

Familial reciprocal non robertsonian translocation t(14;22) resulting in 22q11.2 deletion syndrome

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We report the clinical and genetic characterization of 2 cousins sharing the same chromosomal anomaly; a 22pter-q11.2 deletion and a 14pter-q13 duplication due to an unusual familial reciprocal non robertsonian translocation between 2 acrocentric chromosomes t(14;22)(q13;q11.2), the mother of patient 1 was the first cousin of the father of patient 2. Fluorescent in situ hybridization confirmed the cytogenetic results. The patients showed dysmorphic features and developmental delay with evident intrafamilial phenotypic variability. Reciprocal non robertsonian translocation is a rare event, and has not been reported in patients with 22q11.2 deletions. The mechanism responsible for this rare type of translocation is discussed herein.

Key words: familial reciprocal non robertsonian translocation, 22q11.2 deletion, 14pter-q13 duplication, fluorescent in situ hybridization.

Reciprocal non robertsonian translocation involving acrocentric chromosomes is a rare event with only a few cases reported in the literature.¹ The 22q11.2 deletion syndrome (OMIM 188400; <http://omim.org/>) is the most common microdeletion syndrome affecting approximately 1 in 4,000 live births and involving haploinsufficiency of ~ 50 genes resulting in a multisystem disorder.^{2,3} More than 90% of the probands have a de novo deletion of 22q11.2. Phenotypic expression is highly variable and ranges from severe life threatening conditions to only a few associated features. Most common medical problems include: congenital heart defects, in particular conotruncal anomalies; palatal abnormalities, most frequently velopharyngeal incompetence (VPI); immunodeficiency; hypocalcemia due to hypoparathyroidism; genitourinary anomalies; severe feeding problems; and subtle dysmorphic facial features.^{4,5} Partial trisomy of the long arm of chromosome 14 is a rare chromosomal abnormality with an extremely variable phenotype ranging from mild to severe degrees of malformations including

heart defects, eye anomalies, dysmorphic features, global developmental delay, epilepsy and intellectual disability.⁶⁻⁸

We report a unique family in which a parental reciprocal non robertsonian translocation t(14;22)(q13;q11.2) resulted in 2 cousins sharing the same chromosomal anomaly; a 22pter-q11.2 deletion and a 14pter-q13 duplication.

Clinical Report

The research was reviewed and approved by the Medical Research Institute Ethics

Committee (IORG#: IORG0008812) and participation in the study involved informed consent of participating family members.

Patient 1

A full-term female infant aged 7 months was referred for genetic evaluation due to failure to thrive and delayed milestones. She was the second child of non-consanguineous parents

(Fig. 1). The infant had a repaired cleft palate. Neck support was achieved at the age of 6 months. Mild dysmorphic facial features were evident; a round face, hooded eyelids, wide and prominent nasal root, tubular form of the nose, bulbous nasal tip, hypoplastic alae nasi, downturned corners of the mouth with thin lips, a high arched palate and small low-set ears. Anthropometric measurements included a birth weight of 3.5kgs (p50-75). At 7 months her weight was 5.5kg (p5), length 61cm (p3) and head circumference (HC) 39cm (p3). The patient had rudimentary thymus, suffered from recurrent attacks of otitis media and bronchial asthma. Apart from the facial features, the infant's examination was unremarkable; the echocardiography, abdominal ultrasound and fundus examinations revealed no anomalies.

Patient 2

The cousin of patient 1, a female infant aged 9 months born full-term was the only child of consanguineous parents (Fig 1). She presented with dysmorphic features, delayed milestones and had difficulty in swallowing. Dysmorphic facial features included a round face, wide and prominent nasal root, tubular form of the nose, bulbous nasal tip, hypoplastic alae nasi, thin lips, mild retrognathia and malformed small low-set ears. Her birth weight was

2.5kgs (p3). At 9 months her weight was 5.8kg (< p3), length 64cm (p5) and HC 40cm (p3). The patient suffered recurrent attacks of otitis media and respiratory chest infections. Echocardiography showed VSD, chest X-ray showed absent thymus, fused thoracic vertebrae and duplicated ribs. Endoscopy showed velopharyngeal insufficiency. Fundus examination revealed no anomalies.

Cytogenetics

Giemsa trypsin stained karyotypes were prepared from cultured lymphocytes of the patients, their parents and the sibling of patient 1 according to standard procedures. Karyotypes of the patients revealed a derivative chromosome replacing one of the two chromosomes 22 in all metaphases. Parental karyotypes of the patients showed that the mother of patient 1 and the father of patient 2 (who were cousins) had a translocation $t(14;22)(q13;q11.2)$ (Fig. 2A-D). The karyotype of patient 1 was thus $46,XX,+der(14)t(14;22)(q13;q11.2)mat,-22$ whereas, that of patient 2 was $46,XX,+der(14)t(14;22)(q13;q11.2)pat,-22$. The phenotypically normal 4 year old sibling of patient 1 carried the maternal translocation. FISH using Kreatech MD DiGeorge TUPLE (22q11) Spectrum Orange/22qter Spectrum

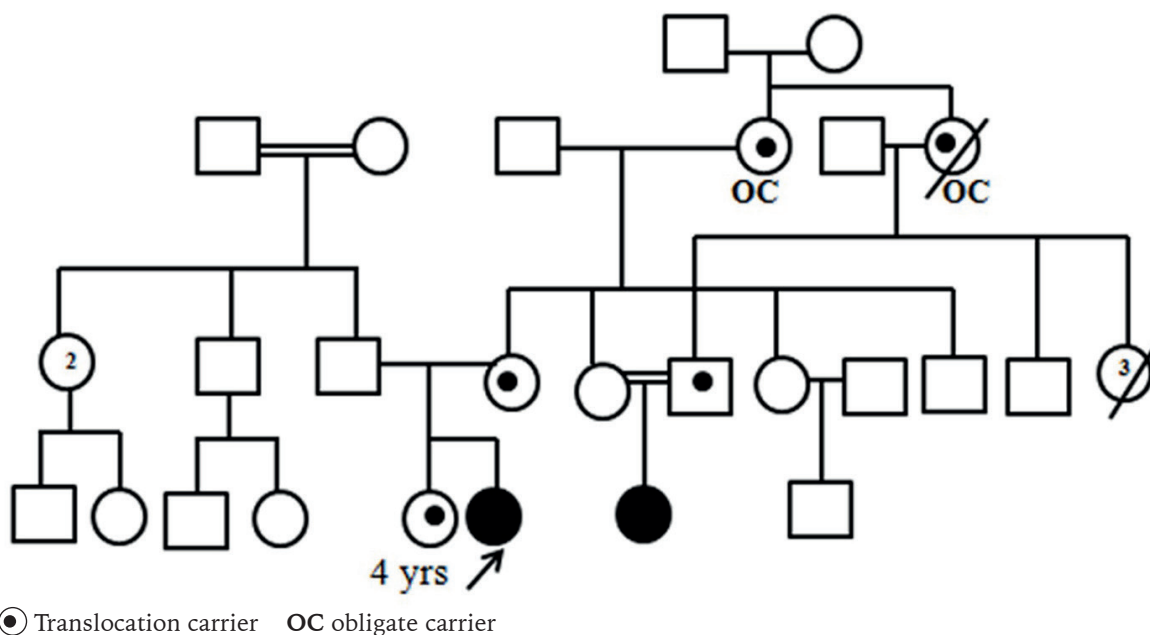


Fig. 1. Pedigree of Family with $t(14;22)(q13;q11.2)$.

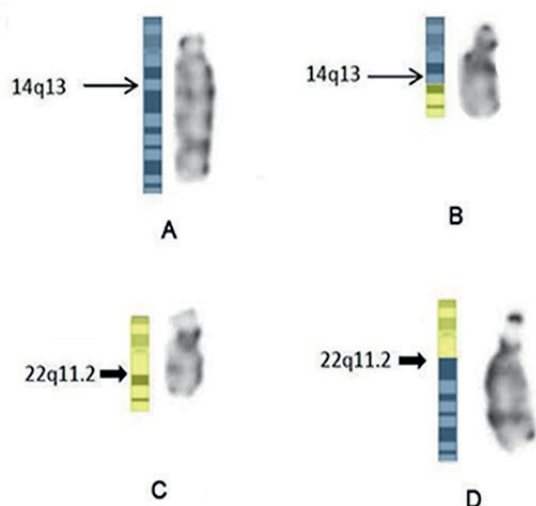
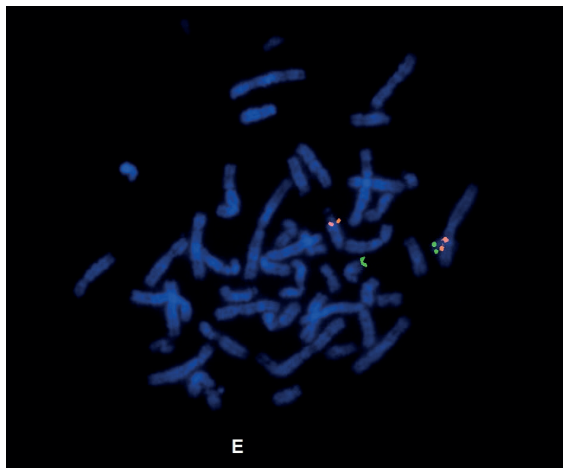


Fig. 2. (A). Normal chromosome 14; the arrow shows the breakpoint
 (B). der(14)t(14;22)(q13;q11.2)
 (C). Normal chromosome 22; the bold arrow shows the breakpoint
 (D). der(22)t((14;22)(q13;q11.2).



(E). FISH using Kreatech MD DiGeorge TUPLE (22q11) Spectrum Orange/22qter Spectrum Green shows 2 red signals; one on chromosome 22 and the other on der (22), 2 green signals; one on chromosome 22 and the other on der (14) (father of patient 2).

Green confirmed the G-banding results of the parents and established the diagnosis of 22q11.2 deletion in the patients. FISH in metaphase chromosomes of the parents and the sibling carrying the translocation showed 2 red signals of the 22q11.2 band; one on the normal chromosome 22 and the other on der(22). The 2 green signals were present on



(F). FISH using Kreatech MD DiGeorge TUPLE (22q11) Spectrum Orange/22qter Spectrum Green shows 1 red signal and 2 green signals confirming the 22q11.2 deletion (patient 1).

the normal chromosome 22 and the der(14) (Fig. 2E). The patients inherited the der(14) thus lacking the red signal of 22q11.2 but retaining the 2 green signals (Fig 2F).

Table I shows the features of our 2 patients compared to previously reported features of patients with 22pter-q11.2 deletions and 14pter-q12~3 duplications.

Discussion

We report the presence of 22pter-q11.2 deletion and 14pter-q13 duplication in first degree cousins due to a familial parental balanced reciprocal non robertsonian translocation t(14;21)(q13;q11.2). To the best

Table I. Comparison of Features Common to Previously Reported Patients with Deletion 22q11.2- or Duplication 14pter-q13.

	22q11.2 deletion ^{9,10}	Patient 1	Patient 2	14pter-q12~13 duplication ^{6,11-13}
Developmental delay	+	+	+	+
Malar-flatness	+	+	+	+
Short palpebral fissure	+	-	+	+
Hooded eyelids	+	+	-	-
Broad nasal bridge	+	+	+	+
Tubular nose	+	+	+	-
Broad/round nasal tip	+	+	+	+
Hypoplasia alae nasae	+	+	+	-
Small mouth	+	+	+	-
Low set ears/Small ears	+	+	+	+
Cleft palate	+	+	-	+
Limb anomalies	Long slender fingers	Long slender fingers-Clinodactyly	-	Clinodactyly-Brachydactyly-Club foot
Rib anomalies	+	-	+	-
Vertebral anomalies	+	-	+	-
Congenital heart disease	+	-	+	+
Feeding difficulties	+	-	+	-
Recurrent infections	+	+	+	+
Absent/hypoplastic thymus	+	+	+	-

of our knowledge this is the first report of 22q11.2 deletion syndrome resulting from a parental balanced reciprocal non robertsonian translocations involving chromosomes 14 and 22. It has been reported that, unless there is a concomitant deletion or duplication of another chromosome, there is no significant phenotypic difference between deletions comprising 22pter-q11.2 and those of only 22q11.2.¹⁴ The 22q11.2 deletion is one of the most common chromosomal anomalies whereas anomalies of chromosome 14 are rare. Clinically 22q11.2 deletions and 14pter-q12~13 duplications share common features including developmental delay, mild dysmorphic features, recurrent infections and congenital heart disease (CHD) Table I.^{6,10,12-13,15} Aside from CHD absent in patient 1, the 2 patients shared the aforementioned features. Our patients showed phenotypic variability previously reported in patients exhibiting 22q11.2 deletions.¹⁶ Patient 2 showed no

hooded eyelids and no palatal anomalies in contrast to patient 1 who presented with hooded eyelids and a repaired cleft palate. Absent thymus, velopharyngeal insufficiency, fused thoracic vertebrae and duplicate ribs were present in patient 2 whereas patient 1 had a rudimentary thymus. Besides inter- and intrafamilial phenotypic variation exhibited by patients with 22q11.2 deletions, phenotypic variability was reported across different population groups such as African, African American, Asian and Latin American, with difficulty diagnosing individuals of African descent.¹⁰ More than 50% of patients of African descent had CHD, ear anomalies and learning problems. Comparing our patients to those of African descent, CHD was present in one patient, both had ear anomalies whereas our patients were too young to assess their learning ability. Genetic modifiers, chance association, or environmental interactions have been proposed to explain the intra-

familial variability. Somatic mosaicism or post zygotic second hit have also been hypothesized as potential mechanisms underlying such phenotypic discordance, even though, to date, no definitive explanation is available.¹⁷

Reciprocal, non-robertsonian constitutional translocations are the result of crossover between two non-homologous chromosomes and most are known to be unique events. Balanced translocations with 22q11 breakpoints represent non-random genomic rearrangements in this region. Most constitutional translocations involving 22q11 share the same 22q11.2 low copy repeat (LCR) breakpoint located within LCR-B.¹⁸ Chromosome 14 and 22 contain *neurofibromatosis 1 (NF1)* pseudogenes that are highly related to each other.¹⁹ The translocation t(14;22) present in our cases may be explained by the homology of the q11 regions of both chromosomes. The interchromosomal transposition events require close contact between chromosomes involved in the rearrangement. It is known that the pericentromeric regions of the acrocentric chromosomes tend to aggregate and that chromosomes occupy defined positions in the cell nucleus.

Genetic counseling is recommended for parents of an affected child with the 22q11.2 deletion to discuss the natural history of this disorder, including the spectrum of medical problems and cognitive difficulties that these infants may encounter.²⁰ The family was counseled about the presence of a familial translocation which resulted in the deletion duplication present in their offspring. The importance of cytogenetic evaluation of all family members was explained since there was a chance that 2 carriers of the balanced translocation would marry. As consanguinity is still high in Egypt, we explained the consequences of consanguineous marriage in a couple where both partners carried the translocation. A marriage between first cousins with the same translocation poses several reproductive problems. A considerable variety of unbalanced gametes may be produced by meiotic segregation of the chromosomes

involved in a reciprocal translocation and their normal homologue. Zygotes carrying extensive imbalances presumably have a very low chance of surviving beyond the first trimester. Balanced zygotes originating from unbalanced gametes with complementary chromosomal sets have been reported.^{21,22}

In conclusion, this is the first report of 22q11.2 deletion syndrome resulting from a parental balanced reciprocal non robertsonian translocations involving chromosomes 14 and 22. This family adds to the previous evidence of intrafamilial phenotypic variation of patients with 22q11.2 deletion.

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