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A novel locus for alopecia with mental retardation syndrome (APMR2) maps to chromosome 3q26.2-q26.31

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Abstract

Congenital alopecia may occur either alone or in association with ectodermal and other abnormalities. On the bases of such associations, several different syndromes featuring congenital alopecia can be distinguished. Alopecia with mental retardation syndrome (APMR) is a rare autosomal recessive disorder, clinically characterized by total or partial hair loss and mental retardation. In the present study, a five-generation Pakistani family with multiple affected individuals with APMR was ascertained. Patients in this family exhibited typical features of APMR syndrome. The disease locus was mapped to chromosome 3q26.2-q26.31 by carrying out a genome scan followed by fine mapping. A maximum two-point logarithm of odds (LOD) score of 2.93 at $\theta = 0.0$ was obtained at markers D3S3053 and D3S2309. Multipoint linkage analysis resulted in a maximum LOD score of 4.57 with several markers, which supports the linkage. The disease locus was flanked by markers D3S1564 and D3S2427, which corresponds to 9.6-cM region according to the Rutgers combined linkage-physical map of the human genome (build 35) and contains 5.6 Mb. The linkage interval of the APMR locus identified here does not overlap with the one described previously; therefore, this locus has been designated as APMR2.

Keywords

3q26.2-q26.31; alopecia with mental retardation syndrome (APMR2); Pakistan

Total or partial absence of hair occurs either alone or in association with other anomalies with a diverse variety of syndromes. Isolated forms of alopecia include Marie Unna hereditary hypotrichosis (MIM 146550), hypotrichosis simplex (MIM 605389), congenital atrichia (MIM 203655), localized hereditary hypotrichosis (LAH; MIM 607903) and autosomal recessive hereditary hypotrichosis (AH; MIM 609167). Loci for all these conditions have been localized but only two genes have been identified; the hairless (*HR*; MIM 602302) gene has been implicated in the etiology of congenital atrichia (1) and desmoglein 4 (*DSG4*; MIM 607892) gene is responsible for LAH (2, 3). The major defects reported to be associated with loss of hair include dwarfism, mental retardation, epilepsy,

nail dystrophy, total or partial anodontia, hyper-keratosis, impaired sweating, cataracts, retinitis pigmentosa etc. (4, 5).

Alopecia with mental retardation syndrome (APMR; MIM 203650) is a rare autosomal recessive disorder characterized by complete hair loss and severe mental retardation. Baraitser et al. (6) reported the combination of total alopecia involving all areas of normal hair growth from birth and severe mental retardation in three cousins who are members of an inbred Middle Eastern family. A similar condition was described by Perniola et al. (7), in two children of consanguineous parents who had the additional phenotype of hearing impairment. Benke and Hajianpour (8) described an inbred Pakistani family in which three consanguineous couples each had a child with alopecia universalis and mental retardation, there were no other phenotypes associated with the syndrome, the patients were not dysmorphic, and hearing, teeth, nails, bone x-rays and sweating were normal. A related phenotype described Woodhouse–Sakati syndrome was first observed in two Saudi Arabian families [Woodhouse and Sakati (9)]. This syndrome is characterized by absence of facial hair, thinning of head and eyebrow hair, mental retardation, hypogonadism, diabetes mellitus and mild sensorineural hearing impairment. An ichthyosis–mental retardation syndrome (MIM 242510) associated with alopecia was described by Jagell et al. (10) in an inbred Swedish family. Shokeir (11) described a syndrome, observed in 12 members of a four-generation pedigree with male-to-male transmission, which included congenital alopecia, mental subnormality, psychomotor epilepsy and pyorrhea. The Amish hair–brain syndrome (MIM 234050) includes mild mental retardation, short stature and brittle hair, which fall out (12–14). This syndrome is caused by mutation in the *TTDN1* gene, also known as *C7ORF11*, that may have a role in transcription (MIM 609188) (15). Recently, John et al. (16) reported the localization of the APMR locus on human chromosome 3q26.33-q27.3 in a large Pakistani family. APMR patients in this family showed absence of hair from all areas of normal hair growth and were severely mentally retarded.

Here, we report on a five-generation consanguineous Pakistani family (Fig. 1) with an autosomal recessive form of the APMR. After exclusion of the known loci involved in the hereditary hair disorders, a genome scan was undertaken, which led to the identification of a novel locus for this form of syndrome (APMR2) on chromosome 3q26.2-q26.31.

Materials and methods

Family history and clinical findings

A large consanguineous Pakistani family (Fig. 1), segregating an autosomal recessive form of alopecia and mental retardation syndrome (APMR2), was studied in which three males and two females were affected. Prior to start of the study, approval was obtained from Quaid-i-Azam University Institutional Review Board. The family members rarely marry outside the community, and consequently consanguineous unions are common. The pedigree (Fig. 1) provided convincing evidence of autosomal recessive mode of inheritance. All the affected individuals underwent examination at Department of Dermatology, Pakistan Institute of Medical Sciences, Islamabad, Pakistan. IQ tests were performed at Children's Hospital, Lahore, Pakistan, using the Wechsler method of calculating IQ values.

DNA extraction and genotyping

Blood samples were collected from four affected and seven unaffected members of the family. Genomic DNA was extracted from peripheral blood leucocytes in ethylenediaminetetraacetic acid-containing tubes by standard method (17).

PCR was carried out in 25- μ l reaction volumes containing 40 ng of genomic DNA, 20 pmol of primers, 200 μ M of each deoxynucleoside tri-phosphate (dNTP), 1 U of Taq DNA polymerase (MBI Fermentas, Gateshead, UK), and 2.5- μ l reaction buffer (KCl 50 mM, Tris–Cl pH 8.3, MgCl₂ 1.5 mM). The thermal cycling conditions used included 95 °C for 5 min, followed by 40 cycles of 95 °C for 1 min, 57–59 °C for 1 min, 72 °C for 1 min, and final extension at 72 °C for 10 min. PCR was performed in thermal cycler ÔGene Amp PCR system 9700' obtained from Applied Biosystems (Foster City, CA). PCR products were resolved on 8% nondenaturing polyacryl-amide gel, and genotypes were assigned by visual inspection.

Linkage analysis

PEDCHECK (18) was used to identify Mendelian inconsistencies. Two-point linkage analysis was carried out using the MLINK program of the FASTLINK computer package (19). The microsatellite markers were ordered according to their sequence-based physical positions from build 35 and the genetic map distances obtained from the Rutgers combined linkage-physical map of the human genome (20). Multipoint linkage analysis was performed using ALLEGRO (21). It was not possible to estimate allele frequencies from the founders because the markers were only genotyped in one family, so equal allele frequencies were initially applied. Because false-positive results can be obtained when analyzing the data using too low of an allele frequency for an allele segregating with the disease locus (22), a sensitivity analysis was carried out for the multipoint linkage analysis by varying the allele frequency of the alleles that segregate with the disease locus from 0.2 to 0.5. Haplotypes were constructed using SIMWALK2 (23, 24). For the analysis, an autosomal recessive mode of inheritance with complete penetrance and a disease allele frequency of 0.001 were used.

Results

Clinical findings

Clinical information was obtained for all family members with particular attention to skin, dentition, sweating, nails, scalp and body hair. All the affected individuals were born with total alopecia. Hairs were completely absent from all areas of normal hair growth including scalp, eyebrows, eyelashes, axillary and pubic hair. Affected individuals showed normal teeth, nails, sweating and hearing. However, all the affected individuals were mentally retarded (Fig. 2). The degree of mental retardation was mild to moderate (IQ ranges from 53 to 61). No other clinical signs including seizures were detected in any of the affected individuals. Heterozygous carrier individuals had normal hairs and were clinically indistinguishable from genotypically normal individuals.

Localization of APMR2 to chromosome 3

To identify the gene underlying the APMR2 phenotype, we followed a classical linkage analysis approach. Prior to embarking on genome-wide scan, we performed cosegregation and homozygosity analysis with microsatellite markers corresponding to candidate genes involved in the related phenotypes. These included ectodermal dysplasia type 2 (MIM 129500) gene *GJB6* (MIM 604418) at 13q12.11 (D13S1316, D13S175, D13S633, D13S250, D13S787); ectodermal dysplasia type 3 (MIM 129490) gene *ectodysplasin1* anhidrotic receptor (MIM 604095) at 2q11-q13 (D2S1343, D2S2954, D2S340, D2S1889, D2S1893, D2S1891); ectodermal dysplasia type 4 (MIM 225060) gene *PVRL1* (MIM 600644) at 11q23.3 (D11S1885, D11S4171, D11S4129, D11S924, D11S1299); human HR (MIM 225060) gene at 8p12 (D8S298, D8S1786, D8S1048); LAH (MIM 607903) gene *DSG4* (MIM 607892) at 18q12.1 (D18S1107, D18S847, D18S478, D18S36, D18S536) and AH (MIM 609167) gene at 3q26.33-q27.3 (D3S2314, D3S3583, D3S3593, D3S1530). Examination of haplotypes showed that the affected individuals were heterozygous for different combinations of the parental alleles. Because of the consanguinity in this pedigree, it is expected that markers that flank the disease locus should be homozygous in all affected pedigree members. Because of lack of homozygosity in candidate regions, linkage was excluded.

After the known genes were excluded, a genome scan was carried out using the DNA samples of four affected individuals (IV-2, V-2, V-3, V-4) of the family. In the course of screening, 358 highly polymorphic microsatellite markers, from linkage mapping set 10 (Invitrogen Co., San Diego, CA), 4 markers including D3S3053 (3q26.31), D11S1304 (11q25), D13S800 (13q22.1) and D18S1106 (18q22.3), were found to be homozygous in all four affected family subjects. Upon testing the rest of the family members, linkage to three of these regions was excluded. All affected members were homozygous and unaffected members heterozygous at marker D3S3053, located at 181.49 cM on chromosome 3q26.31.

For fine mapping, 26 additional markers were selected from the Rutgers combined linkage-physical map (20). Nine markers (D3S1746, D3S3668, D3S1763, D3S1614, D3S1282, D3S3723, D3S1243, D3S1564, D3S3656) were proximal to genome scan marker D3S3053, while 17 markers (D3S1525, D3S3523, D3S2433, D3S1556, D3S1574, D3S3725, D3S2425, D3S2421, D3S1548, D3S1565, D3S2309, D3S3676, D3S2427, D3S3041, D3S2412, D3S3037, D3S3609) lie distal to D3S3053. After genotyping all the family members with these markers, the data were analyzed using two-point and multipoint linkage analysis. Ten of the markers (D3S1282, D3S3723, D3S1243, D3S1525, D3S3523, D3S1574, D3S3725, D3S1548, D3S1565, D3S3676) were uninformative and, therefore, not included in the analysis. Analysis of the marker genotypes within this region with PEDCHECK (18) did not elucidate any genotyping errors.

Table 1 summarizes the two-point LOD score obtained for a total of 17 markers. The maximum two-point LOD score of 2.93 ($\theta=0$) was obtained with two markers D3S3053 and D3S2309. The maximum multipoint LOD score of 4.57 was obtained with several markers, including D3S3656, D3S2433, D3S3053, D3S1556, D3S2425, D3S2421 and D3S2309, which supports linkage to this region. When sensitivity analysis was carried out, the LOD scores varied between 4.6 and 4.4 at these seven markers. The three-unit support interval for

the APMR2 locus is flanked by the markers D3S1564 (174.94 cM) and D3S2427 (184.55 cM). It defines a genetic interval of 9.6 cM on the Rutgers combined linkage-physical map (20) and contains 5.6 Mb according to build 35 of the sequence-based physical map (25). Haplotypes using SIMWALK2 (23, 24) were constructed to determine the critical linkage interval. A recombination event between markers D3S1564 and D3S3656 defined the centromeric boundary of this interval, and this was observed in three affected individuals (IV-2, V-3, V-4). The telomeric boundary is defined by the recombination that occurred between markers D3S2427 and D3S2309 in the affected individual IV-2. The disease interval (region of homozygosity) of APMR2 was the same region contained within the three-unit support interval and flanked by markers D3S1564 and D3S2427.

Discussion

In the present study, we have mapped the second locus for autosomal recessive alopecia and mental retardation syndrome (APMR2) to chromosome 3q26.2-q26.31. Significant evidence of linkage to this chromosomal region was found with maximum multipoint LOD score of 4.57 with several markers. Previously, we have reported the mapping of two different forms of hair loss at 3q26.33-q27.3. A locus for AH (MIM 609167) was mapped between markers D3S3730 (187.52 cM, 180029355 bp) and D3S1314 (208.54 cM, 191574707 bp) (26). Patients in this family showed typical features of hereditary hypotrichosis with no other associated abnormality. The second hair loss locus (APMR; MIM 203650), mapped at 3q26.33-q27.3, was in a family with total alopecia and severe mental retardation (16). This locus spans 11.49 cM and is flanked by markers D3S1232 (189.00 cM, 182902479) and D3S2436 (201.38 cM, 188317914 bp). The APMR2 locus, mapped in the present study, lies proximal to APMR locus and is flanked by markers D3S1564 (174.94 cM, 171671518 bp) and D3S2427 (184.55 cM, 177267503 bp). Recombinations observed in the affected individuals (IV-2, V-2, V-3, V-4) in the family indicate that APMR2 locus does not overlap with AH and APMR loci (Fig. 3). None of the affected individuals is homozygous for markers that overlap with the AH and APMR1 loci (see Fig. 1), and these markers produce negative LOD scores (data not shown).

It should also be noted that there is a difference in the clinical phenotypes of the patients of APMR and APMR2 families. Patients in the APMR family are severely mentally retarded (IQ from 25 to 30), while for those in the APMR2 family, the mental retardation is of mild to moderate (IQ from 53 to 61).

According to sequence-based physical map (25), the linkage interval of APMR2 on chromosome 3q26.2-q26.31 contains 5.6 Mb. Through a database search, we identified several genes mapping between markers D3S1564 and D3S2427. Among these are eIF5A2 protein (MIM 605782) associated with translation initiation factor activity and overexpressed in primary ovarian carcinoma (27); solute carrier family 2 (*SLC2A2*, MIM 138160), which has glucose transporter activity and defects in *SLC2A2* are the cause of Fanconi–Bickel syndrome (MIM 227810); growth hormone secretagogue receptor isoform 1a (MIM 601898) having G protein-coupled receptor activity and involved in control of immune cell activation and inflammation (28); tumor necrosis factor (*TNFSF10*, MIM 603598) involved in induction of apoptosis (29); and neuroligin 1 (*NLGN1*, MIM 600568) involved in the

formation of synaptic junctions (30). None of these appears to be a plausible candidate for APMR2 phenotype.

In conclusion, we report here the localization of a second gene for alopecia with mental retardation syndrome (APMR2) to 9.6 cM region on chromosome 3q26.2-q26.31. Although there is strong evidence for linkage of an autosomal recessive form of AH on chromosome 3q26.33-q27.3 (26) and two different forms of alopecia and mental retardation syndromes, APMR on 3q26.33-q27.3 (16) and APMR2 in the present study on 3q26.2-q26.31, all loci map to large intervals making gene identification difficult. In order to identify the functional genes, we would welcome knowledge of additional families with history of AH, APMR or APMR2.

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Fig. 1.

Drawing of pedigree that segregates APMR2. Filled symbols represent affected individuals. Clear symbols represent unaffected individuals. Map distances are given in centimorgans (cM) according to the Rutgers linkage-physical map of the human genome. The disease-associated haplotypes are shown beneath each symbol. Haplotypes were generated by SIMWALK2.

Fig. 2.
Clinical presentation of APMR2 family. (a) Phenotypic appearance of affected individual V-3 showing complete absence of hair on scalp and missing eyebrows and eyelashes. (b) Complete absence of hair on scalp of affected female V-4 with no eyebrows and eyelashes.

Fig. 3.

Comparison of the linkage interval of AH, APMR and APMR2 on chromosome 3q26 region. Genetic map distances in centimorgans (cM) are according to the Rutgers linkage-physical map of the human genome (20).

Table 1.

Two-point LOD score results between the APMR2 locus and chromosome 3 markers

Marker	Rutgers map (cM) ^a	Physical location (build 35) ^b	LOD score at recombination fraction $\theta = 0$					
			0.00	0.01	0.03	0.05	0.10	0.30
D3S1746	164.04	153,212,439	–Infinity	–3.26	–1.93	–1.35	–0.67	–0.04
D3S3668	171.06	165,829,800	–Infinity	–3.36	–2.02	–1.43	–0.73	–0.06
D3S1763	172.05	168,722,402	–Infinity	–2.98	–1.63	–1.04	–0.34	0.22
D3S1614	173.18	169,692,827	–Infinity	–3.88	–2.51	–1.89	–1.11	–0.18
D3S1564	174.94	171,671,518	–Infinity	–3.26	–1.93	–1.35	–0.67	–0.04
D3S3656	175.27	172,385,646	2.48	2.41	2.28	2.15	1.81	0.57
D3S2433	175.41	173,178,506	2.48	5.41	2.28	2.15	1.81	0.57
D3S3053	175.42	173,233,665	2.93	2.86	2.71	2.57	2.20	0.82
D3S1556	179.57	173,997,424	2.48	2.41	2.28	2.15	1.81	0.57
D3S2425	181.45	175,046,073	2.48	1.451	2.28	2.15	1.81	0.57
D3S2421	183.43	176,557,011	1.58	1.54	1.45	1.36	1.15	0.37
D3S2309	184.55	177,267,438	2.93	2.86	2.71	2.57	2.20	0.82
D3S2427	184.55	177,267,503	–1.20	0.99	1.34	1.43	1.40	0.64
D3S3041	184.55	177,962,785	–1.20	0.99	1.34	1.43	1.40	0.64
D3S2412	184.85	178,547,264	–4.05	–2.16	–1.28	–0.90	–0.45	–0.04
D3S3037	185.85	178,924,373	–4.05	–2.16	–1.28	–0.90	–0.45	–0.04
D3S3609	193.97	185,519,714	–4.05	–2.16	–1.28	–0.90	–0.45	–0.04

Also, displayed are the genetic and sequence-based physical map distances. Markers displayed in bold flank the region of homozygosity.

^a Sex-average Kosambi cM map position from the Rutgers combined linkage-physical map of the human genome (build 35) (20).

^b Sequence-based physical map distance in bases according to the Human Genome Project – Santa Cruz (25).