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Case Report

Genetics Section

Familial Constitutional Rearrangement of Chromosomes 4 & 8: Phenotypically Normal Mother and Abnormal Progeny

FULESH KUNWAR[1], SONAL R. BAKSHI[2]

ABSTRACT

Balanced chromosome translocations carriers mostly do not have recognizable phenotypic expression but may have more risk of recurrent spontaneous abortions &/or children with serious birth defects due to unbalanced chromosome complements. Unbalanced chromosomal rearrangements have variable clinical expression and are rare. We present here a case report of three siblings affected with intellectual disability and minor dysmorphic features of face and limbs, born to a non-consanguineous couple in which mother had 5 abortions. The constitutional chromosome analysis revealed balanced translocation t (4;8) in mother and all the three siblings were karyotypically normal. Chromosomal microarray in one of the probands revealed partial monosomy 8pter-p23 and a partial trisomy 4pter-p16. Phenotypic features were recorded in 3 probands using Human Phenotype Ontology terms to query web-based tool Phenomizer. The harmonized description using globally accepted ontology is very important especially in case of rare genetic conditions and the heterogeneous phenotypes which make it even more challenging. The prevalence of sub-microscopic unbalanced translocations may be under-reported due to lesser use of molecular genetic analysis. The familial expression of abnormal phenotypes including intellectual disability make the individuals candidate for molecular genetic analysis and phenotyping to help defer the status of idiopathic mental retardation and identify sub-entity of genetic condition.

Keywords: Chromosomal microarray, Familial constitutional t(4;8), Intellectual disability, Multiple abortions, Phenomizer

CASE REPORT

We describe here a familial case of idiopathic intellectual disability with low IQ (29% - 35%) based on BKT (Binet Kamat Intelligence Test) and minor dysmorphic features in three siblings born in a non-consanguineous couple with a history of 5 miscarriages [Table/Fig-1]. There was no remarkable history of exposure or illness during pregnancy and post birth. The phenotypic features of three siblings (23/M, 19/M and 9/F) are shown in [Table/Fig-2].

The case research was prospectively reviewed and approved by a duly constituted Institutional Human ethical committee.

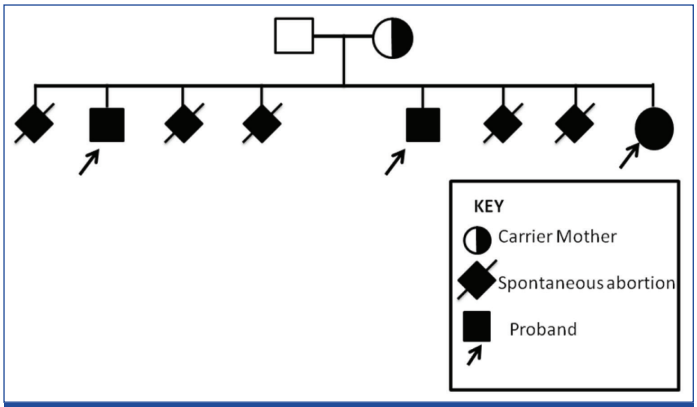
Karyotyping: Standard GTG banding karyotyping procedure was done in siblings and parents after obtaining written informed consent. Karyotype was done as per the ISCN (International System for Human Cytogenetic Nomenclature-2013) [1] using digital image analysis system IKAROS (Metasystems, Germany).

CMA^{HD} (Chromosomal Microarray-High Density): For further characterisation CMA^{HD} (Whole genome oligonucleotide array analysis) was done in one of the three siblings (Proband-2) using lymphocyte genomic DNA. The assay includes high resolution molecular cytogenetic analysis with its 2,690,000 marker content {750,000 polymorphic (SNP) and 1,900,000 non-polymorphic (CNV) markers}. The microchip array used was CytoScan-HD (Affymetrix) for whole genome scan. The array can detect gains and losses at a minimum of 400kb and 200kb, respectively, across the genome, or smaller (≥50Kb) for clinically relevant deletion/duplication syndromes in the subtelomere and pericentromere region or targeted genes.

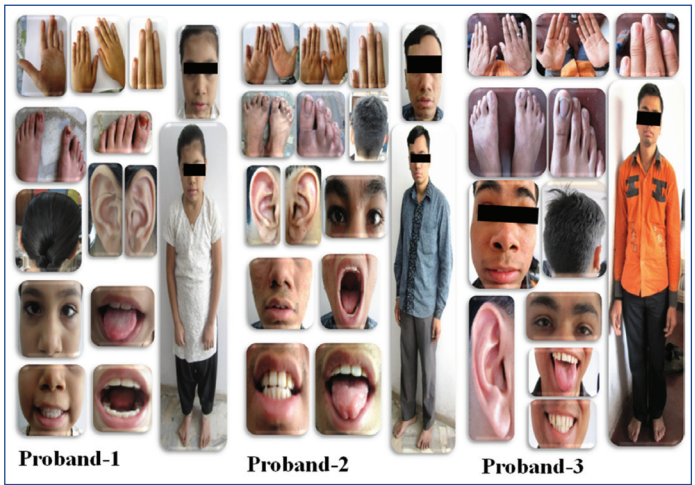
Phenomizer query: Phenotypic features in terms of minor/major abnormalities were recorded and entered in web-based tool Phenomizer [2] [Table/Fig-3]. Variations in body parts with respect to standard were also measured as shown in [Table/Fig-4].

DISCUSSION

The high resolution karyotypes of all the three siblings and father were normal at 550 band level whereas the mother had balanced t(4p;8p) as shown in [Table/Fig-5]. The CM^{HD} result of PB-2 was arr4p16.3p16.1 (68,345-9,520,844)x3, 8p23.3p23.1(158,048-6,982,980)x1. There was an approximately 9.4 Mb gain of the terminal short arm of chromosome 4 and a 6.8 Mb loss of the terminal short arm of chromosome 8. The pattern of imbalance



[Table/Fig-1]: Pedigree of the siblings.



[Table/Fig-2]: The Deep phenotypic features of siblings.

	Proband-1 (09/F)	Proband-2 (19/M)	Proband-3 (23/M)
Hair pattern	Normal	Normal	Single whorl at abnormal position
Skull	High anterior hairline, Broad and large forehead	Microcephaly	Normal
Shape of face	Square face, Pointed chin	Abnormality of the zygomatic arch	Square face, Chin dimple
Tongue	Microglossia	Bifid tongue, Broad uvula	Normal
Nose	Wide nose, Long nose, Wide nasal bridge	Asymmetry of the nares, Low hanging columella, Abnormality of the nasal dorsum	Short nose, Bulbous nose Hypoplastic nasal alae, Broad nasal tip, Flared nostrils
Lips	Thin vermilion border of upper lip, Absent cupid's bow, Everted lower lip vermilion	Curved linear dimple below the lower lip	Normal
Ears	Prominent antitragus, Broad width of superior crus of antihelix, Macrotia	Low-set ears, Abnormality of the tragus, Everted antitragus, Underdeveloped antitragus, Attached earlobe, Angulated antihelix, Abnormality of superior crus of antihelix, Macrotia	Macrotia
Eyes	Strabismus	Strabismus, Up-slanted palpebral fissure	Up-slanted palpebral fissure, Strabismus
Periorbital Region	Telecanthus	Telecanthus	Telecanthus, Epicanthus
Philtrum	Broad philtrum	Smooth philtrum, Malaligned philtral ridges	Broad philtrum
Palate	Normal	High palate	Normal
Neck	Short	Normal	Normal
Palm	Broad palm	Broad palm, Abnormality of the thenar eminence	Normal
Fingers	Clinodactyly of the 5th finger	Normal	Camptodactyly of finger
Nails	Leukonychia	Normal	Normal
Legs	Normal	Short lower limbs	Normal
Feet	Normal	Broad foot	Normal
Toes	Normal	Widely spaced toes	Normal
Chest	Barrel-shaped chest	Barrel-shaped chest	Normal

[Table/Fig-3]: Various phenotypic traits with variation or minor dysmorphic features of siblings using standard terminology.

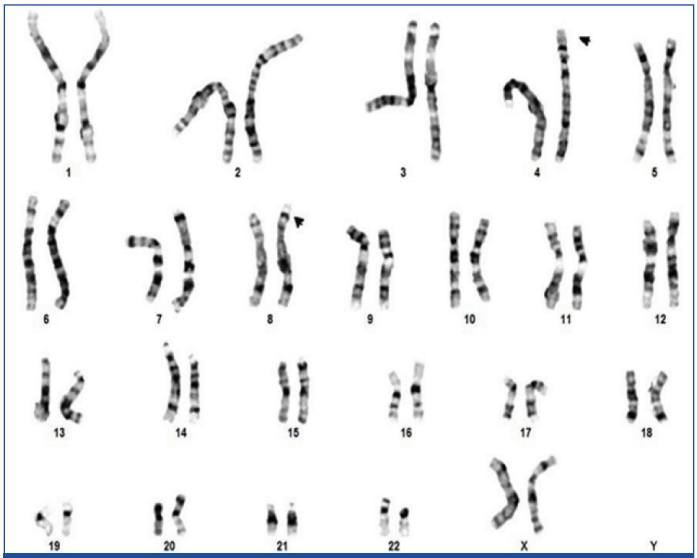
observed in this patient was consistent with an unbalanced chromosome complement resulting from a maternal balanced translocation between the short arms of chromosome 4 and chromosome 8.

Phenomizer scores indicated the most likely diagnoses as Simosa Craniofacial Syndrome (2.5838, 2.8056, 2.1902) that was common for all the three siblings. The results in one female (Proband-1) and one male patient (Proband-2) included four common genetic conditions [Table/Fig-6], in addition to others. The Phenomizer query result did not indicate t(4p;8p) or loss of 8p which may be due to non classical or variant phenotypic features.

Phenotypic expression in segmental aneuploidy generally varies depending on the size of the chromosomal region involved. Genetic factor such as abnormal constitutional karyotype of parental origin or de novo are the reasons for spontaneous abortion. Carriers of balanced chromosomal structural rearrangements are without remarkable phenotypic signature and thus inherited familial cases through the multiple generations can go without detection. The chromosomal translocation involving 4p and 8p has been

Body Parts	Proband-(109/F)	Proband-(219/M)	Proband-(323/M)
Head: Skull Hair	V N	V N	V V
Nose	V	V	V
Neck	V	N	N
Chest appearance	V	V	V
Nails: Finger Toes	V N	N V	V N
Head Circumference Chest Circumference Shoulder Width	N V V	V V V	N V V
Upper Limbs Full Hand Length Palm Length Middle Finger Length	N N N N	N V V V	N V V V
Foot Length	N	N	V
Outer Canthal Inner Canthal Inter Papillary Palpebral Fissure Philtrum Ear Length	V V V V -- V	V V V V V V	V V V V V V

[Table/Fig-4]: Variations in body parts with respect to standard measurement (N=Normal, V=Variation).



[Table/Fig-5]: Karyotype of mother showing t(4p;8p).

reported earlier which are mainly associated with partial trisomy 8p and partial monosmy 4p [3,4], however the reverse is of rare occurrence. Subjects with deletion in 4p; der(4) are reported to have Wolf-Hirschhorn syndrome, whereas cases with deletion at 8p; der(8) are reported to have a milder spectrum of dysmorphic features [3]. There is a wide spectrum of clinical features in people having unbalanced t(4;8) which makes identification of these patients very challenging [5].

Various cryptic translocations can be missed by cytogenetic banding techniques mainly because banding pattern and size are almost similar for both the regions at the 400-500 band resolution. Hence, similar to the widely reported cryptic t(11q;22q); the t(4p;8p) may also be a recurrent translocation [6].

The breakpoint reported in 8p region is within olfactory receptor gene cluster whereas there are two different breakpoints generally reported in 4p; at a distance of approximately 5 and 14Mb from the telomere which may account for the spectrum of phenotypic features that vary with the size of chromosomal region involved [7]. The reports of deletion of 8p generally include common clinical features like developmental delay, low birth weight, congenital heart disease, and a characteristic behaviour like hyperactivity and impulsiveness. The cardiac anomaly reported in these cases is atrioventricular septal defect which could be due to deletion

Score	Disease entry	Known Genes	Score	Disease entry	Known Genes	Score	Disease entry	Known Genes
2.5838	182150 SIMOSA CRANIOFACIAL SYNDROME (OMIM:182150)		3.0583	#212720 MARTSOLF SYNDROME;;CATARACTMENTAL RETARDATION-HYPOGONADISM (OMIM:212720)	RAB3GAP2	2.4526	%277720 WHISTLING FACE SYNDROME, RECESSIVE FORM (OMIM:277720)	
2.5751	#300321 FG SYNDROME 2; FGS2 (OMIM:300321)	FLNA	2.8094	FACIOGENITAL DYSPLASIA (OMIM:305400)	FGD1	2.3832	#614756 CEREBELLAR ATAXIA, NONPROGRESSIVE, WITH MENTAL RETARDATION; CANPMR (OMIM:614756)	CAMTA1
2.5334	%602342 PLANTAR LIPOMATOSIS, UNUSUAL FACIES, AND DEVELOPMENTAL DELAY;; PIERPONT SYNDROME (OMIM:602342)		2.8056	182150 SIMOSA CRANIOFACIAL SYNDROME (OMIM:182150)		2.3712	#193700 ARTHROGRYPOSIS, DISTAL, TYPE 2A; DA2A;; FREEMAN-SHELDON SYNDROME;FSS;; WHISTLING FACE-WINDMILL VANE HAND SYNDROME; ;CRANIOCARPOTARSAL DYSTROPHY;; CRANIOCARPOTARSAL DYSPLASIA (OMIM:193700)	MYH3
2.4915	%164220 SCHILBACH-ROTT SYNDROME;; OCULAR HYPOTELORISM, SUBMUCOSAL CLEFT PALATE, AND HYPOSPADIAS;; CLEFT PALATE, HYPOTELORISM, AND HYPOSPADIAS;; BLEPHAROFACIOSKELETAL SYNDROME; BRSS (OMIM:164220)		2.7673	606155 FRYNS-AFTIMOS SYNDROME;;PACHYGYRIA, MENTAL RETARDATION, EPILEPSY, AND CHARACTERISTIC FACIES;; CEREBROO CULOFACIAL LYMPHATIC SYNDROME;; COFL SYNDROME;;MENTAL RETARDATION WITH EPILEPSY AND CHARACTERISTIC FACIES (OMIM:606155)		2.2532	#300749 MENTAL RETARDATION AND MICROCEPHALY WITH PONTINE AND CEREBELLAR HYPOPLASIA;MICPCH; ;MICPCH SYNDROME;;MENTAL RETARDATION, XLINKED, SYNDROMIC, NAJM TYPE; MRXSNA (OMIM:300749)	CASK
2.4834	FACIOGENITAL DYSPLASIA (OMIM:305400)	FGD1	2.7441	#158170 CHROMOSOME 9P DELETION SYNDROME; ;MONOSOMY 9P SYNDROME (OMIM:158170)		2.1991	612948 STARGARDT MACULAR DEGENERATION, ABSENT OR HYPOPLASTI C CORPUS CALLOSUM,MENTAL RETARDATION, AND DYSMORPHIC FEATURES (OMIM:612948)	
2.3693	%227330 FACIODIGITOGENITAL SYNDROME, AUTOSOMAL RECESSIVE; ;AARSKOG-LIKE SYNDROME;;KUWAIT TYPE FACIODIGITOGENITAL SYNDROME (OMIM:227330)		2.6672	%227330 FACIODIGITOGENITAL SYNDROME, AUTOSOMAL RECESSIVE;;AARSKOG-LIKE SYNDROME;;KUWAIT TYPE FACIODIGITOGENITAL SYNDROME (OMIM:227330)		2.1902	182150 SIMOSA CRANIOFACIAL SYNDROME (OMIM:182150)	
2.3663	KBG SYNDROME (OMIM:148050)	ANKRD11	2.6447	%602342 PLANTAR LIPOMATOSIS, UNUSUAL FACIES, AND DEVELOPMENTAL DELAY;; PIERPONT SYNDROME (OMIM:602342)		2.1806	#613544 CHROMOSOME 6Q11-Q14 DELETION SYNDROMECHROMOSOME 6Q13-Q14 DELETION SYNDROME, INCLUDED (OMIM:613544)	
2.3270	311450 PALLISTER W SYNDROME;;W SYNDROME (OMIM:311450)		2.6052	#610536 MANDIBULOFACIAL DYSOSTOSIS, GUION-ALMEIDA TYPE; MFDGA;;MANDIBULOFACIAL DYSOSTOSIS WITH MICROCEPHALY; MFDM;;GROWTH AND MENTAL RETARDATION, MANDIBULOFACIAL DYSOSTOSIS, MICROCEPHALY, AND CLEFT PALATE (OMIM:610536)	EFTUD2	2.1623	#300143 MENTAL RETARDATION, X-LINKED 21; MRX21;;MENTAL RETARDATION, XLINKED 34; MRX34 (OMIM:300143)	IL1RAPL1
2.2904	606155 FRYNS-AFTIMOS SYNDROME;; PACHYGYRIA, MENTAL RETARDATION, EPILEPSY, AND CHARACTERISTIC FACIES;; CEREBROOCULOFACIAL LYMPHATIC SYNDROME;; COFL SYNDROME; ;MENTAL RETARDATION WITH EPILEPSY AND CHARACTERISTIC FACIES (OMIM:606155)		2.5781	%181270 SCALP-EAR-NIPPLE SYNDROME;;FINLAY-MARKS SYNDROME;; SEN SYNDROME (OMIM:181270)	KCTD1	2.1617	RING CHROMOSOME 1 (ORPHANET:1437)	
2.2733	%145420 HYPERTELORISM, TEEBI TYPE;; BRACHYCEPHAL OFRONTONASAL DYSPLASIA (OMIM:145420)		2.5034	#610954 PITT-HOPKINS SYNDROME; PTHS;; ENCEPHALOPATHY, SEVERE EPILEPTIC, WITH AUTONOMIC DYSFUNCTION;; MENTAL RETARDATION, SYNDROMAL, WITH INTERMITTENT HYPERVENTILATION (OMIM:610954)	TCF4	2.1582	#611091 MENTAL RETARDATION, AUTOSOMAL RECESSIVE 5; MRT5 (OMIM:611091)	NSUN2

[Table/Fig-6]: Result generated by web based software Phenomizer for all the three siblings respectively showing ranked list of possibilities and associated gene based on score

of GATA4 gene present on 8p [8]. But not all the patients have congenital heart defects, the possible reason may be compensatory increases in GATA5 or GATA6 which may mitigate the effects of GATA4 deletion and haploin sufficiency for other cardiac transcription factor genes (e.g. TBX5, NKX2–5) which causes congenital heart disease [8]. The patients having intellectual disability generally also show growth retardation but people with a gain at 4p due to the unbalanced t(4p;8p) are generally tall. This could probably be due to the presence of third copy of FGFR3 gene on the 4p16.3 [9].

According to the Unique database only few cases of der(8) have been reported in medical literature (Unique) [10].

The unbalanced translocation resulting in both partial trisomy for 4p16-pter and partial monosomy for 8p23-pter can be associated with the maternal constitutional t(4;8) (p16;p23). A chromosomal break can cause loss of function of gene if it disrupts the coding sequence or if it separates the coding sequence with cis-acting regulatory sequence. A breakpoint can provide a valuable clue to exact physical location of disease gene. In our case the genetic aberration in Proband-2 involving loss in 8p, the breakpoint region is at 6,982,980 position which occurs between two genes DEFA1 and DEFT1P, probably in the non-coding region but might have affected function of these genes. The gain in 4p might have lead to higher copy number of genes including OR7E83P and LOC101928948 along with others as the breaking region is at 9,520,844 position which occur in between the above two genes [11]. This genomic imbalance observed using CMA may be responsible for congenital minor dysmorphisms and intellectual disabilities due to the dosage effect of genes involved. The rest of the two probands with similar clinical presentation are also likely to carry the similar genomic aberrations though normal at GTG banded karyotype level. The recurrent 8p rearrangements can also occur as a consequence of an inversion polymorphism mediated by two olfactory receptor (OR) gene clusters which can be of parental origin. The olfactory receptor gene clusters exist at 4p16, as well as 8p23 which may be implicated in the genesis of the recurrent t(4;8)(p16;p23) [3]. Giglio S et al., hypothesized that the heterozygous submicroscopic inversions of both 4p and 8p could prevent correct synapsis of the inverted regions at meiosis. As a result, both tetrads might assume a configuration that could result in an illegitimate but “homologous” crossover between the OR-gene clusters present on both 4p and 8p i.e., the double heterozygous inversion will make two nonhomologous chromosomes available to recombine with each other [3].

The unbalanced t(4p;8p) is not always detectable by conventional cytogenetics/multi-colour Fluorescence in situ hybridization techniques [5,12], hence molecular cytogenetic techniques may be helpful to unravel unbalanced chromosomal translocations.

CONCLUSION

It is important to put on record every case of unbalanced t(4;8) along with detailed phenotypic data collected and described in a harmonized way. The high resolution genotyping data in the current era can be more meaningful if matched with phenotyping data collected in detail. The combined study of phenotypic and molecular genetics characterization in abnormal constitutional karyotype cases are required to be pooled to help delineate a subentity of genetic condition. Such efforts can help better clinical management and genetic counselling apart from the molecular pathogenesis studies.

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PARTICULARS OF CONTRIBUTORS:
1. Ph.D. Pursuing, Institute of Science, Nirma University, Sarkhej-Gandhinagar Highway, Ahmedabad, India.
2. Assistant Professor, Institute of Science, Nirma University, Sarkhej-Gandhinagar Highway, Ahmedabad, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sonal R. Bakshi,
Assistant Professor, Institute of Science, Nirma University, Sarkhej-Gandhinagar Highway,
Ahmedabad - 382 481 Gujarat, India.
E-mail: sonal.bakshi@nirmauni.ac.in

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