Distal 3p Duplication and 22q13.3 Deletion with Severe Hypotonia Originating from a Paternal Balanced Translocation (3;22)

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Established Facts

- Balanced translocations may lead to unbalanced gametes in meiosis, which in turn cause unbalanced karyotypes in the offspring.
- In the literature, there are cases with 3p duplication *or* 22q13 deletion.

Novel Insights

- This is the first case with 3p duplication *and* 22q13 deletion.
- Up to date, there is no report on the phenotype of distal 3p duplication and 22q13 deletion.

Keywords

Chromosomal translocation · Hypotonia · Unbalanced segregation · 3p duplication · 22q13 deletion

Abstract

In this study, we present a case with distal 3p duplication and 22q13.3 deletion due to unbalanced meiotic segregation in her father carrying a balanced translocation. The 2-month-old girl was examined for her severe hypotonia, developmental delay, and mild dysmorphic appearance. Clinical features include broad forehead, hypertelorism, laterally extended eyebrows, long eyelashes, a depressed nasal root, bifid nasal

tip, long philtrum, thin lips, posteriorly rotated ears, short neck, partial syndactyly of the right hand (fingers 3, 4), and partial syndactyly of the right foot (toes 2, 3). After examination, the final karyotype was reported as: 46,XX,der(22)del(22)(qter)dup(3)(p22pter), and the array-CGH results showed arr[GRCh37] 3p26.3p22.1(93949_41518607)×3 and arr[GRCh37] 22q13.31q13.33(44554083_51224252)×1. The mother has a 46,XX karyotype, and her father carries a balanced translocation, 46,XY,t(3;22)(p26.3;q13.3). This is the first case with a distal 3p duplication and 22q13.3 deletion with severe hypotonia and developmental delay.

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Fig. 1. Facial appearance of the proband.

Fig. 2. Unilateral partial syndactyly of toes 2 and 3.

Chromosomal abnormalities are divided into numerical and structural irregularities and may affect both autosomal and sex chromosomes [Garzo et al., 2020]. Translocations are the most frequent structural chromosome abnormality, with a frequency of 1/500 [Garzo et al., 2020]. Translocations are divided into 2 groups, balanced and unbalanced, according to loss or gain of genetic material. If there is loss or gain of material, the translocation is considered unbalanced. However, if there is no gain or loss, the translocation is considered to be balanced. Reciprocal translocations occur when the broken parts of nonhomologous chromosomes mutually rejoin [Wang et al., 2020]. Balanced reciprocal translocation carriers generally have a normal phenotype, but they may have recurrent miscarriages or unbalanced gametes. However, unbalanced gametes may appear as a result of the pairing between derivative chromosomes and their normal homologs. In the offspring, phenotypic effects may be observed depending on whether there is partial monosomy or partial trisomy.

Translocations, although not yet known, are based on a homologous recombination mechanism [Boué and Galano, 1984]. It has been reported that a chromosomal transformation is associated with 2 different mechanisms due to double-chain breaks and errors during their repair process [Iwarsson et al., 2000]. Exogenous agents, such as ionizing radiation and chemotherapeutic drugs, and endogenous mechanical stress may cause double-chain breaks [Lee et al., 2019].

Balanced translocation carriers may have healthy offspring that are karyotypically normal or carriers of the same parental balanced translocation, but these offspring

are at increased risk of having gametes with unbalanced chromosome abnormalities, leading to miscarriage or abnormal embryonic, fetal, and postnatal development.

Thus, genetic counseling must be offered to these couples to make them aware of their reproductive risk and to plan an individualized prenatal diagnostic approach.

Here, we present a female patient with severe hypotonia and developmental delay, carrying trisomy 3p26.3p22.1 and monosomy 22q13.31q13.33 with a phenotypically normal father carrying a t(3;22)(p26.3;q13.3) balanced reciprocal translocation. This is the first case in the literature with a 3p26.3p22.1 duplication and a 22q13.31q13.33 deletion.

Case Report

We report on a hypotonic and dysmorphic 2-month-old girl, who was referred to our clinic from a pediatric intensive care unit. She is the first child (first pregnancy) of nonconsanguineous parents. In the prenatal history, the neural tube defect risk was increased in the third-trimester screening test, and bilateral pelvictasia was seen in the prenatal ultrasound. She was born at term via cesarean section due to suspected asphyxia. Her birth weight was 3,850 gr (90–95th percentile); birth length and the occipitofrontal circumference were not reported. After birth, she was admitted to a neonatal intensive care unit.

Upon physical examination, her weight was 4,500 gr (0–25th percentile), length was 55 cm (0–25th percentile), and the occipitofrontal circumference was 39 cm (50–75th centile). She had severe hypotonia with feeding difficulties, growth retardation, respiratory difficulties, and prolonged jaundice, and was hospitalized for an extended period. She had a broad forehead, hypertelorism, laterally extended eyebrows, long eyelashes, a depressed nasal root, bifid nasal tip, long philtrum, thin lips, posteriorly rotated ears, a short neck, partial syndactyly of the right hand (fingers 3, 4), and

Fig. 3. Karyotype of the proband showing 46,XX,der(22)del(22)(qter)dup(3)(p22pter).

partial syndactyly of the right foot (toes 2, 3) (Fig. 1, 2). Echocardiography showed an atrial septal defect and patent ductus arteriosus. A brain MRI was not performed due to the higher risk of anesthesia complications. Transfontanelle ultrasonography revealed no pathology.

Methods and Results

Heparinized peripheral blood was taken from the patient for cytogenetic analysis. For conventional karyotyping, standard 72-h lymphocyte culture and harvesting was performed. The Leishmann-Pancreatin-banding method was used. The results were reported according to the International System for Human Cytogenetic Nomenclature (ISCN 2016). The patient's final karyotype was 46,XX,der(22)del(22)(qter)dup(3)(p22pter) (Fig. 3). The parental chromosome analysis results showed that the mother has a 46,XX karyotype, and the father has a 46,XY,t(3;22)(p26.3;q13.3) karyotype (Fig. 4).

For FISH analysis, slides were prepared using peripheral blood specimens. We used Aquarius® microdeletion syndrome probes, DiGeorge/VCFS TUPLE 1 and 22q13.3 Deletion Syndrome Probe Combination (Cytocell Ltd., Cambridge, UK). FISH was performed according to the manufacturer's instructions. A total of 200

interphase cells were analyzed for each sample with images captured and stored using Applied Imaging/Cytovision system. Final results were reported using the cut-offs established in the laboratory for each of the probes tested, and a 22q13.3 deletion was detected in the proband (Fig. 5).

Whole-genome microarray-based hybridization was performed on an Agilent 4×180K CGH+SNP (Agilent Technologies, Santa Clara, CA, USA) array slide according to the manufacturer's instructions. For analysis and visualization, Feature Extraction software and Cytogenomics version 4.0.3.12 software (Agilent Technologies) were used and evaluation was done based on UCSC build 37 (hg19). It revealed a clinically significant trisomy, arr[GRCh37] 3p26.3p22.1(93,949–41,518,607)×3 (41,425 kb in size), and monosomy, arr[GRCh37] 22q13.31q13.33(44,554,083–51,224,252)×1 (6,670 kb in size) (Fig. 6; Table 1).

Discussion

The patient in our study was first referred to our department for her severe hypotonia and developmental delay. In our clinic, she was diagnosed with an abnormal karyotype, including derivative chromosome 22. A pa-

Fig. 4. Karyotype of the proband's father showing 46,XY,t(3;22)(p26.3;q13.3).

Fig. 5. FISH analysis of the proband with a 22q13.3 deletion. (N25, 22q11.2, red signal; N85A3, 22q13.3, green signal).

Fig. 6. Array-CGH result of the proband revealing arr[GRCh37] 3p26.3p22.1(93949_41518607)×3 and arr[GRCh37] 22q13.31q13.33(44554083_51224252)×1.

rental karyotype analysis revealed that the father had a balanced translocation t(3;22)(p26.3;q13.3). Balanced reciprocal translocation carriers are phenotypically normal but have a significantly increased risk of producing chromosomally unstable gametes [Benet et al., 2005]. During meiosis, balanced reciprocal translocation chromosomes form a quadrivalent shape and match with the homologous segment. Segregation can take place in 5 different ways: alternate (normal or balanced gametes are produced), adjacent 1, adjacent 2, 3:1, and 4:0 (all gametes are unstable). Half of the gametes formed in alternate decomposition are balanced chromosome carriers, whereas the other half has normal chromosome content. Adjacent gametes formed as a result of 1 and 2 segregation can form partial trisomic products with unbalanced chromosome content [Yakut et al., 2006]. Carriers of reciprocal translocations always are at risk of producing unbalanced gametes. This risk is equal for both parental carriers. Balanced translocation carriers may have healthy offspring (both karyotypically normal or carriers of the same pa-

rental balanced translocation) and fetuses with unbalanced chromosome abnormalities, lead to miscarriage or syndromic babies.

To date, only one study has reported an unbalanced segregation of 3;22 balanced translocation from one parent [Zhang K et al., 2018]. The authors reported a 4-generation family with 6 cases carrying t(3;22)(q28;q13) and a normal phenotype. In the same family, 3 cases carrying 3q28q29 duplication and 22q13.33 deletion had severe intellectual disability and developmental delay. In this report, our case has a different karyotype, 46,XX,der(22)del(22)(qter)dup(3)(p22pter), manifesting in a 3p26.3p22.1 duplication and a 22q13.31q13.33 deletion. Two more studies reported patients with chromosomal abnormalities involving the short arm of chromosome 3 at 3p25 and the long arm of chromosome 22 at 22q11. Respectively, Dundar et al. [2010] reported a patient with developmental delay and a de novo karyotype, 45,X,der(3)t(3;22)(p25;q11),-22, while Faed et al. [1987] described a child with de novo monosomy for chromosomes 22

Table 1. The genes in loss and gain regions for the current case

Chromosome	Cytoband	Start	Stop	Probes	Gain	Loss	Genes
Chr3	p26.3p22.1	93,949	41,518,607	1,575	0.595708	0	<p>CHL1, CHL1-AS1, LINC01266, CNTN6, CNTN4, CNTN4-AS2, CNTN4-AS1, IL5RA, TRNT1, CRBN, LRRN1, SETMAR, SUMF1, ITPRI-AS1, ITPRI, EGOT, BHLHE40-AS1, BHLHE40, ARL8B, EDEM1, MIR4790, GRM7-AS3, GRM7, GRM7-AS2, GRM7-AS1, LOC101927394, LMCD1-AS1, LMCD1, LINC00312, SSUH2, CAV3, OXTR, RAD18, SRGAP3, LOC101927416, SRGAP3-AS3, THUMPD3, THUMPD3-AS1, SETD5, LHFPL4, MTMR14, CPNE9, BRPF1, OGG1, CAMK1, TADA3, ARPC4, ARPC4-TTL3, TTL3, RPUSD3, CIDEC, JAGN1, IL17RE, IL17RC, CRELD1, PRRT3, PRRT3-AS1, EMC3, EMC3-AS1, LOC401052, CIDEC, FANCD2, FANCD2OS, BRK1, VHL, IRAK2, TATDN2, GHRLOS, LINC00852, GHRL, SEC13, ATP2B2, MIR378B, MIR885, ATP2B2-IT2, LINC00606, SLC6A11, SLC6A1, SLC6A1-AS1, HRH1, ATG7, VGLL4, TAMM41, SYN2, TIMP4, PPARG, TSEN2, MKRN2OS, MKRN2, RAF1, TMEM40, CAND2, RPL32, SNORA7A, IQSEC1, NUP210, HDAC11-AS1, HDAC11, FBLN2, SNORA93, LINC00620, WNT7A, FGD5P1, TPRXL, CHCHD4, TMEM43, XPC, LSM3, LINC01267, SLC6A6, GRIP2, CCDC174, C3orf20, LOC152274, FGD5, FGD5-AS1, NR2C2, MRPS25, RBSN, COL6A4P1, CAPN7, SH3BP5-AS1, SH3BP5, METTL6, EAF1, COLQ, MIR4270, HAC1, BTDD, ANKRD28, MIR563, GALNT15, DPH3, OXNAD1, RFTN1, LINC00690, DAZL, PLCL2, MIR3714, TBC1D5, LOC339862, SATB1, SATB1-AS1, KCNH8, MIR4791, EFHB, RAB5A, PP2D1, KAT2B, MIR3135A, SGOL1, SGOL1-AS1, LOC101927829, VENTXP7, ZNF385D, ZNF385D-AS1, ZNF385D-AS2, UBE2E2, MIR548AC, UBE2E1-AS1, UBE2E1, NKIRAS1, RPL15, NR1D2, LINC00691, THRB, LOC101927854, THRB-AS1, MIR4792, RARB, LOC105376997, TOP2B, MIR4442, NGLY1, OXSM, LINC00692, LRRC3B, NEK10, SLC4A7, EOMES, LOC100996624, CMC1, AZI2, ZCWPW2, LINC00693, RBMS3-AS3, RBMS3, RBMS3-AS1, TGFB2, GADL1, MIR466, STT3B, OSBPL10, OSBPL10-AS1, ZNF860, GPD1L, CMTM8, CMTM7, CMTM6, DYNCL11, CNOT10, TRIM71, CCR4, GLB1, TMPPE, CRTAP, SUSDS, FBXL2, UBPI, CLASP2, PDCD6IP, LOC101928135, ARPP21, MIR128-2, STAC, DCLK3, TRANK1, EPM2AIP1, MLH1, LRRFIP2, GOLGA4, C3orf35, ITGA9, ITGA9-AS1, CTDSPL, MIR26A1, VILL, PLCD1, DLEC1, ACAA1, MYD88, OXSR1, SLC22A13, SLC22A14, XYLB, ACVR2B-AS1, ACVR2B, EXOG, SCN5A, SCN10A, SCN11A, WDR48, GORASP1, TTC21A, MIR6822, CSRNPI, XIRPI, CX3CR1, CCR8, SLC25A38, RPSA, SNORA6, SNORA62, MOBP, MYRIP, EIF1B-AS1, EIF1B, ENTPD3, ENTPD3-AS1, RPL14, ZNF619, ZNF620, ZNF621, CTNNB1, ULK4</p>
Chr22	q13.31q13.33	44,554,083	51,224,252	313	0	-0.917333	<p>PARVB, PARVG, KIAA1644, LOC101927526, LDOC1L, LINC00207, LINC00229, PRR5, PRR5-ARHGAP8, ARHGAP8, PHF21B, NUP50-AS1, NUP50, KIAA0930, MIR1249, UPK3A, FAM118A, SMC1B, RIBC2, FBLN1, LINC01589, ATXN10, MIR4762, WNT7B, LOC730668, LINC00899, PRR34, PRR34-AS1, MIRLET7BHG, MIR3619, MIRLET7A3, MIR4763, MIRLET7B, PPARA, CDPF1, PKDREJ, TTC38, GTSE1-AS1, GTSE1, TRMU, CELSR1, GRAMD4, CERK, TBC1D22A, TBC1D22A-AS1, LL22NC03-75H12.2, LINC00898, LOC284930, MIR3201, FAM19A5, LOC284933, MIR4535, LINC01310, C22orf34, MIR3667, BRD1, ZBED4, ALG12, CRELD2, PIM3, MIR6821, IL17REL, MLC1, MOV10L1, PANX2, TRABD, SELO, TUBGCP6, HDAC10, MAPK12, MAPK11, PLXNB2, DENND6B, PPP6R2, SBF1, ADM2, MIOX, LMF2, NCAPH2, SCO2, TYMP, ODF3B, KLHDC7B, SYCE3, CPT1B, CHKB-CPT1B, CHKB, CHKB-AS1, MAPK8IP2, ARSA, SHANK3, LOC105373100, ACR, RPL23AP82, RABL2BUPK3A, FAM118A, SMC1B, RIBC2, FBLN1, LINC01589, ATXN10, MIR4762, WNT7B, LOC730668, LINC00899, PRR34, PRR34-AS1, MIRLET7BHG, MIR3619, MIRLET7A3, MIR4763, MIRLET7B, PPARA, CDPF1, PKDREJ, TTC38, GTSE1-AS1, GTSE1, TRMU, CELSR1, GRAMD4, CERK, TBC1D22A, TBC1D22A-AS1, LL22NC03-75H12.2, LINC00898, LOC284930, MIR3201, FAM19A5, LOC284933, MIR4535, LINC01310, C22orf34, MIR3667, BRD1, ZBED4, ALG12, CRELD2, PIM3, MIR6821, IL17REL, MLC1, MOV10L1, PANX2, TRABD, SELO, TUBGCP6, HDAC10, MAPK12, MAPK11, PLXNB2, DENND6B, PPP6R2, SBF1, ADM2, MIOX, LMF2, NCAPH2, SCO2, TYMP, ODF3B, KLHDC7B, SYCE3, CPT1B, CHKB-CPT1B, CHKB, CHKB-AS1, MAPK8IP2, ARSA, SHANK3, LOC105373100, ACR, RPL23AP82, RABL2B</p>

(q11pter) and 3 (p25pter) with phenotypical features of DiGeorge syndrome.

22q11.2 deletion syndrome (also known as DiGeorge syndrome) is one of the most common microdeletion syndromes in the community. Its prevalence is known as 1/4,000, but with new studies, it is stated that the 22q11.2 deletion is more common than estimated [Grati et al., 2015]. As a result of the gene defect at 22q11.2, there is an abnormal development of the 3rd and 4th pharyngeal pouch derivatives including the thymus gland, parathy-

roid glands, aorta, lips, and lower parts of the ears. Thus, most 22q11.2 deletion syndromes manifest with thymus hypoplasia/aplasia, immunodeficiency, cardiovascular anomaly, characteristic facial appearance, intellectual disability, and hypoparathyroidism; behavioral abnormalities, learning difficulties, and psychiatric problems are also common. However, the 22q11.2 deletion syndrome clinical phenotype may be extremely heterogeneous [Ryan et al., 1997], making the diagnosis more difficult in some patients, especially if there is no underlying

congenital heart disease, and the diagnosis may be made in a later stage of life. There is a cluster of low copy repeats (LCRs) in chromosome 22. These LCRs, which facilitate recombination, cause microdeletion and microduplication due to errors that may arise in mutual pairing. Most of the velocardiofacial syndrome/DiGeorge syndrome cases have a deletion region of 1.5–3 Mb, containing 24–30 genes. Because of the variability in deletions due to LCRs, there may also be variability in clinical findings. Differently from the reported case, our proband has a deletion of the distal long arm of chromosome 22 at 22q13.3 including the *SHANK3* gene, coding for a protein involved in postsynaptic densities of excitatory synapse and in neuronal signal transmission. 22q13.3 deletions involving the *SHANK3* gene have been associated with Phelan-McDermid syndrome (OMIM 606232) [Phelan et al., 2001]. The syndrome is characterized by neurological disorders, including developmental disorders, intellectual disability, speech delay, and neonatal hypotonia. More than 50% of the patients show autism or autism-like behaviors; and therefore, it can be classified as a syndromic form of autism spectrum disorders [Görker et al., 2017]. Dysmorphic facial features include dolichocephaly, thick eyebrows, flat midface, broad nose root, bulbous nasal tip, deep-set eyes, ptosis, long lashes, plump cheeks, and prominent ears. Other common physical features include large chubby hands, dysplastic toenails, and a higher pain threshold. There is no life-threatening anomaly. Treatments that increase muscle tone, coordination, strength, cognitive skills, and communication skills are sufficient for many patients.

Although the current case has both 22q13 deletion and 3p duplication, the girl showed some clinical features of 22q13 deletion due to severe neonatal hypotonia, developmental delay, ptosis, long lashes, and plump cheeks. However, regarding that 3p duplication has also been related to cognitive impairment, it is difficult to differentiate the contribution of each rearrangement (3p duplication rather than 22q13 deletion) to her global development and provide any prediction on her neurobehavioral phenotype.

Our proband's duplication at 3p26.3p22.1 (41,425 kb in size) includes several candidate genes for neurodevelopmental disorders such as *CHL1* (OMIM 607416), *CNTN4* (OMIM 607280), and *CNTN6* (OMIM 607220). The *CHL1* gene is highly expressed in peripheral and central nervous systems. It encodes a protein which is part of the L1 gene family and regulates brain cell migration and synaptogenesis. The *CNTN4* gene is important for neuronal function and encodes contactin 4, which is a cell adhesion molecule. In the central nervous system, *CNTN6*

is important for maintenance of neuronal networks. Due to neuronal affection of these genes, we may expect a more severe developmental delay in our patient, compared to Phelan-McDermid syndrome patients.

Chen et al. [2015] presented a 15-WG fetus carrying a distal 3p duplication and terminal 7q deletion with holoprosencephaly (cyclopia). Although holoprosencephaly is also reported in 10% of the 3p duplication syndrome cases [Siebert et al., 1990], our case did not show any brain abnormalities.

Cytogenetic analysis should be offered to parents having a child with complex chromosomal rearrangement and genetic counseling should be provided in order to assess a recurrence risk for chromosomal unbalanced translocations. In cases of parents carrying balanced translocation, the estimated risk is 10–15%. Balanced translocation carriers also have an increased risk of infertility, and recurrent pregnancy losses. This reveals the need for prenatal diagnosis in all subsequent pregnancies of parents with reciprocal translocation [Zhang L et al., 2018]. Pre-implantation genetic diagnosis is recommended to reciprocal translocation carriers as an alternative to prenatal diagnosis and termination of unbalanced fetuses as well as to reduce the number of spontaneous abortions. For these couples, it is of importance to know that the recurrence risk is the same for all further pregnancies and to emphasize that it is necessary to perform chromosome analysis in parents to reduce the risk.

Conclusion

In this study, we report on the first case with a distal 3p duplication and 22q13.3 deletion presenting with severe hypotonia and developmental delay. We aimed to present the phenotype of our patient to the literature and emphasize the importance to define the parental origin of such complex rearrangements and to provide genetic counseling for couples carrying balanced translocations.

Acknowledgment

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Statement of Ethics

Written informed consent form was obtained from the parents of the proband. Ethics approval was not required for this study.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.Y. made substantial contributions to the conception of the work, wrote the manuscript. E.I.A., E.A., and S.D. made substantial contributions to the analysis. N.A.C. and R.D. performed patient diagnosis and management, and revised the intellectual content. J.O. managed literature searching and revised the manuscript. H.G. ensured that the integrity of the whole work was appropriately investigated and resolved and gave approval of the final manuscript.

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