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GENEALOGICAL, BIOCEMICAL AND GENETIC ANALYSIS OF TWO ALBNIAN BROTHERS

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ABSTRACT

The purpose of this paper is to investigate the type of mutation, the genesis of these two cases. This study was included in a sample of 10000 individuals of the Albanian population of Preserve and villages. Albinism is a rare inherited disorder manifested by complete or partial lack of pigment in the skin, hair or eyes due to a defect in melanin biosynthesis. It can be classified as oculocutaneous albinism (OCA), when it involves the hair, skin, and eyes, or ocular albinism (OA), when the phenotype is primarily limited to the eyes and optic system and is therefore associated with specific ocular changes. During family interviews we encountered two cases of oculocutaneous albinism (OCA), due to a reduced amount of melanin in the developing eye.1, 2 where a red light spot is seen. Classical OCA is usually inherited as an autosomal recessive trait due to mutations in four genes known as TYR, 3 P (OCA2), 4 TYRP1,5 and SLC45A2 (MATP), 6 which are responsible for type 1 OCA (OCA1, respectively). MIM 203100), type 2 (OCA2, MIM 203200), type 3 (OCA3, MIM 203290) and type 4 (OCA4, MIM 606574). Based on ophthalmological analysis both of these belong to the oculcutaneus albinism (OC-A) species, thus representing a mild phenotypic variant of OCA.8 OCA. Abnormalities of the eye and optic system are common to all types of albinism and are probably related to melanin reduction during embryonic development and early postpartum life.

Keywords: OC-A albinism, heredity, TYRP 3,4, genetic trees, recessive alleles

INTRODUCTION

This work was performed on the Albanian population in southern Serbia. Based on molecular analysis we think characteristic changes in the optical system include decreased iris pigmentation (iris translucency) and retinal pigment epithelium, fovea hypoplasia, reduced visual acuity, misdirection of optical fibers in chiasm, strabismus, nystagmus refractive. The degree of skin and hair hypopigmentation, when present, varies across a wide clinical spectrum of severe to mild types. The clinical spectrum of OCA varies both within and between genotypes. This type of albinism is at risk for spine bifida carcinoma (SCC).

MATERIAL AND METHODS

Based on molecular, biochemical methods these alpinists have a total lack of melanin pigment even though the melanin cells are the same in number in normal people but they are dysfunctional. In the older brother OCA1 is generally considered a severe form, due to the lack of tyrosine's activity (OCA1A) while in the second brother there is a lower penetration of the gene. This was also the reason why the little one helped his older brother to go to school. Patients show a complete lack of lifelong melanin

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production with light blue irises to almost pink but with very low variations. Those with mutations that determine reduced tyrosinase activity have a milder form (OCA1B) characterized by a blue to green / brown iris which is characterized in the younger brother.3 OCA2, OCA3, and OCA4 show a certain accumulation of pigment over time as in the nerve crest (melanocytes of the skin, iris and choroid). and cells of neuroectodermal origin (RPE cells). Albinism can affect all ethnicities with a total prevalence of approximately 1 in 20,000 people.1 The prevalence of different forms of albinism varies considerably worldwide. Several factors may be involved, including the dissimilar prevalence of different founding gene mutations in different populations. In this case we have 2 albinists per 10000 inhabitants. The diagnostic inclusion criteria of the patients were based on the presence of the following characteristic ophthalmic features: photophobia, nystagmus, reduced visual acuity, strabismus, iris transparency, fundus hypopigmentation and foveal hypoplasia, possibly in combination with varying degrees of hipopigment skin and hair 8; VEP is not considered necessary for the routine diagnosis of albinism.18,19 Syndromic forms of albinism, such as Hermansky-Pudlak, Chediak-Higashi, Griscelli, Tietz, ocular albinism with sensorineural deafness, Wardenburg, Cross, Prader Willie or Angelman. syndromes were ruled out on a clinical basis, based on the lack of additional clinical findings such as deafness; lack of immunity; hematological abnormalities or bleeding diathesis; involvement of the heart, lungs, genitourinary, gastrointestinal or central nervous system; and the presence of obesity and dimorphic features, as reported at the time of clinical diagnosis by the ophthalmologist at the referral center. Both patients analyzed showed variable skin and hair involvement with mild or severe hypo pigmentation, representing the clinical spectrum of OCA phenotypes.

RESULTS AND DISCUSSION

Genealogical analysis:

To discover the genesis of albinism we have done a genealogical analysis of their mother and father. According to this analysis in the first case, figure 1 turns out that until generation III there were no obvious signs of albinism. The genesis of these alpinists starts from their second generation grandfather II with serial number 2.

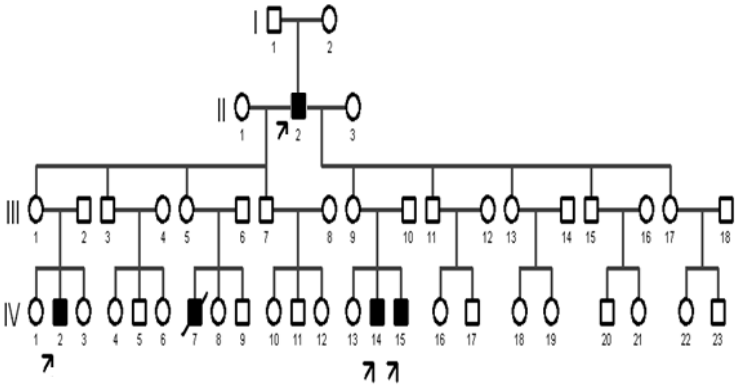

Figure 1. Genealogy of the Albinism brothers by their mother and father

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b) Molecular analysis of mutations

From the genomic DNA analysis of two patients from independent families, referring to ophthalmic institutes in public and private laboratories, we were able to present a clinical diagnosis of non-syndromes albinism. The research adhered to international principles. Informed consent was obtained from the patient's parents after explaining the nature and possible consequences of the patients. To establish a molecular diagnosis, we performed direct DNA sequencing of five genes known to be associated with albinism: TYR, P, TYRP1, MATP, and OA1. Patients were initially screened for TYR and P mutations and, if negative, were subsequently screened for mutations in the TYRP1, MATP, and OA1 genes.

A detailed analysis of the origin of the extended families was conducted to determine the mode of inheritance and in 22 independent families, the division of mutations was confirmed by genetic sequence analysis in all family members.

Genomic DNA was extracted from peripheral whole blood lymphocytes of patients and, where possible, from their parents, using standard techniques. The complete coding sequence and exon-intron boundaries of the OA1, TYR, P, TYRP1 and MATP genes were amplified by standard PCR (Taq Gold DNA polymerase; Roche, Basel, Switzerland). Exon 1 of tyrosine's; Exons 1, 3 and 8 OA1; and exon 3 MATPs, were amplified as a pair of overlapping fragments. Exon 1 of the P and TYRP1 genes, which are not coders, was not analyzed. Human chromosome 11 contains a pseudogen, known as a tyrosine's-like gene (TYRL, 11p11.2; MIM 191270), which shares a 98.55% sequence identity with the 3 'region of TYR (~ 68 kb), including exons 4 and 5. Thus, the identification of nucleotide variants in TYR by PCR and DNA sequencing is a challenging task and can generate false data due to co-amplification from both loci (Lab.Bio-Lab- Kosovo). To allow direct and clear identification of mutations, we used primers for a specific amplification of their TYR location. PCR was performed in 35 cycles with 50 ng of genomic DNA at 94 ° C for 1 minute, at the respective primer firing temperature for 1 minute and at 72 ° C for 1 minute. Primers and PCR amplification reaction conditions are available upon request. The amplifiers were tested for direct sequence mutations (Kit V2.0 for Prism Big Dye Terminator Cycle Sequencing; Applied Biosystems, Inc. [ABI], Foster City, CA) and the reactions were analyzed in a genetic analyzer (Prism 3100; ABI). The mutation nomenclature conforms to the identified nucleotide variations that have been investigated either in the albinism database or in the human gene mutation database.

Figure 2. Albinist brothers

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From phenotypic observation and including measurements of visual acuity, assessment of ocular motility and iris transparency, biomicroscopic examination, fundus examination, fundus autofluorescence (FAF) and retinography, were performed in two patients carrying different gene mutations cause albinism. A 4- and 3-point scale was used to classify iris translucency and macular transparency, respectively.

Autofluorescence was recorded with a standard laser scan with ophthalmic scanning (Heidelberg Retina Angiograph II; Heidelberg Engineering, Heidelberg, Germany). To amplify the autofluorescence signal, we listed the top five images obtained using the integrated system software and calculated an average image.

Figure 3. Albinist brothers in the same school generation.

CONCLUSIONS:

-Based on the analysis made these albinistas belong to the mutation which is the causal variation of DNA (95.6%) from 2 patients analyzed.

- We identified 2 or more causal mutations in 62.2% of 2 patients.

- Two new mutations were discovered in TYR. We also identified mutations in rare locations, including two new mutations in MATP and one in TYRP1.

-New mutations were also identified in rare locations such as TYRP1 and MATP.

-Clinical evaluation revealed that patients with iris and macular pigmentation had significantly higher visual acuity than severe hypopigmented phenotypes.

- The penetration of this gene for albinism has the same effect on the two brothers in terms of pigment, while the ability to see is more pronounced in the older brother than in the second brother.

-For this reason the World Association of Albinists founded in 1992 (AWA - Albinism World Alliance) to appeal to international health institutions to take the problem of albinism more seriously.

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