Clinical findings and molecular cytogenetic characterization of 19q13.42 microduplication: three cases report and literature review

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Case Report

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Abstract

Background

Trisomy 19q is a recognizable syndrome and associated with a wide spectrum of clinical phenotypes in clinic. The purpose of this study was to explore the prenatal phenotypes of 19q13.42 duplication, which was rarely reported in clinic.

Case presentation

Three pregnant women presenting diverse indications for prenatal diagnosis accepted amniocentesis: increased nuchal translucency (case 2) and high risk of trisomy 21 (case 1 and case 3). Case 1 and case 2 shared similar duplicated locus in the region of 19q13.42, encompassing part NLRP12 gene. Case 2 inherited the chromosomal duplication from the mother with normal phenotypes. Case 3 carried a 1.445Mb duplication in the 19q13.42q13.43 region. It was proposed that evolutionary duplication of NLRP12 gene could have a causative role in autoinflammatory diseases development. The genotype-phenotype correlation depends mainly on the duplicated size and functional genes involved, which is still yet to be determined. All pregnant women chose to continue the pregnancy and delivered healthy children with no apparent abnormalities.

Conclusions

The 19q13.42 microduplications in our study are the smallest fragments compared to previous literature. We delineated 19q duplication cases without structural ultrasound anomalies for the first time, which enriched the prenatal phenotypes of this chromosomal aberration. It was proposed that long term follow up analysis should be guaranteed till adulthood to determine whether there will be other emerging clinical symptoms and developmental-behavioral disorders for such carriers.

Background

Chromosomal duplications are regarded to have close association with mental/growth retardation and other genetic disorders. Trisomy 19q, partial or entire duplication of long arm of chromosome 19, was a rare chromosomal anomaly which was first reported in 1976 [1]. Currently, the incidence rate was not clear in clinic. The clinical features of trisomy 19 described in previously reported patients were various and included growth retardation, developmental delay, intellectual disability, microcephaly, heart malformations, anomalies of the genito-urinary tract and/or the gastrointestinal system and seizures, which usually led to poor prognosis [2–5] .

The formation mechanism of trisomy 19q could be due to the presence of a *de novo* duplication, parental balanced reciprocal translocation, pericentric inversion, or small supernumerary marker, which made it difficult to define a distinct genotype-phenotype correlation [6, 7].

For prenatal cases presenting normal karyotypes, chromosomal submicroscopic imbalances of clinic significance could be diagnosed in approximately 1% of structurally normal pregnancies and 6% with structural malformations. Most frequent copy number variants (CNVs) observed in fetuses without structural anomalies included 15q11.2, Xp22.3, Xp21.1, 16p11.2, 1q21.1, 17p12, 16p13.11 and 22q11.21 [8]. To our knowledge, the first case of dup(19q) detected by prenatal diagnosis was reported in 1997 [3]. Herein, we describe three prenatal cases involving 19q13.42 microduplications with no structural anomalies observed, which are the smallest fragments compared to previous cases of trisomy 19q.

Case Presentation

Participants and clinical data

Three pregnant women underwent amniocentesis for cytogenetic and chromosomal microarray analysis (CMA) analysis due to various indications for prenatal diagnosis: increased nuchal translucency (case 2) and high risk of trisomy 21 (case 1 and case 3). All couples were nonconsanguineous and healthy. No family history of diabetes mellitus or congenital malformations were observed. All pregnant women denied any exposure to alcohol, teratogenic agents, irradiation, or infectious diseases during their pregnancies. This study protocol was approved by the Ethics Committee of the First Hospital of Jilin University (No.2019 – 299), and written informed consents were obtained from all couples for publication of this case report and accompanying images.

Methods

Cytogenetic analysis

Amniocentesis was performed for karyotyping analysis with informed consent. Cytogenetic studies were performed on metaphases collected from cultured aminotic fluid cells from three pregnant women. Routine chromosome analysis was performed on G-banding techniques at 300-400 banding resolution prepared from the cultured amniotic fluid cells according to standard protocols. Twenty metaphases were analyzed for all samples. The International System for Human Cytogenetic Nomenclature (ISCN 2016) was used to describe the karyotype [9].

Chromosomal microarray analysis

Genomic DNA was isolated from 10 mL aminotic fluid cells from all three pregnant women. The CytoScan 750K array (Affymetrix, Santa Clara, CA, USA) was applied to detect the known and novel chromosomal CNVs across the entire genome following the manufacturer's protocols and our previous study[10]. The procedures included genomic DNA extraction, digestion and ligation, PCR amplification, PCR product purification, quantification and fragmentation, labeling, array hybridization, washing and scanning. The CNVs detected were totally assessed by comparing them with published literature and the public databases:

(1) Database of Genomic Variants (DGV)(http://dgv.tcag.ca/dgv/app/home),(2)DECIPHER(http://decipher.sanger.ac.uk/), (3) ISCA https://www.iscaconsortium.org/), (4) ECARUCA(http://www.ecaruca.net) and (5) OMIM(http://www.ncbi.nlm.nih.gov/omim).

Results

In our report, three cases with pure interstitial 19q13.42q13.43 microduplications were identified by CMA. G-banding analysis showed that all fetuses showed normal karyotypes, but CMA successfully identified 19q microduplications in the locus between 19q13.42 and 19q13.43. The cytogenetic, CMA results, and clinical features for all three cases were listed in Table 1. Indications for prenatal diagnosis were as follows: increased nuchal translucency (case 2) and high risk of trisomy 21 (case 1 and case 3). No structural abnormalities were detected in ultrasound examination. Among the duplicated regions, case 1 and case 2 shared similar duplicated locus in 19q13.42, encompassing part NLRP12 gene. Only the parents of case 2 opted for CMA to determine the origin of the duplication. It turned out that the fetus inherited the 19q13.42 microduplication from the phenotypically normal mother. All women chose to continue their pregnancies and delivered healthy infants at term. We then carried out a follow-up on their postnatal health conditions, including congenital defects, developmental retardation, body stature, craniofacial dysmorphisms, and skeletal anomalies. All infants were in healthy conditions, and no apparent abnormalities were observed till now, but long term follow up investigation was still necessary.

Discussion And Conclusions

In our study, we described three rare prenatal cases with pure 19q microduplications involving 19q13.42, ranging from 147 kb to 1.445 Mb, which presented no structural abnormalities in sonographic examination. Case 2 was proved to get the 19q13.42 duplication from the healthy mother. To the best of our knowledge, just five cases with prenatally diagnosed trisomy 19q had been described before, and only one case was involved in 19q microduplication. Currently, there is a lack of prenatal manifestations about this chromosomal microscopic imbalance. In our study, all fetuses with various 19q duplicated loci showed no structural anomalies in pregnancy, which were different from previous trisomy 19q cases and enriched the clinic phenotypes of 19q microduplication.

Trisomy 19q, could be regarded as a recognizable syndrome and associated with a wide spectrum of clinical phenotypes, including growth and psychomotor retardation, intellectual disability, low birth weight, microcephaly, short neck, heart malformations, skeletal anomalies, genitourinary anomalies, gastrointestinal defects, seizures and facial dysmorphisms (receding forehead, ptosis, hypertelorism,flat nasal bridge, small nose, short philtrum, down turned mouth, ear anomalies) [4,11,12]. Most trisomy 19q cases also carry monosomy of another chromosome, which makes it difficult to establish a clear phenotype-genotype correlation. Till now, only 19q12-q13.2 duplication is recognized as an obesity-related syndrome with intellectual disability and minor facial findings [13].

Pure 19q duplications, as a rare chromosomal anomaly, can be usually discovered in live borns by molecular genetic technique [1].To better interpret 19q duplication, we made a summary on clinic data observed in postnatal and prenatal cases with pure 19q duplication according to literature review, as shown in Table 1 [1-4,6,11,14-23]. The age of these cases ranged from new born to 39 years. Most trisomy 19q cases (11/19) could be detectable by traditional cytogenetic analysis, with the remainder (8/19) with 19q microduplication identified through molecular cytogenetic techniques. All cases varied in size, ranging from 25 kb to 12.4 Mb, were associated with various loci in 19q. Among these duplications, 12/19 cases were *de novo*, 5/19 cases were parentally inherited, and 2/19 cases were not available. The incidence rate of clinical presentations were as follows: Craniofacial dysmorphism (10/19), development delay (7/19), psychomotor retardation (7/19), brain anomaly (5/19), cardiac malformation (4/19), anomalies of urinary tract (3/19), skeletal anomaly (3/19), obesity (2/19), language disorders (2/19). The deformities of the face and head were the most typical clinic manifestations: ears anomaly (8/19), macrocephaly or microcephaly (6/19), short neck (5/19), nose anomalies (4/19). In addition, some rare anomalies, such as bilateral pronator syndrome, systemic-onset juvenile idiopathic arthritis, Duane retraction syndrome type III and autism spectrum disorder, could also be observed in 19q duplication cases. Generally speaking, postnatal cases usually presented a variety of clinical features with high specificity characterized by growth/psychomotor retardation and craniofacial dysmorphism. It was noteworthy that only five cases were prenatally detected, presenting various degrees of fetal abnormalities [3,4,11,21,22]. However, our cases showed no fetal structural anomalies, which indicated that prenatal trisomy 19q cases might exhibit normal or abnormal ultrasound findings. Although the infants (cases 1 to 3) are now in healthy state, long term follow up analysis is still necessary to confirm whether there will be other emerging clinical symptoms or developmental-behavioral disorders.

To elaborate diverse clinical phenotypes, we also made detailed comparisons of cases harboring 19q13.42 microduplication in DECIPHER and ISCA databases (Fig. 1). Six cases overlapping similar duplicated regions with cases 1 and 2 were recorded. The proportions of pathogenicity were as follows: likely pathogenic (1/6) and uncertain (5/6). The incidence rate of clinical features were as follows: Development delay (3/6), intelligent disability (3/6), and autism (2/6). Seven cases involving similar duplication with case 3 were described in the databases. The clinic pathogenicity in this duplicated locus was uncertain. Only one patient nssv 13649225 presented failure to thrive, hemolytic anemia, short stature and spherocytosis, while no evident phenotypes were observed for other six cases. Generally speaking, more evidence should be accumulated to explore the pathogenicity of 19q13.42 microduplication.

Dosage-sensitive genes with genome alteration would result in phenotypic effects and be associated with human diseases, including heart disease, cancers, diabetes, neuropsychiatric disorders and others [24]. Morbid genes in the region of 19q13.42q13.43 duplication involved in our cases were listed in Table 2. According to the ClinGen database, there are no available evidences that support the triplosensitivity of these genes. Based upon the published literature and public databases, we delineated the potentially pathogenic genes according to their functions and implications to predict the postnatal health conditions for these cases in future.

All CNVs detected in our case 1 and case 2 shared similar 19q13.42 microduplication, encompassing part NLRP12 gene (OMIM 609648; chr19: 54165218-54321990). NLRP12 gene, also known as RNO, PYPAF7, and Monarch-1, encodes the protein of NLRP superfamily, which is implicated in the activation of

proinflammatory caspases and hyperproduction of interleukin-1β [25]. NLRP12 plays critical roles in the regulation of NF-κB signaling, inflammasome activation, dendritic cell migration, and transcription of MHC class I genes [26]. The mutations in NLRP12 have been associated with familial cold autoinflammatory syndrome-2 (FCAS2; OMIM 611762), which displays autosomal dominant inheritance. This syndrome can be induced after exposure to cold and characterized by skin urticaria, arthralgia, conjunctivitis, musculoskeletal symptoms, deafness, lymphadenopathy, and abdominal pain, most of which are accompanied by recurrent fever and serologic evidence of inflammation [27,28]. Till now, there are no related reports on NLRP12 duplication in clinic. However, Galozzi et al. [28] proposed that evolutionary duplication of this gene can have a causative role in autoinflammatory diseases development. Hence, we suggested that these two infants should be followed up regularly on growth and health conditions, especially for autoinflammatory diseases.

In addition, the CMA detected a 19q13.42q13.43 duplication for case 3 , containing 19 OMIM genes. This locus comprises several NLRP (Nucleotide-binding oligomeriztion domain, Leucine rich Repeat and Pyrin domain) family members. NLRP4 is mainly responsible for the inhibition of NF-κB signaling, negative regulation of RLR signaling, autophagy inhibition. NLRP5 is related to the regulation of caspase activation, apoptosis in injured neurons, and embryonic development. The functions of other members (NLRP8, -9, -11, -13) still need to be further investigated [19,26]. As is known, the zinc finger proteins (ZNFs) are the largest transcription factor family in human genome, which contain finger-like protrusions and play critical roles in physiological and pathophysiological mechanisms [29]. Previous research showed that duplications of zinc finger genes commonly occurred during the evolution [30]. The detected duplicated locus in case 3 included ZNF580, -444, -582, -667, -71. Research on the functions of these genes are rare. According to OMIM database, the variations in ZNF582 gene might be associated with intellectual disability, which has yet to be confirmed. ZNF580 is supposed to be involved in endothelial cell proliferation and migration. Enhancing expression of ZNF667 can inhibit the apoptosis via inhibiting Bax and Fas expression. And ZNF667 might be a new oncogene in human hepatocellular carcinoma as a new therapeutic target through enhancing BCL-2 and decreasing BAX expression. Till now, no evidence supported these genes had much relevance to our subject.

In our study, the young ages of our cases and the lacking of comparable individuals limit the assessment of growth and development in future. So long-term follow up analysis should be guaranteed till adulthood. In addition, phenotypic diversity, incomplete penetrance, and the inheritance might be associated with the clinic pathogenicity of 19q microduplication to different degrees, which needs further evidence to illustrate.

In our study, we described three rare prenatal cases consisting of 19q microduplication, encompassing 19q13.42 locus. They presented no ultrasound structural anomalies, which enriched the phenotypic spectrums of 19q duplication. It is believed that more trisomy 19q cases with clinic manifestations and molecular genetic characterization would help to refine clear genotype-phenotype correlations. For prenatally detected 19q duplications, long term follow up should be guaranteed till adulthood to confirm whether there will be other clinical symptoms and developmental-behavioral disorders afterwards.

Abbreviations

Chromosomal microarray analysis=CMA, copy number variants=CNVs, DGV=Database of Genomic Variants, ISCN 2016=International System for Human Cytogenetic Nomenclature, NCBI=National Center for Biotechnology Information, OMIM=Online Mendelian Inheritance in Man

Declarations

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Availability of data and materials

The data and material used or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XZ wrote the first draft of the manuscript. FY and QS collected the data of all the fetuses and couples. YJ, JH and LL participated in analysis and interpretation of data. RL reviewed the manuscript and were involved in its critical revision before submission. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This report was approved by the Ethics Committee of the First Hospital of Jilin University (No.2019-299).The patients provided written informed consent for participating in this study.

Consent for publication

Written informed consents were obtained from couples for publication of this manuscript.

Competing interests

The authors declare that they have no competing interest.

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Tables

Table 1. Clinical features of previously prenatal and postnatal cases with pure 19q duplication

References	Quack et al.[14]	Bhat et al.[15]	Qorri et al.[2]	Zung et al.[16]	Palomares et al.[1]	Lugli, et al.[17]	Rim et al. [18]	Nacinovich al.[6]
Age/sex	2y/M	18m/M	27m/F	14y/M	15m/F	3y/M	5y/M	10y/M
Duplicated region	19q11.05–13.2	19q13.3–13.4	19q13.1–13.3	19q12–13.2	19q12–13.2	19q12–13.2	19q13.32	19q12q13.
Duplication size(Mb)	N.A.	N.A.	N.A.	N.A.	10.8 Mb	12.4 Mb	1.13 Mb	8.17 Mb
Inheritance	Maternal	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*
Karyotype	47,XY,r(19)(q11.05q13.2)	46,XY,dup(19)(q13.3q13.4)	46,XX,dup(19)(q13.1q13.3)	47,XY,+der(19)(q12q13.2)	46,XX,dup(19)(q12q13.2)	46,XY,dup(19)(q12q13.2)	46,XY	46,XY,dup(1(q12q13.2)
Chromosomal microarray results (hg19)	N.A.	N.A.	N.A.	N.A.	From 36.95Mb to 47.75 Mb 19q12q13.2	From 32,964 Mb (19q12) to 45,391 Mb(19q13.2)	chr19:51839641-52967920	19q12q13. (28,740,636 36,906,767
Development delay	+	+	+	+	+	+	+	–
Psychomotor retardation	+	N.A.	+	+	+	+	+	+
Craniofacial dysmorphism	Macrocephaly, hypertelorism, downslanting palpebral fissures, prominent nose, large ears and unusual shaped mouth.	Microcephaly, flat face, high frontal hairline, hypertelorism, epicanthic folds, convergent strabismus, long philtrum, downturned mouth, micrognatia, large ears, short neck with redundant skin folds.	–	Macrocephaly, round face, upslanting palpebral fissures, thick auricles.	Microcephaly, hypertelorism, epicanthic folds, strabismus, long philtrum, downturned mouth, large ears, short neck, sparce hair.	high forehead , midface, trigonocephaly, sparse eyebrows, convergent strabismus, bulbous nose, long philtrum, , high and narrow palate, short neck with redundant skin folds, protruding ears	Microcephaly, broad nasal bridge, high forehead with posterior hair-line, and upward directed corners of the eyes	macrocephaly
Brain anomaly	–	–	–	Cortical atrophy, partial agenesis of corpus callosum.	Thinning of corpus callosum and splenium.	enlargement of the frontal-temporal subarachnoid spaces, partial agenesis of the corpus callosum, dilation of the lateral ventricles, and a large cisterna magna.	–	N.A.
Cardiac malformation	–	Ductus arteriosus, left superior vena cava.	–	–	–	interatrial and interventricular defect	–	N.A.

Anomalies of urinary tract	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Obesity	+	N.A.	–	+	–	–	–	–
Skeletal anomaly	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Language disorders	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	+
Others		Left choanal stenosis			Hypotonia			Bilateral pronator syndrome with valgus knee.

Table 1. Clinical features of previously prenatal and postnatal cases with pure 19q duplication (Continued)

References	Cotter et al[3]	Rombout et al[4]	Tercanli et al[11]	Babic´ et al[21]	Petre et al[22]	Pinto et al[23]	C
Age/sex	TOP	TOP/F	TOP/M	TOP/M	TOP/N.A.	N.A.	7
Duplicated region	19q13.2q13.4	19q13.3qter	19q13.1qter	19q11qter	19q13.42	19q13.42	1
Duplication size(Mb)	N.A.	N.A.	N.A.	N.A.	1.06Mb	25kb	1
Inheritance	*De novo*	*De novo*	*De novo*	Maternal	Paternal	Maternal	N
Karyotype	46,XYdir dup(19) (q13.2;q13.4)	46,XX,der(22)t(19;22) (q13.3;p13)	46,XY,dup(19)(q13.1;qter)	46,XY,der(21) (19;21) (q11;p13)	N.A.	N.A.	4
Chromosomal micro array results (hg19)	N.A.	N.A.	N.A.	N.A.	19q13.42(53759522-54821015)×3	19q13.42(55153092-55178778)×3	1 5
Development delay	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	–
Psychomotor retardation	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	–
Craniofacial dysmorphism	–	Short neck, microretrognathia, flat nose, low set ears	N.A.	Short neck with redundant skin folds, flat nose, low set ears	N.A.	–	–
Brain anomaly	N.A.	Dilatation of the lateral ventricles	N.A.	Moderate dilatation of the IV ventricle	N.A.	–	–
Cardiac malformation	N.A.	VSD, atretic pulmonary artery, hypoplastic right heart.	VSD, aortic coarctation,continuous fusion of the left pulmonary artery with aortic arch, absent right pulmonary artery	N.A.	N.A.	N.A.	–
Anomalies of urinary tract	N.A.	Bilateral pyelo-calical dilatation	Cystic renal dysplasia, renal fusion, hydronephrosis, bilateral absence of ureters	Pyelo-calical dilatation on the left kidney, stenosis at the vesicoureteric junction, horseshoe kidney dilated left ureter	N.A.	N.A.	–
Obesity	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N
Skeletal anomaly	N.A.	Bilateral clinodactyly	Rocker bottom feet	N.A.	N.A.	N.A.	–
Language	N.A.	N.A.	N.A.	N.A.	N.A.	+	N

disorders							
Others	Cystic hygroma	Ultrasound findings: abnormal nuchal translucency	Ultrasound findings: nuchal oedema, mild hydrops fetalis with ascites, oligohydramnion. Heart Malformations,Anomalies of urinary tract	Ultrasound findings: increased nuchal fold, absence of fetal nasal bone, anomalies of central nervous system and urinary tract, intracardial calcifications	Intrauterine growth restriction, intrauterine fetal death	ASD	D

F, female; M, male; m, months; y, years; +, present; –, not present; N.A., not available; DS, Down's syndrome; ASD, Autism Spectrum Disorder; VSD, ventricular septal defect; TOP, termination of pregnancy.

Table 2. Morbid genes in the region of 19q13.42q13.43 duplication involved in our cases.

Gene	OMIM	Description	Disease
NLRP12	609648	NLR family pyrin domain containing 12	Familial cold autoinflammatory syndrome 2
PRKCG	176980	protein kinase C gamma	Spinocerebellar ataxia 14
PRPF31	606419	pre-mRNA processing factor 31	Retinitis pigmentosa 11
CNOT3	604910	CCR4-NOT transcription complex subunit 3	Intellectual developmental disorder with speech delay, autism, and dysmorphic facies
MBOAT7	606048	membrane bound O-acyltransferase domain containing 7	Mental retardation, autosomal recessive 57
TSEN34	608754	tRNA splicing endonuclease subunit 34	Pontocerebellar hypoplasia type 2C
KIR3DL1	604946	killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 1	Human Immunodeficiency Virus Type 1, Susceptibility to
NLRP7	609661	NLR family pyrin domain containing 7	Hydatidiform mole, recurrent, 1
GP6	605546	glycoprotein VI platelet	Bleeding disorder, platelet-type, 11
TNNT1	191041	troponin T1, slow skeletal type	Nemaline myopathy 5, Amish type
TNNI3	191044	troponin I3, cardiac type	Cardiomyopathy, familial restrictive, 1, Cardiomyopathy, dilated, 2A, Cardiomyopathy, dilated, 1FF, Cardiomyopathy, hypertrophic, 7
DNAAF3	614566	dynein axonemal assembly factor 3	Ciliary dyskinesia, primary, 2

Figures

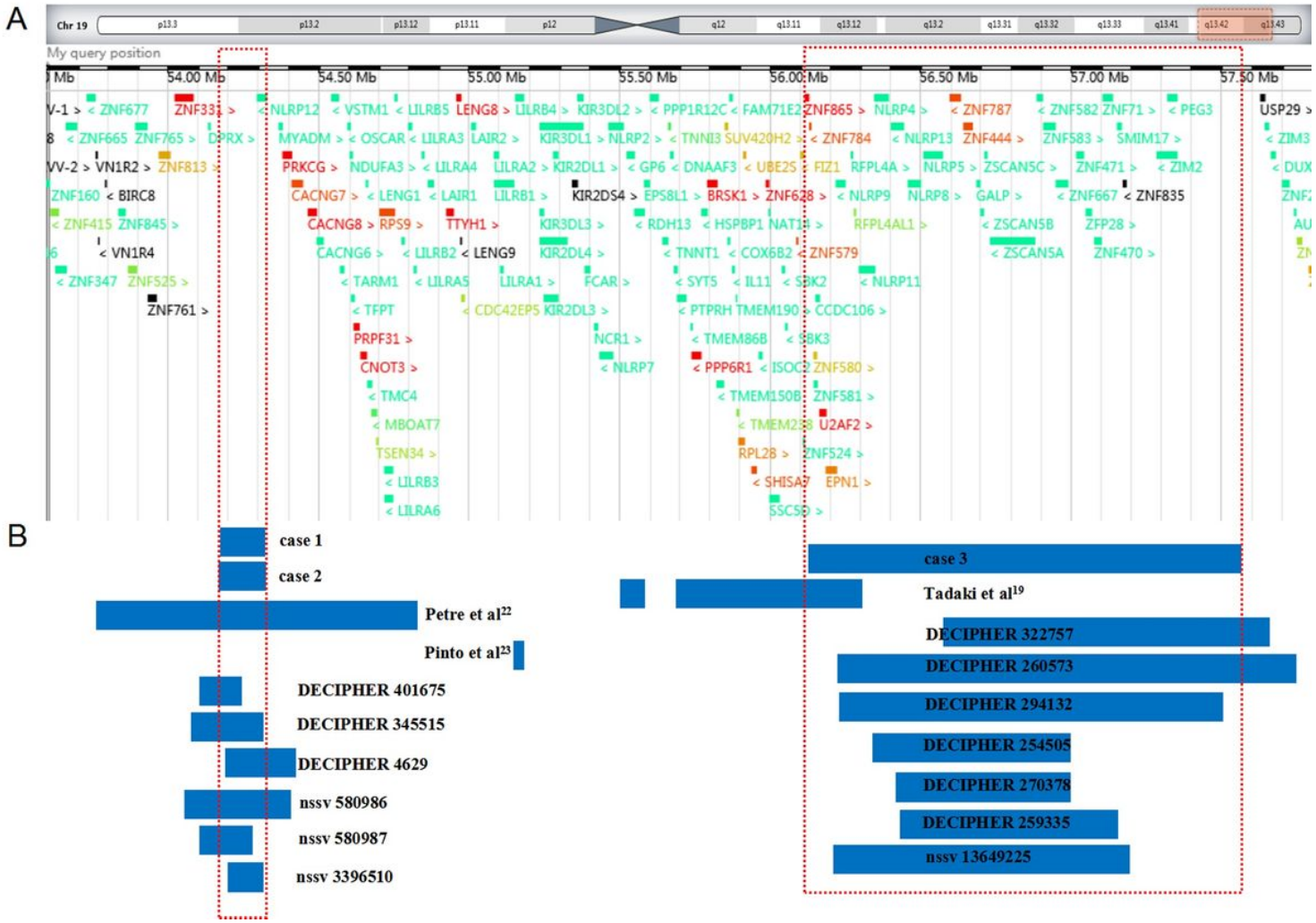

Figure 1

Scale representation of the duplicated region in the long arm of chromosome 19q13.42q13.43 (https://decipher.sanger.ac.uk/) (A) Location of genes in the region. (B) Microduplications detected in the present cases (cases 1 to 3) and previously reported microduplications involving 19q13.42q13.43 in the literature and public databases.