Oculocutaneous albinism (OCA) is a disorder of defective melanin biosynthesis that is characterized by hypopigmentation of skin, hair and retinal pigment epithelium. Phenotypically, OCA patients exhibit white milky skin, whitish to golden hair and deterioration of retinal cells. Until recently, genetic studies have reported seven causative genes (TYR, TYRP1, OCA2, SLC45A2, SLC24A2, C10ORF11 and MCIR) and an uncharacterized OCA5 locus.

Herein we present the medico-genetic study of three Pakistani patients inheriting autosomal recessive OCA. Whole exome sequencing, followed by Sanger DNA sequencing for segregation analysis, revealed recurrent mutations c.346C>T (p.Arg116*) and c.1255G>A (p.Gly419Arg) (family A and B respectively) in TYR gene, while the patient from family C did not reveal any known gene mutation, which suggests the involvement of some novel genetic factor. It is the first report of mapping c.346C>T mutation in a Pakistani patient. Our study further extends the evidence of genetic hotspots regions in TYR gene causing OCA in Pakistani population.

Key word: Oculocutaneous albinism, exome sequencing, genetic analysis, TYR gene

Introduction

Oculocutaneous albinism (OCA) is a pigmentary disorder of defective melanin biosynthesis pathway that is manifested by hypo-pigmentation of skin, hair and retinal pigment epithelium. The clinical features of OCA patients comprise of white milky skin, whitish to golden hair and deterioration of retinal cells. The ophthalmologic consequences in OCA patients usually include photophobia, nystagmus, low visual acuity, Rod and Cone cell deterioration, fovea hypoplasia and misrouting of the optic nerves at the chiasma.1 OCA is a genetically heterogeneous disorder, which mostly segregates in an autosomal recessive manner. Until now, seven genes (TYR, TYRP1, OCA2, SLC45A2, SLC24A2, C10ORF11 and MC1R) and an uncharacterized OCA5 locus have been mapped on the human genome.2 At molecular level, these OCA protein products are involved in melanin metabolism and transport. Epidemiologic studies of Europe and United States indicated that genetically caused OCA affects 1 in 17000 newborns, while this figure may be higher in Pakistani society where rate of consanguineous marriages are over 60% among which the ratio of first cousin union is found in 80% of couples.3

Here in this study, we report on two recurrent mutations in TYR gene, in which c.346C>T is mapped first time in a Pakistani patient. Our study supports the evidence of mutational hotspots in TYR gene causing OCA in Pakistani patients.

Case Report

In this presented investigative study, we ascertained four

Table: The clinical spectrum of OCA patients from family A, B and C.

<table>
<thead>
<tr>
<th>Phenotypic feature</th>
<th>Family A</th>
<th>Family B</th>
<th>Family C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair colour</td>
<td>White</td>
<td>White</td>
<td>Golden</td>
</tr>
<tr>
<td>Skin colour</td>
<td>White</td>
<td>White</td>
<td>White with Redish shade</td>
</tr>
<tr>
<td>Iris colour</td>
<td>Blue</td>
<td>Blue</td>
<td>Brown</td>
</tr>
<tr>
<td>Eye Sight</td>
<td>Weak</td>
<td>Weak</td>
<td>Weak</td>
</tr>
<tr>
<td>Photophobia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Strabismus</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cataract</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Colour blindness</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Impaired Stereoscopic Vision</td>
<td>Minor</td>
<td>No</td>
<td>Minor impairment</td>
</tr>
<tr>
<td>Depth perception</td>
<td>Reduction</td>
<td>Minor Reduction</td>
<td>Moderate Reduction</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Over weight</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Wide tooth spacing</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

1-7Department of Biological Sciences, Faculty of Sciences, 2,3,5,6Gomal Centre of Biochemistry and Biotechnology, Gomal University, Dera Ismail Khan, KPK, Pakistan, 4Department of Cell and Developmental Biology, School of Life Sciences, University of Science and Technology, China, 5Department of Biotechnology and Genetic Engineering, Kohat University of Science and Technology, Kohat, KPK, Pakistan.

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patients for mutation analysis of underlying gene defect causing oculocutaneous albinism. The study was approved by the ethical review board of Gomal Centre of Biochemistry and Biotechnology, Gomal University, D.I. Khan, Pakistan, and the samples were enrolled after obtaining informed written consent for clinico-genetic analysis and data publication. These patients were recruited from different rural parts of Pakistan. Ethnically, three patients (family A and C) were from Saraiki origin, while one patient from family B was Pukhtun by origin. The patients from family A and B were sampled in June 2013 while a single patient from family C was recruited in August 2014. The parents from both families A and B had second degree consanguinity, while the family guardians could not establish the exact degree of kinship in family C. The patients were presenting with non-syndromic form of oculocutaneous albinism. They had depigmented hairs, skin and iris along with reduced visual acuity, photophobia and exhibited continuous symptoms of nystagmus. The reduced pigmentation in the eyes was clearly evident from hazel green to light brown and bluish colouration of the iris but no symptom of heterochromia iridis was observed. The patients also showed progressive loss of vision due to retinal cells degeneration. The detail ophthalmologic examination did not reveal any abnormality of cornea and lens, except the presence of unilateral strabismus in patient from family C. In addition to the presented phenotype, no extra symptoms of biological, radiological or physiological abnormalities were found in any patient. Hence, the gross clinical analysis excluded the possibility of Hermansky-Pudlak, Chediak-Higashi, Waardenburg, Cross-McKusick-Breen, Griscelli syndromes and Elejalde syndromes. The additional clinical spectrum of OCA patients from all three families are presented in Table.

The molecular analysis through whole exome sequencing in two families (A and B) revealed recurrent mutations
colouration. Our study increases the body of evidence that
Pakistanis population.
patient IV-1 presenting with white hair, white skin and blue iris
TYR function effect, which is evident from phenotypic features of
protein truncating mutation in family A has complete loss of
these articles are almost consistent with our findings. The
mitotic recombination and genetic linkage analysis. The
incidence among Pakistanis population. Recently, Shah and
mapped it in a Saraik or origin family. Genetic analysis of family
C indicates the involvement of a novel genetic factor in OCA.
Previously, several researchers have performed extensive
genetics studies on large consanguineous Pakistani families
and reported mutations in TYR, TYRP1, OCA2 and SLC45A2
genes. The TYR gene analyses in these studies have observed that
p.Gly419Arg mutation has the most common incidence among Pakistani population. Recently, Shah and
his colleagues have reported a founder mutation (p.Arg77Gln) in the TYR gene. The clinical data reported in
these articles are almost consistent with our findings. The
protein truncating mutation in family A has complete loss of
function effect, which is evident from phenotypic features of
patient IV-1 presenting with white hair, white skin and blue iris
colouration. Our study increases the body of evidence that
TYR is the most prevalent gene associated with OCA in
Pakistani population.

Discussion
Albinism has an incidence rate of 1 in 20,000 individuals, in
which OCA1 is the most commonly responsible locus world-
wide. OCA1 phenotype is caused due to defective Tyrosinase
(TYR) gene that is positioned on chromosome 11q14. The
TYR gene consist of 5 exons which translate to produce the
529 amino acids long tyrosinase protein. Tyrosinase is an
enzyme that catalyzes the initial two reactions in melanin
biosynthesis mechanism in the pigmentary cells, called
melanocytes. In its first step, the enzyme converts tyrosine
amino acid into dihydroxy phenylalanine (DOPA) and then to
DOPAquinone. Phenotypically, the TYR gene defect is
categorized into OCA1A and OCA1B. OCA1A patients
completely lack tyrosinase activity, while in OCA1B condition
the enzyme shows reduced activity. Mutation studies have
found 351 pathogenic mutations (HGMD Professional 2016.1
total) in TYR gene, in which more than 15 are reported in
Pakistani families. Here, we are presenting the first report
mapping c.346C>T (p.Arg116*) mutation in a Pukhtun origin
Pakistani family, while p.Gly419Arg mutation has previously
been reported in a Punjabi ethnic population and we
mapped it in a Saraik or origin family. Genetic analysis of family
C indicates the involvement of a novel genetic factor in OCA.

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