

Review Article

A novel mosaic 22q11.2 micro-duplication syndrome: clinical report and literature review. Cerebro-oculo-facio-urethrogenito-skeletal syndrome: de novo condition

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Abstract: 22q11.2 duplication syndrome (OMIM #608363) was first described by Edlmann in 1999 and later by other groups. The syndrome presented with clinically normal to varied spectrum of multisystem involvement. The 22q11.2 duplication syndrome in comparison to the 22q11.2 micro-deletion is a relatively rare condition which inherited autosomal dominantly or may occur as de novo condition. This article intends to present a mosaic 22q11.2 microduplication syndrome with novel cerebro-oculo-facio-urethrogenito-skeletal presentation and reviews the literature.

Keywords: 22q11.2, hypospadias, microduplication, microphthalmia, microcornea

Introduction

In 1999 Edlmann et al. reported a four years old patient with modest developmental and language retardation, velopharyngeal insufficiency with 22q11.2 microdeletion/duplication [1]. Four years later Ensenuer et al. described 22q11.2 microduplication as a new syndrome separating from DiGeorge/Velocardiofacial syndrome by implementing FISH analysis of 653 patients with clinical features of DiGeorge/Velocardiofacial syndrome [2] and later by other groups [3-5].

Chromosome 22q11.2 holds numerous region-specific low copy repeats that make it susceptible to DNA rearrangements [6, 7]. This leads to several genetic disorders, including Velocardiofacial syndrome/DiGeorge syndrome (VCF/DGS, #192430; MIM #188400), Cat-eye syndrome (MIM #115470), DER(22)t(11;22) (22) syndrome (MIM #609029), 22q11.2 distal microdeletion syndrome (MIM #611867), and

22q11.2 microduplication syndrome (dup22q11.2, MIM #608363) [8]. Deletion of 22q11 is the most common chromosome aberration ranks after trisomy 21, with an incidence of 1 in every 4000-6000 live births [9, 10].

The dup22q11 syndrome exhibits a broad phenotypic variability, ranging from no abnormalities to severe mental retardation with multiple congenital malformations [4, 10]. The most common reported ophthalmologic findings have included downslanting/upslanting palpebral fissures, ptosis [11-14], and also intellectual disability and neuropsychological problems was reported [15].

We report a case of dup22q11.2 syndrome covering variety of features which as far as the authors are aware have not been reported previously in the literature, namely: microcornea, microphthalmia, cataracts, bilateral cryptorchidism, penile curvature (ventral urethral chordee), ataxia with fine movements coordination



Figure 1. Facial appearance of the patient: left: Front, right: Profile.



Figure 2. The features mimicking Noonan syndrome: minimal webbed neck, mild short neck, wide-set nipples, mild pectus excavatum, kyphoscoliosis, winged scapula, genu valgum.

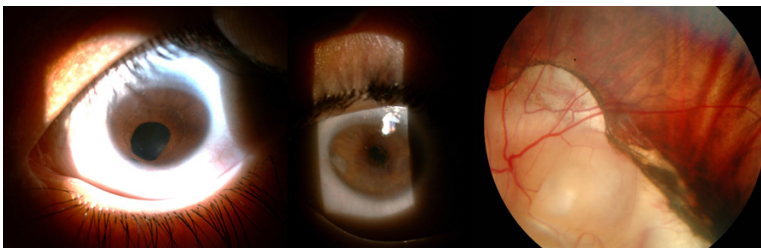


Figure 3. Asymmetric microcornea, left: Left eye, right: Right eye, middle: Coloboma.

difficulties, wide set nipples, superiorly placed eyebrows, long eyelashes, bushy eyebrows and synophrys, narrow forehead, inner strabismus,

dental abnormalities, pectus excavatum and some other skeletal abnormalities.

Case presentation

A 6 years old male patient was admitted to the pediatric surgery ward of our institution due to cryptorchidism, distal hypospadias and downward penile curvature (ventral urethral chordee). The physical examination of the patient was performed and the following data were recorded: weight 19 kg (21 percentile), height 108 cm (11 percentile), narrow forehead, flat face, tinny upper lip, superior placement of eyebrows, long eyelashes, bushy eyebrows and mild synophrys, downslanting palpebral fissures, inner strabismus, bilateral eyelid ptosis, asymmetric microcornea, left microphthalmia, micrognathia, low set ears, high arch palate, dental abnormalities, rhinophonia, bilateral cryptorchidism, downward penile curvature (ventral urethral chordee), hypospadias, minimal webbed neck, mild short neck, wide-set nipples, mild pectus excavatum, mild kypholordosis, mildly broad fingertips, abduction limited fingers 3, 4 and 5 of both hands, laterally curved positioned middle fingers of both hands without camptodactyly, winged right scapula, genu valgum, overlapped 2nd fingers of both feet, left hallus valgus, ataxia with fine movement coordination difficulties (**Figures 1, 2**).

Detailed ophthalmic examination of the patient demonstrated decreased left eye vision (finger count 30 cm), multiple opacities of anterior segment of left eye, papillary extensions into papillary area in left eye (**Figure 3**).

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Table 1. Ophthalmic findings

	Right	Left
Visual acuity	Normal	Decreased
Horizontal corneal diameter (Normal: ≥ 11 mm)	6 mm	7.5 mm
Corneal opacity	Multiple	Cortical cataract
Papillary extensions into the papillary area	Yes	No
Anterior chamber depth (Normal: ≥ 3.32 mm) [1, 2]	1.74 mm (decreased)	2.21 mm (normal)
Total chamber length (Normal: ≥ 22.58 mm) [1, 2]	17 mm (decreased)	21.93 mm (mildly decreased)
Colomba	Retinal	Retinal and inferior iris. Hyperplastic primary vitreous in fundus

1-Zhang Z-Y, et al. (2009), 2-Ojaimi E, et al. (2005).

Ophthalmic findings are summarized in **Table 1**. Audiometric examination showed no hearing impairment. The cardiac examination was in normal limits. Patient prenatal, natal and post-natal past history was not significant. He joined elementary school this year. We planned and performed the operation on penile curvature (ventral urethral chordee), distal hypospadias and cryptorchidism. The operation was satisfactory.

Family history

He is the first child of his mother from her first marriage. The father looks normal without any significant phenotypic abnormalities with negative family history regarding the present case. The patient's stepsister is a normal 4 years old girl and his mother is third child of a family with 10 children (M/F=6/4). Her two older brothers are single and looking healthy individuals. Fourth child is married and gave birth to two children who both underwent ophthalmic operation with unknown nature. Fifth child is a female with one healthy boy. Sixth and seventh children are male and both suffer from epilepsy. The seventh child also has a history of "lop-sided walking and falling down repeatedly". Eighth and ninth children are male, single without any major abnormalities. Tenth child is a 4 years old girl who suffers from scoliosis, stiffness of both elbow joint and difficulty of walking. We were unable to visit these individuals and all information was provided by the parents of the patient.

Laboratory findings

Complete blood count, fasting blood sugar, BUN, creatinine, aspartate aminotransferase and alanine transaminase, total protein and albumin, LDH, gamma glutamyl transferase, C-reactive protein, prothrombin time and International Normalized Ratio, anti-hepatitis Bs,

anti-hepatitis C, anti-HIV, T3, T4, TSH and routine 12 lead surface ECG were in normal range.

Radiological and ultrasound findings

Brain magnetic resonance study revealed normal 3rd, 4th and lateral ventricles without any abnormalities regarding the brain stem, corpus callosum, cerebellum and optic nerves. Left microphthalmia and coloboma, questionable hypoplastic hypophyse, mildly dilated left temporo-fronto-pareital sulci and a mild degree right side cortical atrophy pattern were found. Transthoracic echocardiographic findings were in normal limits. The post-op scrotal ultrasound examination showed both testis with homogeneous appearance, with bilaterally normal size without any abnormality regarding both epididymal and peritesticular structures. The abdominal ultrasound findings including hepatic and renal structures were in normal limits. The X-ray examination showed mild vertebral kyphoscoliosis, left hallus valgus with decreased calcaneal angle.

Denver developmental screening test (DDST)

The DDST demonstrated a personal developmental and social contact of a 4 years age child (mildly delayed), fine motor skill of 4^{6/12} years (lower normal limit), linguistic development of 5^{6/12} years (lower normal limit) and gross motor skill of a 4 years old (mildly delayed).

Chromosomal analyses

Single nucleotide polymorphism chromosomal microarray analysis (Affymetrix 750K) performed in an ISO 15189 approved Clinical Laboratory, using Chromosome Analysis Suite (ChAS) software. The result revealed two nearby tandem non mosaic 2277, 154 and 613, 894 kb interstitial duplication from 22q11.21 (18, 970, 561-21, 247, 715) to 22q11.21 (21,

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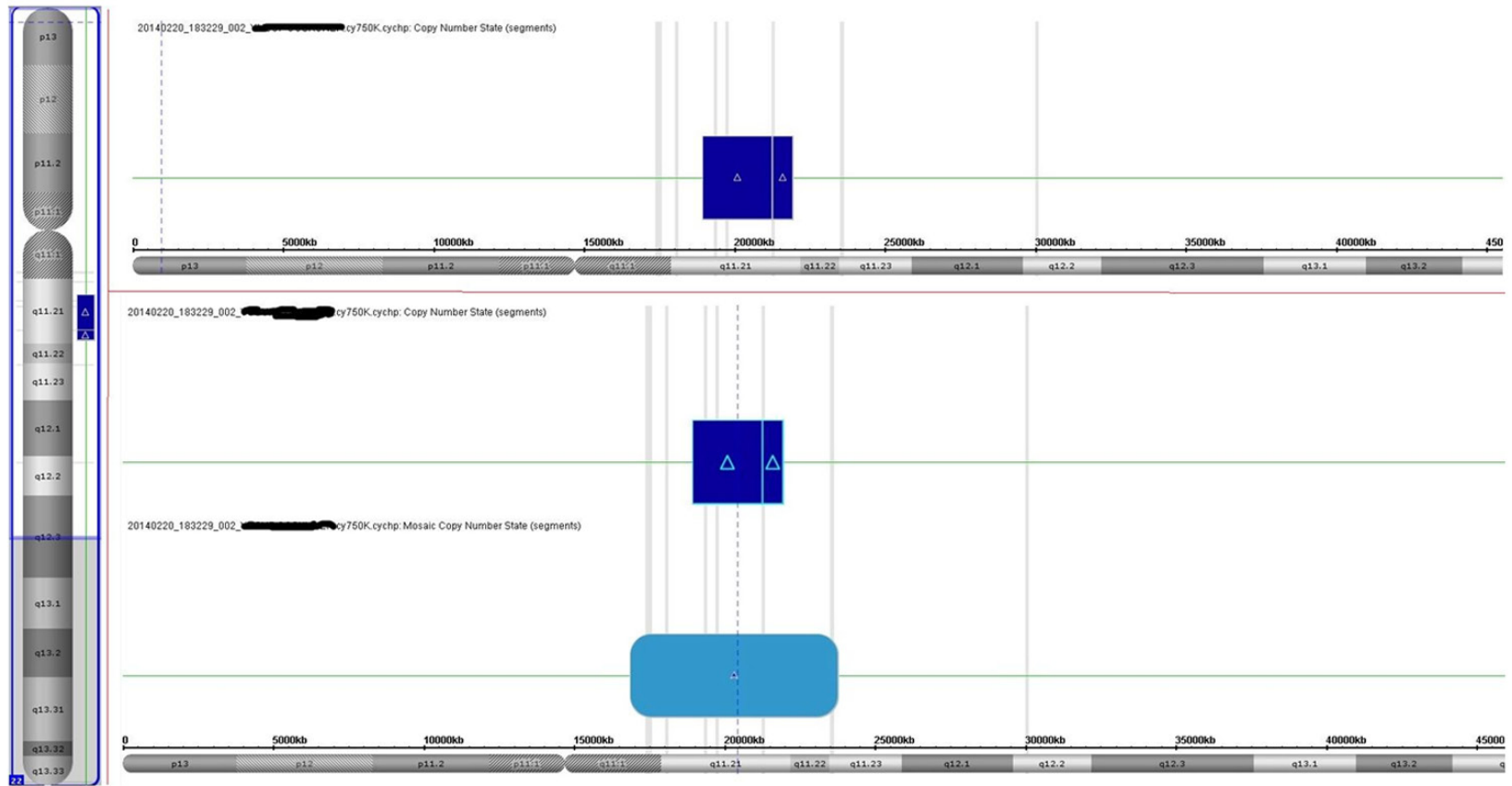


Figure 4. Chromosomal analysis. left: Partial karyogram of the array finding, upper right: Non mosaic neighboring two tandem duplications within 22q11.21, lower right: mosaic finding extending to nearby subbands.

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Table 2. Microarray findings and affected OMIM genes

Findings	Size	OMIM Genes
Arr [hg19] 22q11.21 (18, 970, 561-21, 247, 715)×3	2277,154	DGCR2 (600594), DGCR14 (601755), TSSK2 (610710), GSC2 (601845), SLC25A1 (190315), CLTCL1 (601273), HIRA (600237), MRPL40 (605089), UFD1L (601754), CDC45 (603465), CLDN5 (602101), SEPT5 (602724), GP1BB (138720), TBX1 (602054), GNB1L (610778), TXNRD2 (606448), COMT (116790), ARVCF (602269), DGCR8 (609030), TRMT2A (611151), RANBP1 (601180), ZDHHC8 (608784), RTN4R (605566), DGCR6L (609459), RIMBP3 (612699), ZNF74 (194548), SCARF2 (613619), MED15 (607372), PI4KA (600286), SERPIND1 (142360), SNAP29 (604202)
Arr [hg19] 22q11.21 (21, 301, 313-21, 915, 207)×3	613,894	CRKL (602007), LZTR1 (600574), THAP7 (609518), P2RX6 (608077), SLC7A4 (603752), BCRP2 (113630), RIMBP3C (612701), RIMBP3B (612700), HIC2 (607712), UBE2L3 (603721)

301, 313-21, 915, 207) both spanning in the same chromosomal subband (**Figures 3, 4**). An interesting finding was also observed; that the larger “mosaic” duplication was present spanning more than one subband-area within 22q11.21 to q11.22 (**Figure 4**).

The conventional chromosomal studies on the patient’s mother, father and healthy sister were negative for any gross abnormalities. Array findings of other family members were not available. The OMIM genes within selected regions are listed in **Table 2**.

Discussion

During the first visit of the patient, our first clinical impression was Wolf-Hirschhorn Syndrome due to findings such as hypertelorism, down-slanting palpebral fissures, epicanthal folds, strabismus, coloboma, ptosis, microphthalmia, microcornea, cataracts, cryptorchidism, hypospadias, hypoplastic widely spaced nipples, kyphoscoliosis, dental abnormalities. But the conventional chromosomal analysis and FISH analysis failed to confirm any abnormalities in chromosome 4. Clarke RA et al. first described a case of the association of Klippel-Feil syndrome, Tourette syndrome, motor stereotypies, and obsessive compulsive behavior, with chromosome 22q11.2 duplication syndrome, [16]. This child exhibited short neck with low posterior hairline, abnormal scapulae, and webbing of toes. Beside mild short and webbed neck, although our patient also demonstrated delayed growth, wide-set nipples, pectus excavatum, winged right scapula and hallus valgus-the findings that resemble the Noonan syndrome-we were unable to confirm such diagnosis associated with any gene mutation of PTPN11, KRAS, RAF1, SOS1. A patient with an interstitial inverted duplication of 22q11.2 and typical features of cat eye syndrome including coloboma, preauricular anomalies, heart defect, renal

anomalies, and anal atresia [17]. Our case also resembles LENZ syndrome by demonstrating cryptorchidism, hypospadias, joint mobility reduction, microcornea, microphthalmos, coloboma, ptosis, narrow forehead, short neck, webbed neck, microdontia, hypodontia; teeth, hypoplasia, peg shaped teeth, talipes valgus foot, kyphoscoliosis, growth delay.

In comparison to the 22q11.2 microdeletion, the dup22q11.2 syndrome is relatively rare condition which inherited autosomal dominantly or may occur at lesser ratio as de novo condition. Cotter et al. reviewed 372 patients and identified 30 individuals with 22q11.2 deletion (about 8.1%) but not any microduplication in this series [11]. In a series of 295 patients with clinical features associated with DG/VCFs and implemented cytogenetic and FISH testing, 12 (4%) had the 22q11.2 microdeletion and no microduplication of this region was identified [18]. Sivertsen et al. summarized the previously reported cases of cleft palate only (CPO) who carrying 22q11.2 duplications [15]. According to this report seven of the 35 (20%) cases of 22q11.2 duplications reported in the literature previously had CPO [1-5, 19, 20]. Nevertheless Sivertsen et al. studied 245 babies with CPO in Norway [15]. DNA was available from 174 patients, which 3 patients demonstrate 22-q11.2 deletions and none carried 22q11.2 duplications. Itsara et al. reported the results of their study of 2,500 individuals and identified 31 patients with 22q11.2 microduplications (about 1%) [12]. In a series of 204 patients, 29 (14.2%) was found presented chromosomal abnormalities. Of these 204 patients, 4 cases (2%) demonstrated microdeletion but any with duplication of the 22q11.2 region [21]. Coppinger et al. screened 22096 consecutive individuals with idiopathic mental retardation and/or congenital anomalies, who were submitted to Signature Genomic Laboratories for analysis. They found 18 individu-

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Table 3. Summary of the symptoms, involved organs and case numbers reported in the literature

Clinical findings	Reference ^{feature(case number)}
Growth or developmental delay, failure to thrive	2 ^(5 cases) , 6, 19 ^(2 cases) , 36 ^(2 cases) , 38, 39, 50 ^(11 cases) , 54
Dysmorphic features	2 ^{b,c(7 cases)} ,j(4 cases),a6,a8,mm(6 cases),r(2 cases),u(3 cases),h(7 cases),ee(2 cases),f(5 cases),g(2cases),s(4 cases),i(4 cases),gg(6 cases), 6 ^{f,mm} , 29 ^{h,i,u(2 cases)} ,gg(2 cases),s(2 cases),t(2 cases),v, 30 ^{s,u} , 31 ^{g,h,i,ee} ,33 ^{(2 cases),f,v,ee(3 cases),s} , 34 ^{s,u} , 36 ^{r,s(3cases),gg(3 cases),j(2 cases),mm(3 cases),g,ee,u(2 cases)} , 37 ^(2 cases) ,ee(2 cases),u,j(2 cases),v,a14, 38 ^{gg,s,h} , 39, 43 ^v , 44 ^g , 45 ^{c,d,f,h,i,j,r,u} , 47 ^{v,dd(5 cases)} , 48, 49 ⁱ , 50 ^{a11(9 cases)} , 50 ^(4 cases) , 51 ^{r,v} , 53 ^{b,d,f,g,h,i,j} , 56 ^{f,i,p,h,s}
Velopharyngeal insufficiency	2 ^{6 cases} , 6
Hearing loss	2 ^(5 cases) , 29, 33, 36, 47 ^(5 cases)
Eye anomalies	2 ^{cc} , a7 ^(3 cases) , 2 ^{a10(2 cases)} , 34 ^{cc} , 36 ^{cc} , 37 ^{a10} , 56 ^{k,n,o} , 57 ^y
Brain or SSS abnormality	38 ^{a12} , 44 ^z , 47 ^{z(3 cases)} , 50 ^z , c,v(3 cases),p(3 cases),r(5 cases), 51 ^z , 56 ^m
Cardiovascular Anomalies	2 ^a , a5, 30 ^{pp} , 34 ^{nn,oo} , 38 ^{dd} , 42 ^{aa,dd,hh} , 47 ^{dd} , 50 ^{bb} , 50 ^(2 cases) , 51 ^{aa} , 58 ^a
Urogenital Anomalies	2 ^{zz(2 cases)} ,a1, a2(2 cases), 29 ^w , 37 ^{a13} , 51 ^w , 54 ^w
Intestinal malformation	2 ^{g9} , 46 ^{jj}
Cognitive deficits/Behavior problems	6 ^c , 16 ⁱ , 27 ^{c,d,z} , 29 ^c , 31 ^b , 33 ^{bi(4 cases)} , d(4 cases), 35 ^{kk} , 36 ^{c(3 cases)} , d(3 cases), 37 ^{d(2 cases)} , 38 ^{c,e} , 44 ^c , 48 ^c , 49 ^{c,e,1} , 50 ^{c(10 cases)} , 51 ^c , 55 ^{b,c,d,e}
Psychiatric disorders	2 ^(2 cases) , 53
Others	2 ^{a3,a4} , 28 ^{rr} , 29 ^{uu,vv,yy} , 33 ^(2 cases) , 38 ^{uu} , 41 ⁱⁱ , 43 ^{ff,gg} , 54 ⁱ ,

a: hypoplastic left heart syndrome. b: cognitive deficit. c: delayed language or psychomotor development. d: behavioral problems. e: learning difficulties. f: downslanted palpebral fissures. g: upslanted palpebral fissures. h: abnormal set eyes. i: nasal bone abnormality. j: cleft lip or palate, other palate anomaly. k: abnormal eye movements. l: thyroid hemiagenesis (hypotroidism) or malformation. m: congenital cranial dysinnervation disorder. n: retinal vascular abnormality. o: glaucoma. p: macrocephaly. r: microcephaly. s: ear anomaly. t: hyperactivity and attention deficit. u: retro/micro/macrogathia. v: hypo/hypertelorism. w: cryptorchidism. y: falciiform macular folds. z: seizure. aa: patent ductus arteriosus. bb: atrial septal defect. cc: strabismus. dd: ventricular septal defect. ee: epicanthal folds. ff: amyoplasia. gg: clinodactyly or syndactyly, palmar or finger/toe abnormality. hh: tricuspid atresia. ii: B-Acute lymphoblastic leukemia. jj: anorectal malformations and at least two additional cardinal features of the VACTERL association. kk: autism. mm: narrowed face. nn: D-transposition of the great arteries. oo: Ebstein's anomaly. pp: multiple cardiac anomalies (ex fetus). rr: situs inversus totalis with normal cardiac situs. tt: short palpebral fissures. uu: laryngomalacia. vv: bifida uvula. yy: absence of 12th rib. zz: urethral stenosis. a1: hypospadias. a2: hydronephrosis. a3: absent thymus. a4: asplenia. a5: tetralogy of Fallot. a6: subcutaneous cysts. a7: refractive errors. a8: ankyloglossia. a9: Intestinal malrotation/volvulus. a10: ptosis. a11: general facial dysmorfism. a12: subependymal cysts. a13: vesico-urethral reflux. a14: deviant facial expressions.

Table 4. Some of the duplication size, inheritance mode and techniques of analysis reported in the literature

Duplication Size (Mb) ^{reference}	(0,324) ⁵⁰ , (0,4) ^{26(1 case)} , (0,437) ⁵¹ , (0,614) ⁴³ , (0,619) ⁴¹ , (0,630) ⁴⁴ , (0,8) ⁴⁸ , (1,1) ²⁶ , (1,2) ^{53,55} , (1,158) ⁵⁰ , (1,44) ⁵⁶ , (1,5) ^{29,36(2 cases)} , 36,50, (1,99) ⁵⁰ , (2,1) ^{27,33(3 case),39,47(7 cases)} , (2,107) ⁵⁶ , (2,21) ⁵⁷ , (2,3) ⁵⁸ , (2,5) ^{49,50,52} , (2,51-2,54) ⁴⁶ , (2,63) ⁵⁰ , (2,948) ⁴² , (3) ^{2(7 cases),6} , 29 ^(2 cases) ,30,36 ^(3 cases) ,37 ^(2 cases) ,38 ^(2 cases) , 42,50, (3,070) ⁵⁰ , (3,172) ⁴⁵ , (3,208) ⁵⁰ , (3,4) ^{33(4 cases)} , (3,450) ⁵⁰ , (4) ² , (6) ^{2(2 cases)}
De novo	2 ^{9 cases} , 13, 26, 27, 30, 31, 34, 35, 36 ^(3 cases) , 38, 41, 43, 44, 45, 46, 48, 50 ^{4 cases} , 54, 56, 57, 58
Inherited	2 ^{m,two s(1 case)} , 6 ^{m,m,g,m} , 13 ^{p(11 cases)} , 26, 29 ^{m,p(2 cases)} , 33 ^{p(1 case)} , b(1 case), 33 ^{m(1 case)} , mg ^{f(1 case)} , 36 ^{m,s(1 case)} , p,s(1 case), 37 ^{p,s} , 37 ^{m,m,g,m} , 38 ^{gg} , 42 ^m , 47 ^{p(6 offspring and father)} , 49 ⁿ , 50 ^{p(4 cases)} , m(1 case), 51 ^{m,s} , 52 ^m , 53, 55 ^m
Technic of analysis ^{reference}	(FISH) 2,6,26,29,30,33,34,35,36,41,47,48,51,57,58, (aCGH) 26,27,31,36, 37(2 cases),42,43,44,45,49,50,52,53,54,55,56,57, MLPA ^{26,37(2 cases)} , 38(2 cases), 46

a: Hypoplastic left heart syndrome; b: Cognitive deficit; c: Delayed language or psychomotor development; d: Behavioral problems; e: Learning difficulties; f: Downslanted palpebral fissures; g: Upslanted palpebral fissures; h: Abnormal set eyes; i: Nasal bone abnormality; j: Cleft lip or palate, other palate anomaly; k: Abnormal eye movements; l: Thyroid hemiagenesis (hypotroidism) or malformation; m: Congenital cranial dysinnervation disorder; n: Retinal vascular abnormality; o: Glaucoma; p: Macrocephaly; r: Microcephaly; s: Ear anomaly; t: Hyperactivity and attention deficit; u: Retro/micro/macrogathia; v: Hypo/hypertelorism; w: Cryptorchidism; y: Falciiform macular folds; z: Seizure; aa: Patent ductus arteriosus; bb: Atrial septal defect; cc: Strabismus; dd: Ventricular septal defect; ee: Epicanthal folds; ff: Amyoplasia; gg: Clinodactyly or syndactyly, palmar or finger/toe abnormality; hh: Tricuspid atresia; ii: B-Acute lymphoblastic leukemia; jj: Anorectal malformations and at least two additional cardinal features of the VACTERL association; kk: Autism; mm: Narrowed face; nn: D-transposition of the great arteries; oo: Ebstein's anomaly; pp: Multiple cardiac anomalies (ex fetus); rr: Situs inversus totalis with normal cardiac situs; tt: Short palpebral fissures; uu: Laryngomalacia; vv: Bifida uvula; yy: Absence of 12th rib.

als (8%) had microduplications of 22q11.21-q11.23 [13]. Sahoo et al. analyzed 38,779 individuals and found the 22q11.2 microduplication in 94 individuals (0.24%) which 10 (0.026%) of those were de novo [14]. A large copy number variants case study group consisting of 15,749 of individuals studied by Kaminsky et al. and they identified 32 cases (0.2%) of 22q11.2 duplication [22].

Several methods including FISH, array-CGH, multiplex ligation-dependent probe amplification (MLPA) was used in order to detect duplication of the 22q11.2 region. Mosca et al. demonstrated that cytogenetic studies of their

patient revealed an inverted 9p duplication/deletion and bacterial artificial chromosomes (BACs)-array also showed a 22q11.2 microduplication confirmed by quantitative PCR. They underlined that this case also highlights the efficiency of BACs-array in detecting complex rearrangements [23]. Somerville et al., reported two cases and underlined that their findings illustrate the importance of scanning interphase nuclei when performing FISH analysis for any of the genomic disorders [28].

Many individuals can harbor a duplication of 22q11.2 without any discernible phenotypic effect. Anna Brunet Vega [24] agrees with Yobb

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et al. that the patients with 22q11.2 duplication may present phenotypically extreme diversity, ranging from normal to behavioral abnormalities to multiple defects [4]. According to the Rosa et al. the phenotype of individuals with the reported 22q11.2 duplication is not representative of this condition [21]. Patients with 22q11 microdeletion may exhibit clinical features overlapping with DiGeorge/velocardiofacial syndromes [25, 26].

Cardiac defects do not seem to be a major finding in these individuals, contrarily to what occurs in patients with the del22q11 syndrome [21]. Shimojima et al. recently summarized the clinical features of the patients with dup (22)(q11.2q11.23) reported in four different studies [27].

We summarized some of the clinical features of the patients and the duplication size, inheritance mode and techniques of analysis reported in the literature so far, in **Tables 3** and **4**. [1, 2, 8, 19, 21, 27-58].

Impulsivity, aggression, oppositional defiant disorder, social immaturity, attention deficit disorder, and cognitive deficits and mental retardation have been reported in cases of 22q11.2 microduplication [2-4, 19, 20, 59]. In a series array analysis was performed on 11,463 patients with idiopathic mental retardation, brain malformations, autism spectrum disorders, and/or speech delay, Wincent et al. identified 16 individuals with duplications of chromosome band 22q11.21-q11.23 [60]. Brunet et al. investigated 22q11.2 microduplication using MLPA among 190 patients with schizophrenia and failed to detect 22q11.2 duplication syndrome rearrangement among these patients [61]. Torres et al. screened 200 patients who had been referred for fragile-X determination and 400 healthy control individuals. They found the 5'UTR mutation to be present in three patients with mental retardation or behavioral problems and absent in control individuals of the same ethnic background. They suggest that TBX1 is a candidate causing mental retardation associated with the 22q11.2 duplication syndrome [59].

There are many common features between our proband and the previously reported cases. However, some different and distinct findings observed in our patient which was not reported before in patients with 22q11.2 microduplication

syndrome. The new findings such as microcornea, microphthalmia, cataract, penile curvature (ventral urethral chordee), ataxia with fine movements coordination difficulties, superiorly placed eyebrows, long eyelashes, bushy eyebrows and synophrys, narrow forehead, tinny upper lip, wide set nipples, dental abnormalities, movement and skeletal abnormalities (limitation of abduction of fingers of both hands, kypho-lordosis, laterally curved fingers of both hands, overlapped 2nd finger of both feet, pectus excavatus (mild), genu valgum, hallus valgus, all suggest that the genes within the duplicated area and the molecular pathways which are directly related with these genes may well affect the phenotype.

Mosaicism del (22)(q11.2q11.2)/dup (22)(q11.2q11.2) in a patient with features of 22q11.2 deletion syndrome were reported previously [62]. Our case exhibits mosaicism without any apparent deletion. It is not yet well established whether the mosaic extent of the duplication can also affect the extent of phenotypic features of our patient. This requires further detailed investigations. The genetically analyses of other members of the family, however, with or without clinically positive findings might help in producing more convincing explanation.

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Disclosure of conflict of interest

None.

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