Short communication

A novel mutation in the CNGA3 gene responsible for incomplete achromatopsia

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A R T I C L E   I N F O

Article history:
Received 14 January 2012
Accepted 9 July 2012
Available online 16 June 2014

Keywords:
Achromatopsia
CNGA3
Mutation
Genetic diagnosis
Autosomal recessive

A B S T R A C T

Case report: A 56-year-old male was diagnosed with incomplete achromatopsia. His molecular genetic analysis showed two heterozygous mutations in the CNGA3 gene associated with autosomal recessive achromatopsia.

One of them, c.1495C>T, has not been previously reported in achromatopsia.

Discussion: Achromatopsia is a congenital autosomal recessive retinal disorder. Mutations in the CNGA3 gene, located at chromosome positions 2q11, account for 5–25% of patients affected with this disorder. The vast majority of mutations are missense. This discovery confirms the clinical diagnosis and it allows us to provide genetic counseling.

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Una nueva mutación en el gen CNGA3 causante de acromatopsia incompleta

R E S U M E N

Caso clínico: Varón de 56 años con el diagnóstico clínico de acromatopsia incompleta. En su estudio genético se encontraron dos mutaciones en heterocigosis en el gen CNGA3 relacionado con la acromatopsia recesiva.

Una de ellas la c.1495C>T no ha sido previamente informada en otros casos de acromatopsia.

Discusión: La acromatopsia es una enfermedad retiniana congénita de herencia autosómica recesiva. La tasa de mutaciones en el gen CNGA3, localizado en el cromosoma 2q11, oscila entre el 5 y el 25% de los casos y en su mayoría son producidas por cambios en la secuencia. Este hallazgo confirma el diagnóstico y nos permite realizar un consejo genético.

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Introduction

Achromatopsia is a genetically heterogeneous, autosomic recessive inheritance congenital retinal disease characterized by cone system dysfunction.\(^1\) It exhibits a frequency of 1:30,000–1:50,000.\(^2,3\) Two conditions are distinguished: complete achromatopsia (typical or rod monochromaticism) exhibited by the majority of patients, and incomplete or atypical (IAC).

In IAC, patients preserve slight although abnormal color vision and somewhat better visual acuity (0.1–0.25) than complete achromatopsia cases, as well as photophobia and nystagmus. Some cones probably remain functional, either long and middle wave, or both. Mutations have been identified in genes CNGA3, CNGB3, GNAT2 and PDE6C, all of which encode essential proteins in the cone phototransduction cascade. CNGA3 and CNGB3, respectively located in chromosomes 2q11y 8q21–q22, encode subunits α-3 and β-3 of the channels activated by cyclic GMP cations; GNAT2, located in chromosome 1p13, encodes subunit α-2 of the G protein, transducin; and PDE6C, in chromosome 10q24, encodes subunit α of the phosphodiesterase 6C, GMP cyclic specific.\(^2,3\)

Clinic case

Male, 56, referring photophobia, poor visual equity, nystagmus and poor color vision since childhood. The patient has a sister with the same clinic. The parents are healthy, and had no consanguinity or family history. After ophthalmological examination, color tests, and visual fields, electroretinogram and macular optic coherence tomography, incomplete or atypical congenital achromatopsia was diagnosed.

The genetic molecular study carried out on genomic DNA sample (Tübingen University, Germany) found 2 mutations in heterozygosis in gene CNGA3 related to recessive achromatopsia. Said mutations are: c.1279C>T (previously associated to recessive achromatopsia) and c.1495C>T (not previously related to the disease but probably pathological due to producing truncated protein).

Discussion

Mutations in gene CNGB3 are the most important cause of complete and incomplete achromatopsia and account for 50–87% of cases, depending on the studies.\(^2,3\) The mutations in gene CNGA3 are less frequent and range between 5% and 25%.\(^2,3\)

Gene CNGA3, located in chromosome 2q11, encodes subunit α of the channels activated by cone cyclic GMP cations located in the membrane of the cone external segments and are essential for phototransduction in the 3 cone classes.

Mutations in gene CNGA3 have been detected not only in patients with complete or incomplete achromatopsia but also in patients with progressive cone dystrophy.\(^4\)

Of all identified mutations (over 70), the vast majority (just under 80%) are caused by sequencing changes,\(^7\) and only 3 (Arg427Cys, Arg563His, Thr565Met) were found exclusively in patients with IAC.\(^1,4\) The sequencing changes indicate little tolerance for substitutions for functional and structural maintenance of polypeptide channels.\(^2,4\)

In the case reported herein, DNA was extracted from a peripheral blood sample. Amplification was made with encoding sequence polymerase chain reaction technique and adjacent sequencing of genes CNGA3 and CNGB3, and mutational screening by means of automatic screening thereof.

The analysis has evidenced 2 heterozygosis mutations in gene CNGA3:

- c.1279C>T, consisting in the change of a cytosine by thymine in nucleotide position 1279; said mutation gives rise to truncated protein p.Arg427Cys (substitution of arginine by cysteine in position 427 of the resulting protein), reported previously in other cases of recessive achromatopsia.\(^1,4\)
- c.1495C>T, consisting in the change of a cytosine by thymine in nucleotide position 1495; said mutation gives rise to truncated protein p.Arg499stop which was not previously reported in other cases of recessive achromatopsia.

Achromatopsia follows a recessive autosomic inheritance. For the disease to appear in a patient both parents must provide a mutated copy of the gene, with the risk for siblings of an affected subject being 25% regardless of the number of siblings already exhibiting the disease. Their children are all carriers of one of the paternal mutations but risk for their descendents is low unless the spouse carries a mutation in the same gene, which is more likely in consanguinity.

It is important to establish an adequate clinical diagnostic for a genetic study to enable the identification of the mutation which causes the visual problem. In this way it would be possible to reach an exact diagnostic, define the inheritance pattern and design new specific forms of therapy.

Animal studies suggest that achromatopsia is a good candidate for gene therapy although it would require early application in the first decade of life as cones are progressively lost in a relatively short period of time.\(^5\)

Conflict of interest

No conflict of interest has been declared by the authors.

REFERENCES

