READERS OPINION

# A familial rearrangement(3;5;9) with paternal and maternal transmission leading to a duplication 3p/deletion 5p infant

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We report a complex rea(3;5;9) observed in an unbalanced child who inherited this mutation from his mother and maternal grandfather.

The propositus, a male infant, was the only child of healthy non-consanguineous parents aged 28 (father) and 24 years. There was no history of miscarriages or malformations on either side of the family. The pregnancy and vaginal delivery were normal. The infant's birth weight and length were 2,450 g and 45 cm, respectively. Due to a complex heart defect (PDA, VSD, and ASD) and respiratory insufficiency, he was hospitalized for 30 days. Two months later, he underwent surgery to correct the cardiac defects. His psychomotor development was delayed. Clinical examination at 6 months of age revealed severe growth retardation (weight of 4.9 kg, length of 58 cm, OFC of 37 cm), hypotonia, diminished reflexes, brachycephaly, prominent forehead, bilateral ectropion and blepharophimosis, a small nose with anteverted nares, microstomia, micrognathia, a short neck, dysplastic and cupped ears, an osseous appendix in the sternum, and a single palmar crease in the left hand. The abdomen and external genitalia were normal. The patient had neither a cat-like cry nor telecanthus. One month later, the patient died of hypoventilation; no autopsy was performed.

The karyotypes of the patient and several relatives were determined using G-banding and Fluorescence in situ hybridization (FISH). The probes 3p (Vysis, Abbott Laboratories, Abbott Park, IL, USA)/5p (Cytocell, Cytocell Ltd., Cambridge, UK) subtel, ABL/BCR (Vysis, Abbott Laboratories, Abbott Park, IL, USA), and cri du chat/Sotos (Cytocell, Cytocell Ltd., Cambridge, UK) were used to test both the child and his mother; the mother was also tested with painting probes for chromosomes 3 and 9 (Cytocell, Cytocell Ltd., Cambridge, UK). This combined analysis led to the diagnosis of a familial 4-breakpoint rea(3;5;9) in both balanced and unbalanced forms (Figures 1 and 2). The patient had a duplication for 3p24.3→pter concomitant with a deletion for 5p15.2→pter due to a 46,XY,der(5)der(9)rea(3;5;9)(p24;p13.1p15.2;q22)mat.ish der(5)(5psubtel–,cri du chat–,ABL+)der(9)(3psubtel+,5psubtel–,ABL–) karyotype. In contrast, the mother's balanced complement was 46,XX,rea(3;5;9)(3qter→3p24.3::5p15.2→5pter;5qter→5p13.1::9q22→9qter;9pter→9q22::5p13.1→5p15.2::3p24.3→3pter).ish der(3)(3psubtel–,5psubtel+,cri du chat+)der(5)(5psubtel–,cri du chat–,ABL+,wcp9+)der(9)(3psubtel+,cri du chat–,ABL–,wcp3+). The patient's maternal grandfather was also a balanced carrier, and the patient's father had a normal 46,XY karyotype.

The non-specific phenotype of the patient, including the lack of the cry and facies characteristic of the 5p deletion syndrome, can more parsimoniously be ascribed to his compound imbalance (1). The complex heart defect and death in infancy appear to be related to the 3p duplication (2).

Because the 5p segment can be regarded as ''inserted'' into the der(9), our observation may support the contention that complex chromosome rearrangements (CCR) with at least one insertional translocation can be transmitted either paternally or maternally and are refractory to recombination


**Figure 1** - Partial G-banded karyotypes of the familial rea(3;5;9)(p24.3;p13.1p15.2;q22). *Upper row*: the child's unbalanced karyotype, with only the 5 and 9 derivatives; the patient had a duplication of 3p24.3→pter concomitant with a deletion of 5p15.2→pter. *Lower row*: the mother's balanced karyotype, with all three derivatives. Except for the patient's normal pair 3, the derivative is on the *right* in each pair.



No potential conflict of interest was reported.

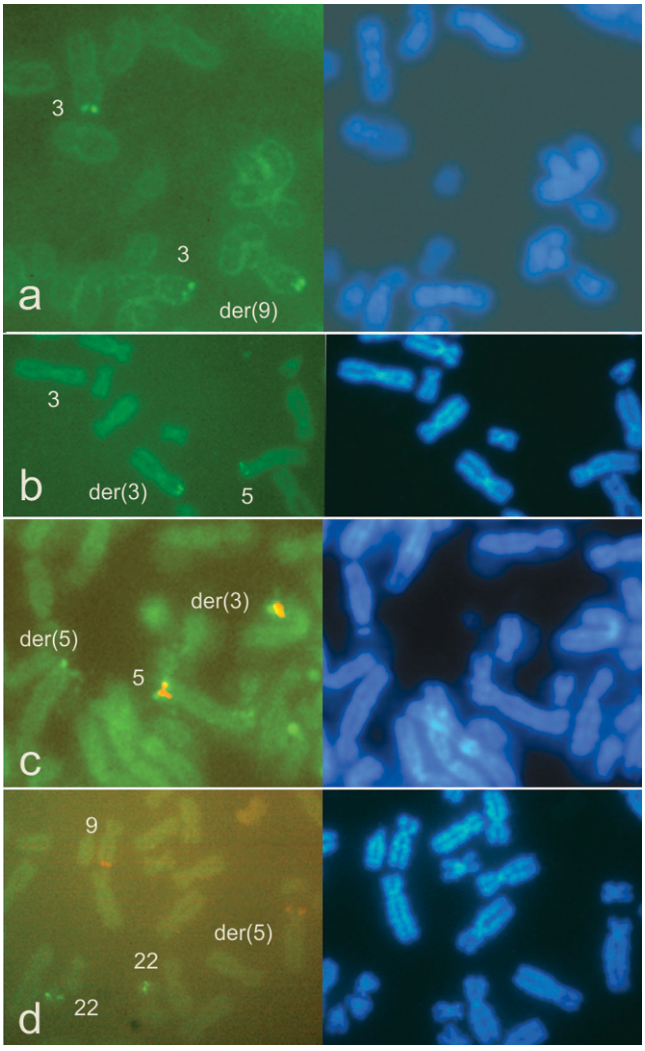


**Figure 2 -** FISH karyotype analyses of the patient (a) and his balanced mother (b-d). a: The 3p subtel probe (*green*) hybridized to both the normal 3 and the der(9). b: The 5p subtel probe (*green*) hybridized to both the normal 5 and the der(3). c: The combined cri du chat (*green*/*red*)/Sotos (*green*) probe confirmed the translocation of 5p15.2→pter onto 3p24.3; i.e., the der(3) had both 5p or cri du chat signals, whereas the der(5) exhibited only the 5q35 Sotos signal. d: The ABL (*red*)/BCR probe (*green*) hybridized to both the normal 9 and the der(5) and to both copies of chromosome 22. DAPI counterstained images are on the *right*.

(3). The CCR of this patient — like other 3-chromosome rearrangements (4,5) — is expected to lead to imbalances predominantly via improper segregation.

Even if the unique nature of most CCRs requires the determination of the specific reproductive risks in each individual case (4,5), in general these risks appear to be greater than the corresponding empirical risks associated with reciprocal translocations, amounting to a ~50% risk of miscarriage and a ~20% risk of an unbalanced live infant (6). In addition to the gamete that led to the double imbalance in our patient, there are five other ''adjacent-1'' gametes that can be produced by carriers of the present CCR; notably, the counterpart der(3)/5/9 gamete would result in a viable del 3p/dup 5p unbalanced child. The theoretical ''adjacent-2'' (12 different gametes) and asymmetric 4:2, 5:1, or 6:0 segregations (44 gametes) are unlikely to be compatible with postnatal survival (except perhaps trisomy 9).

The involvement of chromosomes 3, 5, and 9 in the present CCR is consistent with the disproportionate participation of these chromosomes among the ~250 CCRs reported to date (5,7,8); the involvement of these chromosomes is even more disproportionate if all ~40 prenatally diagnosed instances are considered (9,10). Yet, this specific chromosomal combination has not apparently been described even though these three chromosomes were involved in a single more complex karyotype (11).

Finally, the fact that four de novo CCRs (12-15) and one de novo double balanced translocation (16) have been documented in fetuses (four female, one male) conceived after intracytoplasmic sperm injection should not be disregarded.

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## AUTHOR CONTRIBUTIONS

Rivera H designed the study and wrote the report. Domínguez MG performed the chromosomal analyses and critically reviewed the manuscript. Both authors approved the final version of the manuscript.

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