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SHORT REPORT

4q34.1–q35.2 deletion in a boy with phenotype resembling 22q11.2 deletion syndrome

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Abstract Small terminal or interstitial deletions involving bands 4q34 and 4q35 have been described in several patients with a relatively mild phenotype such as mild to moderate intellectual disability and minor dysmorphic features. We present a boy born from unrelated parents with a de novo 4q34.1–q35.2 deletion and clinical features resembling 22q11.2 deletion syndrome. To the best of our knowledge, this is the first reported patient with 4q34–q35 deletion and phenotype resembling 22q11.2 deletion syndrome without fifth finger anomalies as a specific feature of 4q- syndrome. G-banding karyotyping disclosed the deletion, which was further delineated by microarray comparative genomic hybridization. Fluorescence in situ hybridization and multiplex ligation-dependent probe amplification analyses did not reveal rearrangements of 22q11.2 region. MLPA confirmed the deletion within the 4q35.2 region. *Conclusion*: Given the considerable clinical overlaps between the 22q11.2 deletion syndrome and clinical manifestation of the patient described in this study, we propose that region 4q34.1–q35.2 should be considered as another region associated with phenotype resembling 22q11.2 deletion syndrome. We also propose that distal 4q deletions should be considered in the evaluation of patients with phenotypic manifestations resembling 22q11.2 deletion syndrome in whom no 22q11.2 microdeletion was detected, even in the absence of distinctive fifth finger anomalies. Additionally, we underline the importance of applying array CGH that enables simultaneous genome-wide detection and delineation of copy number changes (e.g., deletions and duplications).

Keywords 4q34.1–q35.2 deletion · 22q11.2 deletion syndrome · Array CGH · MLPA

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Introduction

Microscopically visible interstitial and terminal deletions of the long arm of chromosome 4 often cause a recognizable pattern of malformations known as 4q- syndrome [28, 30, 32]. This syndrome is usually associated with growth retardation, mild to moderate mental retardation, craniofacial anomalies (microcephaly, low-set and malformed pinnae, short nose with a low nasal bridge and micrognathia), palatal, skeletal and fifth finger anomalies (clinodactyly, ulnar ray defects, stiff fifth finger with hypoplastic or tapering distal phalanx, hooked or

volar nail), as well as urogenital and cardiovascular malformations (mostly atrial or ventricular septal defects) [1, 11, 17, 30]. Several authors have suggested that the critical region for most of the 4q- common characteristics might be assigned to the 4q31–q34 interval [16, 26, 28, 29]. Smaller terminal or interstitial deletions involving bands 4q34–q35 have also been described in several cases [2, 5–7, 10, 17, 24, 33–35]. These smaller deletions usually do not lead to major anomalies, but rather give mild to moderate mental retardation and minor dysmorphic features such as coarse face, ear malformations and fifth finger anomalies [6]. Major anomalies have been described in a few cases associated with smaller deletions and the most common are congenital heart defects, genitourinary anomalies and cleft palate [2, 33]. An association of the 4q34.2–qter deletions and the phenotype of velocardiofacial syndrome has been suggested by several authors [5, 7, 10, 25, 33]. So far, no consistent clinical phenotype for 4q34–q35 deletions could be delineated [2]. It has, however, been suggested that the severity of the phenotype correlates with the size of deletion [17].

22q11.2 deletion syndrome (MIM# 188400) is the most common deletion disorder in humans with an incidence of approximately 1/4,000 per live births [9]. This syndrome is characterized by a broad spectrum of features including conotruncal heart anomalies, craniofacial dysmorphism (long face with malar flattening and mandibular retrusion, narrow palpebral fissures, small and malformed pinnae, prominent nasal bridge and small mouth), cleft palate, absent or small thymus with T lymphocyte dysfunction and hypoparathyroidism [11, 14].

Here, we report a patient initially suspected of having 22q11.2 deletion syndrome because of facial dysmorphism, tetralogy of Fallot, right aortic arch and normal growth and development. Routine cytogenetic analysis, however, identified a microscopically visible distal 4q deletion. In order to delineate this chromosomal deletion, we applied microarray comparative genomic hybridization (array CGH). Array CGH confirmed the distal deletion of the long arm of chromosome 4. The deletion is approximately 17.4 Mb in size and extends from 4q34.1 to the subtelomeric region of 4q35.2. The 22q11.2 microdeletion was not detectable by fluorescence in situ hybridization (FISH) and multiplex ligation-dependent probe amplification (MLPA). Additionally, MLPA confirmed the deletion within the 4q35.2 region. Considering that this patient with clinical features of 22q11.2 deletion syndrome has a large 4q deletion and no fifth finger anomalies as specific feature of 4q-syndrome, we propose that 4q34.1–q35.2 region should be considered as another region associated with the phenotype resembling 22q11.2 deletion syndrome.

Case report

A 6-month-old male infant was referred for genetic counseling because of tetralogy of Fallot, right aortic arch and facial dysmorphism. He was the first child of a young, healthy and unrelated couple. Family history as well as the histories of pregnancy and delivery were unremarkable, without consanguinity or exposure to teratogenic factors.

Physical examination revealed a small mouth and prominent ears. Height and weight were between the 25th and 50th centile and head circumference at 50th centile. Heart auscultation disclosed a grade 4/6 systolic murmur at upper left sternal border, accompanied with central cyanosis. He was mildly hypotonic, with otherwise normal motor and cognitive development.

At the age of 8 months, a complete correction of tetralogy of Fallot was undertaken. Postoperative course was complicated by junctional ectopic tachycardia, which was successfully treated with amiodarone. The motor milestones of the patient were within wider range of normal. He was able to sit unassisted at 9–10 months, shortly after surgical intervention, and walked at the age of 15–16 months.

Presently, at the age of 2 years and 2 months, previously observed facial dysmorphism persists. Growth and psychomotor development are normal, with height 90.5 cm (75th centile), weight 14.3 kg (between 75th and 90th centile) and head circumference 52 cm (between 75th and 90th centile). He speaks short sentences and smiles occasionally during examination. The hair, as well as, skull form is normal. The palpebral fissures and distance between eyes also appear normal. The outer canthal distance is 7.8 cm (75th centile), the inner canthal distance is 2.9 cm (between 75th and 90th centile), the interpupillary distance is 5.1 cm (75th centile) and the length of palpebral fissures is 2.5 cm (between 50th and 75th centile). The nasal root and bridge, as well as, length and form of the filtrum are normal. The ears are anteverted with otherwise normal morphology and dimensions. The mouth appears small and the chin pointed. The boy is not suffering any disturbance of heart rhythm, having only a mild residual pulmonary stenosis detected on the most recent echocardiographic examination.

G-banding cytogenetic analysis of the patient identified a distal deletion within the long arm of one chromosome 4, with the breakpoints assigned between 4q34 and 4q35 (data not shown). Parental chromosomes were normal, indicating that deletion in the patient had arisen de novo (data not shown). The array CGH analysis provided precise delineation of the chromosomal rearrangement, showing an interstitial deletion approximately 17.4 Mb in size in the distal part of chromosome 4 (chr4: 172,977,872–190,351,861; genome build 18), extending from 4q34.1 to the subtelomeric region of 4q35.2 (Fig. 1). Copy number

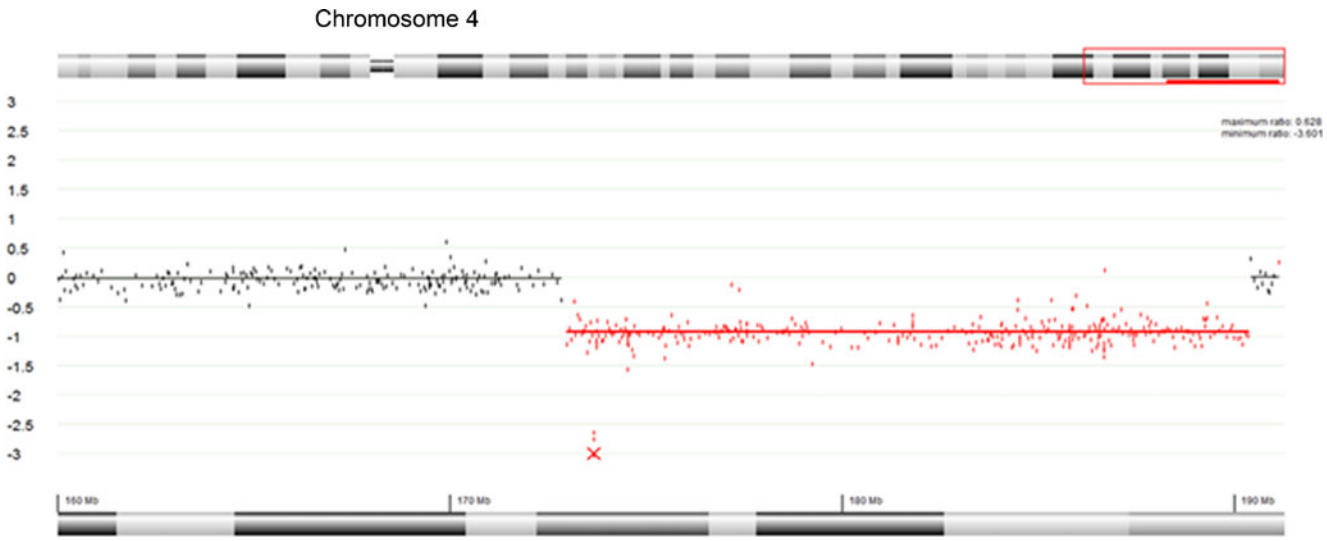

Fig. 1 Enlarged array CGH profile of the distal part of chromosome 4 of the patient. The *red* reporters on the distal part of chromosome 4 represent the deleted region. *X axis* represents physical location in Mb. *Y axis* represents log2 intensity ratio, with a single copy loss at value of −1

profiling was performed on an Agilent Human Genome CGH Microarray 60K (AMADID# 021924, hg18, NCBI build 36.1, March 2006) as previously described [4]. Microarray slides were scanned using an Agilent microarray scanner, quantified with Feature Extraction software 9.5.1 and further analyzed with arrayCGHbase (http://medgen.ugent.be/arraycghbase/) [20]. No other copy number variations and cryptic chromosomal rearrangements could be detected by array CGH. In addition, FISH with TUPLE1 probe and MLPA (kit P250-A1 DiGeorge; MRC-Holland) analyses were performed. Neither of these two analyses revealed rearrangements of 22q11.2 region. MLPA confirmed the deletion of the KLKB1 probe within the 4q35.2 region and rearrangements in other four regions at chromosomes 8, 9, 10 and 17 were not detectable (data not shown).

Discussion

It has been proposed that distal deletions of chromosome 4q involving 4q34-qter are usually characterized with relatively mild phenotypic abnormalities, such as mild to moderate mental retardation and minor dysmorphic features [6, 33]. We have identified a de novo interstitial deletion, spanning the 4q34.1–q35.2 region, in a boy with a phenotype resembling the 22q11.2 deletion syndrome. The approximate size of 17.4 Mb and breakpoints of the deletion have been determined by array CGH.

Based on literature analysis, only a few authors have postulated that distal 4q deletions might be associated with a phenotype resembling the 22q11.2 deletion syndrome [10, 25, 33]. Tsai et al. described a boy with 4q34.2-qter deletion, having velocardiofacial syndrome-like phenotype accompanied by typical 4q- syndrome anomaly, i.e., dysplastic and duplicated nail of the fifth finger [33]. A second report describes two patients with distal 4q deletions, initially suspected of having 22q11.2 deletion syndrome [10]. The first patient was presented with intellectual disability, congenital heart defect, cutaneous syndactyly of fingers, omphalocele and deletion of the 4q33-qter region. The second reported patient had a milder phenotype and haploinsufficiency of both 4q35-qter and 4p16 regions. A third report by Ravnan et al. described a patient with suspected 22q11.2 deletion syndrome and a deletion of the 4q31–q33 region, located more proximal comparing to deletion of the patient presented in this study [25]. Furthermore, certain craniofacial characteristics of velocardiofacial syndrome were described in four patients with 4q34 deletions [5, 7].

The patient presented here has normal growth as well as normal motor and cognitive development, with no major extracardiac malformations. In association with tetralogy of Fallot, right aortic arch, small mouth appearance and protuberant ears, such characteristic clinical findings initially suggested the 22q11.2 deletion syndrome (Table 1). To the best of our knowledge, this is the first reported case having 4q34–q35 deletion and phenotype resembling 22q11.2 deletion syndrome without fifth finger anomalies as a specific feature of 4q-syndrome. Given the considerable clinical overlap between the 22q11.2 deletion syndrome and clinical manifestation of the patient described in this study (Table 1), we propose that region 4q34.1–q35.2 should be considered as another region associated with a phenotype resembling 22q11.2 deletion syndrome.

Table 1 Comparison of phenotypic characteristics of distal 4q34–q35 deletions, 22q11.2 deletion syndrome and presented patient

Phenotypic feature	4q34–q35 deletions (%)[a]	22q11.2 deletion syndrome (%)[b]	Presented patient
Growth retardation	10	36	–
Cognitive/motor delay	65	Absent or mild in 62	–
Small mouth/prominent nasal bridge and root/short palpebral fissures	5	Typical	+
Frontal bossing/broad nasal bridge/ micrognathia	25	n/s	–
Congenital heart disease	15	85	+
Tetralogy of Fallot	0	21	+
Right aortic arch	0	52	+
ASD/VSD/DAP	15	>60	+
Digital defects	25	2	–
Genitourinary anomalies	5	12	–
Cleft palate	15	12	–
Hypocalcemia	0	60 (mostly neonatal)	–
T cell deficiency	0	Occasional	–

Estimated frequencies of phenotypic characteristics in patients with 4q34–q35 deletions [2, 5, 7, 17, 24, 27, 31, 33] and 22q11.2 deletion syndrome [14]

ASD atrial septal defect, *VSD* ventricular septal defect, *DAP* ductus arteriosus persistens, *n/s* not stated as a common phenotypic characteristic of the syndrome

[a] 4q34–q35 deletions [2, 5, 7, 17, 24, 27, 31, 33]

[b] 22q11.2 deletion syndrome [14]

Additionally, a phenotypically normal patient with a deletion approximately 10.7 Mb in size spanning the 4q34.1–q34.3 region (chr4: 172,142,000–182,840,000) has been described recently [1]. The deletion in this patient overlaps with the one described in our patient. By comparing the breakpoints in the asymptomatic patient having a 4q34.1–q34.3 deletion [1] and the patient presented in this study, we hypothesize that the deletion of the distal 4q34.3–q35.2 region might be responsible for the heart defects and phenotypic manifestation resembling the 22q11.2 deletion syndrome.

HAND2 (heart and neural crest derivatives expressed 2) gene, which is previously reported to play an essential role in cardiac morphogenesis [22], is among the genes affected by both deletions (4q34.1–q34.3 and 4q34.1–q35.2). The absence of any cardiac abnormality in the patient with 4q34.1–q34.3 deletion [1] further supports the observation that haploinsufficiency of the *HAND2* gene is either non-causative or shows incomplete penetrance [13, 15, 36]. The absence of cardiac features has been described in several patients having 4q deletions involving the *HAND2* gene [1, 13, 15, 36]. Accordingly, it has been suggested that other genes residing in the distal 4q interval, including micro-RNA has-mir-1305, might be involved in cardiac morphogenesis [27, 36].

Interestingly, although the deletion of 4q approximately 17 Mb in size is delineated in our patient, no obvious cognitive impairment could be observed. Literature analysis of 20 patients reported with deletions located solely within 4q34–q35 region (Table 1) showed that 11 of them (55%) had normal or near normal cognitive development [2, 7, 31] while 13 (65%) had normal motor development [2, 7, 27, 31, 33]. Among patients with normal or near normal cognitive development, six patients were found to have large deletions of this region ranging from approximately 7–13 Mb [2, 31]. On the other hand, the deletions of such extent in other genomic regions have been described very rarely in individuals with a normal cognitive development [i.e., chromosomes 18q21.3-qter (17 Mb) and 21q11.2–q21.3 (14 Mb)] [18, 23, 37]. One of possible explanations for no cognitive delay in our patient may lie in the fact that such sizeable imbalance comprises one of the longest human gene deserts 6 Mb in size located within the region 4q34.3 [12]. Gene deserts are segments devoid of protein-coding genes or segments with low gene density and thus remain largely unknown regarding their function. Furthermore, the unusual clinical presentation of our patient could be a consequence of somatic mosaicism, as recently postulated by Mkrtchyan et al. [21].

The comparison of phenotypic characteristics of distal 4q34–q35 deletions and 22q11.2 deletion syndrome (Table 1) suggests that correct establishment of proper diagnosis could be challenging, especially in patients with normal or near normal development, conotruncal heart defects and the absence of digital anomalies.

Our findings support observations that the analysis of only one locus in patients with suspected 22q11.2 deletion syndrome or any other idiopathic malformation syndrome might be insufficient [3, 8, 19]. Thus, we underline the importance of applying array CGH that enables simultaneous genome-wide detection and delineation of copy number changes. Our findings further indicate that distal 4q deletion should be considered in patients with phenotypic manifestations resembling 22q11.2 deletion syndrome in whom no 22q11.2 microdeletion was detected [36]. We further suggest that distal 4q deletion should be considered in such patients even in the absence of distinctive fifth finger anomalies. The precise delineation of deletion breakpoints in cases of 4q deletions, together with studies focused on potential influence of yet unidentified modifying genes and epigenetic factors, should clarify which genes and pathways are responsible for the pathogenesis of heart defects and phenotype of patients with 4q deletions.

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