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Clinical Report

Microduplication 22q11.2: A Benign Polymorphism or a Syndrome With a Very Large Clinical Variability and Reduced Penetrance? —Report of Two Families

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We report on two unrelated families where the probands presented with learning difficulties and a microduplication 22q11.2. In the first family the proband was a 7-year-old boy who was referred because of psychomotor retardation, behavioral problems, large weight and height, and mild dysmorphism. His father and one brother also had mental retardation and behavioral anomalies, and presented the same microduplication. In the second family only the proband had mild learning difficulties, but the same microduplication 22q11.2 was discovered in her sister, her asymptomatic mother and grandfather. No distinctly recognizable phenotype has been observed in the individuals from our two families diagnosed with microduplication 22q11.2. The marked clinical variability both inter- and intrafamilial, including the presence of a complete normal phenotype and the presence of high intellectual possibilities in two individuals with this microdupllication 22q11.2 is remarkable. So far, 63 patients, corresponding to 35 families, with microduplication 22q11.2 have been described. The fact that microduplication 22q11.2 can be seen in individuals with a normal/near normal phenotype has been previously reported as well. We postulate that the clinical findings described so far could be due to ascertainment bias, since the most common reason for performing FISH 22 analyses is to exclude microdeletion. Future reports are needed to answer the question whether microduplication could be a non-pathogenic polymorphism or whether it is a real syndrome with a very large clinical variability and reduced penetrance. © 2008 Wiley-Liss, Inc.

Key words: microduplication 22q11.2; learning difficulties; behavioral anomalies

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INTRODUCTION

Microduplications of the 22q11.2 region have only recently been observed examining interphase cells by FISH with TUPLE1 probe in patients referred for DiGeorge/Velocardiofacial syndrome (DG/VCFS). Ensenauer et al. [2003] found a microduplication in 1.5% of unrelated patients. So far, 63 patients, corresponding to 35 families, with microduplication 22q11.2 have been described (Table I). The clinical phenotype of these patients ranges from isolated mild learning disability to the presence of severe congenital malformations, some of which are reminiscent of the DG/VCFS/22q11.2 deletion syndrome. Mild dysmorphic findings reported in these patients include hypertelorism, broad nasal bridge, epicanthal folds, high forehead, downslanting palpebral fissures, clinodactyly of the 5th fingers, micrognathia and microcephaly. Other findings reported in these patients are urogenital anomalies, hypotonia, scoliosis, seizures or abnormal EEG.

Here, we report on two unrelated families with microduplication 22q11.2 in which both probands presented with learning difficulties and an attention deficit disorder.

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TABLE I. Clinical Findings in Patients With Microduplication 22q11.2

Clinical findings	Literature findings[a]	Family 1 (this study)	Family 2 (this study)	Total
Total number of patients	56	3	4	63
Total number of families	33	1	1	35
Cognitive deficits	31/47 (66%)	3/3	1/4	35/54 (65%)
Behavior problems[b]	15/44 (34%)	3/3 (AB + ADHD)	1/4 (ADHD)	19/51 (37%)
Postnatal growth retardation	16/50 (32%)	0/3[c]	0/4	16/57 (28%)
Cleft palate	9/53 (17%)	0/3	0/4	9/60 (15%)
Velo-pharyngeal insufficiency without cleft palate[b]	10/38 (26%)	0/3	0/4	10/45 (22%)
Postnatal dysmorphic facial features	39/51 (76%)	3/3	2/4	44/58 (76%)
Congenital heart defect	12/54 (22%)	0/3	0/4	12/61 (20%)
Hearing loss[d]	13/49 (26%)	1/3	0/4	14/56 (25%)
Thyroid problems?	—	1/3	1/4	2/7

[a]As reviewed by de La Rochebrochard et al. [2006], Engels et al. [2007] and Menten et al. [2007].
[b]Include aggressive behavior (AB) and/or attention deficit hyperactivity disorder (ADHD) in patients over 2 years.
[c]Weight, length and OFC at the upper normal range or above.
[d]Reviewed on the basis of papers reporting patients with microduplication 22q11, as cited by de La Rochebrochard et al. [2006], Engels et al. [2007] and Menten et al. [2007].

CLINICAL REPORT

Family 1

Proband 1 was a 7-year-old boy referred because of psychomotor retardation, behavioral problems, large weight and height, and facial dysmorphism. He was the second child of a healthy 23-year-old G2P2 mother and a 26-year-old unrelated father. Both parents had a history of learning difficulties and had followed special education. The father had behavioral problems comparable to those of his son. The proband had two brothers; the youngest one also had learning difficulties and behavioral problems. The older brother was normal. Further family history was unremarkable. Pregnancy was normal. He was born at term with BW 3.980 kg (90th centile), BL 52.5 cm (90th centile) and OFC 39 cm (>97th centile). Delivery was reported as difficult, with Apgar score 1 after 1 min; he required intubation and ventilation because of respiratory insufficiency and hypovolemic shock. He also presented neonatal hypoglycemia and received phototherapy for neonatal icterus. Clinical examination at birth showed axial hypotonia. Cerebral ultrasounds and EEG performed in the neonatal period were normal. He was operated on for pyloric stenosis at the age of 6 weeks. He often had otitis media. His psychomotor development was retarded. From the age of 5 months on, he received special training to improve his motor skills. He walked independently at age 15 months. Psychomotor testing at the age of 2 years revealed a global developmental age of 18–19 months. His global developmental quotient (DQ) at the age of 4.3 years was 80 (with performance DQ 79 and verbal DQ 86). He was hyperactive, and had occasional outbursts of violent behavior, for which he received treatment with Rilatine® (methylphenidate). He also had problems of nocturnal and diurnal incontinence. He attended a special school for children with mental retardation and behavioral problems. At age 7 years, his weight, length and OFC were 28.5 kg (>97th centile), 134.5 cm (>97th centile) and 54.3 cm (90–97th centile), respectively. He had a systolic heart murmur 1/6, and a mild syndactyly of toes 2–3. There was a mild facial dysmorphism consisting of a high forehead, downslanting palpebral fissures, and hypertelorism (Fig. 1). His DQ at age 7 years was evaluated at 57. Brain MRI showed two aspecific white matter anomalies in the left occipital and right parietal region. EEG was abnormal (slow pattern with frequently high voltage theta and delta components). Auditive evoked potentials disclosed asymmetric perceptive hearing loss (left side: 35 dB; right side: 25 dB). Renal ultrasounds showed a small right kidney. Cardiac ultrasounds and an ophthalmological examination were normal. DNA analysis

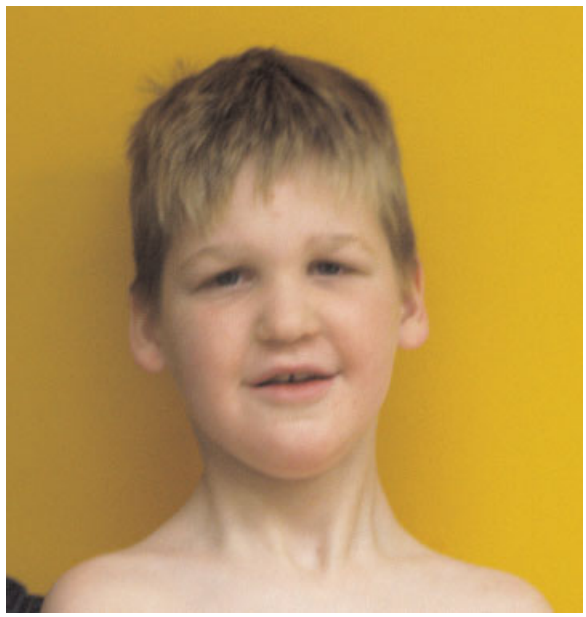

FIG. 1. General appearance of the propositus (Family 1), at the age of 7 years, showing high forehead, broad nasal bridge, and downslanting palpebral fissures. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

excluded the fragile X syndrome. His standard karyotype was 46,XY normal, but FISH 22q11.2 analyses showed the presence of three signals for TUPLE1 in all interphase nuclei (Fig. 2).

The proband's father and youngest brother had the same microduplication 22q11.2. The father had special education as a child, in the same school as his two children. His DQ at the ages of 8 and 11 years, was evaluated at 65 (with VIQ 69; PIQ 70) and 77, respectively. Major behavioral problems, similar as in his two affected children, were recorded, including outbursts of violent behavior. EEG performed at the age of 10 years showed a mild to moderate disturbed pattern without lateralization. His hearing was normal. Weight, length and OFC were 91 kg, 1.86 cm, and 58 cm, respectively. He had mild 5th left finger clinodactyly and a mild facial dysmorphism (Fig. 3). Recently a cold thyroid nodule was detected, followed by treatment with thyroid hormone. Ophthalmological examination, cardiac and renal ultrasounds were all normal.

The 4-year-old affected brother was born at term after a normal pregnancy and an uneventful delivery, with normal birth measurements (W 3.740 kg, L 51 cm, OFC 37 cm). He had a history of gastro-esophageal reflux. His development was normal and he walked independently at age 13 months. He was, as the proband, hyperactive, had an attention deficit disorder with occasional outbursts of violent behavior in school, and a tendency to run away from school or home. Psychomotor testing at the age of 4.1 years revealed a global developmental age of 3 years with delayed speech and delayed motor abilities especially for fine motor skills. Presently he receives special education and special training to improve his language in the same school as the proband. Brain MRI, auditive evoked potentials, ophthalmological examination, cardiac and renal ultrasounds were all normal. His weight, length and OFC were 19 kg (97th centile), 110 cm (97th centile) and 53.5 cm (>97th centile), respectively. He had clinodactyly of the fifth fingers, flat feet and a mild facial dysmorphism, resembling the proband and his father, including a high forehead, frontal upsweep, hypertelorism, and epicanthus (Fig. 4).

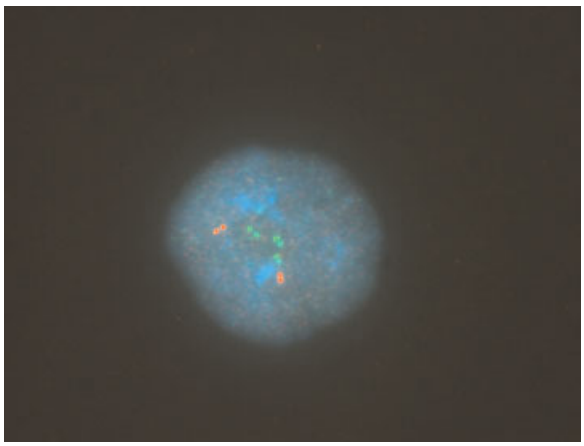

Fig. 2. FISH analysis 22q11.2 showed the presence of three signals for the TUPLE 1 probe in all interphase nuclei (TUPLE 1: green signal; control probe at 22q13: red signal). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Fig. 3. The affected father (Family 1). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Family 2

Proband 2 was an 8-year-old girl with learning difficulties. She was the second child of a healthy

Fig. 4. The affected brother (Family 1), at the age of 4 years, showing a high forehead, frontal upsweep, hypertelorism, and epicanthus. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

28-year-old G2P2 mother and a 31-year-old unrelated father. Family history was unremarkable. The pregnancy was uneventful, delivery occurred spontaneously at term, and she had normal birth measurements. During infancy, she often had respiratory infections and otitis media for which ear drains were placed and adeno-amygdalectomy was performed. She walked independently at the age of 17 months. She said her first words at age 12 months, but very soon a delay in language was diagnosed. At the age of 3 years testing confirmed a language delay (evaluated between 1 and 2 years), followed by a special training to improve her language. Psychomotor testing at the age of 4 and 6 years showed a DQ of 86 and 100 (with VIQ 98, PIQ 103), respectively. She had concentration difficulties and mild hyperactivity, but no behavioral problems. She was recently treated with Rilatine® with favorable results. Her weight, length and OFC were all within the normal range. She had a broad nasal bridge, epicanthus, low-set ears (Fig. 5), relatively short first toes and a mild scoliosis. Skeletal X-rays confirmed this mild scoliosis but no anomalies of the vertebrae were seen. Brain MRI, auditory testing, ophthalmological examination, cardiac and renal ultrasounds were all normal. Abdominal ultrasounds showed a mild aspecific enlargement of the liver, but further testings were normal. DNA analyses for fragile X syndrome and subtelomeric deletions were normal. Standard karyotype was 46,XX normal, but FISH 22q11.2 analyses showed the presence of three signals for TUPLE1 in all interphase nuclei, as well as in some metaphases (Fig. 6).

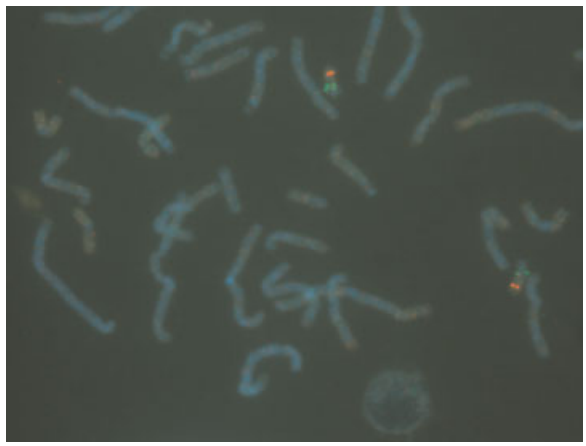

FIG. 6. FISH analysis 22q11.2 showed the presence of three signals for TUPLE 1 in some metaphases (TUPLE 1: green signal; control probe at 22q13: red signal). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The same microduplication was discovered in her mother (Fig. 7) and maternal grandfather (Fig. 8), who both were completely asymptomatic. Both succeeded their university studies, and obtained two university degrees (the grandfather even obtained both degrees simultaneously). Both were myopic. The healthy mother was born at term with normal birth measurements, had during childhood recurrent otitis media treated with ear drains, and a spina bifida occulta. The grandfather also was in good health, had never been operated on, and had no medical problems.

The youngest 4-year-old sister of the proband also had the microduplication 22q11.2. She was also born at term with normal birth measurements. Hypothyroidism caused by thyroid agenesis was diagnosed soon after birth, and she was treated since then with thyroid hormone. Her psychomotor development was reported as normal. She walked alone at the age of 18 months. She had no history

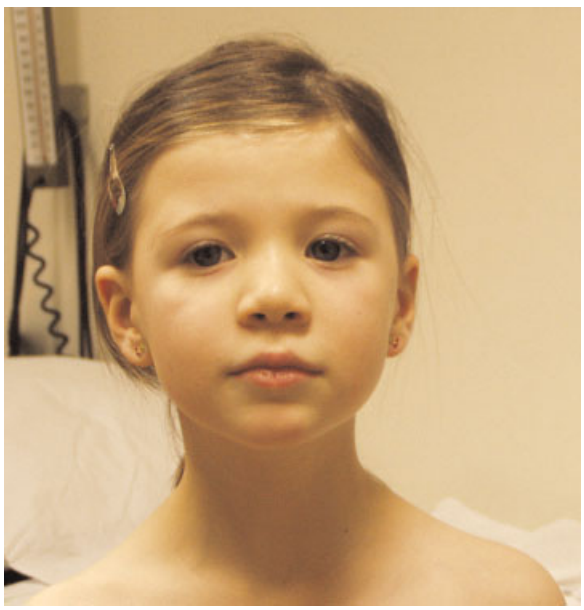

FIG. 5. General appearance of the proposita (Family 2), at the age of 8 years, showing a broad nasal bridge, epicanthus, and low-set ears. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

FIG. 7. The mother (Family 2), carrier of the microduplication 22q11.2. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

FIG. 8. The maternal grandfather (Family 2), carrier of the microduplication 22q11.2. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

of otitis, had no concentration difficulties, no behavioral problems, and was a quiet girl. Her weight, length and head circumference were in the low-normal range. She was not really dysmorphic, but had epicanthal folds, a high forehead (Fig. 9) and a shortened big toe unilaterally.

The maternal grandfather had five sisters and two brothers. One of the sisters anamnestically had learning difficulties but no behavioral problems. Both brothers were normal but each of them had one son with learning difficulties (also without behavioral anomalies) on a total of 5 and 3 children, respectively. They were unfortunately not available for testing. Both parents of the grandfather were intellectually normal (his father was a medical doctor).

FIG. 9. The sister (Family 2), carrier of the microduplication 22q11.2, at the age of 4 years, showing a high forehead and epicanthal folds. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

FISH Analyses

Three signals for TUPLE1 probe in all interphase nuclei (Fig. 2), and in some of the metaphases (Fig. 6) were present in both probands and some of their family members (cf. supra). FISH analysis with specific probes in the probands of both families confirmed the presence of three signals for probes RP11-1057H19 and RP11-278E23, located at 17.8 and 19.9 Mb according to the NCBI genome database (http://www.ncbi.nlm.nih.gov/mapview/map_search.cgi). Only two signals were obtained for the other probes including RP11-66F9, RP11-172D7, RP11-91O6, RP11-81B3 (16.9 Mb) (proximal) and RP11-36N5 (20.3 Mb), RP11-22M5, RP11-297B9 (distal). The size of the duplication can thus be estimated between 2.1 and 3.4 Mb in both probands, based upon the physical location of the duplicated markers.

DISCUSSION

There is a marked clinical variability in the seven cases from these two families, both inter- and intrafamilial. No distinctly recognizable phenotype has been observed in the individuals from both families diagnosed with microduplication 22q11.2. In the first family the proband, his affected father and brother all had mental retardation, a mild facial dysmorphism, short concentration span, hyperactivity, and behavioral problems consisting of impulsivity and aggressive behavior. These findings were all described in other patients with microduplication 22q11.2 [Ensenauer et al., 2003; Yobb et al., 2005; de La Rochebrochard et al., 2006]. In the second family only the proband showed mild learning difficulties. In addition, the dysmorphic findings were very mild in Proband 2 and in her youngest sister, and were even lacking in the mother and grandfather. Proband 1 also had an asymmetric perceptive hearing loss and a small right kidney. Hearing impairment has also been frequently reported in patients with microduplication 22q11.2 (Table I). Two rather unusual findings not described in patients with microduplication 22q11.2 so far are (1) the large weight, length and head circumference of the three affected patients from the first family, and (2) the thyroid problems, both treated with thyroid hormone, occurring in the affected father of the first family and the "affected" sister of the second family. The occurrence of these problems could be a coincidence, but the possibility that these problems could be related to the microduplication is not

excluded, since hyperthyroidism is known to occur in patients with a 22q11.2 deletion syndrome. Whether thyroid problems, including agenesis, could be related to the 22q11.2 microduplication currently remains unknown. Clinical investigation of additional patients is needed to answer this question.

Amongst the seven cases with microduplication 22q11.2 in our two families, there are two individuals (mother and maternal grandfather) with a complete normal phenotype and high intellectual capacities. Individuals with microduplication 22q11.2 and a normal/near-normal phenotype have been described in a significant number of reported families [Ensenauer et al., 2003; Yobb et al., 2005; de La Rochebrochard et al., 2006; Engels et al., 2007; Menten et al., 2007].

Possible causes for such wide clinical variability and penetrance are as yet unknown. Interfamilial variability could of course partly be explained by the variability of the size of the microduplication 22q, usually varying between 3 and 6 Mb [Yobb et al., 2005; de La Rochebrochard et al., 2006]. In our two families the size of the microduplication appears however to be similar, most likely corresponding to the classical 3 Mb duplication (and deletion), resulting from abnormal pairing and homologous recombination mediated by low-copy repeats (LCRs) [Edelmann et al., 1999]. The variability might be explained by the influence of other interfering genes, presently unknown, and/or by epigenetic factors. The clinical findings described so far in microduplication 22q11.2 (Table I) could be due to ascertainment bias, since the most common reason for performing FISH 22 analyses is to exclude microdeletion, as it was the case in the probands of these two families. Recent studies confirmed furthermore the rather low incidence of 22q11.2 microduplication amongst patients referred for DG/VCFS [Lamb et al., 2004; Cotter et al., 2005; Brunet et al., 2006].

We postulate that microduplication 22q11.2 could be present more frequently in persons without clinical symptoms having a normal to even high intelligence. So far, microduplication 22q11.2 may be largely undetected as a result of an aspecific/unpredictable/mild phenotype leading to problems with ascertainment and choosing the patient cohort to search microduplication 22q11.2. This duplication could even be a rather rare but non-pathogenic polymorphism with each of the reported individuals/families having unrelated, and as yet undiscovered causes for their disabilities. Future reports of other families with microduplication 22q11.2 are needed to answer the question whether the delineation of this microduplication 22q11.2 "syndrome" might be an ascertainment bias or whether it is a real "syndrome" with a very large clinical variability and reduced penetrance.

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