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.
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.

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 psychiatric 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.
Case Report 22q11.2 Duplication

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 Pinchesky 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

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 70 (5 years)                      |
|                                | IQ 101 (33 years, MWT-B)      |                                      |
| 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                  | Hypertelorism                        |
|                                | Broad nose                    | Broad nose                           |
|                                | Dysplastic ears                | Large ears                           |
|                                | Prominent forehead            | 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.

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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 [Winston 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.
Case Report 22q11.2 Duplication

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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 molekular-biologischer 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.

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