

Familial complex chromosomal rearrangement in a dysmorphic child with global developmental delay

Ngim C F, Keng W T, Ariffin R

ABSTRACT

We report the unusual case of a dysmorphic child with global developmental delay secondary to a familial complex chromosomal rearrangement (CCR). His chromosomal analysis using G-banding and dual colour fluorescence *in situ* hybridisation with whole chromosome paint revealed a supernumerary marker chromosome as a result of malsegregation of a familial CCR involving chromosomes 7, 12 and 14. The balanced form of this familial CCR was also carried by the patient's mother and maternal grandmother, both of whom had a history of recurrent spontaneous abortions, as well as his maternal uncle, who was infertile. To the best of our knowledge, this is the first reported case of familial CCR involving chromosomes 7, 12 and 14. This case also highlights the importance of chromosomal analysis in children with dysmorphism and developmental delay as well as in adults who suffer from recurrent spontaneous abortions or infertility.

Keywords: complex chromosomal rearrangement, developmental delay, dysmorphic, recurrent spontaneous abortions, supernumerary marker chromosome

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INTRODUCTION

Complex chromosomal rearrangements (CCRs) are structural rearrangements involving at least three chromosomes and three or more chromosome breakpoints. CCRs can be categorised by the method of transmission (familial or *de novo*) or their structure, based on the number of breakpoints and type of rearrangement. The three-way CCRs, in which three segments from three chromosomes break off, translocate and unite, are the most common type, as illustrated in this case. CCRs may also be categorised as balanced (where there is no loss or gain of chromosome material) or unbalanced. Balanced carriers are healthy but at risk of infertility, recurrent spontaneous abortions and producing an offspring with

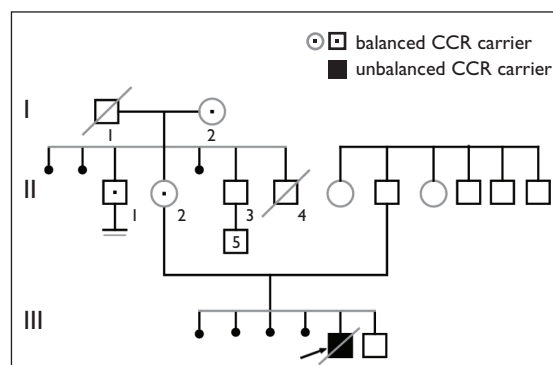


Fig. 1 Pedigree of the family.

an unbalanced CCR. The carrier of an unbalanced CCR has a high risk of global developmental delay, craniofacial dysmorphism and multiple malformations. We report a case of familial CCR that affected three generations of a family, ultimately resulting in balanced and unbalanced carriers.

CASE REPORT

The proband was the first male child born after a series of four spontaneous abortions to healthy, unrelated parents (Fig. 1). His maternal grandmother (I 2) had three spontaneous abortions and four healthy children. His maternal uncle (II 1), who was oligospermic, had no offspring after 13 years of marriage. His mother's youngest brother (II 4) was healthy but died in a road traffic accident at 18 years of age. Except for the proband, all the other family members were phenotypically normal and healthy. After an uneventful antenatal period, the proband was delivered at term with a birth weight of 2.4 kg (third percentile), a length of 45 cm (third percentile) and a head circumference of 34 cm (10th–25th percentile). He had a flat facial profile with prominent eyes, up-slanting palpebral fissures, low-set small ears and bilateral structural talipes equinovarus (Fig. 2). Since birth, he had severe global developmental delay. He rolled over at 16 months and sat with support at 18 months of age. At two-and-a-half years of age, he was unable to sit on his own, stand with support or reach out to grasp objects. He exhibited a social smile at six months of age. Although he has vocalised since

Department of Paediatrics, Monash University Malaysia, JKR 1235, Bukit Azah, Johor Bahru 80100, Malaysia

Ngim CF, BSc, MBBS, MRCP Paediatrician and Senior Lecturer

Department of Paediatrics and Clinical Genetics, Kuala Lumpur Hospital, Jalan Pahang, Kuala Lumpur 50586, Malaysia

Keng WT, MBBS, MRCP, CCST Consultant and Metabolic Specialist

Genetics Department

Ariffin R, MD, MPath, AM Consultant and Head

Correspondence to: Dr Chin Fang Ngim Tel: (60) 7 219 0600 Fax: (60) 7 219 0600 Email: ngim.chin.fang@med.monash.edu.my



Fig. 2 Photograph of the proband at two years of age. Note the prominent eyes, upslanting palpebral fissures and low set ears.

eight months of age, he has never babbled or shown much response when spoken to. Audiologic evaluation with brainstem evoked response showed bilateral sensorineural deafness. Magnetic resonance (MR) imaging of the brain at seven months was normal, as was the MR imaging of the lumbosacral spine, except for a T11 butterfly vertebra. Abdominal ultrasonography and cardiac and ophthalmologic evaluations were normal. During infancy, the proband had recurrent pneumonia that required monthly hospitalisation secondary to gastroesophageal reflux disease, which had been confirmed by barium studies. His immunoglobulin levels and neutrophil counts were normal. At five months of age, he experienced generalised tonic seizures, and electroencephalogram revealed abnormal background, with frequent independent multifocal epileptiform discharges suggestive of symptomatic generalised epilepsy. When the proband was two years and nine months old, he passed away after a bout of pneumonia that was complicated by septicaemic shock.

The proband's G-banding chromosome analysis at 550 band levels showed an extra supernumerary marker chromosome (SMC) (Fig. 3a). His father's karyotyping was normal, but his mother was found to carry a balanced three-way exchange involving chromosomes 7, 12 and 14 (Fig. 3b). Her karyotype was 46,XX,t(7;12;14)(q21.2;q24.2;q13). This finding was confirmed with a dual colour fluorescence *in situ* hybridisation (FISH) with whole chromosome paint (WCP) on chromosomes 7, 12 and 14, which selectively painted two chromosomes in each experiment. Based on the WCP FISH analysis, the

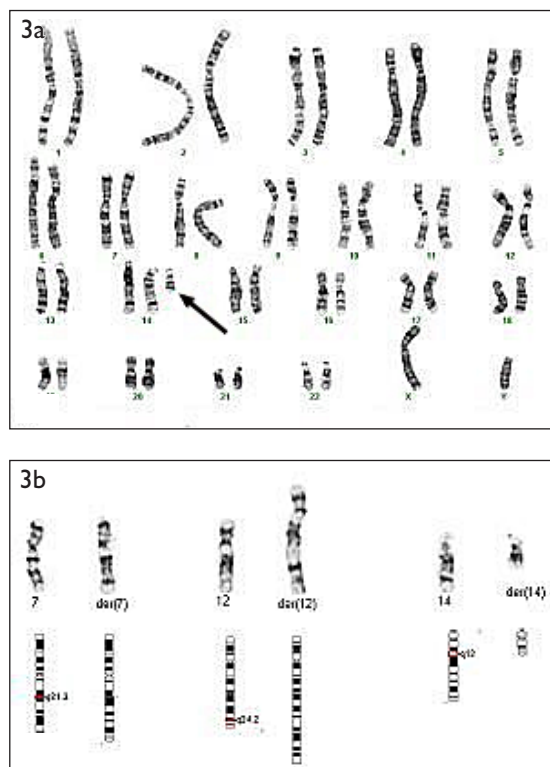


Fig. 3 G-banded karyotype. (a) Proband's karyotype shows the supernumerary marker chromosome (arrow). (b) His mother's partial karyotype with corresponding ideograms shows balanced translocation t(7;12;14)(q21.2;q24.2;q13).

mother's translocation was confirmed to be that of 7, 12 and 14 in origin. In addition, FISH using subtelomeric probes 7qtel and 14qtel was carried out in the metaphase spread, which confirmed that one subtelomeric probe 7q was translocated onto chromosome 12 and one subtelomeric probe 14q was translocated onto chromosome 7. Molecular cytogenetic analysis further characterised the chromosomal rearrangements on the proband, where a dual colour FISH with WCP 7, 12 and 14 revealed that the proband's SMC was a derivative chromosome 14 (Fig. 4). This resulted in trisomy for the region 14pter→14q13 and 12q24.2→12qter. Thus, his karyotype was 47,XY,+der(14)t(7;12;14)(q21.2;q24.2;q13) mat. The balanced form of CCR carried by the proband's mother was also identified in his maternal grandmother (I 2) and maternal uncle (II 1). His uncle II 3, who was healthy and had five healthy sons, declined chromosomal analysis. The proband's younger brother, at ten months of age, carried no evidence of craniofacial dysmorphism or developmental problems. His parents agreed to have his testing deferred till he reaches the age of consent.

DISCUSSION

Structural chromosomal abnormalities can occur as a result of damage to the structural integrity of one or

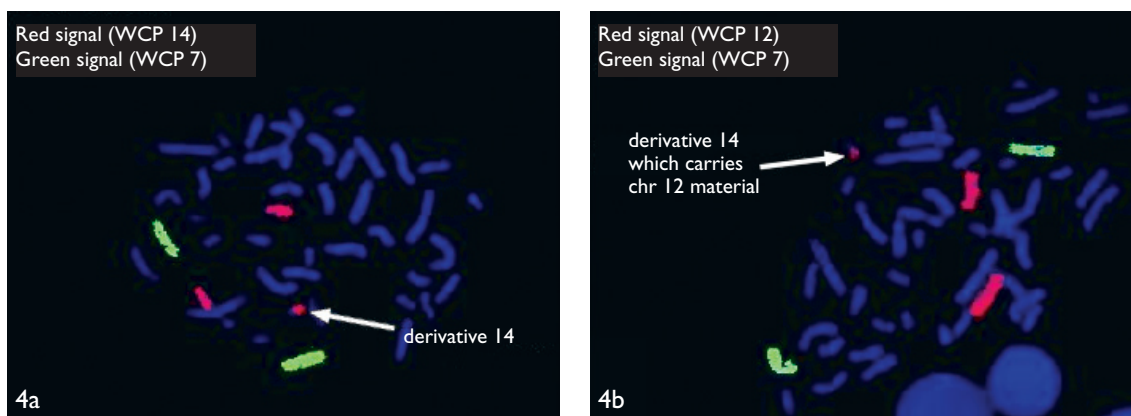


Fig. 4 Dual colour fluorescence *in situ* hybridisation with whole chromosome paint (a) 7 and 14; and (b) 7 and 12. Note that the proband's supernumerary marker chromosome (arrows) was a derivative chromosome 14 with chromosome 12 material.

more chromosomes. The causes include deletion, insertion, inversions and translocations; they may be balanced or unbalanced. Among the structural chromosomal abnormalities, CCRs relate to situations where more than two breakpoints and/or more than two chromosomes are involved. CCRs are rare events. In 1998, Batanian and Esvara conducted a literature survey and listed 114 cases of CCRs.⁽¹⁾ The most common category of CCR is a three-way exchange, in which three chromosomes break off, translocate and unite, as was seen in this case involving chromosomes 7, 12 and 14. As in most three-way CCRs, this case was a familial one and was transmitted through the mother, who in turn had inherited it from her own mother.

Carriers of balanced CCR have normal phenotypes but are at risk of infertility, recurrent abortions and producing offspring with unbalanced rearrangements due to either malsegregation of the derivative chromosomes or formation of a recombinant chromosome. Madan et al determined a carrier's empiric risk for spontaneous abortions as 50% and the risk for a liveborn abnormal child as 20%.⁽²⁾ Further risk assessment would also be determined by patterns in the family. For example, if multiple miscarriages have occurred in the past, there is a tendency for this pattern to continue, as it is likely that all unbalanced forms lead to miscarriage.⁽³⁾ Carriers who have abnormal liveborns carry a higher risk for similar occurrences. Such arguments would predict that the maternal uncle II 3, who had five normal children, was likely to have a normal karyotype.

Carriers of unbalanced CCR are at risk of developmental abnormalities, craniofacial dysmorphism and multiple organ malformations. In the present case, an SMC had occurred as a result of malsegregation of a familial CCR during meiosis, thus resulting in trisomy for the region 14pter→14q13 and 12q24.2→12qter. In

our case, the proband had dysmorphism, severe global developmental delay and epilepsy.

Chromosomal analysis was not conducted on the proband's mother despite her history of recurrent spontaneous abortions. She was only investigated after the proband's abnormal karyotype was noted. Although no cytogenetic study had been carried out on the aborted foetuses, it is reasonable to associate her spontaneous abortions to the foetuses' unbalanced karyotypes. Carp et al reported that in cases of recurrent spontaneous abortions, 10.8% of parental chromosomal aberrations are found.⁽⁴⁾ Most other published series in the literature reported a 3%–5% prevalence rate.⁽⁵⁻⁷⁾ This highlights the importance of karyotyping a woman with recurrent abortions, where the aetiology is undetermined after preliminary investigations, as appropriate genetic counselling and antenatal diagnosis could then be offered to the affected woman.

Males with oligospermia should be offered karyotyping as well. Chromosomal abnormalities have been detected in the karyotypes of 10%–15% of men with azoospermia and 5% with oligospermia, but in less than 1% of normal men.⁽⁸⁾ In a study by Van Assche et al, the overall incidence of structural chromosomal anomalies is 4.6% in oligospermic men and 13.7% in azoospermic men.⁽⁹⁾ The infertility affecting the maternal uncle in the current study also substantiates the general observation that CCRs are rarely transmitted through spermatogenesis.

In conclusion, CCR is a rare type of chromosomal aberration that can be inherited. Techniques are now available to further characterise CCRs. Chromosomal analysis should be considered in any child with dysmorphic features, global developmental delay or multiple organ malformation, as well as in adults who present with recurrent spontaneous abortions or infertility.

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