ORIGINAL ARTICLE

Homozygosity mapping in albinism patients using a novel panel of 13 STR markers inside the nonsyndromic OCA genes: introducing 5 novel mutations

Faravareh Khordadpoor-Deilamani¹, Mohammad Taghi Akbari^{2,3}, Morteza Karimipoor^{3,4} and Gholam Reza Javadi¹

Albinism is a heterogeneous genetic disorder of melanin synthesis that results in hypopigmented hair, skin and eyes. It is associated with decreased visual acuity, nystagmus, strabismus and photophobia. Six genes are known to be involved in nonsyndromic oculocutaneous albinism (OCA). In this study, we aimed to find the disease causing mutations in albinism patients using homozygosity mapping. Twenty three unrelated patients with nonsyndromic OCA or autosomal recessive ocular albinism were recruited in this study. All of the patients' parents had consanguineous marriage and all were screened for *TYR* mutations previously. At first, we performed homozygosity mapping using fluorescently labeled primers to amplify a novel panel of 13 STR markers inside the OCA genes and then the screened loci in each family were studied using PCR and cycle sequencing methods. We found five mutations including three mutations in *OCA2*, one mutation in *SLC45A2* and one mutation in *C10ORF11* genes, all of which were novel. In cases where the disease causing mutations are identical by descent due to a common ancestor, these STR markers can enable us to screen for the responsible genes.

Journal of Human Genetics (2016) 61, 373–379; doi:10.1038/jhg.2015.167; published online 28 January 2016

INTRODUCTION

Albinism is a rare genetic disorder which affects ~1 in 20 000 individuals worldwide, although the prevalence of the different subtypes of albinism varies considerably among different populations. Melanin production which occurs in melanocytes is closely regulated. Defects in the melanin biosynthesis or transport result in hypopigmentation.^{1–4}

Oculocutaneous albinism (OCA) is a heterogeneous and autosomal recessive disorder with the symptoms of lack of pigment in the skin, hair and eyes, and optic defects such as photophobia, strabismus, poor vision and nystagmus.^{2,5,6}

Mutations in *HPS1*, *AP3B1*, *HPS3*, *HPS4*, *HPS5*, *HPS6*, *DTNBP1*, *BLOC1S3*, *BLOC1S6* (*PLDN*), *LYST* and genes result in syndromic OCA, while mutations in *TYR* (OMIM:606933), *OCA2* (OMIM:611409), *TYRP1* (OMIM:115501), and *SLC45A2* (OMIM:606202), *SLC24A5* (OMIM:609802) and *C10ORF11* (OMIM:614537) genes cause nonsyndromic forms of this disease (OCA1, OCA2, OCA3, OCA4, OCA6 and OCA7, respectively). Also an OCA locus is mapped to 4q24 in a consanguineous Pakistani family, which may be responsible for OCA5 (OMIM:615312), but the gene has not been described.^{1,7–10}

OCA1A (tyrosinase-negative OCA) (OMIM:203100) is caused by *TYR* null mutations and melanin formation never occurs throughout the patient's life. In contrast, hair of individuals with OCA1B (OMIM:606952) in which mutations produce a partially active or hypomorphic tyrosinase enzyme turns to yellow or blonde with age.^{3,4,11}

The OCA2 (OMIM:203200) patients have generally less severe clinical phenotype than OCA1 and most affected patients accumulate pigment with age. It is caused by mutations in the *P* (*OCA2*) gene, which codes for a melanosomal membrane protein. P protein plays a role in regulating the pH of melanosomes and may be involved in the transport of tyrosine or some other small molecule into the melanosome.^{2,12}

Mutations in *TYRP1* gene cause OCA3 (OMIM:203290). *TYRP1* has partial tyrosinase hydroxylase activity and catalyzes the oxidation of 5,6-dihydroxyindole-2- carboxylic acid in the melanin biosynthesis pathway.^{13,14}

OCA4 (OMIM:606574) is due to mutations in *SLC45A2* (*MATP*) that probably acts as a melanosomal protein and substance transporter.^{13,15}

¹Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran; ²Department of Medical Genetics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran; ³Tehran Medical Genetics Laboratory, Tehran, Iran and ⁴Department of Molecular Medicine, Biotechnology Research Center, Pasteur Institute of Iran, Tehran, Iran

Correspondence: Dr MT Akbari, Department of Medical Genetics, Faculty of Medical Sciences, Tarbiat Modares University, P.O. Box: 14115-331, Tehran 02182884555, Iran. E-mail: mtakbari@modares.ac.ir

Received 8 October 2015; revised 16 November 2015; accepted 26 November 2015; published online 28 January 2016

Table 1 Thirteen STR markers inside the oculocutaneous albinism (OCA) genes were selected for homozygosity mapping

Gene/RefSeq	STR markers and their probe accession numbers	STR location inside the gene	Consensus sequence	Primer sequence	Size (bp)	Fluorescent label
TYR NG_008748.1	S1 = Pr032754300	Between exons 2 and 3	TCTA	F: 5'-AGTTGGCATCGTCGATGGTTAC-3' R: 5'-GGTGATACCATGGGCAAATTCTG-3'	262	FAM
	S2 = Pr032754301	Between exons 4 and 5	AC	F: 5'-TGCTTTTAGGAATTTACAACTGTTCA-3' R: 5'-GCGTTTATCCTAAGGACCATTCTG-3'	351	FAM
OCA2 (P) NG_009846.1	S1 = Pr032754296	Between exons 2 and 3	TG	F: 5'-GTTGATTTATGTAACATTCTGCTGG-3' R: 5'-GAGGTTACATAAAGCTACCCAAGTGA-3'	109	FAM
	S2 = Pr032754297	Between exons 17 and 18	GT	F: 5'-AAGTTCATACAGATTATGCCTGCCT-3' R: 5'-AGTACTTCACTGGTCACCAAGTCC-3'	306	FAM
TYRP1 NG_011705.1	S1 = Pr032754302	Before exon 1	TG	F: 5'-ACGTTCCAGAGTAAGTAGCATATGGT-3' R: 5'-GAGATGTGTGGCACTGGATGGA-3'	456	HEX
	S2 = Pr032754303	Between exons 5 and 6	TG	F: 5'-ACAATCCCTGATCTCAACCCTC-3' R: 5'-GCTTAAGTTGCCAGATGTTACTTCAG-3'	384	HEX
MATP NG_011691.1	S1 = Pr032754294	Between exons 2 and 3	TG	F: 5'-AACCAATGGGGAAGATATAAGAAGAGT-3' R: 5'-GTCTTGTAGAAGGTTAACCAGGTTC-3'	153	FAM
	S2 = Pr032754295	Between exons 3 and 4	GT	F: 5'-TGTGCATTTTCCATTACATATTGAAG-3' R: 5'-CTCCCTGTTCTTAGCCAGATGTCT-3'	194	FAM
SLC24A5 NG_011500.1	S1 = Pr032754298	Before exon 1	TG	F: 5'-TGTGTATGAAAGAAAGGGGACACAG-3' R: 5'-CAACTGGGTTGGTCATCGTTTC-3'	224	HEX
	S2 = Pr032754299	Before exon 1	GAAA	F: 5'-AAGCACTTACTCCGTTCCATCAG-3' R: 5'-CGACCTCTGGCTGACGTCCTC-3'	408	FAM
C10ORF11 NG_042180.1	S1 = Pr032754291	Between exons 2 and 3	GT	F: 5'-TAATCAGAGTGCTCGCATGTTCT-3' R: 5'-CTTTCAGCTGTGCAGATGACTGTG-3'	118	HEX
	S2 = Pr032754292	Between exons 5 and 6	AC	F: 5'-GCAACAAGACTCTCAGCATCACAG-3' R: 5'-ACAAATTCTCATAGTACCTGGGAACC-3'	294	HEX
	S3 = Pr032754293	Between exons 6 and 7	TTA	F: 5'-TGGGGAAGTCCAAAGTCTTTCTG-3' R: 5'-GTAACTGAGGGTTCTAGTGTCTTGAGT-3'	326	HEX

The size of the fragments are presented according to the mentioned accession numbers. Forward primers were labeled with the FAM or HEX fluorophores.

OCA6 (OMIM:113750) occurs due to mutations in *SLC24A5* that has a role in skin pigmentation.^{16,17} The *SLC24A5* protein belongs to a family of potassium-dependent sodium/calcium exchangers.¹⁸

Mutations in *C10ORF11* result in OCA7 (OMIM:615179). The protein encoded by this gene is an LRRs (leucine-rich repeats) containing protein and may be involved in cell adhesion and signaling, extracellular-matrix assembly, platelet aggregation, neuronal development, RNA processing and immune response.¹⁵

Eye findings in Ocular albinism (OA) and OCA patients are similar, but the hair and skin are not affected in OA.¹⁹ Both X-linked recessive (OA1) and autosomal recessive (AROA) forms of OA are reported.²⁰ The latter may be a clinically mild form of OCA, due to mutations in either the *TYR* or *OCA2* genes.²¹

Because of the observed range of phenotypic variation in albinism patients, genetic analysis may be helpful with respect to a more accurate diagnosis and genetic counseling.^{2,22}

Mutations that are detected by molecular genetics methods can be analyzed *in silico* to determine their effects. Several *in silico* mutation analysis of OCA genes are reported such as mutational analysis of *TYR* gene and its protein structural or functional consequences,^{23,24} Bioinformatic analysis of mutations in *TYRP1* gene^{25,26} and computational screening of mutations in *OCA2* gene.²⁷

In this study, we performed homozygosity mapping using STR markers in order to pinpoint the genes involved and to find the mutations in the families with consanguineous marriage.

MATERIALS AND METHODS

Twenty three unrelated Iranian albinism patients, including 2 AROA and 21 nonsyndromic OCA patients from unrelated families were recruited in this

study. All of them were previously screened for *TYR* gene mutations.²⁸ The study was approved by the local ethics committee and the informed written consent was obtained from all patients and their parents.

Genomic DNA was extracted from peripheral whole blood of the patients and their parents using salting out method.

Tandem repeats were selected inside the *TYR*, *OCA2*, *TYRP1*, *SLC45A2* (*MATP*), *SLC24A5* and *C10ORF11* genes using TRF (<https://tandem.bu.edu/trf/trf.html>)²⁹ and SERV (<http://www.igs.cnrs-mrs.fr/SERV/>)³⁰ programs. These STR markers were later submitted to the Probe database (<http://www.ncbi.nlm.nih.gov/probe>) and registered with the probe accession numbers presented in Table 1. Thirteen primer pairs were designed and fluorescently labeled to amplify these STR markers (Table 1).

The STR markers in the patients, their parents and siblings (if available) were amplified performing two multiplex PCR. The fragments were separated on 3130 Genetic Analyzer (Foster City, CA, USA) using 500 ROX size standard and the data were analyzed by GeneMarker software (State College, PA, USA). Homozygous loci in each family were selected for further studies by PCR and cycle sequencing. The primers were designed for all exons and intron-exon boundaries of screened genes using gene runner software and primer blast website <http://www.ncbi.nlm.nih.gov/tools/primer-blast/> (Supplementary Table 1). Novel mutations were analyzed using tools such as SIFT, PolyPhen and MutationTaster and were interpreted based on ACMG (American College of Medical Genetics) standards and guideline.³¹ Their pathogenicity was confirmed by ascertaining co-segregation in the families and by screening a panel of population-matched healthy controls.

RESULTS

In this study, we performed mutation analysis of the nonsyndromic OCA genes in 23 unrelated albinism patients (2 AROA and 21 OCA patients) in families with consanguineous marriage. All patients were studied for *TYR* mutations previously.²⁸ 14 out of 23 patients

Figure 1 Families with homozygous mutations in *TYR* gene. Only the sizes of the STRs inside the *TYR* gene are displayed.

Figure 2 Family 12 with the deletion of exons 3–18 of the *OCA2* gene. (a) The pedigree and the results of the homozygosity mapping. All patients had homozygous allele of OCA2-S1 (109 bp) and homozygous deletion of OCA2-S2. (b) The electropherogram data of a patient on the 3130 Genetic Analyzer. The arrow shows the deletion of the OCA2-S2. (c) Left, PCR products of the exon 2 (701 bp) in the healthy person (1), the patients (2 and 3) and blank (4), exon 3 (534 bp) in the healthy people (5 and 6), the patients (7–10) and blank (11), 50 bp size marker (12), exon 9 (489 bp) in healthy person (13), the patients (14 and 15) and the blank (16). Right, PCR products of the exon 18 (575 bp) in healthy person (1), the patients (2–5) and the blank (6), 50 bp size marker (7), and the exon 19 (572 bp) in the healthy person (8), the patients (9–12) and the blank (13). Exon 8 of *SLC24A5* (377 bp) was used as an internal control for exons 3,9,18 and 19. A full color version of this figure is available at the *Journal of Human Genetics* journal online.

Figure 3 Family 6 with p.G657R in *OCA2* gene, family 20 with IVS9+1G>T in *OCA2* gene, family 2 with c.1273delC in *SLC45A2* (*MATP*) gene and family 23 with p.N89K in *C10ORF11*. A full color version of this figure is available at the *Journal of Human Genetics* journal online.

were recognized to have mutations in *TYR* gene, from which 11 were homozygous, 2 were compound heterozygous and 1 had only one mutation (p.P406L). For nine remaining patients no mutation was found.

Using fluorescently labeled primers to amplify STR markers existing inside the six OCA genes, all families were first screened for the homozygous loci in the patient, and then the screened loci in each family were sequenced. In addition to confirming our findings on *TYR* gene (Figure 1), we found five novel mutations in homozygous form, including three mutations in *OCA2* (p.G657R, Del exons 3–18 and IVS9+1G>T in patients 6, 12 and 20, respectively), one mutation in *SLC45A2* gene (c.1273delC in patient 2) and one mutation in *C10ORF11* (p.N89K in patient 23) (Figures 2,3 and Table 2).

The mutations co-segregated in the families and did not exist in the 50 healthy controls.

DISCUSSION

Due to the consanguineous marriage in Iran (with the overall rate of about 38.6%),^{32,33} the probability of the genetic disorders due to common ancestors is increased.

To our knowledge, it is the first comprehensive genetic analysis of the OCA patients in which all six nonsyndromic OCA genes are studied by homozygosity mapping using STR markers inside the relevant genes. Although this approach has been used and for the diagnosis of genetically heterogeneous disorders such as genodermatoses and ichthyosis.^{34,35}

In some families (such as families 2 and 17), some STR markers were semi-informative or not informative. However, we sequenced all the genes that showed homozygous pattern for STR markers in those families irrespective of being genuinely informative with respect to being disease causing or not.

Five mutations were found in this study, all of which were novel. Three patients had mutations in *OCA2* gene. Patient 6 had p.G657R mutation, which is a missense variant in one of the transmembrane domains of *OCA2* protein. Tools such as SIFT, Polyphen-2 and MutationTaster, predict p.G657R as a disease causing mutation. According to the ACMG standards and guidelines for interpretation of sequence variants, this novel mutation is likely pathogenic.

Deletion of exons 3–18 of *OCA2* gene was observed in patients of pedigree 12 that is one of the biggest pedigrees we studied. Gross deletions in *OCA2* have been reported^{36–39} and the largest reported deletion covered the entire gene.⁴⁰

Patient 20 had IVS9+1G>T in his *OCA2* gene. Human splicing finder tool predicted that the wild type donor site is broken, so intron retention probably occurs. According to the ACMG standards and guidelines these two latter variants are pathogenic.

Patient 2 who was heterozygous for p.P406L in *TYR* gene, had also c.1273delC (p.Leu425Trpfs) in her *SLC45A2* gene in homozygous form. This mutation is a frameshifting one and causes a termination signal in ninth codon after. Although patients with digenic OCA who have mutations in *TYR* and *SLC45A2* genes are reported,⁵ the mother of this patient (heterozygous for p.P406L mutation in *TYR* and

Table 2 Mutations in 23 albinism patients and the clinical and molecular diagnosis of OCA

Pedigree	Clinical diagnosis	Loci screened		Molecular diagnosis	Heterozygous mutations in TYR gene
		by homozygosity mapping	Homozygous mutations		
1	OCA	TYR	c.286dupA	OCA1A	p.P406L
2	OCA	SLC24A5 MATP	No mutation c.1273delC (p.Leu425Trpfs)	OCA4	
3	AROA	SLC24A5 OCA2	No mutation No mutation	ND	
4	OCA	SLC24A5	No mutation	ND	p.G47S and c.del1276-82
5	OCA	TYR	p.M332I	OCA1B	
6	OCA	OCA2	p.G657R (c.1969G>C)	OCA2	
7	OCA	TYR	p.M332I	OCA1B	p.R239W and p.M332I
8	OCA	TYR MATP C10ORF11	No mutation No mutation No mutation	ND	
9	OCA	—	—	OCA1	
10	OCA	—	—	ND	p.G47S and c.del1276-82
11	OCA	TYR	c.286dupA	OCA1A	
12	OCA	OCA2	Del exons 3–18	OCA2	
13	OCA	TYR	c.286dupA	OCA1A	p.G47S and c.del1276-82
14	OCA	TYR	p.R77Q	OCA1A	
15	OCA	—	—	OCA1A	
16	OCA	TYR	p.P21S	OCA1A	p.G47S and c.del1276-82
17	OCA	TYR	p.R77Q	OCA1A	
18	OCA	TYR C10ORF11	p.G419R No mutation	OCA1A	
19	OCA	TYR	p.P301L	OCA1A	p.G47S and c.del1276-82
20	OCA	SLC24A5 OCA2	No mutation IVS9+1G>T (c.1044+1G>T)	OCA2	
21	OCA	TYR	c.286dupA	OCA1A	
22	OCA	SLC24A5	No mutation	ND	p.G47S and c.del1276-82
23	AROA	MATP C10ORF11	No mutation p.N89K (c.267C>A)	OCA7	

Abbreviations: ND, not determined; OCA, oculocutaneous albinism. Mutations in TYR gene are derived from our previous study.

c.1273delC in *SLC45A2* gene) and also her father (heterozygous for p.R402Q polymorphism in *TYR* and c.1273delC in *SLC45A2* gene) were both healthy. However, these findings do not contradict the pathogenicity of p.P406L.

Patient 23 who suffered from AROA was homozygous for p.N89K in *C10ORF11* (NM_032024). This mutation occurred in the LRR4 domain of the protein. Mentioned bioinformatics tools (MutationTaster, PolyPhen-2, PROVEN and I-Mutant2) predicted p.N89K to be a disease causing mutation. According to the ACMG standards and guidelines, this novel mutation is likely pathogenic. Although functional studies are needed in order to confirm its pathogenicity. Grønskov *et al.* for the first time reported mutations in *C10orf11* cause autosomal recessive albinism (OCA7).¹⁵ Also some cases with AROA have mutations in either the *TYR* or *OCA2* (*P*) genes.²¹ Here for the first time, we reported a patient with AROA (which can be a mild form of OCA) who had a mutation in *C10ORF11*.

No mutation was found in *SLC24A5* gene and none of the families showed homozygosity for in *TYRP1* gene. Mutations in five patients remained unidentified. This may be due to the involvement of other genes, variants in the promoter or other regulatory elements that were not covered in this study or compound heterozygote or digenic OCA.

These STR markers can enable us to screen for the responsible genes in OCA patients in inbred families with homozygosity mapping. Also, they can be used for linkage analysis in the families with compound heterozygous patients or without consanguinity marriage. However, the increase of the markers inside or adjacent to the genes are suggested in order to ease the further analysis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank the albinism families for their collaboration. The personnel of Tehran Medical Genetics Laboratory are appreciated for their help and support. This project was financially supported by Tehran Medical Genetics Laboratory, grant number 93003.

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Supplementary Information accompanies the paper on Journal of Human Genetics website (<http://www.nature.com/jhg>)