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ARTICLE

Tyrosinase (TYR) gene sequencing and literature review reveals recurrent mutations and multiple population founder gene mutations as causative of oculocutaneous albinism (OCA) in Pakistani families

Muhammad Shakil[1,2,3] · Gaurav V. Harlalka[2] · Shamshad Ali[4] · Siying Lin[2] · Ilaria D'Atri[2] · Shabbir Hussain[1] · Abdul Nasir[5] · Muhammad Aiman Shahzad[6] · Muhammad Ikram Ullah[1,7] · Jay E. Self[8] · Emma L. Baple[2] · Andrew H. Crosby[2] · Saqib Mahmood[6,9]

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Abstract

Purpose To investigate eight previously unreported Pakistani families with genetically undefined OCA for mutations in *TYR*.

Methods Sanger sequencing of *TYR* has been performed in eight families with OCA phenotype. Mutation analysis was performed to establish the pathogenic role of novel mutation. Bioinformatics analysis was performed to predict the structural and functional impacts on protein due to the mutation.

Results In this study, we identified six likely pathogenic variants of *TYR* (c.272 G>A, c.308 G>A, c.346C>T, c.715 C>T, c.832 C>T and c.1255 G>A), including one novel variant (c.308 G>A; p.Cys103Tyr), segregating as appropriate in each family. Cys103 lies in the highly conserved region of the tyrosinase enzyme, and p.Cys103Tyr is predicted to disturb enzymatic function via alteration of the configurational orientation of *TYR* leading to a more rigid polypeptide structure. We have also reviewed the mutation spectrum of TYR in Pakistani ethnicity. Published data on OCA families proposed that ~40% have been associated with genetic variations in the *TYR* gene. The mutations reported in this study have now been described with varying frequencies in Pakistani families, including very rare/unique mutations.

Conclusion A literature review of *TYR* gene mutations in Pakistani populations, combined with our genetic data, identified a number of gene mutations likely to represent regional ancestral founder mutations of relevance to Pakistani populations, in addition to sporadic and recurrent 'hotspot' mutations present repeatedly in other regions worldwide.

Introduction

Non-syndromic oculocutaneous albinism (nsOCA) is an autosomal recessive disorder characterised by the partial or

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✉ Saqib Mahmood
sqb_medgen@yahoo.com

1 Department of Biochemistry, University of Health Sciences (UHS), Lahore, Pakistan

2 RD&E (Wonford) NHS Foundation Trust, University of Exeter Medical School, Barrack Road, Exeter, Devon EX2 5DW, UK

3 Department of Biochemistry, Services Institute of Medical Sciences, Services Hospital, Lahore, Pakistan

4 Department of Ophthalmology, Services Institute of Medical Sciences, Services Hospital, Lahore, Pakistan

5 Synthetic Protein Engineering Lab (SPEL), Department of Molecular Science and Technology, Ajou University, Suwon 443-749, South Korea

6 Department of Human Genetics and Molecular Biology, University of Health Sciences (UHS), Lahore, Pakistan

7 Department of Clinical Laboratory Sciences, Jouf University, Sakaka-2014, Saudi Arabia

8 Clinical and Experimental Sciences, University of Southampton, Southampton, UK

9 Institute of Biomedical and Allied Health Sciences, University of Health Sciences (UHS), Lahore, Pakistan

complete loss of pigmentation in the skin, hair and ocular tissues that is due to a decrease or absence of melanin production [1]. Other clinically important features associated with OCA are foveal hypoplasia, misrouting of the optic nerves at the chiasm, photophobia, nystagmus and vision impairment [2]. The prevalence of albinism worldwide has been estimated at 1 in 17,000, indicating that ~1 in 70 people are carriers of the *OCA* allele globally [3].

Non-syndromic OCA is further divided into seven subtypes (OCA1–7) on the basis of genetic testing. Oculocutaneous albinism type 1 (OCA1) is the most common OCA variant affecting almost 50% of affected individuals worldwide [4, 5]. Clinically, OCA has a broad clinical presentation, with OCA1A being the most severe subtype with absolute lack of melanin biosynthesis throughout life resulting in completely white hair and skin. Other OCA subtypes (OCA1B, OCA2, OCA3, OCA4 and OCA7) display a degree of melanin pigmentation with advancing age, giving rise to a wide range of the skin, hair and eyes colour, although pigmentation remains typically less than unaffected individuals. Due to the indistinguishable clinical phenotypes and the involvement of different genes, molecular diagnosis has become an important tool to accurately identify the type and severity of OCA to aid genetic diagnosis, counselling and for considering therapeutic development [6, 7].

To date, the pathogenic variants in six genes, *TYR, OCA2, TYRP1, SLC45A2, SLC24A5* and *C10orf11*, have been identified in individuals with nsOCA [8]. In a Pakistani family, possible locus for a form of nsOCA on chromosome 4q24 [9] has been previously identified, for which the gene remains undefined. In published population studies, however, the detection rate of alleles causing albinism varies from 60 to 90% [10, 11]. OCA type 1 is associated by mutation in the tyrosinase *TYR* (MIM# 606933) gene, which encompasses five coding exons and is located on chromosome 11q14.3. Tyrosinase enzyme has a pivotal role in the biosynthesis of melanin in melanocytes as it catalyses the first two reactions of the melanin synthesis pathway: formation of L-3,4-dihydroxyphenylalanine (L-DOPA) by hydroxylation of tyrosine and dopaquinone production by the oxidation of L-DOPA. These two steps are crucial for melanin synthesis [12], and defects in tyrosinase catalytic activity due to *TYR* mutation may result into complete absence or decreased pigmentation of the skin, eyes and hair, depending on residual enzyme activity [13]. OCA1A (MIM# 203100) is the most severe clinical phenotype characterised by an almost complete absence of the skin, hair and iris pigmentation, and associated with pathogenic or null alleles in *TYR*. Less severe *TYR* mutations may manifest as OCA1B (MIM# 606952), which results in a milder, extremely variable phenotype due to decreased but not completely abrogated tyrosinase activity and low-to-moderate levels of melanin pigmentation in affected individuals [4, 14].

Materials and methods

Patients and family members

This study entails the genetic investigation of eight Pakistani families recruited with informed consent with ethical approval (Ethical board of University of Health Sciences, Lahore). All families originate from the Punjab Province, with distinct ethnic backgrounds: (1) Khokhar (Sahiwal), (2) Chadhar Jutt (Chiniot), (3) Arain (Gujranwala), (4) Malik Awan (Lahore), (5) Mughal (Lahore), (6) Gujjar (Lahore), (7) Saraki Somro (Rahim Yar khan) and (8) Turk Pathan (RYK). The families diagnosed with OCA and having two or more affected members were included in this study, while the families with ocular albinism and syndromic OCA were excluded. Following diagnosis of a proband in each pedigree, further clinical details for each family were obtained by visiting ophthalmologists from local collaborating hospitals. Clinical images of the affected individuals were taken with consent in order to document phenotypic features and confirm disease status. Videos were also taken for further study. Ophthalmic examinations were completed using the best locally available resources, including: visual acuity testing using LogMAR Visual Acuity Chart (LVRC) Numbers Distance, colour vision testing using Ishihara charts and funduscopic examination by direct ophthalmoscopy. Findings were recorded on the specified data forms.

Molecular genetic analysis

Peripheral venous blood samples were taken in EDTA containing vacutainer tubes from each participating individual for genomic DNA extraction, as previously described [4]. One affected individual from each family was sequenced for all five coding exons and associated intron–exon junctions in the *TYR* gene. Sequence reads were aligned to the human genome reference sequence [hg19] to observe base-pair changes using BioEdit software, CLC sequence viewer (https://www.qiagenbioinformatics.com/products/clc-sequence-viewer/) and Chromas Lite (http://technelysium.com.au/wp/chromas/) software. DNA samples from the families of those probands who showed putative mutations in one affected individual were sequenced in order to confirm segregation with the disease phenotype. The in silico pathogenicity prediction tools applied were SIFT (<0.05), PolyPhen2 Hum Var (possibly damaging and probably damaging) and GERP++ (>2) [14]. Crystal structure of human tyrosinase protein (PDB ID

5M8Q) [15] was used as a template for the construction of three-dimensional (3D) structure of wild and mutant tyrosinase protein. The models were visualised using UCSF-chimera (https://www.cgl.ucsf.edu/chimera/). RAMPAGE was used for evaluation and validation of the modelled 3-D structures [16].

Results

Clinical findings

Eight families with congenital nsOCA were enrolled from different cities within the Punjab province of Pakistan (family 1 from the Sahiwal, family 2 from Chiniot, family 3 from Gujranwala, families 5, 6, 7 from Lahore, families 7 and 8 from Rahim Yar Khan). The apparent mode of inheritance in all families was consistent with an autosomal recessive disorder, and all affected individuals exhibited the cardinal clinical features of OCA with white-to-golden blonde hair, pale-to-reddish white skin, decreased visual acuity of variable extent, nystagmus, strabismus and photophobia. Ophthalmological examination of all affected individuals revealed the classical ophthalmic features of albinism namely: foveal hypoplasia, nystagmus, strabismus and a hypopigmented fundus. The clinical findings are summarised in Table 1.

Genetic findings

Sequencing of the coding regions of *TYR* gene revealed a novel missense mutation chr11:88911429G>A [hg19]; c.308G>A; p.Cys103Tyr in the first coding exon of *TYR* in pedigree of family 1 of OCA (Fig. 1a, b), which co-segregated appropriately on sequencing (Fig. 1c). In silico analyses were undertaken using various pathogenicity prediction tools, such as PolyPhen-2 and SIFT, indicating that this variant is likely deleterious (Table 2). Five other *TYR* missense variants were identified; chr11:89018011G>A [hg19]; NM_000372.4: c.1255 G>A; p.Gly419Arg in families 2, 3 and 4, chr11:88911393 G>A [hg19]; NM_000372.4: c.272 G>A; p.Cys91Tyr in family 7, and c.715 C>T; p.Arg239Trp in family 8, and two nonsense mutations were also identified; c.346 C>T; p.Arg116Ter in

Table 1 Clinical features observed in OCA families

Parameters	Family 1 IV:1	Family 2: V:6	Family 3: IV:1	Family 4: IV:8	Family 5: IV:2	Family 6: IV:4	Family 7: IV:2	Family 8: IV:1
Gender	Male	Male	Male	Female	Male	Male	Male	Male
Age (years)	30	25	9	16	12	22	26	25
Caste	Khokhar	Chudhar JUtt	Arain	Malik Awan	Mughal	Gujjar	Somro	Turk
Region	Sahiwal	Chiniot	Gujranwala	Lahore	Lahore	Lahore	RYK	RYK
Hair colour	White	White	White	Golden	Golden Blond	White	White	Golden blond
Skin colour	Reddish white	Reddish white	Reddish white	white	Reddish white	Reddish white	Reddish white	Red
Skin rashes	On sunlight exposure	Present in childhood only. Thick dry skin	On sunlight exposure	On sunlight exposure	On sunlight exposure	On sunlight exposure	On sunlight exposure	No
Iris colour	Dark grey	Light grey	Dark grey	Light grey	Grey	Grey	Light Grey	Light Grey
Visual acuity (BCVA LogMar)								
Right eye	1.4	1.7	1	1	0.8	0.7	1.3	1
Left eye	1.4	1.7	0.9	0.9	0.8	0.7	1.1	1
Refractive error								
R	−3.5	−16	8.o/ + 1 × 95°	+ 4.5/ + 0.5 × 90°	+ 3.0/ + 1.5 × 80°	+ 6.5/ + 1.5 × 100°	−13/−2.0 × 30°	+ 3.5/ + 3 × 90°
L	−6	−16/ + 2 × 40°	+ 8/ + 2 × 95°	+ 4.5/ + 0.5 × 90°	+ 2.5/ + 4.5 × 100°	+ 6.5/ + 2.0 × 80°	−12	+ 2.5/ + 3 × 85°
Photophobia	Present	Present	Present	Present	Present	Present	Present	Present
Nystagmus	Present	Present	Present	Present	Present	Present	Present	Present
Foveal hypoplasia	Present	Present	Present	Present	Present	Present	Present	Present
Fundus	Albiniotic	Albiniotic	Albiniotic	Albiniotic	Albiniotic	Albiniotic	Albiniotic	Albiniotic

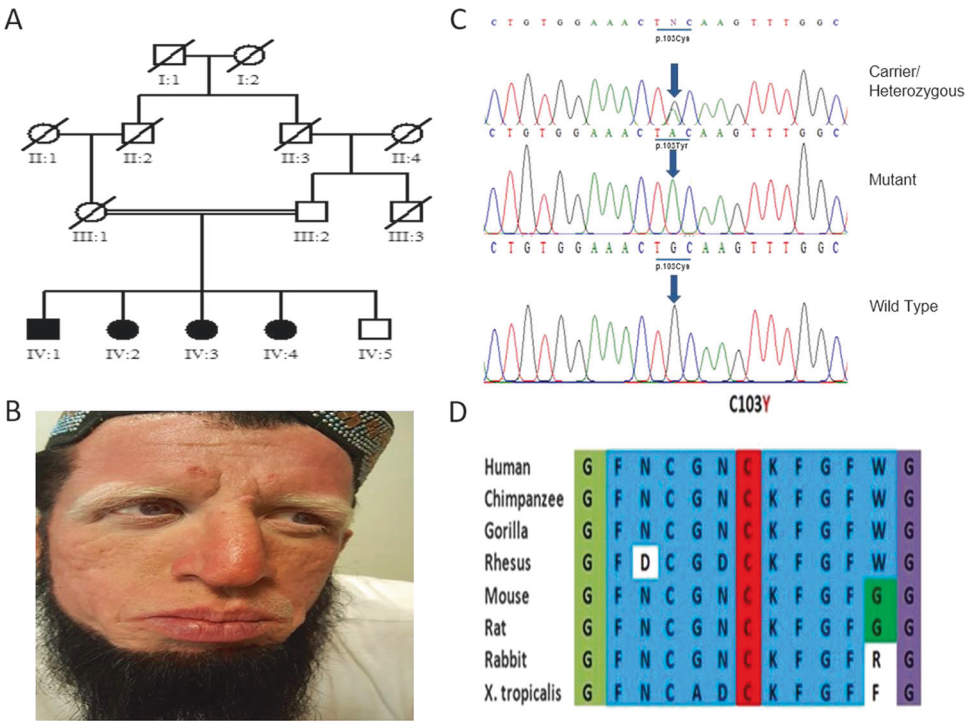

Fig. 1 **a** Family pedigree showing *TYR* c.308 G> A variant and **b** image of affected individuals. **c** co-segregation analysis of this family establish the *TYR* variant chr11:88911429 G >A [hg19]; c.308 G >A; p. Cys103Tyr. Parental samples were heterozygous, and unaffected siblings were either WT or heterozygous carriers and **d** amino acid alignment using ClustalW showing high conservation of the Cys103 residue across vertebrates

Table 2 Novel and reported TYR (NM_000372.4) variants identified in OCA families of this study

	Family 1 IV:1	Family 2 V:6	Family 3 IV:1	Family 4 IV:8	Family 5 IV:2	Family 6 IV:4	Family 7 IV:2	*Family 8 IV:1*
Nucleotide variant	c.308 G>A	c.1255 G>A	c.1255 G>A	c.1255 G>A	c.346 C>T	c.832 C>T	c.272 G>A	c.715 C>T
Protein variant	p. Cys 103Tyr	p.Gly419Arg	p.Gly419Arg	p.Gly419Arg	p.Arg116Ter	p.Arg278Ter	p.Cys91Tyr	p.Arg239Trp
Status	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous
Type of mutation	Missense	Missense	Missense	Missense	Nonsense	Nonsense	Missense	Missense
Previously reported	Novel (this study)	Yes [14]	Yes	Yes	Yes	Yes [15]	Yes	Yes
Sift	Damaging	Damaging	Damaging	Damaging	Damaging	Damaging	Damaging	Damaging
PolyPhen-2	Possibly damaging	Probably damaging	Probably damaging	Probably damaging	Probably damaging	Probably damaging	Probably damaging	Probably damaging
Homozygous in gnomAD	No	No	No	No	No	No	No	No
gnomAD MAF		0.00006155	0.00006155	0.00006155	0.00002887	0.000177		0.0000285

family 5, and g.89191214;NM_000372.4: c.832 C>T; p. Arg278Ter in family 6 (Fig. 2a–g). The *TYR* variant, c.308 G>A, identified in this study is not listed in homozygous form in online gnomAD genomic database (http://gnomad.broadinstitute.org), and the variant was also absent in age- and sex-matched 150 chromosomes of Pakistani ancestry.

Comparative homology and protein homology analysis

Clustal W alignment of tyrosinase proteins from various species showed the conservation of residues cysteine at position 103 among eight species. The conserved amino acids are shown with a dark grey background, and the non-conserved amino acids are shown with a white background (Fig. 1d). In case of wild-type structure, the Cys103 established the disulphide bond with nearby Cys112 (Fig. 3a, b). Due to the substitution of cystine with tyrosine at position 112 loss the disulphide bond (Fig. 3c). This structural disruption might influence the function of protein and thus the reason to cause OCA1. The RAMPAGE server generated the Ramachandran plot for wild-type displayed 90.3% of residues are in the most favoured region, while 8.6% of amino acids reside in the generously allowed

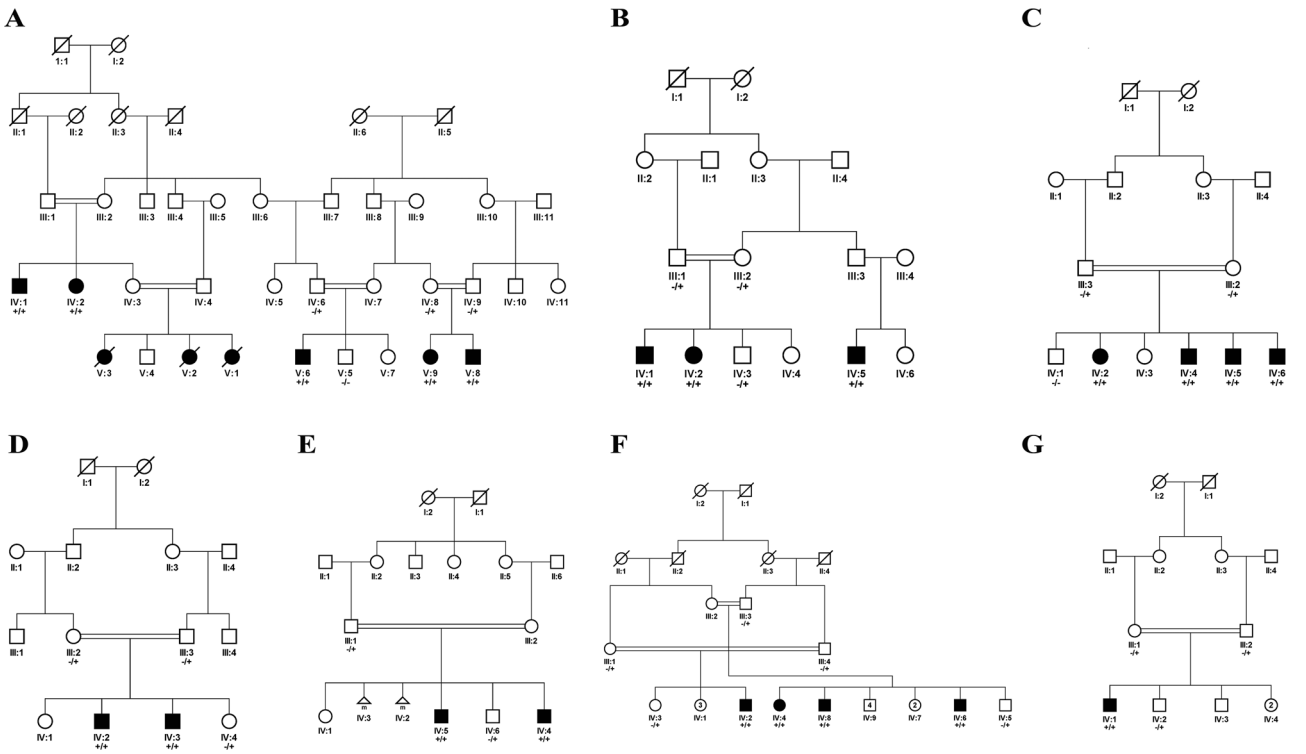

Fig. 2 Pedigrees of seven families with oculocutaneous albinism co-segregating for TYR (MIM# 606933) mutations. Presence or absence of the variant is indicated by a + or − sign, respectively. **a**–**c**. Pedigree representation of three families (family 2–4) with c.1255G>A mutation, **d**. pedigree with c.346C>T variant, **e**. family 6 with c.832C>T mutation, **f**. family 7 with c. 272G>A and **g**. family 8 with c. 715C>T mutations

region (Fig. 3d). According to the Ramachandran plot generated for the structure with missense mutation 91.3% of residues are found in the most favoured region, while 7.4% of amino acids reside in the generously allowed region (Fig. 3e).

Discussion

Our study highlights the importance of the genetic burden of *TYR* gene mutation to the prevalence of albinism families from Pakistan. Pakistanis have a rich anthropogenic background owing to successive waves of invasions and emigrations, although most groups did not intermingle with the original local population and practiced endogamy, giving rise to genetic isolates that persist today. Parental consanguinity has been documented to lead to an increased incidence of recessive genetic disorders [17]. In Pakistan, 62.7% of marriages are consanguineous, ~80% of which are between first cousins [18], and marriage within clans and high consanguinity in Pakistan are a common cause of increased incidences of recessive disorders, including OCA.

Tyrosinase, a copper containing oxidase, is the rate-limiting enzyme in the melanin biosynthesis pathway. It catalyses the first two reactions of the melanin synthesis pathway: formation of DOPA and then DOPA quinone subsequently. About one-third of OCA cases in Pakistan are due to mutation in *TYR* [7]. In this study, we identified one novel and five previously reported mutations in *TYR* associated with OCA in families from different regions of Pakistan. The novel *TYR* mutation (c.308 G>A; p. Cys103Tyr) was identified in a family from the Sahiwal district (Punjab Province) of Pakistan. Affected individuals in this family presented with typical features, including white hair (dyed black at the time of sampling), reddish white to white skin with sunburn scars on face and arms, nystagmus, severe photophobia (cannot go outside in day time) and de-pigmented transparent grey irides with decreased visual acuity. The variant is not listed in online genome databases indicating that this is likely to be very rare in this population. In silico pathogenic tools establish the deleterious effect of this novel mutation. Amino acid sequence alignment using the programme ClustalW 2.1 showed high conservation of the Cys103 residue in related vertebrates. The mutation p.Cys103Tyr lies in the highly conserved region of this enzyme tyrosinase, predicted to disturb the enzymatic function. Due to this mutation, the configurational orientation of TYR was reformed and lead to the rigid structure in nature.

This study also identified previously reported mutations in seven OCA families, which include c.272 G>A, c.346 C>T, c.715 C>T, c.832C> T and c.1255 G>A. To date, published data describe >200 OCA families from Pakistani populations that have undergone genetic analysis. Out of

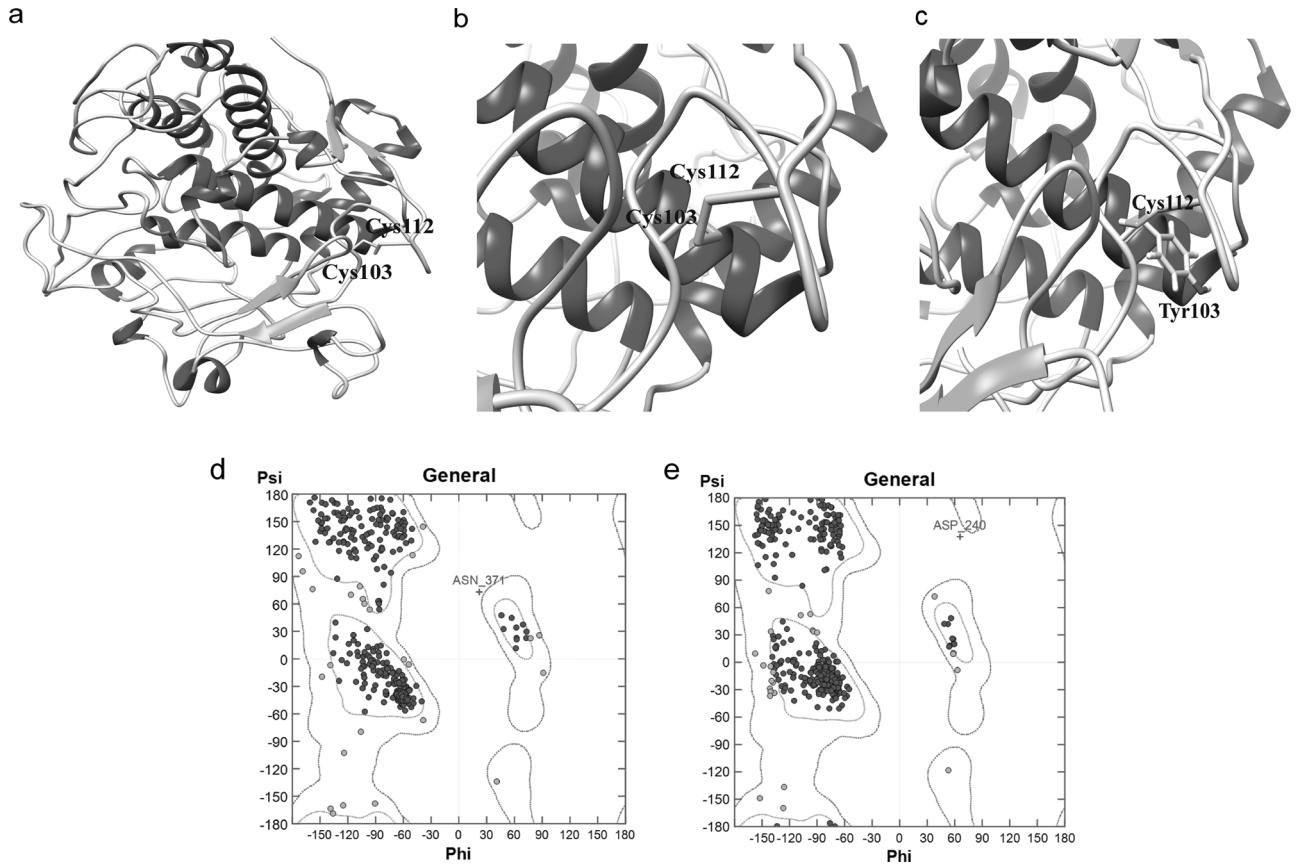

Fig. 3 **a** Three-dimensional structure of tyrosinase showing the position of residue Cys103 through the stick model, **b** Close-up view of normal, and **c** mutant-type tyrosinase, **d** the Ramachandran plot for the modelled wild-type AAAS protein presenting 90.3% of residues are found in the most favoured regions, 8.6% of residues are in the most allowed regions, and 1.1% of residues are found in the outlier regions, **e** the Ramachandran plot for the modelled mutant variant c.308 G>A, 91.3% of residues are found in the most favoured regions, 7.4% of residues are in the most allowed regions, and 1.3% of residues are found in the outlier regions

these families, 81 families (~40%) have been associated with genetic variations in the *TYR* gene (Supplementary Table 1). The mutations reported in this study have now been described with varying frequencies in Pakistani families, including very rare/unique mutations (Supplementary Table 1): c.346 C>T and c.715 C>T [19] in just 2 families [20], as well as more common mutations: c.832 C>T in 17 families [4, 7, 20–22] and c.1255 G>A in 16 families [4, 7, 19, 22]. While it is not possible to conclusively determine whether common *TYR* mutations represent mutation hotspots versus founder gene mutations without more detailed genetic analyses, evidence to support both mechanisms is present in the literature. Several of the *TYR* mutations described in our study are commonly associated with OCA in Pakistan, and likely represent both regional founder as well as recurrent (hotspot) mutations. For example, the c.832 C> T; p.Arg278Ter c.1255 G>A; p. Gly419Arg variants in *TYR* identified in families 2, 3, 4 and 6, account for 21%, and 19.75% of all families with known *TYR* variants in Pakistan, respectively [4, 7]. While the frequency of the c.832 C>T variant is higher in the Pakistani population, the mutation has also been identified in many other populations worldwide, indicating that it has likely occurred recurrently, although an increased frequency of the variant in some areas may indicate it has also accumulated as a regional founder mutation (Guayanan 12.5%; Jewish 2.6%; Japanese 22.2%; European 2.5%; Mexican 0.83%; Indian 0.83% and 4.34%; Eastern Indian 8.3%; Syrian 0.83%; Chinese 18.75%) [22]. Consistent with this, the variant is listed in online genome databases, occurring (in gnomAD) more frequently in the South Asian population (allele frequency = 0.0013) than in other regions (for example, allele frequencies in African and European populations are 0.0001249 and 0.00002372, respectively).

The current study identified the c.1255 G>A variant as the most common allele of *TYR* present in the Punjabi ethnic group. Three families from this study, and five families from previous studies with c.1255 G>A, originate from the same geographical area (Punjab) and the same ethnic group (Punjabi language group). This variant has also been documented in other Pakistani ethnicities, including Sindhi, Kashmiri and Balochi backgrounds, and together accounts for 19.75%, of all families from Pakistan known to have *TYR* mutation (Supplementary Table 1). The high

frequency of the variant in the Pakistani population is similar to the frequency in the Indian population (Indian 20%; South Indian 16.6%), although notably this mutation occurs much less commonly in the white Caucasian population (0.83%; of families identified) [23]. Together this may indicate that the c.1255 G>A variant may represent a founder mutation which has accumulated in the Indo–Pakistan subcontinent region, and consistent with this the variant occurs most commonly in South Asian populations in online databases (GnomAD South Asian population is 0.0003899, as compared with European frequency of 0.00003967). Consistent with this, the variant has not as yet been reported in other populations outside of these regions.

We also determined that the c.230 G>A variant has been reported in Japanese, Korean, Chinese and European populations [12, 23–27]. While this may indicate that the variant has occurred recurrently, it has only been reported in communities in the Pakistani Kashmir region [19], and so while occurring recurrently may again represent a regional founder mutation of importance in this area of Pakistan. Similarly, c.62 C>T; p.Pro21Leu, c.103 T>C; p.Cys35Arg, c.1231 T>C; p.Tyr411His [24], c.240 G>C; p.Trp80Cys [3], c.308 G>A; p.Cys103Tyr (associated with severe photophobia, thisstudy) and c.593 T>C; p.Ile198Thr [20] have only been reported in specific Pakistani communities, and not outside of Pakistan. This likely indicates that each variant may also represent regional founder variants. Conversely, variants c.346 C>T; p.Arg116Ter [19], c.649 C>T; p.Arg217Trp [7, 23], c.896 G>A; p.Arg299His [7, 22] and splice site variant c.1037–7 T>A [7, 19–22] have all been reported in different ethnic groups from Pakistan, as well as from other countries. These (and several other) variants may therefore represent *TYR* mutations recurring worldwide.

Overall, the prevalence of *TYR* alleles in Pakistan (37%) is similar to frequencies in families from Europe (46%), although largely different to studies in different populations. For instance, *TYR* and *OCA2* variants account for 70 and 10% of OCA in a study of 127 patients from a Chinese population, with a notable regional variation [23]. In India, a study of 82 OCA patients revealed ~60% prevalence of *TYR* mutation [28]. Similarly, in the US, Europe, Italy, Japan and Korea, the alleles of *TYR* are the most common cause of OCA [25]. In contrast, variants in *OCA2* account for ~80% of the OCA cases in an African population [29, 30].

In conclusion, it is clear that the clinical presentation of OCA is caused by a wide variety of mutations in multiple genes. Thus for economic and geographical reasons, it is not feasible to routinely perform Sanger sequencing of all the known OCA genes to detect underlying genetic defects. Together our data and studies highlight the importance and expand current knowledge of the molecular spectrum and specific frequencies of *TYR* gene mutation in OCA in Pakistani communities, indicating that a number of TYR gene mutations likely involve founder gene mutations. Due to the frequency of mutations in the *TYR* gene which comprises only five coding exons, targeted sequencing of *TYR* may be appropriate (where broader sequencing panels are prohibitively expensive), to provide valuable information to aid the diagnosis and counselling of affected individuals and family members throughout Pakistan.

Summary

What was known before

- Non-syndromic oculocutaneous albinism (nsOCA) is an autosomal recessive disorder characterised by the partial or complete loss of pigmentation in the skin, hair and ocular tissues. Non-syndromic OCA is further divided into seven subtypes (OCA1–7), on the basis of genetic testing. About 300 mutations in *TYR* has been identified.

What this study adds

- A novel c.308 G>A; p.Cys103Tyr mutation of *TYR* can cause Oculocutaneous albinism. Protein modelling predicted the change in configuration of the protein structure and function. An update on the review of *TYR* mutations for the founder effect in different ethnic groups of Pakistani population.

Data availability

Data supporting the conclusions of this article are included within the article.

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Author contributions MS, SA, MIU and SH provided samples and clinical details. GVH, MS, ID, JES, AN and MAS performed genetic studies, and analysed data along with SL and ID. SM, JES, AHC, ELB and MIU designed and conceived studies. SL aided compilation and analysis of clinical information, and edited the paper with AHC, ELB, JES and SM.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Consent for publication Written consent was obtained from all patients or their relatives for publication.

Ethics approval and consent to participate This study was approved by the ethical approval committee institutional review board of the University of Health Sciences, Lahore, Pakistan.

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