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Novel Insights from Clinical Practice

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# Extensive, 3.8 Mb-Sized Deletion of 22q12 in a Patient with Bilateral Schwannoma, Intellectual Disability, Sensorineural Hearing Loss, and Epilepsy

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### Established Facts

- 22q12 cytogenetic region contains genes for cell cycle control, chromatin modification, transmembrane signaling, neural development as well as cancer predisposition genes, notably *CHEK2* and *NF2*.
- Patients present with craniofacial anomalies including cleft palate, intellectual disability, epilepsy, cardiac defects, and schwannommas if *NF2* is affected.
- While *NF2* deletions as a cause of schwannomas are undisputed, there is a lack of genotype-phenotype correlation for other clinical signs. In previous reports, deletions including *MN1* gene region were deemed responsible for cleft palate.

### Novel Insights

- Patient in our case presents with cleft palate, despite the absence of *MN1* gene deletion. Therefore, multiple 22q12 regions may be responsible for the development of craniofacial abnormalities.
- While epilepsy is one of the rarer symptoms occurring in patients with 22q12 deletions, these cases invariably included *DEPDC5* deletion. It is very likely that heterozygous loss of *DEPDC5* is responsible for seizure disorders in these patients.

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**Keywords**
22q12 deletion · Microdeletion syndrome · Bilateral schwannoma · NF2

**Abstract**
***Introduction:*** In contrast with the well-known and described deletion of the 22q11 chromosome region responsible for DiGeorge syndrome, 22q12 deletions are much rarer. Only a few dozen cases have been reported so far. This region contains genes responsible for cell cycle control, chromatin modification, transmembrane signaling, cell adhesion, and neural development, as well as several cancer predisposition genes. ***Case Presentation:*** We present a patient with cleft palate, sensorineural hearing loss, vestibular dysfunction, epilepsy, mild to moderate intellectual disability, divergent strabism, pes equinovarus, platyspondylia, and bilateral schwannoma. Using Microarray-based Comparative Genomic Hybridization (aCGH), we identified the de novo 3.8 Mb interstitial deletion at 22q12.1→22q12.3. We confirmed deletion of the critical *NF2* region by MLPA analysis. ***Discussion:*** Large 22q12 deletion in the proband encases the critical *NF2* region, responsible for development of bilateral schwannoma. We compared the phenotype of the patient with previously reported cases. Interestingly, our patient developed cleft palate even without deletion of the *MN1* gene, deemed responsible in previous studies. We also strongly suspect the *DEPDC5* gene deletion to be responsible for seizures, consistent with previously reported cases.



## Introduction

Chromosome 22 is the second smallest human chromosome, spanning more than 51 million DNA base pairs and representing between 1.5 and 2 percent of the total DNA in cells. Chromosome 22 contains over 800 genes that provide instructions for making proteins, performing a variety of different roles in the body, such as cell cycle control, cell-cell adhesion, transmembrane signaling, and sensorineural development. It also contains several well-described oncogenes. Structural abnormalities of chromosome 22 are responsible for various conditions. 22q11.2 deletion syndrome (velocardiofacial, DiGeorge syndrome) is probably the most recognized. Chromosome 22 harbors loci for several other Mendelian disorders – amyotrophic lateral sclerosis, breast cancer susceptibility, cat-eye syndrome, 22q11.2 distal deletion syndrome, 22q13 deletion syndrome, Phelan-McDermid syndrome, Liberfarb syndrome, and type 2 neurofibromatosis [Kaplan et al., 1987; Gilbert, 1998; Dunham et al., 1999; Yu et al., 2012; Peter et al., 2019].

## Case Report

*Personal History*

We report a male patient with sensorineural hearing loss, mild intellectual disability, epilepsy, and multiple congenital abnormalities. The proband came from third physiological pregnancy. Amniocentesis performed because of the mother's age showed no chromosomal abnormality. Patient was born to term by forceps delivery due to intrauterine asphyxiation. He was resuscitated and spent 4 days in neonatal ICU. Birth weight and height were 3,500 g and 50 cm. Shortly after birth, clinical investigation recognized a cleft palate. Brain CT scan described dilation of the lateral brain ventricles. In the following years, clinicians reported a delay in psychomotor development – the child achieved milestones significantly later than normal. The patient had surgical intervention at the age of 2 years for the reconstruction of the cleft palate and at the age of 6 years for dental surgery.

During childhood, the patient suffered from recurrent ENT infections (rhinitis, sinusitis, otitis media). At the age of 10 years, the patient developed progressive bilateral sensorineural hearing loss – severe hearing loss on the right side and complete deafness on the left side. A cochlear implant was necessary to facilitate hearing. At the age of 13 years, the patient developed epileptic seizures – focal complex paroxysms, successfully treated with lamotrigine. Furthermore, the patient continued showing signs of mild intellectual disability: expressive and perceptive dysphasia, disharmony, dysgraphy. He also suffered from vestibular dysfunction, velopharyngeal insufficiency, and rhinolalia. At the age of 15 years, NMR imaging identified spinal canal stenosis without any clinical symptoms.

*Manifestation of Malignancy*

At the age of 25 years, the patient presented with bilateral schwannoma of the acoustic nerve (Fig. 1). Surgery resulted in partial resection of the tumors, complicated by bleeding and residual paresis of the right facial (VII) nerve. The attending clinician proposed watch-and-wait strategy.

*Family History*

The patient's half-siblings did not show any congenital abnormalities or delayed development: the half-brother presented only with bronchial asthma and the half-sister was completely healthy. The mother of the proband was not particularly ill, apart from infection with Lyme disease. The mother's mother presented with lymphoma. The father of the proband suffered from upper gastrointestinal tract difficulties, as well as his mother. There was no further family history of hearing loss, congenital malformations, or other neoplasms (Fig. 2).

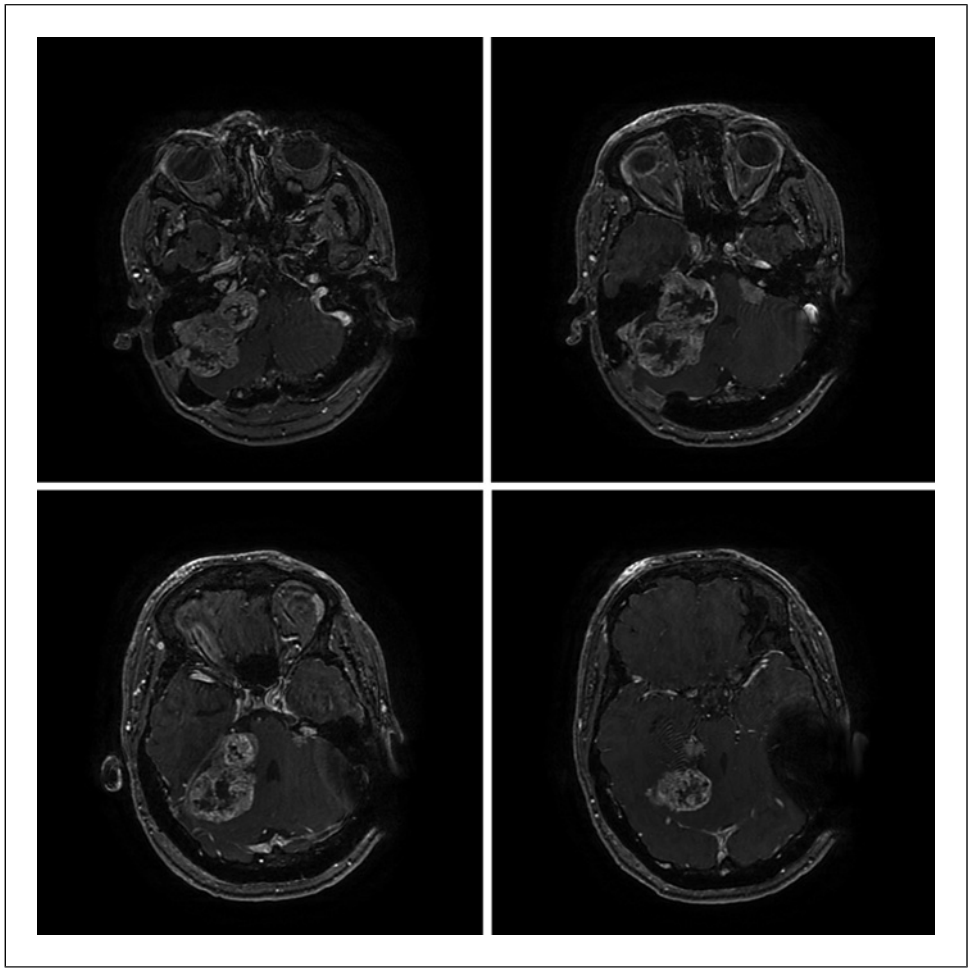

**Fig. 1.** T1 contrast MR imaging appearances of CN VIII schwannoma in the cerebellopontine angle (CPA) in a 25-year-old male. Artifacts caused by the presence of cochlear implant.

*Phenotype*

At the time of the investigation, the proband was 25 years old and measured 160 cm and 52 kg. We observed pyknic habitus and hypotrophic musculature, as well as posture affected by flattened thoracic kyphosis and accentuated lumbar lordosis. Gynecomastia was present. Shoulders were narrow and dropped. Knee joints were in a vagous position. The skin of the torso and upper extremities was speckled with multiple fibromas and affected by secondary acne and conglobata. Facial stigmata were present: asymmetry due to paresis of the facial nerve on the right side, ptosis of the eyelid, divergent strabism, drooping, hypertelorism, epicanthal folds, broad nasal root, and narrow lips. Earlobes were in a lower position and dorsally rotated. The hair border was lower on the neck. Limbs were proportional to the torso. Secondary sexual characteristics were underdeveloped. External genitalia were male (Fig. 3).

*Mutational Screening and Confirmation*

We performed NGS analysis for cancer susceptibility genes. The sequencing library (custom panel BRONCO containing 296 genes) was prepared using the SureSelectXT HS target enrichment system from Agilent (Ref.1 in online suppl. material; for all online suppl. material, see https://doi.org/10.1159/000528744). Sequence analysis did not detect any abnormalities apart from fumarate hydratase heterozygous carrier status (likely pathogenic variant NM_000143.4[FH]:c.2T>A, p.Met1?). However, CNV analysis of the sequencing data discovered a heterozygous loss of all exons of *CHEK2* tumor suppressor gene and heterozygous loss of the neurofibromin 2 (NF2) gene. We confirmed the *NF2* deletion by MLPA analysis (Fig. 4a, Ref.2 in online suppl. material). Close cytogenetic distance and possible gene linkage suggested a larger chromosome 22 deletion.

*Cytogenetic Studies*

Conventional karyotyping determined normal male karyotype (46, XY) in the proband. However, Array-CGH, SurePrint G3 Cancer CGH + SNP Microarray Kit, 4 × 180K (Agilent Technologies) (Ref.3 in online suppl. material) determined an extensive, 3.8 Mb-sized, 22q12.1-22q12.3 heterozygous deletion, arr [GRCh37] 22q12.1q12.3(28421280_32254899)x1, including the *CHEK2* and *NF2* regions (Fig. 4b). For the complete list of deleted genes, see Table 1. We did not detect the deletion in either parent, so we presume a de novo origin of the deletion.

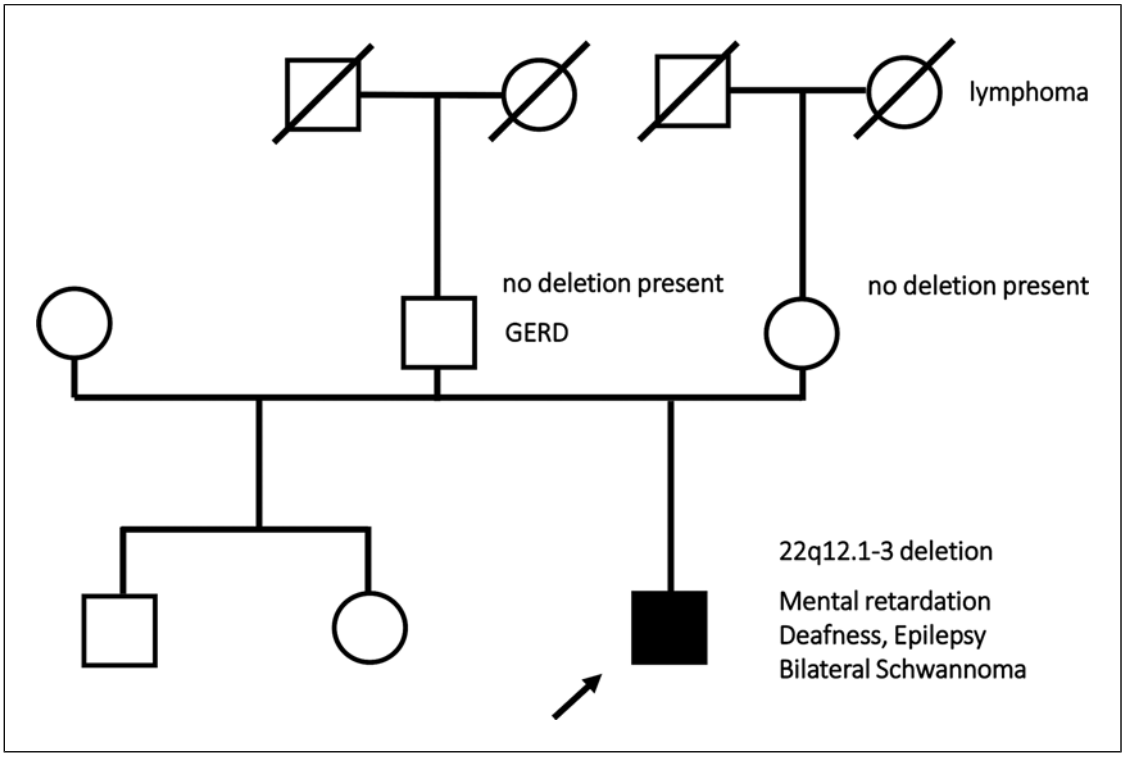


**Fig. 2.** Pedigree of the proband, presenting with de novo 22q12.1-12.3 extensive deletion.

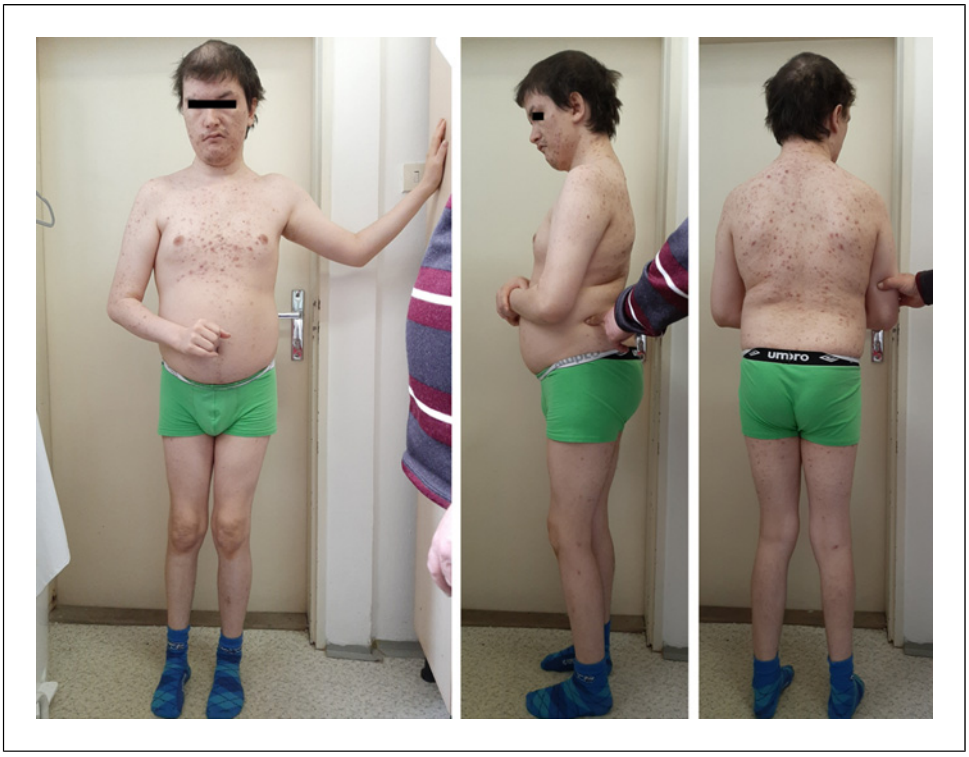

**Fig. 3.** Images of the proband with intellectual disability and type 2 neurofibromatosis. Paresis of the right facial nerve resulted from surgical intervention.

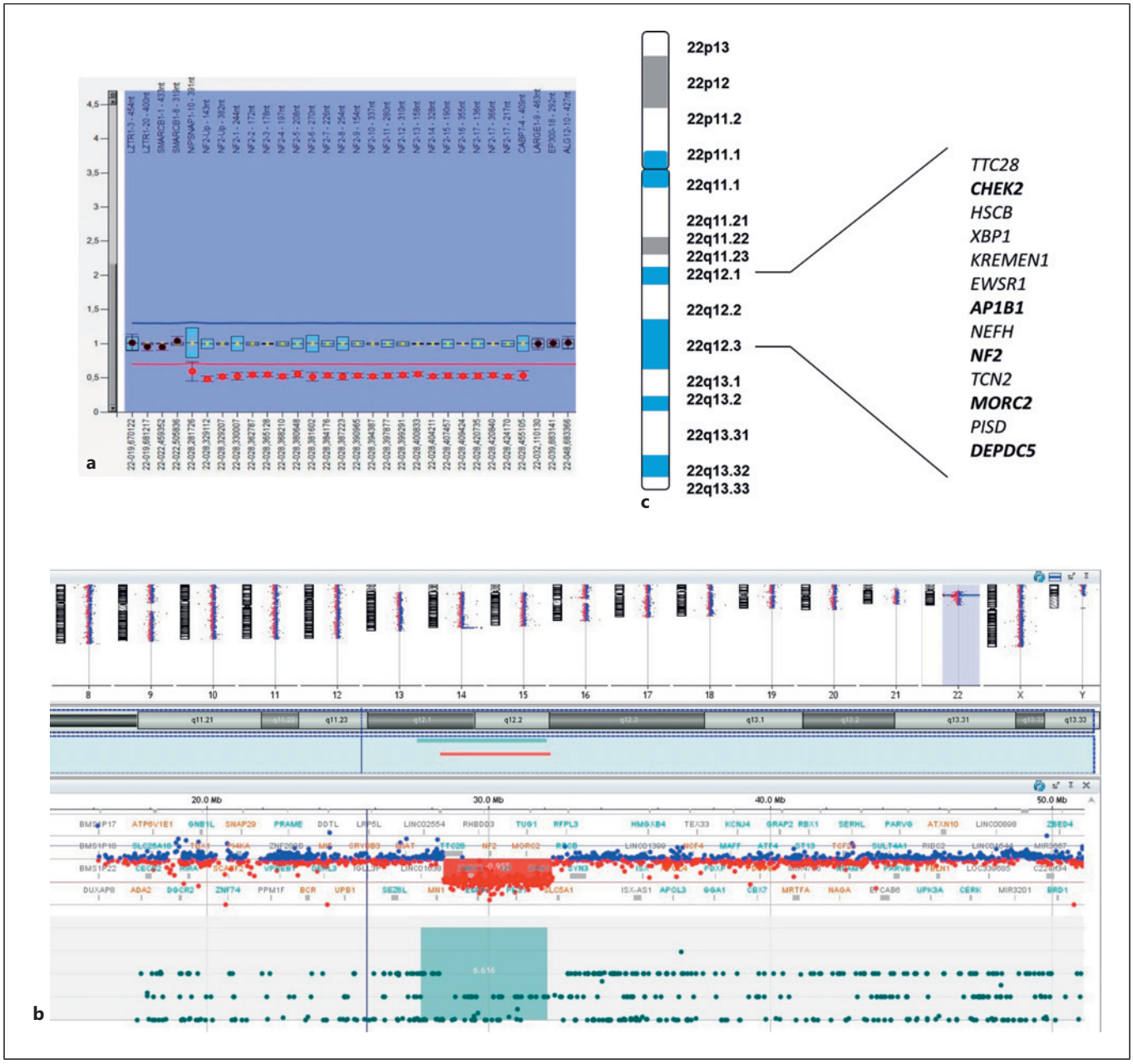


**Fig. 4. a** Heterozygous loss of the NF2 gene, confirmed by MLPA analysis. **b** Oligonucleotide array-CGH, detecting extensive 3.8 Mb-sized 22q12.1→22q12.3 de novo interstitial deletion. **c** Schematic map of chromosome 22, showing selected disease-associated genes.

## Discussion

We report a 25-year-old man with 22q12 de novo deletion, bilateral schwannoma, intellectual disability, sensorineural hearing loss, and epilepsy. This large deletion encompasses 58 known protein-coding genes, particularly *NF2* (neurofibromin 2, OMIM #607379) and *CHEK2* (checkpoint kinase 2, OMIM #604373) (Fig. 4c). *MN1* (OMIM #156100) oncogene was not included in the deletion. We searched the DECIPHER database for large deletions involving the affected region, with a 30 kB deletion size cut off. We identified 20 CNV variants

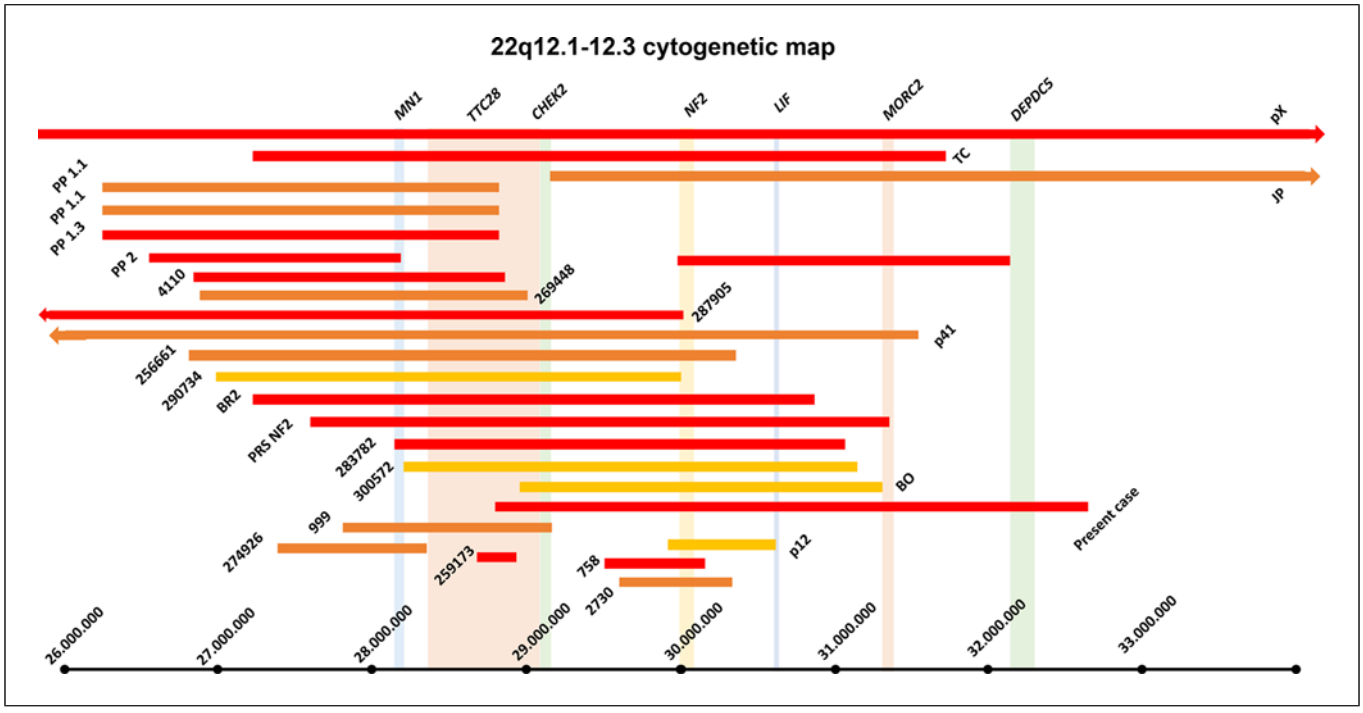


**Fig. 5.** Large deletions of the 22q12.1-12.3 region as reported in the literature and in the DECIPHER database, arranged by phenotypic effects. Red blocks mark the patients presenting with cleft palate or bifid uvula, orange blocks indicate patients with craniofacial anomalies but without cleft palate, and yellow blocks show patients without craniofacial anomalies. The present case is clearly marked. Patients PRS-NF2, TC, pX, p41, JP, p12, 999, and 4,110 were reviewed by Davidson et al. [2012]. Patients PP1.1, PP1.2, PP1.3, and PP2 were reported by Beck et al. [2015]. Patient BO was reported by Bosson et al. [2015]. Patients BR2; 256,661; 269,448; 290,734; 287,905 were reported by Breckpot et al. [2016]. Patients 758; 2,730; 259,173; 283,782; 287,905; and 300,572 are recorded entries in the DECIPHER database. Selected genes causing mendelian disorders are represented with columns: MN1: light blue, TTC28: light green, CHEK2: turquoise, NF2: pink, LIF: purple, MORC2: light gray, DEPDC5: dark gray. The coordinates of all variants were based on the UCSC GRCh37/hg19 assembly.

**Table 1.** Table of genes involved in 22q12.1–3 deletion, in alphabetical order

| Coding, high pLI | Coding, low pLI | | Coding, no pLI score | Non-coding |
|---|---|---|---|---|
| *AP1B1* | *ASCC2* | *RFPL1* | *CHEK2* | *HORMAD2-AS1* |
| *CCDC117* | *C22orf31* | *RHBDD3* | *HSCB* | *KIAA1656* |
| *DEPDC5* | *CABP7* | *RNF185* | *KREMEN1* | *LIF-AS1* |
| *EIF4ENIF1* | *CASTOR1* | *RNF215* | *NEFH* | *LINC01521* |
| *EWSR1* | *CCDC157* | *SE142L* | *PISD* | *LOC105372990* |
| *GAL3ST1* | *DRG1* | *SEC143L* | *TCN2* | *LOC107985544* |
| *GAS2L1* | *DUSP18* | *SEC14L4* | | *LOC91370* |
| *LIF* | *EMID1* | *SEC14L6* | | *MIR3200* |
| *MORC2* | *HORMAD2* | *SELENOM* | | *MIR3928* |
| *MTMR3* | *INPP5J* | *SFI1* | | *MIR5739* |
| *NF2* | *LIMK2* | *SLC35E4* | | *MIR6818* |
| *OSM* | *MTFP1* | *SMTN* | | *MIR7109* |
| *PATZ1* | *NIPSNAP1* | *TBC1D10A* | | *MORC2-AS1* |
| *PES1* | *OSBP2* | *TCN2* | | *PIK3IP1-AS1* |
| *PRR14L* | *PIK3IP1* | *THOC5* | | *RFPL1S* |
| *SF3A1* | *PLA2G3* | *UQCR10* | | *SDC4P* |
| *TTC28* | *PRR14L* | *XBP1* | | *SNORD125* |
| *ZNRF3* | *RASL10A* | *ZMAT5* | | *TUG1* |
| | | | | *ZNRF3-AS1* |

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**Table 2.** Phenotypic comparison of reported patients

| Patient | 22q12 deletion coordinates | Deletion size | Deleted genes | Decipher database | Inheritance | Cleft palate | Microcephaly | Micrognathia | Hypertelorism | Intellectual disability | Cardiac defect | Corpus callosum hypoplasia | Schwannoma | Epilepsy | Hearing loss | Other features | Author |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| JM (proband) | chr22:28817269-32650888 | 3.8 Mb | *NF2 and others* | No | De novo | + | – | – | + | + | – | Large ventricles | + | + | + | Pes cavus, scoliosis | Trizuljak et al. |
| pX | chr22:25843214-34411312 | 8.0 Mb | *MN1, PITPNB, TTC28, NF2, CHEK2, 51 others* | No | De novo | + | – | + | + | + | + | + | ? | – | – | | Barbi et al., 2002 |
| TC | chr22:27407968-31732873 | 6.0 Mb | *MN1, PITPNB, TTC28, NF2, CHEK* | No | De novo | + | – | + | + | + | + | + | + | + | – | Single palmar crease, accessory nipple, pectus excavatum, hypoplastic terminal phalanges | Said et al., 2011 |
| PRS NF2 | chr22:27607541-31305842 | 3.7 Mb | *MN1, PITPNB, TTC28, NF2, CHEK2 and others* | No | Unknown | + | + | + | + | + | + | + | + | – | + | | Davidson et al., 2012 |
| 4110 | chr22:26877538-28885620 + 2 other deletions and 1 duplication on chr22 | 2.01 Mb | *CRYBA4, CRYBB1, HSP4, MN1, PITPNB, SRRD, TFIP11, TPST2, TTC28* | Yes | De novo | + | – | – | – | + | – | – | ? | – | + | Cataracts, proptosis, short phalanges | Davidson et al., 2012 |
| PP 1.3 | chr22:26025041-28837082 | 2.76 Mb | *MN1 and 12 others* | No | Inherited | + | – | – | – | ? | – | – | – | – | – | | Beck et al., 2012 |
| PP2 | chr22:29939719-32217179, chr22:26552234-28165965 | 1.61 Mb | *MN1 and 16 others* | No | De novo | + | – | – | – | + | – | – | – | – | – | | Beck et al., 2012 |
| 283,782 | chr22:28172328-31061168 | 2.89 Mb | *CHEK, NF2, MN1, PITPNB, TTC28 and 39 others* | Yes | De novo | Bifid uvula | – | – | + | – | – | – | ? | – | – | Pes cavus, scoliosis, camptodactyly | Bosson et al., 2016 |
| 259,173 | chr22:28675022-28959281 | 0.28 Mb | *TTC28* | Yes | Unknown | + | + | – | – | – | – | – | ? | – | – | | Bosson et al., 2016 |
| 758 | chr22:29512535-30221049 | 0.71 Mb | *NF2 and 15 others* | Yes | Unknown | Bifid uvula | – | – | – | + | + | – | + | – | + | | Bosson et al., 2016 |
| 287,905 | chr22:25689977–30038041 | 4.3 Mb | *MN1, NF2?* | Yes | De novo | + | – | + | + | + | – | + | – | ? | + | Hypoplastic terminal phalanges | Breckpot et al., 2016 |
| BR2 | chr22:27266032–30848647 | 3.58 Mb | *MN1, NF2* | No | De novo | + | – | + | – | + | + | + | – | ? | – | Short stature, atrial septal defect, ectopic kidney, long slender fingers | Breckpot et al., 2016 |
| JP | chr22:29143604-36019401 | 7.4 Mb | *NF2 and others* | No | Unknown | VPI | ? | ? | ? | + | – | – | + | + | – | | Bruder et al., 1999 |
| p41 | chr22:29909878-31509382 | Unknown | *MN1, PITPNB, TTC28, NF2, CHEK2, and others* | No | De novo | + | + | + | + | + | – | – | + | – | – | Cataracts, pes cavus, facial palsy, cerebral palsy | Bruder et al., 2001 |
| 999 | chr22:27814209-29227971 | 1.41 Mb | *CCDC117, CHEK2, HSCB, MN1, PITPNB, TTC28, XBP1* | Yes | De novo | - | + | – | – | + | – | – | ? | – | – | | Davidson et al., 2012 |

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**Table 2** (continued)

| Patient | 22q12 deletion coordinates | Deletion size | Deleted genes | Decipher database | Inheritance | Cleft palate | Microcephaly | Micrognathia | Hypertelorism | Intellectual disability | Cardiac defect | Corpus callosum hypoplasia | Schwannoma | Epilepsy | Hearing loss | Other features | Author |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PP 1.1 | chr22:26025041-28837082 | 2.76 Mb | *MN1 and 12 others* | No | Inherited | High palate | – | – | – | + | – | – | – | – | – | | Beck et al., 2012 |
| PP 1.2 | chr22:26025041-28837082 | 2.76 Mb | *MN1 and 12 others* | No | Inherited | VPI | – | – | – | + | – | – | – | – | – | | Beck et al., 2012 |
| 274,296 | chr22:27375542-28307008 | 0.93 Mb | *MN1, PITPNB* | Yes | Unknown | VPI | – | – | – | + | – | Large ventricles | ? | – | – | Vocal cord paralysis, arthrogryposis | Bosson et al., 2016; Breckpot et al., 2016 |
| 2730 | chr22:29617783-30353083 | 0.74 Mb | *NF2 and 15 others* | Yes | Unknown | - | – | – | – | – | – | - | ? | – | – | | Bosson et al., 2016; Breckpot et al., 2016 |
| 256,661 | chr22: 26727554–30313733 | 3.59 Mb | *MN1, NF2* | Yes | De novo | High palate, VPI | + | + | + | + | – | - | + | ? | + | Unilateral choanal atresia, café au lait spots | Breckpot et al. 2016 |
| 269,448 | chr22: 26857719–29029963 | 2.17 Mb | *MN1* | Yes | De novo | VPI | + | – | – | + | – | ? | ? | ? | + | Epicanthus, webbed neck, narrow ear canals | Breckpot et al., 2016 |
| p12 | chr22:29909878-30695471 | 0.53 Mb | *NF2 and others* | No | De novo | ? | ? | ? | ? | + | – | - | + | – | – | | Bruder et al., 2001 |
| BO | chr22:28967413-31385775 | 2.4 Mb | *CHEK2, NF2, TTC28, and 41 others* | No | De novo | – | – | + | – | + | – | + | – | – | – | Hypospadia, exotropia, VSD | Bosson et al., 2016 |
| 300,572 | chr22:28247776-31223581 | 2.98 Mb | *CHEK2, NF2, TTC28, PITPNB, and 40 others* | Yes | De novo | – | – | – | – | + | – | - | ? | – | – | | Bosson et al., 2016 |
| 290,734 | chr22: 26980074–30016888 | 3.04 Mb | *MN1, NF2?* | Yes | De novo | – | – | – | – | + | – | ? | ? | ? | – | Short stature, broad hallux, tapered fingers, laryngomalacia | Breckpot et al., 2016 |

Coordinates of all variants are based on the UCSC GRCh37/hg19 assembly. Black color marks the patients presenting with cleft palate or bifid uvula. Dark gray color marks patients with craniofacial anomalies but without cleft palate, and light gray color marks patients without craniofacial anomalies. The present case is marked as JM. VPI, velopharyngeal insufficiency; VSD, ventricular septal defect.

containing 22q12 deletions, while ClinVar entries yielded another 11 large 22q12 deletions in the literature [Miller et al., 2010; Kaminsky et al., 2011; Yatsenko et al., 2020]. The average deletion size was 2.01 Mb, and median deletion size was 1.84 Mb. Only a select few DECIPHER entries had phenotypic description in the literature [Sanson et al., 1993; Bruder et al., 1999; Bruder et al., 2001; Barbi et al., 2002; Firth et al., 2009; Said et al., 2011; Davidson et al., 2012; Bosson et al., 2016; Breckpot et al., 2016].

We compared the phenotype of our patient with previously reported subjects in the literature (Table 2). Out of seventeen reported patients with deletions involving the *NF2* gene (including our patient), eight developed schwannoma at the time of publication. According to the literature, the median age of onset varies between 17 and 22 years. Even though the penetrance of the disease is >95%, most of the reported cases were described in early childhood and may have not developed neurofibromas yet [Zucman-Rossi et al., 1998; Kluwe et al., 2005; Evans, 2009].

One of the most common features reported in patients with large 22q12 deletions was cleft palate and velopharyngeal insufficiency. 11/25 patients (including our patient) were diagnosed with cleft palate, while eight other patients were reported with bifid uvula, high arched palate, and/or velopharyngeal insufficiency. Beck et al. [2015] proposed a critical region, spanning Chr22: 27607000-28166000, including the *MN1* gene, associated with cleft palate. This was confirmed in further publications [Breckpot et al., 2016]. However, in contrast with previous findings, Bosson et al. [2016] present a case report of patients with cleft palate and velopharyngeal insufficiency without deletions of the *MN1* gene. Therefore, multiple regions of 22q12 may be responsible for the development of craniofacial abnormalities (Fig. 5). However, we cannot rule out a variant of potential clinical significance in other genes associated with cleft palate, as we did not perform a study specifically targeted for this trait.

In the reported subset of patients, only three patients (marked as pX, JP, and the present case) developed epilepsy. All of these patients had deletions including the *DEPDC5* gene (at the distal part of the deletion in the present case). Loss-of-function (nonsense or truncating mutations) in *DEPDC5* causes familial focal epilepsy with variable foci characterized by focal seizures arising from different cortical regions in different family members [Dibbens et al., 2013; Zhang et al., 2021]. Neurological findings in the present case are consistent with this diagnosis. It is very likely that heterozygous loss of *DEPDC5* is responsible for seizure disorders in these patients.

The involvement of multiple cancer predisposition genes in the deletion (*CHEK2*, *NF2*) increases the risk of further malignancies. We provided comprehensive genetic counseling according to the current guidelines [Foretová et al., 2019] and the patient will be followed up by a multidisciplinary team of clinicians (neurologist, neurosurgeon, dermatologist, oncologist).

In conclusion, we present a case with a novel 22q12.1–12.3 deletion, cleft palate, sensorineural hearing loss, vestibular dysfunction, epilepsy, mild to moderate intellectual disability, divergent strabism, pes equinovarus, and platyspondylia. Extensive deletions encompassing *NF2* and *CHEK2* genes cause an elevated risk of cancer, such as our case developing bilateral schwannoma. Correct diagnosis using microarray techniques significantly improves management, risk assessment, prognosis, follow-up, and ultimately survival of affected patients.

## Statement of Ethics

According to the currently valid Czech legislation, ethics approval was not required for this study, as all results were obtained within the framework of the provision of health care. All genetic analyses were performed with the informed consent of proband's legal representatives. Informed consent for publication of the medical details and accompanying images was obtained from proband's legal representatives according to Declaration of Helsinki.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


## Funding Sources

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## Author Contributions

Jakub Trizuljak and Jakub Duben performed the initial clinical evaluation of the proband, literature research, and comparison with previously reported cases. Ivana Blaháková, Zuzana Vrzalová, Jiří Štika, and Lenka Radová performed NGS analyses. Veronika Bergerová and Soňa Mejstříková performed cytogenetic analyses.

Kateřina Staňo Kozubík reviewed the article and provided ethical guidelines. Radim Jančálek supplied and described NMR imaging studies. Michael Doubek and Šárka Pospíšilová revised the article and contributed to discussion.

## Data Availability Statement

Cytogenetic data were received from publicly available databases (DECIPHER).

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