Received: 22 March 2021 | Revised: 7 May 2021 | Accepted: 8 July 2021

DOI: 10.1002/mgg3.1755

Molecular Genetics & Genomic Medicine Open Access WILEY

CLINICAL REPORT

Interstitial duplication of 20q11.22q13.11: A case report and review of literature

Logan Goetzinger[1] | **Rachel D. Starks**[2] | **Kyle Dillahunt**[3] | **Heather Major**[3] | **Jaime M. Nagy**[3] | **Alpa Sidhu**[3]

[1]Carver College of Medicine, University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA

[2]Department of Pathology, University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA

[3]Division of Medical Genetics and Genomics, The Stead Family Department of Pediatrics, University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA

Correspondence
Alpa Sidhu, Division of Medical Genetics and Genomics, The Stead Family Department of Pediatrics, University of Iowa Hospitals and Clinics, Iowa City, IA 52246, USA.
Email: alpa-sidhu@uiowa.edu

Abstract

Background: Reports of interstitial duplication of chromosome 20q11 are rare with only nine published patients to date.

Methods: We performed karyotype and chromosomal microarray analysis on a peripheral blood sample for our patient and reviewed the genes in the region to provide genotype–phenotype correlation.

Results: Clinical features of the patient include minor dysmorphic facial features, shorthands and feet, bilateral conductive hearing loss, global developmental delay, and behavioral issues with attention deficit hyperactivity disorder. Together with previously published cases of 20q11 duplication, we show that patients with overlapping duplications share a similar clinical phenotype of dysmorphic craniofacial features and developmental delay.

Conclusion: We report an 8-year-old girl with a 9.1 Mb interstitial duplication of chromosome 20q11.22q13.11. Our observations suggest that a novel duplication syndrome and documentation of similar cases will further help clarify the phenotype.

KEYWORDS

chromosome 20q duplication, developmental delay, dysmorphic facial features

1 | CASE REPORT

Interstitial duplications of the long arm of chromosome 20 are rare. Previously published cases of isolated trisomy 20q have suggested a novel duplication syndrome, but only a few cases have been reported so far (Avila et al., 2013; Blanc et al., 2008; Breen et al., 1999; Cebi et al., 2016; Iglesias et al., 2006; Wanderley et al., 2005). Previous publications by Avila et al., (2013) and Cebi et al., (2016) reference another case report but we were unable to find this in the literature (referenced as Burbridge J, Reid E, Swanton S, 2003. A novel duplication of the long arm of chromosome 20 in a newborn. J Med Genet 40; pS57). Common features reported previously include dysmorphic facial features with metopic ridging, small and retracted jaw, shorthands, developmental delay, and intellectual disability. In this case report, we present an 8-year-old girl with isolated 9.1 Mb duplication of chromosome 20q11.22q13.22 inserted into chromosome 21 at 21q22.3. We go on to compare the previously reported cases with our patient and propose candidate genes within the smallest region of overlap (SRO) that may contribute to the phenotype.

The proband is an 8-year-old girl born full-term at 40 weeks gestation to a gravida six mother. The pregnancy, birth, and postnatal history are largely unknown due to separation from

biological parents and resultant placement in the foster care setting with subsequent adoption. Reported history provided by the adoptive parents includes methamphetamine abuse during pregnancy. The duplication was identified when amniocentesis was performed due to suspected chromosomal abnormality in a sibling and confirmed postnatally by a chromosomal microarray with a limited 5-cell karyotype. At the age of 3 years, the patient presented to our clinic with known chromosomal abnormality and global developmental delay. Her clinical picture at that visit included bilateral mild–moderate conductive hearing loss, dysmorphic features of posteriorly rotated ears, wide nasal tip, and shorthands. Hearing aids were subsequently placed at age 4 years and developmental interventions continued with physical, occupational, and speech therapies. The patient later returned for follow-up at the age of 8 years. Her clinical picture now included behavioral issues with a diagnosis of attention deficit hyperactivity disorder and aggression. She also struggled with nocturnal enuresis and chronic constipation. She was in a special education classroom and received speech therapy. Physical examination revealed posteriorly rotated ears, tubular nose with bulbous tip, and shorthands and feet (Figure 1a). Chromosomal microarray was obtained and detected a 9.1 Mb likely pathogenic duplication at 20q11.22q13.11 {arr[GRCh37] 20q11.22q13.11(32831962–41996173) x 3}. The duplication was reported as likely pathogenic due to gene content and similarity to previously reported cases. However, the duplication did not completely overlap previously reported cases and there is currently no established critical region for pathogenic duplications of proximal 20q. No additional copy number variants were identified. Karyotype analysis demonstrated that the chromosome 20 material was directly inserted into a derivative chromosome 21 at band q22.3 [46,XX,der(21)ins(21;20)(q22.3;q11.2q13.1)] (Figure 1b).

Despite repeated attempts to contact biological parents, parental karyotypes were unable to be obtained. The adoptive mother reported that our patient's paternal half-sibling had a chromosomal abnormality that is unconfirmed. The inheritance pattern of the duplication is unknown.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

This study was conducted in accordance with the Declaration of Helsinki and national guidelines. Written informed consent for participation and publication was obtained from the adoptive parent.

2.2 | Karyotype analysis

Lymphocytes from a peripheral blood specimen were stimulated with phytohemagglutinin and cultured for 72 h. Cells were arrested in metaphase by Colcemid treatment for 30 min followed by incubation for 30 min at room temperature with hypotonic solution (0.075 molar potassium chloride). Cells were then fixed three times with 3:1 methanol/acetic acid. Chromosomes were banded using the G-band method. Metaphase images were captured in CytoVision computerized imaging system (Leica Microsystems). Five G-banded metaphases were analyzed and karyograms prepared from computer-assisted digital images of these metaphases.

2.3 | Chromosomal microarray

Chromosomal oligonucleotide microarray and SNP analysis were done using an Affymetrix CytoScanHD hg19 (NCBI build 37) whole-genome array consisting of 1.9 million non-polymorphic markers and 750,000 SNP probes, with an average probe spacing of about 1.2 kb. Data were extracted and processed using Affymetrix ChAS software (Affymetrix, version 1.2.2) and Nexus Copy Number (BioDiscovery, version 7) software.

3 | DISCUSSION

Here we report an 8-year-old girl with a 9.1 Mb duplication of chromosome 20q11.2 and compare the phenotypic presentation with other published reports of interstitial duplications in the region. Comparisons between case reports suggest common clinical features of shorthands, developmental delay, and dysmorphic facial features. To this date, cases of isolated 20q duplication are rare, involving approximately seven previously published reports with a total of nine patients (Avila et al., 2013; Blanc et al., 2008; Breen et al., 1999; Cebi et al., 2016; Iglesias et al., 2006; Wanderley et al., 2005). Of these nine patients, two were excluded from further comparison due to insufficient phenotypic information, lack of clearly defined breakpoints, and inability to review the publication (Breen et al., 1999) (case report referenced as Burbridge J, Reid E, Swanton S, 2003. A novel duplication of the long arm of chromosome 20 in a newborn. J Med Genet 40;pS57). An additional two were excluded due to them having more distal duplications of chromosome 20 than that found in our patient (Blanc et al., 2008; Iglesias et al., 2006). Our patient is unique from previously reported cases as the duplicated chromosome 20 material is inserted into the long arm of chromosome 21. The observed phenotype overlaps with other cases of tandem 20q duplications suggesting copy gain of this region is responsible for clinical findings. However, the possibility of disruption of a gene or regulatory element at the 21q insertion breakpoint that contributes to our patient's clinical picture cannot be ruled out.

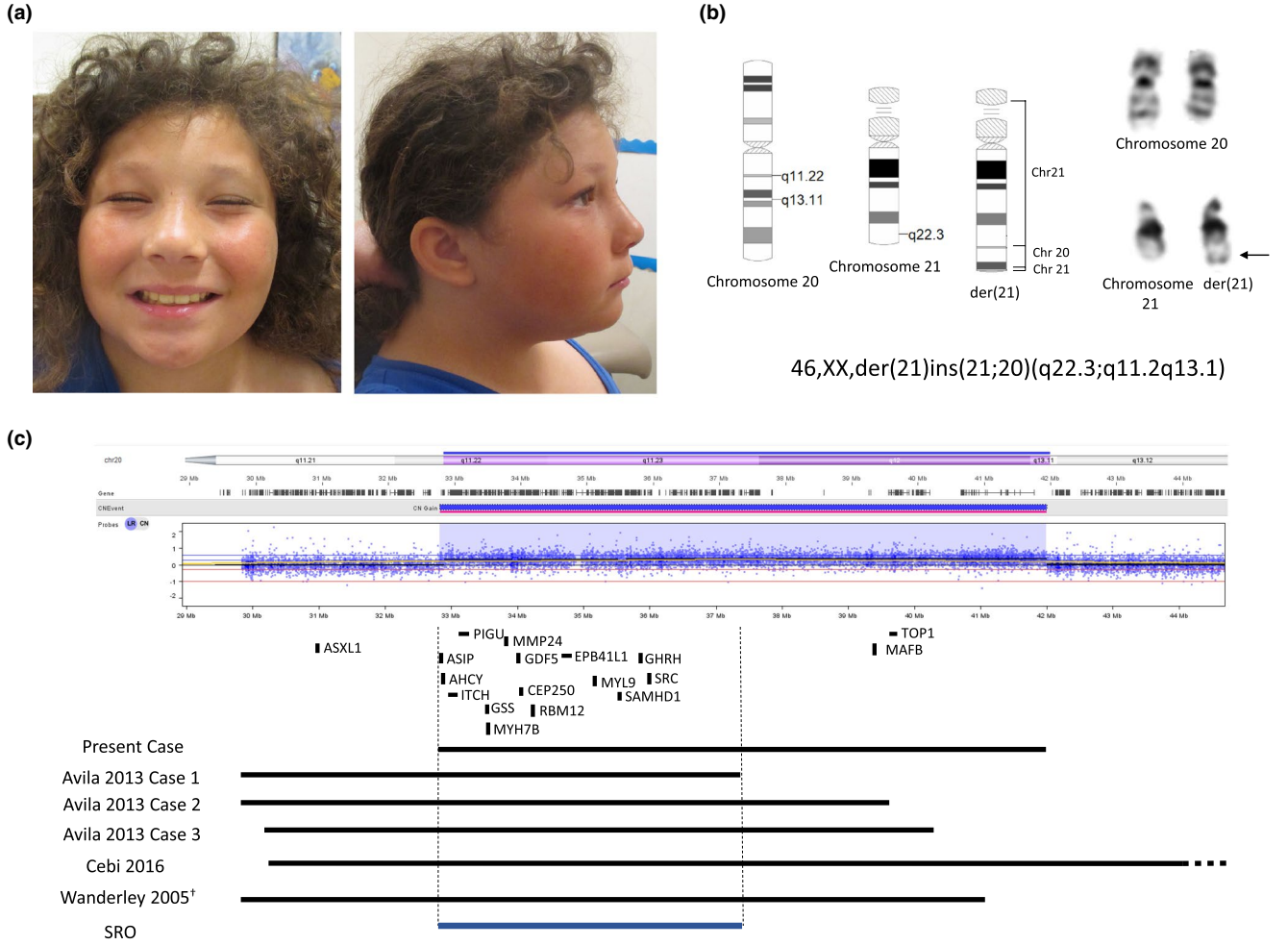

FIGURE 1 (a) Facial appearance of our patient at age 8 years. Dysmorphic facial features include low-set and posteriorly rotated ears and tubular nose with bulbous tip. (b) Chromosome analysis depicting normal chromosome 20 pair and derivative chromosome 21 showing interstitial duplication of 20q11.22q13.22 [46,XX,der(21)ins(21;20)(q22.3;q11.22q13.11)]. (c) Chromosomal microarray depicting 9.1 Mb duplication of chromosome 20q. Solid lines represent the respective duplication regions of the present case and compare five previously reported cases. Breakpoints for patients reported in Wanderley et al. had to be approximated from the karyotype designation. The smallest region of overlap (SRO) is the solid blue line. †Breakpoints approximated from karyotype designation

Table 1 outlines and compares our patient to five other cases with overlapping duplications of 20q. Common clinical findings include dysmorphic features, shorthands, and developmental delay. In comparison with other reports, our patient had minor dysmorphic facial features of low-set and posteriorly rotated ears and tubular nose with bulbous tip. In addition, our patient had a normal 2-dimensional echocardiogram and a normal retroperitoneal ultrasound demonstrating an absence of major organ defect.

We attempted to identify candidate genes responsible for clinical features seen in both our patient and other reported cases. Figure 1c outlines the duplicated region with the involved genes and compares it to five reported cases to outline the smallest region of overlap (SRO). Previous reports have suggested *ASXL1* (OMIM#612990) as a candidate gene (Avila et al., 2013). The *ASXL1* gene is a homolog of the *Asx* homeotic gene in Drosophila and is thought to be involved in the maintenance of *HOX* group of genes, particularly in those involving body patterning and chromatin remodeling. Mutations in this gene have been identified in at least half of patients with Borhing-Opitz syndrome (BOS) (Hoischen et al., 2011; Magini et al., 2012). Given the comparable clinical features among previously published 20q duplications and those with BOS, Avila et al., (2013) hypothesized that *ASXL1* duplication may be associated with a milder phenotype comparable with BOS. The features of patients attributed to the gene *ASXL1* include trigonocephaly, prominent metopic suture, exophthalmos, anteverted nostrils, growth retardation, and developmental delay. However, the *ASXL1* gene is not present in the duplication identified in our patient. In keeping with previous reports, our patient does not exhibit the craniofacial features described in patients with duplication of the *ASXL1* gene.

Similar duplications were not found either in the DGV gold data set or in the ClinVar. A DECIPHER database search

TABLE 1 Clinical Features of isolated 20q duplication cases in comparison with our patient

	Present case	Cebi 2016	Avila (1) 2013	Avila (2) 2013	Avila (3) 2013	Wanderley 2005
Karyotype	46,XX,der(21)ins(21;20)(q22.3;q11.22q13.11)	46,XY,dup(20)(20q11.21-q13.13) de novo	46,XY,dup(20) (q11.21q11.23) de novo	NR	46,XY,dup(20)(q11.2q12) de novo	46,XY,dup(20)(q11.2q12) de novo
CMA	hg19 (32,831,962–41,996,173)	hg19 (31,146,232–48,340,036)	hg19(29,833,609–37,354,404)	hg19 (29,833,609–39,615,698)	hg19 (30,193,414–40,199,371)	NR
Parental testing	Not completed	Completed	Completed	Completed	Completed	Completed
Size	9.1 Mb	17.1 Mb	7.5–8.5 Mb	9.78–9.98 Mb	10.0–10.14 Mb	NR
Sex	Female	Male	Male	Male	Male	Male
Age	8 years	15 years	8 years	4.5 years	1.5 years	16 months
Ethnicity	African American/Caucasian	NR	Caucasian	Caucasian	Caucasian	NR
Craniofacial features						
Coarse face	−	−	+	−	+	NR
Microcephaly	−	−	−	+	-	−
Metopic ridging	−	NR	+	+	+	+
Epicanthus	−	+	+	+	+	+
Depressed nasal bridge	−	−	+	+	+	−
Low set ears	+	+	+	+	+	−
Retrognathia	−	+	+	−	+	+
Musculoskeletal features						
Shorthands	+	+	+	+	+	+
Short Feet	+	NR	+	−	−	+
Clinodactyly	+	NR	+	−	−	−
Neurological features						
Developmental delay	+	+	+	+	+	+
Intellectual disability	−	+	+	+	+	+
Attention deficit disorder	+	NR	+	−	−	NR
Myopia	−	+	−	−	−	+
Hypotonia	+	NR	NR	NR	NR	NR
Other						
Cryptorchidism	N/A	+	−	+	+	+
Cardiac malformation	−	−	-	−	−	−
Growth delay	−	NR	−	−	+	+
Sacral dimple	−	NR	−	−	−	+
Hearing loss	+	NR	NR	NR	NR	NR

Abbreviations: −, not present; +, present; N/A, not applicable; NR, not reported.

showed seven overlapping duplications (Firth et al., 2009). Five of the duplications found in DECIPHER were similar to those reported in Avila et al. and included the gene *ASXL1*. Limited phenotypic information reported for the remaining two included developmental delay and dysmorphic facial features. Examination of the overlapping region seen in our patient and in previously described cases of 20q duplication revealed 63 protein-coding genes, including 10 genes associated with human disorders. However, none of the genes in this region are presently known to cause a phenotype when duplicated. Among the genes identified, the most striking of these include those related to the development and maintenance of connective tissue and signaling from the extracellular matrix to the nucleus. Within this region is *GDF5* (OMIM #601146), which encodes a growth factor and signaling molecule involved in bone and cartilage formation that is a member of the TGF-beta superfamily. Loss-of-function pathogenic variants in *GDF5* are associated with both autosomal dominant and recessive disorders including brachydactyly, Grebe type chondrodysplasia, and Hunter-Thompson type acromesomelic dysplasia. The dominant negative effect of a missense mutation in *GDF5* in a family with Grebe type chondrodysplasia was shown to be caused by the inability to secrete other related BMP family members (Thomas et al., 1997). Gain-of-function pathogenic variants in *GDF5* are associated with type 2 multiple synostoses syndrome and proximal symphalangism (Degenkolbe et al., 2013; Plett et al., 2008). It is possible that duplication of this gene alters GDF5 signaling and contributes to the shorthands and feet seen in our and other patients. Also identified within this region are *MYH7B* (OMIM #609928) encoding myosin heavy chain 7B, a subunit of a conventional myosin complex, and the *MYL9* (OMIM #609905) gene encoding myosin light chain 9, a regulatory subunit involved in the regulation of both smooth muscle and nonmuscle cell contractility. *MMP24* (OMIM #604871) encodes a matrix metalloproteinase, which is involved in the regulation of neuroimmune interactions between neurites and mast cells and in neural stem cell quiescence (Uniprot.org). Finally, *SRC* (OMIM #190090) encodes a nonreceptor tyrosine kinase involved in multiple signaling pathways ranging from gene transcription, cellular adhesion, apoptosis, migration, and transformation (Uniprot.org). Although no triplosensitive effect is reported for *GDF5*, concomitant duplication of regulatory genes involved in connective tissue and extracellular matrix enzymes may together result in phenotypic changes seen in our patient and others with 20q duplication.

Our patient is the sixth case reported to carry a duplication of this region to date. Unfortunately, parental testing could not be performed for our patient, but previously reported cases have all been de novo. Common clinical findings include dysmorphic facial features, shorthands, and developmental delay. Interestingly, our patient does not exhibit the craniofacial features described in previous reports, highlighting that the proposed gene, *ASXL1*, could be responsible for the facial profile in those patients. The neurodevelopmental features are common in all patients with duplication of this region. The smallest region of overlap, however, does not include the *ASXL1* gene, suggesting that genes other than *ASXL1* are contributing to developmental delay and behavioral concerns. No specific candidate gene was identified for the neurodevelopmental phenotype. However, the simultaneous duplication of multiple genes in this region may contribute to the clinical picture. Additionally, it is possible that the gene *GDF5* may be responsible for the shorthands and feet, given its known function in bone and cartilage formation. Bilateral conductive hearing loss, observed in our patient, has not been previously reported and may represent an expansion of the phenotypic spectrum associated with duplication of the 20q11.22q13.1 region. In conclusion, our patient adds to the known literature with similar duplications. Further reporting of cases in this region would be important to continue to elucidate the clinical picture and underlying etiology of this rare duplication.

ACKNOWLEDGMENTS

The authors would like to thank the family for their willingness to participate in this case report and The Shivanand R. Patil Cytogenetics and Molecular Laboratory for performing karyotype and CMA for the patient as well as for providing the pictures for the figure. This study makes use of data generated by the DECIPHER community. A full list of centers that contributed to the generation of the data is available from http://decipher.sanger.ac.uk and via email from decipher@sanger.ac.uk. Funding for the project was provided by the Wellcome Trust.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

LG: drafted the original manuscript and table. RDS: searched the Online Mendelian Inheritance in Man (OMIM) database for the function and description of genes in the duplicated region. KD: obtained consent and performed counseling for the testing coordinated in the patient. JMN: contributed to the research testing performed on the patient and figure for the manuscript. AS: provided patient information, created figure, and performed manuscript revisions.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable for this article as no new data were created or analyzed in this study.

ORCID

Kyle Dillahunt https://orcid.org/0000-0001-6383-5417
Alpa Sidhu https://orcid.org/0000-0002-8980-5029

REFERENCES

Avila, M., Kirchhoff, M., Marle, N., Hove, H. D., Chouchane, M., Thauvin-Robinet, C., … Faivre, L. (2013). Delineation of a new chromosome 20q11.2 duplication syndrome including the ASXL1 gene. *American Journal of Medical Genetics. Part A*, *161A*(7), 1594–1598. https://doi.org/10.1002/ajmg.a.35970

Blanc, P., Gouas, L., Francannet, C., Giollant, M., Vago, P., & Goumy, C. (2008). Trisomy 20q caused by interstitial duplication 20q13.2: Clinical report and literature review. *American Journal of Medical Genetics. Part A*, *146A*(10), 1307–1311. https://doi.org/10.1002/ajmg.a.32278.

Breen, C. J., Barton, L., Carey, A., Dunlop, A., Glancy, M., Hall, K., … Stallings, R. L. (1999). Applications of comparative genomic hybridisation in constitutional chromosome studies. *Journal of Medical Genetics*, *36*(7), 511–517.

Cebi, A. H., Karaguzel, G., Karakus, M., Polat, R., Seyhan, S., Onder, H., & Ikbal, M. (2016). A new isolated 20q interstitial duplication case and its clinical comparison with similar isolated cases. *Genetic Counseling*, *27*(3), 393–397.

Degenkolbe, E., König, J., Zimmer, J., Walther, M., Reißner, C., Nickel, J., Plöger, F., Raspopovic, J., Sharpe, J., Dathe, K., Hecht, J. T., Mundlos, S., Doelken, S. C., & Seemann, P. (2013). A GDF5 point mutation strikes twice–causing BDA1 and SYNS2. *PLoS Genetics*, *9*(10), e1003846. https://doi.org/10.1371/journal.pgen.1003846

Firth, H. V., Richards, S. M., Bevan, A. P., Clayton, S., Corpas, M., Rajan, D., Vooren, S. V., Moreau, Y., Pettett, R. M., & Carter, N. P. (2009). DECIPHER: Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources. *American Journal of Human Genetics*, *84*(4), 524–533. https://doi.org/10.1016/j.ajhg.2009.03.010

Hoischen, A., van Bon, B. W. M., Rodríguez-Santiago, B., Gilissen, C., Vissers, L. E. L. M., de Vries, P., Janssen, I., van Lier, B., Hastings, R., Smithson, S. F., Newbury-Ecob, R., Kjaergaard, S., Goodship, J., McGowan, R., Bartholdi, D., Rauch, A., Peippo, M., Cobben, J. M., Wieczorek, D., … de Vries, B. B. B. A. (2011). De novo nonsense mutations in ASXL1 cause Bohring-Opitz syndrome. *Nature Genetics*, *43*(8), 729–731. https://doi.org/10.1038/ng.868

Iglesias, A., Rauen, K. A., Albertson, D. G., Pinkel, D., & Cotter, P. D. (2006). Duplication of distal 20q: Clinical, cytogenetic and array CGH. Characterization of a new case. *Clinical Dysmorphology*, *15*(1), 19–23. https://doi.org/10.1097/01.mcd.0000184969.84280.e1

Magini, P., Monica, M. D., Uzielli, M. L. G., Mongelli, P., Scarselli, G., Gambineri, E., Scarano, G., & Seri, M. (2012). Two novel patients with Bohring-Opitz syndrome caused by de novo ASXL1 mutations. *American Journal of Medical Genetics. Part A*, *158A*(4), 917–921. https://doi.org/10.1002/ajmg.a.35265

Plett, S. K., Berdon, W. E., Cowles, R. A., Oklu, R., & Campbell, J. B. (2008). Cushing proximal symphalangism and the NOG and GDF5 genes. *Pediatric Radiology*, *38*(2), 209–215. https://doi.org/10.1007/s00247-007-0675-y

Thomas, J. T., Kilpatrick, M. W., Lin, K., Erlacher, L., Lembessis, P., Costa, T., Tsipouras, P., & Luyten, F. P. (1997). Disruption of human limb morphogenesis by a dominant negative mutation in CDMP1. *Nature Genetics*, *17*(1), 58–64. https://doi.org/10.1038/ng0997-58

Wanderley, H. Y., Schrander-Stumpel, C. T., Visser, M. O., Van Maanen-Op Het Roodt, E. A., Loneus, W. H., & Engelen, J. J. (2005). Report of a patient with a trisomy of chromosome region 20q11.2–>20q12 and characterization with FISH. *Genetic Counseling*, *16*(3), 277–282.

How to cite this article: Goetzinger, L., Starks, R. D., Dillahunt, K., Major, H., Nagy, J. M., & Sidhu, A. (2021). Interstitial duplication of 20q11.22q13.11: A case report and review of literature. *Molecular Genetics & Genomic Medicine*, 9, e1755. https://doi.org/10.1002/mgg3.1755