Duplication of 19p13.3 in 11-Year-Old Male Patient with Dysmorphic Features and Intellectual Disability: A Review

Irina Novikova¹ Paushpala Sen¹ Ann Manzardo¹ Merlin G. Butler¹

¹Departments of Psychiatry and Behavioral Sciences and Pediatrics, University of Kansas Medical Center, Kansas City, Kansas, United States

Address for correspondence Merlin G. Butler, MD, PhD, Departments of Psychiatry and Behavioral Sciences and Pediatrics, University of Kansas Medical Center, 3901 Rainbow Boulevard, MS 4015, Kansas City, KS 66160, United States (e-mail: mbutler4@kumc.edu).

J Pediatr Genet 2017;6:227–233.

Abstract

Keywords

- ▶ partial chromosome 19p13.3 duplication
- ▶ microarray
- ▶ microcephaly
- ▶ dysmorphic features
- ▶ intellectual disability
- ▶ review

We present a clinical report of an 11-year-old male patient with an interstitial duplication of 19p13.3 (829 kb in size) at genomic coordinates 3,804,495–4,033,722 bp (hg19) identified by chromosomal microarray analysis and review the literature from nine published reports adding knowledge regarding this chromosomal anomaly and clinical outcomes. The size of the duplication ranged from 0.83 to 8.9 Mb in the nine individuals. The young boy in our report was dysmorphic with microcephaly, abnormal craniofacial features, intellectual disability, aggression, and a heart murmur. All patients were found to have a psychomotor developmental delay and/or intellectual disability with the majority having microcephaly, intrauterine growth retardation, and hypotonia. Common craniofacial findings included a tall, prominent forehead, an elongated face, epicanthal folds, hypertelorism, prominent low-set ears, philtrum anomaly, and a small mouth. Other less common features included abnormal digits, sparse hair, and cardiac defects. Clinical features, chromosome duplication sizes, locations, and the number of genes will be summarized in a tabular form.

Introduction

A small but growing body of scientific literature is emerging about the clinical findings of those with the 19p13.3 micro-deletion or duplication. Most reported individuals with a submicroscopic 19p13.3 rearrangement have a deletion as opposed to a duplication.¹ Clinical findings in patients with the rare 19p13.3 duplication include intrauterine growth restriction, developmental delay, intellectual disability, hypotonia, feeding difficulties, microcephaly, proportional short stature, ear anomalies, tall, or prominent forehead, wide nasal bridge, and abnormal fingers and/or toes with syndactyly.^{1–6} Rarely, cardiac problems, skeletal malformations, and early-onset puberty were reported.^{1–4} Nevado et al¹ reported that patients with either the deletion or duplication of the 19p13.3 chromosomal region had similar

findings; however, those with the duplication showed fewer dysmorphic features and less severe intellectual disability.¹ Due to a paucity of knowledge, the full spectrum of clinical findings associated with the 19p13.3 duplication is yet to be fully elucidated. Hence, we report an 11-year-old male patient with an interstitial duplication of chromosome 19p13.3 that included 21 disease-causing genes recorded in the Online Mendelian Inheritance in Man (OMIM) database (available at: www.omim.org), reviewed the medical literature, and summarized the clinical and genetic findings to delineate this rare cytogenetic duplication further.

Clinical Report

Our 11-year-old male patient lived in a foster home and removed from the care of his biological parents due to

received

February 28, 2017

accepted after revision

April 28, 2017

published online

June 2, 2017

Copyright © 2017 by Georg Thieme
Verlag KG, Stuttgart · New York

DOI <https://doi.org/10.1055/s-0037-1603650>.
ISSN 2146-4596.

neglect; therefore, limited information was available about his earlier personal, family, or medical histories. He was born without congenital defects. He had a history of developmental delays but without chronic health problems. He had ear tubes placed at 5 years of age and currently wears eyeglasses to correct myopia. He has a 10-year-old biological sister who reportedly resembles the proband in physical appearance and also has cognitive problems (IQ score of 61). Also, the biological parents have unexplained learning disabilities. Our patient has trouble sleeping and was diagnosed with attention-deficit/hyperactivity disorder, posttraumatic stress disorder, and an unexplained learning disability. He exhibited features of autism, such as repetitive play, and the need for routine. The foster mother now homeschools the patient due to a history of disruptive and aggressive behaviors in the school setting where he was previously enrolled in an Individualized Education Program.

Cognitive evaluation at 9 years of age showed delay for his chronological age with a score at the sixth percentile on the Peabody Picture Vocabulary Test, Fourth Edition (PPVT-IV) and an age equivalent of 4.9 years. He scored at the first percentile on the Expressive Vocabulary Test (age equivalent 6.0 years) and less than first percentile on the Structured Photographic Expressive Language Test (SPELT-3) (age equivalent <4.0 years). According to the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV), his full-scale IQ was 51 (<0.5th percentile). His verbal comprehension was at the 0.5th percentile, perceptual reasoning at the 2nd percentile, working memory at the 0.3rd percentile, and processing speed recorded at less than the 0.5th percentile. He also received low or moderately low ratings for communication, daily living skills, socialization, interpersonal relationships, and adaptive behavior domains using the Vineland Adaptive Behavior Scales II–Teacher Rating Form.

During his clinical genetics evaluation at the age of 11 years, 5 months, his height was 132.5 cm (<3rd percentile), weight was 26.8 kg (<10th percentile), and head circumference was 50.5 cm (5th percentile). Other measurements included: ear length 5.3 cm (15th percentile), inner canthal distance 2.5 cm (<3rd percentile), outer canthal distance 7 cm (<3rd percentile), total hand length 13.7 cm (<3rd percentile), and middle finger length 5.5 cm (<3rd percentile). He had two posterior hair whorls at 5 cm apart that were displaced anteriorly. He had prominent appearing fleshy, soft ears with simple architecture, and attached ear lobes bilaterally. He had an elongated triangular-shaped face, a prominent forehead, a stellate iris pattern bilaterally, epicanthal folds, a prominent nose with malar hypoplasia, a flat appearing philtrum with a thin appearing upper lip, high-arched palate with a single uvula, a small chin, and small appearing mouth (►Fig. 1). He exhibited normal strength of both upper and lower extremities with no leg length asymmetry. He had a pigmented birthmark (2 cm by 6 cm) on his right lower leg with generalized skin marbling, a protruding right scapula, bilateral single palmar creases, hypotonia, and generalized hyperflexibility of joints with two to three toe syndactyly bilaterally. A systolic heart murmur was heard best at the left sternal border (grade II/VI) with radiation to the neck

Fig. 1 Our patient at 11 years, 5 months with a 19p13.3 duplication showing frontal and facial views illustrating an elongated triangular-shaped face, a prominent forehead, epicanthal folds, and a wide-appearing neck. His nose was prominent with malar hypoplasia, a flat appearing philtrum, a thin upper lip, high-arched palate with a single uvula, a small chin, and small appearing mouth.

area. Normal distal pulses and heart rhythm were noted without cyanosis.

A chromosomal microarray consisting of 180,000 copy number probes (Agilent Technologies, Santa Clara, California, United States) was previously performed and detected an 829 kb interstitial duplication of chromosome 19p13.3 [3,804,495–4,633,772bp, GRCh37, hg19] (►Fig. 2). This chromosomal anomaly was described previously in either a deletion or duplication form and included the following genes collectively: *ATCAY*, *NMRK2*, *DAPK3*, *EEF2*, *PIAS4*, *ZBTB7A*, and *MAP2K2*. No other chromosomal abnormality or copy number variant were detected. The biological parents were not available for genetic testing. Informed consent was obtained for this report from the designated guardian for the patient in accordance with institutional standards for the protection of human research subjects.

Discussion

Our patient has a rare chromosome 19p13.3 duplication reported previously in the literature in nine individuals (see ►Table 1). This duplication included 21 OMIM categorized genes: *ATCAY*, *NMRK2*, *DAPK3*, *EEF2*, *PIAS4*, *ZBTB7A*, *MAP2K2*, *CREB3L3*, *SIRT6*, *EBI3*, *SHD*, *TMIGD2*, *FSD1*, *STAP2*, *SH3GL1*, *CHAF1A*, *UBXN6*, *PLIN4*, *PLIN5*, *LRG1*, and *SEMA6BS*. This duplication varied in size in those reported in the literature with potentially several genes playing a role in our patient's phenotype. For example, one of the genes is

Fig. 2 Chromosomal microarray analysis showing the copy number probes and location of the 0.83 Mb interstitial duplication of chromosome 19p13.3 (chr19:3,804,495–4,633,722bp with hg build 19) found in our patient and position of the involved 21 genes. The copy number state represents the duplication identified by the chromosomal microarray analysis (performed by Lineagen Laboratory, Salt Lake City, Utah, United States) with the copy number state identified by the signals of copy number variant probes represented as dots found above the horizontal line indicating a duplication within the chromosome 19p13.3 band. The location of genes is represented within this chromosomal region by the cluster of vertical bars arranged above the chromosome 19p13.3 band at the bottom. The numbers represent the genomic coordinates for chromosome 19. The chromosome 19 ideogram (on the right) shows the location of the duplicated region.

PIAS4 (protein inhibitor of activated Stat 4), and Nevado et al¹ reported an association with macro/microcephaly in individuals with the 19p13.3 microdeletion/microduplication syndrome; the duplication is associated with microcephaly while a single copy of this gene is associated with macrocephaly.¹ Our patient's head size was small (50.5 cm, fifth percentile) which is in line with the observation mentioned above. In the review of the literature, we found that seven out of nine individuals with the 19p13.3 microduplication had microcephaly (see ►Table 1). One subject reported by Nevado et al¹ was normocephalic, but her microduplication did not include the *PIAS4* gene. A second individual with a normal head circumference (30.5 cm, 10th percentile) at birth was reported, but it is unknown whether this patient's chromosome duplication included the *PIAS4* gene.⁴

The *ATCAY* (cerebellar ataxia, Cayman type) gene is reportedly important for neural development⁷ and associated with autosomal recessive Cayman cerebellar ataxia, a disorder first discovered in individuals living on the Grand Cayman Island. Individuals with this condition have hypotonia, psychomotor impairment, nystagmus, ataxia, and intention tremor.⁸ Our patient and all individuals reported with the 19p13.3 duplication had a psychomotor developmental delay (see ►Table 1), and possibly having an extra copy of the *ATCAY* gene may have a deleterious effect on psychomotor development.

The *EEF2* (eukaryotic translation elongation factor 2) gene is recognized to be critical for protein synthesis.⁹ A heterozygous

missense mutation in the *EEF2* gene was found in a five generation family with "autosomal dominant late-onset spinocerebellar ataxia-26." The mutation was segregating with the disease in most cases: 24 affected and 2 unaffected family members carried the mutation.¹⁰ Neither our patient nor cases in the literature were reported to have a history of ataxia. However, all but one of the subjects (age 39 years) were children at the time of the report, and it is unknown whether having an extra copy of the *EEF2* gene may put them at risk of developing late-onset spinocerebellar ataxia in the future.

The *MAP2K2* (mitogen-activated protein kinase 2) gene when disturbed is associated with the cardiofaciocutaneous syndrome. Cardiac problems in this syndrome include pulmonic stenosis, atrial septal defect, and hypertrophic cardiomyopathy. Individuals with this condition may also have a long appearing face with a high forehead, hypertelorism, down-slanting eyes, low-set ears, and a small chin. Most people with the cardiofaciocutaneous syndrome have skin findings including dry skin, dark-colored pigmented area, and keratosis pilaris. Individuals with this syndrome usually have developmental delays and intellectual disability.¹⁰

Certain features of the cardiofaciocutaneous syndrome overlap with those seen in our patient and individuals with the 19p13.3 duplication reported in the literature including developmental delays, intellectual disability, low-set ears, a tall forehead, a long appearing face, and hypertelorism. The overlapping features seen in individuals with the cardiofaciocutaneous syndrome and the 19p13.3 duplication may be

Table 1 Demographics, clinical, and molecular genetics of individuals with 19p13.3 duplication

References	Andries et al (2002)	Lybaek et al (2009)	Sigberg et al (2011)	Ishikawa et al (2013)	Nevado et al (2015)	Orellana et al (2015)	Present case	Total	%
Cases reported	1	1	1	1	2	3	1	10	
Demographics									
Age	21 m	2.5 y	9 y	3 y	6 y	10 y	39 y	11.5 y	Mean = 9.2 y
Gender	M	F	M	F	F	M	F	M	5 M, 5 F
Growth									
Height	N/A	Short stature at birth, 42.5 cm (3%)	N/A	75 cm (−5 SD)	N/A	N/A	N/A	132.5 cm (<3%)	
Weight	N/A	At birth 1.79 kg (3%)	N/A	7.68 kg (−3.4 SD)	N/A	N/A	N/A	26.8 kg (<10%)	
Head circumference	−3 SD	At birth 30.5 cm (10%)	Microcephaly	42 cm (−4.0 SD)	−4.4 SD	<3%	<3%	50.5 cm (5%)	
Intrauterine growth restriction	−	+	N/A	+	N/A	+	+	N/A	83
C-section	−	+	−	+	−	+	−	−	3/10
Neurodevelopmental features									
Psychomotor developmental delay/intellectual disability	+	+	+	+	+	+	+	+	10/10
Hypotonia	N/A	N/A	+	+	+	+	+	+	88
Microcephaly	+	−	+	+	+	+	+	+	8/10
Craniofacial features									
Abnormal nose	Short	+	Wide-based	+	+	+	+	Wide-based	10/10
Tall, prominent forehead	+	+	+	+	+	+	+	+	10/10
Small mouth	+	+	N/A	+	N/A	+	+	+	6/6
Philtrum anomaly	+	Short	Short	Short	Short	+	Flat	Flat	9/10
Hypertelorism	+	+	+	+	+	+	+	+	8/9
Abnormal digits	Long toes	Small feet, asymmetric length	−	−	+	Long fingers	Long fingers	Small hands	8/10
Prominent low-set ears	+	−	N/A	+	−	+	+	+	7/8
Elongated face	−	+	N/A	−	+	+	+	+	6/8
Epicanthal folds	N/A	−	+	+	−	+	−	+	6/9

Table 1 (Continued)

References	Andries et al (2002)	Lybaek et al (2009)	Siggberg et al (2011)	Ishikawa et al (2013)	Nevado et al (2015)		Orellana et al (2015)	Present case	Total	%	
Abnormal hair pattern	Sparse	Sparse	N/A	Sparse	–	–	–	Curly	Coarse	5/9	56
Upper lip anomaly	+	–	Thin	+	+	–	–	–	Thin	5/10	50
Other											
		Bilateral hip dysplasia, cardiac defect	Short, down-slanting fissures	Strabismus, short, down-slanting fissures, small chin, precocious puberty, kyphoscoliosis, bilateral hip dislocations, cardiac defects, pulmonary hypertension	1st cousins				High-arched palate, heart murmur, ptosis, ADHD, small chin, hypermobility, aggression, pigmented birthmark		
Genetics											
Genetic testing	FISH	Microarray	Microarray	Microarray	Microarray		Microarray	Microarray			
Duplication area	19p13.3-pter	19p13.2-p13.3 8.9 Mb	19p13.3 0.81 Mb	19p13.3 6.1 Mb	19p13.3 2.39 Mb	19p13.3 1.48 Mb	19p13.3 4.95 Mb	19p13.3 0.83 Mb			
19p13.3 number of genes	N/A	215	N/A	150	N/A	N/A	253	21			
Duplication coordinates	N/A	1,489,000–10,449,000bp (hg19)	3,976,000–4,790,000bp (hg19)	327,273–6,106,229bp (hg19)	2,487,767–4,882,351-bp (hg19)	2,329,320–3,808,325-bp (hg19)	1,952,590-6,908,729bp (hg19)	3,804,495-4,633,722bp (hg19)			

Abbreviation: FISH, fluorescence in situ hybridization.

Fig. 3 The location and size of the individual chromosome 19p duplications are shown for the reported cases including genomic coordinates with respect to our present case. The 21 OMIM genes duplicated in our case are represented with bands 19p13.2 and 19p13.3 shown on the left. OMIM, Online Mendelian Inheritance in Man.

due to abnormalities of the *MAP2K2* gene although mutations are noted in the cardiofaciocutaneous syndrome and not deletions or duplications encompassing this gene.

In the review of the literature, nine other patients (five females and four males) were identified ranging in age from 21 months to 39 years with an average age of 9.2 years. They all had short stature and decreased weight. The 19p13.3 duplication was identified by microarray analysis in eight subjects while fluorescence in situ hybridization was utilized in one subject. The size of the duplication ranged from 0.83 to 8.9 Mb and involved 21 to 253 genes. All patients were found to have a psychomotor developmental delay and/or intellectual disability. The majority of subjects had microcephaly (80%), intrauterine growth retardation (83%), and hypotonia (88%). Common craniofacial findings included a tall, prominent forehead (100%), a small mouth (100%), philtrum anomaly (90%), hypertelorism (89%), abnormal digits, generally long (80%), prominent low-set ears (78%), an elongated face (75%), epicanthal folds (67%), abnormal hair pattern, generally sparse (56%), and upper lip anomaly (50%). Other features seen in some individuals included early-onset puberty, joint findings (hip dislocations, hypermobility), high-arched palate, and cardiac defects. The collection of overlapping features recognized are components of the 19p13.3 duplication.

The sizes of the 19p13.3 duplication seen in our summary of reported cases were variable or inconsistent in size excluding the duplication reported in the cousins from an extended family by Orellana et al (2015) (→ **Fig. 3**). This family carried an interstitial intrachromosomal 19 insertional translocation resulting in a 19p13.3 duplication in three affected members. The variability of duplication size in sporadic cases suggests the absence of common chromosome breakpoints contributing to deletions or duplications within a chromosome region as noted in other syndromes such as Prader-Willi syndrome where the 15q11-q13 region is deleted due to common breakpoints contributing to the deletion process.^{11,12}

Genetic aberrations including deletions, duplications, or translocations can influence the severity of clinical presentation and recurrence risks depending on the type of chromosomal anomaly.¹³ Clinical correlates of autosomal chromosomal abnormality databases linked to genome-wide association studies (GWAS) have been used to identify potentially associated clinical findings. For example, Jouni et al (2013) reported a GWAS of 3,336 adults and 0.75% had autosomal chromosomal abnormalities, and nearly one-third of them had hematological malignancies, specifically 20q deletions, and myeloproliferative disorders.¹⁴ Furthermore, whole exome sequencing has been used to implicate

gene mutations in the causation of uncharacterized syndromes such as *INO80D* in aortic hypoplasia, premature atherosclerosis, and arterial stiffness.¹⁵ We were unable to study other family members or perform a karyotype on our patient at this time which could impact on genetic counseling when approaching reproductive age. A karyotype or exome sequencing would be recommended in the future to assist in identifying the chromosomal anomaly leading to the 19p13.3 duplication such as chromosome translocations which could impact recurrence risk by involving chromosome 19 or other chromosome rearrangements in the offspring. The authors recommend the reporting of other patients with the 19p13.3 duplication to further characterize the clinical phenotype and variation with relationship to the size and location of the chromosomal anomaly, genes involved, and clinical presentation.

Acknowledgment

The authors thank the foster family and patient with the 19p13.3 duplication and Charlotte Weber for technical support. The authors acknowledge the National Institute of Child Health and Human Development for support including grant no. HD02528.

References

- 1 Nevado J, Rosenfeld JA, Mena R, et al. PIAS4 is associated with macro/microcephaly in the novel interstitial 19p13.3 microdeletion/microduplication syndrome. *Eur J Hum Genet* 2015;23(12):1615–1626
- 2 Andries S, Sartenaer D, Rack K, et al. Pure terminal duplication of the short arm of chromosome 19 in a boy with mild microcephaly. *J Med Genet* 2002;39(10):E60. Doi: 10.1136/jmg.39.10.e60
- 3 Ishikawa A, Enomoto K, Tominaga M, et al. Pure duplication of 19p13.3. *Am J Med Genet A* 2013;161A(09):2300–2304
- 4 Lybaek H, Ørstavik KH, Prescott T, et al. An 8.9 Mb 19p13 duplication associated with precocious puberty and a sporadic 3.9 Mb 2q23.3q24.1 deletion containing NR4A2 in mentally retarded members of a family with an intrachromosomal 19p-into-19q between-arm insertion. *Eur J Hum Genet* 2009;17(07):904–910
- 5 Orellana C, Roselló M, Monfort S, Mayo S, Oltra S, Martínez F. Pure duplication of 19p13.3 in three members of a family with intellectual disability and literature review. Definition of a new microduplication syndrome. *Am J Med Genet A* 2015;167(07):1614–1620
- 6 Siggberg L, Olsén P, Nantö-Salonen K, Knuutila S. 19p13.3 aberrations are associated with dysmorphic features and deviant psychomotor development. *Cytogenet Genome Res* 2011;132(1-2):8–15
- 7 Online Mendelian Inheritance in Man. MIM Number: 601238. Available at: <https://omim.org/entry/601238?search=MIM%20Number%3A%20601238&highlight=mim%20601238%20number>. Accessed December 21, 2016
- 8 National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda, MD: The Library; ATCAY gene [reviewed 2016 Dec. 21; cited 2016 Dec. 27]. Available at: <https://ghr.nlm.nih.gov/gene/ATCAY>. Accessed December 21, 2016
- 9 National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda, MD: The Library; EEF2 gene [reviewed 2016 Dec. 21; cited 2016 Dec. 27]. Available at: <https://ghr.nlm.nih.gov/gene/EEF2>. Accessed December 21, 2016
- 10 National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda, MD: The Library; cardiofaciocutaneous syndrome [reviewed May 2012; cited 2016 Dec. 27]. Available at: <https://ghr.nlm.nih.gov/condition/cardiofaciocutaneous-syndrome#>. Accessed December 21, 2016
- 11 Angulo MA, Butler MG, Cataletto ME. Prader-Willi syndrome: a review of clinical, genetic, and endocrine findings. *J Endocrinol Invest* 2015;38(12):1249–1263
- 12 Butler MG. Single gene and syndromic causes of obesity: illustrative examples. *Prog Mol Biol Transl Sci* 2016;140:1–45
- 13 Carvalho CM, Lupski JR. Mechanisms underlying structural variant formation in genomic disorders. *Nat Rev Genet* 2016;17(04):224–238
- 14 Jouni H, Shameer K, Asmann YW, Hazin R, de Andrade M, Kullo IJ. Clinical correlates of autosomal chromosomal abnormalities in an electronic medical record-linked genome-wide association study: A case series. *J Investig Med* 2013;1(04). Doi: 10.1177/2324709613508932
- 15 Shameer K, Klee EW, Dalenberg AK, Kullo IJ. Whole exome sequencing implicates an *INO80D* mutation in a syndrome of aortic hypoplasia, premature atherosclerosis, and arterial stiffness. *Circ Cardiovasc Genet* 2014;7(05):607–614