Molecular Cytogenetics

CASE REPORT

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Phenotypic and genotypic insights into concurrent tertiary trisomy for 9p and 18p

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Abstract

Background Carriers of balanced reciprocal translocation are usually phenotypically normal; however, they have an increased risk of producing gametes with chromosomal imbalance through different types of meiotic segregation of the translocation quadrivalent. The genetically imbalanced gametes when they survive can result in embryos with chromosomal abnormalities. Here we report a family with two siblings inheriting partial trisomy for 9p and 18p concurrently resulting from a 3:1 meiotic segregation of a maternal balanced translocation involving chromosome 9q and 18p, and the associated phenotype.

The family - case presentation The family was ascertained because of severe congenital anomalies in a newborn male (sibling 1). The karyotype of this patient was 47,XY,+del(9)(q13q34). Cytogenetic analysis revealed that the phenotypically normal mother harbored a balanced translocation 46,XX,t(9;18)(q13;p11.21). Chromosomal microarray analysis (CMA) of the abnormal child detected segmental trisomy for 9p and 18p. In conjunction with conventional cytogenetic results of the mother and CMA results of the affected child, the final karyotype of sibling one was 47,XY,+der(9)t(9;18)(q13;p11.22)dmat. arr[GRCh36] 9p24.3q13(199254_70163189)× 3, 18p11.32p11.22(131491_9640590)× 3; this resulted in segmental duplication of 69.96 Mb on 9pter->q13 and 9.51 Mb on 18p. There was a subsequent birth of a female sibling (sibling two) with multiple anomalies, including dysmorphic facial features, kidney aberration, cardiac defects, and abnormal brain MRI. The G-banded karyotype of this sibling was 47,XX,+del(9)(q13q34). The final karyotype of this sibling after CMA results was 47,XX,+der(9)t(9;18)(q13;p11.22)dmat. arr[GRCh37] 9p24.3p13.1(209020_38763958)× 3; 18p11.32p11.22(146484_9640912)× 3. The apparent discrepancy between the array results of the two siblings is attributed to difference in the design of array chips and genome builds used for these patients (NimbleGen/Roche v2.0 3-plex and GRCh36 for sibling one, and GGXChip + SNP array and GRCh37 of Agilent Technologies for sibling two). There are 182 OMIM genes in the duplicated region of 9p and 33 OMIM genes in the duplicated region of 18p which may have contributed to the clinical features of the affected siblings.

Conclusions To our knowledge, we report the first two cases of concurrent partial trisomy 9p and 18p in the same family. This report adds more information about phenotypic effects of these chromosomal copy number gains and supports chromosomal microarray analysis as the standard for precise identification or demarking regions of duplications, particularly when the translocation involves at least one subterminal segment. In view of the recurring infants with congenital anomalies the couple may benefit from prenatal chromosome analysis of future pregnancies or opting to assisted reproductive methods and transferring normal embryos for implantation.

Keywords Familial t(9;18)(q13;p11.2), Concurrent trisomy 9p and 18p, CMA anlysis

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Introduction

Balanced translocations are seen in 5–10% of couples experiencing recurrent pregnancy loss [1]. Carriers of a balanced translocation have a risk of abnormal chromosome segregation during gamete formation. During

meiosis, the translocated chromosomes form an association of four chromosomes or a quadrivalent that segregates through one of five cytologic types of meiotic orientation. Adjacent and alternate segregation result in euploid gametes (normal, balanced, or abnormal), 3:1 segregation result in tertiary trisomic and monosomic gametes, whereas a 4:0 segregation may not produce viable gametes. The unbalanced gametes when viable produce a viable embryo and a newborn with congenital anomalies.

Trisomy 9p is the fourth most common chromosome anomaly in liveborn infants and occurs in less than 1 in 1,000,000 live births [2, 3],Orpha.net, 4.

The resultant phenotype is brachycephaly, dysmorphic facial features, hypoplasia, and abnormalities of the fingers and toes, developmental and intellectual disabilities [5, 6]. Trisomy 18p is rare and has only been reported in approximately thirty-five cases. The resultant phenotype is epilepsy, dysmorphic facial features, developmental delay, and intellectual disability [7]. Most commonly these imbalances are inherited from a parent with a balanced translocation [8]. While 9p deletion and duplication syndrome, particularly involving 9p22 and 9p24, has been reviewed recently [9], there have been no reports on the phenotypic-genotypic features of concurrent trisomy for 9p and 18p. Here we report two siblings with partial trisomy for 9p and 18p concurrently resulting from 3:1 meiotic segregation of a maternal balanced translocation. This is the first documented kindred of concurrent trisomy 9p and 18p providing new insights into phenotypic and genotypic correlations. Furthermore, we highlight the need to use high resolution genomic assays such as CMA to define the gnomic imbalances more precisely.

Patient and methods

Case presentation

The family has three children, one phenotypically unaffected and the other two with congenital anomalies. They were born to nonconsanguineous healthy parents. The phenotype of sibling one (male) included polycystic kidney disease, a solitary right kidney, hypothyroidism, hiatal hernia, short stature, dysmorphic facial features, seizures, global developmental delay, and neurocognitive impairments. He has severe feeding difficulties and is gastrostomy tube dependent. At age 9 years he was diagnosed with non-intractable epilepsy without status epilepticus. This was controlled with medication, and he was successfully weaned off without recurrence of seizures. At the age of 12 the patient current diagnosis is likely focal epilepsy. Sibling two, a newborn female, was referred for clinical evaluation of pulmonary valve atresia and a family history of other congenital malformations. Phenotypic features include critical pulmonary valve stenosis, fetal growth restriction, choroid plexus cysts, enlarged adrenal glands, and bilateral clubfoot, and relies on a nasogastric tube for feeding.

Materials and methods

Chromosomal analysis

Chromosomal analysis was performed on metaphase spreads obtained from peripheral blood lymphocyte cultures using standard karyotyping techniques with G-banding. The analysis was performed using karyotyping software (GenASIs, Applied Spectral Imaging, Carlsbad, CA). Metaphases were analyzed and described according to the International System for Human Cytogenetic Nomenclature (McGowan-Jordan, 10.

Chromosomal microarray analysis

Chromosomal microarray analysis was performed on DNA extracted from peripheral blood from both affected siblings. Microarray analysis of sibling one was performed using the NimbleGen/Roche v2.0 3-plex (Pleasanton, CA) and microarray analysis of sibling two was performed using the GnGxChip + SNP array and Surescan G4900DA Microarray Scanner System (Agilent Technologies, Santa Clara, CA). The copy number variants for sibling one was analyzed and reported using the NCBI human genome build 36 (GRCh36/hg18), and for sibling two, NCBI human genome build 37 (GRCh37/hg19) was used; Genoglyphix analysis software (PerkinElmer, Waltham, MA) was used to assess the pathogenicity of the copy number variants.

Gene and protein enrichment analysis

GeneScout [11], a web-based tool, was used to identify genes and their associated phenotypes within the duplicated regions of 9p and 18p. GeneScout catalogs genes inherited in an autosomal dominant or recessive manner within a specific genomic region. By cross-referencing genetic findings with phenotypic databases, it may help establish links between genes and phenotypes. This analysis further enables identifying a set of genes for further investigation for their association with the clinical findings in affected patients. The hg19/GRCh37 chromosome coordinates for the abnormal regions of sibling 2 (chr9:209020_3863958 and chr18:146484_9640912) were input into GeneScout and the output was a list of genes and associated phenotypes for both regions (Table 1, Supplemental Table 1). Protein enrichment analyses were performed using the stringAPP [12] in the Cytoscape software [13]. StringAPP imports STRING protein networks, which are known and predicted protein-protein interactions for more than 2000 organisms, into Cytoscape for network analysis and visualization (http://apps.cytoscape.org/apps/stringapp). This analysis can

Table 1 Genes of clinical significance on the duplicated segments of 9p (chr9: 209020_38763958) and 18p (chr18:146484_9640912)

Genomic location	Gene	Gene name	OMIM #	Phenotype	Inheritance
chr9:2,621,787-2,660,056	VLDLR	Very low density lipoprotein receptor	192977	Cerebellar hypoplasia, impaired intellectual development	AR
chr9:4,984,390-5,129,948	JAK2	Janus kinase 2	147796	Hematologic neoplasia, Budd-Chiari syndrome	Somatic, AD
chr9:14,081,842-14,532,075	NFIB	Nuclear factor I B	600728	Macrocephaly, acquired with impaired intellectual development	AD
chr9:26,903,370-26,947,240	PLAA	Phospholipase A2 activating protein	603873	Neurodevelopmental disorders	AR
chr9:27,109,223-27,230,172	TEK	TEK receptor tyrosine kinase	600221	Glaucoma 3, Venous malformations	AD
chr9:35,056,061-35,072,622	VCP	Valosin containing protein	601023	Charcot-Marie-Tooth disease, type 2Y, Frontotemporal dementia	AD
chr9:35,490,108-35,561,892	RUSC2	RUN and SH3 domain containing 2 testis associated actin remodeling kinase 1	611053	Intellectual developmental disorder, autosomal recessive 61	AR
chr9:35,791,588-35,809,728	NPR2	Natriuretic peptide receptor 2	108961	Acromesomelic dysplasia 1, Maroteaux type Epiphyseal chondrodysplasia, Miura type Short stature with nonspecific skeletal abnormalities	AD
chr9:36,833,266-37,034,265	PAX5	Paired box 5	167414	Leukemia, acute lymphoblastic, susceptibility to, 3	NA
chr9:39,064,707-39,288,164	CNTNAP3	Contactin associated protein family member 3	NA	?	
chr18:2,655,725-2,805,015	SMCHD1	Structural maintenance of chromosomes flexible hinge domain containing 1	614982	Bosma arrhinia microphthalmia syndrome	AD
chr18:3,412,007-3,459,976	TGIF1	TGFB induced factor homeobox 1	602630	Holoprosencephaly 4	AD

identify over-represented pathways and highlight their contribution to phenotypic outcomes like inflammation or immune modulation. This was used to identify potential functional pathways within the list of genes retrieved in GeneScout analysis.

Results

Cytogentic results

Chromosome analysis of cultured peripheral blood lymphocytes of the mother revealed 46,XX,t(9;18)(q13;p11.21) (Fig. 1A), that of the affected sibling two revealed 47,XX,+der(9)t(9;18)(q13;p11.21)dmat (Fig. 1B). Chromosome analysis of the phenotypically unaffected child was not performed.

Chromosomal microarray analysis

Microarray analysis of sibling one identified segmental duplication for chromosome 9 from 9p24.3 (the distal end of the short arm) to 9q13 (69.96 Mb) (Fig. 2A) and segmental duplication for chromosome 18 from 18p11.32 (distal end of the short) to 18p11.22 (9.51 Mb) (Fig. 2B). However, a closer look at the distribution of probes on the duplicated region of 9p indicated that the actual region of duplication was from 9p24.3 to 9p13.1 (Fig 2.A) which is 38.7 Mb in size; this is similar to that detected in sibling two by Genoglyphix. Microarray analysis of sibling two identified segmental duplication for chromosome 9 from 9p24.3 to 9p13.1 (38.55 Mb) (Fig. 2C) and segmental duplication for chromosome 18 from 18p11.32 to 18p11.22 (9.50 Mb) (Fig. 2D). The small difference in the size of the duplicated segment on 9 between the two siblings can be attributed to the difference in the design of the chips used (NimbleGen design in 2012 vs. Agilent design in 2023) and the genome builds used for the analysis.

Gene enrichment and protein network analysis

Duplication of 9p and 18p caused significant genetic imbalance due to the presence of several genes in these regions. GeneScout analysis revealed 182 genes in the duplicated 9p24.3-p13.1 region and 33 genes in the duplicated 18p region (Supplemental Tables 1 and 2). Among these genes 48 on 9p and seven on 18p were OMIM genes with either dominant (29 conditions) or recessive (41 conditions) inheritance (Supplemenatl Table 3). We hypothesize that abundance of the product of these genes is responsible for the clinical features of siblings.

We performed protein enrichment analysis to determine functional networks of the proteins of the genes in the duplicated regions using the STRING package in Cytoscape. The 182 OMIM genes identified on 9p24.3-q13 using GeneScout were used for the input gene list into the STRING protein network analysis. Multiple pathways involved in immune system response such as type interferon receptor binding (FDR=2.71E-21), JAK-STAT signaling pathways (FDR=1.4E-13), and Toll-like

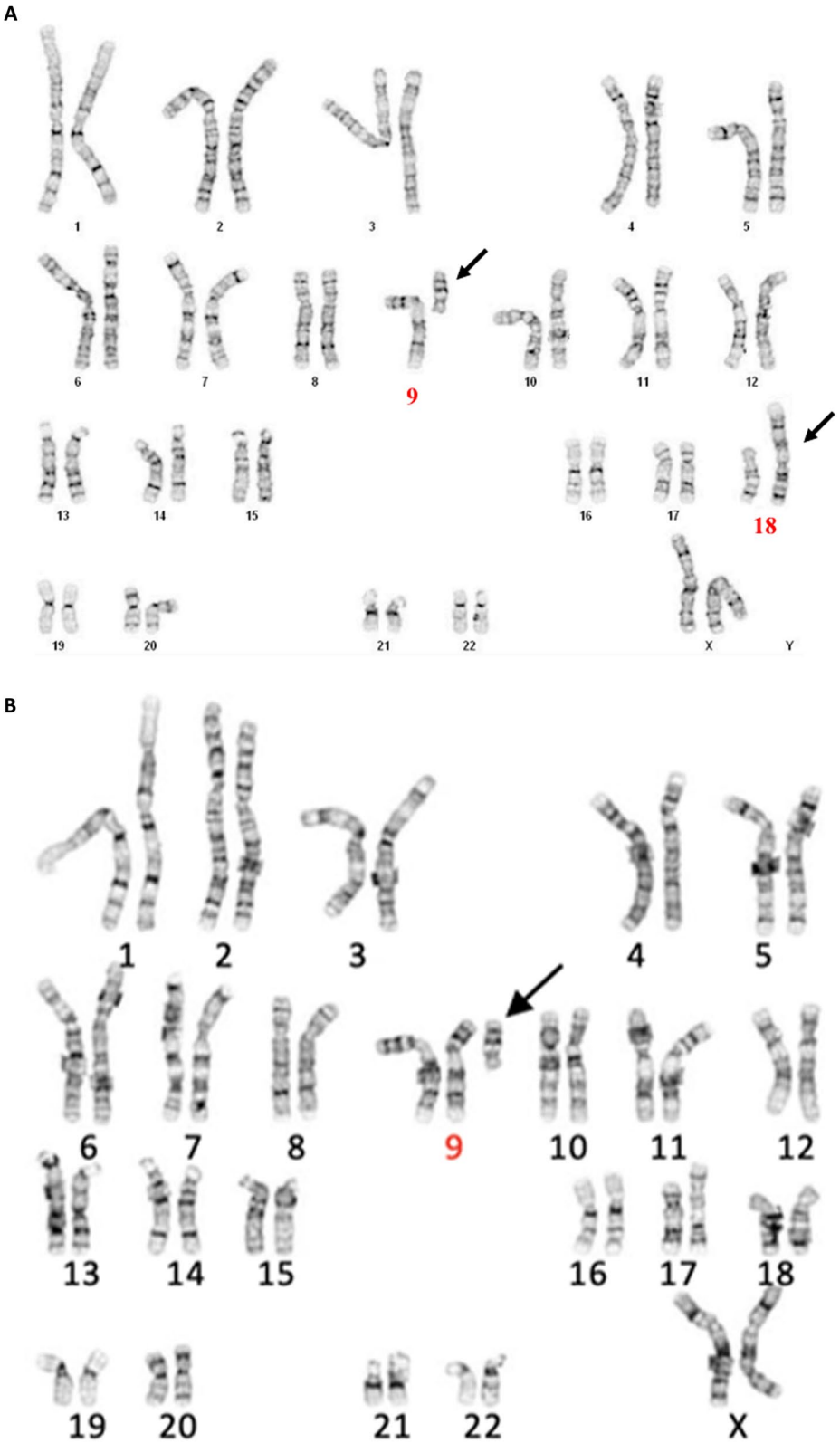
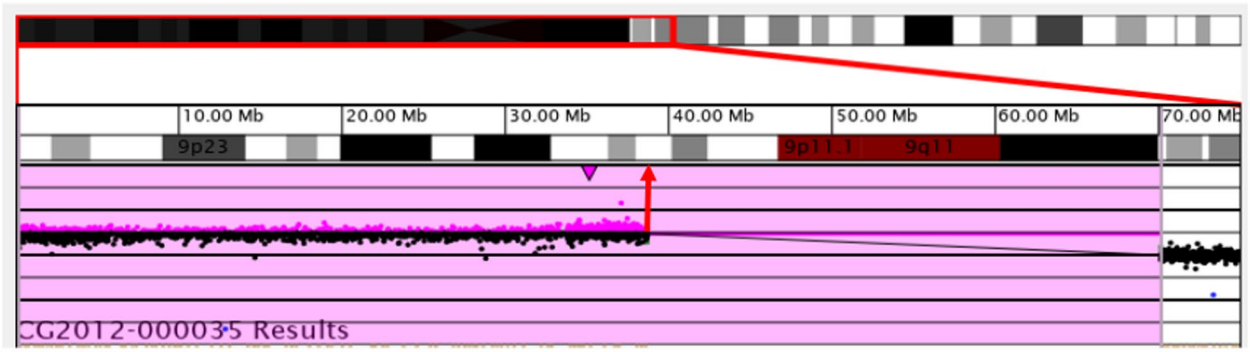
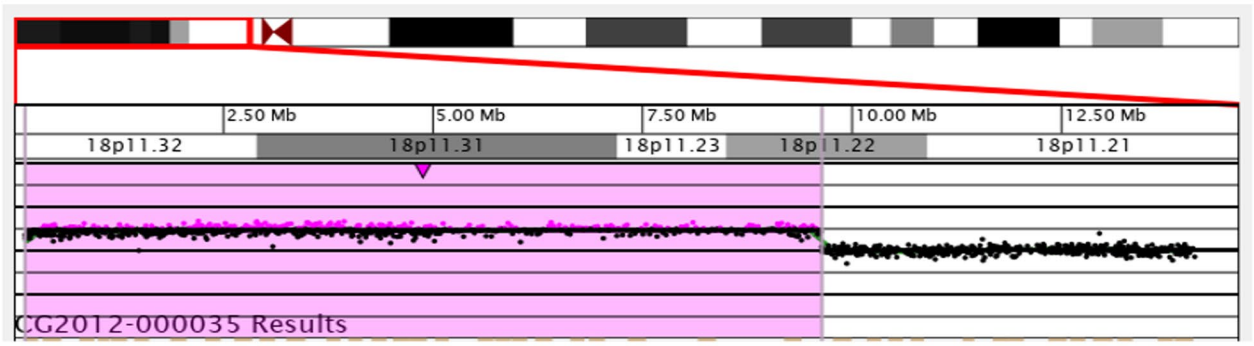


Fig 1 G-banded karyotypes (475–500 band level) showing maternal balanced translocation 46,XX,t(9;18)(q13;p11.21) (arrows point to interchanged chromosomes) (**A**), and sibling two karyotype: 47,XX,+der(9)t(9;18)(q13;p11.22)dmat (arrow point to the der(9) chromosome inherited from the mother) (**B**)

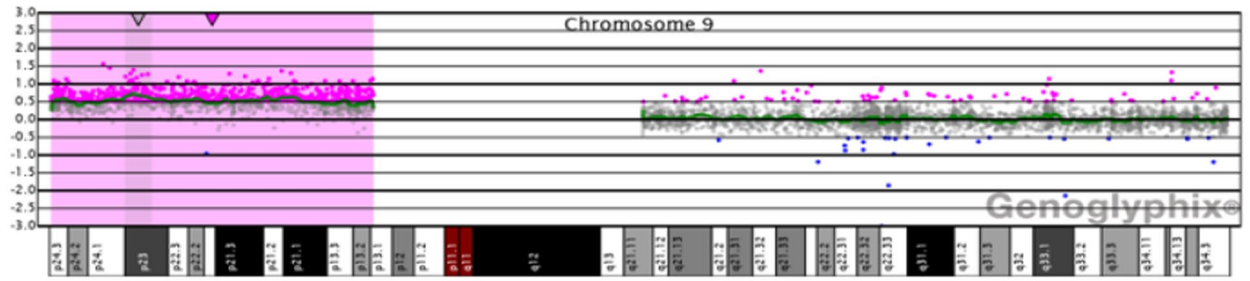
A. Sibling one, derived chromosome 9



B. Sibling one, derived chromosome 18



C. Sibling two, derived chromosome 9



D. Sibling two, derived chromosome 18

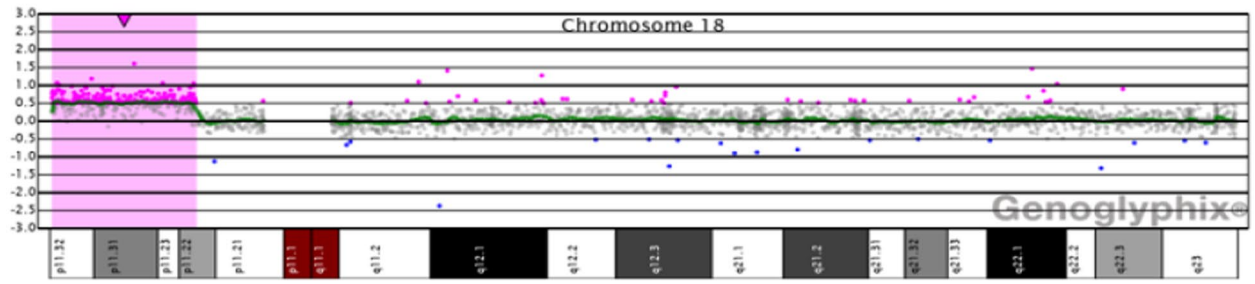


Fig 2 Microarray results of peripheral blood from sibling one (**A**, **B**), and from sibling two (**C**, **D**). **A**. Duplication of 9p24.3q13.arr [GRCh36] (199254_70163189) × 3. Note that the genomic region of duplication extended to 9q13, but the probe coverage ended at 9p13.1 (red arrow). **B**. Duplication of 18p11.32p11.22.arr [GRCh36] (131491_9640590) × 3 **C**. Duplication of 9p24.3p13.1.arr [GRCh37](209020_38763958)× 3 **D**. Duplication of 18p11.32p11.22 [GRCh37] (146484_9640912)× 3

receptor binding (FDR=7.06E-10) were significant (FDR<0.05) (Supplemental Table 4). We observed an enrichment of IFNA genes which are involved in immune function. Similar analysis for the genes identified on 18p portion did not yield any significant pathways.

Discussion

Meiotic segregation of a translocation quadrivalent is influenced by the size of the translocated segments, chromosomes involved, quadrivalent structure and gender of the carrier [1, 14–16]. Translocations with terminal break point(s) may have an increased tendency to undergo 3:1 disjunction [15]. Survival of a gamete or an embryo is inversely related to the extent of genetic imbalance contributed by the unbalanced chromosome. Although G-banded karyotype analysis is a standard method to evaluate the karyotype of these patients, accuracy of this method is limited to the band resolution obtained and has the potential to yield erroneous results particularly when the abnormal segment is(are) small and/or have a similar G-band pattern. Wu et al [17] reported an infant with a normal G-banded karyotype, whereas molecular karyotyping detected an unbalanced karyotype with a der(X)t(X;9)(q27;p23). Li et al [18] used high resolution copy number variation method to precisely detect chromosomal gain or loss in an infant with 46,XX,der(7)t(7;9)(p22;p21). Ing et al [19] reported a family with t(9;19)(q12;p13.3) in which an affected child carried the der(9)t(9;19) chromosome in addition to normal 9 and 19. This imbalance was first detected by array comparative genomic hybridization. Interpretation of the G-banded karyotypes of the two kindreds in this study although acceptable, this method did not precisely define the composition of the der(9) chromosome, whereas CMA analysis identified the presence of 18p segment on the der(9). Thus, the present study and previous reports document the necessity to use high resolution genomic assays to gain precise insight into molecular imbalances underlying congenital anomalies.

The t(11;22)(q23;q11.2) and t(8;22)(q24.13;q11.21) are two constitutional translocations segregating through multiple families and identified through the birth of a child with tertiary trisomy resulting from meiotic 3:1 segregation in the carrier parent [20]. All reported cases of tertiary trisomy in these families were due to a +der(22) chromosome that carried a minimal region on proximal 22q and the distal portion of 11q or distal portion of 8q. This chromosome causes minimal genetic imbalance to the gamete and in the embryo and therefore leads to live birth with congenital anomalies. In fact, Armstrong et al [21] detected all types of segregation products in the chromosomes of sperm of t(11;22) carrier males and concluded that the frequent recovery of tertiary trisomic newborn was due to preferential survival of these embryo rather than preferential 3:1 segregation of the translocation quadrivalent. This is analogous to our observation in the two kindred that inherited der(9). The der(9) carried a very small segment of 18p (33 OMIM genes), whereas the der(18) carried almost the entire long arm of chromosome 9, and therefore had greater genetic imbalance. In the context of a 47-chromosome embryo, biologically the embryo with der(9) has a greater potential to survive compared to the embryo carrying der(18) chromosome. Recently Ming et al [22] reported a family with a t(9;12)(q13;p11.2) in which a 3:1 segregation in the carrier mother resulted in an infant with concurrent trisomy for 9p and 12p with the karyotype 47,XX,der(9)(t(9;12)(q13;p11.2)dmat. Cytogenetically the duplicated segment of 9p is similar

to that seen in the current patients. This further supports that an embryo with minimal genetic imbalance due to inheritance of an unbalanced chromosome such as der(9) in the current patients has a greater potential to survive.

Over 200 cases of trisomy 9p and approximately 35 cases of trisomy 18p are documented in the literature. To our knowledge, this is the first report of concurrent partial trisomy for 9p and 18p in two siblings of a family. The short arm of chromosome 9 is a gene poor region likely contributing to compatibility with survival when present in trisomy [9, 23]. Trisomy 9p most commonly is a result of a parental reciprocal translocation between chromosome 9 and another autosome that is passed on to the offspring [23]. This duplicated genomic material can contain part of the short arm, the entire short arm, or the short arm and part of the long arm. Clinical severity is associated with the size of the duplicated region. For example, craniofacial characteristics were more severe in patients with trisomy 9p and involving the proximal 9q compared to those with no long arm involvement [23]. Genotype-phenotype studies have suggested that the minimal critical region of partial trisomy 9 is 9p22-p24 [9, 24], however others have suggested this region is 9p22.1-p23 [25].

Duplication of a gene can affect the phenotype by altering gene dosage. An increase in the copy number of genes can lead to excess protein production contributing to the clinical phenotype of the patients [26]. Duplication of genes can also contribute to autosomal dominant inheritance by gain-of-function effects, dominant-negative effects, or in rare cases by haploinsufficiency. Duplication of a haploinsufficient gene is often deleterious [27]. Thus, the phenotypic heterogeneity of trisomy 9p can be a result of expression of different duplicated genes [28]. Some of these genes, such as *TEK*, *NFIB*, and *NPR2*, are linked to autosomal dominant conditions consistent with

the phenotypes observed in our patients. These conditions include hereditary vascular anomalies, macrocephaly associated with intellectual disability, and short stature without specific skeletal abnormalities, respectively (Online Mendelian Inheritance in Man, [29–31]. *PAX5* and *CNTNAP3*, genes in the duplicated 9p region, are involved in central nervous system development and play a role in learning processes [26].

Pure trisomy for 18p is rare [32], and no specific clinical phenotype is associated with it due to variability in the size of the duplicated 18p in the few patients it is reported. Craniofacial anomalies and developmental disabilities are common features in these patients [33]. Cognitive profile in these patients is variable ranging from normal intelligence to moderate intellectual disability [34]. Over half of individuals with chromosome 18 abnormalities, specifically duplication or trisomy, exhibit epilepsy, like sibling one. Upregulation of *TGIF1* mapped at 18p11.31 has been associated with seizure frequency [35]. Although genes on chromosome 18, like *TGIF1*, have been linked to seizures, no key candidate genes critical for neurotransmission or seizure predisposition, such as sodium channel subunits, have been identified [36]. Further studies are warranted to better characterize the genes in the implicated region associated with these phenotypic features.

Our study enhances the understanding of partial trisomy 9 and partial trisomy 18 and demonstrates that combining CMA with chromosomal analysis is effective in the precise identifying structural chromosome abnormalities underlying congenital anomalies. Furthermore, in view of the recurrent liveborn offspring with chromosome abnormality, this family may benefit by prenatal chromosome testing of the fetus or opting for assisted reproductive methods followed by screening for embryos with normal chromosome complement.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13039-025-00704-9.

Additional file 1.

Additional file 2.

Additional file 3.

Additional file 4.

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Author contributions
PK, RG and KSW are involved in performing clinical tests, interpretation of test results and contributed to manuscript preparation. AES is involved in clinical diagnosis of patients and their management and contributed to manuscript preparation. CAW gathered information necessary to include in the manuscript, literature review and generated the manuscript.

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

Declarations

Ethics approval and consent to participate
Consent from the patient and/or guardian is obtained to perform laboratory tests necessary to establish the diagnosis and/or management, and to use these results for academic activity if interesting. This study did not require any additional material from subjects.

Competing interests
The authors declare that they have no competing interests.

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