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Short Report

Identification of critical regions for clinical features of distal 10q deletion syndrome

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Array comparative genomic hybridization studies were performed to further characterize cytogenetic abnormalities found originally by karyotype and fluorescence *in situ* hybridization in five clinical cases of distal 10q deletions, including several with complex cytogenetic rearrangements and one with a partial male-to-female sex-reversal phenotype. These results have enabled us to narrow the previously proposed critical regions for the craniofacial, urogenital, and neuropsychiatric disease-related manifestations associated with distal 10q deletion syndrome. Furthermore, we propose that haploinsufficiency of the *DOCK1* gene may play a crucial role in the pathogenesis of the 10q deletion syndrome. We hypothesize that alteration of *DOCK1* and/or other genes involved in regulation and signaling of multiple pathways can explain the wide range of phenotypic variability between patients with similar or identical cytogenetic abnormalities.

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Key words: array comparative genomic hybridization – chromosome rearrangement – critical region – deletion 10q – *DOCK1* gene – genotype-phenotype correlation

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Partial deletion of the long arm of chromosome 10 is a relatively frequent cytogenetic abnormality with more than 100 patients described in the literature. The vast majority of studies have reported terminal deletions, with breakpoints ranging from 10q23.3 to 10q26.3 as determined by conventional cytogenetic techniques, and only a few cases of 10q interstitial deletions have been previously identified (1–5). A distinctive distal 10q deletion syndrome has been proposed (5–11), but as with other microdeletion syndromes, such as DiGeorge (OMIM 188400) and Smith–Magenis syndrome

(OMIM 182290), considerable heterogeneity exists in the clinical presentation of 10q deletion syndrome, even among family members who share the same deletion boundaries (5). Relatively consistent features for deletion 10q syndrome include a common facial appearance, cardiac and urogenital anomalies, and a high incidence of neurodevelopmental deficits (5, 6). It is unclear if the severity of the phenotype correlates with the size of the deletion or with involvement of the more proximal 10q region. Previous efforts to establish genotype–phenotype correlations have been hampered by the respective limitations of standard GTG-banding, telomeric fluorescence *in situ* hybridization (FISH) analyses and fine breakpoint mapping (12, 13). Newer molecular technologies such as array comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) genotyping analyses are able to define breakpoints at high resolution and, therefore, enable improved genotype–phenotype correlation. To more precisely define the critical regions for the common clinical features associated with deletions of distal 10q, we have conducted clinical, cytogenetic and high-resolution molecular studies of five patients in four families.

Materials and methods

Patient samples

Informed consents approved by the Institutional Review Board for Human Subject Research at Baylor College of Medicine were obtained for further delineation of breakpoints and publication of photographs.

Cytogenetic and FISH analyses

Chromosomes for G-banding and FISH analyses were obtained from peripheral blood lymphocytes using standard procedures to verify the findings detected by aCGH.

Targeted aCGH analyses

Patients' genomic DNAs were extracted using the PureGen kit (Gentra Systems, Minneapolis, MN) according to the manufacturer's instructions. The initial aCGH studies were conducted on clinically available microarrays (Baylor College of Medicine, Chromosome Microarray Analysis, bacterial artificial chromosome (BAC) array version 4 to version 6, http://www.bcm.edu/geneticlabs/cma/tables.html) (14). The aCGH procedures and data analysis were performed as previously described (15).

Genome wide array analysis

(1) The HumanHap550 BeadChip (Illumina Inc) was used for genomic profiling in cases 1 and 2. This Bead Chip employs the single base extension assay (Infinium® II) as previously described (16, 17).
(2) A genome wide BAC-derived aCGH (WG aCGH) containing a set of 21,658 RP11 BAC clones (18) was used for patient 3 as described previously (19).
(3) Whole Human Genome Oligo Microarray Kits 244K (Agilent Technologies, Inc, CA) were used in patient 4 to further refine the breakpoint region. The procedures for DNA digestion, labeling, and hybridization were performed according to the manufacturer's instructions with some modifications (20).

Clinical reports and results

Case 1

The patient was born at 29 weeks of gestation to a 37-year-old G_2P_1 healthy mother. The patient was small for a gestational age (<third percentile) and had multiple congenital anomalies (Table 1 and Fig. 1), including dysmorphic features, imperforate anus, distal rectal atresia, and ambiguous genitalia characterized by partially fused labioscrotal folds and the absence of a phallus or clitoris. Patient 1 exhibits many of the characteristic facial features of the 10q deletion syndrome, including a broad, prominent nose, facial asymmetry, and ear anomalies (Fig. 1a). The presence of male gonadal tissue was confirmed by serum testosterone measurement, although testes were unable to be visualized by ultrasound. A pineal cyst was identified by head ultrasonography. Bilateral absence of the inferior-most rib was noted radiographically. Renal ultrasound demonstrated bilateral hydronephrosis, with a dilated right ureter. A moderate sensorineural hearing loss was identified.

Previous G-banding chromosome analysis revealed a 46,XY,del(10)(q25.2),t(12;15)(p13;q24)*dn* chromosome pattern (Fig. 2a). A targeted aCGH showed an interstitial deletion at band 10q25.13-q26.3 using BAC (V.5) involving 12 BAC clones in the subtelomeric region at band 10q26.13-q26.3 estimated at 15–20 Mb in size. A high-resolution SNP array determined the breakpoint intervals of the deleted region (UCSC Genome database, 2006; http://genome.ucsc.edu/) as shown in Fig. 2b and Table 1.

Table 1. Clinical manifestations in patients with distal deletion of 10q

Findings	Reported previously		Case 1	Case 2	Case 3	Case 4	Case 5	Courtens et al. 2006 (23)	Ogata et al. 2000, case1 (13)	Chen et al. 2005 (24)
Deletion region	10q25-qter	10q26-qter	10q26.13-q26.3	10q26.2-qter	10q26.2-q26.3	10q26.12-q26.2	10q26.12-q26.2	10q26.2-qter	10q26.12-qter	10q25.3-qter
Deletion size, Mb			17.22	7.29	3.51	5.8	5.8			
Deletion interval, hg18			chr10: 116253478-133508337	chr10:128058517-135318924	chr10:128246920-131836090	chr10:122878779-128720232	Same as case 4			
Karyotypic gender			Male	Female	Male	Female	Male	Female	Male	Male
Craniofacial dysmorphism			+	+	+	+	+	+	+	+
Broad nose	16/16	32/39	+	+	+	+	+	+		+
Ear anomalies	14/16	30/37	+	−	+	+	+	+		+
Hypertelorism	7/14	24/35	+	−	−	+	+	+		+
Microcephaly	10/16	13/29	+	+	−	+	+	+		
Strabismus	6/14	25/32	−	+	+	−	−	+		
Congenital heart disease	10/16	12/40	+	+	−	−	+	−		−
PDA	1/5	3/8	+	+	−		+	−		
Urinary tract/renal anomalies	2/16	3/40	+	+	−	−	−	−	_	
Anogenital anomalies	9/10	16/32	+	−	−	−	−	−	+	+
Cryptorchidism	6/6	21/24	+	−	−	na	−	na	+	
Ambiguous genitalia/sex reversal	2/3	1/13	+	−	−	na	−	na	−	+
Anal atresia			−	−	−	−	−		+	−
Attention-deficit hyperactivity disorder	7/9	5/7		+	−	+	+	+		na
ODD-like spectrum	6/9	2/7		+	−	−	−			na
Autism spectrum disorder	1/9	4/7		+	−	−	−			na
Mental retardation	9/9	6/6		+		+	+	+		na

+, feature present; −, feature absent; na, not applicable; ODD, oppositional defiant disorder; PDA, patent ductus arteriosus.

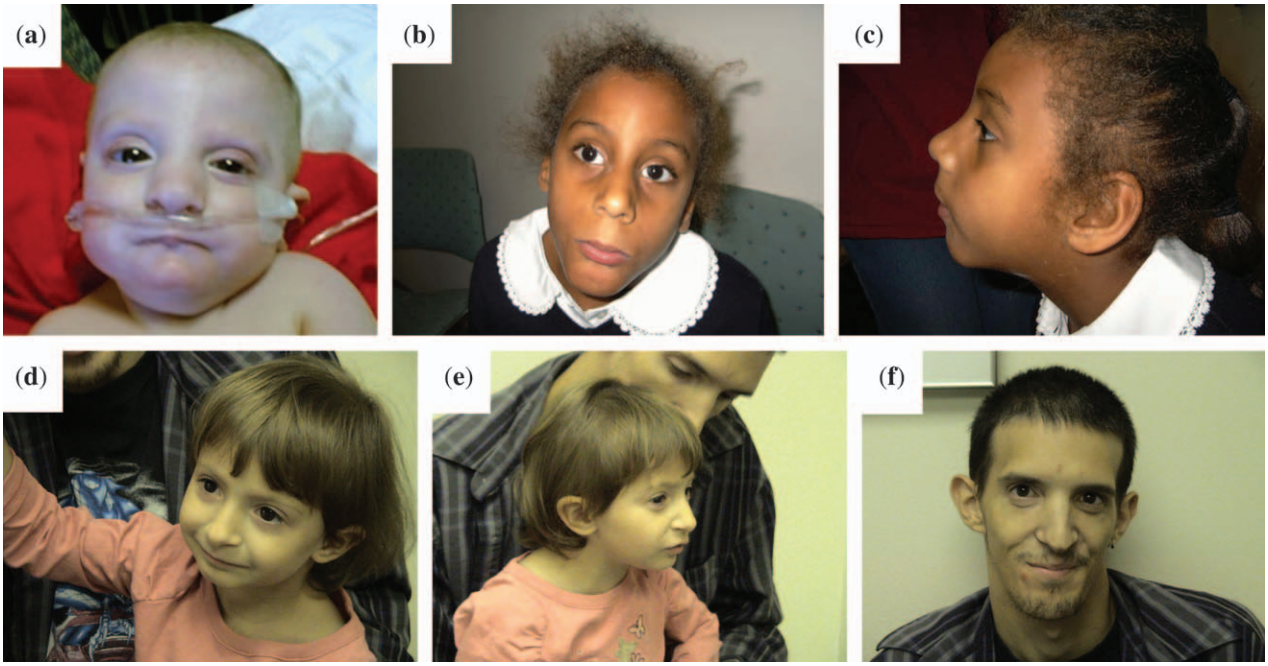

Fig. 1. Affected probands. (**a**) Patient 1 at age 6 months. (**b** and **c**) Patient 2 at age 6 years. (**d** and **e**) Patient 4 at age 2 years presented with triangular-shaped face, prominent nose, low-set ears with simplified helices, and micrognathia, clinodactyly of the fifth finger and syndactyly of the 2nd and 3rd toes bilaterally. She had many features in common with her father. (**f**) Patient 5, father of patient 4.

Case 2

This 6-year-old girl presented for neuropsychiatric evaluation with a history of developmental delay, poor balance and impaired adaptive functioning. Auditory and tactile sensitivity and a preoccupation with parts of objects were reported. She would often mouth or lick objects and engage in repetitive movements. Her social interactions were characterized by impaired understanding of social boundaries, difficulty with socially appropriate conversation, perseveration on topics of interest, and inability to play independently or imaginatively. Concrete thinking, as well as a poor appreciation of cause and effect, was evident. Her behavior was characterized by hyperactivity, impulsivity, poor concentration, and distractibility. She was diagnosed with mild mental retardation (MR), attention-deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD). Physical findings were significant for short stature (−3 SD), microcephaly (−4 SD), dysmorphic features (Table 1 and Fig. 1b,c), and clinodactyly. An aortopulmonary window was identified by echocardiography, and renal ultrasound demonstrated a hypoechoic right kidney.

Previous chromosome analysis showed a 46,XX,inv(10)(p11.23q21.2)*dn* chromosome pattern (Fig. 2c). A deletion of 10q26.2-q26.3 with nine probes (RP11-422P15 to RP11-140A10), encompassing approximately 7 Mb of the subtelomeric region was detected by targeted aCGH and confirmed by FISH analysis to be on the inverted chromosome 10 (data not shown). The subsequent study using SNP array refined a deletion boundary (Fig. 2d and Table 1).

Case 3

A 3-year-old Caucasian boy born at 35 weeks gestation to a 21-year-old G_1P_0 mother was referred for evaluation of hypotonia and developmental delay. Mild persistent elevation of creatine kinase and paroxysmal alternating torticollis, suspected to be secondary to a dystonic process, were also noted. Motor skills were significantly delayed; he was able to crawl but unable to walk. Deep tendon reflexes were increased, and his axial tone was diminished. Magnetic resonance imaging of the brain was normal at 10 months of age. His weight, height and head circumference were all at the 50th percentile. Mild dysmorphic features (Table 1) included asymmetric positioning of the ears, incomplete curvature of the helices bilaterally, pinched nasal tip with small nares, a thin upper lip, and downturned corners of the mouth. He had clinodactyly, short fifth metacarpal bones, and tapering of the fingers bilaterally.

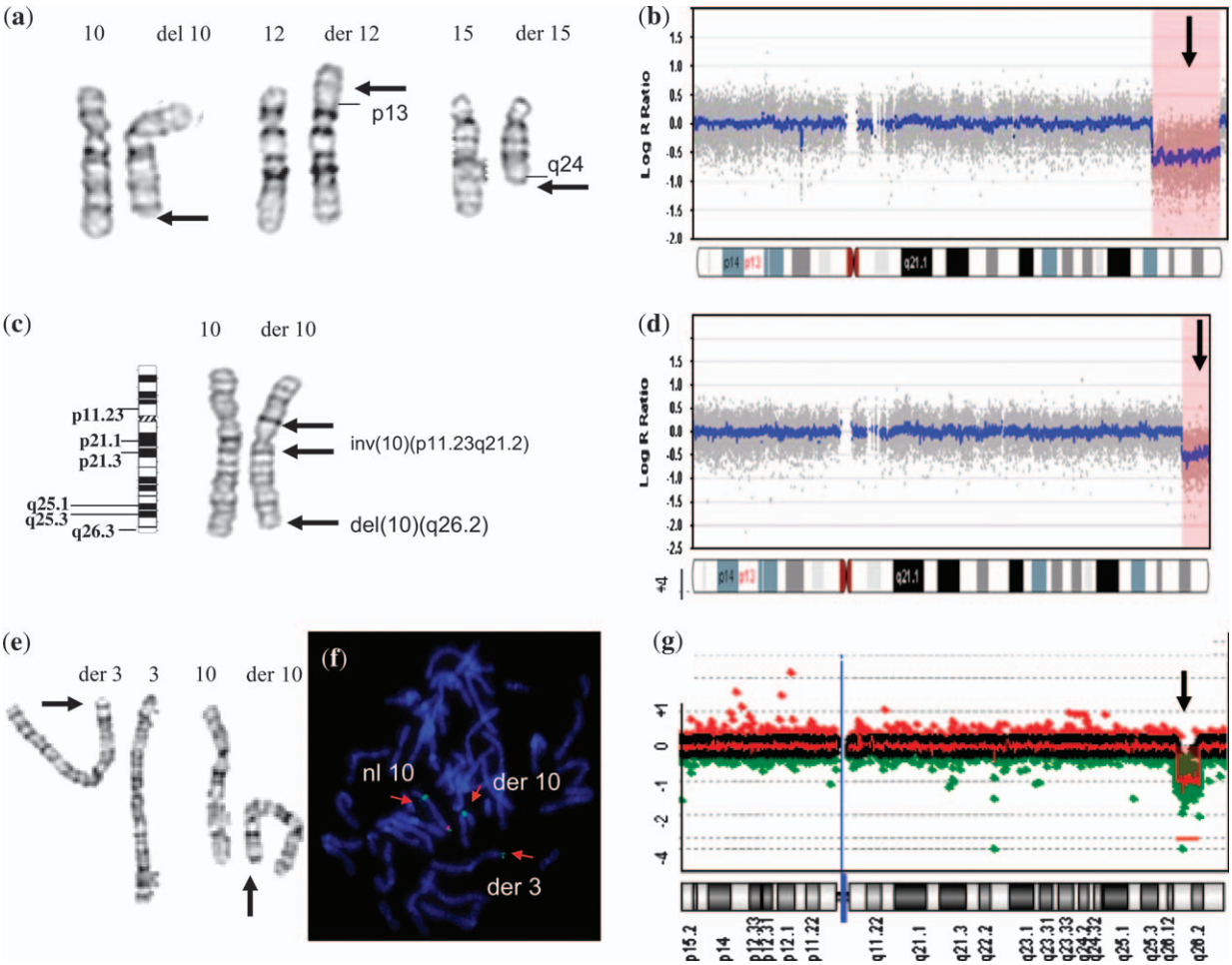

Fig. 2. (**a**) Partial karyotype with del(10)(q25.2),t(12;15)(p13;q24) in case 1. (**b**) High-resolution single nucleotide polymorphisms (SNPs) array from Illumina in case 1 showed the deletion encompassing a 17.22 Mb segment containing 113 known genes and putative gene products. There were no additional imbalances detected at the chromosome 12 and 15 breakpoints (data not shown). (**c**) Partial karyotype with der(10)del(10)(q26.2)inv(10)(p11.23q21.2) (arrows indicate identified breakpoints) in case 2. (**d**) The results from the Illumina SNP array in case 2 delineate the deletion to a 7.29 Mb segment that includes ~70 genes. There were no gains or losses of genomic material identified at the inversion breakpoints (data not shown). (**e**) Partial karyotype with t(3;10)(p26.2;q26.3)*dn* in case 3. (**f**) Fluorescence *in situ* hybridization analysis with clone RP11-9019 (in red; deleted) and a 10q subtelomere-specific clone (in green, present on derivative chromosome 3) confirmed the deletion of 10q due to translocation event in case 3 (the aqua signals represent the probe for the centromeres 10). The patient's karyotype was designated as 46,XX,der(10)del(10)(q26.2q26.3) t(3;10)(p26.2;q26.3)*dn*. (**g**) Results of a whole genome oligoarray CGH analysis from Agilent in patient 4 showing an interstitial deletion within the 10q26.12-q26.2 region, spanning an approximately 5.84 Mb segment that encompasses at least 53 known and/or predicted genes.

Previous chromosome analysis revealed an apparently balanced translocation t(3;10)(p26.2;q26.3)*dn* (Fig. 2e). A single clone loss (RP11-90B19) in the breakpoint region of chromosome 10q26.2 (BAC V.4) was detected by targeted aCGH and confirmed by FISH analysis (Fig. 2f). Subsequently, an interstitial deletion del(10)(q26.2q26.3) encompassing approximately 3.59 Mb was delineated by whole genome BAC array (Table 1). Interestingly, the proximal breakpoint in case 3 is located ~130 kb distal to the proximal breakpoint in case 2.

Case 4

A 2-year-old girl was referred for evaluation of failure to thrive, developmental delay and dysmorphic features (Table 1 and Fig. 1d,e). She was born at term to a 20-year-old G3P0 mother by spontaneous vaginal delivery after an uncomplicated pregnancy. She was noted to have a dislocated left hip that was treated surgically. Developmentally, she sat at 6 months of age and began cruising at 10–11 months of age. She was walking at 13 months. She had a vocabulary of 10 words but usually needed to be prompted to speak. On examination at the age of 2 years, her

height, weight and head circumference were all below the third percentile. She had slightly reduced muscle tone. She was able to stand; her left hip was rotated internally.

Previous chromosome analysis had been reportedly normal (46,XX). An interstitial deletion on 10q26.12-q26.2 was initially identified by targeted aCGH and delineated by the high density array (Fig. 2g and Table 1). A deletion was also present in the patient's father (case 5), as determined by FISH analysis using four clones at the boundaries.

Case 5

This 25-year-old man is the father of case 4 (Table 1 and Fig. 1f). He is 5 feet 9 inches tall. He always had difficulty in gaining weight. He had a congenital heart defect, described as a patent ductus arteriosus (PDA), which was corrected at 5 years of age. He had a history of frequent episodes of pneumonia and bronchitis as an infant. He had bilateral hip dysplasia, requiring casting. He also has a history of an anxiety disorder. He had learning difficulties and graduated from high school with special education services. His dysmorphic features were similar to those described in his daughter. Chromosome analysis was reportedly normal (46,XY). FISH analysis confirmed a deletion as observed in his child (case 4).

Discussion

We report five patients in four families with deletions involving the distal long arm of one chromosome 10. In cases 1, 2 and 3, apparently balanced chromosome rearrangements not involving the distal 10q region were identified by standard chromosome analysis, while the deletions of the 10q were detected by aCGH studies (Fig. 2a,c,e). Recent studies showed that cryptic imbalances are present in up to 40% of patients with abnormal phenotype and apparently balanced rearrangements, thus highlighting the importance of high-resolution microarray analysis (21, 22).

In this study, we characterized cytogenetic abnormalities using high-resolution aCGH technology that enables more conclusive genotype–phenotype correlations. It has been proposed that facial dysmorphism is associated with a deletion of *FGFR2*, a craniosynostosis-associated gene (5). However, *FGFR2* was neither deleted in our case 2 nor in the patient reported by Courtens et al. (23) (Fig. 3). Based on molecular studies for eight patients [our patients 1–5 and those reported by Ogata et al., case 1 (13), Chen et al. (24), and Courtens et al. (23)], we can assign the apparent critical region to an approximately 600 kb segment in 10q26.2, the smallest region of deletion overlap (SRO) (Fig. 3). All these patients shared a deletion of an approximately 600 kb segment at the 10q26.2 region, encompassing two genes, *DOCK1 and C10orf90* (Fig. 3), and have craniofacial dysmorphism, various degrees of MR, and growth failure in common.

This 600 kb SRO contains only two annotated transcripts: *C10orf90* and *DOCK1*, a dedicator of cytokinesis 1. Studies in mammalian cell lines suggest that *Dock1* is involved in regulation of several cellular activities including control of cell morphology, polarity, migration, adhesion to extracellular matrix proteins or other cells, proliferation, apoptosis, tumorigenesis, phagocytosis, vesicular transport and transcription. Interestingly, it has been proposed that the critical region associated with urinary anomalies resides distal to *D10S186* marker (13), which corresponds to the physical location of the *DOCK1* gene. Therefore, *DOCK1* deficiency could be responsible for urinary defects as well. Thus, we hypothesize that through multiple signal transduction pathways, *DOCK1* appears to influence diverse cellular processes critical to normal development. The *DOCK1* haploinsufficiency can result in craniofacial dysmorphism as well as the spectrum of other clinical manifestations, such as cardiac and urinary anomalies, associated with 10q deletion syndrome. The clinical heterogeneity can be due to incomplete penetrance or the influence of other genes involved in the multiple signal transduction pathways or can result from other genetic, epigenetic, or environmental causes.

Genital anomalies including cryptorchidism, hypoplastic labia majora, micropenis, and ambiguous genitalia have been previously reported in patients with partial monosomy of 10q. A complete male-to-female sex-reversal phenotype is very rare with only four reported cases among 10q deletion patients; our case 1 represented a partial sex-reversal phenotype, with ambiguous genitalia. This occurrence has previously been associated with deletion of the 10q25.3-26.1 segment (24–26). Prior investigators have postulated four genes *PAX2* (10q24.3-q25.1), *GFRA1* (10q25.3), *EMX2* (10q26.11), and *FGFR2* (10q26.12) to be associated with sex reversal in patients with deletions of 10q (13). Based on the defined critical region between *RH119261* and *D10S294* (Fig. 3b), the *EMX2* and *GFRA1* genes are potential sex-determining candidate genes. The *EMX2* gene, a homeodomain transcription factor, has been linked to murine genitourinary

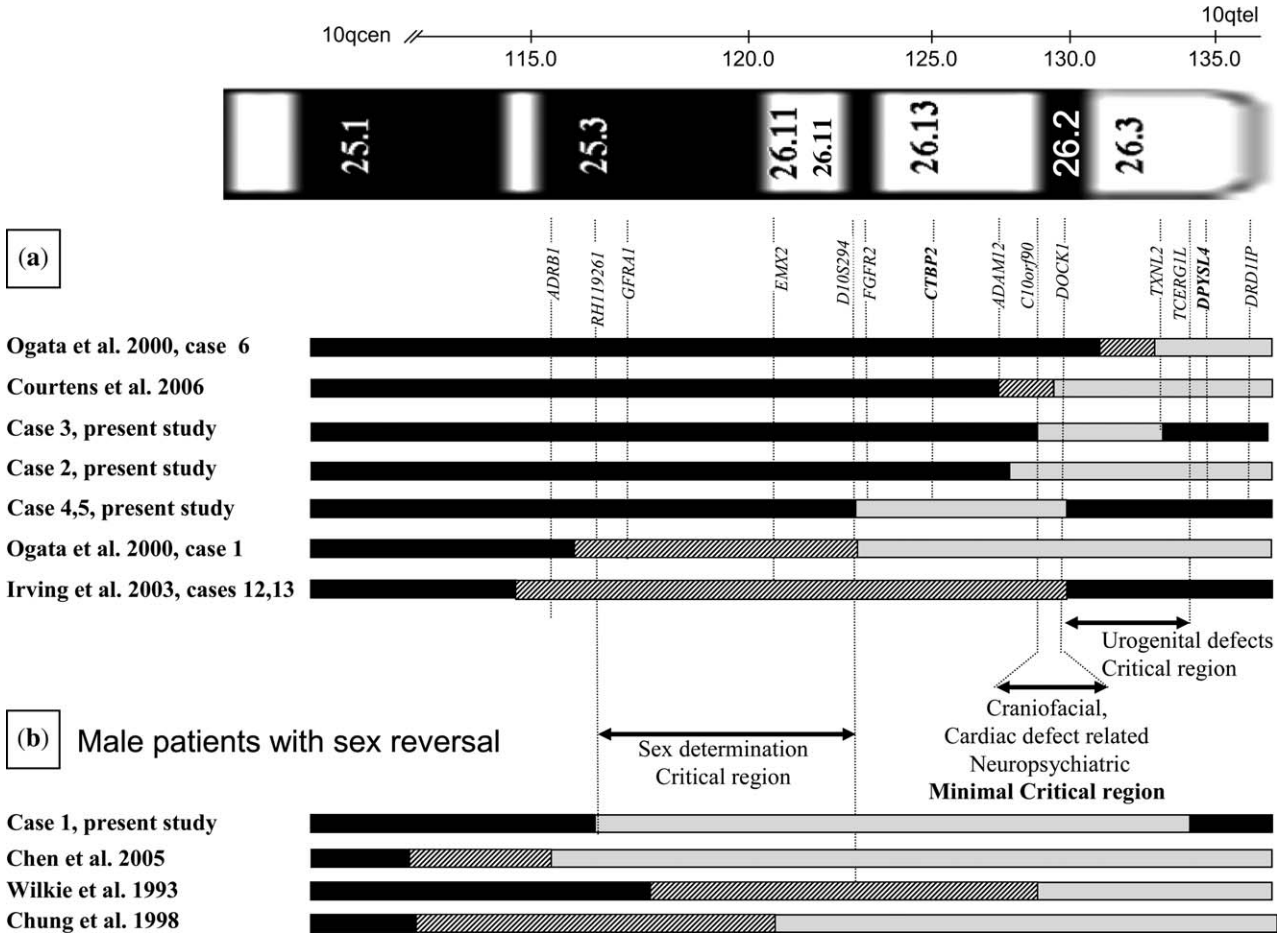

Fig. 3. (**a**) Schematic presentation of the chromosome 10q23-q26 region, including known genes of interest (in scale). Open bars represent the extent of the 10q deletion in five patients studied by microarray analysis, as well as in five informative patients reported previously. Black vertical bars represent non-deleted regions. Hatched bars identify either uninformative or inconclusive areas. Double-headed arrows indicate the proposed critical regions. Only three reported cases did not involve the 10q26.2 region: case 6 reported by Ogata et al. (13) and cases 12 and 13 reported by Irving et al. (1). Clinical manifestations greatly depend upon the 10q deletion size and region of 10q monosomy; however, many patients have a characteristic facial appearance, with microcephaly, a broad nasal bridge, prominent nose, hypertelorism, low-set ears, and a thin upper lip. Haploinsufficiency of a gene(s) located in the minimal critical region most likely is responsible for the common dysmorphic features, congenital heart defects and neuropsychiatric manifestations. (**b**) Schematic presentation of deletions in patients with sex reversal. Patient 1 reported in this study had the largest deletion 10q25.3-qter and sex reversal. In three male patients reported previously (21, 22, 24), deletions of 10q25-qter were also associated with sex reversal or ambiguous genitalia. Based on combined data, we propose a sex determination critical region on 10q between *RH119261* and *D10S294*.

development (27) and thus represents a particularly attractive candidate.

Neurobehavioral manifestations, including ADHD, disruptive and affectionate behavior, and bipolar disorder-like syndromes, have been well described in 10q deletion patients. A few candidate genes associated with bipolar disorder were proposed within the distal 10q region including C-terminal binding protein 2 (*CTBP2*) and dopamine receptor D1-interacting protein (*DRD1IP*) (23, 28). In addition, variant haplotypes of the *DRD1IP* gene were recently shown to be associated with the inattentive and hyperactive/impulsive variants of ADHD (29). Although behavioral disturbances can be non-specifically associated with MR, ASD and ADHD were the most clinically salient features associated with the presented herein case 2. The *DRD1IP* gene was deleted in the patient 2, supporting the idea that copy number abnormalities may also contribute to ADHD pathogenesis. Other candidate genes include *INPP5A*, a Li^+-sensitive second messenger-inducing enzyme, and *DSPYL4*, a dihydropyrimidase-like enzyme involved in central nervous system (CNS) development.

To our knowledge, the ASD has not been previously associated with the deletions of distal 10q. Potential candidate genes that may confer autism

susceptibility are distinct from those described above for ADHD and include *GPR123*, a G-protein coupled secretin family receptor; *ADAM8*, a metalloprotease that facilitates cell–cell adhesion during neurogenesis and neurodegeneration; and *DSPYL4*, involved in CNS development.

In conclusion, we define a ~600 kb SRO for 10q deletion syndrome that encompasses the *C10orf90* and *DOCK1* genes associated with craniofacial dysmorphism, various degrees of MR, and growth failure. We hypothesize the wide range of phenotypic variability between patients with similar or identical 10q deletions results from alteration of *DOCK1*, a gene involved in signaling and regulation of multiple pathways. Further high-resolution studies of patients with extended deletions, small interstitial deletions, and translocations involving 10q25-q26 region will facilitate genotype–phenotype correlations for specific genes critical to the 10q deletion syndrome.

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