

# Shank3 Duplication in Patient with an Unbalanced Translocation (20;22)(Q13.33;Q13.33)



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## Abstract

We report subtelomeric deletion of 20q13.33 and duplication 22q13.33 resulting from unbalanced de novo translocation t(20;22)(q13.33;q13.33) in 6-year-old girl with mild mental disability, speech delay, behavioural problems, growth delay, microcephaly, minor dysmorphic features, detected by MLPA and SNParray. Deletion spanning 1,6 Mb included, apart from ARFGAP1 and MYT1, genes KCNQ2 and CHRNA4, which are linked to autosomal dominant epilepsy. Duplicated area included genes RABL2B, ARSA and SHANK3 spans approx. 190 kb and is associated with autistic spectrum disorders, severe speech impairment, ADHD and schizophrenia. Whereas the terminal deletion of 22q is known as Phelan McDermid syndrome, the duplication of the same region is not so frequently reported. Subtelomeric 20q deletions are rare, and deletions resulting from translocation were reported only in a few cases. We review the clinical and behavioural phenotype of subtelomeric 20q deletion and 22q duplication.

## Introduction

Subtelomeric rearrangements contribute to idiopathic mental insufficiency and human malformation, sometimes as distinct mental retardation syndromes. However, for most subtelomeric defects characteristic clinical phenotype remains to be elucidated. With the use of modern techniques, such as molecular karyotyping (aCGH) or multiple ligation-dependent probe amplification (MLPA), chromosome abnormalities can be identified in individuals with nonspecific symptoms, such as developmental delay, in whom no particular disorder is suspected. In "genotype-first" approach, individuals with similar genotypes or genetic constitution can be detected, and typical phenotype, or collection of clinical features can be determined. We describe a patient with subtelomeric 20q deletion and 22q duplication. Our report can contribute to characterization of the clinical picture of subtelomeric microdeletion 20q and 22q microduplication.

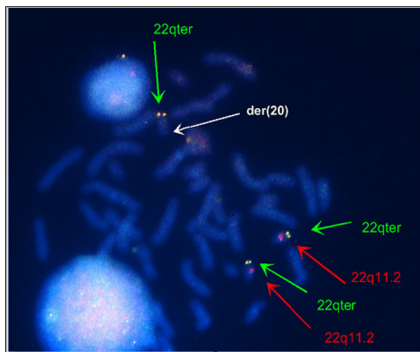
## Clinical Report

The proband was the second child of nonconsanguineous, healthy parents; the mother was 28 years old and father 33 years. Pregnancy was uneventful; delivery was at 38<sup>th</sup> week gestation; Apgar score was 10-10-10, birth weight 2805 g, length 46 cm and head circumference 33 cm (10<sup>th</sup> percentile). Paediatrician noted

the first signs of developmental delay (motoric delay) at 3 months of life. The proband underwent physiotherapeutic interventions according to Vojta and then Bobath concepts. At one year, she was diagnosed with truncal hypotonia and developmental delay. At two years on clinical examination, there was persisting hypotonia, growth deficiency, developmental delay and hyperreflexia of lower extremities. At three years, speech delay and behavioural problems (affective behaviour and negativistic behaviour, moodiness, frustration/anger if the things go in other than her way, she requires attention) were noted. She was showing a speech delay, but the hearing loss was ruled out. MRI scan (four years and 7 months) showed a structurally normal brain with slightly expanded space of temporal lobe of the right ventricle.

At five years, she used to say up to 20 words, after that she used simple sentences. She used to smear the stool on her body and the bed linen. At five years and eight months, she was referred to our Medical Genetics unit because of speech delay, mental insufficiency and failure to thrive. She was still suffering from enuresis. Growth parameters were as follows: weight 18 kg (-0.93 SD), height 110 cm (-1.2 SD), OFC 47 cm (-2.64 SD). She was not willing to tolerate physical examination (from any physician). Clinical examination shown presence of flat occiput, slightly posteriorly rotated ears,

otapostasis, almond shaped eyes, slight inner epicanthal fold at the left and prominent pinna (Figure 1). She actually looks like her younger sister. She had clinodactyly of the 4th digits of lower limb but no major dysmorphic features. At this time (8 years and 4 months) she still has the intermittent problem with enuresis but she is getting better. Her mental status matches moderate mental disability.



**Figure 1:** Photographs of the patient at age 5 years 8 months.

Some signs of autistic spectrum disorder are present. She repeatedly uses some sounds to satisfy herself. She repeats new favourite sentences even in the inappropriate situations. Behaviour is frequently negativistic and aggressive, she has a tendency to react like “see no evil, hear no evil”, she turn back on mother and pretend, that the mother is not in the room. She is obstinate and impatient; e.g. she is obsessively asking about planned appointments. She may have an elevated level of pain sensitivity - she uses to stare at TV in a rigid position (knees bended to the chest), and she is squeezing her thighs without pain reaction.

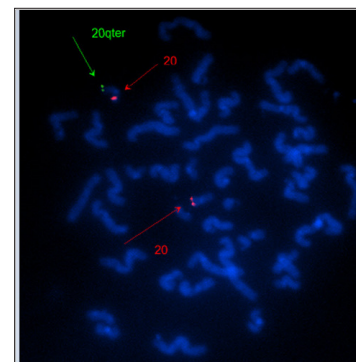
**Methods**

Metaphase chromosomes preparations from a peripheral blood lymphocyte culture were obtained according to standard procedures. Chromosomes analysis was carried out on GTG banded chromosomes at a resolution of 550 bands. For MLPA (Multiplex ligation-dependent probe amplification), DNA was extracted from peripheral blood by standard salting out methods. The telomere kits (SALSA MLPA P036 and P070- Telomere 3 and 5)(MRC - Holland) were used for screening of subtelomeric rearrangements in the sample and SALSA MLPA P245 Microdeletions and P343 Autism-kit for confirmation of duplication 22q13.33. Procedures were performed according manufacturer’s protocol. SNP array (HumanCytoSNP-12v2.1, Illumina, Inc., San Diego, CA) and FISH with probes JAG1(Alagille)/qter (Cytocell) and probe DiGeorge VCFS TUPLE 1/22q13.33 (Cytocell) were used for confirmation of the MLPA results.

**Results**

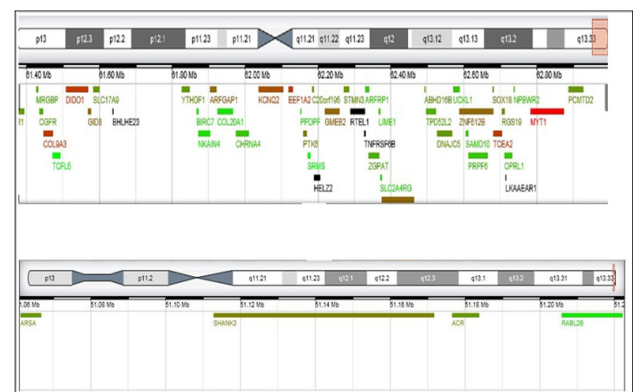
The karyotype of the patient was 46,XX. SNP array revealed subtelomeric microdeletion of 20q13.33 in patient, thus the karyotype was 46, XX, arr 20q13.33(61,323,418-62,909,908) x1. SALSA MLPA Telomere 3 and 5 however detected not only microdeletion 20q13.33 (OPRL1, UCKL1) but also duplication 22q13.33 (RABL2B, ARSA). Duplication 22q was not detected by SNP array as its size is relatively small (0,2 Mb resolution of duplications

are guaranteed by Human CytoSNP-12v2.1 Illumina), and SNP coverage of that region does not ensure duplication detection. We, therefore, performed confirmation with another SALSA MLPA kits (SALSA MLPA P245 - Microdeletions and P343 - Autism1), which showed duplication of SHANK3 gene. We also verified the detected imbalance by FISH. The results are as follows: MLPA - 46,XX, rsa20q13.33(P036,P070)x1;22q13.33(P036,P070,P245,P343) x3;FISH- 46,XX, ish der(20)t(20;22)(qter-;qter+). Microdeletion 20q13.33 spans 1.6 Mband involves genes AFRGAP1, CHRNA4 and KCNQ2,MYT1, OPRL1. The size of 22q13.33 microduplication is approximately 190 kb and involves genes RABL2B, ARSA and SHANK3 (Figure 2) The karyotype (G band and FISH) of the parents, sister and stepbrother were normal.



**Figure 2:** Relevant genes involved in translocation of chromosomes 20 and 22 (<https://decipher.sanger.ac.uk>).

**Discussion**



**Figure 3**

We report a case of de novo 1.6 Mb subtelomeric deletion of chromosome 20q13.33 and duplication of chromosome 22q13.33 as a result of unbalanced chromosomal translocation in the patient with speech delay and mental disability, but without major dysmorphic features and epileptic seizures. Up to 20 cases of the microdeletion 20q13.33 were reported so far [1-4] (Figure 3). Subtelomeric deletions of the long arm of chromosome 20 are rare. Clinical features of individuals with these microdeletions include severe limb malformations, skeletal abnormalities, growth insufficiency, developmental and speech delay, mental insufficiency and seizures. There does not appear to be a clinically recognisable constellation of dysmorphic features among individuals with subtelomeric 20q microdeletions [5]. In our patient developmental and transient growth delays were observed.

However, severe limb malformations were not present. Several studies report seizures or epilepsy in the individuals with microdeletion 20q especially deletion KCNQ2 and CHRNA4 [5,6]. KCNQ2 encodes a subunit of voltage-gate potassium channel and mutations in one allele have been noted in some patients with benign familial neonatal seizures [7,8]. Recently mutations in KCNQ2 were described in patient with unexplained neonatal or infantile epileptic encephalopathy [9]. CHRNA4 encodes the  $\alpha 4$  subunit of the neuronal nicotinic acetylcholine receptor. Mutations in this gene leading to a gain of function were found in some patients suffering from AD nocturnal frontal lobe epilepsy, disorder that is characterized by a variety of paroxysmal behaviours that generally arise out of non-REM sleep [10]. CHRNA4 knockout mice show heightened anxiety-like behaviour [11]. No seizures or sleep disturbances were observed in our patient so far. Lack of seizures in our patient suggests deletion of these genes may show incomplete penetrance [5]. However, we cannot exclude the later onset the seizures as our patient is still young.

The haploinsufficiency MYT1 - myelin transcription factor that is highly expressed in the developing brain - and OPRL1 (encoding opiate-like G-protein-coupled receptor that is thought to be involved in the regulation of instinctive and emotional behaviours) are mentioned to have the possible role in behavioural problems and neuro developmental delay [12]. Behavioural problems associated with the chromosomal aberration [5,13] were noted at the age of three years in our patient, but at the time of first clinical evaluation they were not related to the autistic spectrum disorders (ASD). Whereas deletion 22q13.33 is well known as Phelan McDermid syndrome, the duplication the same region has been less frequently observed [14-16] usually as a result of unbalanced translocation [17,18]. The duplication detected in our patient encompasses genes SHANK3, ACR, ARSA and RABL2B.

The 22q13 duplications have been reported in patients diagnosed with Asperger syndrome, attention deficit-hyperactivity disorder (ADHD) or schizophrenia [16,19,20]. Hyperkinetic neuropsychiatric disorder is caused by heterozygous interstitial duplication in chromosome 22q13 involving the SHANK3 gene [14]. SHANK3 was first identified in rats [15] and then in humans as a gene expressed predominantly in cerebral cortex and cerebellum. Patients with duplication of SHANK3 are essentially nonverbal and showed poor social interactions and repetitive behaviours [21]. As discussed elsewhere [19,22,23], fine tuning of the gene expression of critical genes such as SHANK3 can be crucial for the development of speech and language and/or social communication in humans.

Whereas a child, who inherited the 22q13 deletion, developed an ASD phenotype, her sister who inherited a 22q13 partial trisomy presented with ADHD. Similarly, in a family with a paternal balanced translocation described by [19], the daughter with a 22q13 deletion developed autism, severe language delay, whereas her brother with a 22q13 partial trisomy, albeit the diagnosis of Asperger syndrome, demonstrated precocious language development and fluent speech. The additional copy of 22q/SHANK3 seems to do not cause language disability but can lead to impairment in social communication [19]. However, some authors reported the poor

language development in the case of dup 22qter (see Figure 2). Marked irritability and unstable temper present in our patient were also reported previously [16]. SHANK3 gene encodes a protein of the postsynaptic density (PSD) of excitatory synapses, where it may function as a master scaffolding forming large sheets that may represent the platform for the construction of the PSD complex [24]. At the PSD complex, SHANK3 has been shown to bind to neuroligins [25] which, together with the neurexins form a complex at glutamatergic synapses. Presumably the 22q13 duplication causes overexpression SHANK3 resulting in interference with proper synaptic development, such as developmental deficiency.

Okamoto et al. [18] suggested that the 22q13 duplication is a recognisable clinical entity with hypotonia, developmental delay and growth deficiency. All these symptoms were observed in our patient. Moreover microcephaly, which was also noted in our patient, has also been reported to accompany frequently the duplication 22q13 [15-18]. As the microcephaly was mentioned only in the Beri-Deixheimer's (Table 1) report of 20q13.33 microdeletion, we can assume that this abnormality is more common for duplication 22q13.33. Craniofacial abnormalities are less characteristic for 22q13.33 duplication except for prominent forehead, hypertelorism and flat nasal bridge which are frequently reported in this case (Table 2). But we can not confirm the presence of these in our patient. Poor language development and mental insufficiency/developmental delay are reported in both aberrations - 22q13 duplication and 20q13 deletion - so it is difficult to ascribe these abnormalities to the particular aberration.

## Conclusion

Autistic behaviour was reported in patients with sub telomeric micro deletion 20q13 [5,26,27] Some of the neuro behavioural problems in our patient may result from the 22q13 duplication (moodiness) but she does not suffer from Asperger syndrome or ADHD. Hyperactivity or ADHD is common in this case [14,16]. Contemporary failure, to thrive, has been described in 20q13 subtelomeric deletions (Table 1). The extension of the subtelomeric deletion 20q13 in all reviewed reports is rather similar, but we concluded that except for the presence of seizures and mild brain anomalies is impossible to distinguish any subtypes.

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Beri-Deixheimer 1	approx 1.0	KCNQ2, SOX18, MYT1	del(20) (q13.33) FISH	61.2-62.9	7y (F)	-	+	+	temporal narrow-wing	-	hypertelorism, mongoloid slant	down-turned corners, thin upper lip	anteverted nares	brachycephaly	-	+	normal	-	phonological abnormalities, nystagmus	
2	approx 1.33	ARFGAP1, CHRNA4, KCNQ2, SOX18, MYT1	del(20) (q13.33) FISH		4y (F)	1 episode, irregular sleep	?	+	temporal narrow-wing	-	hypertelorism, epicanthic folds	-	-	trigonocephaly	thin corpus callosum, abnormal ECG	-	autistic, poor language and social interaction	-	-	
Mefford	1.5	ARFGAP1, CHRNA4, KCNQ2, SOX18, MYT1	del(20) (q13.33) aCGH	60.7-62.4	7y(M)	irregular sleep	+	+	-	-	-	-	-	-	delay/eye++ initiation of temporal lobes, abnormal ECG	?	axial	-	blind, nystagmus	
																				+
Leeuw	2006	ARFGAP1, CHRNA4, KCNQ2, SOX18, MYT1	der(20) t(17;20) aCGH, FISH	61.6-62.4	5y4m (M)	+	?	+	narrow	low-set, small thin helix	deep-set, hypertelorism	short philtrum, micrognathia	notched	thin	abnormal ECG	-	failure to thrive	+	+	congenital abnorm. of kidneys, cryptorchidism
Roberts	?		del(20) (q13.33) FISH	?	9y(M)	-	+	+	-	-	mongoloid slant	thin upper lip, smooth short philtrum	bulbous	-	-	?	-	-	syndactyly, clinodactyly	
Ardalan	1.6	ARFGAP1, CHRNA4, KCNQ2, SOX18, MYT1	del(20) (q13.33) and dup(20) (p13) FISH	?	7y(F)	tonic, seizures, mild ataxia	+	++	large	dysplastic	hypertelorism	short upper lip	long prominent	-	mild asymmetry and ventricular enlargement with cerebral atrophy, abnormal ECG	-	aggressive, self-injurious beh.	-	anterior anal placement	
Frassse	?		del(20) (q13) conventional karyotyping	?	3m (M)	+	?	+	prominent	low-set, malformed	mongoloid slant, epicanthic folds	long upper lip, thick lower lip	broad bridge, anteverted nostrils	-	?	?	++	+	?	
GD growth delay, PMD psychomotoric delay, MI mental insufficiency																				

Table 2: Clinical characterization of microduplication 22q(q13.33) in the literature.

author	size of dup [Mb]	genes of interest	Karyotype method	Age (gen-der)	Seizures/epilepsy	Speech delay	PMD/MR	fore-head	ears	eyes	mouth	nose	Face	micro-cephaly	behaviour	hypo-tonia	short stature/growth delay	others
Capkova	0.19	ARSA, SHANK3, RAB12B	der(20)(20:22)(q13.33;q13.33)dn SNParray, MLPA, FISH	5y7m (F)	-	+	+	-	otopostasis, posteriorly rotated	almond shaped, slight mongoloid slant on the left	-	prominent pinnna	square	+	anxious, mild negativistic, affective	+	+	clinodactyly of 4th toes, flat feet
Okamoto 1	6.0	ARSA, SHANK3, RAB12B	dup(22)(q13-qter)dn aCGH, FISH	4m (F)	-	+	+	prominent	low-set, deformed	hypertelorism	shallow philtrum, high-arched palate	broad, flat nasal bridge	round	+	affective, friendly	+	+	hypopigmentation skin and hair
2	>2.0	ARSA, SHANK3, RAB12B	der(17)(17:22)(p13;q13)pat aCGH, FISH	6y (F)	-	+	+	prominent	low-set, deformed	hypertelorism, epicanthus	high-arched palate	broad, flat nasal bridge	round	-	feeding difficulty	-	+	-
Bon/2007 ECARUCA	4.3	ARSA, SHANK3, RAB12B	der(10)(10:22)(q13.31;q13.33)ma microarray, FISH, MLPA	3y7m (F)	-	+	+	-	-	strabismus	micrognathia, microstomia	trigono-cephaly	-	-	hyperactivity	+	+	skin syndactyly
Wu	0.258	ARSA, SHANK3, RAB12B	dup(22)(q13.33) SNP array, MLPA	7m (F)	-	?	+	-	prominent	small palpebral fissures	-	flat nasal bridge	-	+	?	?	+	CHD
Feenstra 1	?	?	der(21)(21:22)(p13;q13.2)pat FISH	3y6m (F)	-	+	+	prominent	low-set	epicanthus, small palpebral fissures, hypertelorism	submucose palate cleft	flat midface	+	+	hyperactive, pleasant	+	+	ysplastic hip, pulmonicar valve stenosis, ectopic kidney
2	?	?	der(21)(21:22)(p10;q13.3)pat MLPA, FISH	3y11m (M)	+	+	+	prominent	-	deep-set	prominent upper lip, down-turned corners	depressed bridge	flat midface	+	hyperactivity, feeding difficulty	-	+	-
Failla	5.4	ARSA, RAB12B, SHANK3	dup(22)(q13.33) aCGH, FISH	20y (F)	-	incoherent-	+	-	helix hyperplasia	hypertelorism, myopia, down-slanting palpebral fissures	rethognathia, thick lips	deviation of nasal septa	-	+	ADHD, schizofrenia, restlessness, aggressive reaction	+	?	sciosis, splay foot with valgus, myopia, some ECG abnormalites
Han 1	.064-0.24	SHANK3, RAB12B,	dup(22)(q13.33) aCGH	11y (F)	+	?	-	-	-	Epicanthus small palpebral fissures	-	Pinched anteverted nares	-	-	ADHD, destructive behaviour	-	-	auditory overstimulation, hyperphagia
2	0.115-0.3	ARSA, SHANK3, RAB12B	dup(22)(q13.33) aCGH	35y (M)	+	?	-	-	-	-	-	-	-	-	bipolar mood swing	-	-	--



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