Trisomy Chromosome (22)(q13.1-qter) as a Result of Paternal Inversion (22)(p11q13.1) Proved Using Region-Specific FISH Probes

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We present a male infant with multiple congenital anomalies including severe growth retardation, microcephaly, hypertelorism, low-set ears, bilateral cleft lip and palate, micrognathia, cryptorchidism with hypospadias, hemivertebrae, and complex heart defects. The karyotype was 46, XY, rec(22) dup(22q) inv(22)(p11q13)pat. The duplicated segment (q13.1 →qter), a result of an unbalanced recombinant derived from the paternal inversion (22)(p11q13.1), was confirmed using results of silver staining for nucleolar organizer regions (NOR) and fluorescence in situ hybridization with region-specific probes (D22S75/D22S39 and Mbcr). This case further delineated the clinical entity of duplicated 22q13 or distal trisomy 22. *(Chang Gung Med J 2005;28:657-61)*

Key words: Chromosome 22, inv(22), dup(22), distal trisomy 22.

Complete trisomy 22 is very rare in liveborn infants, although it is a common finding in spontaneous abortions. The existence of such chromosomal abnormalities has been questioned. Previously the supernumerary marker chromosomes such as inv dup(15) or der(22)t(11;22) may look like chromosome 22 using G-banding but was elucidated after the advent of fluorescence in situ hybridization (FISH).[1-3] Only mosaic or partial trisomy of either proximal or distal segment of the long arm of chromosome 22 could survive.[4,5] Some of those cases were caused by unbalanced translocations involving chromosome 22.[1,3,4] A new case of a duplication of the distal part of the long arm of chromosome 22 (q13.1-qter) due to paternal inversion confirmed using FISH with the specific painting and cosmid probes from chromosome 22 is reported.

CASE REPORT

The male patient was the first child of unrelated, healthy Taiwanese parents. His birth weight at term was 1300 g, length was 40 cm, and head circumference was 26 cm (all were far below the 3rd percentile for a term male infant). Intrauterine growth retardation (IUGR) was noted at 20 weeks' gestation, with sonography showing simultaneous oligohydramnios. His mother denied any history of smoking, alcohol, drug, radiation exposure, or diabetes. However, there was a long history of secondary infertility with two episodes of early trimester spontaneous abortion. After birth, the baby showed generalized cyanosis, respiratory distress and bradycardia. In addition to severe growth retardation, multiple congenital anomalies were found as follows: microcephaly, hypertelorism, low-set ears, bilateral complete cleft lip and palate, micrognathia, clenched hands, cryptorchidism, and penoscrotal hypospadias. A grade II/VI systolic murmur over the left sternal border was noted. Radiographs showed cardiomegaly and thoracic hemivertebrae. Cardiac echocardiography revealed type I truncus arteriosus

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Received: May 1, 2004; Accepted: Aug. 16, 2004
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with major aortico-pulmonary collateral arteries, an atrial septal defect, a ventricular septal defect and a large patent ductus arteriosus. Brain echocardiography showed mild ventriculomegaly. Renal echocardiography showed normal kidneys and ureters.

Chromosome study of the patient from the peripheral lymphocytes stimulated by phytohaemagglutinin showed 46, XY, $22p^+$ using G-banding (Fig. 1). The possibility of a large satellite short arm on chromosome 22 (i.e., 22p13) was eliminated by Q-banding and the nucleolus organizer region (NOR) staining (Fig. 1). The use of the painting probe "Coatasome 22" (Oncor) confirmed that all of the additional material was derived from chromosome 22 (Fig. 2A). By using the DiGeorge chromosome region (D22S75) and a control probe (D22S39) (Oncor), the D22S75 signals (locus: 22q11.2) were intact but three copies of D22S39 (locus: 22q13.3) existed (Fig. 2B). Thus the specific chromosome 22q11.2 deletion syndrome was excluded. The Mbcr probe (Major breakpoint region locus: 22q11, proximal to D22S75) also confirmed this finding. There was one copy on the abnormal chromosome, and therefore by inference that is D22S39 in two copies on this chromosome and not D22S75 (Fig. 2C). Thus, the karyotypes of both parents were examined. His father's karyotype showed a metacentric inverted chromosome 22 without NOR signals (Fig. 1) and the mother was 46, XX. FISH of the probes described above also confirmed the nature of inv(22) in the father (Figs. 2D-E). Therefore, the karyotype of the proband was established: 46, XY, dup inv(22) (qter→q13.1::p11→qter) representing duplication of the segment 22q13.1→qter, as an unbalanced recombinant derived from the paternal inversion (22) (p11q13.1).

Progressive heart failure with subsequent hepatomegaly and renal failure developed, and he responded poorly to diuretics and inotropic agents. No hypocalcemia or evidence of thymic hypoplasia was noted. The patient died at 1 month of age due to multiple organ failure.

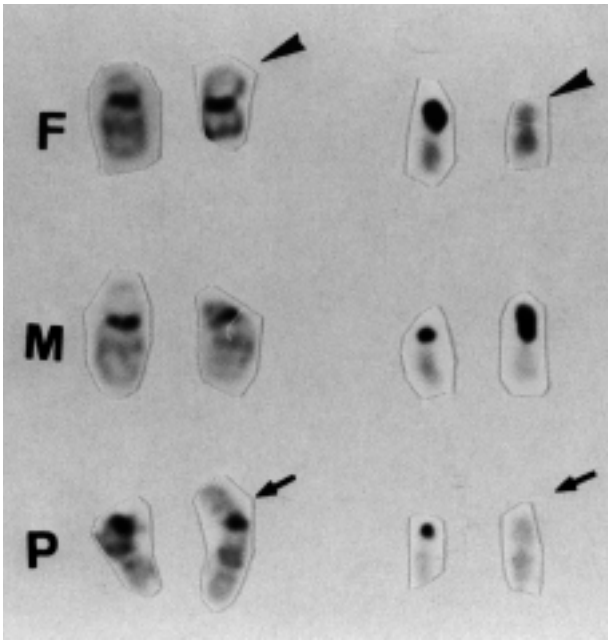

Fig. 1 Partial karyotypes of the mother (M), father (F) and proband (P), illustrating the abnormal chromosome 22 (arrowhead) derived from paternal inversion 22 (arrow). Note the indicated inverted and abnormal 22s show no NOR staining.

DISCUSSION

This case represents a "pure" duplication of 22q, from q13.1 to qter, without involvement of any other chromosome segment proved using results of FISH studies. The derivative chromosome exhibited three signals (for D22S39) with the D22S75/D22S39 probe combination (Fig. 2). In order to investigate the inversion breakpoints, we also performed FISH with the cosmid Mbcr in the region 22q11. Mbcr cosmids showed normal hybridization signals, suggesting the existence of trisomy in D22S39 region. The rearranged chromosome was thus interpreted as a result of an inverted duplication of part of the long arm of chromosome 22 (from q13.1 to qter) followed by an unbalanced recombinant derived from the paternal metacentric inversion (Fig. 3). Thus, the patient is apparently trisomic for the region 22q13.1 to 22qter.

Pericentric inversions of human chromosomes are not rare, especially in 1, 9, 16 Y. They are often familial and benign, but can lead to unbalanced recombinants in many instances.[6] Structural chromosomal rearrangements may preferentially involve specific regions or segments. The chromosome involved (the amount of constitutive heterochromatic material), the size of the inverted segment, the sex of the carrier parent, and the specific breakpoints in the

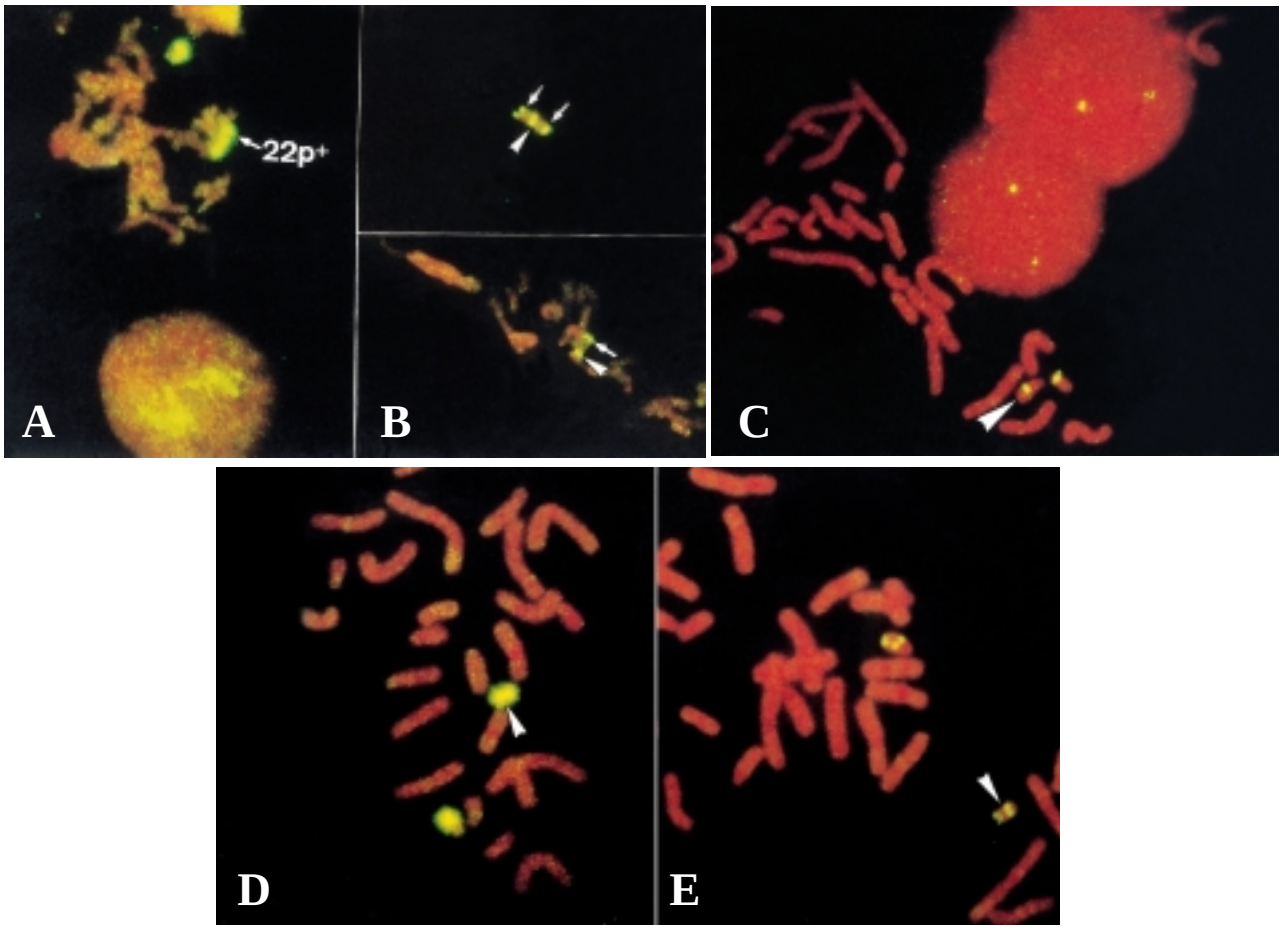

Fig. 2 FISH studies showing (A) whole chromosome 22 painting probe confirming the origin of the 22p^{+} segment (arrow); (B) D22S75/D22S39 showing intact D22S75 (arrowheads) but trisomic D22S39 (arrows); (C) Mbcr showing intact 22q11 in the proband (arrowhead); and (D, E) describing the nature of paternal inverted chromosome 22 (arrowheads) with the probes as in A & B, respectively.

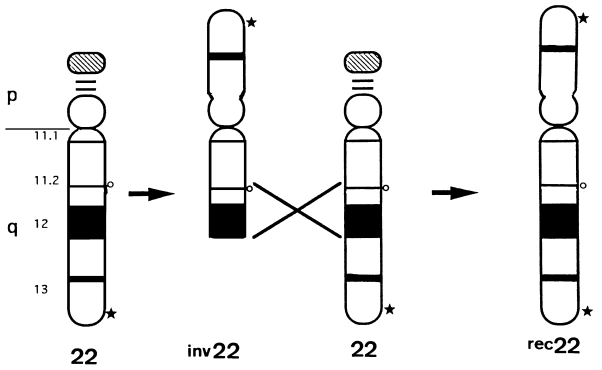

Fig. 3 Diagramatic representation of the recombinants from the inverted 22.

inverted chromosome appear to influence the formation of unbalanced recombinants.[6] Chromosome 22 contains several unique repeated gene families.[7] Unequal crossing-over between multiple members of these gene families may produce *de novo* deletions or other alterations of chromosome 22 such as complex inversions. The results of previous reports[5,8-10] and this case show that both male and female carriers of inversion (22)(p13q12) or (p11q13) are at risk for having unbalanced recombinant offspring. Any instance of odd numbers of crossing-over at the time of pairing up of the normal and inverted 22 during meiosis within the inverted segment may result in either duplicated or deleted 22q13→13qter. Carriers

of derivative inverted chromosomes are usually at risk for producing gametes of unbalanced chromosome complements. The poor reproductive history of the mother of the proband may have resulted from fetal chromosome unbalance. In fact, the paternal inverted (22)(p11q13.1) appears to be the cause of fetal wastage and abnormal offspring or pregnancy in the family.

The majority of duplicated chromosome 22 involve the proximal segment, such as cat-eye syndrome or der(22)t(11;22).[11] Duplications of the distal segment have been reported in a few cases and they allowed the delineation of a distal 22q syndrome.[9,10] Severe mental and growth retardation, microcephaly, dysmorphic facies, low-set ears, cleft lip and palate and micrognathia, cryptorchidism were seen in patients with duplicated 22q12 → qter.[5,8,10] Meanwhile, preauricular skin tags or sinuses, the cat eye syndrome (anal atresia and coloboma) were absent, which were present in complete trisomy 22 or proximal trisomy 22.[4,12] The phenotypic features of the present case have a number of similarities with the distal 22q syndrome, notably cleft lip and palate, micrognathia, heart defects, skeletal defects and severe IUGR. Several syndromes with overlapping features should be differentiated, including velocardiofacial syndrome (or the acronym CATCH 22),[13] Goldenhar syndrome, and trisomy 13 or 18. Since the recombinant chromosome looks like an acrocentric chromosome with a large satellite or a translocated segment from other chromosomes, G-banding along with NOR-staining should be routine tests for both patient and parents. FISH with specific probes such as whole chromosome 22 painting probe, specific cosmids (D22S75, D22S39 or M-bcr) could be used to confirm the nature of the rearranged chromosome 22.

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以區域特異性 FISH 探針證實源於父親倒轉染色體 22p11q13.1 之染色體 22q13.1-qter 三體症

侯家瑋

一名男嬰有多重先天畸形，包括嚴重生長遲滯、小頭症、眼距過寬、低位耳、雙側唇顎裂、小下巴、隱睪症合併尿道下裂、脊椎缺損，與複雜型心臟病。他的染色體核型爲 46, XY, rec(22) dup(22q) inv(22)(p11q13)pat，其複製染色體片段 (q13.1→qter) 之產生乃源於父親倒轉第二十二號染色體 (22)(p11q13.1) 之不平衡構造重整所致。由 NOR 特殊染色及使用染色體特異探針 (D22S75/D22S39 和 Mbcr) 之螢光性原位雜合法已作進一步確認。本病例更可描述複製染色體 22q13 或遠端染色體 22 三體症之臨床特徵。(長庚醫誌 2005;28:657-61)

關鍵字：第二十二號染色體，倒轉染色體二十二，複製染色體二十二，遠端染色體 22 三體症。

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受文日期：民國93年5月1日；接受刊載：民國93年8月16日
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