Delineation of a de novo 7q21.3q31.1 Deletion by CGH-SNP Arrays in a Girl with Multiple Congenital Anomalies Including Severe Glaucoma

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Key Words

Array-CGH · Candidate genes · Delineation del(7q) · Ectrodactyly region

Abstract

In this study, we present a female patient with a constitutional de novo deletion in 7q21.3q31.1 as determined by G-banding and CGH-SNP arrays. She exhibited, among other features, psychomotor retardation, congenital severe bilateral glaucoma, a cleft palate, and heart defect. Microarray assay disclosed a deleted 12.5-Mb region roughly 88 kb downstream the ectrodactyly critical region; thus, the patient's final karyotype was 46,XX, arr 7q21.3q31.1(96,742,140–109,246,085)×1 dn. This girl represents the fourth patient described so far with congenital glaucoma and a deletion encompassing or overlapping the 7q21.3q31.1 region, and confirms the presence of a locus or loci related to such a clinical feature. According to our results, the proneness to ocular defects secondary to 7q intermediate deletions could be caused by co-deletion of *TAC1*, *HBP1*, and a small cluster of cytochrome P450 genes (subfamily 3A). This conclusion is supported by their functional roles and expression locations

as well as because *TAC1* is related to the functional pathway of the *MYOC* gene whose mutations are linked to glaucoma. Moreover, given that this girl is clinically reminiscent of several phenotypes related to diverse deletions within 7q21q32, our results and observations offer a general overview of the gene content of deletions/phenotypes overlapping 7q21.3q31.1 and confirm that loci distal to *DLX* genes including the *CUX1* gene and potential regulatory elements downstream from *DLX5* are unrelated to ectrodactyly.

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Introduction

Constitutional 7q deletions are rather common but heterogeneous. Altogether, these deletions encompass the whole 7q (DECIPHER database) and usually are classified in proximal (q11→21), intermediate (q21→31/32) and terminal (q32→qter) [Gibson et al., 1982; Young et al., 1984; Cheong et al., 2008].

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Diverse deletions within the 7q21q32 segment have often been associated with ectrodactyly and multiple clinical features, such as intellectual disability/developmental delay, ear/hearing anomalies, low birth weight, feeding problems, unusual cry, microcephaly, micrognathia, cardiac and palate defects, recurrent infections, abnormal palmar creases, and eye abnormalities [Young et al., 1984; Rivera et al., 1991; Scherer et al., 1994; Montgomery et al., 2000; Bernardini et al., 2008; Cheong et al., 2008; van Silfhout et al., 2009]. This phenotypic consistency along with the apparent overlapping of the deleted regions may indeed represent a recognizable deletion syndrome [Fagan et al., 1989]. Here, we report on a girl with a 7q21.3q31.1 deletion and congenital severe glaucoma (but not ectrodactyly) in order to refine the mapping of and provide further insights on ocular phenotypes related to intermediate (q21→31/32) deletions.

Patient Description

The patient, a 1-year-old girl, is the second child of healthy non-consanguineous parents. The family history was unremarkable. Foetal growth retardation, short femur and calcification of the placenta were detected in the third trimester; she was born by caesarean section at 35 weeks of gestation due to increased foetal risk. Birth weight was 2,300 g (<3rd percentile), length was 43 cm (<3rd percentile) and the only Apgar score referred to was 8. Congenital glaucoma was detected and treated by trabeculectomy in 2 different interventions. The patient still remains with elevated intraocular pressure. Brain magnetic resonance imaging revealed increased subarachnoid space, altered myelination process and bilateral optic nerve oedema. At the age of 7 months, her weight was 4,300 g (between 10 and 25th percentile) and length 57.3 cm (<3rd percentile). She presented with big eyes, blue sclerae, wide fontanelles, prominent eyebrows, low-set ears with overfolded helix, upslanting palpebral fissures, apparent telecanthus, bulbous nasal tip, hypoplastic nasal alae, short columella, apparently increased distance between nasal base and midline upper lip vermilion border, thin lips, marked Cupid's bow, cleft soft palate, micrognathia, bilateral single palmar crease, and bilateral fifth finger clinodactyly (fig. 1A). In addition, she had foramen ovale, patent ductus arteriosus and tricuspid regurgitation. At 12 months, she is still unable to control her head. Her reaction to auditory stimuli is poor, but she follows light stimuli. She has not developed any teeth, has a weak cry, and her weight, length and OFC were 5,500 g (<3rd percentile), 67.5 cm (<3rd percentile) and 42 cm (<3 percentile), respectively. An ophthalmological evaluation described bilateral primary congenital glaucoma characterised by buphthalmos, elevated intraocular pressure, thin and bluish anterior sclera, and corneal oedema with corneal opacification. Uveal structures, including iris, were apparently normal, although iris implantation could not be defined. Currently, she is recovering from episodes of recurrent respiratory infection.

Material and Methods

Chromosomal Analysis

Initial cytogenetic analyses of the patient and her parents were made on GTG-banded metaphase chromosomes obtained from 72 h lymphocyte cultures. Further blood samples from the patient and her parents, taken under informed consent, were used to perform the molecular studies.

Array CGH

Initially, genomic DNA from the patient and her parents was obtained from 3 ml of peripheral blood with the Qiagen Gentra® Puregene Blood core Kit. Medium-density microarray analysis was performed using the Agilent SurePrint G3 Hmn CGH+SNP 4x180K Microarray Kit (contains ~120,000 CGH probes and 60,000 SNP probes with median spacing of 25 kb). Briefly, genomic DNA (~1 mg) from the patient and her parents and from sex-matched controls was digested by *AluI* and *RsaI* restriction enzymes (Promega, Madison, Wisc., USA) for 2 h at 37°C. The digested products were labelled with Cy3-dUTP and Cy5-dUTP fluorochromes using the Sure tag DNA Labelling Kit (Agilent Technologies). The labelled products were purified, hybridised and washed according to Agilent protocols. Each slide was scanned on a Nimblegen MS 200 scanner (Roche), and the resulting images were converted by image conversion software and imaged by Feature Extraction software (Agilent technologies). Results were analysed using default analysis method – CGH+SNP v2 with the ADM-2 aberration algorithm by Agilent CytoGenomics software v.2.5.

Results

The patient's G-banded karyotype was 46,XX,del(7)(q22q22)dn; parental karyotypes were normal. The corresponding microarray assay disclosed a deleted 12.5-Mb region (genomic position 96,742,140–109,246,085), embracing 500 markers and 229 genes (including miRNAs and hypothetical proteins) with *ACN9* being the more proximal and *C7orf66* the more distal (GRCh37/hg19); thus, there was a partial monosomy for 7q21.3q31.1 (fig. 1B). This deletion overlaps with the ectrodactyly original critical region [Scherer et al., 1994], but did not include *DLX5* and *DLX6* genes, the major candidates for such clinical feature. No other remarkable genomic change was observed. Microarray results from the parents were normal. The patient's final karyotype was 46,XX,arr 7q21.3q31.1(96,742,140–109,246,085)×1 dn.

Discussion

In this study, the fourth patient described so far with congenital glaucoma related to a constitutional de novo deletion involving or overlapping the 7q21.3q31.1 region

Fig. 1. A Craniofacial, hand and mouth features of the patient. **B** Loss profile analysis indicated by log₂ ratio (plotting and line) visualisation from Agilent CytoGenomics software v.2.5. **C** Diagram (not to scale) denoting cases with or without an ocular abnormality and carriers of a 7q deletion overlapping 7q21.3q31.1. Most of all these chromosomal aberrations were not molecularly refined, so we are making an approximation from breakpoints originally assigned (i.e. we have placed the breakpoints in proximal or distal endings of bands, but not of sub-bands). Cases below 'present case' correspond to DECIPHER's cases with a major overlapping to the present deletion. Vertical blue lines indicate the potential minimum region for ocular abnormalities; both the first blue line (left) and the dotted line delimit the regions of overlap with our case. Grey lines delimit some sub-regions of overlapping. * This case reported neither ocular anomalies, nor ectrodactyly (the original breakpoints were 7q21q31). ** Imprecise breakpoints (no ectrodactyly). ? = Unknown ocular involvement, since the foetus was not autopsied. **D** UCSC browser screenshot containing all imbalance cases reported by DECIPHER and ISCA overlapping the 7q21.3q31.1 region (red = deletions, blue = amplifications). Two ISCA deletions (IDs nssv578163 and nssv582318) seem to span the region 7q21.3q31.1 completely, but actually they correspond to chromosome 7 monosomies.

Table 1. Clinical features from deletion cases reported within 7q21q32 but with an apparent major overlapping to the 7q21.3q31.1 region

Clinical features		Cases/references																	present case
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15*	16	17	
General																			
Low birth weight	-	+	-	-	+	-	-	+	-	+	+	+	+	+	+	-	-	+	
ID/DD	+	+	+	+	+	+	+	+	+	+	+ ^a	+	+	+	+ ^b	+	+	+	
Growth retardation/short stature	-	-	-	+	+	+	-	+	-	+	-	+	-	+	-	-	-	+	
Speech delay	-	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	?	+	
Hypotonia	-	+	-	+	+	-	-	-	-	+	-	-	+	-	-	-	-	+	
Abnormal EEG/seizures	-	+	-	-	+	-	-	+	-	+	+	-	-	-	-	-	-	-	
Recurrent infections	+	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	+	
Head/periorbital																			
Broad/prominent forehead	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	
Microcephaly	+	+	-	-	+	-	-	-	-	-	-	+	-	+	-	-	+	-	
Upward slant	-	+	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+	
Epicanthic folds	-	-	-	+	-	-	-	+	-	-	-	-	-	-	-	-	-	NA	
Prominent eyebrows	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	
Hypertelorism/telecanthus	-	-	-	-	-	-	-	-	-	-	+	-	+	-	+	-	+	apparently	
Ears/hearing																			
Low set	+	+	-	+	-	-	-	-	-	-	+	-	+	+	-	-	+	+	
Malformations	+	+	-	+	+	+	+	-	-	-	+	+	+	-	-	-	-	+	
Deafness/hearing loss	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	apparently	
Nose																			
Flat/broad nasal bridge	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	
Bulbous nasal tip	+	-	-	-	+	-	-	+	-	-	+	-	-	-	-	-	-	+	
Eye anomalies	+	+	G	-	-	+	-	+	+	+	G	+	+	G	?	-	-	G	
Mouth																			
Large	+	+	-	+	+	-	+	+	-	+	+	-	+	-	-	-	-	-	
Thin upper lip	-	-	-	+	-	-	-	+	-	?	?	-	?	-	-	-	-	+	
Long philtrum	+	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	apparently	
Cleft/high/narrow palate	-	-	+	+	-	-	-	-	-	-	-	+	-	+	-	-	-	+	
Micrognathia	+	+	-	-	-	-	-	-	-	+	-	+	+	-	-	-	-	+	
Feeding problems	-	+	-	-	+	+	+	+	-	+	+	-	+	-	-	-	-	mild ^c	
Neck																			
Short	-	-	-	+	-	+	-	-	-	-	+	-	-	-	-	-	-	-	
Extremities/hands																			
Fifth finger clinodactyly	-	+	-	-	-	-	mild	+	-	-	-	-	-	-	-	-	+	+	
Splithand/splitfoot	-	-	-	-	-	-	-	-	-	-	-	+	+	+	-	-	-	-	
Abnormal palmar creases	-	+	-	-	+	-	-	+	-	-	+	-	-	-	+	-	-	+	
Cardiovascular																			
ASD/VSD	-	+	+	-	-	-	-	-	-	-	+	-	+	+	-	-	-	-	
PDA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	
Pulmonar stenosis	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	+	-	-	
Other	-	-	-	-	-	-	-	-	-	+	+	-	-	-	+	-	-	+ ^e	
Gastrointestinal																			
Hernia	-	-	-	-	-	-	-	+	-	-	-	+	+	-	-	-	-	-	
Urogenital																			
Genital abnormalities	-	-	+	-	-	+	-	+	-	-	-	+	-	+	-	+	-	-	

¹ Ayraud et al. [1976]; ² Higginson et al. [1976]; ³ Dennis et al. [1977]; ⁴ Hull et al. [1979]; ⁵ Klep-de Pater et al. [1979]; ⁶ Serup [1980]; ⁷ Abuelo and Padre-Mendoza [1982]; ⁸ Young et al. [1984]; ⁹ Chitayat et al. [1988]; ¹⁰ Fagan et al. [1989]; ¹¹ Franceschini et al. [1978]; ¹² Tajara et al. [1989]; ¹³ Morey and Higgins [1990]; ¹⁴ Montgomery et al. [2000]; ¹⁵ Cheong et al. [2008]; ¹⁶ ID 253694; ¹⁷ ID 255298.

ID/DD = Intellectual disability/developmental delay; NA = not available; G = glaucoma; ? = unknown/imprecise.

* Foetus delivered at 22 weeks and not available for further evaluations.

^a Suggested by us (early death). ^b Suggested by authors (early death). ^c Initially poor suck. ^d This patient presented pre-axial polydactyly in the hands.

After this review, a very similar deletion to our case was described in a 24-week-old foetus who presented a cleft lip and palate, hypertelorism, a broad nasal bridge, micrognathia, low-set ears, a micropenis and cryptorchidism [Chen et al., 2013]. In this table, features presented in >30% of cases are: ID/DD (~18/18), eye anomalies (12/18), low birth weight (10/18), ear malformations (10/18), heart defects (9/18), large mouth (9/18), feeding problems (9/18), low-set ears (8/18), growth retardation/short stature (8/18), hypotonia (6/18), microcephaly (6/18), micrognathia (6/18), abnormal palmar creases (6/18), and genital anomalies (6/18). The feature 'weak cry' or 'unusual cry' was not included in the present table, but it was present in ~5 patients including the present one.

(fig. 1C; table 1) is presented. Our results suggest that co-deletion of at least 3 eye-related loci (*TAC1*, *CYP3A43* and *HBPI*) mapped in this region could account for glaucoma and other ocular abnormalities.

Glaucoma, a clinically and genetically heterogeneous condition, is characterised by loss of retinal ganglion cells and atrophy of the optic nerve [Izzotti et al., 2011; Mookherjee et al., 2012]. The major clinical criterion of increased intraocular pressure usually results from resistance of the trabecular meshwork to the aqueous humour [Kennedy et al., 2012]. The trabecular meshwork is located around the base of the cornea and plays an important role in regulating the aqueous humour outflow [Izzotti et al., 2011]. Alterations in trabecular meshwork have frequently been found in patients with congenital glaucoma. Congenital glaucoma, cloudy cornea, primary open-angle glaucoma, and juvenile open-angle glaucoma are some of the subtypes of glaucoma and have been related to diverse loci such as *GLC1A* or *MYOC* (1q24.3), *CYP1B1* (2p22.2), and *CAV1/CAV2* (7q31.2) [Stoilov et al., 1997; Alward et al., 1998; Thorleifsson et al., 2010; Kennedy et al., 2012; Mookherjee et al., 2012].

The *CYP1B1* gene has been linked to primary congenital glaucoma with cytochrome-P450-dependent metabolites regulating corneal transparency and aqueous humour secretion (OMIM 231300). Furthermore, *CYP1B1* was downregulated and *CYP26B1* upregulated in human trabecular meshwork cells with a mutated *MYOC* gene [Kennedy et al., 2012]. These facts suggest that other genes of the cytochrome P450s family could be related as well. Actually, a small cluster of cytochrome P450 genes at 7q22.1 (*CYP3A4*, *CYP3A5*, *CYP3A7*, and *CYP3A43*) was deleted in our patient; in fact, most of the deletions in 7q associated with glaucoma or other ocular abnormalities such as cloudy corneas, macrocornea or abnormal pupils involved q22 and likely, *CYPs* genes [Young et al., 1984; Montgomery et al., 2000]. Remarkably, *CYP3A43* was found differentially expressed in human cornea epithelium tissue [Turner et al., 2007]. In general, members of the subfamily 3A were found expressed in human iris, ciliary body and cornea [Zhang et al., 2008; Volotinen et al., 2011]. Another candidate gene for glaucoma appears to be *TAC1*, also deleted in our patient, which has recently been suggested as a possible physiological biomarker for glaucomatous injury. The *TAC1* gene was related to the functional pathway of the *MYOC* gene, which is a glycoprotein induced by stress conditions in trabecular meshwork. Actually, *TAC1* expression was also strongly altered in *MYOC* mutant cells [Kennedy et al., 2012]. The *TAC1* gene (7q21.3) encodes for precur-

sors of hormones that act as neurotransmitters (UCSC genome browser) and has been identified as a mechanosensible gene in the human trabecular meshwork [Kennedy et al., 2012].

Another gene also deleted in this patient, namely *HBPI*, is a transcriptional repressor that participates in the WNT pathway and is expressed in retina, cornea and ciliary bodies (EMBL-EBI and GeneCards databases). The WNT pathway has been associated to intraocular pressure regulation [Kennedy et al., 2012]. Coincidentally, the *HBPI* (high mobility group box transcription factor) gene is alike to *HMGB1* (high-mobility group box 1 protein) that is known to be an endogenous molecule for signalling of retinal damage and inflammatory stress [Lee et al., 2012].

Although most cases with ocular defects and deletions within or overlapping the 7q21.3q31.1 region were reported before methods for a precise genetic delineation were available, it seems feasible that in at least 9 patients with glaucoma or other ocular abnormalities [Ayraud et al., 1976; Dennis et al., 1977; Franceschini et al., 1978; Serup, 1980; Young et al., 1984; Fagan et al., 1989; Tajara et al., 1989; Morey et al., 1990; Montgomery et al., 2000], the respective deletions involved all the above-mentioned genes (fig. 1C). A further detailed review in DECIPHER and ISCA showed that among ~39 deletions of or overlapping the 7q21.3q31.1 region (fig. 1D), none exhibited the breakpoints here defined or included all 3 genes here proposed. The most similar 7q deletion, molecularly defined (98,423,469–111,872,943), was very recently reported by Chen et al. [2013], but it did not include *TAC1* and neither ocular abnormalities were reported in the foetus. The non-deleted status of *CAV1/CAV2* loci in our patient is consistent with the lack of ocular abnormalities seen in 8 patients with *CAV1/CAV2* hemizygosity. Accordingly, it is tempting to speculate that the proneness to ocular defects inherent to 7q intermediate deletions could largely be caused by co-deletion of the critical genes proposed here. It is worth noting, however, that practically all of the imbalances were related to intellectual disability/developmental delay and multiple sub-regions overlapped (fig. 1C, D; table 1).

In spite of the wide phenotypical spectrum of 7q21q32 deletions, several recurrent clinical features have been observed (table 1). According to the information gathered in table 1, at least 14 features had a frequency >30% in those patients (table 1). For instance, the child in this study described exhibited at least 11 of these features, including intellectual disability/developmental delay, growth retardation, and craniofacial, heart and eye defects. Addition-

Table 2. Deleted genes in 7q21.3q31.1 potentially related to some frequent clinical features seen in other similar deletion cases

Related to	Gene/protein	References
Brain/ID/DD	<i>ACHE</i> , <i>ATXNL7</i> , <i>BHLHA15</i> , <i>COG5</i> , <i>GPC2</i> , <i>MLL5*</i> , <i>NPTX2</i> , <i>NRCAM</i> , <i>PNPLA8</i> , <i>RELN</i> , <i>SRPK2</i> , <i>SYPL1</i> , <i>TAC1</i> , <i>THAP5</i> , <i>TMEM130</i> , <i>VEGF</i> , <i>NYAPI</i> ^a	UCSC genome browser; Al-Hassnan et al. [2011]; Rymen et al. [2012]; DECIPHER ID 263273; Vincent et al. [2008]; Uliana et al. [2010]
Craniofacial alterations	<i>MLL5*</i> , <i>PLOD3**</i> , <i>RELN</i>	Al-Hassnan et al. [2011]; Salo et al. [2008]
Deafness/hearing loss	<i>GJC3</i> , <i>LHFPL3</i> , <i>MLL5*</i> , <i>PLOD3**</i> , <i>SLC26A4</i> , <i>SLC26A5</i>	UCSC genome browser; ID 263273; Salo et al. [2008]; Albert et al. [2006]
Ocular abnormalities	<i>CLDN15</i> , <i>CYP3A4</i> , <i>CYP3A43</i> , <i>CYP3A5</i> , <i>CYP3A7</i> , <i>HBPI</i> , <i>NRCAM</i> , <i>TAC1</i> , <i>TMEM130</i>	EMBL-EBI; Volotinen et al. [2011]; Lee et al. [2012]; Demyanenko et al. [2011]; Kennedy et al. [2012]
Heart/cardiac defects	<i>MOSPD3</i> , <i>NPTX2</i> , <i>PNPLA8</i> , <i>SRPK2</i> , <i>THAP5</i>	UCSC genome browser; Pall et al. [2004]
Gastrointestinal alterations/ growth retardation/short stature	<i>CLDN15</i> , <i>MUC3A</i> , <i>MUCB</i> , <i>MUC17</i> , <i>MOGAT3</i>	UCSC genome browser; Wada et al. [2013]

These associations were performed according to the gene functions and expression locations, gene/phenotype overlap with other cases, or previous association. Note that some genes may be linked to more than one clinical feature. Actually, some monogenic lesions were seemingly responsible for various clinical features (e.g. *MLL5** or *PLOD3***).

^a Deleted in an ISCA microdeletion case (ID nssv578204).

ally, breakpoints analysis revealed that the proximal breakpoint of the present deletion lies just 88 kb downstream of the *DLX5* gene. Because haploinsufficiency for *DLX5* and *DLX6* genes appears to be responsible for ectrodactyly [Scherer et al., 1994; van Silfhout et al., 2009], our observation indirectly confirms the exclusion of the *CUX1* gene (as suggested by Bernardini et al. [2008]) and potential regulatory elements (as suggested by Tzschach et al. [2007]) downstream of *DLX5* and *ACN9* (between RP11-800O14 and D7S618) in determining such a limb defect.

Overall, our findings confirm that 7q21.3q31.1 is a gene-rich region crucial for brain, heart, growth, and eye physiology/development (table 2), offer a general over-

view of the gene content of deletions/phenotypes overlapping 7q21.3q31.1, and further strengthen that loci distal to *DLX* genes are unrelated to ectrodactyly.

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