Recurrent 1q21.1 deletion syndrome: report on variable expression, nonpenetrance and review of literature

Priyanka Upadhyai[a], Eram Fatima Amiri[a], Vishal Singh Guleria[a], Stephanie L. Bielas[b], Katta Mohan Girisha[a] and Anju Shukla[a]

The clinical phenotype of 1q21.1 microdeletion syndrome is highly heterogeneous. It is characterized by dysmorphic facial features, microcephaly, and developmental delay. Several congenital defects, including cardiac, ocular, skeletal anomalies, and psychiatric or behavioural abnormalities, have also been described. Here, we report on two siblings with substantial intrafamilial phenotypic variability carrying a heterozygous deletion of the 1q21.1 region spanning a known critical genomic area (~1.35 Mb). The microdeletion was inherited from the unaffected father. Patients described here show a spectrum of clinical features, a portion of which overlap with those previously reported in patients with 1q21.1 microdeletions. In addition, we review the clinical reports of 66 individuals with this condition. These findings extend and substantiate the current clinical understanding of recurrent copy number variations in the 1q21.1 region. *Clin Dysmorphol* 29: 127–131

Clinical Dysmorphology 2020, **29**:127–131

Keywords: 1q21.1, chromosomal microarray, nonpenetrance

[a]Department of Medical Genetics, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India and [b]Department of Human Genetics, University of Michigan, Ann Arbor, Michigan, USA

Correspondence to Anju Shukla, MD, DM, Department of Medical Genetics, Kasturba Medical College, Manipal Academy of Higher Education, Manipal 576104, Karnataka, India
Tel: +918202922726; fax: +918202571927; e-mail: anju.shukla@manipal.edu

Received 1 August 2019 **Accepted** 27 April 2020

Introduction

Individuals with recurrent 1q21.1 copy number variations (CNVs) show a high degree of phenotypic variability from unaffected to severe clinical manifestation. The 1q21.1 microdeletion syndrome (OMIM612474) has been associated with various phenotypic features including microcephaly, intellectual disability, developmental delay, craniofacial dysmorphism, congenital anomalies such as congenital heart disease (CHD), eye abnormalities, genitourinary, and skeletal aberrations (Christiansen *et al.*, 2004; Brunetti-Pierri *et al.*, 2008; Mefford *et al.*, 2008; Brunet *et al.*, 2009; Digilio *et al.*, 2013; Busè *et al.*, 2017). In addition, behavioural and psychiatric conditions including attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), schizophrenia, and seizures have also been reported in a subset of patients with this condition (Sebat *et al.*, 2007; Stefansson *et al.*, 2008; Crespi and Crofts, 2012).

Furthermore, the reciprocal 1q21.1 microduplication has been associated with macrocephaly or relative macrocephaly, frontal bossing, hypertelorism, developmental delay, intellectual disability, and ASD (Brunetti-Pierri *et al.*, 2008; Mefford *et al.*, 2008; Bernier *et al.*, 2016; Busè *et al.*, 2017). Both inherited and de-novo 1q21.1 microdeletions and microduplications have been identified. Herein, we report on two siblings with 1.3 and 2 Mb 1q21.1 microdeletions inherited from their unaffected father.

Methods

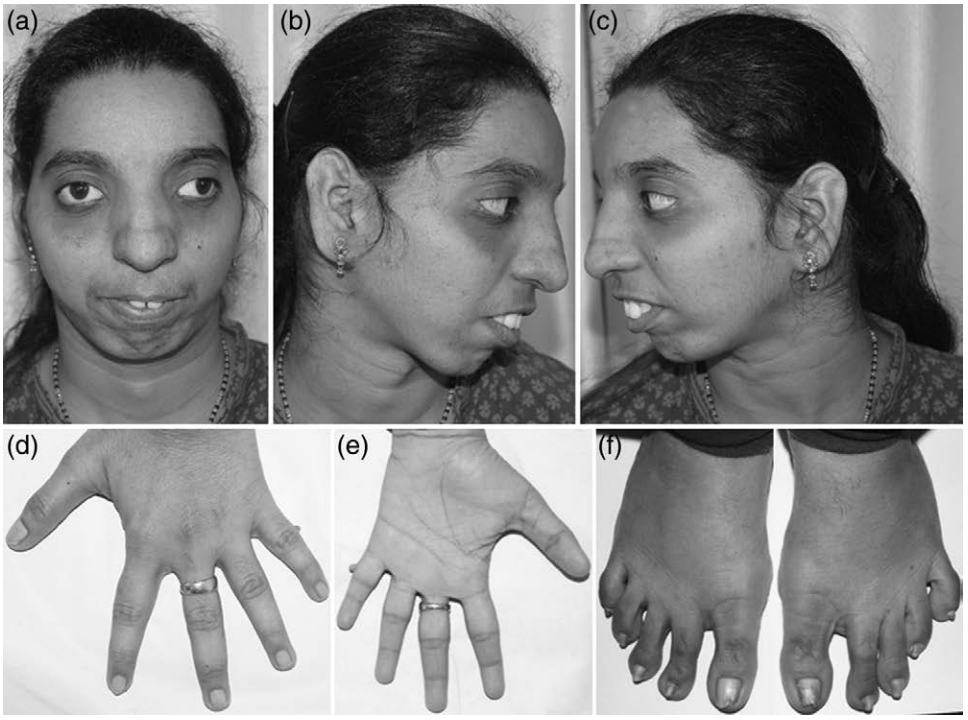
Clinical report

A 27-year-old female patient (P1) was evaluated upon referral for facial dysmorphism. She is the first-born to nonconsanguineous, unaffected parents (Fig. 1). She was born at term via vaginal delivery with a normal antenatal period. Her developmental history was normal. Upon examination, her head circumference was 49.2 cm (–5 SD) and height was 146 cm (–2.8 SD). She had tall forehead, telecanthus, strabismus, everted lateral half of lower eyelid, prominent nose with broad root, bridge, and ridge, microretrognathia, and large ears with underdeveloped helix. At 16 years of age, she had an operation for microretrognathia. In addition, she had bilateral and rudimentary postaxial polydactyly of both hands, a short fifth digit with clinodactyly, dystrophic nails, and mild joint laxity.

The affected male sibling (P2) of P1 was also evaluated at 22 years of age (Fig. 2). Similar to P1, P2 was also born at term via vaginal delivery with normal antenatal period. Facial dysmorphism, cleft lip, and cleft palate were noted at birth. He had significant developmental delay. At two years of age, he achieved neck holding and independent sitting. He spoke using bisyllables at three years old and walked without support at three and a half years. Currently, he is able to speak using short sentences. At 15 years age, he had an episode of seizures and has since been on medication. Upon examination, his head circumference was 49.7 cm (–4.9 SD) and height was 151 cm

0962-8827 DOI: 10.1097/MCD.0000000000000327

Fig. 1



P1 at 27 years of age. (a–c) Note dysmorphic facial features; (d) postaxial polydactyly; (e) short fifth finger with clinodactyly; and (f) dystrophic nails.

(–4.4 SD). He has a tall forehead, asymmetric facies with more severe microphthalmia on the right eye, microcornea and corneal opacity in the left eye, a broad nose with deviated septum, repaired cleft lip, dysmorphic ears with deficient helix, and irregular dentition. His cleft lip was surgically corrected at four months and 15 years of age. Furthermore, he has intellectual disability, mild webbing in upper limbs, partial syndactyly of the second and third toes, elbow and distal joint laxity, and abnormal fat pads on lower back.

Chromosomal microarray analysis

EDTA blood samples were collected from P1, P2, and both parents after obtaining written informed consent. Chromosomal microarray was performed using Illumina HumanCytoSNP-12 on DNA obtained from peripheral blood samples of both affected siblings. The genome-wide resolution of this array is ~30 kb.

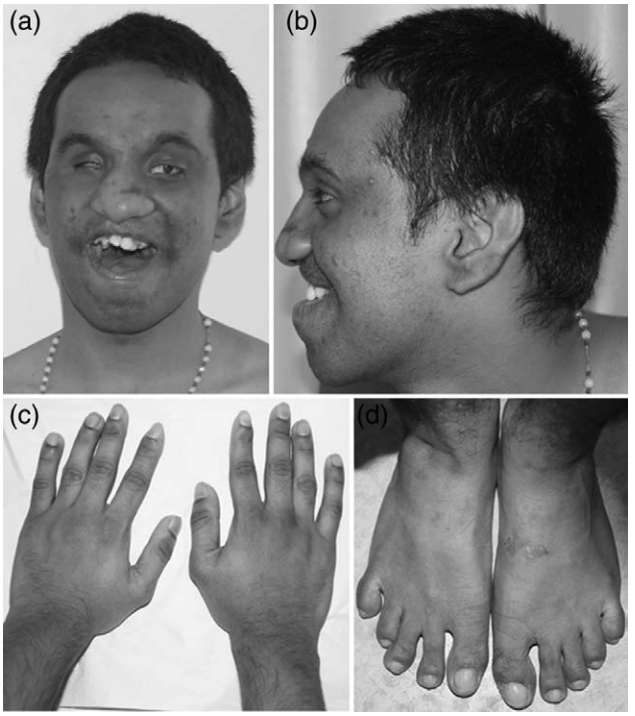
Real-time PCR analysis

Genomic DNA (gDNA) was extracted from whole blood for the affected siblings and both parents using a standard phenol-chloroform method. Real-time quantitative PCR was carried out on gDNA using StepOne (Applied Biosystems, Thermo Fisher Scientific, Foster City, California, USA) with a final reaction volume of 10 µl. All reactions were prepared with 5 µl of 2× PowerUP SYBR Green Mastermix (Applied Biosystems, Thermo Fisher Scientific) and 500 nM of forward and reverse primers for target genes *BCL9* and *CHD1L* within the 1q21.1 critical genomic region that is commonly affected in patients with 1q21.1 microdeletion/microduplication syndromes and is deleted in both P1 and P2 siblings in this report. Primer sequences are available upon request. Exon 4 of *CFTR* was used as an internal control. For each sample, a total of 12.5 ng of DNA was used as template and samples were analysed in duplicate in four independent experiments. Thermal cycling conditions included a prerun of 50°C for 2 min and 95°C for 2 min. Cycle conditions were 95°C for 15 s and 60°C for 1 min for 40 cycles. Relative quantification of copy numbers on genomic DNA was carried out using the comparative threshold cycle ($\Delta\Delta C_T$) method (Bierhals *et al.*, 2013). The relative exon copy number was calculated by the expression $2 \times 2^{-(\Delta\Delta C_T)}$ and is approximately two for a diploid sample and one for heterozygous deletion.

Results

Chromosomal microarray analysis revealed a heterozygous deletion of 2 Mb (chr1: 145 755 813–147 828 939; hg19, GRch37) and 1.3 Mb (chr1: 146 516 199–147 828 939; hg19, GRch37) in P1 and P2, respectively. This difference appears technical due to the lower density of single nucleotide polymorphism markers in this region of the microarray platform utilized. To confirm these findings

Fig. 2



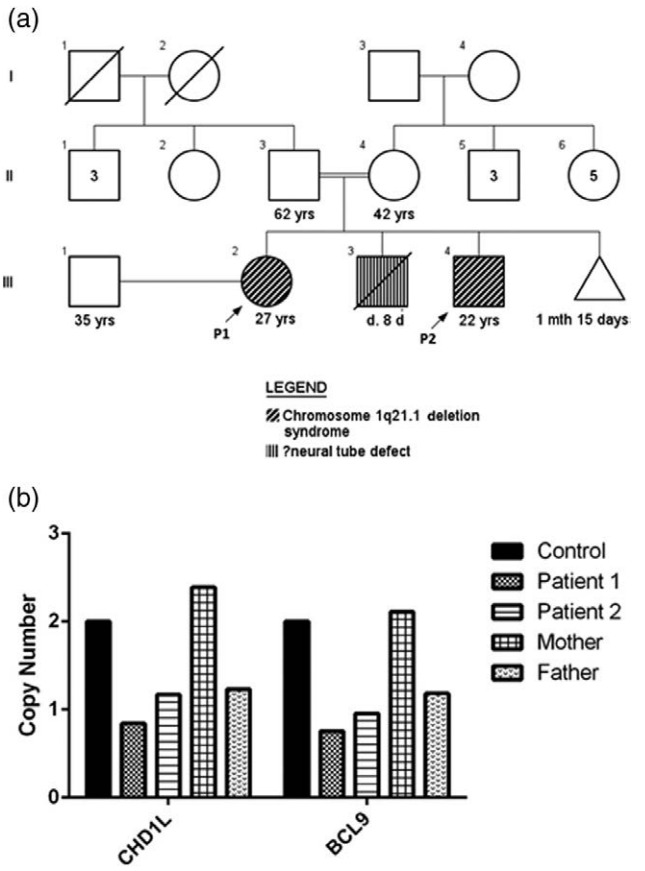
P2 at 22 years of age. (a and b) Facial dysmorphism; (c) proximally placed thumbs; and (d) mild cutaneous syndactyly between second and third toes.

within the siblings and evaluate the unaffected parents, we performed real-time PCR on gDNA templates for comparative quantification of copy number of two genes, *BCL9* and *CHD1L*. Both target genes lie within the critical 1q21.1 genomic region affected in several patients with 1q21.1 microdeletions/microduplications and that is deleted in both affected siblings. *CHD1L* and *BCL9* copy number estimates equate to approximately one in both siblings and the unaffected father, indicating heterozygous deletion, whereas the copy number in the mother is comparable to that expected for diploid copy number (Fig. 3). These results suggest paternal inheritance of the 1q21.1 heterozygous deletion in both affected siblings, and the unaffected status of the father is consistent with previous reports of 1q21.1 microdeletion inheritance from mildly affected or apparently unaffected parents (Brunetti-Pierri *et al.*, 2008; Mefford *et al.*, 2008; Bernier *et al.*, 2016; Busè *et al.*, 2017).

Discussion

Individuals with the 1q21.1 microdeletion syndrome display a diversity of clinical phenotypes. In the present study, a significant intrafamilial variability in the expression of clinical features is observed in the affected siblings P1 and P2. In addition to these variable clinical manifestations, they also share several features with other subjects previously described for this syndrome.

Fig. 3



(a) Pedigree of the family; (b) relative quantification of copy numbers of *CHD1L* and *BCL9* by real-time PCR on genomic DNA of the patients revealed one copy number of both amplicons in both the patients and their father, while values of both amplicons in the patient's mother are comparable to that of a diploid sample.

Table 1 Clinical summary of patients with 1q21.1 microdeletion syndrome

Clinical features	Frequency (%)
Growth abnormalities	44/68 (64.7)
Developmental delay	27/68 (39.7)
Intellectual disability	15/68 (22.1)
Facial dysmorphism	40/68 (58.8)
Skeletal abnormalities	29/68 (42.6)
Ocular involvement	19/68 (27.9)
Cardiac anomalies	10/59 (16.9)
Dental involvement	2/68 (2.9)
Nail involvement	3/68 (4.4)
Genitourinary abnormalities	8/68 (11.8)
Seizures	9/68 (13.23)
Behavioural anomalies	23/68 (33.8)

Here, we review a total 68 affected individuals with detailed clinical outcomes in the literature, including the two affected subjects described above. The suite of clinical features characterized in the present study and elsewhere (Brunetti-Pierri *et al.*, 2008; Mefford *et al.*, 2008; Bernier *et al.*, 2016; Gamba *et al.*, 2016; Busè *et al.*, 2017) are summarized in Table 1.

Growth abnormalities are commonly associated with the 1q21.1 microdeletion syndrome, and are observed in 64.7% of the 68 reviewed patients. Notably, microcephaly and short stature reported in both affected siblings are observed in 35.3 and 44.1% of the 68 patients, respectively.

Dysmorphic facial features were observed in 58.8% of the 68 subjects. P1 and P2 in the present study have large ears with deficient helix and a prominent nose, features present in 4.4 and 7.4% of the 68 subjects, respectively. In addition, microretrognathia and irregular dentition are observed in P1 and P2. Dental deformities are reported in 10.3% of the 68 subjects. Cleft lip/palate is described in 4.4% of all 68 reviewed subjects, features seen in P2 but absent in P1.

Skeletal abnormalities have been described in 42.6% of all 68 subjects. Polydactyly and clinodactyly are seen in P1, but not P2, and are reported in 8.8% of the 68 reviewed subjects. Syndactyly, observed in P2 but not P1, is present in 5.9% of all 68 subjects. Mild joint laxity is noted in both P1 and P2, and in 7.4% of all 68 subjects, whereas scoliosis reported in 5.9% of the 68 subjects is not seen in P1 and P2. Furthermore, nail dystrophy is described in P1 but not in P2, and is reported in 4.4% of the 68 subjects.

Developmental delay and intellectual disability are described in 39.7 and 22.1% of all 68 subjects, respectively, and compared to reported cases (Brunetti-Pierri *et al.*, 2008; Mefford *et al.*, 2008; Gamba *et al.*, 2016; Busè *et al.*, 2017), both phenotypes were more severe in P2. Broadly, ocular abnormalities are noted in P1 and P2, and in 27.9% of all 68 subjects. Eye anomalies reported in previous subjects include hypermetropia, convergent squint, cataracts, strabismus, micropthalmia, Duane anomaly, exophoria, dry eyes, chorioretinal and iris coloboma, and lens subluxation. Notably, microcornea, nystagmus, and corneal opacity are seen in P2 and are not reported in the other 67 subjects. Strabismus is observed in P1 but not P2, and is described in 10.3% of all 68 subjects. Furthermore, telecanthus is observed in P1 and has not been reported for the other subjects reviewed here. An isolated episode of seizure was noted in P2, and observed in 13.2% of all 68 subjects. Last, cardiac, genitourinary, and behavioural abnormalities are described in 16.9, 11.8 and 33.8%, respectively, of all 68 subjects, yet are not noted in P1 and P2.

Previous studies have reported the 1q21.1 deleted region ranges in size from 1.2 to 1.7 Mb in subjects with the 1q21.1 microdeletion syndrome (Brunetti-Pierri *et al.*, 2008; Mefford *et al.*, 2008; Gamba *et al.*, 2016; Busè *et al.*, 2017). A patient with larger and atypical deletion of ~5.5 Mb extending proximally towards the centromere compared to the more commonly observed deleted region has also been reported (Mefford *et al.*, 2008). Chromosomal microarray analysis revealed a heterozygous deletion of 2 and 1.3 Mb of 1q21, in P1 and P2, respectively, with suggestive evidence of inheritance from the unaffected father by quantitative real-time PCR. The genomic region deleted in both siblings encompasses nine genes: *NBPF11; PRKAB2; FMO5; CHD1L; BCL9; ACP6; GJA5; GJA8* and *GPR89B*. This deletion overlaps a ~1.35 Mb (145–146.35 Mb) critical region that is commonly deleted in individuals with the 1q21 microdeletion syndrome (Mefford *et al.*, 2008; Busè *et al.*, 2017), but not all subjects. No other clinically significant CNVs were detected.

.

Conclusion

Here, we report on the phenotypes of two siblings with heterozygous 1q21.1 microdeletions, as well as review and summarize the spectrum of clinical features previously published for individuals reported with this condition. Our report substantiates the marked variation in expressivity of 1q21.1 microdeletion phenotypes in affected patients, as well as reduced/nonpenetrance of heterozygous 1q21.1 microdeletion carriers. Finally, the variable intrafamilial phenotypic expression observed among the affected siblings in this study, as well as the spectra of clinical phenotypes previously reported among individuals with 1q21.1 microdeletions may be attributed to genetic factors, such as variants in modifier genes, epigenetic, or environmental influences. In addition, it is unclear the extent to which alterations in gene dosage or disruption to 1q21.1 chromatin regulatory landscapes contribute to variation in expressivity and penetrance. Inclusion of additional patients with detailed clinical findings such as the present study is crucial for advancing the understanding of reciprocal 1q21.1 microdeletion and microduplication syndromes.

Acknowledgement

We thank the family for their cooperation and consent for participation in this study.

This work was funded by the US National Institutes of Health funded project entitled 'Genetic Diagnosis of Heritable Neurodevelopmental Disorders in India: Investigating the Use of Whole Exome Sequencing and Genetic Counseling to Address the High Burden of Neurodevelopmental Disorders' (1R21NS094047-01).

Conflicts of interest

There are no conflicts of interest.

References

Bernier R, Steinman KJ, Reilly B, Wallace AS, Sherr EH, Pojman N, *et al.*; Simons VIP Consortium (2016). Clinical phenotype of the recurrent 1q21.1 copy-number variant. *Genet Med* **18**:341–349.

Bierhals T, Maddukuri SB, Kutsche K, Girisha KM (2013). Expanding the phenotype associated with 17q12 duplication: case report and review of the literature. *Am J Med Genet A* **161A**:352–359.

Brunet A, Armengol L, Heine D, Rosell J, García-Aragonés M, Gabau E, *et al.* (2009). BAC array CGH in patients with velocardiofacial syndrome-like features reveals genomic aberrations on chromosome region 1q21.1. *BMC Med Genet* **10**:144.

Brunetti-Pierri N, Berg JS, Scaglia F, Belmont J, Bacino CA, Sahoo T, *et al.* (2008). Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities. *Nat Genet* **40**:1466–1471.

Busè M, Cuttaia HC, Palazzo D, Mazara MV, Lauricella SA, Malacarne M, *et al.* (2017). Expanding the phenotype of reciprocal 1q21.1 deletions and duplications: a case series. *Ital J Pediatr* **43**:61.

Christiansen J, Dyck JD, Elyas BG, Lilley M, Bamforth JS, Hicks M, *et al.* (2004). Chromosome 1q21.1 contiguous gene deletion is associated with congenital heart disease. *Circ Res* **94**:1429–1435.

Crespi BJ, Crofts HJ (2012). Association testing of copy number variants in schizophrenia and autism spectrum disorders. *J Neurodev Disord* **4**:15.

Digilio MC, Bernardini L, Consoli F, Lepri FR, Giuffrida MG, Baban A, *et al.* (2013). Congenital heart defects in recurrent reciprocal 1q21.1 deletion and duplication syndromes: rare association with pulmonary valve stenosis. *Eur J Med Genet* **56**:144–149.

Gamba BF, Zechi-Ceide RM, Kokitsu-Nakata NM, Vendramini-Pittoli S, Rosenberg C, Krepischi Santos AC, *et al.* (2016). Interstitial 1q21.1 microdeletion is associated with severe skeletal anomalies, dysmorphic face and moderate intellectual disability. *Mol Syndromol* **7**:344–348.

Mefford HC, Sharp AJ, Baker C, Itsara A, Jiang Z, Buysse K, *et al.* (2008). Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes. *N Engl J Med* **359**:1685–1699.

Sebat J, Lakshmi B, Malhotra D, Troge J, Lese-Martin C, Walsh T, *et al.* (2007). Strong association of de novo copy number mutations with autism. *Science* **316**:445–449.

Stefansson H, Rujescu D, Cichon S, Pietiläinen OP, Ingason A, Steinberg S, *et al.*; GROUP (2008). Large recurrent microdeletions associated with schizophrenia. *Nature* **455**:232–236.