biotech).

PCR Analysis

Twenty-eight X chromosome–specific microsatellite markers were used in this study (table 2). Samples of 10 ng genomic DNA were amplified in 10 μl of buffer, containing 10 mM Tris-HCl pH 8.3, 50 mM KCl, 1.5 mM $MgCl_2$, 200 μM each of dATP, dTTP, dCTP, and dGTP, 12.5 ng bovine serum albumin/μl, and 0.035 units/μl of Ampli *Taq* (Perkin Elmer Cetus). Primers were added to a final concentration of 0.1 μM (MAOA, MAOB, DXS453, DXS454, DMD45, DXS425, DXS737, DXS102, and DXS458); 0.2 μM (AR, DXS1242, DXS426, DXYS1, DXS456, DXS297, PFC, DXS1114, DXS691, DXS692, DXS441, DXS1187, DXS1122, DXS998, and HPRT); 0.3 μM (ALAS2 and DXS1243); or 0.4 μM (DXS365 and DXS451). One of the primers in each pair was 5′-labeled with γ-^{32}ATP.

Table 1

Summary of Data Obtained from Biochemical and Psychological Assessment of Six Affected Males with X-Linked Recessive Panhypopituitarism

Individual	Thyroid Hormone[a]	GH	Serum Cortisol	Prolactin	Hypogonadal	IQ Score	Intellectual Ability
II:5	Low	Low	Normal	Low	Yes	...	Mild intellectual disability
III:3	Low to normal	Low[b]	Normal	Low to normal	No	86	Low/average ability with specific auditory memory deficit
III:9	Low	Low[b]	Low	Low	Yes	70	Mild intellectual disability with particularly low language skills
IV:1	Normal	Low[b]	Normal	...	Uncertain[c]	74	Mild intellectual disability
IV:4	Low to normal	Low[b]	Normal	...	Uncertain[c]	...	Mild intellectual disability
IV:5	Normal	Low to normal[b]	Normal	Normal	Uncertain[c]	53	Mild intellectual disability with particularly low language skills

[a] All subjects had a normal serum TSH.
[b] Treated with human growth hormone: low = peak stimulated GH < 10 mIU/liter; low to normal = peak stimulated between 10 and 20 mIU/liter.
[c] Uncertain gonadal status, since the subjects are prepubertal.

Table 2

X-Chromosome Marker Loci Used in Linkage Analysis

Locus (Probe)	Location	Reference
DXS365	Xp21.2-p22.3	Browne et al. (1992)
DXS451	Xp21.2-p22.3	Browne et al. (1992)
DMD 3′ (DMD45)	Xp21	Clemens et al. (1991)
DXS1243	Xp21	Oudet et al. (1991)
DXS1242	Xp21	Feener et al. (1991)
MAOA	Xp11.3	Black et al. (1991)
MAOB	Xp11.3-11.4	Konradi et al. (1992)
DXS426	Xp11.21-21.2	Luty et al. (1990)
PFC	Xp21.1-11.23	Coleman et al. (1991)
DXS255	Xp11.3-Xcen	Fraser et al. (1987)
ALAS2	Xp11.21	Cox et al. (1992)
AR	Xq11-12	Sleddens et al. (1992)
DXS453	Xp11.23-q21.1	Weber et al. (1990)
DXS441	Xq13.3	Ram et al. (1992)
DXYS1	Xq21.31	Browne et al. (1991)
DXS458	Xq21.1-q23	Weber et al. (1990)
DXS454	Xq21.1-q23	Weber et al. (1990)
DXS456	Xq21-q22	Luty et al. (1990)
DXS425	Xq26-27.1	Luty et al. (1990)
DXS737	Xq25	Hudson et al. (1992)
DXS1187	Xq26	Gerken et al. (1994); GDB
DXS1122	Xq25-q26	Donnelly et al. (1994); GDB
DXS692	Xq25-q26.2	Lasser et al. (1993)
DXS1114	Xq26.1	Weber et al. (1993)
HPRT	Xq26.1	Hearne and Todd (1991)
DXS102	Xq26.3-q27.1	Gedeon et al. (1992)
DXS691	Xq26.2-q27	Lasser et al. (1993)
DXS297	Xq27.3	Richards et al. (1991)
DXS998	Xq27-q28	Smahi et al. (1994)

NOTE.—The marker DXS255 detects an RFLP, whereas all others are microsatellites and detect VNTRs.

After an initial denaturation for 4 min at 93°C, the temperature was varied between 93°C for 30 s, 55°C for 30 s, and 72°C for 30 s. For the primers DXS737, DXS441, ALAS2, and DXS102, an annealing temperature of 60°C was used. The samples were incubated for 26 temperature cycles, and, during the last cycle, the incubation at 72°C was extended to 4 min. Ten microliters of formamide-containing loading buffer was added to the samples, and 2 μl of each sample was loaded on a 6% polyacrylamide/7 M urea sequencing gel. After electrophoresis, the gel was dried and autoradiographed overnight.

Linkage Analysis

Two-point linkage analysis was performed using the FASTLINK program (Cottingham et al. 1993). The disease was assumed to be completely penetrant, and the gene frequency for XPH was set to 0.0005. Microsatellite allele frequencies were as previously published (Cuticchia et al. 1993), except for the markers DXS255, DXS425, DXS426, DXS451, DXS456, DXS737, DXS998, DXS1187, DXS1122, DXS1243, and PFC, which were set to $1/n$ (n = number of known alleles for the marker).

Allele Quantification

For the quantitative analysis, one of the primers of the microsatellite marker DXS102 was 5′-labeled with fluorescein. PCR was performed as described above. Thirty microliters of loading dye were added to the reactions, and 2 μl of each sample was loaded on a Pharmacia ALF automated sequencer. Data were analyzed using the Pharmacia Fragment Manager software.

Table 3

LOD Scores at Different Recombination Fractions for Markers in the Xq25-27 Region in the Family with X-Linked Recessive Panhypopituitarism

	LOD Score at θ =						
Locus	0	.01	.05	.10	.20	.30	.40
DXS425	−∞	−.83	.40	.79	.92	.77	.45
DXS737	4.12	4.05	3.79	3.44	2.69	1.84	.90
DXS1187	4.12	4.05	3.79	3.44	2.69	1.84	.90
DXS1122	3.82	3.75	3.49	3.14	2.40	1.57	.71
DXS1114	3.89	3.82	3.56	3.21	2.47	1.64	.75
HPRT	1.81	1.78	1.67	1.53	1.22	.88	.48
DXS102	−∞	.28	.84	.96	.87	.61	.30
DXS691	2.41	2.37	2.23	2.04	1.63	1.17	.63
DXS297	−∞	−.53	.67	1.02	1.08	.83	.44
DXS998	−∞	−1.32	−.05	.39	.63	.58	.36
DXS692	1.81	1.78	1.67	1.53	1.22	.88	.48

Results

Individuals from the family with XPH were analyzed using markers distributed along the X chromosome (table 2). Twenty-eight of the investigated microsatellite markers and one RFLP marker were informative in this family. Table 3 summarizes the relevant results. No recombination events were observed between the disease locus and seven markers in the Xq25-q26 region (DXS737, DXS1187, DXS1122, DXS692, DXS1114, HPRT, and DXS691). The highest LOD scores (Z_{max}) were obtained with the markers from the DXS737 and DXS1187 loci. A two-point peak LOD score of 4.12 was observed at a peak recombination fraction (θ_{max}) of 0 for each of the two loci. The loci DXS1122 and DXS1114, located distal to DXS737, gave Z_{max} values of 3.82 (θ_{max} = 0) and 3.89 (θ_{max} = 0), respectively. These markers gave lower LOD scores, since fewer individuals were informative for them. The marker DXS102, located proximal of DXS691, had recombined with the disease locus in one individual, who was uninformative for DXS691.

Additional information regarding the location of the XPH locus relative to the markers used was obtained by analyzing individual crossover events. The segregation patterns for four of the markers surrounding the XPH locus are presented in figure 1. The order of loci was assumed to be Xcen–DXS425–DXS737–DXS102–DXS998–Xqter (Willard et al. 1994; GDB framework map number CXM117).

The carrier female II:1 is informative for the marker DXS998. Her two daughters, III:1 and III:2, are both obligate carriers, but they have inherited the unaffected grandpaternal 120 allele, implying that a recombination took place in both meioses giving rise to III:1 and III:2. In addition, the affected son of III:1, IV:1, has inherited the unaffected grandparental allele 116. This indicates a recombination between the disease locus and DXS998 in the meiosis leading to IV:1 (fig. 1). On the basis of these observations, the XPH locus appears to be located proximal to DXS998. A total of three recombinations have taken place between the markers DXS737 and DXS998 among nine informative meioses in this pedigree. This agrees well with the estimated genetic distance of 35.4 cM between corresponding loci (Wang et al. 1994).

Analysis of the unaffected male II:4 and the carrier

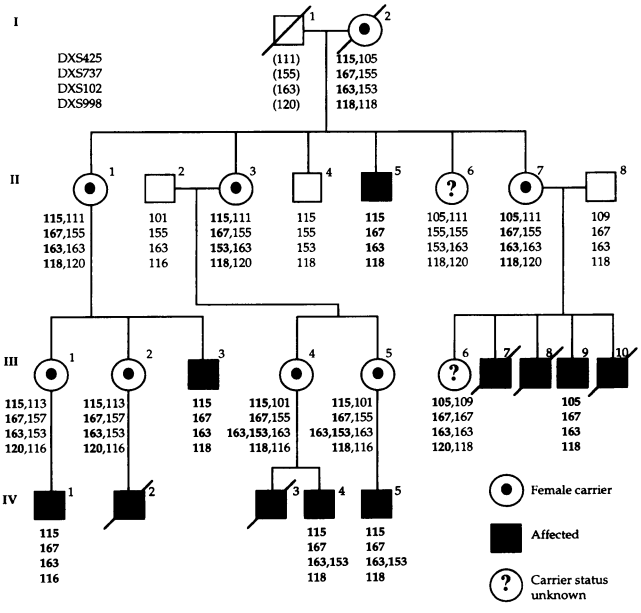

Figure 1 Pedigree of the family with XPH. The segregation pattern of four markers in the Xq25-q27 region are indicated. The predicted haplotype of I:1 is marked within parentheses. Haplotypes segregating with the disorder are indicated in bold. The pedigree includes all family members subjected to linkage analysis.

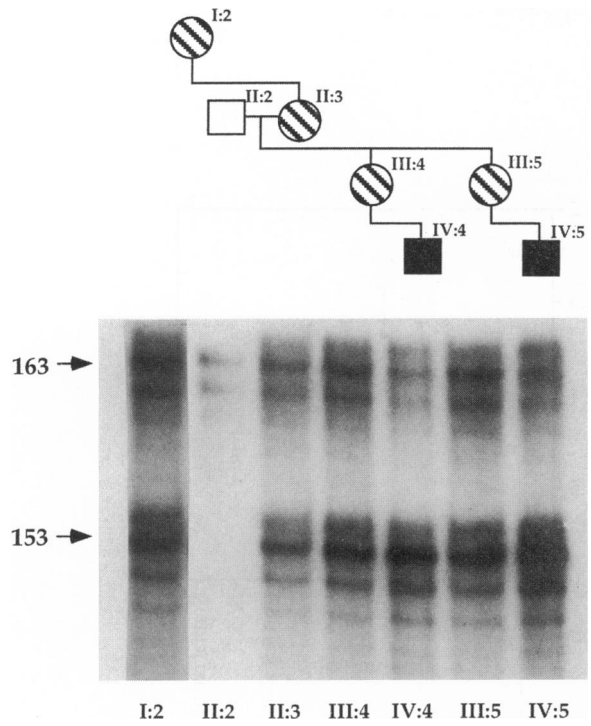

Figure 2 Autoradiogram representing the amplified microsatellite marker DXS102, separated by polyacrylamide gel electrophoresis. The two affected males, IV:4 and IV:5, appear heterozygous for this X-chromosome marker in that they have both 153 and 163 alleles.

female II:7 offers some additional clues to the relative position of the XPH locus. Their mother, I:2, is informative for the marker DXS425 (fig. 1). The carrier sisters, II:1 and II:3, their affected brother, II:5, and also their unaffected brother, II:4, have inherited the same 115 allele from their mother. By contrast, II:4 has inherited different alleles than two of his carrier sisters and the affected brother for markers located distal to DXS425. The carrier female II:7 has inherited the 105 allele for the same marker. This is a different allele than that of her carrier sisters and the affected brother, whereas for the markers located distal to DXS425 she has inherited the same alleles as her affected brother and one of her carrier sisters. These data imply that the XPH locus is located distal to the DXS425 locus. On the basis of the crossover events in this family, we conclude that the disease gene is most likely located proximal to DXS998 and distal to DXS425.

Unexpectedly, two affected males, IV:4 and IV:5, appear to be heterozygous for the marker DXS102, because they exhibit two different alleles (figs. 1 and 2). The results have been reproduced with DNA prepared from an independent blood sample of IV:5, and we have also analyzed the same marker by RFLP (data not shown), confirming that both males have two different copies of this X-linked marker.

A possible interpretation of this result is that a region including the DXS102 locus is duplicated in the two affected boys, IV:4 and IV:5, and that this duplication causes their disease. An observation that speaks against this interpretation is that all the other affected members of the pedigree showed a single allele from the DXS102 locus. However, inspection of the genotypes in the pedigree depicted in figure 1 revealed that a recombination has taken place in the meiosis that gave rise to individual II:3, the grandmother of IV:4 and IV:5 (fig. 3). It is thus possible that the carrier I:2 had two copies of the 163 allele from the DXS102 locus in addition to one 153 allele and that the duplicated 163 allele was transmitted to all affected branches of the family except the one that originates from carrier II:3. The recombination event in the meiosis leading to II:3 may have taken place between one of the duplicated 163 alleles and the 153 allele on the opposite chromosome, as depicted in figure 3.

To test the hypothesis that individuals who carry the mutation have an extra copy of DXS102, we have quantitated fluorescent amplification products of the DXS102 marker, using an automated DNA sequencer. A supernumerary 163 allele was identified in the heterozygous carrier females 1:2, II:3, III:1, III:2, III:4, and III:5 (fig. 4*A*, *B*). The extra allele was evident as an increase in signal for the 163 allele compared with that of the 153 allele present in a single copy. Three of the females in the family, II:1, II:7, and III:6, are homozygous for the genetic marker defining the DXS102 locus and thus could not be evaluated in this manner. This is also true for the other affected males, II:5, III:3, III:9, and IV:1. The female II:6 does not appear to have an extra allele for the marker (fig. 4*A*, *B*). This is consistent with our linkage data, which indicate that she is not a carrier of the disorder, and with the fact that she has given birth to four sons, none of them affected by XPH.

Discussion

By definition, the group of disorders known as "familial panhypopituitarism" is characterized by deficiencies

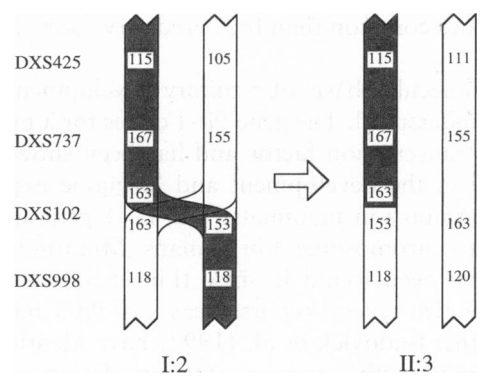

Figure 3 Schematic drawing of a region in the X chromosomes involving a putative duplication of the DXS102 locus. A hypothetical crossover in the meiosis in I:2, giving rise to II:3, is indicated.

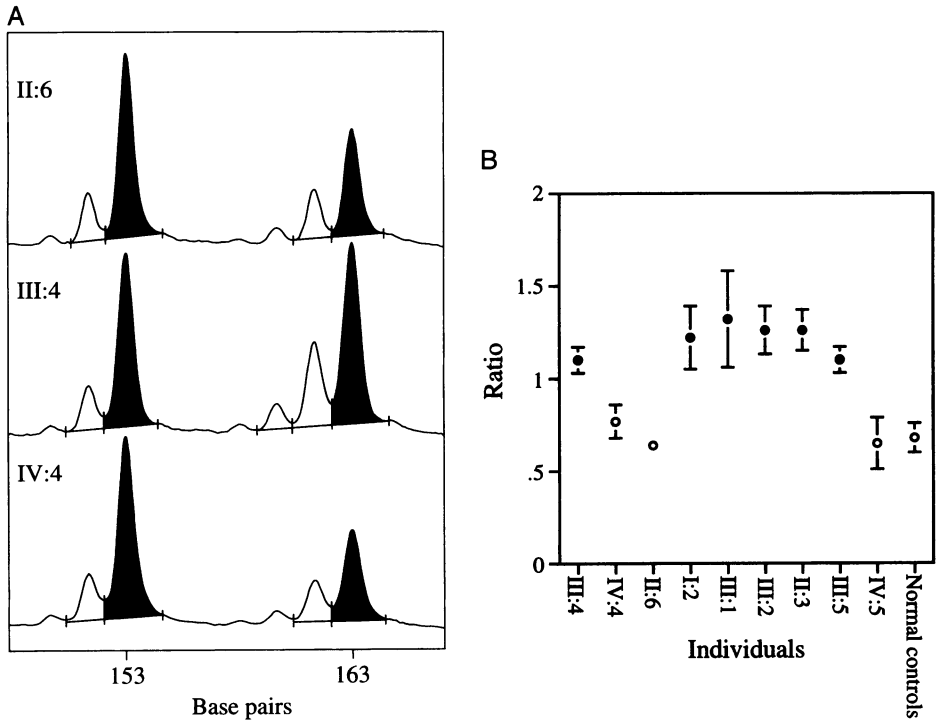

Figure 4 *A*, Quantitation of amplified alleles of the DXS102 locus. The fluorogram illustrates two alleles of the DXS102 locus in DNA samples from three XPH family members. The sizes of the shaded areas, representing the 163 and the 153 alleles, were estimated using the Fragment Manager software. On the basis of the segregation of the suspected duplication, individual II:6 is expected to have one copy each of the 153 and the 163 alleles, while the carrier female III:4 has two copies of the 163 allele and one copy of the 153 allele. Her affected son, IV:4, has one 153 allele and one 163 allele. *B*, Ratios of the areas of the peaks representing the 163 and the 153 alleles, which were calculated for the indicated members of the XPH family. Black circles represent DNA samples from individuals expected to have two 163 alleles and one 153 alleles, and open circles represent DNA samples with one 153 allele and one 163 allele. The standard errors of a minimum of four determinations are indicated. DNA samples from 11 individuals unrelated to the XPH family were used as normal controls.

of GH and at least one more pituitary hormone. The associated hormone insufficiencies tend to vary not only between, but also within, families (Rimoin 1971). The family we have investigated exhibits X-linked recessive inheritance, but autosomal recessive inheritance of similar conditions has been reported (Rischbieth and Barrington 1912; Trygstad and Seip 1964). There are also nonhereditary forms of the disease, considered to be much more common than the hereditary forms (Rimoin 1971).

The molecular basis of pituitary development is still poorly understood. The gene Pit-1 codes for a pituitary-specific transcription factor and has been shown to be involved in the development and hormone expression of the pituitary in mammals. The Pit-1 gene has been located to chromosome 3 in humans. Mutations in this gene have been found in mice (Lin et al. 1992), and there are also several reported cases of Pit-1 mutations in humans: Radovick et al. (1992) have identified one such patient with severe mental retardation and deficiency of GH, prolactin (Prl), and thyroid-stimulating hormone (TSH). In addition, Pfäffle et al. (1992) and Tatsumi et al. (1992) have reported families demonstrating inheritance of a disorder characterized by deficiency of GH, Prl, and TSH.

It is clear that a mutation in another gene of importance in the regulation of pituitary development is segregating in our family with XPH. Patients in this family present a clinical picture that in some ways resembles that caused by mutations in Pit-1. All affected males have GH deficiency, and they show mild intellectual disability. In addition, some have variable combinations of deficiencies of other hormones such as adrenocorticothrophin, FSH, and luteinizing hormome. The X-linked recessive mode of inheritance in the family investigated by us demonstrates that the disease is caused by a mutation in a gene distinct from Pit-1. The family we have investigated is the only one so far reported to exhibit this specific syndrome.

We have performed genetic linkage analysis of the XPH family and mapped the disease locus to the q25-q26 region of the X chromosome. By analyzing individual crossover events in the family, the region of interest was limited to a segment of ~14 cM, according to the integrated gene map published by Wang et al. in 1994. It is unlikely that the region could be delimited much

further by linkage analysis, since only 14 informative meioses are available. The increasing availability of mapped expressed sequenced tagged sites of known tissue distribution offers, however, a possibility to identify candidate genes in the region.

Two affected males, IV:4 and IV:5, appear to be heterozygous for the DXS102 marker located near the disease locus (fig. 2). Quantitative analysis of the marker cX38.1 in DNA samples from family members revealed an extra copy of the marker in all affected individuals and carrier females who were informative by our analysis (fig. 4*A*, *B*). This strongly suggests that a gene duplication at the disease locus segregates with the disorder in this family. If a duplicated chromosomal segment indeed causes the disease in the present family, this segment is likely to be located next to the normal copy of the segment, since this is the most common outcome of a duplication event and since the mutation in this family maps to that region on the X chromosome where the duplicated marker is located in an unrearranged chromosome.

A recombination was observed between the disease locus and DXS102 in one individual, II:3. This carrier female is the grandmother of the two affected male cousins who appear heterozygous for this marker. We have preliminary data suggesting that two additional markers in the region are duplicated in affected males and carrier females. Together, these three duplicated markers span a region of ~4 cM, according to the integrated X-chromosome map (Wang et al. 1994). It is therefore not unexpected that a recombination should have taken place within the duplicated region in this family.

There are several models to explain how a DNA duplication could give rise to genetic disease. The altered localization of a gene in a duplicated region can interfere with its regulation (Lupski et al. 1991), or the breakpoints of the duplicated segment could interrupt the coding region of a critical gene. The apparent size of the duplicated region argues against the notion of a critical gene spanning both duplication breakpoints. If the gene is interrupted by only one of the breakpoints, there should still remain one intact copy of the gene, but, since the disorder in the present family is inherited as a recessive trait, no intact copy of the gene is expected to remain in affected males. It is possible, however, that a duplicated gene, interrupted by a breakpoint, exerts a dominant effect, interfering with the development of the pituitary. In this hypothetical case, those cells in carrier females where the X chromosome carrying the mutation remains active could fail to develop into pituitary cells, but cells with the reciprocal inactivation pattern might still allow this tissue to develop. This would give rise to the X-linked pattern of inheritance observed in the present family. One further model that could account for the characteristics of the disease is a gene-dosage effect involving one or several genes in the duplicated region. This mechanism has been demonstrated in Charcot-Marie-Tooth disease type 1A, an autosomal dominant disease. In the majority of patients with this disease, a 1.5-Mb duplication of a region on chromosome 17 is seen. The gene PMP22, causing the disease, was isolated on the basis of the observed duplication (Valentijn et al. 1992). Since the disease in our family segregates as an X-linked recessive trait, affected males would be expected to have twice the normal level of expression of a duplicated gene(s), while carrier females, with a hypothetical average 1.5-fold increase in expression, appear clinically normal.

We are currently investigating more X-chromosome markers in the region of interest to find other markers with supernumerary alleles in affected individuals and carrier females, in order to determine the extent of the duplication in this family and to locate the duplication breakpoints. DNA samples from affected individuals are also examined through pulse-field gel electrophoresis and FISH analysis in order to characterize any rearrangements in the relevant region of the X chromosome.

Acknowledgments

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References

Black GCM, Chen Z-Y, Craig IW, Powell JF (1991) Dinucleotide repeat polymorphism at the MAOA locus. Nucleic Acids Res 19:689

Browne D, Barker D, Litt M (1992) Dinucleotide repeat polymorphisms at the DXS365, DXS443 and DXS451 loci. Hum Mol Genet 1:213

Browne DL, Zonana J, Litt M (1991) Dinucleotide repeat polymorphism at the DXYS1X locus. Nucleic Acids Res 19:1721

Clemens PR, Fenwick RG, Chamberlain JS, Gibbs RA, de Anrade M, Chakraborty R, Caskey CT (1991) Carrier detection and prenatal diagnosis in Duchenne and Becker muscular dystrophy families, using dinucleotide repeat polymorphisms. Am J Hum Genet 49:951–961

Coleman MP, Murray JC, Willard HF, Nolan KF, Reid KBM, Blake DJ, Lindsay S, et al (1991) Genetic mapping around the Properdin P gene. Genomics 11:991–996

Cottingham RWJ, Idury RM, Schäffer AA (1993) Faster sequential genetic linkage computations. Am J Hum Genet 53:252–263

Cox TC, Kozman HM, Raskind WH, May BK, Mulley JC (1992) Identification of a highly polymorphic marker within

intron 7 of the ALAS2 gene and suggestion of at least two loci for X-linked sideroblastic anaemia. Hum Mol Genet 1: 639–641

Cuticchia AJ, Fasman KH, Kingsbury DT, Robbins RJ, Pearson PL (1993) The GDB human genome data base anno 1993. Nucleic Acids Res 21:3003–3006

Feener CA, Boyce FM, Kunkel LM (1991) Rapid detection of CA polymorphisms in cloned DNA: application to the 5′ region of the dystrophin gene. Am J Hum Genet 48: 621–627

Fraser N, Buckle V, Levy E, Ballabio A, Rollo M, Persico G, Craig I (1987) Localization of STS coding sequences to Xp22.3 and to Yq11.2: evidence for an ancestral pseudoautosomal gene? Cytogenet Cell Genet 46:615–616

Gedeon AK, Holman K, Richards RI, Mulley JC (1992) Characerization of new PCR based markers for mapping and diagnosis: AC dinucleotide markers at the DXS237 (GMGX9) and DXS102 (cX38.1) loci. Am J Med Genet 43:255–260

Hearne CM, Todd JA (1991) Tetranucleotide repeat polymorphism at the HPRT locus. Nucleic Acids Res 19:5450

Hudson TJ, Engelstein M, Lee MK, Ho EC, Rubenfield MJ, Adams CP, Housman DE, et al (1992) Isolation and chromosomal assignment of 100 highly informative human simple sequence repeat polymorphisms. Genomics 13:622–629

Konradi C, Ozelius L, Breakefield XO (1992) Highly polymorphic (GT)n repeat sequence in intron II of the human MAOB gene. Genomics 12:176–177

Lasser DM, Wilhelmsen KC, Nygaard TG, Tantravahi U (1993) Characerization of microsatellite polymorphisms DXS691 and DXS692: genetic mapping to Xq26.2-Xq27 and Xq25-Xq26.2. Genomics 16:785–786

Lin C, Lin S-C, Chang C-P, Rosenfeld MG (1992) Pit-1 dependent expression of the receptor for growth hormone releasing factor mediates pituitary cell growth. Nature 360: 765–768

Lupski JR, Montes de Oca-Luna R, Slaugenhaupt S, Pentao L, Guzzetta V, Trask BJ, Saucedo-Cardenas O, et al (1991) DNA duplication associated with Charcot-Marie-Tooth disease type 1A. Cell 66:219–232

Luty JA, Guo Z, Willard HF, Ledbetter DH, Ledbetter S, Litt M (1990) Five polymorphic microsatellite VNTRs on the human X chromosome. Am J Hum Genet 46:776–783

Oudet C, Heilig R, Hanauer A, Mandel J-L (1991) Nonradioactive assay for new microsatellite polymorphisms at the 5′ end of the dystrophin gene, and estimation of intragenic recombination. Am J Hum Genet 49:311–319

Pfäffle RW, diMattia GE, Parks JS, Brown MR, Wit JM, Jansen M, Van der Nar H, et al (1992) Mutation of the POU-specific domain of Pit-1 and hypopituitarism without pituitary hypoplasia. Science 257:1118–1121

Phelan PD, Connelly MDJ, Martin FIR, Wettenhall HNB (1971) X-linked recessive hypopituitarism. Birth Defects 7:24–27

Radovick S, Nations M, Du Y, Berg LA, Weintraub BD, Wondisford FE (1992) A mutation in the POU-homeodomain of Pit-1 responsible for combined pituitary hormone deficiency. Science 257:1115–1118

Ram KT, Barker DF, Puck JM (1992) Dinucleotide repeat polymorphism at the DXS441 locus. Nucleic Acids Res 20:1428

Richards RI, Shen Y, Holman K, Kozman H, Hyland V, Mulley JC, Sutherland GR (1991) Fragile X syndrome: diagnosis using highly polymorphic microsatellite markers. Am J Hum Genet 48:1051–1057

Rimoin DL (1971) Genetic form of pituitary dwarfism. Birth Defects 7:12–23

Rischbieth H, Barrington A (1912) Dwarfism. In: Galton F (ed) Treasury of human inheritance. Dulau, London, sec XV

Sleddens HFBM, Oostra BA, Brinkmann AO, Trapman J (1992) Trinucleotide repeat polymorphism in the androgen receptor gene (AR). Nucleic Acids Res 20:1427

Smahi A, Peterlin B, Onodera O, Tsuji S, Fulchignoni-Lataud MC (1994) Use of radiation-reduced hybrid panel for the localization of seven markers in the Xq28 region of the human genome. Ann Genet 37:11–13

Southern EM (1975) Detection of specific sequences among DNA fragments separated by gel electrophoresis. J Mol Biol 98:503–517

Tatsumi K, Miyai K, Notomi T, Kaibe K, Amino N, Mizuno Y, Kohno H (1992) Cretinism with combined hormone deficiency caused by a mutation in the PIT1 gene. Hum Mol Genet 1:56–58

Trygstad O, Seip M (1964) Hereditary pituitary dwarfism treated with human growth hormone. Acta Paediatr 53: 527–531

Valentijn LJ, Bolhuis PA, Zorn I, Hoogendijk JE, van de Basch N, Hensels GW, Stanton VP Jr (1992) The peripheral myelin gene PMP-22/GAS-3 is duplicated in Charcot-Marie-Tooth disease type 1A. Nat Genet 1:166–170

Wang LH, Collins A, Lawrence S, Keats BJ, Morton NE (1994) Integration of gene maps: chromosome X. Genomics 22: 590–604

Weber C, Oudet C, Johnson S, Pilia G, Schlessinger D, Hanauer A (1993) Dinucleotide polymorphism at Xq26.1 (DXS1114). Hum Mol Genet 2:612

Weber JL, Kwitek AE, May PE, Polymeropoulos MH, Ledbetter S (1990) Dinucleotide repeat polymorphisms at the DXS453, DXS454 and DXS458 loci. Nucleic Acids Res 18:4037

Willard HF, Cremens F, Mandel JL, Monaco AP, Nelson DL, Schlessinger D (1994). Report on the Fifth International Workshop on Human X-Chromosome Mapping 1994. Cytogenet Cell Genet 67:296–319