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Complex genomic rearrangements of the Y chromosome in a premature infant

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Abstract

Background Chromoanagenesis is an umbrella term used to describe catastrophic "all at once" cellular events leading to the chaotic reconstruction of chromosomes. It is characterized by numerous rearrangements involving a small number of chromosomes/loci, copy number gains in combination with deletions, reconstruction of chromosomal fragments with improper order/orientation, and preserved heterozygosity in copy number neutral regions. Chromoanagesis is frequently described in association with cancer; however, it has also been described in the germline. The clinical features associated with constitutional chromoanagenesis are typically due to copy number changes and/or disruption of genes or regulatory regions.

Case presentation We present an 8-year-old male patient with complex rearrangements of the Y chromosome including a ring Y chromosome, a derivative Y;21 chromosome, and a complex rearranged Y chromosome. These chromosomes were characterized by G-banded chromosome analysis, SNP microarray, interphase FISH, and metaphase FISH. The mechanism(s) by which these rearrangements occurred is unclear; however, it is evocative of chromoanagenesis.

Conclusion This case is a novel example of suspected germline chromoanagenesis leading to large copy number changes that are well-tolerated, possibly because only the sex chromosomes are affected.

Keywords Y chromosome, Chromoanagenesis, Chromothripsis, Mosaicism, Complex chromosome rearrangements

Background

Complex chromosome rearrangements (CCRs) are currently defined as structural variations involving at least three breakpoints and/or at least three chromosomes. Most CCRs seem to be without apparent phenotypic effect [20, 7] however, mechanisms for CCR pathogenicity include haploinsufficiency or triplosensitivity of involved genes and breakpoints that disrupt genes and/or regulatory regions.

Chromoanagenesis is an umbrella term used to describe catastrophic "all at once" cellular events leading to the chaotic reconstruction of chromosomes. One form of chromoanagenesis known as chromothripsis was first described in cancer cells [24], but has since been

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described in the germline [10, 14]. Chromothripsis consists of chromosome shattering and reassembly resulting in copy number losses. Another form of chromoanagenesis, chromoanasynthesis, refers to the creation of a chromosome with multiple copy number gains occasionally associated with copy number losses resulting from fork stalling and template switching (FoSTeS). To date, it is unclear whether chromothripsis and chromoanasynthesis are completely distinct events, and some have used the terms interchangeably. Most chromoanagenesis events arise *de novo* on paternally derived chromosomes, likely due to sperm susceptibility to DNA damage and relative lack of DNA repair mechanisms [10]. CCRs consistent with chromothripsis have been maternally inherited in several cases (constitutional CCRs are known to negatively affect spermatogenesis) [4, 8].

Y chromosome abnormalities are known to cause defects in male reproductive function [23]. Ring Y chromosomes, Y chromosome translocations, and complex rearrangements of monocentric Y chromosomes have all been described in individuals with azoospermia, many with the azoospermia factor (AZF) region still intact [9]. Phenotypic consequences beyond infertility are only rarely observed, and typically in cases of unbalanced translocations involving autosomes [17].

Structurally abnormal Y chromosomes are frequently identified in association with 45,X/46,XY mosaicism [13, 27]. Individuals with 45,X/46,XY mosaicism have a range of clinical presentations, and gonadal sex is typically determined by the ratio and distribution of XY cells to cells with monosomy X [6]. Males with 45,X/46,XY mosaicism typically have spontaneous puberty, but may experience clinical features overlapping with Turner syndrome including short stature, genital differences, renal and cardiac anomalies, developmental delays, learning disabilities, and attention deficit disorders [1, 13]. Previous studies suggest that up to 95% of prenatally diagnosed cases of 45,X/46,XY mosaicism are phenotypically normal males [5, 26].

Gains of Y chromosome material including 47,XYY have been reported with variable phenotypes including social-emotional difficulties, attention-deficit disorders, autism spectrum disorder, tall stature, macrocephaly, macroorchidism, hypotonia, hypertelorism, and tremors [2, 22]. Prenatally diagnosed individuals are more likely to have mild phenotypes or be unaffected [3, 28].

We present an 8-year-old male patient with complex rearrangements of the Y chromosome including a ring Y chromosome, a derivative Y;21 chromosome, and a complex rearranged Y chromosome. These abnormal Y chromosomes were characterized by G-banded chromosome analysis, SNP microarray analysis, and interphase and metaphase fluorescence in situ hybridization (FISH) analyses. The mechanism(s) by which these rearrangements occurred is unclear; however, it is evocative of chromoanagenesis.

Case presentation

The patient is an 8-year-old male and the child of healthy non-consanguineous parents. His mother presented to genetics prenatally with an abnormal non-invasive prenatal screening result indicating a high risk for Turner syndrome. The family history was unremarkable. Ultrasound performed at 15 weeks was suggestive of male genitalia. Non-invasive prenatal screening was repeated, with results again indicating a high risk for Turner syndrome. Ultrasound performed at 19w6d gestation was again suggestive of male genitalia. Amniocentesis was performed at the 19w6d ultrasound. Ultrasound performed at 24w0d was concerning for ambiguous genitalia. The patient was born at 25w3d gestation by Caesarean section due to preterm premature rupture of membranes (PPROM) and breech presentation. His presentation was complicated by premature delivery, grade III intraventricular hemorrhage, and bronchopulmonary dysplasia. The patient's birth weight was 0.71 kg and birth length was 31.5 cm. A clinical examination found no signs of under-virilization or Turner syndrome. He was discharged from the NICU after 87 days weighing 7.95 kg.

The patient's surgical history includes tracheostomy shortly after birth followed by airway reconstruction with rib cartilage graft at age 4 years, and a tracheocutaneous fistula closure with decannulation at age 5 years. He has a history of chronic constipation, mild hypothyroidism, and mild bilateral hyperopic astigmatism. He has global developmental delays and began walking just before age 3 years and had his first words around 4 years of age. He was most recently assessed by a developmental pediatrician at age 7 years and 8 months, where he was noted to have delayed receptive and expressive speech as well as difficulties with articulation. He was also noted to have ongoing gross and fine motor delays that included difficulties with balance, dressing himself, and writing. He was noted to receive special education in school. At his most recent clinical evaluation at age 8 years and 9 months, he weighed 23.9 kg (14th percentile, Z = -1.07) and was 123.8 cm tall (7th percentile, Z= -1.46). His external genitalia were noted to be normal male with no concern for micropenis and testes descended bilaterally. This medical history is complicated by severe prematurity, and determining the relative contribution of sex chromosome abnormalities to specific phenotypes is challenging.

Methods

Chromosome analysis was performed according to standard protocols and analysed using CytoVision Imaging Software (Leica Microsystems). FISH analysis was

completed using the SRY probe LSI SRY SpectrumOrange/ CEP X SpectrumGreen (Abbott Molecular), CEP X/Y Probe (DXZ1/DYZ1, Abbott Molecular), Aneuvysion Assay (CEP18/X/Y - alpha-satellite/ LSI 13/21, Abbott Molecular), Yq11.221 (RP11-38N21 custom probe, Empire Genomics), and Yp11.2 (RP11-62H15 custom probe, Empire Genomics). The analysis was completed per manufacturer's recommendations. FISH images were captured using a Zeiss Axio Imager Z2 microscope and analysed using CytoVision Imaging Software (Leica Microsystems). Genomic SNP chromosomal microarray analysis (SNP-CMA) was completed using the Infinium Assay with the Illumina Infinium CytoSNP-850 K Beadchip Platform. The data was analysed using the Illumina Genome Studio Genotyping Module V3.2 (Illumina Inc). Linear positions of abnormalities are listed according to the Human Genome Build GRCh37/hg19. The International System for Human Cytogenomic Nomenclature (ISCN) 2020 recommendations were used for all clone and karyotype designations.

Results

Interphase FISH studies detected multiple signal patterns consistent with Y chromosome mosaicism in the uncultured amniocytes including zero copies of the Y chromosome centromere (CEP Y) in 28% of cells, one copy of the Y chromosome centromere (CEP Y) in 22% of cells, two copies of Y chromosome centromere (DYZ1) in 18% of cells, three copies of Y chromosome centromere (CEP Y) in 30% of cells, and four copies of Y centromere (CEP Y) in 2% of cells. All cells had a signal pattern consistent with one copy of the X chromosome centromere (CEP X). There was no evidence of aneuploidy for chromosome X, chromosome 13, chromosome 18, or chromosome 21 (Supplemental Fig. 1).

G-banded chromosome analysis of 15 amniocyte colonies identified three abnormal clones. The largest clone of 12 colonies (70.6%) featured only monosomy X (Supplemental Fig. 2A). The second clone of two colonies (11.8%) featured material of unknown origin added to the short arm of chromosome 21 and what appeared to be a possible isodicentric chromosome Y (Fig. 1A). The last clone of three colonies (17.6%) featured both the previously described abnormal chromosome Y and chromosome 21 with an additional abnormality in the form of a ring chromosome (Fig. 1B). An XY male karyotype was not identified in any of the colonies examined.

Given the clinical indication of prenatal ambiguous genitalia, metaphase FISH analysis was used to determine whether *SRY* (Yp11.3) was present in any of the three clones. *SRY* (Yp11.3) was not detected in the clone with only monosomy X (Supplemental Fig. 2B). In both the second and third clones, *SRY* (Yp11.3) was detected on the short arm of one copy of chromosome 21 (21p), characterizing the unknown additional material on chromosome 21 and suggested the presence of a derivative Y;21 chromosome. *SRY* (Yp11.3) also was detected near both telomeres on the suspected isodicentric Y chromosome (Fig. 1C and D) for a total of three copies.

To confirm the prenatal findings, postnatal genetic testing was completed. Chromosome analysis on the patient's peripheral blood identified the same three abnormal clones, though they were present in different percentages. The first clone featuring only one copy of the X chromosome was present in 3/70 cells (4.3%), the second clone featuring abnormalities of both chromosome 21 and chromosome Y was present in 27/70 cells (38.6%), while the final clone featuring the ring chromosome was present in in 40/70 cells (57.1%) (Supplemental Table 1). This change in clone prevalence was also confirmed by X/Y centromere FISH studies (data not provided).

To further clarify the structures of the abnormal chromosome 21, chromosome Y, and ring chromosome, a series of FISH studies were completed using probes to various regions of the Y chromosome including *SRY* (Yp11.3), Yp11.2, the Y centromere (DYZ3), and Yq11.221.

Consistent with the FISH studies on the amniocytes, one copy of the *SRY* probe (Yp11.3) was detected on the short arm of abnormal chromosome 21 and two copies of the *SRY* probe (Yp11.3) were detected on the suspected isodicentric chromosome Y with one copy located near the telomere on each arm. A copy of *SRY* (Yp11.3) was not detected on the ring chromosome (data not shown). One copy of the Y centromere probe (DYZ3) was detected on all three abnormal chromosomes (Fig. 2A), including the short arm of chromosome 21. This confirmed our theory that the abnormal chromosome 21 was a derivative Y;21 chromosome. Surprisingly, the presence of only one Y chromosome centromere on the suspected isodicentric Y chromosome prompted us to change our designation to a complex rearranged Y chromosome (Fig. 2D).

A probe targeting the short arm of chromosome Y (Yp11.2) was detected in a total of two copies on the complex rearranged Y chromosome with one copy near the middle of each arm, but it was absent from both the ring chromosome and, unexpectedly, from the abnormal chromosome 21 (Fig. 2B). One copy of the RP11-38N21 (Yq11.221) probe was detected on the ring chromosome while two copies of the RP11-38N21 (Yq11.221) probe were detected (one on each arm) on the complex rearranged Y chromosome (Fig. 2C and D).

SNP-CMA was performed to better characterize the genomic regions of gain and loss. SNP-CMA identified dosage changes involving the entire Y chromosome; this included both pseudoautosomal (PAR) regions. Of note, PAR1 and PAR2 probes map to both chromosome X and chromosome Y but are reflected predominantly on

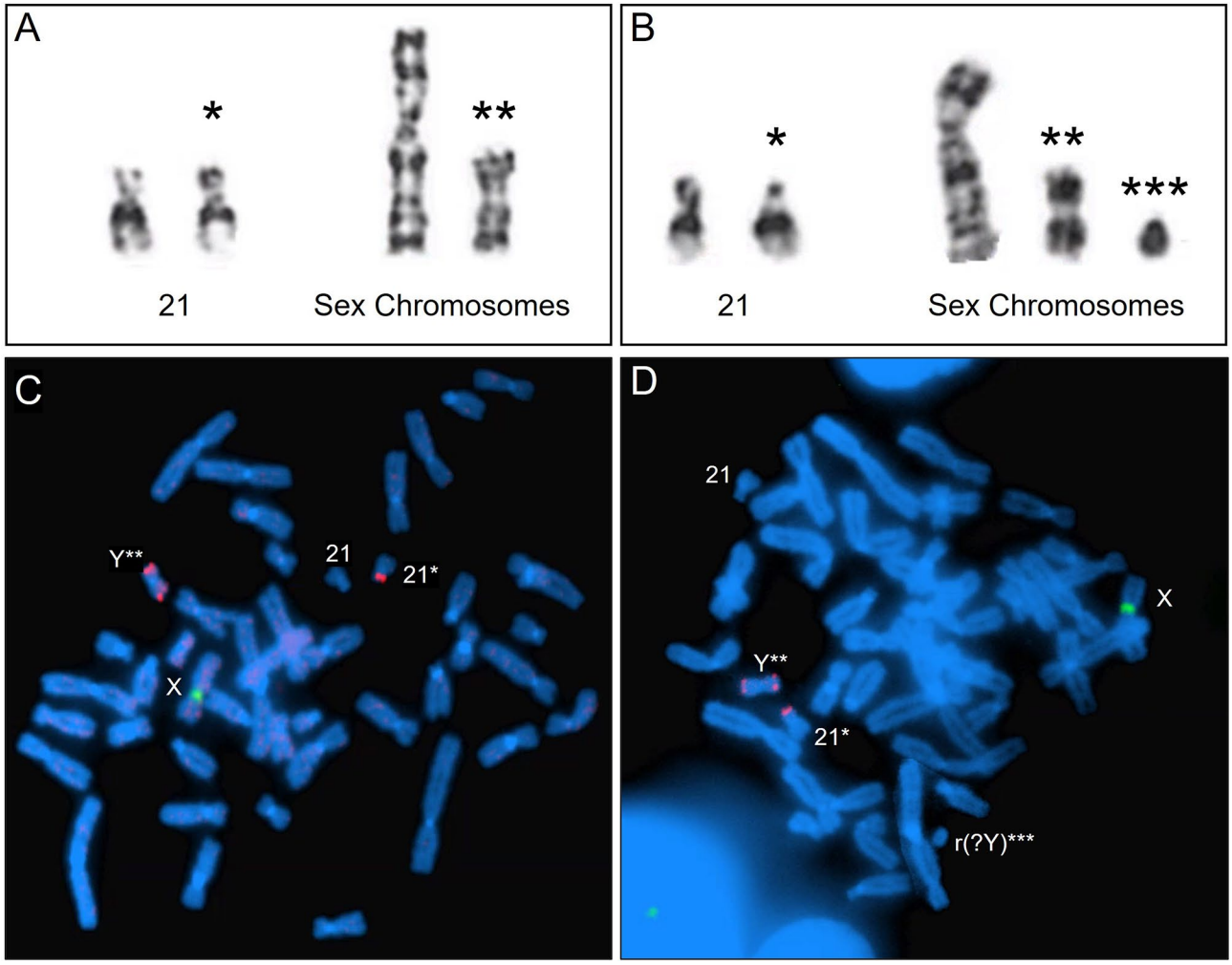

Fig. 1 G-banded chromosome analysis of the cultured amniocytes identified two clones with structural abnormalities. One clone featured material of unknown origin added to the short arm of chromosome 21 (**A**, 21*) and a possible isodicentric Y chromosome (A, Y**). The second clone featured material of unknown origin added on the short arm of chromosome 21 (B, 21*), a possible isodicentric Y chromosome (B, Y**), and a ring chromosome of unknown origin (**B**, r(?Y)***). Metaphase FISH analysis was performed on each of the two clones using probes targeting *SRY* (Yp11.2, red) and the X chromosome centromere (DXZ1, green) (**C**, **D**)

chromosome X in the Genome Studio software. A 2.6 Mb mosaic gain of Xp22.33/Yp11.32 was detected, representing PAR1 (chrX:60814-2667033) (Fig. 3A). Additionally, a 24.5 Mb mosaic gain from Yp11.31→Yq11.23 (chrY:2655180–27197855) was identified (Fig. 3C); the Log-R ratio indicated that the region was present in 0 to 4 copies. Furthermore, SNP-CMA detected deletions from the long arm of chromosome Y including a 0.3 Mb deletion of Yq11.23 (chrY:28538592–28817458) and a 0.3 Mb deletion of Xq28/Yq12 (chrX:154933691–155254881) mapping to PAR2 (Fig. 3B and C). Of note, genomic imbalances of chromosome 21 material were not identified, due to the region affected being the short arm of chromosome 21. This region is not represented on the array (data not shown).

To rule out whether these abnormalities were inherited from either a balanced or unbalanced rearrangement in the patient's parents, G-banded chromosome analysis was performed on 10 cells. Peripheral blood analyses for both parents were normal (data not shown).

Discussion/conclusions

We report a patient with mosaicism for novel complex rearrangements involving chromosome 21 and chromosome Y. From both amniotic fluid and peripheral blood specimens, we detected three different abnormal clones. Utilizing a combination of FISH, G-banded chromosomes, and SNP-CMA analyses, we characterized each of these clones and determined their prevalence in both sample types. A summary of this patient's final peripheral blood results and karyotype designations is available in Supplemental Table 2.

The Y chromosome rearrangements detected in our patient have the following characteristics suggestive of

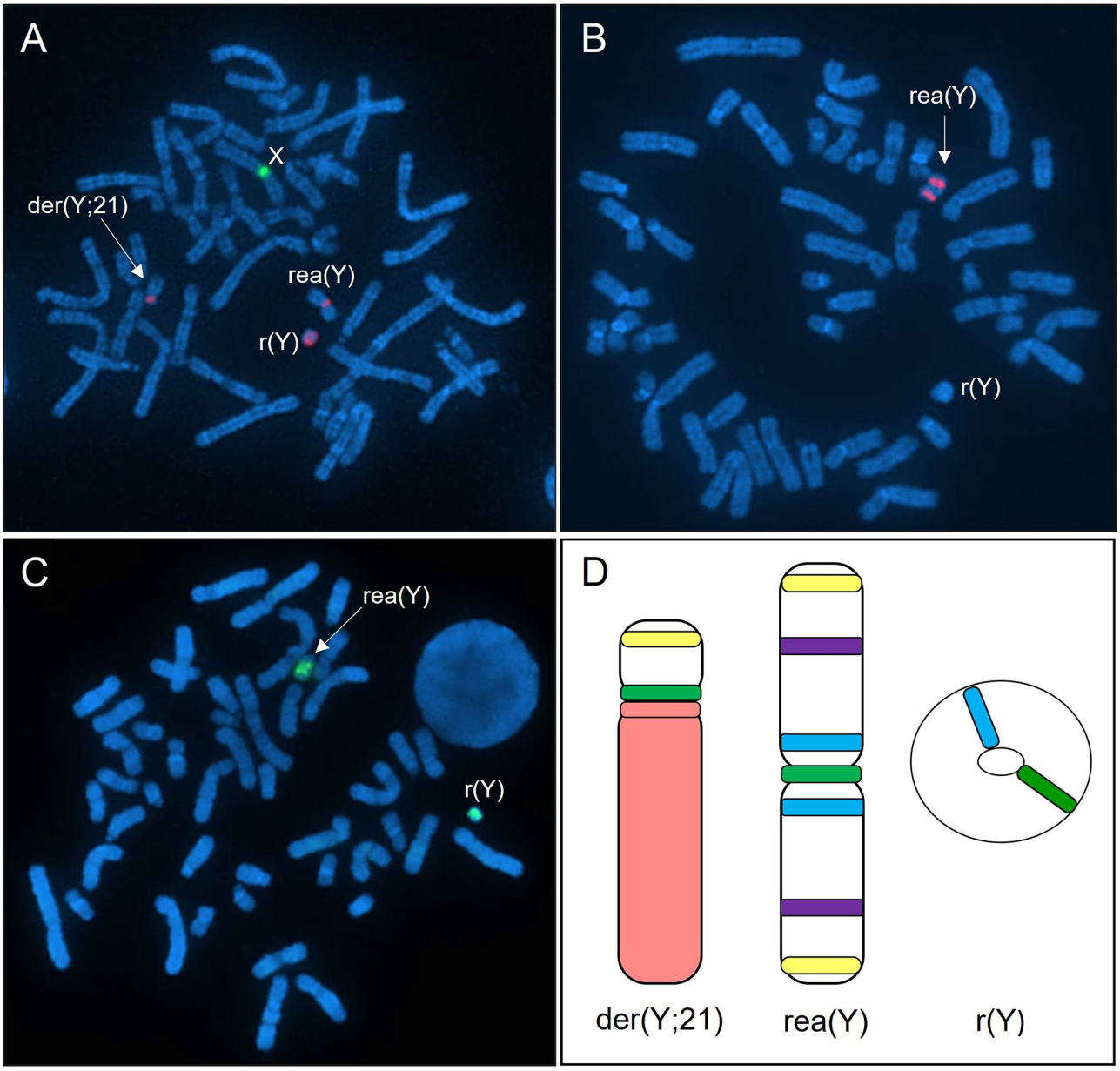

Fig. 2 Metaphase FISH analyses of a postnatal peripheral blood sample helped clarify the chromosomal abnormalities of the most complex clone with the abnormal chromosome 21, abnormal Y chromosome, and the ring chromosome. Metaphase FISH analysis of this clone was performed using probes targeting both the X centromere (DZX1, green) and the Y centromere (DZY1, red) (**A**), the chromosome region Yp11.2 (RP11-62H15, red) (**B**), and the chromosome region Yq11.221 (RP11-384N21, red) (**C**). A proposed model for the rearrangements in this patient's complex clones based on results from the G-banded chromosome, the SNP-CMA, and metaphase FISH analyses. The colored bars are representative of the metaphase FISH results included *SRY* (Yp11.2, yellow), Y centromere (DZY1, green), Yp11.2 (purple), and Yq11.221 (aqua). Red shading indicates chromosome 21 material (**D**)

chromoanagenesis: numerous rearrangements involving a small number of chromosomes/loci, copy number gains in combination with deletions, reconstruction of chromosomal fragments with improper order/orientation, and preserved heterozygosity in copy number neutral regions. Furthermore, ring chromosomes and atypical translocations have both been described previously in association with suspected chromoanagenesis [11, 12]. Typically, clinical features associated with constitutional chromoanagenesis are due to haploinsufficiency/triplosensitivity of deleted/duplicated regions and/or disruption of genes or regulatory regions. Previously reported cases of constitutional chromoanagenesis usually involve smaller copy number imbalances, as large imbalances are not tolerated in the germline. However, sex chromosomes are known exceptions to this principle, as larger copy number changes can be tolerated.

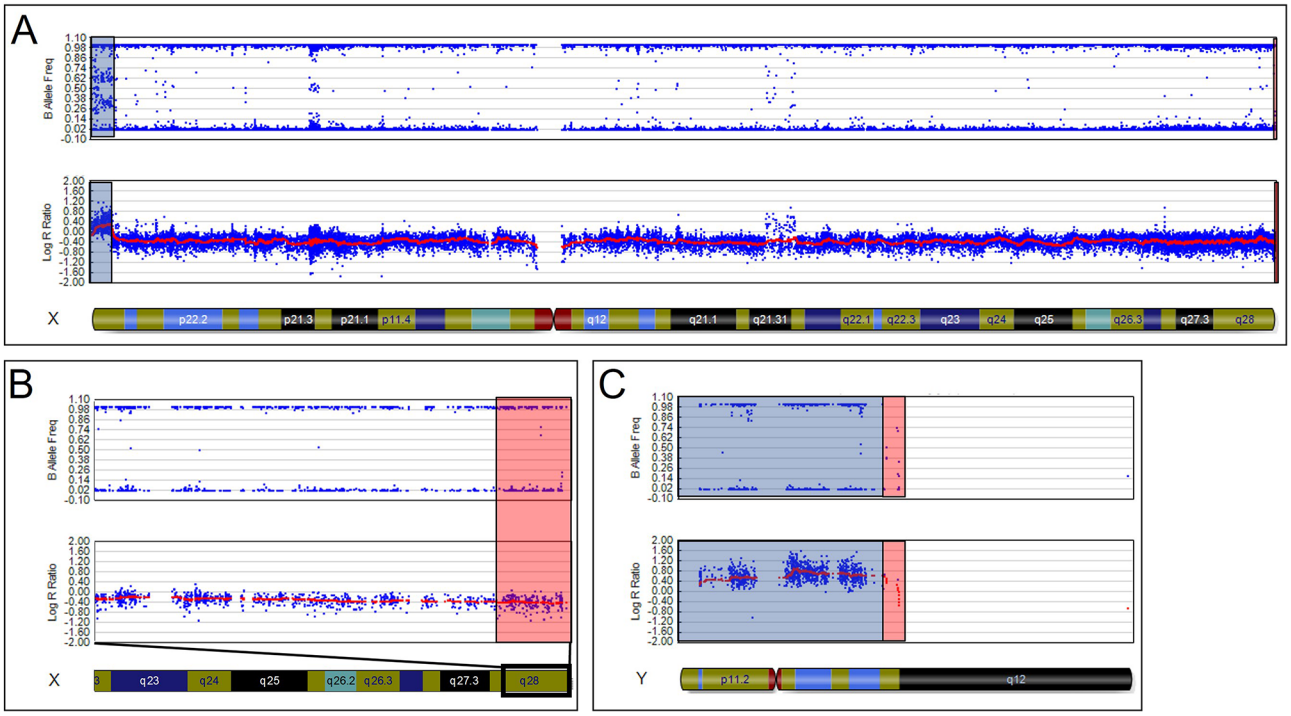

Fig. 3 SNP-CMA analysis identified copy number variants in the X/Y pseudoautosomal regions (PAR) and the Y chromosome during a postnatal peripheral blood analysis. A 2.6 Mb mosaic gain was identified in the Xp22.33/Yp11.32 region corresponding to PAR1 (**A**, blue region). A smaller deletion 0.3 Mb deletion was detected in the Xq28/Yq region corresponding to PAR2 (**B**, red region). SNP-CMA analysis of the Y chromosome detected both a large 24.5 Mb gain of material from Yp11.31→Yq11.23 (C, blue region) and a 0.3 Mb deletion of Yq11.23 (**C**, red region)

The patient's mosaic gain of 24.5 Mb from Yp11.31→Yq12 includes at least 374 protein-coding genes as well as azoospermia factor (AZF) regions (AZFa, AzFb, and AZFc). Each of these AZF regions contains several genes thought to play a role in spermatogenesis, and deletions of these regions are a known cause of infertility. Additional studies have suggested that duplication of these regions may be enriched in individuals with spermatogenic failure [29, 15]. However, duplications of these regions also have been reported in fertile males. This duplication also involves two disease-associated genes: *UISP9Y* (spermatogenic failure) and exon 1 of *SRY* (46,XY sex reversal). Neither of these genes have known triplosensitivity. The effect of partial gene duplication on *SRY* function is unknown.

The patient's mosaic gain of Xp22.33/Yp11.32 includes at least 15 protein-coding genes including two disease associated genes: *CSF2RA* (pulmonary surfactant metabolism dysfunction-44) and *SHOX* (idiopathic familial short stature, Leri-Weill dyschondrosteosis, and Langer mesomelic dysplasia). Neither of these genes has known triplosensitivity. The patient's mosaic 0.3 Mb Xq28/Yq12 deletion contains at least five protein-coding genes, none of which have been associated with human disease. The 0.3 Mb deletion of Yq11.23 contains no protein-coding genes and has no known dosage sensitivity. Furthermore, it is assumed that the Yq12 heterochromatin region between these two deletions also was deleted; however, this cannot be stated with certainty given lack of SNP microarray probe coverage in this region.

This patient is mosaic for a 45,X cell line. While many phenotypically male individuals with 45,X/46,XY mosaicism are apparently unaffected, this may be a contributing factor to the patient's reported developmental delays, learning difficulties, attention deficits, and short stature. In addition, this patient's Y chromosome material gain may be a contributing factor to clinical features overlapping with 47, XYY syndrome including developmental delays, learning difficulties, and attention deficits. Due to the patient's prematurity and associated complications, it is difficult to attribute his clinical features to the complex chromosomal rearrangements. In addition, structural Y chromosome abnormalities often lead to azoospermia and meiotic failure independent of haploinsufficiency/triplosensitivity of affected genes/regions. Therefore, this patient may experience reduced fertility in the future.

This case is a novel example of suspected germline chromoanagenesis leading to large copy number changes on the Y chromosome. Long-read whole genome sequencing or optical genome mapping would be useful in the future to clarify breakpoints and further elucidate the mechanism by which these rearrangements took place.

Abbreviations

CCRs	Complex chromosome rearrangements
FISH	Fluorescence in situ hybridization
SNP-CMA	Single nucleotide polymorphism chromosomal microarray analysis
PPROM	Preterm premature rupture of the membranes
Mb	Megabase
FoSTeS	Fork stalling and template switching mechanism
MMBIR	Microhomology-mediated break-induced repair
NHEJ	Breakage-fusion-bridge cycle prompting non-homologous end joining
PAR	Pseudoautosomal region

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13039-024-00689-x.

Supplementary Material 1: Supplemental Figure 1: Interphase FISH studies on uncultured amniocytes revealed a variable number of Y chromosome centromere signals (CEP Y alpha satellite, orange) consistent with mosaicism in the fetus. Five different signal patterns identified involving the Y chromosome including a loss of Y in 28% of cells (A), one copy of Y in 22% of cells (B), two copies of Y in 18% of cells (C), three copies of Y in 30% of cells (D), and four copies of Y in 2% of cells (E). There was no evidence of aneuploidy for the centromere of chromosome X (CEP X alpha satellite, green) or chromosome 18 (CEP 18 alpha satellite, aqua) in these cells (A-E). There was no evidence of aneuploidy for the probes for chromosome 13 (LSI 13, green) or chromosome 21 (LSI 21, orange) (F)

Supplementary Material 2: Supplemental Figure 2: G-banded chromosome analysis of the cultured amniocytes identified three clones. The only abnormality identified in the largest clone was the presence of a single sex chromosome, chromosome X (A). Metaphase FISH of this clone was performed using probes targeting SRY (Yp11.2, red) and the X chromosome centromere (DXZ1, green) (B)

Supplementary Material 3: Supplemental Table 1: Comparison of clonal percentages identified in amniocytes versus peripheral blood during chromosome analysis

Supplementary Material 4: Supplemental Table 2: Summary of cytogenetic characterization using patient's peripheral blood

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Author contributions
SB-substantial contributions to the conception or design of the work and interpretation of the data, drafting the work, revising the work critically for important intellectual content, final approval of the version to be published. AC- substantial contributions to the conception or design of the work and interpretation of the data, drafting the work, revising the work critically for important intellectual content, final approval of the version to be published. NS- substantial contributions to clinical data, revising the work critically for important intellectual content, final approval of the version to be published. BR- substantial contributions to clinical data, revising the work critically for important intellectual content, final approval of the version to be published. DM- substantial contributions to clinical data, revising the work critically for important intellectual content, final approval of the version to be published. RH- substantial contributions to clinical data, revising the work critically for important intellectual content, final approval of the version to be published. TS- substantial contributions to the conception or design of the work and interpretation of data, revising the work critically for important intellectual content, final approval of the version to be published.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Cincinnati Children's Hospital Medical Center's Institutional Review Board exempts case reports on a single patient.

Consent for publication
Mother consented for publication of this case report.

Competing interests
The authors declare no competing interests.

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