

Lessons learned from the study of pigmentation and eye diseases

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Oculocutaneous albinism

- Oculocutaneous albinism (OCA) types 1, 2, 3, and 4 (OMIM 203100, 203200, 203290, 611409), are characterized by hypopigmentation of eyes, skin and hair, and are considered to be autosomal recessive disorders.
- Two unanswered questions about the OCA spectrum
- --- 1: the P gene paradox
- --- 2: A significant portion of Caucasian OCA patients have only one identifiable mutation.

P gene paradox

- PWS and AS patients with a deletion of *P* gene are hypopigmented; however, OCA2 carriers who are heterozygous for the 2.7-kb deletion in the sub-Saharan African population are not hypopigmented.

Evidence Suggesting the Inheritance Mode of the Human *P* Gene in Skin Complexion Is Not Strictly Recessive

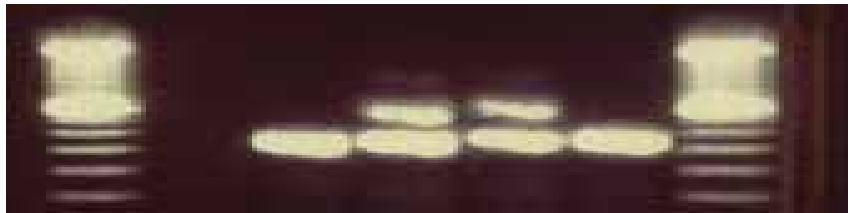
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1 2 3 4 5



6 7 8 9 10 11 12



Red hair color should be considered as a differential diagnosis of OCA3

A case of Asian Indian OCA3 patient

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Father



Patient at 5 months old



14 months old



Mother



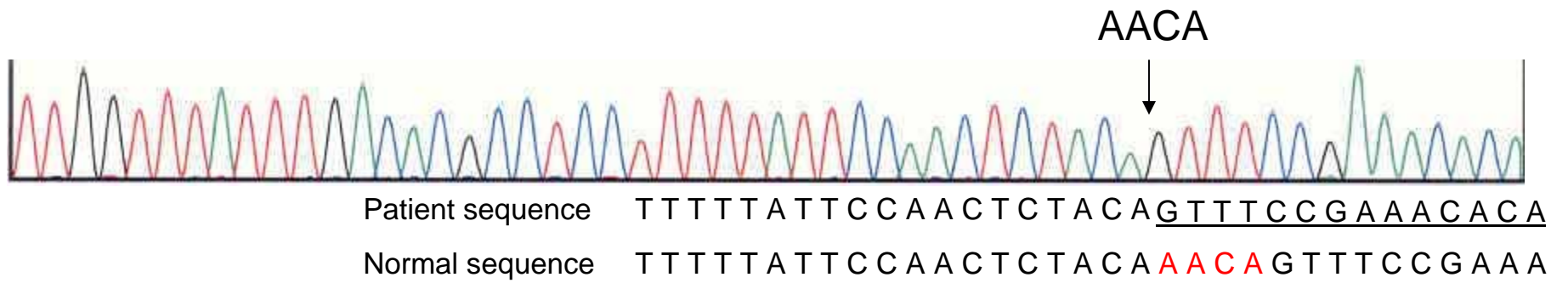
26 months old



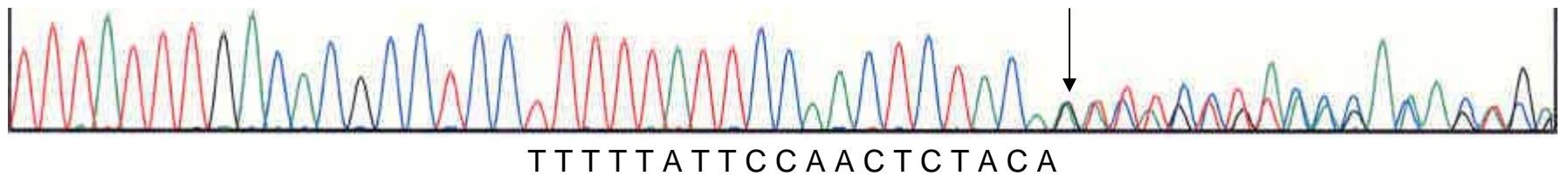
39 months old



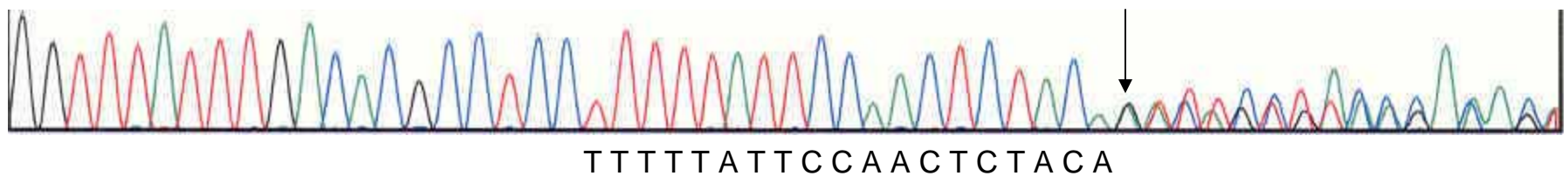
Propositus



Mother



Father



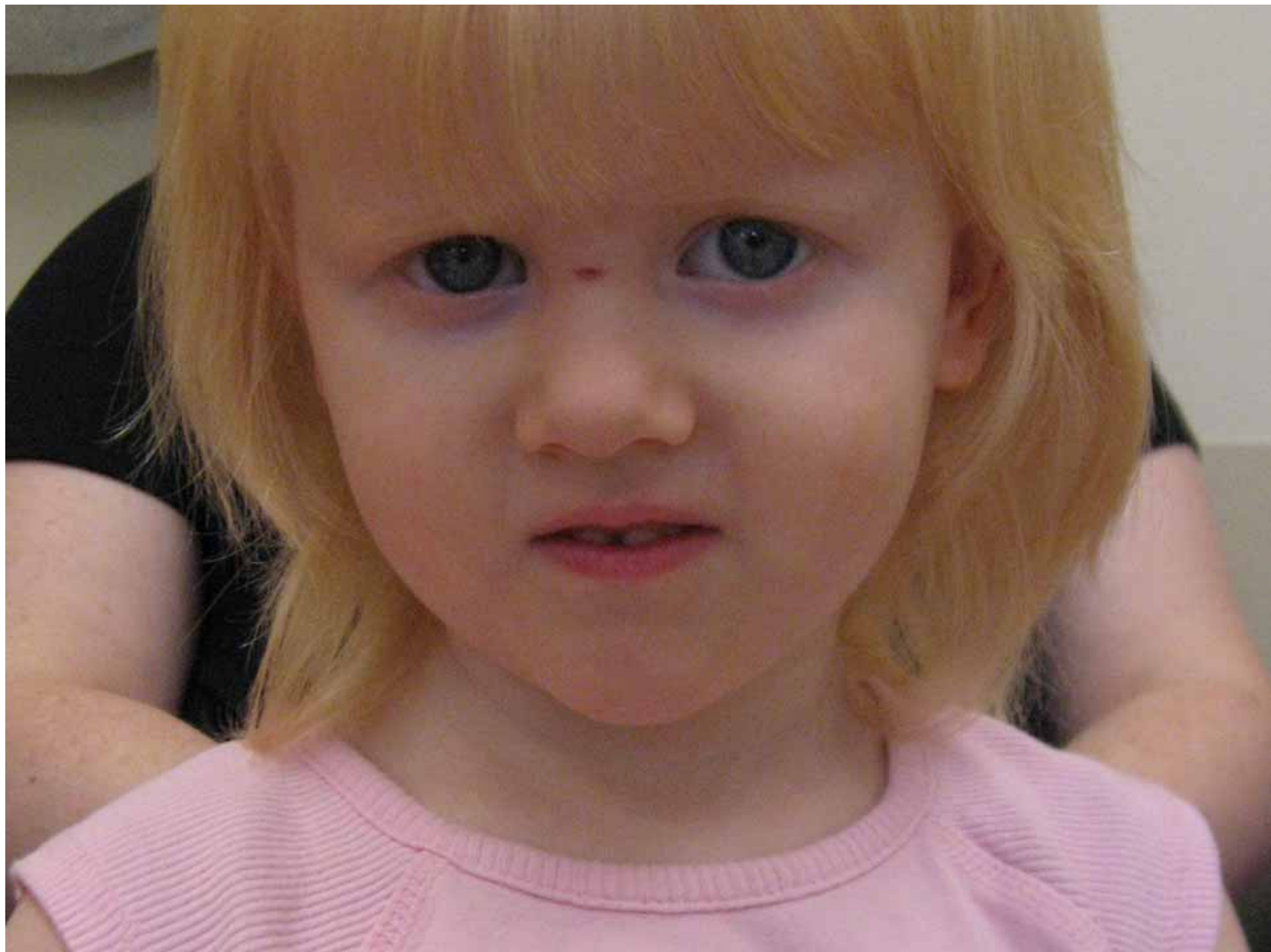
Phenotype of OCA3 in Caucasians: Report of Second European Patient

Pei-Wen Chiang,¹ Jennifer Roggenbuck,² Rebecca K Willaert,³ Elaine Spector,¹
Nancy Mendelsohn²

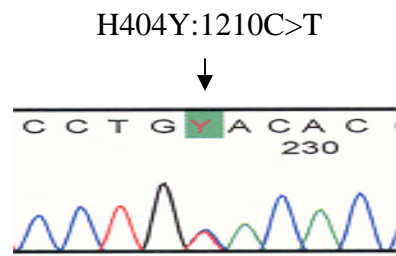
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²Children's Hospitals & Clinics of Minnesota, Minneapolis,
Minneapolis, MN, ³University of Minnesota, Minneapolis, MN.

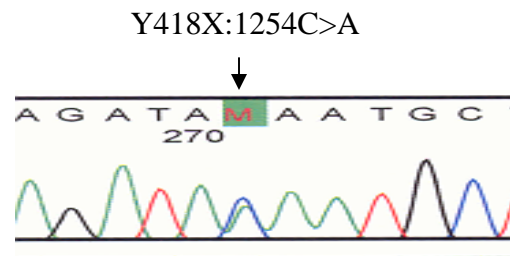




(A)



(B)



OCA spectrum

- non-syndromic patients with various eye, skin and hair phenotypes; from the mildest end being pure OA (strabismus to nystagmus with or without fovea hypoplasia and variable eye color) to variable degrees of OCA with eye, skin and hair involvement
- On one end of the spectrum, eye phenotypes are the main clinical diagnosis. This group of patients, mainly Caucasians, can have mutation(s) in *OA1*, *OCA1-4* or other unidentified gene(s). Some of these patients may only have one mutation plus a hypomorphic allele and other modifier(s)
- On the opposite end of the spectrum, such as African American OCA patients, two mutations are most likely present.

Evidence suggesting digenic inheritance of Waardenburg syndrome type II with ocular albinism

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²Department of Pediatrics, Division of Genetics and Genomic Medicine,
Vanderbilt University School of Medicine, Nashville, Tennessee

proband



father



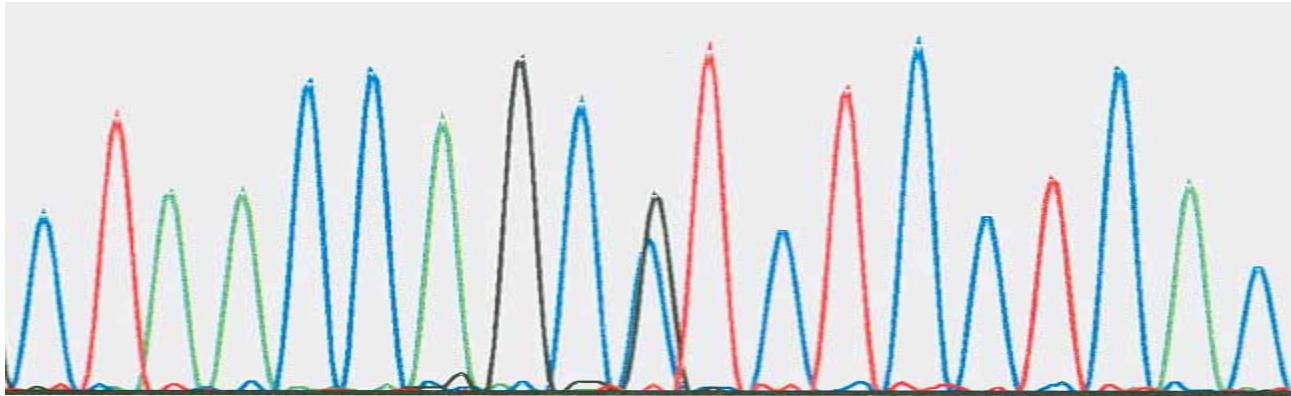
mother



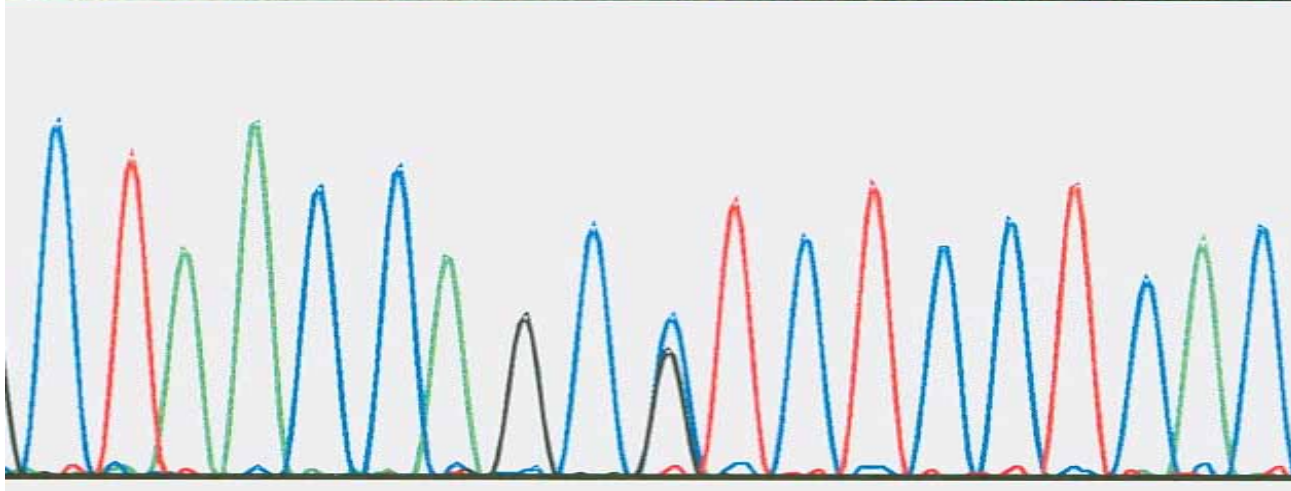
OCA3

	Codon	Amino acid
Normal	C C T	Proline
Mutant	C G T	Arginine

Forward



Reverse



Waardenburg syndrome with OA – A new mutation mechanism

- We present a second WS2 family with OA and provide evidence suggesting the *OCA1/TYRR402Q* allele could not cause OA in this family.
- We hypothesize the presence of a novel *OCA3* mutation together with the *MITF* del R217 mutation account for the OA phenotype in this family.
- Since *MITF* is a transcription factor for pigmentation genes, a mutation in *MITF* plus a heterozygous mutation in *OCA3* together provide an adverse effect crossing a quantitative threshold; therefore, WS2 with OA occurs.
- We have hypothesized previously that the clinical spectrum and mutation mechanism of OCA depend on the pigmentation threshold of an affected individual. This unique family has provided further evidence supporting this hypothesis.

A new hypothesis of OCA

- the clinical spectrum of patients with OCA spectrum depends upon the combined effects of mutation(s) acting with various modifiers and crossing a threshold to produce a phenotype in a patient.
- In some Caucasian patients with OCA, the presence of one mutation, a hypomorphic allele/haplotype and extra unknown modifier(s) from other gene(s) are the likely cause of OCA spectrum in these patients.
- OCA spectrum should not be treated as a purely recessive disease.

Eye diseases

- RP and LCA
- Many genes are involved
- Currently, tests for limited numbers of genes are available
- Variable expression, severity and onset
- Modifiers

Toward comprehensive molecular diagnosis of Retinitis Pigmentosa

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Young TL,² Spector E,⁵ Chiang PW.⁵

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What we have learned

- Reported mutations and/or novel SNPs were found in every patient we studied
- Every patient has a few novel SNPs
- We are investigating the biological significance of these sequence changes by studying additional family members
- RP may be an excellent disease model to elucidate phenotypic modifiers due to the large numbers of known genes involved in the specific pathway.