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A Case Series of Double Segment Imbalances: Delineation of Phenotypes and Comparison with Phenotypes of Isolated Copy Number Variations

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Abstract

This study undertaken at a tertiary hospital documents the phenotypes of patients with double segment chromosomal imbalances (DSI) and compares the phenotypes with those of the isolated copy number variations (CNV) of the concerned regions. Twenty cases diagnosed as DSI in our department over the last four years using cytogenetic microarray (CMA) and/or multiplex ligation-dependent probe amplification (MLPA), were included in the study. In some cases, phenotype of one CNV may predominate as was observed in four cases of this series. However, the other CNV may modify the phenotype. Five cases had a blend of phenotypes corresponding to deleted/duplicated chromosomal segments while 6 cases had nonspecific features like intellectual disability or developmental delay. In five cases the phenotype could not be delineated in detail as they were prenatally detected. Out of the 16 families, there were 5 families showing recurrence which suggested an inherited chromosomal abnormality. Identification of DSI is important as one of the parents may be a carrier of a balanced chromosomal rearrangement. Cytogenetic microarray is the gold standard technique to identify such submicroscopic chromosomal imbalances; however, MLPA with subtelomeric probes is an alternative option for a developing country like ours due to cost constraints. Both these techniques thus help to identify the families at risk of recurrence of chromosomal abnormalities, aiding in prenatal diagnosis and genetic counseling.

Introduction

With the evolution of molecular cytogenetic techniques, many micro-deletion / micro-duplication syndromes are getting delineated. Fluorescence in situ hybridization (FISH) identified sub-telomeric deletions / duplications long before the era of cytogenetic microarray (CMA). Multiplex ligation-dependent probe amplification (MLPA) interrogates ends of all chromosomes in one go and the subtelomeric MLPA probe set identifies copy number variations (CNVs) in 6 to 7% of patients (Boggula et al., 2014) with intellectual disability and developmental delay. Some of these, usually double segment imbalances, are inherited from a balanced translocation in one of the parents. Balanced translocations are common with an incidence of 1 in 500 (Redin et al., 2017). Phenotypes of double segment imbalances are influenced by the chromosomes involved and the sizes of the imbalances. The phenotype of the patient with a common microdeletion syndrome may get modified by the CNV on another chromosome making the clinical diagnosis difficult. Double segment imbalances can also lead to spontaneous abortions and fetal losses. Hence, a technique which can target multiple regions in one go like MLPA or CMA is preferable as compared to FISH which probes one or few regions based on clinical suspicion. Here, we review cases with double segment imbalances identified by chromosomal microarray and / or MLPA. An attempt is made to do some genotype-phenotype correlation. Features of syndromes with specific

Table 1 Comparison of phenotype of cases with double segment imbalance with respective isolated deleted / duplicated chromosomal segment phenotype as documented previously in literature** [The features documented in literature and also seen in our patient are highlighted in bold font].

Case No.	Age / Sex CMA / MLPA Result	CNV loss [Phenotype reported with isolated CNV loss]	CNV gain Phenotype reported with isolated CNV gain	Dominant phenotype (CNV) Patient's phenotype
1	1 year / Female Arr[hg19] 20p13p12.3(61,661-6,355,181)x3, 6q27(167,609,282-170,914,297)x1	Het 3.3 Mb Del 6q27 16 OMIM genes [Mild GDD, Motor delay]	Het 6.2 Mb Dup 20p13-p12.3 64 OMIM genes **[ID, poor motor coordination and speech**, broad nasal bridge]	Dup at 20p13-p12.3 **[GDD**, seizures, **ataxia]**
2	Fetus of 17 Weeks gestation (Sibling of case 1) Arr[hg19] 20p13p12.3(61,661-6,316,301)x3, 6q27(167,609,282-170,914,297)x1	Het 3.3 Mb Del at 6q27 16 OMIM genes- [Mild GDD, Motor delay)	Het 6.2 Mb Dup at 20p13-p12.3 64 OMIM genes [ID, poor motor coordination, poor speech, broad nasal bridge]	**Phenotype yet to evolve** No dysmorphism, no gross malformations
3*	7 months / Male Arr[hg19] 22q13.31q13.33(45,143,535-51,197,766)x1, 17q25.1q25.3(74,126,271-81,041,823)x3	Het 6 Mb Del 22q13.31-q13.33 44 OMIM genes including *SHANK3* [Phelan McDermid syndrome, **hypotonia, GDD**, severe speech delay, prognathism, dysplastic ears, ptosis, saddle nose, normal to advanced growth, autism] (OMIM 606232)	Het 6.9 Mb Dup 17q25.1-q25.3 86 OMIM genes **[GDD**, FTT, **distal arthrogryposis**]	Blended phenotype **GDD**, **clenched fist**, bushy straight eyebrows, low set ears, triangular face, broad thumb, **hypotonia**
4*	30 months / Female Arr[hg19] 6q25.3q27(158,628,326-170,914,297)x1, 7q36.3(155,277,221-159,119,707)x3	Het 12.28 Mb Del at 6q25.3q27 46 OMIM genes **[ID**, **hypotonia**, epilepsy, cardiac defects, retinal abnormalities, **ear anomalies**, **facial dysmorphisms**, brain, spinal cord, and vertebrae malformations]	Het 3.8 Mb Dup at 7q36.3 12 OMIM genes. **[Mild ID**, macrocephaly, broad forehead, **hypertelorism**, muscular hypertrophy, corpus callosum agenesis]	Del 6q25.3-q27 phenotype. **GDD**, **hypotonia**, microcephaly, prominent metopic sutures, **hypotelorism**, micropthalmia, microcornea, **smooth philtrum, and dysplastic posteriorly rotated low set ears, short neck, low posterior hairline,** and bilateral talipo-equinovalgus.

5	5 years / Female (Sibling of case 4) Heterozygous deletion at 7q36.3 and Heterozygous duplication at 6q27	Het Del 7q36.3 #gene - *VIPR2* **[Speech delay, ID**, short stature, holoproscencephaly, microcephaly, ptosis, sacral agenesis]	Het Dup 6q27 #gene - *TBP2* **[Speech delay, ID**, Autistic behavior]	**Predominantly social and language delay**, dysmorphism
6*	8 days / Male Arr[hg19] 5p15.33p14.3(113,576-19,902,278)x1, 7p22.3p22.2(43,376-4,156,704)x3	Het 19.7 Mb Del 5p15.33-p14.3 54 OMIM genes **[Microcephaly, round face, hypertelorism, micrognathia, epicanthal folds, low-set ears, hypotonia, and severe psychomotor and mental retardation, Cri–du-Chat syndrome]**	Het 4.1 Mb Dup 7p22.3-p22.2 26 OMIM genes [ID and GDD]	**Prominent Cri-du-Chat syndrome** phenotype **Blepharophimosis, prominent nasal bridge, left auricular tags, low set ears, retrognathia, thin tented upper lip, right 2nd and 3rd toe syndactyly**
7*	30 months / Male Arr[hg19] 8p23.3p23.1(158,048-6,962,251)x1, 8q24.11q24.3(118,514,344-146,295,771)x3	Het 6.8Mb Del 8p23.3-p23.1 15 OMIM genes **[GDD, ID]**	Het 27.7Mb Dup 8q24.11-q24.3 132 OMIM genes **[GDD, facial dysmorphism]**	**GDD**, **facial dysmorphism**, Rigidity
8*	9 months / Female Arr[hg19] 4p16.3p15.1(68,345-30,758,135)x3, 9p24.3p23(208,454-11,007,250)x1	Het 10.8 Mb Del 9p24.3-p23 **[Sex reversal syndrome]**	Het 30.7 Mb Dup 4p16.3-p15.1 **[GDD**, minor heart defects, mild ptosis]	Blended phenotype Microcephaly, **GDD**, feeding difficulty, **46XY with female genitalia (sex reversal)**
9	3 months / Female Arr7q36.1q36.3 (149770238-159118443)x1, 11q24.1-25 (121769912-134926021)x3	Het 9 Mb, loss 7q36.1 53 OMIM Genes- *ASB10, SHH, XRCC2* LBW, mental retardation, GDD, **facial dysmorphism**, genitourinary malformations, **holoprosencephaly**, sacral agenesis, Currarino syndrome	Het 13Mb gain 11q24.1-25 25 OMIM genes - *JAM3* Autistic behavior, Seizures, **FTT**, GDD, Microcephaly, IUGR, hypotonia	Blended phenotype **Micro-retrognathia**, **FTT**, **agenesis of corpus callosum**
10	5 years/ Female (Second cousin of case number 9) Arr7q36.1q36.3(149698257-159118443) x3, 11q24.1-25(121769912-134926021] x1	Het 13 Mb Del 11q24.1-25 25 OMIM genes including *JAM3* **[Jacobsen syndrome thrombocytopenia joint contractures, CHD,** chorio-retinal coloboma]	Het 9 Mb gain at 7q36.1 53 OMIM Genes- *ASB10, SHH, XRCC2* [Triphalangeal thumb, polysyndactyly syndrome]	Del 11q24.1-25 Phenotype **GDD**, **facial dysmorphism**, broad halluces, **camptodactyly**, **CHD**

11	4 years / Male Heterozygous deletion at 18q23 and Heterozygous duplication at 17q13.3	Het Del 18q23 #gene - *CTDP1* [Congenital aural atresia, **mild to severe developmental delay**, malformation of the external ears] (OMIM 607842)	Het Dup 17q13.3 #genes - *SECTM1, TBCD*	[Microcephaly, **GDD**, telecanthus, depressed nasal bridge with flat facial profile, low set ears, sandal gap with **clinodactyly of toes**, agenesis of corpus callosum, atrial septal defect]
12	Prenatal testing 16 weeks fetus Heterozygous deletion at 12p13.33 and Heterozygous duplication at 18p11.32	Het Del 12p13.33 #gene - *KDM5A* Speech delay, ID, variable psychiatric manifestations	Het Dup 18p11.32, #gene - *THOC1* Mild and nonspecific phenotype	**History of one spontaneous abortion, history of intellectual disability in family**. Mother's Karyotype- 46, XX, t(12;18)(p13.3;p11.2)
13	Prenatal testing 11 weeks fetus (Sibling of fetus 12) Heterozygous duplication at 12p13.33 and Heterozygous deletion at 18p11.32	Het Del 18p11.32, #gene - *THOC1* ID, mild and nonspecific phenotype	Het Dup 12p13.33 #gene - *KDM5A* Facial dysmorphism, umbilical hernia, CNS malformations, seizures, premature ischemic stroke.	
14	Products of conception spontaneously aborted Heterozygous deletion at 15q26.3and Heterozygous duplication at 20p13	Het Del 15q26.3 #gene - *TM2D3* IUGR, postnatal growth retardation.	Het Dup 20p13 #gene - *ZCCHC3* **ID, poor motor coordination and speech**, broad nasal bridge	**History of four recurrent spontaneous abortions.**
15	4 year / Male Heterozygous deletion at 11q25 and Heterozygous duplication at 2q37.3	Het Del 11q25 #gene - *IGSF9B* Developmental delay, **short stature**, CHD, thrombocytopenia, **genitourinary anomalies**, pyloric stenosis, and ophthalmologic anomalies	Het Dup 2q37.3 #gene - *ATG4B* **Facial dysmorphism**, hypotonia, feeding difficulties	Blended phenotype **Short stature, hypertelorism,** clinodactyly, fingerization of thumb with widening of wrist, **bilateral undescended testes**
16	10 months / Female Heterozygous deletion at 5q35.3 and Heterozygous duplication at 19q13.43	Del 5q35.3 #gene - *GNB2L1* Developmental delay, hypotonia, **FTT**, postnatal short stature, **CHD**	Dup 19q13.43 #gene - *CHMP2A* **Mild dysmorphic features**, ID, seizures	Blended phenotype **FTT**, **telecanthus, frontal bossing, depressed nasal bridge, smooth long philtrum, tented upper lips**, spatulated nails, **CHD - atrial septal defect**

17*	1 month / Male Arr[hg19] 11q24.1q25(121,709,028-134,937,416)x1, 10p15.3p15.1(100,047-4,254,167)x3 Heterozygous deletion at 11q25 and Heterozygous duplication at 10p15.3	Del 11q25 61 OMIM genes including *FLI1* Developmental delay, short stature, **CHD**, **facial dysmorphism**, thrombocytopenia, genitourinary anomalies, pyloric stenosis, eye anomalies	Dup 10p15.3 33 OMIM genes Learning disability, dolichocephaly, wide sutures, frontal bossing, micro/retrognathia and renal defects	Del 11q25 phenotype **Hypertelorism**, over-riding of great toes, **CHD (ASD with VSD)**, thrombocytopenia
18	1 year 4 months / Female Heterozygous deletion at 4p16.3 and Heterozygous duplication at 8p23.3	Del 4p16.3 #genes - *PIGG* **Wolf-Hirschhorn syndrome** (OMIM 194190)	Dup 8p23.3 #genes - *FBXO25* GDD, ID	Del 4p16.3 phenotype **GDD, facial asymmetry, bushy eyelashes, hypertelorism, broad nasal bridge, pointed low set ears, discontinuous simian crease, short stubby digits, lower limb asymmetry, pes planus, ostium secundum ASD with moderate PS with dilated RA and RV**
19	Prenatal testing 16 weeks fetus Heterozygous deletion at **13q34** and Heterozygous duplication at **11q25**	**Het Del 13q34** #gene - *CDC16* GDD, ID, obesity, and mild facial dysmorphism.	**Het Dup 11q25** #gene - *IGSF9B* Dysmorphic facial features, microcephaly, micrognathia, dysplastic ears, pre/postnatal growth retardation, speech delay, mental retardation, hypotonia, NTD, cardiac, vertebral, limb, urinary tract, genital anomalies.	**Bad obstetric history- one first trimester spontaneous abortion and one IUD** Husband's Karyotype - 46,XY, t(11;13)(q32;q25). Previous child with 13q deletion syndrome(GDD, prenatal growth retardation, FTT, anal atresia, with recto vaginal fistula)
20	4 years / Male Heterozygous deletion at 8p23.3 and Heterozygous duplication at 3p26.3	Het Del 8p23.3 #gene - *FBX025* **GDD, ID,** hypotonia, childhood onset epilepsy, autistic features	Het Dup 3p26.3 #gene - *CHL1* **GDD, ID, facial dysmorphism, seizures**	Blended phenotype **GDD**, ataxia, inappropriate laughter, wooly curly hair, **broad forehead, overhanging and broad nasal tip, slightly hypoplastic ala nasi, thin upper lip,** MRI brain – frontal cortical atrophy.

Note: ASD – atrial septal defect, CHD – congenital heart disease, CNV – copy number variation, CMA – cytogenetic microarray, Del- deletion, Dup – duplication, FTT – failure to thrive, GDD – global developmental delay, Het – heterozygous, ID – intellectual disability, IUD – intrauterine fetal demise, PS – pulmonary stenosis, RA – right atrium, RV – right ventricle, VSD – ventricular septal defect, IUGR – intrauterine growth retardation, MLPA – multiplex ligation-dependent probe amplification.
* Cases where both MLPA and CMA done
# Name of the genes in the respective MLPA probes
** The phenotypic features given are from the published literature for which references are not listed.

phenotypes appear to reflect in the cases though the nonspecific features with developmental abnormalities or blended phenotypes are seen in some. The aim is to stress the importance of identification of double segment chromosomal imbalances (DSI) for genetic counseling.

Materials & Methods

The study was conducted in the medical genetics department of a tertiary hospital. It was a retrospective descriptive study. Patients presenting to the medical genetics outpatient department and detected to have double segment chromosomal imbalance (DSI) by CMA and/or MLPA during the past four years were included in the study. Data was obtained from the medical records, case files, hospital information system and the genetic laboratory records. In each individual with DSI, the phenotypic presentation of the isolated chromosomal segment (deleted and duplicated) as reported earlier in literature was compared to the individual's phenotype to attempt genotype phenotype correlation. Deletions and duplications detected by MLPA were not confirmed by CMA in all cases. The data from published literature about reported deletion/ duplication of the particular end of the chromosome was taken as evidence to decide whether a particular chromosomal imbalance detected by MLPA was pathogenic. The interpretation of pathogenic nature of CNVs detected by CMA used the criteria of the genes involved within the CNVs as well as previous reports of CNVs in published databases, namely DECIPHER (https://decipher.sanger.ac.uk/), OMIM (https://omim.org/) and PubMed (https://pubmed.ncbi.nlm.nih.gov/).

Results

The total number of samples subjected to MLPA for sub-telomeric regions was 355. Out of them microdeletions and micro-duplications were identified in 18 cases (5%) and 6 cases (1.6%), respectively, while 16 patients (4.5%) had DSI. In addition, CMA identified DSI in another 4 cases. We were also able to perform CMA in 6 cases of DSI detected by MLPA. The data including phenotypes of cases detected by MLPA and/or CMA is provided in Table 1. The clinical photographs of representative cases are shown in Figure 1. The total number of cases with DSI was 20 and they were from 16 families. These include two pairs of siblings (case numbers 1 and 2; 4 and 5), a pair of second cousins (case numbers 9 and 10) and prenatal samples of two separate pregnancies in a mother (cases 12 and 13). Case 2 was the fetus in the next pregnancy of the mother of case number 1. The typical phenotypic features of isolated deletion/duplication of the concerned chromosome from the published literature are also given in Table 1 for comparison with the phenotype of the case with DSI. In three families (case nos. 12, 13, 14 and 19), only the fetal sample was tested, one of them being products of conception (case 14). For case 19, amniotic fluid DNA was studied by MLPA and the fetal USG did not reveal any abnormality. The indication for prenatal testing in case 19 was balanced translocation in the husband and there was bad obstetric history (previous one spontaneous abortion and one intrauterine fetal death) in his wife. The couple also had a child affected with 13q deletion syndrome. Fetal autopsy could not be done for cases 12, 13 and 19. In two families with two children each (cases 4 and 5 & cases 9 and 10) with DSI, the chromosomal imbalances involved the same set of 2 chromosomes, but were reciprocal in nature. Case 4 (Figure 1a), had a 12.28 Mb deletion at 6q25.3q27 and 3.8 Mb duplication at 7q36.3 (Figure 2, 3) while her sister (case 5 - Figure 1b) had heterozygous duplication at 6q27 with heterozygous deletion at 7q36.3 (on MLPA). Case 9 had 13 Mb duplication at 11q 24.1-25 along with 9.2 Mb deletion at 7q 36.1 – 36.3 region, while her second cousin (case 10) had 9.4 Mb gain of 7q36.1-36.3 and 13.16 Mb loss at 11q24.1-25. Cases 9 and 10 have been reported earlier by Tuteja et al. from our center (Tuteja et al., 2017). Out of the 20 cases, there were 5 families with 2 offspring/fetuses with DSI which suggested an inherited chromosomal abnormality. In the parents, balanced translocation was confirmed in all except one (case 4 and 5). For other cases with one child with DSI, evaluation of the parents for balanced rearrangement could not be done.

Discussion

Unbalanced chromosomal abnormalities in DSI, in which there is a net gain and loss of genetic material, often disrupt large numbers of dosage-sensitive, developmentally important genes and result in specific and complex

Figure 1 Dysmorphism noted in the patients. 1a. Case 4 (heterozygous 12.28 Mb deletion at 6q25.3q27 and heterozygous 3.8 Mb duplication at 7q36.3): Hypotelorism, smooth philtrum, dysplastic posteriorly rotated low set ears, short neck; 1b. Case 5 (heterozygous deletion at 7q36.3 and heterozygous duplication at 6q27): Smooth philtrum, thin upper lip; 1c. Case 18 (heterozygous deletion at 4p16.3 and heterozygous duplication at 8p23.3): Facial asymmetry, bushy eyelashes, hypertelorism, broad nasal bridge, pointed low set ears; 1d. & e. Case 6 (heterozygous deletion 5p15.33-p14.3 and heterozygous duplication 7p22.3-p22.2): Blepharophimosis, prominent nasal bridge, retrognathia, thin tented upper lip, left auricular tags, low set ears; 1f. Case 11 (heterozygous deletion at 18q23 and heterozygous duplication at 17q13.3): Microcephaly, telecanthus, depressed nasal bridge with flat facial profile, low set ears, sandal gap with clinodactyly of toes.

phenotypes. Even if the sizes of the unbalanced segments are large, detection by traditional karyotyping may be difficult due to duplicated segment compensating for the size of the deleted segment. The phenotypes of DSI are combined effects of both the imbalances. In our case series, there were five prenatal samples without adequate information of phenotypes. The DSI with characteristic phenotypes seen in this series are Phelan-McDermid syndrome (case 3), Cri-du-chat syndrome (case 6), sex reversal syndrome (case 8) and Wolf-Hirschhorn syndrome (Case 18). Even in these cases, the phenotype had representation of the associated imbalance of the other chromosome. In case 3, the child had dysplastic ears as seen in Phelan-McDermid syndrome as well as distal arthrogryposis seen in duplication 17q25.1-q25.3. Five cases had blended hybrid phenotypes (Case 9,10,15,16 and 20). Case 10 had phenotype suggestive of Jacobsen syndrome (Del 11q24.1-25); however, she did not have thrombocytopenia. Most of the submicroscopic chromosomal imbalances have intellectual disability or developmental delay as features and such a non-specific phenotype was seen in six of the fifteen postnatal cases (cases 1, 4, 5, 7, 11 and 17). Predominance of phenotype of the deleted chromosomal segment was seen in some cases probably because deletion is considered more harmful than duplication. Cases of blended phenotype resulting from DSI of various chromosomal regions have been described in literature (Colangelo et al., 2018).

Phenotypic variability in combined or complex chromosomal aberrations in DSI makes it difficult to perform genotype-phenotype correlations. Hence the syndromes with characteristic phenotype may not be clinically suspected. The double segment imbalances mostly are from inherited derivative chromosomes from the parents with a balanced chromosomal rearrangement. Hence there may be history of previous spontaneous abortions, unexplained fetal losses, stillbirths or similarly affected family

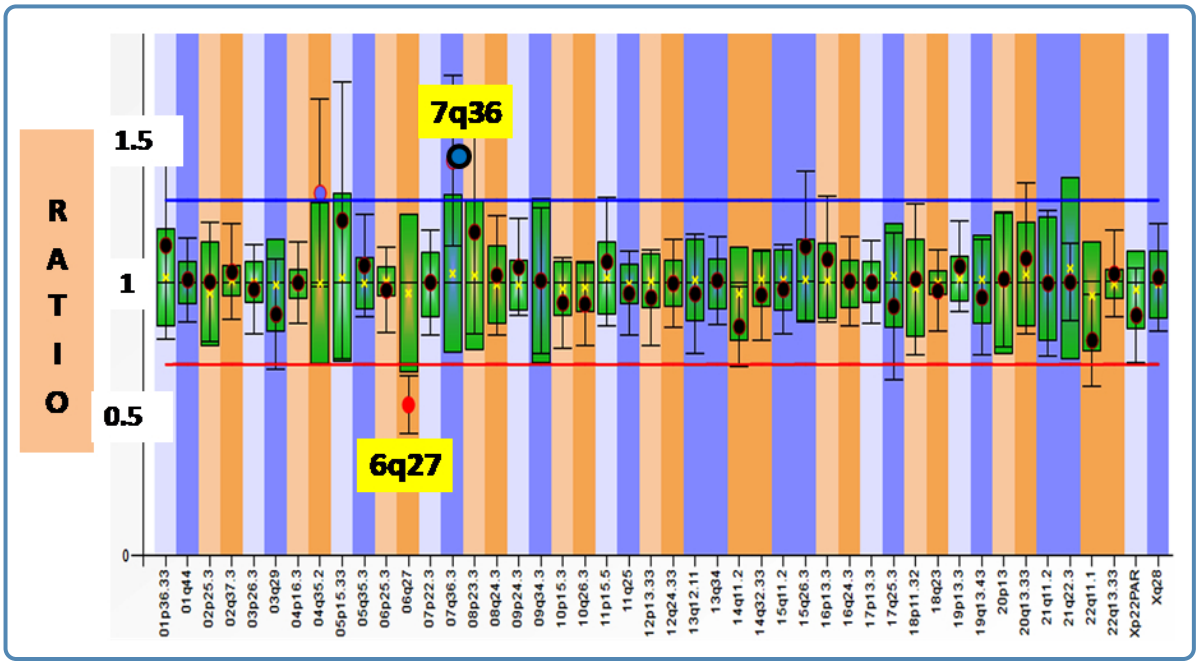

Figure 2 MLPA showing double segment imbalance: Case 4 (Heterozygous deletion at 6q27 and heterozygous duplication at 7q36.3).

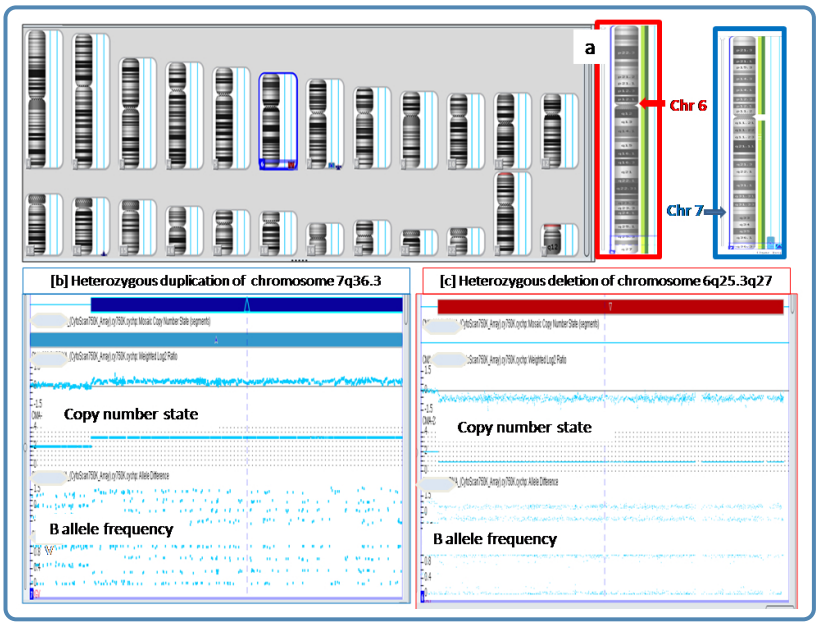

Figure 3 Cytogenetic microarray showing double segment imbalance for Case 4 - Arr [hg19] 6q25.3q27 (158,628,326-170,914,297) x1 & 7q36.3 (155,277,221-159,119,707) x3; 3a. Ideogram showing involved chromosomal segments; 3b & c. Copy number status and B allele frequencies of duplicated and deleted segments of 7q and 6q respectively.

member. We were not able to study all the parents for carrier status by fluorescence in situ hybridization. Five of the 16 families had recurrences. The recurrence may have the same type of imbalance (cases 1 and 2) or may have the other reciprocal imbalance as was the situation in the cousins (cases 9 and 10) and the pair of sisters (cases 4 and 5). The phenotype may be

similar in the recurrences as neuro-developmental disability or recurrent fetal loses. But both situations may occur in one family. Identification of these chromosomal abnormalities is of utmost importance to prevent recurrences in the family. The siblings and cousins of a carrier may be harboring the same balanced chromosomal abnormality and recurrences are expected in the extended family members. Hence, they should be offered genetic counseling and predictive testing.

Recently Iype et al. described south Indian kindred with double segment imbalance spanning five generations with t(3;4)(p26.3;p16.1), in which several individuals had either del(3p)/dup(4p) or del(4p)/dup(3p). The individuals in the family had variable phenotypes and reciprocal double segment imbalances as well. Interestingly there was no history of recurrent spontaneous abortions reported in the family (Iype et al., 2015). Nucaro et al. reported a family from Italy spanning three generations, with karyotype 46, der(3)t(3;10)(p26;p12). There was history of several miscarriages and phenotype of the patients was more likely attributable to the 10p duplication (19Mb) than to the 3p deletion (2.6 Mb) (Nucaro et al., 2008).

Rarely such a family may present with infertility in males and recurrent spontaneous abortions in female carriers (Goel & Phadke, 2011). Prenatal screening using cell-free DNA in maternal plasma or pre-implantation genetic testing are options for carriers of DSI in addition to the traditional prenatal diagnosis through fetal sampling by chorionic villus sampling or amniocentesis. Chromosomal breakpoints in the parents are important for predicting the segregation pattern and estimating the risk in the fetus. Thus, in cases of DSI, screening of the parents by karyotype or FISH is important as the risk of recurrence is high if the parent is a carrier. Many carriers of such balanced translocations may not be detectable by karyotype as the difference in the sizes of deleted and duplicated segments may not be significant and detectable by traditional karyotype.

Conclusion

Clinical suspicion based on phenotypes may be difficult in cases with DSI. The presence of DSI suggests a possibility of balanced chromosomal rearrangement in either of the parents. Hence identification of DSI in children, fetuses and products of conception is important. Cytogenetic microarray being a genomic technique is the best option to detect submicroscopic chromosomal imbalances. However, if it cannot be done due to cost constraints, MLPA with subtelomeric probes can be used as a substitute as it can detect DSI and thus help to identify the families at high risk of recurrence of chromosomal abnormalities.

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Conflict of interest

The authors declare that they have no conflict of interest.

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