SNP Array and Genome Sequencing Demonstrated Revertant Mosaicism via Postzygotic Rescue as the Main Mechanism of Mosaic Chromosomal Terminal Duplications

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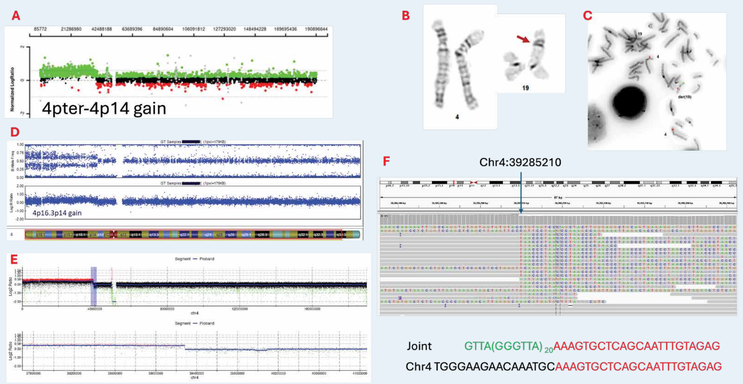
INTRODUCTION

- Trisomy rescue is a well-known mechanism of generating a normal cell line. Here, we describe revertant mosaicism, in which all cells initially carry chromosomal structural rearrangement instead of aneuploidy, and a subset reverts to normal cells without rearrangement – resulting in a mosaic population composed of both abnormal and genetically corrected cells.
- Recognizing this mechanism reframes how we interpret mosaic structural variation in rare diseases.
- Mosaicism for a normal cell population and a pure terminal duplication is extremely rare.
- We previously reported two siblings with features of Down syndrome and mosaicism for an inherited chromosome 8 with additional chromosome 21 material attached to the end of 8q; interstitial telomeric sequences (ITS) were present at the junction. The normal cells are proposed to arise through a reversion of the abnormal chromosome 8 due to ITS instability.[1]
- In this study, we further investigated the formation mechanism of mosaic chromosomal rearrangements.

METHODS

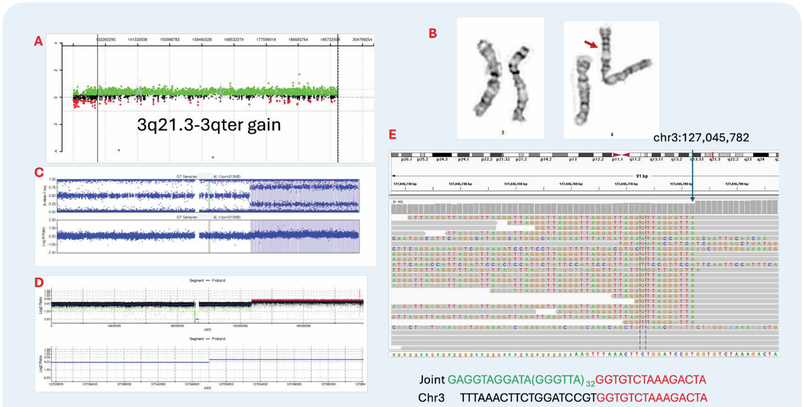
- Three unrelated pediatric patients with mosaicism for a terminal duplication due to unbalanced translocation were revealed by chromosomal microarray analysis (CMA) and cytogenetics studies at Baylor Genetics. The DNA samples were de-identified for breakpoint and mechanistic studies. Parental studies were performed for patient 3.
- SNP array: Infinium CoreExome-24 (Illumina, inc.) – ~268k exonic and ~152k intronic markers
- Genome sequencing (GS): Ultima sequencer; analyzed with VizCNV2 and Integrative Genomics Viewer (IGV)



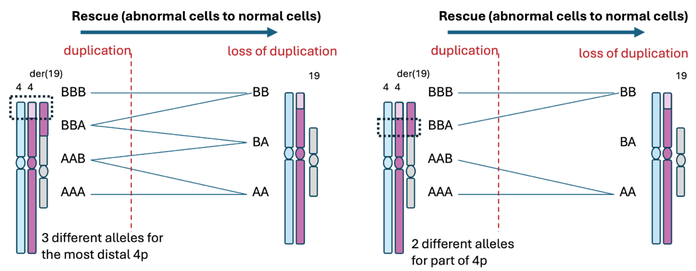
Patient 1: 57% mosaicism for a *de novo* extra copy of 4p attached to 19q (A-C). SNP array patten (D) is consistent with a recombination within the duplicated region in 4p. The interval of the duplication was defined and visualized using VizCNV (E) and the breakpoint was viewed using IGV where ITS was detected at the junction (F).

RESULTS

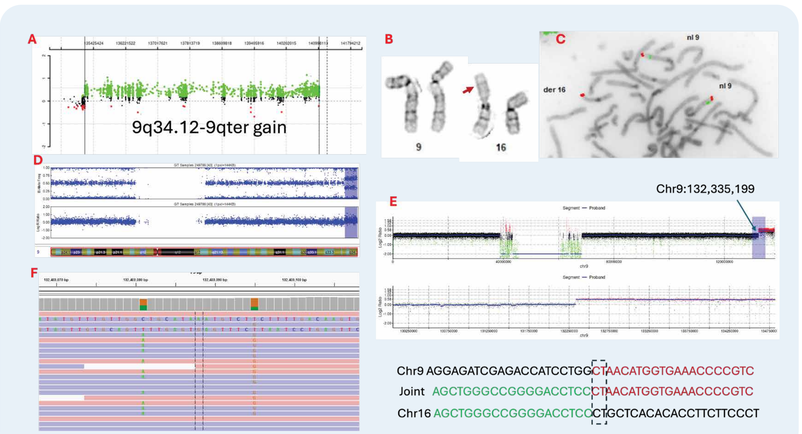
- For all the three patients with mosaicism for a terminal duplication, SNP array and/or GS indicated revertant mosaicism with a germline unbalanced translocation followed by postzygotic rescue to generate a normal cell line.
- The SNP array data indicated postzygotic rescue in patients 1 and 2 with three and two alleles respectively, but B-allele frequency was consistent with segmental uniparental isodisomy for this region in the normal cells. Trio GS showed three different alleles (SNP array inconclusive).
- GS on patients 1 and 2 detected the TTAGGG telomeric repeat at the junction, supporting ITS-driven instability causing the reversion to a normal chromosome.



Patient 2: 50% mosaicism for trisomy of terminal 3q due to an unbalanced 3;4 translocation (A-B). SNP array patten (C) is consistent with segmental uniparental isodisomy for this region in the normal cells. The interval of the duplication was defined and visualized using VizCNV (D) and the breakpoint was viewed using IGV where ITS was detected at the junction (E).



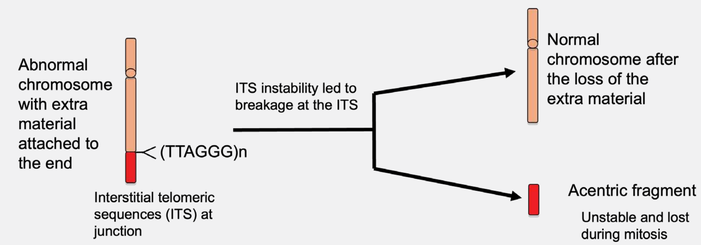
Graphic illustration of the B-allele frequence pattern seen in the SNP array for patient 1 due to recombination in the duplicated region in 4p and the postzygotic rescue leading to reversion of the derivative chromosome 19 to a normal chromosome 19.



Patient 3: 91% mosaicism for a *de novo* unbalanced paternal 9q-to-16 translocation (A-C). SNP array patten (D) is consistent with two alleles in the duplicated region. The interval of the duplication was defined and visualized using VizCNV (E) and a microhomology of 2 bp was detected at the junction. Trio GS showed three different alleles as shown in (F) in which reference G-A were seen in 32 reads, G-G in 31 reads, and A-G in 46 reads.

CONCLUSIONS

- Our results indicate that revertant mosaicism via postzygotic rescue is the main mechanism for mosaic terminal duplications.
- Detection of ITS at the translocation junctions further supports ITS instability as a driver for reversion.
- For ITS-associated terminal duplications, additional investigations may uncover cryptic low-level revertant mosaicism.



Model of revertant mosaicism due to ITS instability

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Reference:
1) Bi W, et al. Recurring germline mosaicism in a family due to reversion of an inherited derivative chromosome 8 from an 8;21 translocation with interstitial telomeric sequences. J Med Genet. 2023. PMID: 36150828.
2) Du H, etc. VizCNV: An integrated platform for concurrent phased BAF and CNV analysis with trio genome sequencing data. bioRxiv [Preprint]. 2024 PMID: 39553991.