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Original article

Clinical variability of the 22q11.2 duplication syndrome

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Abstract

The 22q11.2 duplication syndrome is an extremely variable disorder with a phenotype ranging from normal to learning disability and congenital defects. Both patients with a *de novo* 22q11.2 duplication and patients in whom the duplication has been inherited from a phenotypically normal parent have been reported.

In this study we present two familial cases with a 3 Mb 22q11.2 duplication detected by array-CGH.

We also review the findings in 36 reported cases with the aim of delineating the phenotype of the 22q11.2 duplication syndrome. In a majority of the reported cases where parents have been tested, the duplication seems to have been inherited from a normal parent with minor abnormalities. With this in mind we recommend that family members of patients with a 22q11.2 duplication to be tested for this genetic defect.

Keywords: 22q11.2 Duplication; Syndrome; Mental retardation; Children; Array-CGH; MLPA

1. Introduction

Deletion 22q11.2 syndrome, which includes the well-known genomic disorders DiGeorge and Velo-Cardio-Facial syndrome (MIM 188400, 192430), is familiar to most paediatricians

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with a prevalence of 4/10 000 births. The phenotype of patients with deletion 22q11.2 syndrome varies enormously, even within a family. A majority of the 22q11.2 microdeletions are *de novo*, but some of them are inherited from a mildly affected or normal parent. Recently patients with duplications of the same region at 22q11.2 have been reported [1,3–9,14,15]. The phenotype of these patients seems to vary in the same way as that of the deletion syndrome with symptoms ranging from severe mental retardation, dysmorphic facial features, and heart malformations to no symptoms at all. Although some of the features of the 22q11 duplication syndrome overlap with the deletion syndrome it has become clear that most of the symptoms are distinct from the 22q11.2 deletion syndrome.

The sizes of the duplications, like those of the deletions, range between 1.5 and 6 Mb. The rearrangements in the 22q11.2 region are most likely the result of unequal crossing-over of segmental duplications (SD) (LCR22s) during meiosis that can lead to either duplications or deletions in the above-mentioned region [10].

Recent data suggest that the frequency of the duplications is approximately half that of the deletions [12]. However, up till now only about 34 cases of 22q11.2 duplications have been reported [1,3–9,14,15], a low number compared to the large number of cases reported with 22q11.2 deletion syndrome. This difference might be explained either by the wide range of and sometimes mild phenotypes of the patients, which will give less reason to suspect and test for 22q11.2 duplication or to technical difficulties in detecting microduplications by fluorescent in situ hybridisation (FISH) on metaphase spreads. With the clinical implementation of multiplex ligation-dependent probe amplification (MLPA) or of genomic microarrays, the number of patients detected with 22q11.2 duplication is almost certainly going to increase.

In this report we describe on two patients from different families with 22q11.2 duplication syndrome. Both patients inherited the duplication from almost phenotypically healthy parents. In addition, we review the findings in 34 previously described cases with the aim of delineating the phenotype of the 22q11.2 duplication syndrome.

2. Material and methods

2.1. Array-CGH

Microarray based comparative genomic hybridisation (array-CGH) was performed using the CytoChip (BlueGnome Ltd, Cambridge, UK) with a resolution of 1 Mb. Array-CGH was performed as previously described with some modifications [11]. Briefly, 500 μg test and reference DNA was labelled by random priming with Cy-3 dCTP and Cy-5 dCTP (GE HealthCare, UK), respectively, using the BioPrime Array-CGH Genomic Labelling System (Invitrogen, Carlsbad, CA). The reaction was incubated overnight at 37 °C. Unincorporated nucleotides were removed using the BioPrime purification kit (GE HealthCare, UK). Labelled test and reference DNA were mixed with 60 μg of Cot1 DNA (Invitrogen, Carlsbad, CA), and hybridised to the array for 16–18 h at 45 °C. Slides were washed in 2× SSC, 0.1% SDS, 25% formamide for 20 min. at 45 °C, followed by 1× PBS for 20 min. at RT, 0.2× SSC for 15 s at RT and finally deionised water for 15 s at RT, and were immediately dried with compressed air. A pool of sex-matched DNA from eight normal male or female blood donors was used for the reference samples.

Arrays were analysed using a GenePix 4000B scanner (Axon Instruments Inc, Union City, CA) and BlueFuse software (v3.5) (BlueGnome Ltd, Cambridge, UK).

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2.2. MLPA

Array-CGH data were confirmed by using MLPA with the SALSA MLPA kit P250 DiGeorge (MRC Holland, Amsterdam, The Netherlands), as previously described [11]. Analysis was performed with GeneMarker software 1.6 (Softgenetics, USA).

3. Results

3.1. Case reports

3.1.1. Case 1

The index patient was a 3-year old girl (Fig. 1A and B), first child of non-consanguineous parents. The father had a brother who was mentally retarded and autistic, probably as a result of hypoxia during birth. Otherwise there are no reports on mental retardation or abnormal genetic conditions in the family. The mother had a nasal speech and dyslexia. She was able to follow normal school with extra help. Both the maternal grandmother and the mother's brother were normal.

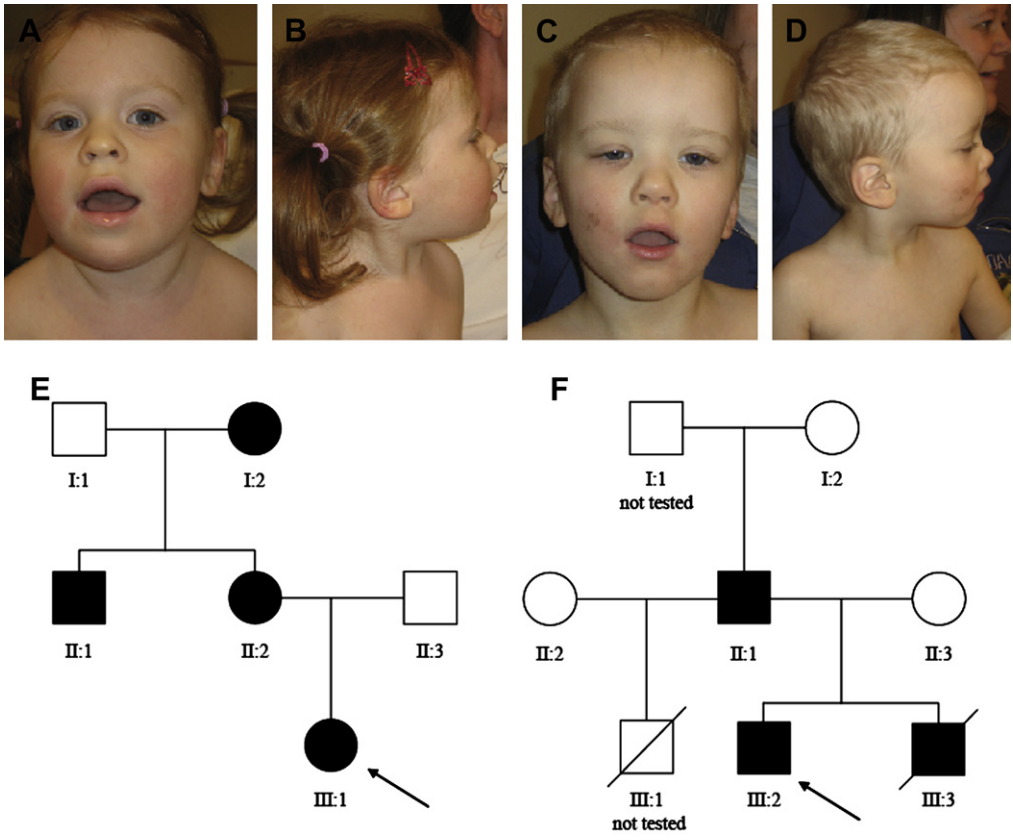

Fig. 1. Photographs and family pedigrees of patients and families carrying a 3 Mb 22q11.2 duplication: (A and B) case 1, (C and D) case 2, (E) pedigree of family 1, and (F) pedigree of family 2.

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The patient was born by emergency caesarean section because of pre-eclampsia after 40 + 4 weeks' gestation. The mother's health was good during early pregnancy. There were no reports on use of drugs or alcohol. The girl's birth weight was 3055 g. Her Apgar scores were 7–9–10. The neonatal period was normal. At age 1.5 years she had a seizure in connection with a urinary tract infection, secondary to bilateral vesico-urethral reflux of grade 4 on the right kidney and grade 3 on the left.

Her psychomotor development was delayed. At the age of 1 year she was able to roll over but not to sit up. She crawled at 20 months and started to walk without support at 2 years and 3 months. Her speech and language development was delayed. At 3 years and 3 months she spoke a few single words. Brain MRI and metabolic screening were both normal.

At clinical examination at 3 years and 3 months, her weight was −1 SD, height −2 SD and head circumference was −0.5 SD. The following dysmorphic features were noted: full lips, epicanthic folds, a flat nasal bridge, prognathism, thick ear helixes, high-arched palate and muscular hypotonia (Table 1).

Array-CGH analysis of case 1 (III:1) (Fig. 1E) revealed a duplication spanning four clones, RP11-800B02 through RP11-441P13, at 22q11.21, which was verified by MLPA-analysis. The size of the duplication was estimated by the same method to be 2.09–3.06 Mb, with a centromeric breakpoint between *USP18* and *CLTCL1* and a telomeric breakpoint between *LZTR1* and *HIC2* (Fig. 2B). The duplication is most likely the result of nonallelic homologous recombination (NAHR) between LCR22A and LCR22D. MLPA-analysis disclosed an identical duplication in the mother (II:2), maternal grandmother (I:2) and maternal uncle (II:1). This duplication was not detected in either the father (II:3) or the maternal grandfather (I:1).

3.1.2. Case 2

The proband was a 3-year old boy (Fig. 1C and D), second son of non-consanguineous parents. Both parents required special education in school, as both were diagnosed with borderline mental retardation. Three years after the birth of the index patient the parents gave birth to a boy, who was born after 25 + 3 weeks of pregnancy as a result of severe maternal toxicosis, with a birth weight of 600 g. He died at the age of 30 weeks of gastrointestinal bleeding. The mother had insulin-dependent diabetes mellitus and had been treated with insulin since 1991. The father had a son from a former relationship, who was born after 28 weeks of pregnancy with a birth weight of 630 g. That child died after 38 h.

The index patient was born after 34 (35 + 4) weeks of gestation by caesarean section, performed because of toxicosis. The boy was small for gestational age with a birth weight of 1400 g. He was mentally retarded and his language development was delayed. Motor development was normal and he walked at the age of 1 year. He spoke his first word at the age of 2.5 years and at the age of 3.5 years he only said a few single words.

At 3.5 years of age, he showed the following dysmorphic features (Table 1): His height was 94.4 cm, −2 SD, weight 14 kg, −1.5 SD and head circumference 48 cm, −3 SD. He had bilateral ptosis, more pronounced on the right eye, a square-shaped head with a large prominent forehead, slight hypertelorism, epicanthal folds and a flat nose. He also had a high-arched palate, low-set ears with thick helixes, and deviant facial expressions. He had muscular hypotonia, and a nasal speech.

Array-CGH (Fig. 2A) and MLPA-analyses of case 2 (III:2) (Fig. 1F) showed the same duplication at 22q11.21 as detected in family 1. MLPA-analysis of family 2 identified the same duplication in the father (II:1) and also in the proband's deceased younger brother (III:3). This

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Table 1
Summary of clinical features of present and previously reported cases with 22q11.21 microduplication syndrome

	Ensenauer et al. [6]	Yobb et al. [14] [a]	Portnoi et al. [9]	de La Rochenbrochrad et al. [3]	Alberti et al. [1]	Engels et al. [5]	Mukaddes et al. [7]	Yu et al. [15]	Ou et al. [8]	Present case#1	Present case#2	Total results
Parental studies	2 familial, 5 *de novo*	3 familial	2 familial	1 familial	1 *de novo*	1 familial	1 familial	2 familial	2 familial, 1 *de novo*	1 familial	1 familial	16 familial, 7 *de novo*
Duplication size	7 × 3 Mb 4 × 4 Mb 2 × 6 Mb	–	2 × 3 Mb	3 Mb	1.5 Mb	3 × 2.8 Mb	–	1 × 3 Mb 1 × 1.5 Mb	3 × 3 Mb 2 × 1.5 Mb	3 Mb	3 Mb	
Relatives with duplication who show cognitive deficits												18/26
Sex	7M/5F	2M/5F	1M/1F	F	F	1M/2F	F	2F	3M/2F	F	M	21F/15M
Poor growth	7/11	3/7	1/2	–				0/2	1/5	Height −2 SD Weight −1 SD, Head −0.5 SD	Height −2 SD Weight −1.5 SD, Head −3 SD	19/30
Microcephaly	2/11	2/3	0/2			1/3		1/2	1/5	–	+	2/28
Cognitive deficits	10/10	5/5	2/2		+	3/3	+	1/2	5/5	+	+	30/31
Behavioral problems	2/8	3/4			+	1/3	+	0/2	3/5	+	+	13/26
Motor delays	7/9				+	1/3	+	0/2		+	+	12/18
Hypotonia	1/10	3/7	2/2		+					+	+	9/21
Seizures	2/11	3/4					+			–	–	6/18
Hearing impairment	5/11	4/7	1/2		+		–		3/5	–	–	14/29
Visual impairment			0/1		+	3/3	+			–	–	5/8
Susceptibility to infections	1/11	0/6				3/3				–	–	4/22
Urogenital anomalies	4/10	0/6	0/2	–				0/2	0/1	+	–	5/24

(*continued on next page*)

Table 1 (*continued*)

	Ensenauer et al. [6]	Yobb et al. [14] [a]	Portnoi et al. [9]	de La Rochenbrochrad et al. [3]	Alberti et al. [1]	Engels et al. [5]	Mukaddes et al. [7]	Yu et al. [15]	Ou et al. [8]	Present case#1	Present case#2	Total results
Parental studies	2 familial, 5 *de novo*	3 familial	2 familial	1 familial	1 *de novo*	1 familial	1 familial	2 familial	2 familial, 1 *de novo*	1 familial	1 familial	16 familial, 7 *de novo*
Duplication size	7 × 3 Mb 4 × 4 Mb 2 × 6 Mb	−	2 × 3 Mb	3 Mb	1.5 Mb	3 × 2.8 Mb	−	1 × 3 Mb 1 × 1.5 Mb	3 × 3 Mb 2 × 1.5 Mb	3 Mb	3 Mb	
Heart defects	2/11	2/7	0/2	+			+	1/2	0/5	−	−	7/31
Palatal defects	5/12	1/5	2/2				+	0/2	0/5	+	+	11/29
Velopharyngeal insufficiency	7/10	1/5	2/2				+	0/2	2/5	−	−	13/27
Micrognathia	5/10	3/4	2/2	+	+			0/2	2/5	−	−	14/27
Prognathism			0/5				+	0/2	0/5	+	+	3/12
Downslanting palpebral fissures	7/10		0/2	+				0/2	1/5	−	−	9/22
Ptosis	3/10		0/2					0/2		−	+	4/16
Epicanthal folds	2/10	2/2			+	2/3		0/2	1/5	+	+	11/26
Hypertelorism	8/11	3/3	2/2					0/2		−	+	14/20
Dysplastic ears	4/10		2/2	+				0/2	3/5	−	−	10/22
Broad flat nose	4/11	4/4	1/2		+	2/3		0/2	2/5	+	+	16/30
Anomalies of hands/feet	5/10	4/7	1/2			1/3		1/2	3/5	−	−	15/31
Abnormal palmar creases	3/11	4/7							0/5	−	−	7/25

+ = Feature present, − = feature absent, P = percentile, SD = standard deviation, F = female, and M = male.

[a] Including patient from Edelmann et al. [4].

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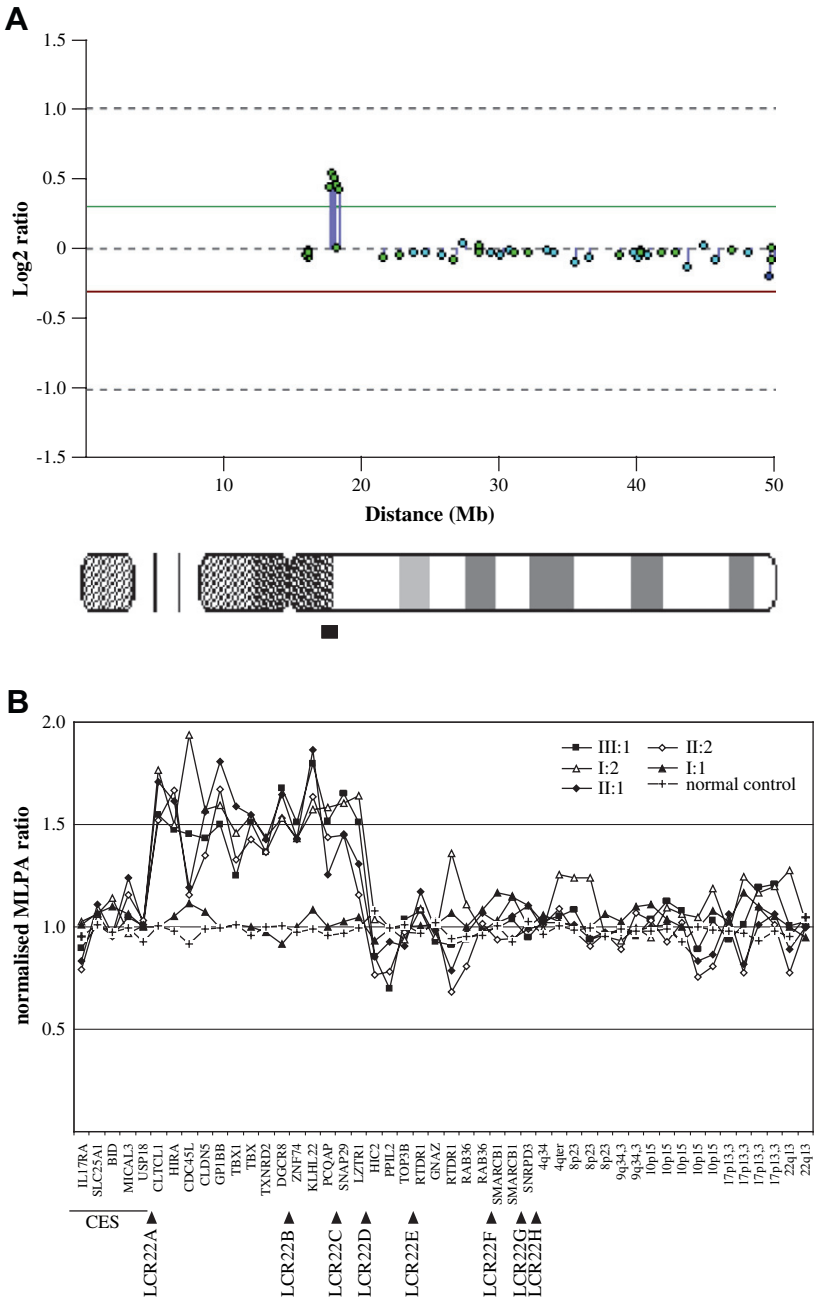

Fig. 2. (A) Array-CGH profile from chromosome 22 displaying a duplication at 22q11.2 in case 2. The green line indicates the threshold for duplication and the red line a deletion (±0.3). (B) MLPA results from family 1, displaying a duplication of 14 probes located in the 22q.11.2 region. Probes IL17RA to USP18 are located in the region for Cat Eye Syndrome (CES). Probes CLTCL1 to SNRPD3 are located in the critical region for 22q11.2 deletion/duplication syndrome. Probes 4q34 to 22q13 are used as controls. Arrows point at the different locations for the LCRs in the 22q11.2 region. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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duplication was not detected in the proband's mother (II:3) or maternal grandmother (I:2). The deceased older brother (III:1) was not analysed because of lack of genomic DNA.

4. Discussion

In this study we present two familial cases of 22q11.2 microduplications. In case 1 we found that the mother, maternal grandmother and healthy maternal uncle all carried the same 22q11.2 duplication as the index patient. The mother had severe dyslexia, nasal speech and slight learning difficulties, but otherwise had a normal mental development. The maternal grandmother and the maternal uncle were unaffected.

The father of case 2 also carried the duplication and had mild learning problems, but no other symptoms. The present two patients have many similarities to patients reported in other publications with 22q11.2 duplication syndrome (Table 1) [1,3–9,14,15]. They had mental and growth retardation, and showed facial features as broad flat nose, a high palate and epicanthal folds which are commonly found in other patients with the syndrome. In addition both of our patients had prognathism, which has only been reported in one other case. Neither of our patients had heart malformations, visual or hearing impairment, seizures, downslanting palpebral fissures, micrognathia or abnormal hands or feet, symptoms that have been reported frequently in other cases.

In Table 1 the abnormal findings in previous and present cases of 22q11.2 duplication syndrome are reviewed [1,3–9,14,15]. In the 36 cases there is clearly a very wide phenotypic variation, ranging from no abnormality or mild learning disabilities to severe mental retardation with multiple congenital malformations.

The most frequently reported symptoms in the 22q11.2 duplication syndrome are mental retardation/learning difficulties (cognitive deficits such as deficits of memory performance, perceptual organisation and verbal comprehension, ADHD and speech impairment) (97%), delayed psychomotor development (67%), growth retardation (63%) and muscular hypotonia (43%). The most common dysmorphic features detected are hypertelorism (70%), broad flat nose (53%), micrognathia (52%), velopharyngeal insufficiency (48%), dysplastic ears (45%), epicanthal folds (42%) and downslanting palpebral fissures (41%). Other reported symptoms are congenital heart malformation, visual and hearing impairment, seizures, microcephaly, ptosis, and urogenital abnormalities.

In a number of patients in the different studies, the parents have not been tested. However, in those cases where parents of patients with a detected 22q11.2 duplication were tested, a majority of the duplications seemed to have been inherited from a parent with no or only minor abnormalities (18/26; 69%). Aberrations inherited from a phenotypically normal parent are usually considered as benign. However, if the region contains known disease genes and if the region has also been detected as the site of aberrations considered as *de novo*, much care has to be taken in the interpretation of these aberrations.

The reason for the wide phenotypic variation is not known, but possible explanations might be that the 22q11.2 deletion syndrome phenotype could be due to other genetic mutations or that other genes not involved in the duplication may compensate for or inhibit the pathogenesis of the duplication. It has also been speculated that epigenetic factors as well as non-penetrance [14] might be involved. One of the genes in the commonly deleted region at 22q11.2, *TBX1*, has been suggested as the gene causing the phenotype of the 22q11.2 deletion syndrome [2,13]. A recent study showed that some of the missense mutation in *TBX1* resulted in increased expression levels and a gain of function [16]. Although this is a gene dosage more in

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concordance with the 22q11.2 duplication syndrome, these patients displayed symptoms more similar to the 22q11.2 deletion syndrome. The reason for this is not known but one explanation could be that deletion or duplication of one or more critical genes have the same phenotypic effect. That could also be an explanation to why there are so many similar symptoms between the 22q11.2 deletion and duplication syndrome. The increased expression of *TBX1* together with epigenetic factors or regulation by other genes has been suggested as possible explanations for the wide phenotypic variation seen in the 22q11.2 duplication syndrome [8]. Other explanations that have been discussed are that altered gene dosage of *TBX1* might result in down regulation of the gene targets of *TBX1*[2].

In conclusion, the phenotype of the 22q11.2 duplication syndrome is very heterogeneous, with a phenotype ranging from very mild symptoms to severe mental retardation. Although it is possible to perform prenatal testing it is impossible to predict the phenotypic outcome of a 22q11.2 duplication.

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