

—Report on Experiments and Clinical Cases—

Congenital Bilateral Severe Microphthalmia with Mental Retardation and Cerebral Palsy: Chromosome Aberration, 46, XY, t(2;6)(q31;q24)

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Abstract

Congenital bilateral anophthalmia and microphthalmia are rare conditions, with overall prevalence in one study set at 1.0 per 10,000 births⁹. We report here a case of congenital bilateral severe microphthalmia with mental retardation and cerebral palsy. The patient was a man aged 38 years with a chromosome aberration, namely a balanced translocation: 46, XY, t(2;6)(q31;q24). He had no other malformations apart from the severe microphthalmia. CT of the head showed no significant abnormal findings in the brain, but rudimentary eyeballs and external ocular muscles in the bilateral orbits. There was no family history of anophthalmia, microphthalmia, mental retardation or cerebral palsy. His mother had not used any medications or excessive alcohol during gestation.

Putative genes of anophthalmia and microphthalmia reported to date include *PAX6* (Glaser T et al 1994⁶) and *CHX10* (Ferda Percin E et al 2000⁵). Further, some loci of these conditions have been reported (Graham CA et al 1991⁷; Bessant DAR et al 1998³; Morle L et al 2000⁴; Forrester S et al 2001¹; Ng D et al 2002⁸). To our knowledge, however, this is the first report of nonsyndromic microphthalmia or anophthalmia with chromosome 2q31 or 6q24 aberration. We consider that the putative gene may be located on the break points of chromosome 2 and 6. (J Nippon Med Sch 2005; 72: 242–244)

Key words: chromosome aberration, anophthalmia, microphthalmia, mental retardation, cerebral palsy

Introduction

Congenital severe anophthalmia and microphthalmia are rare autosomal chromosome aberrations which generally have a severe impact on development and growth, often causing an array of severe malformations and severe to profound mental retardation. Candidate genes for anophthalmia and

microphthalmia reported to date are *CHX10* (Ferda Percin E et al 2000⁵), *PAX6* (Gaser T et al 1994⁶) and *ANOPI* (Graham CA et al 1991⁷; Ng D et al 2002⁸), respectively. Here, we report a man with congenital bilateral severe microphthalmia, mental retardation and cerebral palsy with a balanced translocation: 46, XY, t(2;6)(q31;q24) and no family history of anophthalmia, microphthalmia, mental retardation or cerebral palsy.

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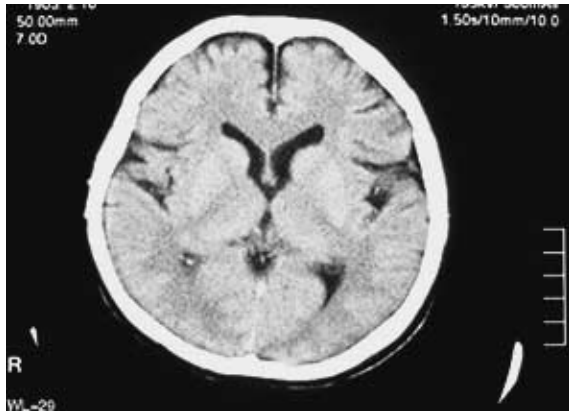


Fig. 1 Head CT: No significant findings in the brain.

Case Report

The patient was born in December 1964 weighing 3,500 g. No significant problems were encountered in the perinatal period. In the neonatal period, his parents reported his eyelids did not open, and a diagnosis of bilateral severe microphthalmia was made. He showed psycho-motor delay, with head control noted at age 1 year and sitting on the floor at age 5 (1969), at which time he first entered our hospital. On initial examination, he could not stand up unaided and had a highly limited vocabulary. Other development findings included height 102 cm (-1SD), weight 14.5 kg (-1.8SD) and head circumference 49.5 cm (-1SD). He had no other malformations apart from the bilateral severe microphthalmia. At age 38 (2002), CT of the head (Fig. 1) showed no significant abnormal findings in the brain, but rudimentary eyeballs and external ocular muscles in the bilateral orbits (Fig. 2). G-banding analysis showed a balanced translocation: 46, XY, t(2;6)(q31;q24). He did not experience seizures. He always had chronic aerophagia, and sometimes experienced repeated hematemesis due to reflux esophagitis. His parents were cousins. There was no family history of anophthalmia, microphthalmia, cerebral palsy or mental retardation.

Discussion

Congenital microphthalmia and anophthalmia are

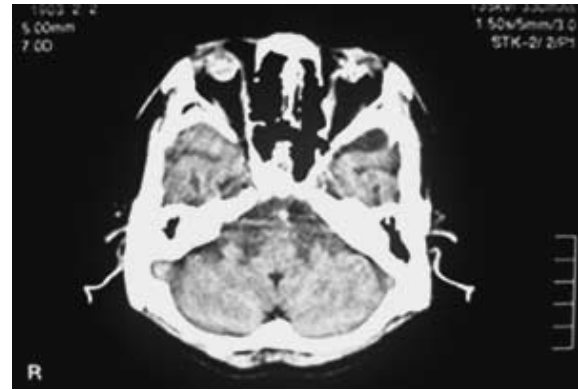


Fig. 2 Head CT: Rudimentary eyeballs and external ocular muscles in the bilateral orbits.

rare conditions. In one study, overall prevalence of the two in England from 1988~94 was 1.0 per 10,000 births⁹. About 10% of mentally retarded patients with coloboma or microphthalmia have chromosomal aberrations¹⁰. Pinsky et al (1965) described three sisters with microphthalmia, severe mental retardation and spastic cerebral palsy, who did not, however, have chromosome aberrations¹¹.

Candidate genes for anophthalmia and microphthalmia reported to date are *CHX10* (Fedra Percin E et al 2000⁵), *PAX6* (Graser T et al 1994⁶) and *ANOP1* (Graham CA et al 1991⁷; Ng D et al 2002⁸). Fedra Percin E et al reported the mapping of a human microphthalmia locus on chromosome 14q24.3, the cloning of *CHX10* at this locus and the identification of recessive *CHX10* mutations in two families with non-syndromic microphthalmia, cataracts and severe abnormalities of the iris. It has also been reported that human *CHX10* is expressed in progenitor cells of developing neuroretina and in the inner nuclear layer of mature retina⁵.

Graser T et al (1994) described how the human eye malformation aniridia resulted from haploinsufficiency of *PAX6*, a paired box DNA-binding protein. The *PAX6* gene is located on 11p13. In a previous study, a patient with severe craniofacial and central nervous system defects and no eyes was found to be a compound heterozygote, suggesting that *PAX6* plays a critical role in controlling the migration and differentiation of specific neuronal progenitor cells in the brain⁶.

A second malformation, autosomal dominant nanophthalmos, is characterized by a small eye, as

indicated by short axial length, high hyperopia, high lens/eye volume ratio, and a high incidence of angle-closure glaucoma. Othman et al (1998) clinically and genetically evaluated members of a large family with the dominant form of nanophthalmos¹². Linkage analysis assigned the locus of the defect, which was symbolized NNO1, to chromosome 11. These findings rule out the involvement of *PAX6*, however, because it was not located within the NNO1 genetic inclusion interval.

A third condition is Lenz syndrome, which comprises microphthalmia with mental retardation, malformed ear and skeletal anomalies. This condition is inherited in an X-linked recessive pattern. Graham et al (1991) described seven anophthalmic males, three of whom were deceased at the time of study, and showed that the pattern was consistent with X-linked recessive inheritance, and that multipoint linkage analysis suggested that the gene involved was localized to the Xq27~q28 region (ANOP1)⁷. Clinically affected males with bilateral disease had fusion of the eyelid margins (ankyloblepharon) and radiologically demonstrable underdevelopment of the bony orbits. All males had mental retardation (IQ less than 50) and one was born with preauricular skin tags and a cleft soft palate. Ng et al (2002) described a five-generation African-American family with microphthalmia or anophthalmia, mental retardation and urogenital anomalies, in an X-linked recessive inheritance pattern which was consistent with Lenz syndrome⁸. An X-chromosome scan revealed linkage to a 10 cM region between markers DXS228 and DXS992 in Xp11.4~p21.2 (ANOP2). These findings all show that X-linked recessive syndromic microphthalmia exhibits genetic heterogeneity.

We report here a case of congenital bilateral severe microphthalmia with mental retardation and cerebral palsy. This patient has a chromosome aberration, balanced translocation: 46, XY, t(2;6)(q31;q24). To our knowledge, this is the first description of congenital severe anophthalmia or microphthalmia with chromosome 2q31 or 6q24 aberration. Although confirmation will require the accumulation of further cases, it may be supposed

that the putative gene is located on the brake points of chromosomes 2 and 6.

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