HEALTH SERVICES LABORATORIES

A rare familial intrachromosomal insertion elucidated by Fluorescence in situ Hybridization (FISH) studies

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Summary

Here we present a rare case of a familial intrachromossomal insertion, clarified by FISH studies, initially misinterpreted as a paracentric inversion by karyotyping. We discuss challenges in diagnosing these abnormalities and their clinical implications.

Introduction

Karyotyping parents of children with congenital malformations and/or developmental delay can reveal balanced rearrangements causative of unbalanced chromosomes in their progeny[1]. Different abnormality types infer different levels of reproductive risk. Precise identification of these rearrangements is essential for genetic counselling, prenatal diagnosis, and wider familial studies[2].

Within-arm insertions involving the insertion of a segment within the same chromosome arm, are rarely reported. In contrast, paracentric inversions where an inverted segment reinserts within the arm, are common[3]. Both can cause a similar G-banding pattern making it difficult to distinguish them by karyotyping alone. This distinction is crucial because their different meiotic behaviors infer high versus minimal reproductive risk, respectively[4]. Within-arm insertions can produce gametes with a gain or loss of the inserted segment, possibly leading to viable unbalanced offspring. In paracentric inversions, crossing-over within the inverted loop results in dicentric and acentric chromosomes, which are unstable and unlikely to produce viable unbalanced progeny[1].

Case details

The proband was a 21-week-old fetus with structural malformations on ultrasound scan. Analysis revealed a ~6 Mb deletion of chromosome 1 at bands 1q41-q42.13.

Maternal karyotype analysis revealed a balanced rearrangement of this 1q region, initially interpreted as a paracentric inversion. Karyotyping of the maternal sister, who had an affected baby with a gain of this 1q region, showed she carried the same "paracentric inversion" (Fig 1).

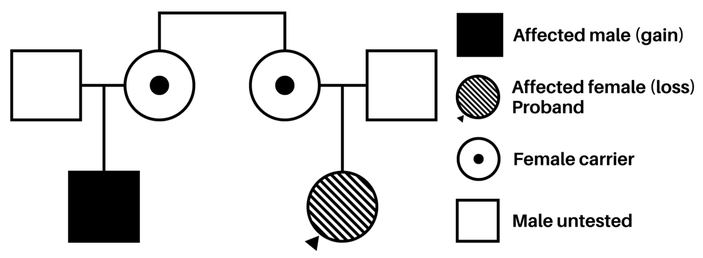

Figure 1. Family pedigree.

Detection of complimentary 1q gain and loss within the progeny is consistent with the meiotic behavior of a within-arm insertion rather than a paracentric inversion[5].

FISH studies & meiotic origin

To differentiate between an inversion & insertion, FISH probes located across the 1q region where used. The resulting signal pattern indicated an insertion confirming this hypothesis (Fig 2).

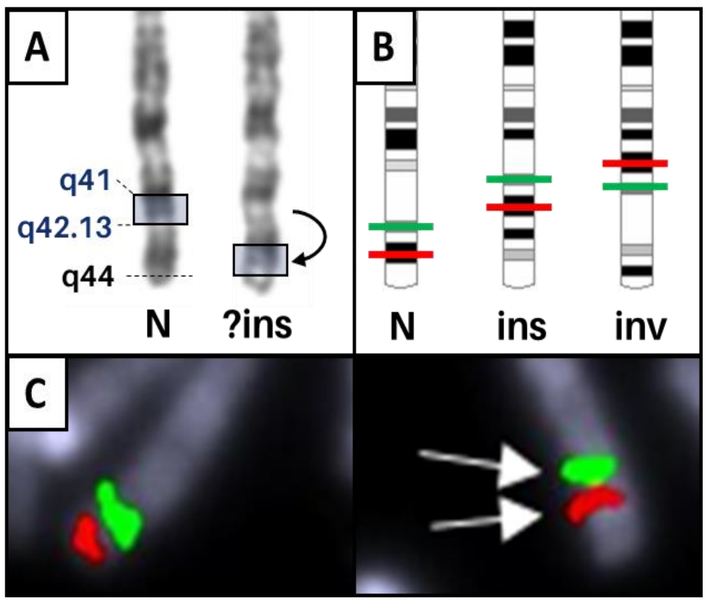

Figure 2. A: G-banded region of chromosome 1 of the proband's mother. N: normal, ?ins: possible insertion. B: Idiogram showing expected FISH patterns for normal (N), within-arm insertion (ins), and paracentric inversion (inv), using probes targeting bands 1q42.2 (green) and 1q43 (red). C: FISH results for normal (left) and inserted (right) chromosomes 1.

Gain and loss of the same 1q region in the progeny can arise by maternal meiotic recombination at segment 1q42.13q44 during incomplete or complete synapsis between the normal & inserted chromosome 1 (Fig 3).

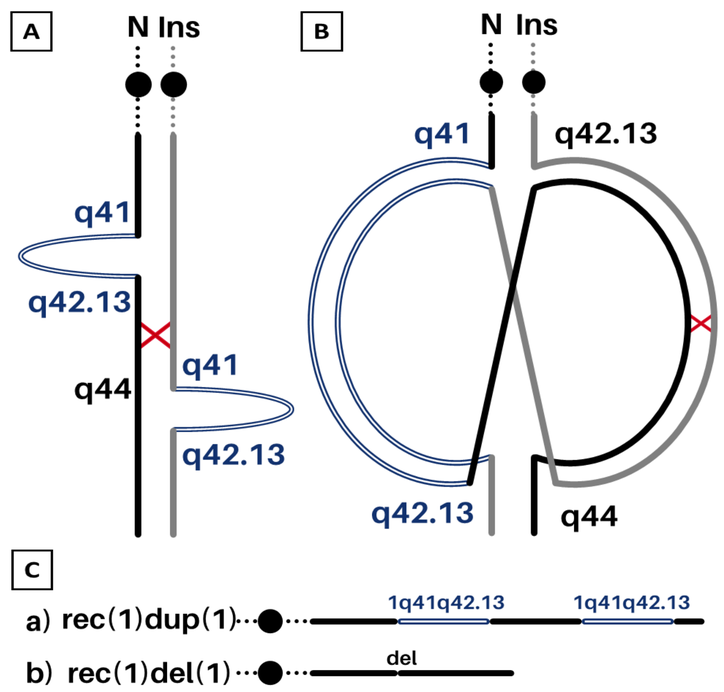

Figure 3. A: Incomplete synapsis (folding out). B: Complete synapsis (double-loop). N: normal chromosome 1, ins: inserted chromosome 1. C: Recombinants resulting from crossing-over at the x. a) Duplication of segment 1q41q42.13, b) Deletion of segment 1q41q42.13.

Discussion/Conclusion

This case highlights how within-arm insertions can be misinterpreted as paracentric inversions by karyotyping alone. A comprehensive family history, combined with tailored FISH studies, was essential for differentiating between a low risk paracentric inversion and a within arm insertion which infers significant reproductive risk for recurrence in subsequent pregnancies. This enables effective genetic counseling, ensuring families receive accurate information about recurrence risks and the potential genetic implications for future generations.

References

1. Gardner RJM, Amor DJ. *Gardner and Sutherland's Chromosome Abnormalities and Genetic Counseling*. 5th ed. New York: Oxford Academic; 2018.
2. Madan K. Paracentric inversions: a review. *Hum Genet* 1995;96(5):503–15. doi:10.1007/BF00197403.
3. Madan K, Nieuwint AW. Reproductive risks for paracentric inversion heterozygotes: inversion or insertion? *Am J Med Genet* 2002;107(4):3403.
4. Ardalan A, Prieur M, Choiset A, Turleau C, Goutieres F, Girard-Orgeolet S. Intrachromosomal insertion mimicking a pericentric inversion: molecular cytogenetic characterization of a three-break rearrangement of chromosome 20. *Am J Med Genet A* 2005;138A(3):288–93. doi:10.1002/ajmg.a.30966.
5. Madan K, Menko FH. Intrachromosomal insertions: a case report and a review. *Hum Genet* 1992;89(1):1–9. doi:10.1007/BF00207032.