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Novel Insights from Clinical Practice

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Atypical 22q11.2 Microduplication with "Typical" Signs and Overgrowth

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Established Facts

- 22q11.2 duplication syndrome has a variable clinical phenotype with similarities to the well-known 22q11.2 deletion syndrome.
- Due to this variability it is a big challenge for clinicians to predict the phenotypic consequences.
- A patient with an atypically small 22q11.2 duplication and an 8q22.1 duplication with overgrowth has previously been reported.

Novel Insights

- Very small rearrangements with atypical breakpoints can cause a clinical picture of the 22q11.2 duplication syndrome as described in larger and typical 22q11.2 duplication patients.
- The 22q11.2 duplication is probably responsible for the overgrowth phenotype and not the additional one in 8q22.1 of the previously published case.
- A "second hit" concerning CNVs seems not to be necessary for a severe phenotype in a 22q11.2 duplication patient.
- Since only few information exists about atypical duplications of chromosome 22q11.2, this report of a similar duplication like an already published one, also with overgrowth, increases the spectrum of known cases.

Keywords
22q11.2 · Duplication · Overgrowth · Atypical breakpoints · Macrocephaly

Abstract
The 22q11.2 microduplication syndrome shows variable phenotypes with reduced penetrance compared to the 22q11.2 deletion syndrome. We report a woman with overgrowth and macrocephaly, mild mental retardation, heart defect, kidney anomalies, and dysmorphic features. Array-CGH analysis revealed a 246-kb duplication at the 22q11.2 region. No additional clinically significant CNVs were found. The case resembles a previously published case also showing overgrowth and macrocephaly with an almost identical 22q11.2 duplication of 252 kb.

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Introduction

It is becoming more and more clear, that a duplication in the chromosomal region 22q11.2 (chromosome 22q11.2 duplication syndrome; MIM #608363) has many overlapping features with the well-known 22q11.2 deletion syndrome, i.e., dysmorphic features like a high forehead, a broad nasal bridge, down-slanting palpebral fissures, congenital heart defect, velopharyngeal insufficiency, speech delay, hearing loss, intellectual deficits, behavioral problems, and psychiatric disorders like depression and attention-deficit hyperactivity disorder [Portnoi, 2009; Hoeffding et al., 2017]. The rate of autism seems to be especially high [Wenger et al., 2016]. Psychosis may also occur [Amelsvoort et al., 2016]. These medical problems are, however, less frequent than in the 22q11.2 deletion syndrome patients, and some patients have a normal or very mild phenotype [Portnoi, 2009]. As in the 22q11.2 deletion syndrome, the penetrance and expressivity of this syndrome are highly variable, and there is no correlation between the size of the duplication and the clinical phenotype [Van Campenhout et al., 2012; McDonald-McGinn et al., 2015; Yu et al., 2019]. In a Danish population study, the prevalence for duplications was even higher than for deletions (1:1,606 and 1:3,672, respectively) [Olsen et al., 2018]. Relatively few reports about duplications have been published, especially about distal or atypical duplications. The variable phenotype of distal duplications includes developmental and intellectual delay, behavioral problems including hyperactivity, epilepsy, hypotonia, and congenital heart defects [Ou et al., 2008; Coppinger et al., 2009; Pinchefsky et al., 2017]. There is little knowledge about the phenotypic consequences of very small rearrangements, as presented in this report. Thus, more information about the phenotypic spectrum of such atypical duplications is important for clinicians and patients.

Case Presentation

We report a 33-year-old female, born after an uncomplicated pregnancy with a birth weight of 3,580 g, length 51 cm, and occipitofrontal circumference 37.5 cm. Her Apgar score was 9–10. Umbilical artery blood pH was 2.33. A ventricular septal defect was surgically corrected at the age of 6 months. Early development was slightly delayed. Because of a nasal voice she received speech therapy.

At the age of 12 years the patient presented with tall stature (172 cm; >P97) and obesity. Hyperkyphosis, muscular hypotonia, weak musculature of arms, hands, and feet were reported. Facial dysmorphisms including hypertelorism, broad nose, prominent forehead, and slightly dysplastic ears were observed (Fig. 1). A duplex kidney was found with ultrasound. Due to hypothyroidism she was prescribed L-thyroxine, due to arterial hypertension lisinopril. She presented with coordination and balance problems, coxa valga, lymphedema of legs with swellings of the feet, and obesity. MRI of the brain revealed a small pituitary adenoma in 2019.

Fig. 1. Frontal view of the patient at the age of about 14 years (left) and 1 year (right).

After the death of her mother in 1994, at the age of 10, psychological problems and difficulties in sports classes required a change from a regular school to a school for disabled children. At school, she was bullied because of her obesity and handicap and did not have many social contacts. Between age 12 and 14 years she lived in a residential group. An IQ of 84 was measured at the age of 15.

At the age of about 26 years, she developed depressive symptoms with depressed mood, reduced drive, social withdrawal, rumination, low self-esteem, and concerns about making mistakes. Because of these symptoms she was treated in a psychiatric hospital for 2 months with the diagnoses depressive episode and social phobia. She got sertraline as antidepressant and still takes 100 mg/day. Symptoms subsided after inpatient treatment and 45 sessions of psychotherapy. She never had developed any psychotic symptoms. The psychological problems after death of her mother during her childhood may have been caused by a depression as well as a reaction to this negative life event. This might have influenced the development of psychiatric problems later in her life. Patients with genetic syndromes can have reactive aspects in their depression caused by suffering from being "different" and disabled as well as from such possibly traumatic life events. Posttraumatic stress disorder is relatively rare in 22q11.2 deletion syndrome patients, however [Schneider et al., 2014].

She got the qualification as a healthcare management assistant but failed to find a job. She is working part time in a cleaning company, living in an apartment by herself.

With regard to family history, her mother died suddenly for an unknown reason when the patient was 8 years old. Her father is still alive. She has one older paternal half-sister. Her mother has 2 brothers. One of them has 2 daughters and 2 sons. Our patient was unaware of any family members with mental retardation or syndrome-specific features and could not provide any additional information about the pedigree, for example, on her father's side.

When she came to our specialized center for deletion syndrome 22q11.2 in 2017 she still thought to have a *deletion* syndrome

Table 1. Comparison of phenotypes of our patient and the patient reported previously by Tarsitano et al. [2014]

	Our patient	Patient from Tarsitano et al. [2014]
Sex	Female	Male
Intellectual development	IQ 84 (infancy) IQ 101 (33 years, MWT-B)	IQ 70 (5 years)
Psychiatric diagnosis (at the age of)	Depression (26 years)	ADHD (5 years)
Length	Overgrowth (172 cm at age 12 years)	Overgrowth (177 cm at age 13 years)
Occipitofrontal circumference	Macrocephaly at birth (37.5 cm)	Macrocephaly at birth (38 cm)
Facial dysmorphism	Hypertelorism Broad nose Dysplastic ears Prominent forehead	Hypertelorism Broad nose Large ears Prominent forehead
Heart anomalies	Ventricular septal defect	
Palatal anomalies	Nasal voice	
Urogenital anomalies	Duplex kidney	Abnormal external genitalia
Musculoskeletal anomalies	Coxa valga, hyperkyphosis, muscular hypotonia	Flat feet
Other	Lymphedema, hypothyroidism	

MWT-B, a vocabulary intelligence test; ADHD; attention-deficit hyperactivity disorder.

22q11.2, which had been diagnosed clinically already at young age, but had never been confirmed by genetic testing.

Conventional karyotyping and FISH analysis with a locus-specific probe yielded normal results [46,XX.ish 22q11(D22S1660×2)]. Oligonucleotide-based array-CGH analysis of genomic DNA from an EDTA blood sample was conducted using CGX-HD™ array (Perkin Elmer). Female genomic DNA by Promega was used as reference. The CGX-HD™ array contains 180K oligonucleotides but does not cover regions specific to centromeres, heterochromatin (1, 9, 16, Y), and the short arms of the acrocentric chromosomes (13–15, 21, 22). Data were analyzed using CytoGenomics 2.5 (Agilent) and Genoglyphix 3.0 (Perkin Elmer) software with annotations of Genome Build 37/hg19. The achieved practical resolution is ~50 kb.

The array-CGH analysis detected a gain (microduplication) of about 246 kb in the genomic region 22q11.22, arr[GRCh37] 22q11.22(22320654_22566333)×3 [ISCN, 2016]. This gain includes the 5' region of the DNA topoisomerase III beta gene (*TOP3B;* MIM 603582). The breakpoints in this case do not localize within "classical" low-copy repeats (LCRs). The gain is located to the distal part of the genomic region between LCR22D–E (genomic coordinates of LCRs according to Mikhail et al. [2014]).

Since familial cases of duplication syndrome 22q11.2 are probably more common than in the deletion syndrome (for example, 11 out of 12 cases were inherited in Coppinger et al. [2009], 70% in Pinchefsky et al. [2017], and most cases as well in Wincent et al. [2010]), we initiated genetic testing of family members. Only her father agreed to be tested. He did not show any copy number change in the quantitative PCR analysis except for the control amplicon located outside the aberrant region detected in his daughter (hg19, chr22:22,221,601–22,221,683). This variant is not present in his daughter and represents a clinically not relevant variant.

Discussion

The less severe clinical phenotype of the 22q11.2 duplication syndrome compared to the 22q11.2 deletion syndrome may be a reason for the duplication syndrome being underdiagnosed to date. Besides the challenging clinical diagnosis, there is in addition a technical reason since these duplications are not detectable by conventional cytogenetics and FISH analysis which used to be the standard diagnostic methods. Using molecular karyotyping techniques (array-CGH and SNP arrays) more cases will be detected and enable a genotype-phenotype correlation.

Due to non-allelic homologous recombination between LCRs (LCR22A–H) at the 22q11.2 locus, recurrent CNVs occur more frequently, with reciprocal deletions or duplications between LCR22A and LCR22D being the most common recombinants [Burnside, 2015]. Besides the more common typical ~3-Mb microduplications or microdeletions (LCR22A–D), atypical duplications and deletions of smaller or larger regions or further distal than LCR22D (MIM 611867) with differing breakpoints in other LCRs have been reported [Fagerberg et al., 2013]. In the review by Burnside [2015], CNVs at the 22q11.2 locus are classified and a standardized nomenclature for the deletions is suggested, that is, proximal deletions (common proximal breakpoint in LCR22A), central

("nested") deletions, and distal deletions type I–III. Atypical duplications have been classified in Pinchefsky et al. [2017] within 3 groups (LCR F–H, LCR E–G/H, and LCR D–F/G), but showing no correlation with any phenotype. Ou et al. [2008] proposed a more detailed molecular characterization for a clearer identification of the region.

The duplication detected in our patient, which is the smallest described so far, resembles the ~252-kb microduplication described by Tarsitano et al. [2014]. In this published case the mother is carrier of the duplication. In addition, this patient carries a second CNV (~142-kb duplication in 8q22.1) which was inherited from the father. Clinically this patient showed similar phenotypes like our patient (Table 1): macrocephaly at birth and at 5 years of age, overgrowth as an adolescent, and facial dysmorphic features. In addition, the boy was diagnosed with mild cognitive impairment and attention-deficit hyperactivity disorder. Notably, we did not identify any additional significant CNVs in our patient. Nevertheless our patient shows a more severe phenotype with the exception of cognitive impairment, resembling in many symptoms the typical duplication and deletion syndrome. A heart defect is present, whereas none of 16 patients with a distal 22q11.2 duplication had a congenital heart defect [Wincent et al., 2010]. Moreover, a nasal speech, kidney abnormalities, and hypothyreosis, presented by our patient, are further typical clinical signs in patients with 22q11.2 duplications and deletions.

There are reports about VACTERL (vertebral defects, anorectal malformation, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities) association in 22q11.2 duplication syndrome [Schramm et al., 2011; Nguyen et al., 2017]. However, our patient only presented 3 of the 6 features: cardiac defects, renal anomaly, and limb abnormality (coxa valga). Vertebral defects have not been investigated in detail, but hyperkyphosis may be a fourth feature.

We conclude that also small rearrangements with atypical breakpoints can cause the clinical picture of the 22q11.2 duplication syndrome as described in larger and typical 22q11.2 duplication patients. We can exclude that quite frequently occurring additional CNVs could have caused the observed phenotype. While in the patient reported by Tarsitano et al. [2014] also the 8q22.1 region could have contributed to the phenotype, our patient showed a similar clinical picture with additional symptoms without a "second hit." The male patient's father in Tarsitano et al. also had macrocephaly, however, which could point to the 8q22.1 duplication to be the reason, which is common to both.

Unfortunately, the mother of our patient was not available for testing to exclude a maternally inherited duplication, and we have no relevant clinical information about her. Our patient could not remember any dysmorphic features or other symptoms of her. In Tarsitano et al. [2014], the mother with the same duplication had only mild dysmorphic facial features, showing again, that due to reduced penetrance there is no direct link from the duplication to the phenotype, that is, a rather or totally normal phenotype of parental carriers.

Tarsitano et al. [2014] mention 2 unpublished cases (DECIPHER database 251380 and 257341; https://decipher.sanger.ac.uk/) with similar duplications, one de novo duplication encompassing the complete *TOP3B* gene (MIM *603582) with mental retardation and microcephaly, the other with no phenotypic or inheritance information. In the case of a deletion with similar length to our duplication (268 kb) of chromosome 22q11.22 including *TOP3B* and almost identical location (genomic coordinates 22,311,348–22,578,983), autism, cognitive impairment, behavioral problems, and dysmorphic features have been reported [Kaufman et al., 2016]. This patient did not show overgrowth at the age of 11 years and no macrocephaly at birth like the 2 patients with the duplication of this genomic area. Overgrowth has so far not been published in other 22q11.2 duplication patients. Macrocephaly was seen in 21% out of 30 patients [Pinchefsky et al., 2017]. A smaller deletion than that described by Kaufman et al. [2016], also including the *TOP3B* gene, was reported to be associated with a similar phenotype with learning difficulties [Tan et al., 2011]. In addition, another 240-kb deletion of chromosome 22q11.22 disrupting *TOP3B,* reported in a Northern Finnish sub-isolate, leads to intellectual deficits and was found to be associated with schizophrenia if present in homozygous form [Stoll et al., 2013]. Deletion of this region seems to lead to more similar phenotypes than the duplication, however.

In conclusion, we report a second case of a very small 22q11.2 microduplication, which is with 246 kb the smallest reported to date. While information is rare about symptoms in atypical duplications of chromosome 22q11.2, this report increases the spectrum of known cases also showing, that "typical" signs for a 22q11.2 CNV like heart defect, kidney and endocrinological anomalies, and nasal speech can be present in an atypical duplication without additional clinically significant CNVs.

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Statement of Ethics

The described patient has given written informed consent to publish her case including publication of her images. The MWT-B test was performed as part of the study „Untersuchung molekularbiologischer und hirnfunktioneller Charakteristika seltener genetischer Syndrome im Hinblick auf kinder-, jugend- und erwachsenenpsychische Komorbiditäten" that was approved by the committee on human research of the University of Wuerzburg (study number 76/14). Research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.F. examined and treated the patient as a medical doctor, E.K. performed the genetic analyses, and both authors wrote the manuscript.

References

Amelsvoort TV, Denayer A, Boermans J, Swillen A. Psychotic disorder associated with 22q11.2 duplication syndrome. Psychiatry Res. 2016; 236:206–7.

Burnside RD. 22q11.21 Deletion Syndromes: A Review of Proximal, Central, and Distal Deletions and Their Associated Features. Cytogenet Genome Res. 2015;146(2):89–99.

Coppinger J, McDonald-McGinn D, Zackai E, Shane K, Atkin JF, Asamoah A, et al. Identification of familial and de novo microduplications of 22q11.21-q11.23 distal to the 22q11.21 microdeletion syndrome region. Hum Mol Genet. 2009;18(8):1377–83.

Fagerberg CR, Graakjaer J, Heinl UD, Ousager LB, Dreyer I, Kirchhoff M, et al. Heart defects and other features of the 22q11 distal deletion syndrome. Eur J Med Genet. 2013;56(2):98–107.

Hoeffding LK, Trabjerg BB, Olsen L, Mazin W, Sparsø T, Vangkilde A, et al. Risk of Psychiatric Disorders Among Individuals With the 22q11.2 Deletion or Duplication: A Danish Nationwide, Register-Based Study. JAMA Psychiatry. 2017;74(3):282–90.

ISCN 2016. An International System for Human Cytogenomic Nomenclature. McGowan-Jordan J, Simons A, Schmid M, editors. Cytogenet Genome Res. 2016;149(1-2):1–140.

Kaufman CS, Genovese A, Butler MG. Deletion of TOP3B Is Associated with Cognitive Impairment and Facial Dysmorphism. Cytogenet Genome Res. 2016;150(2):106–11.

McDonald-McGinn DM, Sullivan KE, Marino B, Philip N, Swillen A, Vorstman JA, et al. 22q11.2 deletion syndrome. Nat Rev Dis Primers. 2015;1:15071.

Mikhail FM, Burnside RD, Rush B, Ibrahim J, Godshalk R, Rutledge SL, et al. The recurrent distal 22q11.2 microdeletions are often de novo and do not represent a single clinical entity: a proposed categorization system. Genet Med. 2014;16(1):92–100.

Nguyen LT, Fleishman R, Flynn E, Prasad R, Moulick A, Mesia CI, et al. 22q11.2 microduplication syndrome with associated esophageal atresia/tracheo-esophageal fistula and vascular ring. Clin Case Rep. 2017;5(3):351–6.

Olsen L, Sparsø T, Weinsheimer SM, Dos Santos MBQ, Mazin W, Rosengren A, et al. Prevalence of rearrangements in the 22q11.2 region and population-based risk of neuropsychiatric and developmental disorders in a Danish population: a case-cohort study. Lancet Psychiatry. 2018;5(7):573–80.

Ou Z, Berg JS, Yonath H, Enciso VB, Miller DT, Picker J, et al. Microduplications of 22q11.2 are frequently inherited and are associated with variable phenotypes. Genet Med. 2008; 10(4):267–77.

Pinchefsky E, Laneuville L, Srour M. Distal 22q11.2 Microduplication: Case Report and Review of the Literature. Child Neurol Open. 2017;4: 2329048X17737651.

Portnoi MF. Microduplication 22q11.2: a new chromosomal syndrome. Eur J Med Genet. 2009;52(2-3):88–93.

Schneider M, Debbané M, Bassett AS, Chow EW, Fung WL, van den Bree M, et al. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. Am J Psychiatry. 2014;171(6):627–39.

Schramm C, Draaken M, Bartels E, Boemers TM, Aretz S, Brockschmidt FF, et al. De novo microduplication at 22q11.21 in a patient with VACTERL association. Eur J Med Genet. 2011;54(1):9–13.

Stoll G, Pietiläinen OPH, Linder B, Suvisaari J, Brosi C, Hennah W, et al. Deletion of TOP3β, a component of FMRP-containing mRNPs, contributes to neurodevelopmental disorders. Nat Neurosci. 2013;16(9):1228–37.

Tan TY, Collins A, James PA, McGillivray G, Stark Z, Gordon CT, et al. Phenotypic variability of distal 22q11.2 copy number abnormalities. Am J Med Genet A. 2011;155A(7): 1623–33.

Tarsitano M, Ceglia C, Novelli A, Capalbo A, Lombardo B, Pastore L, et al. Microduplications in 22q11.2 and 8q22.1 associated with mild mental retardation and generalized overgrowth. Gene. 2014;536(1):213–6.

Van Campenhout S, Devriendt K, Breckpot J, Frijns JP, Peeters H, Van Buggenhout G, et al. Microduplication 22q11.2: a description of the clinical, developmental and behavioral characteristics during childhood. Genet Couns. 2012;23(2):135–48.

Wenger TL, Miller JS, DePolo LM, de Marchena AB, Clements CC, Emanuel BS, et al. 22q11.2 duplication syndrome: elevated rate of autism spectrum disorder and need for medical screening. Mol Autism. 2016;7:27.

Wincent J, Bruno DL, van Bon BW, Bremer A, Stewart H, Bongers EM, et al. Sixteen New Cases Contributing to the Characterization of Patients with Distal 22q11.2 Microduplications. Mol Syndromol. 2010;1(5):246–54.

Yu A, Turbiville D, Xu F, Ray JW, Britt AD, Lupo PJ, et al. Genotypic and phenotypic variability of 22q11.2 microduplications: An institutional experience. Am J Med Genet A. 2019; 179(11):2178–89.