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Distinctive Phenotypic Abnormalities Associated with Submicroscopic 21q22 Deletion Including *DYRK1A*

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Key Words
21q2 · Chromosome 21 · *DYRK1A* · Mental retardation · Microdeletion syndrome · Periventricular nodular heterotopia · Polymicrogyria

Abstract
Partial monosomy 21 has been reported, but the phenotypes described are variable with location and size of the deletion. We present 2 patients with a partially overlapping microdeletion of 21q22 and a striking phenotypic resemblance. They both presented with severe psychomotor delay, behavioral problems, no speech, microcephaly, feeding problems with frequent regurgitation, idiopathic thrombocytopenia, obesity, deep set eyes, down turned corners of the mouth, dysplastic ears, and small chin. Brain MRI showed cerebral atrophy mostly evident in frontal and temporal lobes, widened ventricles and thin corpus callosum in both cases, and in one patient evidence of a migration disorder. The first patient also presented with epilepsy and a ventricular septum defect. The second patient had a unilateral Peters anomaly. Microarray analysis showed a partially overlapping microdeletion spanning about 2.5 Mb in the 21q22.1–q22.2 region including the *DYRK1A* gene and excluding *RUNX1*. These patients present with a recognizable phenotype specific for this 21q22.1–q22.2 locus. We searched the literature for patients with overlapping deletions including the *DYRK1A* gene, in order to define other genes responsible for this presentation.

Chromosome 21 has been the subject of extensive studies. Trisomy 21 causing Down syndrome [DS, OMIM #190685] is one of the few trisomy syndromes compatible with life and is common with an incidence of about 1 in 800 live births. However, (partial) monosomy 21 is much rarer and few patients have been reported in literature [Holbek et al., 1974; Fryns et al., 1977; Matsui et al., 1978; Yamamoto et al., 1979; Pellissier et al., 1987; Korenberg et al., 1991; Krasikov et al., 1992; Chettouh et al., 1995; Huret et al., 1995; Theodoropoulos et al., 1995; Bartsch et al., 1997; Joosten et al., 1997; Matsumoto et al., 1997; Ehling

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et al., 2004; Mori et al., 2004; Yao et al., 2006; Tuschl et al., 2007; Beri-Dexheimer et al., 2008; Dobyns et al., 2008; Lyle et al., 2009; Miller et al., 2009; Fujita et al., 2010; Lindstrand et al., 2010]. The region of the monosomy and the phenotype of reported cases are variable. The 21q22 region seems associated with the most severe phenotype exhibiting mental retardation and microcephaly [Yamamoto et al., 1979]. Disruption of *DYRK1A* (*Drosophila minibrain* homologue gene, OMIM *600855) in this region has been associated with microcephaly, mental retardation and dysmorphisms in 2 patients [Møller et al., 2008]. Studying similar patients potentially reveals valuable information regarding the function of the chromosome 21 genes.

We present 2 unrelated individuals with a partial monosomy 21 with strikingly similar facial features giving them a 'moody' appearance, similar brain imaging and a partially overlapping 21q22 microdeletion. This overlapping 2.5-Mb region contains amongst others the *DYRK1A* gene and covers the DS critical region [OMIM #190685]. Combining our data with previously published reports by others, we delineate a recognizable phenotype of chromosome 21q22.1–q22.2 microdeletion including the *DYRK1A* gene.

Clinical Reports

Patient 1

Patient 1 was referred to our department at 18 months of age. Clinical data are summarized in table 1. He was born after an uneventful pregnancy at 38 weeks of gestation as the 10th child to non-consanguineous healthy Dutch parents. His birth weight was 2,140 g (–2 SD) and head circumference 31 cm (–2.8 SD). The neonatal period was complicated by cardiac decompensation due to a persistent ductus arteriosus and a perimembranous ventricular septum defect (VSD). The duct closed spontaneously at cardiologic follow-up, the VSD was managed conservatively.

Clinical genetic examination at the age of 18 months showed micro- and brachycephaly, square forehead, deep-set eyes with long eyelashes, small nose, large pupils, thin lips with down-turned corners of the mouth, micrognathia, large, low-set ears, and weight and head circumference at –4 SD (fig. 1).

His developmental milestones were delayed. Severe feeding problems and gastro-esophageal reflux necessitated gastric tube feeding and Nissen fundoplication. He suffered from recurrent upper respiratory tract infections and had severe constipation. He developed epilepsy with tonic-clonic seizures requiring antiepileptic drug (AED) therapy.

At follow-up at the age of 7 years he was severely mentally retarded and exhibited no speech. He had a flat forehead, broad eyebrows extending onto the eyelids, deep-set eyes with long eyelashes, large pupils, wide nasal ridge, large, low-set ears, full cheeks, dental caries, micrognathia, small hands and feet, a sandal gap between 1st and 2nd toes, joint hyperlaxity, pectus excavatum, truncal obesity, and cryptorchidism (fig. 1). His height was 110 cm (–3 SD), weight 20 kg (+1 SD), and head circumference 45.5 cm (–4 SD).

Abdominal ultrasound and skeletal X-rays revealed no abnormalities. A post-operative (tonsillectomy) hemorrhage prompted studies of bleeding diathesis, this revealed low platelet counts ranging from 82–149 $\times$ 10^9/l (normal range: 199–369 $\times$ 10^9/l).

Brain MRI performed at 1 year of age (fig. 3A, B) showed small frontal lobes, enlarged lateral and third ventricles with high signal of periventricular white matter on T2 weighted images, a thin corpus callosum and brain stem, and delayed myelination. At two years of age, brain MRI showed similar features, although myelination had progressed.

He died at age 11 of a bronchopneumonia complicated by pulmonary hemorrhage.

Patient 2

Patient 2 was referred to our department of Clinical Genetics at the age of 8 months because of progressive microcephaly and dysmorphic features. She was born after an uneventful pregnancy at 42 weeks of gestation as the first child of non-consanguineous healthy Chinese parents. Her birth weight was 2,765 g (–2 SD), length 46 cm (–3 SD) and head circumference 31 cm (–3.5 SD). She had a systolic murmur due to a persistent ductus arteriosus. It closed spontaneously on follow-up. In infancy she suffered from episodic attacks of blue discoloration of the extremities. She has had two seizures suggestive of epilepsy and one EEG showed dubious epileptic activity, requiring AED therapy.

On clinical examination dysmorphic features included square forehead with nevus flammeus, low-set and thick eyebrows, long eyelashes, peri-orbital fullness with deep set eyes, wide nasal ridge, anteverted nares, down-turned corners of the mouth, small chin, round ears with broad helices and a left-sided ear pit, inverted nipples, a closed sacral dimple, a congenital nevus on the back, a single palmar crease on the left hand, a contracture of the left thumb, deep set nails of the toes, and bilateral short proximally implanted first toes (fig. 2).

Her developmental milestones were delayed. She started walking independently at age 2. She suffered from feeding problems which required gastric tube feeding in infancy. During follow-up up to 7 years of age she exhibited severe mental retardation with absent speech, no eye contact, hyperactive behavior and poor interaction with people. Teeth grinding was noted and diffuse dental decay was striking. At that age, her height was 110 cm (–3 SD), weight 25 kg (2.5 SD), and head circumference 48 cm (–2 SD). She had severe constipation.

Ophthalmic examination revealed bilateral hypermetropia, amblyopia of the right eye, and a unilateral corneal opacity area consistent with a Peters anomaly. Her platelet counts were below normal range on 2 separate occasions, 104 and 137 $\times$ 10^9/l (normal range: 199–369 $\times$ 10^9/l). Craniosynostosis was excluded with a skull X-ray. Congenital CMV-infection was excluded by PCR of neonatal screening blood spot. No skeletal abnormalities were detected.

Brain MRI performed at the age of 5 months and repeated MRI at the age of 15 months (fig. 3C, D) showed cerebral atrophy with deep sulci, mostly evident in frontal and temporal lobes, underdeveloped frontal gyri, a thin corpus callosum with loss of periventricular white matter and widened lateral and third ven-

Table 1. Summary of patients described in the literature with an 21q22 (micro)deletion including *DYRK1A*

	Patient 1 (this study)	Patient 2 (this study)	Bartsch et al. [1997]	Fujita et al. [2010]	Matsumoto et al. [1997]	Shinawi et al. [2008], patient 3	Theodoropoulos et al. [1995]	Yao et al. [2006], case 2	Yao et al. [2006] case 3
Chromosomal aberration	del(21)(q22.13q22.2) (mosaic)	del(21)(q22.12q22.2)	der(21)t(18;21)(q23;q22.1)	Del(21)(q22.12q22.2)	del(21)(q22.1)	del(21)(q22.1) (mosaic)	del(21)(q22)	del(21)(q22.1)	del(21)(q22.1q22.3) (mosaic)
Deletion size	4.1 Mb	4.2 Mb	> 10.4 Mb <12.1 Mb	3.97 Mb		19.8 Mb		12.87 Mb	12.6 Mb
Sex	M	F	F	M	M	F	F	F	F
MR/DD	Y	Y	Y	Y	Y	Y		Y	Y
IUGR	Y	Y	Y	Y	Y	Y		Y	Y
Height (SD)	<–3 SD	<2.5 SD	–2.5 SD	–3 SD	–1.4 SD				
Obesity	Y	Y	N	N	N				
OFC at birth	<–2.5 SD	<–2.5 SD	–3 SD	–3.2 SD	–1.5 SD		p25		
OFC	–4 SD	–2 SD	–2.3 SD	<p3	–2.5 SD	<p3/<–2 SD		Microcephaly	Microcephaly
Facial dysmorphism									
Full eyebrows	Y	Y		Y					
Long eyelashes	Y	Y							
Deep-set eyes	Y	Y	Y			Y			
Peri-orbital fullness	Y	Y	Y	Y		Y			
Epicanthal folds	N	Y	N	Y		Y		Y	Y
Hypertelorism				Y		Y			
Deep nasal bridge	Y	Y	Broad			Y	N	Broad	N
Prominent nose					Y				
Anteverted nares	Y	Y	Y						
Featureless/prominent philtrum	Y	Y	Y	N					
Down-turned corners of the mouth	Y	Y	Y	Y					
Teeth	Decay	Decay, abnormal	Small, widely spaced	Peg-shaped, prominent incisors					
Retro-/micrognathia	Y	Y	Y	Y	Y		Y	Y	Y
Low-set/dysplastic ears	Y, large	Y, earpit	Y	Y, earpit	Y	Small ears	Y, cup-shaped, tag	N	Y
Neurology									
Epilepsy/seizures	Y	Y	Y	N		Y		Y	Y
Speech	N	N	N	N		Y			
Brain imaging (MRI if not stated otherwise)	EV, decreased WM, underdeveloped frontal lobes, hypoplastic CC	EV, decreased WM, underdeveloped frontal lobes, thin optic chiasm and CC		CT-scan: normal		Normal	Ultrasound: germinal matrix bleed, EV, thin CC	CD, CC and WM, hypoplasia	CT-scan: hydrocephalus ex vacuo, CD, WM and CC hypoplasia, cerebellar hypoplasia
Other features									
Thrombocytopenia	Y	N		N		Y			
Heart	VSD, Persistent DAB	Persistent DAB	Murmur	N		Murmur	Coarctation aorta, hypoplastic left heart, thick valves, PFO	Unknown defect	Unknown defect
Extremities	Small hands and feet	Trigger finger, single palmar crease	Short hands and legs, small flat feet	Thick toenails			Camptodactyly, overlapping fingers		
Miscellaneous	Cryptorchism	Peters anomaly, inverted nipples	Abnormal cervical vertebrae	Hypospadias, corneal clouding, bifid uvula	Short neck	Strabismus, inverted nipples, thin/sparse hair	Microphthalmia, cloudy cornea, short neck, anterior anus, kidney dysplasia, skeletal abnormalities	Webbed neck	Webbed neck

Unknown features are left blank. CC: Corpus callosum, CD: cortical dysplasia, DAB: ductus arteriosus Botalli, EV: enlarged ventricles, ITP: idiopathic thrombocytopenia, MR/DD: mental retardation/developmental delay, N: no, NA: not applicable, PFO: patent foramen ovale, PVL: periventricular leukomalacia, WM: white matter, Y: yes.

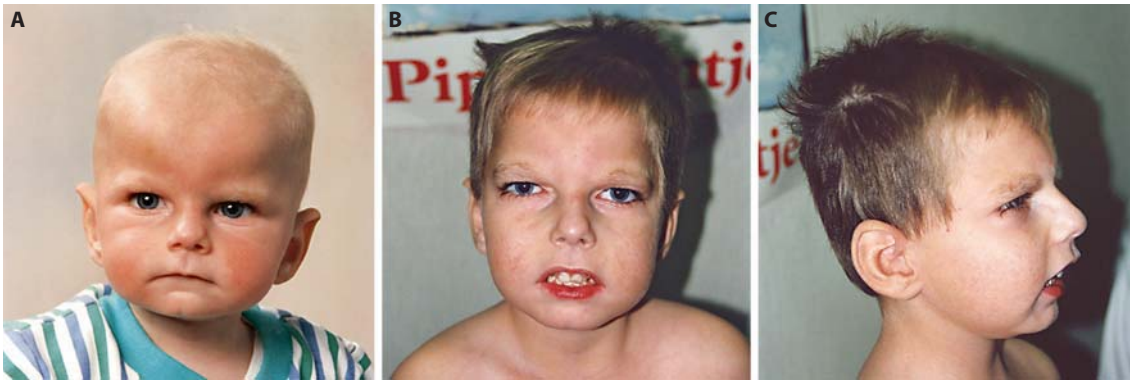

Fig. 1. Facial features of patient 1. **A** Age unknown. Note the full upper eyelids and cheeks, anteverted nares, down-turned corners of the mouth and large ears. **B**, **C** Age 7 years. Note thick eyebrows, full upper eyelids and cheeks, slightly anteverted nares, down-turned corners of the mouth, dental decay and large, low-set ears.

tricles both at frontal and occipito-temporal areas, a thin brain stem, and no evidence for active demyelination.

Recent brain MRI at the age of 8 years showed evidence of a periventricular nodular heterotopia located in the frontal horn of the right lateral ventricle. The inferior part of the right frontal cortex is abnormal and suggestive of polymicrogyria (fig. 3E, F).

Cytogenetic and Microarray Results

Routine cytogenetic analysis of patients 1 and 2 revealed a normal karyotype. DNA of the patients was hybridized to Affymetrix 250K SNP arrays according to the Affymetrix standard protocol for the GeneChip Mapping 250K *Nsp*I arrays. Copy number analysis using the Copy Number Analyzer for GeneChip (CNAG) v 3.0 [Nannya et al., 2005] indicated in patient 1 a 4.1-Mb deletion (arr 21q22.13–q22.2 (37053718–41102161 [hg18]) ×1, see fig. 4). In patient 2, a 4.2-Mb deletion (arr 21q22.12q22.2 (35337577–39585051 [hg18]) ×1) was observed, (fig. 4). In both cases parental DNA analysis by quantitative PCR showed a de novo origin of the deletion. The deletions were confirmed by fluorescent in situ hybridization (FISH) with chromosome 21 BAC clones (RP11–166F15 absent, RP1–63H24 present). Analysis of the B allele ratio of the Affymetrix array in Nexus Copy Number software (Biodiscovery) revealed the possibility that in patient 1 the deletion was present in mosaic form in leukocyte DNA. Additional FISH analysis confirmed the mosaic in cultured lymphocytes where 50% of the nuclei showed the presence of 2 normal copies of chromosome 21. In order to define the deletion breakpoint in patient 2 more precisely, qPCR experiments were performed on patient DNA (primer sequences available on request). This resulted in refinement of the borders, defining the deletion from basepair 35346296 to 39576472 (NCBI built 36.3), and, using extra- and intragenic probes, *RUNX1* was excluded from the proximal end of the deletion.

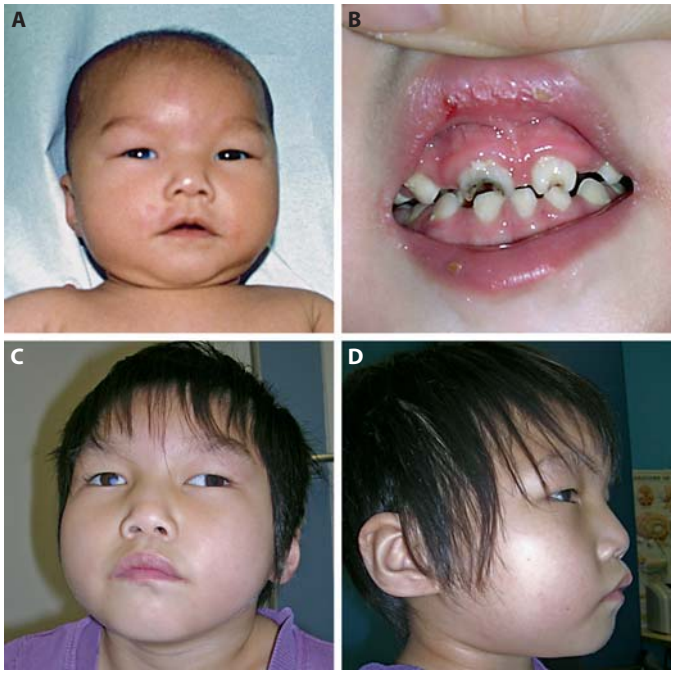

Fig. 2. Facial features of patient 2. **A** Age 8 months. Note the full upper eyelids and cheeks, anteverted nares and down-turned corners of the mouth. **B** Severe dental decay and malshaped teeth. **C**, **D** Age 7 years. Note thick eyebrows, Peters anomaly of the right eye, full upper eyelids and cheeks, anteverted nares and down-turned corners of the mouth, malformed ears and moody expression.

The deletion areas of the 2 patients partially overlap from base pair 37053718 to 39585051 spanning 2.5 Mb on chromosome 21q22.13–q22.2, encompassing 27 genes (15 protein coding genes, 3 non-protein coding genes, 4 pseudogenes and 5 hypothetical genes) according to the NCBI and Ensembl database annotation build 36.3 (table 2). The *DYRK1A* gene, previously associated with neurodevelopmental anomalies and microcephaly [Møller et al., 2008], is included in the shared deletion area.

Review of 21q22 Deletions Including *DYRK1A*

Several features have been repeatedly described in partial monosomy 21 including intrauterine and postnatal growth retardation, down-slanting palpebral fissures, low-set ears, arthrogryposis-like signs, hypertonia, heart defect, and mental retardation [Chettouh et al., 1995]. In order to delineate a more specific phenotype relating to 21q22 deletions we searched PubMed, Decipher and Ensembl databases for patients with these deletions. Most of the patients reported in the literature have microscopic deletions with poorly defined breakpoints. We review only those where we can deduce overlap with the 21q22.13–q22.2 critical region of our patients and where the phenotypic description is sufficient for comparison. These are summarized in table 1. The findings are fairly consistent regarding intra-uterine growth retardation (IUGR), microcephaly, mental retardation, seizures, corpus callosum abnormalities and facial features (deep-set eyes, micrognathia, and dysplastic ears).

Of note, also one patient described by Shinawi et al. [2008] and one by Yao et al. [2006] show the deletion in mosaic form.

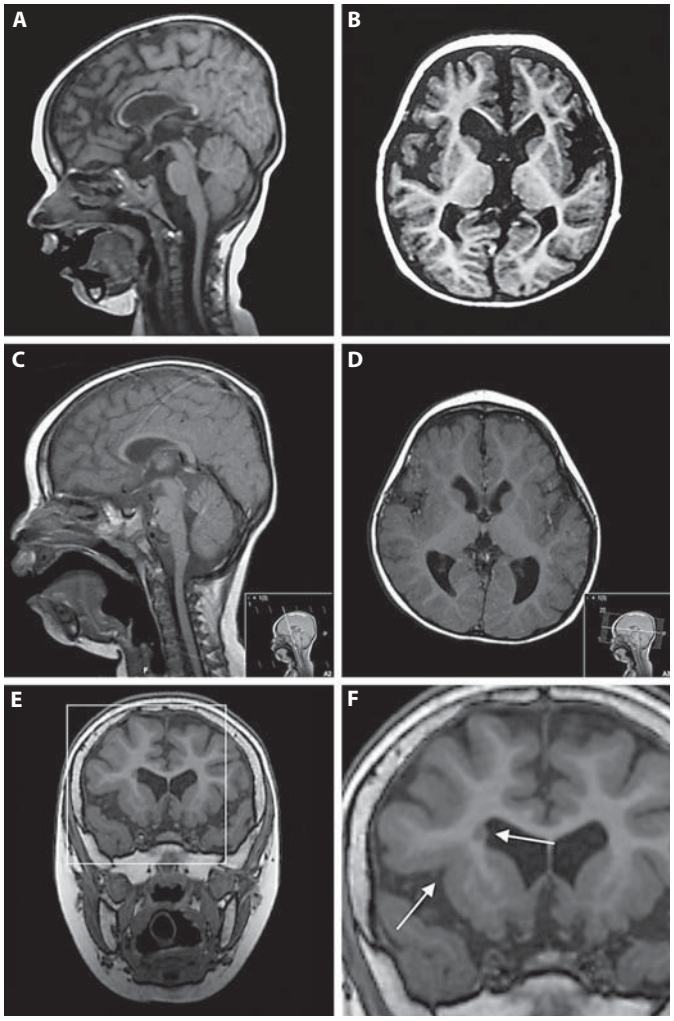

Fig. 3. Brain T1 weighed MRI images. **A–D** Note cerebral atrophy/underdevelopment of frontal and temporal lobes, widened ventricles including the 3rd ventricle, thin corpus callosum and brain stem. **A** Patient 1, midsaggital section. **B** Patient 1, transversal section. **C** Patient 2, midsagittal section. **D** Patient 2, transversal section. **E**, **F** Patient 2, note periventricular nodular heterotopia and area suspected of polymicrogyria in the right frontal lobe (**E**). Coronal section (**F**). Magnification of **E**, upper arrow points to heterotopia, lower arrow points to the area suspected of polymicrogyria.

Discussion

The 2 patients presented in this study show a distinctive phenotype that to our knowledge has not previously been recognized in patients with 21q22 deletions. They exhibit severe mental retardation with absence of speech, microcephaly, short stature, and distinct cerebral abnormalities. Their facial features with square forehead, full eyebrows and eyelids, deep-set eyes, broad nasal ridge, and down-turned corners of the mouth are strikingly alike and give them a 'moody' appearance. Brain MRI findings are quite similar in the patients, showing underdevelopment of frontal lobes with evidence of a migration disorder in patient 2, deep frontotemporal sulci, large lateral and third ventricles, loss of periventricular white matter, callosal dysgenesis and thin brain stem. The low resolution MRI of patient 1 did not allow recognition of minor cortical malformations.

Because of their resembling features, it is likely that genes in their common deleted area are causative of their phenotype. *DYRK1A* [OMIM 600855] maps to chromosome 21q22.13 and is included in the deleted area of both patients. With its location within the Down syndrome

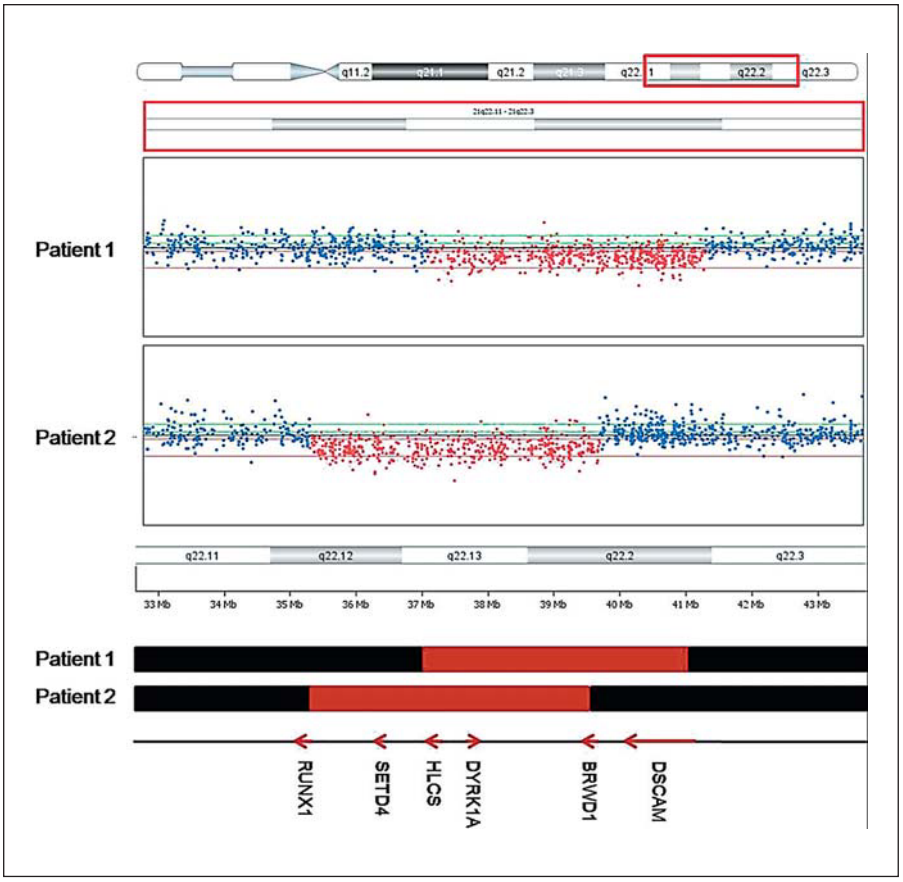

Fig. 4. Array results. Under the schematic representation of chromosome 21 the actual results in the 21q22.11–q22.3 region of the two 250K SNP arrays are shown. In the bottom panel the overlapping segments and several genes in the area are depicted.

Table 2. Known genes in overlapping deletion area

Gene symbol	Name	OMIM
HLCS	Holocarboxylase synthethase	609018
DSCR6	Down syndrome critical region gene 6	609892
PIGP	Phosphatidylinositol glycan anchor biosynthesis, class P	605938
TTC3	Tetratricopeptide repeat domain 3	602259
DSCR9	Down syndrome critical region gene 9	–
DSCR3	Down syndrome critical region gene 3	605298
DYRK1A	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	600855
KCNJ6	Potassium channel, inwardly rectifying, subfamily J, member 6	600877
DSCR4	Down syndrome critical region gene 4	604829
DSCR8	Down syndrome critical region gene 8	–
DSCR10	Down syndrome critical region gene 10	–
KCNJ15	Potassium channel, inwardly rectifying, subfamily J, member 15	602106
ERG	V-ets erythroblastosis virus E26 onco gene homolog	165080
C21orf24	Chromosome 21 open reading frame 24	611723
ETS2	V-ets erythroblastosis virus E26 onco gene homolog 2	164740
AP001042.1	FLJ45139 protein	–
PSMG1	Proteasome assembly chaperone 1 (DSCR2)	605296
BRWD1	Bromodomain and WD repeat domain 1	–

critical region, *DYRK1A* has been suggested to play a crucial role in brain alterations both in trisomy and monosomy 21 patients [Song et al., 1996]. Møller et al. [2008] reported 2 patients with a translocation truncating the *DYRK1A* gene. Both patients exhibited prenatal onset microcephaly, intrauterine growth retardation, feeding problems, developmental delay and seizures. In the first patient retardation was mild, and he had large, low-set ears, long philtrum, and micrognathia. On brain MRI hypogenesis of the corpus callosum was described without other abnormalities. The second patient had severe mental retardation, absent speech, large ears, flat philtrum and a ventricular septum defect. Brain MRI showed enlarged ventricles. The *DYRK1A* gene is the human homolog of the *Drosophila minibrain* gene [Tejedor et al., 1995]. It is highly conserved in mammals. In mice, *Dyrk1a* haploinsuffiency leads to a reduced body size with a disproportionate brain reduction, and developmental delay [Fotaki et al., 2002]. In particular, underdevelopment of the ventral mid- and hindbrain structures was present in *Dyrk1A*$^{+/-}$ mice. The MRI findings of our patients with large third ventricle, thin corpus callosum and brain stem might relate to the *DYRK1A* haploinsufficiency.

Besides *DYRK1A*, there are 14 protein coding and 3 non-protein coding genes annotated in the common deleted area, each of which might contribute to the phenotype. Six of these are Down-syndrome critical region (DSCR) genes of unknown function. Among the genes with known function, *TTC3*, *KCNJ6* and *BRDW1* are also interesting candidates.

The *TTC3* (tetratricopeptide repeat domain 3) gene is involved in neuronal cell differentiation and particularly in regulation of neurite extension [Berto et al., 2007], suggesting that absence of *TTC3* could be related to in cognitive problems and brain underdevelopment. The tetratricopeptide domain is also present in kinesins responsible for the organization of axonal microtubules and cytoskeleton dynamics and in *KIAA1279*, the gene mutated in Goldberg-Shprintzen syndrome [Brooks et al., 2005].

KCNJ6 [OMIM 600877], also known as *GIRK2*, is expressed in the brain and the pancreatic β-cell. Homozygous *Girk2* missense mutation in *weaver* mice causes severe cerebellar ataxia and altered behavioral pattern [Patil et al., 1995; Pravetoni and Wickman, 2008]. Heterozygous *weaver* mice have a decreased number of surviving granule cells and suffer sporadically from tonic-clonic seizures [Patil et al., 1995]. Also, homozygous *weaver* mice have decreased levels of circulating IGF1 and responded to GH-treatment [Yao et al., 2007]. The postnatal growth retardation in our patients might be partially explained by a deficient GH/IGF1 axis, as seen in mutant *weaver* mice.

Mutations in the *RUNX1* gene [OMIM 151385] cause familial platelet disorder with propensity to acute myeloid leukemia [FPD/AML; OMIM 601399]. Shinawi et al. [2008] reviewed platelet pool storage disease caused by *RUNX1* haploinsufficiency and described multiple problems of microdeletions at 21q22 ascribed to *RUNX1* and *DYRK1A*. Surprisingly, both our patients were diagnosed with low platelet counts, although *RUNX1* is not deleted. Possibly, regulatory elements of *RUNX1* are affected by the deletion or other genes in the critical area are involved in platelet disorders. In mice, regulatory elements have been identified distant (300 kb) from *Runx1* [Soler et al., 2010].

Periventricular nodular heterotopia (PNH) are a new finding in 21q22 deletion. PNH is considered a malformation of cortical development. Of note, other cortical malformations, that is polymicrogyria [Yao et al., 2006; Beri-Dexheimer et al., 2008; Dobyns et al., 2008] and lissencephaly [Miller et al., 2009], have been associated with 21q deletions. Yao et al. [2006] propose that an 8.4-Mb region on 21q22.11–q22.3 is associated with cortical dysplasia. However, the large size of this area and lack of breakpoint details make the comparison of these patients with ours incomplete.

Our findings suggest that a minimum 2.5-Mb microdeletion at chromosome 21q22.13–q22.2 including *DYRK1A* and excluding *RUNX1* is responsible for a characteristic syndrome with recognizable facial features, severe developmental delay, brain abnormalities, IUGR, and eye and platelet abnormalities. Our observation reduces the chromosomal area to which these abnormalities have been previously ascribed, and should encourage high resolution array analysis in patients with a similar phenotype. It could be worthwhile searching for mutations in *DYRK1A* in patients with a similar phenotype in whom microdeletions have been excluded.

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