

Mild form of oculocutaneous albinism type 1: phenotypic analysis of compound heterozygous patients with the R402Q variant of the *TYR* gene

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ABSTRACT

Aim Oculocutaneous albinism type 1 (OCA1) is due to *TYR* mutations. c.1205G>A/p.Arg402Gln (R402Q) is a thermosensitive variant of the *TYR* gene that has been reported to be responsible for mild forms of OCA1. The aim of our study was to define the phenotype associated with this variant.

Methods In our retrospective series, among 268 patients diagnosed with OCA1, 122 (45.5%) harboured one pathogenic variant of *TYR*, and the R402Q variant ensured to be in trans by segregation analysis in 69 patients (25.7%), constituting the 'R402Q-OCA1' group. 146 patients harboured two pathogenic variants of the *TYR* gene other than R402Q. Clinical records were available for 119 of them, constituting the 'Classical-OCA1' group.

Results Most R402Q-OCA1 patients presented with white or yellow-white hair at birth (71.43%), blond hair later (46.97%), a light phototype but with residual pigmentation (69.64%), and blue eyes (76.56%). Their pigmentation was significantly higher than in the classical-OCA1 group. All patients from the R402Q-OCA1 group presented with ocular features of albinism. However the prevalence of photophobia (78.13%) and iris transillumination (83.87%) and the severity scores of iris transillumination, retinal hypopigmentation and foveal hypoplasia were lower in the R402Q-OCA1 group. Visual acuity was higher in the R402Q-OCA1 group (0.38±0.21 logarithm of the minimum angle of resolution vs 0.76±0.24). Investigations concerning a possible additive effect of the c.575C>A/p.Ser192 (S192Y) variant of *TYR* in cis with R402Q, suggested by others, showed no significant impact on the phenotype.

Conclusion The R402Q variant leads to variable but generally mild forms of albinism whose less typical presentation may lead to underdiagnosis.

INTRODUCTION

Albinism is a heterogeneous group of genetic abnormalities that presents with various degrees of congenital hypopigmentation of the skin, hair and eyes, and with ophthalmological disorders that include decreased visual acuity (VA), refractive errors, strabismus, photophobia, nystagmus, hypopigmentation and iris transillumination, retinal hypopigmentation, foveal hypoplasia, anomalies of

the optic nerve head, and an excess of optic nerve fibre decussation at the chiasm. The common pathophysiology consists in an absent or reduced melanin synthesis.¹⁻³

Albinism is a genetically heterogeneous condition with 19 genes identified to date.^{4,5}

Oculocutaneous albinism type 1 (OCA1) is the most common subtype in the Caucasian population, in which it accounts for more than 50% of all cases.^{5,6} OCA1 is inherited in an autosomal recessive manner and is clinically heterogeneous, ranging from the most severe form associated with no melanin synthesis, to a phenotype associated with residual melanin synthesis.

The c.1205G>A/p.Arg402Gln variant (hereafter called R402Q) is a common variant of the *TYR* gene with a worldwide prevalence of 17.7%, particularly frequent in Caucasian populations (allele frequency of 26.48% in Europe⁷). R402Q is widely regarded as a neutral polymorphism rather than as a pathogenic variant since it does not lead to albinism in the homozygous state. Indeed its prevalence in the homozygous state is about 7.01% (0.2648²) in the general European population.⁷ However its role in mild forms of OCA1 has been suspected since 1991.⁸⁻¹²

The R402Q variant encodes a thermosensitive tyrosinase, with only 25% of normal catalytic activity at a body temperature of 37°C due to its retention in the endoplasmic reticulum, whereas it is released at a temperature of 31°C–32°C.^{13,14}

c.575C>A/p.Ser192 (S192Y) is another common *TYR* variant.⁷ A synergistic effect of S192Y and R402Q on the reduction of tyrosinase enzymatic activity has been described.^{14,15}

A phenotypic analysis of a large series of compound heterozygotes with one deleterious *TYR* variant and the R402Q variant has not been reported so far. This was the main aim of our study. The possible additive effect of the S192Y variants was also investigated.

SUBJECTS AND METHODS

Subjects

Patients originated from all parts of the world but were mainly from France.



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Patients with a clinical diagnosis of albinism who were compound heterozygotes for the R402Q variant and another pathogenic variant of the *TYR* gene in trans constituted what is called hereafter the R402Q-OCA1 group. Patients with a clinical diagnosis of albinism and who had two pathogenic variants of the *TYR* gene other than R402Q constituted the control group, called hereafter the classical-OCA1 group.

Genetic analysis and their use for genetic research were performed under conditions established by French law. Informed consent was obtained from all participants or their parents in the case of minors.

Molecular genetic analysis

DNA was extracted from peripheral blood lymphocytes.

Patients' genotypes were established by Sanger sequencing (*TYR*, *OCA2*, *TYRP1*, *SLC45A2*, *GPR143*, *HPS 1*) (before 2013) or by next-generation sequencing (NGS) using a panel of genes involved in syndromic and non-syndromic albinism (*TYR*, *OCA2*, *TYRP1*, *SLC45A2*, *SLC24A5*, *C10ORF11*, *GPR143*, *HPS 1 to 10*, *LYST*, *SLC38A8*) (after 2013) using the Ion Torrent technology with an AmpliSeq panel (Thermo Scientific-Life Technologies) that covered all exons of the targeted genes including 25 bp of flanking intronic sequences.

The NGS coverage was 97.43% of the targeted genes, with an average depth of 300. Missed bases were covered by Sanger sequencing. Gene rearrangements (deletions, duplications) in all 19 albinism genes were searched for by high-resolution array-comparative genomic hybridisation and confirmed by quantitative multiplex fluorescent PCR.^{5–16} Sequences were run on a Personal Genome Machine (Thermo Scientific-Life Technologies). Experimental conditions are available from the authors on request. Pathogenicity of single nucleotide variants was evaluated using the bioinformatics tools Cartagenia (Agilent Technologies) and Alamut (Interactive BioSoftware) based on the criteria including allele frequency, conservation, pathogenicity prediction algorithms and effect on splicing, as described in Lasseaux *et al.*⁵

The parents of all patients were analysed to allow segregation analysis of the variants.

Phenotypic data

Demographic and phenotypic data included age at last description, sex, ethnicity, hair colour at birth and evolution, skin colour and ability to tan, presence of pigmented nevi, best-corrected distance visual acuity, refraction, presence of strabismus, nystagmus, photophobia, iris transillumination and its intensity, retinal hypopigmentation and its intensity, foveal hypoplasia and its severity, and presence of a characteristic crossed asymmetry on visual evoked potentials (VEP).

Clinical data were collected from a standardised questionnaire filled in by practitioners at the time of genetic test prescription and/or from consultation reports including the most recent ophthalmological descriptions. Portrait photographs, iris photographs, retinophotography and optical coherence tomography (OCT) images were collected when available.

Phototype description was based on the Fitzpatrick Classification Scale,¹⁷ but the skin, hair and eye pigmentations were analysed independently.

Hair colour was analysed at birth and at last description in patients aged 12 months or more to take into account possible changes within early childhood.

VA was tested using age-appropriate methods chosen by clinicians and converted into logarithm of the minimum angle of

resolution (logMAR) for statistical analyses. The study focused on the acuity of the better eye and on patients aged 5 years or more (since VA is immature and its measurement unreliable in very young children¹⁸).

Refraction data corresponded to autorefractor measurements or to correction worn in glasses. The cycloplegic refraction was preferentially selected when available. Refractive errors were considered as significant with myopia ≤ -0.75 D or hypermetropia ≥ 1 D and astigmatism ≥ 1 D.

A patient was assigned a diagnosis of nystagmus if a nystagmus had been noticed at any time of his/her medical history, even if it had disappeared later.

Iris transillumination and retinal hypopigmentation were analysed from clinical descriptions or photographs and classified according to simplified versions of, respectively, Summer *et al.*'s grading scale¹⁹ and Käsman-Kellner *et al.*'s grading scale,²⁰ presented in figure 1.

Foveal hypoplasia analysis relied on macular OCT slides. A majority was obtained by spectral domain-OCT (SD-OCT), but some by time domain-OCT. Our grading scale, described in figure 1, was inspired by Thomas *et al.*'s²¹ grading scale but does not take into account outer nuclear layer widening, which was considered too difficult to appreciate on many OCT slides whose resolution was not sufficient, possibly because of nystagmus or of the use of time domain-OCT instead of SD-OCT.²¹

Statistical analysis

The prevalence of most phenotypical features was compared between R402Q-OCA1 and classical-OCA1 patients using χ^2 test. A Fisher's exact test was used to compare the prevalence of nystagmus and retinal hypopigmentation due to the small sample size for these features. The mean VAs were compared using a Student's t-test. Grading scale scores were considered as ordinal data so that a Mann-Whitney U test was used for comparisons. The correlation between VA and the severity of foveal hypoplasia was evaluated using Pearson's correlation test. Among R402Q-OCA1 patients, comparison between subgroups relied on Student's t-tests to compare mean VAs and Fisher's exact test for categorical data. Values of $p < 0.05$ were considered significant.

The correlation between VA and the severity of foveal hypoplasia was evaluated using Pearson's correlation test.

RESULTS

Genetic study

In our series of patients, 268 patients were diagnosed with OCA1. One hundred and twenty-two (45.5%) harboured one pathogenic variant of *TYR* and the R402Q variant. Segregation analysis allowed to assure that the R402Q variant and the other variant were in trans in 69 patients (25.7%), who were therefore included in the 'R402Q-OCA1' group. One hundred and forty-six patients harboured two pathogenic variants of the *TYR* gene, other than R402Q. No clinical report was available for 27 patients so that only 119 could be included in the phenotypic analysis in the 'classical-OCA1' group.

Table 1 presents the pathogenic variants found in R402Q-OCA1 patients and in classical-OCA1 patients.

Phenotypic study

Figure 2 illustrates the wide spectrum of possible phenotypes in R402Q-OCA1 patients. It can be noted that the level of hypopigmentation, with regard to the skin, hair and eyes, is

A) Grade of iris transillumination		Clinical description
Grade 1		Marked amount of iris pigment and a minimal punctuated transillumination
Grade 2		Moderate amount of iris pigment and a diffuse punctuated iris transillumination
Grade 3		Minimal amount or absence of iris pigment and almost complete or complete transillumination

B) Grade of retinal hypopigmentation		Clinical description
Grade 1		Only peripheral hypopigmentation (restricted to outside vascular arcs)
Grade 2		Both peripheral and central hypopigmentation (outside and inside vascular arcs)

C) Grade of foveal hypoplasia	Foveal structural features detectable using optical coherence tomography	Illustrations
Grade 0 = Normal structures of the fovea	RNFL = retinal nerve fiber layer; GCL = ganglion cell layer; IPL = inner plexiform layer; INL = inner nuclear layer; OPL = outer plexiform layer; ONL = outer nuclear layer; ELM = external limiting membrane; PIS and POS = photoreceptors inner segments and photoreceptors outer segments; RPE = retinal pigment epithelium.	
Grade 1	Absence of a complete extrusion of the inner retinal layers and OPL, leading to an incomplete foveal pit, still surrounded by two more convex areas corresponding to a local juxtafoveolar thickening of the inner retinal layers.	
Grade 2	A discreet pit, allows identifying the location of the fovea but it is shallow, with no juxtafoveolar thickening of the inner retinal layers.	
Grade 3	No pit at all but remaining central outer nuclear layer widening at the fovea.	
Grade 4	No widening of the outer nuclear layer at the fovea. The fovea cannot be distinguished from the rest of the retina.	

Figure 1 (A) Iris transillumination severity scale. (B) Retinal hypopigmentation severity scale. (C) Illustration of the normal foveal structural features detectable using optical coherence tomography and foveal hypoplasia severity scale according to those structural features detectable using optical coherence tomography.

highly variable, ranging from noticeable hypopigmentation to apparently 'normal' pigmentation.

Table 2 presents the comparative description of R402Q-OCA1 and classical-OCA1 patients.

Skin, hair and eye colours, the presence and score of iris transillumination, and the level of retinal hypopigmentation differed significantly between the two groups, with a more pigmented phenotype in R402Q-OCA1 patients. VA was significantly higher and photophobia less frequent in R402Q-OCA1 patients. All patients with an available macular OCT imaging had foveal hypoplasia, whose severity was however significantly lower in the R402Q-OCA1 group. All patients presented with refractive errors, hyperopia and astigmatism being the most frequent. The prevalence of nystagmus and retinal hypopigmentation was high but did not significantly differ between the two groups.

Figure 3 illustrates the various morphological aspects of the macula revealed by macular OCT imaging in R402Q-OCA1 patients.

A statistically significant correlation between VA and the grade of foveal hypoplasia was found among R402Q-OCA1 patients. VA appears to decrease with the rise of the severity grade of foveal hypoplasia ($r=0.577$ (95% CI 0.260 to 0.782), $p=0.001$).

Assuming that the type of mutation in trans with the R402Q variant may impact the phenotype, we compared two groups of R402Q-OCA1 patients, those with missense variants ($n=50$) and those with supposedly more deleterious variants (ie, nonsense, frameshift, splicing variants, intragenic deletions) ($n=19$) of the TYR gene, in trans of R402Q. Patients with a missense variant were found to have a higher mean VA (0.35 ± 0.19 logMAR (about 20/45 Snellen) ($n=30$) vs 0.46 ± 0.21 logMAR (about

Table 1 Genotypes of all patients with two mutations identified in the *TYR* gene

Kind of mutation	<i>TYR</i> mutation sequence name	Protein name	Allele (n)
Mutations associated with the c.1205G>A/p.Arg402Gln (R402Q) variant among R402Q-OCA1 patients (69 patients, 69 alleles)			
Missense (n=88, 72.1%)	c.62C>T	p.Pro21Leu	2
	c.71G>A	p.Cys24Tyr	1
	c.107G>A	p.Cys36Tyr	1
	c.140G>A	p.Gly47Asp	2
	c.230G>A	p.Arg77Gln	1
	c.242C>T	p.Pro81Leu	2
	c.290G>T	p.Gly97Val	1
	c.415A>C	p.Thr139Pro	1
	c.595G>T	p.Asp199Tyr	2
	c.649C>T	p.Arg217Trp	2
	c.650G>A	p.Arg217Gln	1
	c.715C>T	p.Arg239Trp	2
	c.823G>T	p.Val275Phe	2
	c.1111A>G	p.Asn371Asp	1
	c.1118C>A	p.Thr373Lys	20
	c.1138T>C	p.Ser380Pro	1
	c.1146C>A	p.Asn382Lys	3
	c.1306G>T	p.Gly436Cys	1
	c.1315T>G	p.Phe439Val	1
	c.1336G>A	p.Gly446Ser	1
c.1454G>A	p.Gly485Gln	1	
c.1469C>A	p.Ala490Asp	1	
Nonsense (n=11, 9%)	c.239G>A	p.Trp80*	1
	c.655G>T	p.Glu219*	1
	c.732_733delTG	p.Cys244*	1
	c.1204C>T	p.Arg402*	1
	c.1392_1393insT	p.Lys465*	2
Frameshift (n=8, 6.6%)	c.216delA	p.Val74Trpfs*46	1
	c.1386_1387insAA	p.Tyr463Asnfs*23	3
	c.1467dupT	p.Ala490Cysfs*20	3
Splice site mutation (n=13, 10.7%)	c.1A>G	p.?	3
	c.1037-2A>G	p.?	1
	c.1037-7T>A	p.?	1
Deletion of exons (n=2, 1.6%)	Deletion exon 2	P.?	1
Mutations found among classical OCA1 patients (146 patients, 292 alleles): part 1			
Missense (n=167, 57.2%)	c.56 A>G	p.His 19 Arg	1
	c.61C>T	p.Pro21Ser	5
	c.71G>C	p.Cys24Ser	1
	c.98 A>C	p.Lys 33 Thr	3
	c.107G>A	p.Cys36Tyr	1
	c.124G>A	p.Asp42Asn	1
	c.136T>C	p.Cys46Arg	1
	c.140G>A	p.Gly47Asp	11
	c.164G>A	p.Cys55Tyr	1
	c.229C>T	p.Arg77Trp	5
	c.230G>A	p.Arg77Gln	4
	c.241C>T	p.Pro81Ser	1
	c.242C>T	p.Pro81Leu	4

Continued

Table 1 Continued

Kind of mutation	<i>TYR</i> mutation sequence name	Protein name	Allele (n)
	c.272G>A	p.Cys91Tyr	1
	c.325G>A	p.Gly109Arg	1
	c.451A>T	p.Ile151Phe	1
	c.547G>T	p.Val183Leu	1
	c.613C>A	p.Pro205Thr	1
	c.616G>A	p.Ala206Thr	5
	c.617C>T	p.Ala206Val	4
	c.635G>A	p.Arg212Lys	2
	c.649C>T	p.Arg217Trp	5
	c.650G>A	p.Arg217Gln	3
	c.679G>A	p.Gly227Arg	1
	c.710A>C	p.Asp237Ala	1
	c.715C>T	p.Arg239Trp	2
	c.755T>G	p.Met252Arg	2
	c.816G>C	p.Trp272Cys	2
	c.823G>T	p.Val275Phe	8
	c.866 G>C	p.Cys289Ser	1
	c.895C>T	p.Arg299Cys	1
	c.896 G>A	p.Arg 299 His	3
	c.982G>C	p.Glu328Gln	2
	c.996 G>A	p.Met332Ile	1
	c.1012T>G	p.Phe338Val	2
	c.1036G>A	p.Gly346Arg	1
	c.1037 G>A	p.Gly346Glu	1
	c.1058 G>A	p.Gly353Glu	1
	c.1064C>T	p.Ala355Val	3
	c.1111A>T	p.Asn371Tyr	6
	c.1118C>A	p.Thr373Lys	29
	c.1146C>A	p.Asn382Lys	6
	c.1147G>A	p.Asp383Asn	3
	c.1171_1172delinsTT	p.Ala391Leu	2
	c.1200G>T	p.Trp400Cys	1
	c.1217 C>T	p.Pro406Leu	6
	c.1255G>A	p.Gly419Arg	1
	c.1264C>T	p.Arg422Trp	1
	c.1265G>A	p.Arg422Gln	2
	c.1336G>A	p.Gly446Ser	8
	c.1342G>A	p.Asp448Asn	5
	c.1432C>T	p.Leu478Phe	1
	c.1469C>A	p.Ala490Asp	1
Nonsense (n=37, 12.7%)	c.255T>A	p.Tyr85*	1
	c.273C>A	p.Cys91*	1
	c.346C>T	p.Arg116*	4
	c.488C>G	p.Ser163*	1
	c.571G>T	p.Gly191*	2
	c.732_733delGT	p.Cys244*	6
	c.741C>A	p.Cys247*	2
	c.753C>A	p.Tyr251*	1
	c.815G>A	p.Trp272*	2
	c.832C>T	p.Arg 278*	8
	c.1204C>T	p.Arg402*	4
	c.1392dup	p.Lys465*	5
	Mutations found among classical-OCA1 patients (146 patients, 292 alleles): part 2		

Continued

Table 1 Continued

Kind of mutation	TYR mutation sequence name	Protein name	Allele (n)
Frameshift (n=26, 8.9%)	c.286 dupA	p.Met96Asnfs*73	1
	c.326del	p.Gly109Aspfs*11	1
	c.334delT	p.Cys112Alafs*8	1
	c.338_339del	p.Thr113Argfs*55	1
	c.505_507delGAC	p.Asp169del	1
	c.525_527dup	p.Phe176dup	1
	c.567_571delTGGGG	p.Gly190Ilefs*2	1
	c.573delA	p.Ser192Leufs*34	4
	c.649delC	p.Arg217Glyfs*9	1
	c.773_774delCA	p.Thr258Lysfs*3	1
	c.841delG	p.Glu281Serfs*38	1
	c.911_914del	p.His304Profs*14	1
	c.1164delT	p.His389Thrfs*96	1
	c.1177delG	p.Val393fs*92	1
	c.1386_1387insAA	p.Tyr463Asnfs*23	2
	c.1467dup	p.Ala490Cysfs*20	6
	c.1472dupT	p.Leu492Alafs*18	1
Splice site mutation (n=57, 19.5%)	c.-111_-109dup	p.?	1
	c.1037-1G>A	p.?	1
	c.1037-7T>A	p.?	25
	c.1184+1G>A	p.?	2
	c.1185-1 G>T	p.?	6
	c.1366+1 G>A	p.?	1
	c.1A>G	p.?	16
	c.2T>C	p.?	3
	c.820-1_820delinsTG	p.?	1
	c.820-3delC	p.?	1
Deletion of exon or of the gene (n=5, 1.7%)	Deletion exon 1	p.?	1
	Deletion exon 2	p.?	1
	Deletion 3-4-5	p.?	1
	Deletion TYR	p.?	1
	Deletion 11q14.3	p.?	1

20/55 Snellen) (n=11)). However, this difference was not significant ($p=0.104$).

Investigation of a possible additive effect of the S192Y variant

Among the 69 patients of the R402Q-OCA1 group, 52 were either heterozygous or homozygous for the S192Y variant, a common TYR variant. For 31 of those, segregation analysis ensured that the S192Y variant was in cis with the R402Q variant (p.[S192Y;R402Q] haplotype) and in trans with the classical pathogenic variant. Seventeen patients did not harbour the S192Y variant.

The phenotypes of the 31 patients carrying p.[S192Y;R402Q] were compared with those of the 17 patients who did not carry the S192Y variant. No significant differences were found regarding the phototype and VA. These data therefore do not seem to confirm the additive effect of the S192Y and R402Q alleles on the phenotype observed by others.¹⁶

It should be noted that other variants may be missed because they located in the introns or in regulatory flanking sequences, which are not routinely sequenced in clinical laboratories. As a pilot study, however, we sequenced the entirety of the TYR gene in six patients heterozygote for a pathogenic TYR variant, but did not identify any additional pathogenic variant.

DISCUSSION

This study is shedding light on the specific phenotype observed in R402Q-OCA1 patients, which represents a significant part of OCA1 patients (45.5% in our study).

Clinical prognosis

The R402Q-OCA1 phenotype significantly differs from the classical-OCA1 phenotype. The prognosis of the disease, chiefly determined by ophthalmological impairments, appears on average better in the R402Q-OCA1 group.

R402Q-OCA1 patients had a mean VA of 0.38 logMAR (about 20/45 on Snellen chart), significantly higher than classical-OCA1 patients (0.76 logMAR (20/100–20/125 on Snellen) $p<0.0001$). Of them 32.56% had a VA $\geq 20/40$, which is the threshold for driving, whereas only 4.55% reached this threshold in the classical-OCA1 group. All R402Q-OCA1 patients aged 5 years or more had a VA higher than 20/200, which is, since 2006, the definition of blindness according to the International Statistical Classification of Diseases, whereas only three had VA $>20/200$ and nine had VA=20/200 in the classical-OCA1 group.

Photophobia was also less frequent in R402Q-OCA1 patients. Nystagmus had a high prevalence in both groups. It was slightly less frequent in the R402Q-OCA1 group, but this difference was not significant. Nevertheless, the nystagmus was probably less intense in the latter group according to some descriptions evoking 'subtle' nystagmus, 'micronystagmus' or a decline or disappearance with time in some patients.

The frequency of refractive errors was high in both groups. Astigmatism was the most frequent refractive error and hyperopia more frequent than myopia. These results are consistent with those of previous studies.²²

The lower frequency of strabismus in classical-OCA1 patients may result from an underestimation due to the more frequent and more intense nystagmus in this group, making the evaluation of strabismus more difficult.

The severity of foveal hypoplasia was significantly lower in the R402Q-OCA1 group. Its evaluation with OCT has a prognostic interest since the severity of foveal hypoplasia is correlated with VA, as demonstrated in the present study as well as in previous ones.^{21 23 24}

Risk of underdiagnosis

If the prognosis seems better, the diagnosis of albinism may be more difficult in the R402Q-OCA1 group with a risk of underdiagnosis. Diagnostic signs are sometimes more subtle, or even missing, especially in Caucasians, with a fair phototype.

Skin and hair colours are often fair at birth in R402Q-OCA1 patients, but less systematically as in classical-OCA1 patients, and generally tend to darken over the years. Eye colour may be green or brown. Iris transillumination may be missing and when present is less severe and notably seldom total (22.58% grade 3 vs 96.67% in classical-OCA1 patients). Nystagmus is slightly less frequent in the R402Q-OCA1 group (89.06% vs 95.19%). Retinal hypopigmentation may be missing or very mild (only 70.45% grade 2 vs 94.44%).

This explains why the diagnosis of albinism was made belatedly in adolescence or adulthood in some R402Q-OCA1 patients. Ophthalmologists have a predominant role in the diagnosis of this specific form of albinism, whereas in more severe forms the diagnosis is generally made earlier by the paediatrician or dermatologist.

The foveal hypoplasia documented by OCT since the early 2000s²⁵ appears to be very sensitive for the diagnosis of albinism



Figure 2 Representative sample of the hair, iris and retinal pigmentation phenotypes in oculocutaneous type 1 patients, compound heterozygous with one classical Tyr mutation and the c.1205G>A/p.Arg402Gln (R402Q) variant. The first row presents the variety of hair colour in this population with different shades of blond (patient c.[649C>T];[1205G>A]) (A), ginger (patient c.[1386_1387insAA];[1205G>A]) (B) and brown (patient c.[649C>T];[1205G>A]) (C). The second row presents the variety of iris colour from blue (patient c.[1306G>T];[1205G>A]) (D) and (patient c.[823G>T];[1205G>A]) (E) to green or brown (patient c.[649C>T];[1205G>A]) (F), and iris transillumination severity ranging from total or almost total transillumination (grade 3 in our classification) (D) to punctate transillumination (grade 1) (E) and to no transillumination at all (grade 0) (F). The third row presents the variable severity of retinal hypopigmentation which may extend to the whole retina including the macular zone (patient c.[649C>T];[1205G>A]) (G) or sparing partially the macular region (patient c.[655G>T];[1205G>A]) (H) (combined into grade 2 in our classification), which also may be restricted to outside vascular arcs (grade 1) (patient c.[823G>T];[1205G>A]) (I) and (patient c.[649C>T];[1205G>A]) (J) or may be absent.

when suspected, notably in patients with congenital nystagmus, as reported previously,^{26–28} with handheld models being useful when examining young children.²⁸ The foveal hypoplasia is nevertheless not specific of albinism and may be observed in other ophthalmological disorders such as aniridia due to PAX6 mutations, or even be idiopathic.^{27,28} Recent devices with OCT-angiography also show the reduced or absent foveal avascular zone accompanying foveal hypoplasia,²⁹ as shown in figure 3.

Penetrance studies

Fourteen parents of patients from our series had a genotype associating the R402Q variant and another pathogenic variant of the TYR gene. For eight of them the segregation analysis assured that the R402Q and the other pathogenic variant were in trans. As in Oetting *et al*'s study,³⁰ none of them was initially reported to have albinism, but no complete clinical records were available initially.

We obtained the clinical description for one mother whose diagnosis of albinism had never been identified before but was confirmed both clinically and genetically after her daughters were diagnosed. She had an R402Q-OCA1 genotype (c.[1386_1387insAA];[1205G>A]), and presented with fair phototype, yellow-blond hair, blue transilluminable iris, nystagmus, photophobia, divergent strabismus, VA=20/40, grade 2 retinal hypopigmentation, grade 3 foveal hypoplasia and crossed asymmetry on VEP recording. The hypothesis of similar cases of undiagnosed

parents should not be excluded in the absence of a complete clinical examination.

Two patients' mothers (segregation analysis uncompleted) underwent clinical examination and did not reach a diagnosis of albinism. They nevertheless both reported difficulties to tan and one presented with a very mild iris transillumination. These cases suggest a very low expressivity of the R402Q variant and an incomplete penetrance.

Limitations

We acknowledge that there are limitations in our study.

First, there is a high level of missing data partially explained by the retrospective study design. OCT slides were available for only 50 out of 188 patients, which could be explained by the recentness of this tool and by its difficult implementation in children and patients with a marked nystagmus.

VEP recordings were often missing, possibly because they were not performed. The typical crossed asymmetry^{19,31} was less frequent than non-specific anomalies which may arise from poor VA, nystagmus or incorrect VEP implementation.³¹

The collection of data from multiple practitioners was responsible for heterogeneity, which we tried to compensate by simplifying the grading scales and restricting foveal hypoplasia grading to patients with OCT slides available.

Binocular acuity would have been more pertinent in patients with nystagmus but was often missing.

Table 2 Demographic and phenotypic characteristics of patients with oculocutaneous albinism due to *TYR* mutations (OCA1)

	Classical-OCA1 (N=119) n (%)	R402Q-OCA1 (N=69) n (%)	P values
Age at the last description available	<1 month to 81 years: <1 year: n=30 1–4 years: n=23 ≥5 years: n=66	<1 month to 36 years: <1 year: n=11 1–4 years: n=12 ≥5 years: n=46	
Ethnicity	n=109 4=Maghreb sure or supposed/1=Maghreb-Caucasian/104=Caucasians/Other: Caucasian origin generally suspected	n=65 2=Maghreb/63=Caucasian	
Hair colour at birth	n=96	n=56	<0.001
'white', 'white-yellow'	89 (92.71)	40 (71.43)	
'yellow', 'yellow blond', 'blond'	7 (7.29)	8 (14.29)	
'ginger'	0 (0.00)	6 (10.71)	
'light brown'	0 (0.00)	2 (3.57)	
Hair colour at last description and at least 1 year	n=81	n=66	<0.001
'white', 'white-yellow'	57 (70.37)	17 (25.76)	
'yellow', 'light blond', 'blond', 'dark-blond'	17 (20.99)	31 (46.97)	
'yellow-ginger', 'ginger', 'ginger-brown'	4 (4.94)	11 (16.67)	
'light brown', 'brown'	3 (3.70)	7 (10.60)	
Skin colour at last description and at least 1 year	n=82	n=56	<0.001
White AND no nevi (or not pigmented) AND no ability to tan	65 (79.27)	17 (30.36)	
Other than 'white' ('creamy', 'rose') OR presence of nevi (except if not pigmented) OR tendency to tan	17 (20.73)	39 (69.64)	
Iris colour	n=99	n=64	<0.001
'grey', 'blue-grey', 'blue', 'blue-green'	94 (94.95)	49 (76.56)	
'green', 'green-brown', 'brown'	5 (5.05)	15 (23.44)	
Presence of iris transillumination	n=84	n=62	0.045
Yes	79 (94.05)	52 (83.87)	
Severity score of iris transillumination if present	n=30	n=31	<0.001
Stage 1	0 (0.00)	10 (32.26)	
Stage 2	1 (3.33)	14 (45.16)	
Stage 3	29 (96.67)	7 (22.58)	
Photophobia	n=91	n=49	<0.001
Yes	88 (96.70)	37 (75.51)	
Nystagmus	n=104	n=64	0.215
Yes	99 (95.19)	57 (89.06)	
Strabismus	n=75	n=62	0.408
Yes	31 (40.79)	30 (48.39)	
Refractive error (patient at least 1 year)	n=61 (60 for astigmatism)	n=53	
None	0 (0.00)	0 (0.00)	
Myopia (≤ -0.75 D)	16 (26.23)	6 (11.32)	0.044
Hyperopia (≥ 1 D)	44 (72.13)	43 (81.13)	0.260
Astigmatism (≥ 1 D)	46 (76.67)	44 (83.02)	0.320
Visual acuity (logMAR) (patients ≥ 5 years)	n=44	n=43	<0.001
Mean \pm SD	0.76 \pm 0.24	0.38 \pm 0.20	
Median (min–max)	0.70 (1.3–0.15)	0.35 (0.9–0.15)	
% with VA $\geq 20/40$ Snellen (logMAR=0.3)	4.55	32.56	
Presence of retinal hypopigmentation	n=80	n=59	0.074
Yes	80 (100.00)	56 (94.92)	
Severity score of retinal hypopigmentation if present	n=36	n=44	0.006
Stage 1	2 (5.56)	13 (29.55)	
Stage 2	34 (94.44)	31 (70.45)	
Presence and severity score of foveal hypoplasia if OCT available	n=19	n=31	<0.001
Stage 0	0 (0.00)	0 (0.00)	
Stage 1	1 (5.26)	3 (9.68)	
Stage 2	1 (5.26)	6 (19.35)	
Stage 3	2 (10.53)	15 (48.39)	
Stage 4	15 (78.95)	7 (22.58)	

Continued

Table 2 Continued

	Classical-OCA1 (N=119) n (%)	R402Q-OCA1 (N=69) n (%)	P values
Mean score±SD	3.63±0.81	2.84±0.88	
Visual evoked potential	n=31	n=15	0.495
Presence of a crossed asymmetry	8 (25.80)	6 (0.40)	

Comparison between compound heterozygotes for one pathogenic variant and the c.1205G>A/p.Arg402Gln variant (R402Q variant) of the *TYR* gene (R402Q-OCA1), and patients with two pathogenic variants of the *TYR* gene other than R402Q (classical-OCA1). OCA1, oculocutaneous albinism type 1; OCT, optical coherence tomography; logMAR, logarithm of the minimum angle of resolution.

Lastly, clinical reports were rarely available for patients' parents, and only few of them underwent complete examination for the purpose of this study. A more exhaustive analysis of patients' parents, including carriers of R402Q and another pathogenic variant, would be of interest in order to better evaluate expressivity and penetrance of the R402Q variant.

CONCLUSION

There are strong arguments in favour of R402Q being a mildly pathogenic, but definitely pathogenic, *TYR* variant when associated in trans with another pathogenic variant. First, the mild phenotype of R402Q-OCA1 patients would not be compatible with the presence of two deleterious variants, which would lead to more severe OCA1 phenotypes. Second, all patients included after 2013 have had an extensive analysis of the 18 known albinism genes and *SLC38A8*, thus excluding another form of albinism than OCA1. The only possibility that cannot be ruled out is the presence of another variant(s) in the introns or regulatory regions of the gene that are not explored in our diagnostic set-up. Considering the high number of R402Q-OCA1 patients

analysed, it seems unlikely however that non-exonic variants are responsible for the disease in all of them. One patient had complete sequencing of the *TYR*, *OCA2*, *TYRP1* and *SLC45A2* genes including 25 kb of flanking sequences, exons and introns (data not shown). No pathogenic variant was identified in any of the introns or flanking sequences of the four genes. Third, in a large series of patients with albinism, the R402Q variant was far more common in OCA patients with one *TYR* pathogenic variant (139/158; 88%) than in patients with two pathogenic variants (26/161; 16.0%).⁵ Finally the R402Q variant explains a significant part of OCA1 (45.5% in our series).

Albinism is known to be clinically heterogeneous and corresponds to a continuum of phenotypes that ranges from mild to severe. The phenotypes observed in R402Q-OCA1 patients reside at the mild or very mild end of this continuum but is variable and may overlap with that of classical-OCA1 or other forms of albinism.

A clinical diagnosis of albinism can be easily overlooked in patients in whom hypopigmentation is unremarkable and in whom the ocular phenotype is and appears atypical. A complete

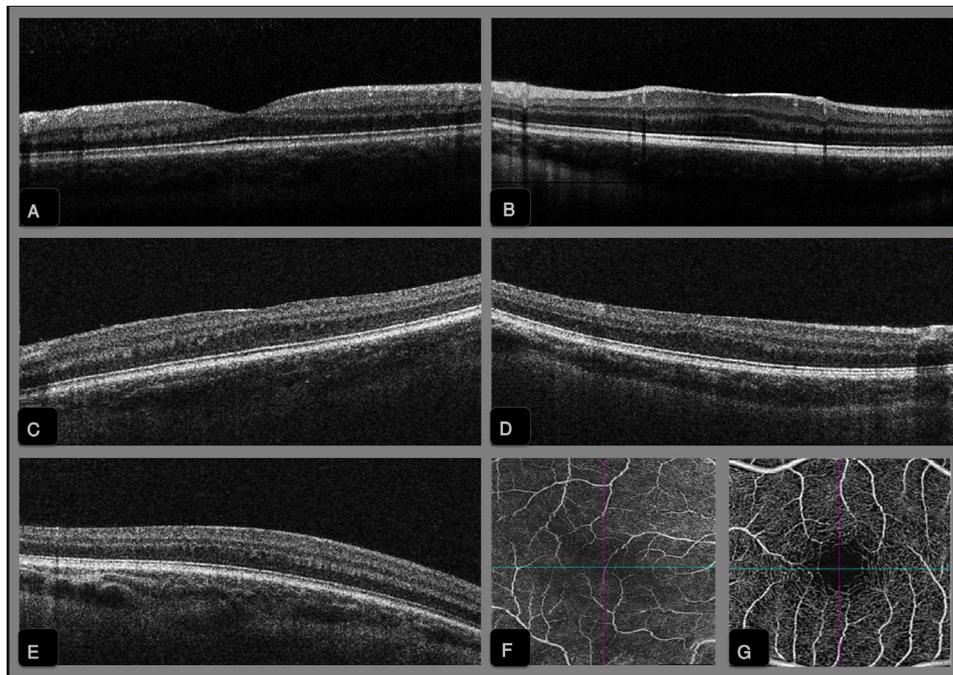


Figure 3 Representative sample of foveal morphologies in oculocutaneous type 1 patients, compound heterozygous with one classical *Tyr* mutation and the c.1205G>A/p.Arg402Gln (R402Q) variant (R201QOCA1 patients). A to E correspond to spectral domain optical coherence tomography (OCT) imaging of a normal fovea (A) and R402Q-OCA1 patients' fovea (B–E), illustrating our classification for foveal hypoplasia. Grade 0 (A), grade 1 (patient c.[1469C>A];[1205G>A]) (B), grade 2 (patient c.[649C>T];[1205G>A]) (C), grade 3 (patient c.239G>A);[120G>A]) (D) and grade 4 (patient c.[655G>T];[1205G>A]) (E). F is an OCT-angiography imaging of the fovea of an R402Q-OCA1 patient compared with a normal fovea (G). It confirms the clinically suspected vascular modifications of the macular region in albino patients, mainly characterised by the absence of a normal foveal avascular zone.

ophthalmological examination will in such cases be the key to clinical diagnosis.

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