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Case Report

Association between a new 3q;5q chromosomal translocation and dystrophy of human retinal pigment epithelium

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ABSTRACT. Retinitis pigmentosa (RP) is a heterogeneous group of inherited retinal degeneration. This group of disorders essentially leads to blindness due to mutations in different genes. The genetic basis affected by sporadic and inherited autosomal dominant, autosomal recessive or X-linked mutations is complex. In humans, RP is in most cases associated with missense mutations in the rhodopsin gene (RHO). RHO plays an important role in phototransduction pathways. So far, few studies have described associations between chromosomal alterations and RP. In this study, we present a case report of a premature, 32-week-old male baby who suffered from retinopathy, facial dysmorphisms and other disorders. His chromosomes were analyzed by conventional and high-resolution chromosomal techniques. This analysis revealed structural aberrations on chromosomes 3 and 5 with an apparently balanced chromosomal translocation with karyotype 46,XY,t(3;5)(q25;q11.2). Remarkably, the 3q breakpoint on the long arm of chromosome 3 is located close to the physical RHO chromosomal gene location. In this study, we describe presumably for the first time a possible association between a 3q;5q

chromosomal alteration and RP. We conclude that the new detected chromosomal translocation may lead either to loss or inactivation of the intragenic RHO gene or its respective gene regulatory region. As a consequence, the chromosomal aberration may be responsible for retinitis pigmentosa.

Key words: Retinal dystrophy, Retinitis pigmentosa, Chromosomal translocation 3q;5q

INTRODUCTION

Genetic factors play a role in many illnesses, such as retinal diseases. Retinitis pigmentosa (RP) refers to a group of retinal diseases with a heterogeneous phenotypic and genetic background (Bhatti, 2006). The disease is characterized by a progressive visual loss and affects approximately 1.5 million people throughout the world. The degeneration of photoreceptor cells causes blindness. Genetic studies have identified 120 loci and 56 genes associated with human retinopathies (Sohocki et al., 2001). RP mutations can occur in a sporadic or familial manner (Rivolta et al., 2002; Kalloniatis and Fletcher, 2004; Wang et al., 2005; Mordes et al., 2006). A number of genes defective in RP patients have been cloned. Many RP genes are expressed predominantly or specifically in the retina (Mordes et al., 2006). Recently, several non-retina-specific autosomal dominant RP genes that encode ubiquitously expressed proteins essential for RNA processing have been identified in different tissues (Mordes et al., 2006; Comitato et al., 2007). The most important RP mutations, including the rhodopsin (RHO) gene, occur in genes involved in visual transduction pathways (Mordes et al., 2006).

RP-like pigment deficits also occur as a component of other clinical syndromes, such as Usher's syndrome (Mordes et al., 2006). Syndromic forms occur in which the disease can be characterized as a multiple disorder (Bardet-Biedl's syndromes and Refsum's disease) and are oligogenic (Kalloniatis and Fletcher, 2004). Furthermore, a polygenic inheritance may also occur, in which an interaction between multiple genes and environmental factors seems to be likely, although this interaction is not well characterized (Stone et al., 2001). Chromosomal alterations, such as partial monosomy (6q) and 1;6(q44;q27) translocation, and non-classical inheritance, such as uniparental disomy, can also result in dystrophy of the retinal pigment (Tranebjaerg et al., 1986; McLeod et al., 1990; Rivolta et al., 2002; Wang et al., 2005).

Inherited retinal disease has been associated with gene mutations in the integral membrane proteins of RHO, peripherin/retinal degeneration slow as well as retinitis pigmentosa 1, cone rod homeobox, and aryl hydrocarbon receptor interacting protein-like 1. However, association studies showed that RHO mutations are the most common cause of RP (Sohocki et al., 2001; Illing et al., 2002). These mutations are linked to the loss of night vision and the progressive constriction of the visual field (Chen et al., 2006). The RHO gene encodes the photoreceptor-specific RHO protein that plays an essential role in the visual transduction cascade (Kalloniatis and Fletcher, 2004). Mutations in RHO are responsible for 20 to 25% of the RP disorders and are transmitted in an autosomal dominant manner. Amongst these, more than 100 different mutations have been detected so far, including deletions, insertions and substitutions (Wang et al., 2005).

MATERIAL AND METHODS

Cytogenetic analysis

A short-term culture of peripheral blood lymphocytes was carried out for conventional analysis (Ford and Hamerton, 1956) and for high-resolution chromosomal analysis (Yunis, 1976). Fifty metaphases were analyzed with GTG banding for the presentation of the family's karyotypes (proband, his mother and his brother).

Case report

The study was approved by the Ethics Committee of the University Hospital/UFMA, with an informed consent form being signed by the child's guardian. The patient with the described structural chromosomal aberration was a premature male baby with 32 weeks. The baby weighed 1680 g, had a height of 40.5 cm and a cephalic perimeter of 30.5 cm. The child was treated in the intensive care unit of the hospital for a period of 12 weeks, since he suffered from respiratory distress, which required artificial ventilation, and from various other clinical symptoms. These clinical symptoms included anemia, which was corrected by transfusion of blood products, cardiac insufficiency and septicemia.

RESULTS

A delayed development in crawling and walking was observed. Dysmorphic facial features included ocular hypertelorism, convergent strabismus, long philtrum, and low-set and dysplastic ears (Figure 1). The patient also exhibited low implantation of hair, mammary

Figure 1. Patient with dystrophy of the retinal pigment epithelium and exhibiting facial dysmorphisms (ocular hypertelorism, convergent strabismus, long philtrum, low-set and dysplastic ears).

hypertelorism and brachydactyly of the hands and feet.

In order to examine a suspected premature retinopathy, the baby at 6 months old was examined by binocular ophthalmoscopy. In the retinal epithelium, "clumps" that suggested retinal epithelium dystrophy were observed. As a consequence, a possible premature retinopathy was excluded.

Cytogenetic analysis of the young patient revealed an apparently balanced chromosomal translocation with 46,XY,t(3;5)(q25;q11.2) karyotype (Figure 2). The karyotypes of the mother and brother were found to be normal. Although it was impossible to perform a karyotype of the father, he did not reveal signs of any clinical abnormality.

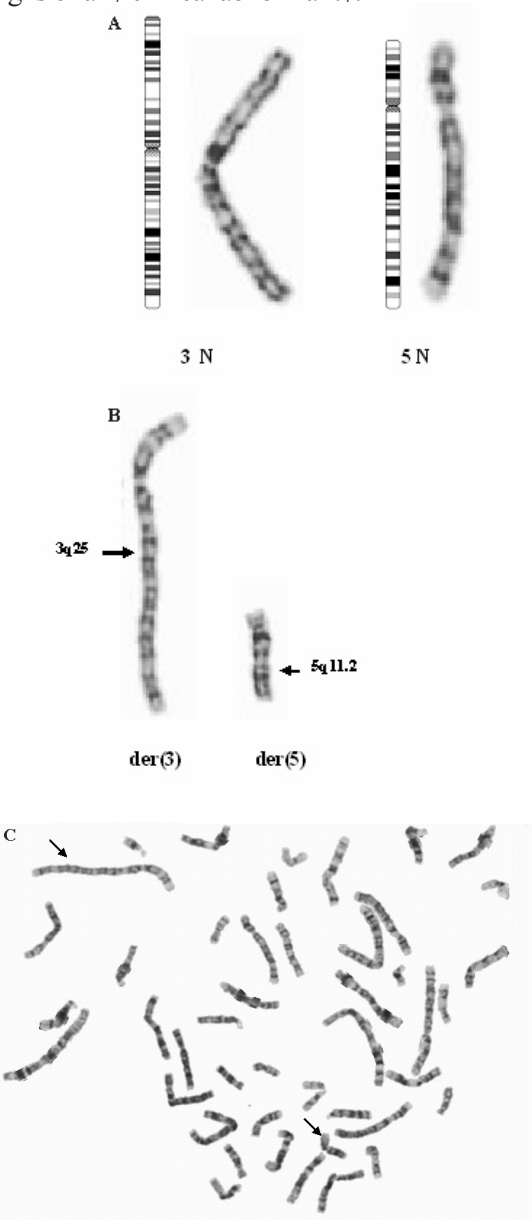

Figure 2. A. Normal chromosomes 3 and 5. **B.** Derivative chromosomes 3 and 5 and their respective break points. **C.** Metaphase (arrows).

DISCUSSION

The most common form of retinal degeneration is RP. The most prominent pathological finding of RP is the loss of photoreceptor cells, often followed by alterations in the retinal pigmented epithelium and retinal glia (Mordes et al., 2006). So far, there is no prevention or cure for the disease. RP mutations can be involved in spontaneous alterations in genes or can be responsible for inherited disorders. By means of cytogenetics, it was possible to recognize a subtle chromosomal abnormality. In a premature patient suffering from dystrophy of the retinal pigment epithelium and exhibiting facial dysmorphism, a piece on the long arm of chromosome 3 at position 3q25 had been translocated to chromosome 5 at position 5q11.2.

Here, we present, to our knowledge for the first time, a patient carrying a 3q;5q chromosomal translocation associated with a dystrophy of the retinal pigment epithelium and facial dysmorphisms. In contrast to the patient, the mother and brother had a normal karyotype with no detection of chromosomal aberrations. Unfortunately, the father of the proband did not agree to a karyotype analysis. However, the father did not reveal any signs of abnormalities, as identified in his son. High-resolution cytogenetic analysis identified an apparently balanced translocation. However, with our analysis we cannot exclude the possibility of undetectable submicroscopic deletions.

Genetic studies on familial forms have improved our understanding of retinal degeneration. Familial RP displays all three modes of Mendelian inheritance: autosomal dominant, autosomal recessive and X-linked (Rivolta et al., 2002; Wang et al., 2005). The most important autosomal dominant RP mutations are located in the RHO gene and play a prominent role in phototransduction (Mordes et al., 2006). RHO on the long arm of chromosome 3 is located at position 3q21-25 coding for the seven transmembrane plasma membrane RHO protein which is coupled to heterotrimeric G proteins (Chen et al., 2006). Therefore, the chromosomal RHO gene position is located near the chromosomal break point of the patient.

The chromosomal translocation may lead to the loss or inactivation of the RHO gene resulting in a non-functional protein or could according to possible nucleotide changes in the respective gene regulatory sequence may lead to an insufficient synthesis of RHO. Thus, it is very likely that RP of the patient is caused by the detected *de novo* chromosomal translocation during chromosomal rearrangement. The suggested association between RP and facial dysmorphisms with the chromosomal alteration infers the loss or inactivation of structural intragenic RHO nucleotide sequences or gene regulatory sequences of the respective gene. However, we cannot exclude the possibility that other genes located on the long arm of chromosome 3 have a prominent role in the regulation of the RHO gene and thus may be responsible for the described pathology.

Syndromic forms of RP are linked to mutations such as in the gene alpha-methylacyl-CoA racemase located on chromosome 5p13.2-5q11.1 (NCBI GenBank accession NM014324) causing Refsum's disease. Mutations in the clarin-1 (USH3) gene (NCBI, GenBank accession AF495717), located on chromosomes 5q14 and 3q21-25 cause the Usher's syndrome (types 2C and 3) (Ferdinandusse et al., 2000; Pieke-Dahl et al., 2000; Aller et al., 2004). However, in contrast to the dominant RHO mutations, these mutations are inherited in an autosomal recessive manner. The patient described in this study did not manifest additional clinical signs

(e.g., deafness) that are diagnosed for both Refsum's disease and Usher's syndrome. We assume that it is not likely that recessive mutations caused the retinal epithelium dystrophy and facial dysmorphisms, as described here.

In future studies, nucleotide sequence analysis of the described chromosomal translocation sites should be performed in order to examine whether indeed a likely intragenic or a nearby extragenic RHO gene regulatory mutation can cause retinitis pigmentosa.

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