







CLINICAL REPORT

A novel unbalanced translocation between chromosomes 5p and 18q leading to dysmorphology and global developmental delay

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Funding information

St. George's University Small Research Grant Initiative 18,017

Abstract

Background: Individuals with various sized terminal duplications of chromosome 5p or terminal deletions of chromosome 18q have been described. These aberrations may cause congenital malformations and intellectual disability of varying severity.

Methods: Via an international collaborative effort, we obtained a cytogenetic diagnosis for a 5-year-old boy of Afro-Caribbean ancestry who has global developmental delay, dysmorphology, hypotonia, feeding difficulties, bilateral club feet, and intellectual disability.

Results: Conventional G-banded karyotyping showed additional chromatin of unknown origin on the long arm of chromosome 18. SNP microarray confirmed the loss of ~6.4 Mb from chromosome 18q: arr[hg19] 18q22.3-q23(71,518,518-77,943,115)x1. The source of the additional chromatin was determined from the microarray to be ~32 Mb from the short arm of chromosome 5 (arr[hg19] 5p13.3-p15.33(51,045-32,062,984)x3). The unbalanced translocation was verified by fluorescent in situ hybridization (FISH). Both parents are healthy and have normal karyotypes suggesting that this abnormality arose *de novo* in the proband, although gonadal mosaicism in a parent cannot be excluded.

Abbreviations: ID, intellectual disability.

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Conclusion: The combination of clinical features in this individual is most likely due to the partial deletion of 18q and partial duplication of 5p, which to our knowledge has not been previously described.

KEYWORDS

developing economy, dysmorphology, global developmental delay, low-income nation, middle-income nation, resource-limited community, unbalanced translocation

1 | INTRODUCTION

Unbalanced chromosome rearrangements that are cytogenetically visible account for ~3% of all recognized chromosome abnormalities (Shaffer & Lupski, 2000). These structural chromosome abnormalities include both interchromosomal rearrangements, such as balanced and unbalanced translocations, and intrachromosomal rearrangements, such as deletions, tandem duplications, inversions, and isochromosomes. Detection of a derivative chromosome in which a segment from one chromosome has been attached to the end of another chromosome in a patient with congenital anomalies often leads to the detection of a parental balanced translocation that has been transmitted in the unbalanced form to the child. However, up to 40% of unbalanced translocations have been determined to be *de novo* on the basis of normal parental chromosome analyses of blood samples. Of course, the possibility of gonadal mosaicism cannot be excluded. *De novo* unbalanced translocations may be generated by various mechanisms including nonallelic homologous recombination (NAHR), nonhomologous end-joining (NHEJ), and microhomology-mediated break-induced replication (MMBIR) (Weckselblatt et al., 2015).

Balanced chromosomal translocations are the exchange of segments between chromosomes, resulting in neither loss nor gain in genetic material (Berend et al., 2002; Pettenati et al., 2002). This type of chromosomal abnormality is found in approximately one in 500 individuals, with a higher occurrence in patients with a history of recurrent pregnancy losses (Morin et al., 2017). Carriers usually appear phenotypically normal but may have a higher risk of adverse reproductive outcomes including fetal death or pregnancy loss, infertility, or multiple miscarriages due to transmission and fertilization of a gamete harboring an unbalanced chromosomal rearrangement (Verdoni et al., 2021).

Molecular and/or cytogenetic diagnosis is important to help inform parents of the recurrence risk of future clinically affected children. Individuals who are known asymptomatic carriers of balanced translocations have a relatively high risk of having another child with

unbalanced translocations. This risk applies both to parents who already have an affected child and to other potential carriers in the family (Batista et al., 1994). Parents who have a child with an apparently *de novo* unbalanced translocation are also at higher baseline risk of having another affected child compared to the general population (Campbell et al., 2014; Hasanzadeh-NazarAbadi et al., 2014).

Here, we describe a 5-year-old boy who had multiple congenital abnormalities and a suspected genetic syndrome. He is from an underserved small West Indian island community that typically does not have access to specialty medical services (Charles et al., 2017; Sobering et al., 2017; Wardeh et al., 2018; Yearwood et al., 2018), or genetic testing (Roach et al., 2015). After clinical evaluation and laboratory investigation, he was found to have an apparently *de novo* unbalanced translocation with duplication of the terminal region of chromosome 5p and deletion of the terminal region of chromosome 18q.

2 | CASE REPORT

A 5-year-old boy of Afro-Caribbean ancestry who was suspected to have a genetic syndrome presented to a *pro bono* pediatric genetics outreach clinic (Sobering et al., 2020). He was born at full-term to a 32-year-old father and a 22-year-old G3P2 > 3 mother by spontaneous vaginal delivery with no complications during the pregnancy or labor. At birth he weighed 2.75 kg, his length was 46 cm, and he had a head circumference of 32 cm. At this time, there was a concern for Down syndrome due to low muscle tone, feeding difficulties, and facial features, but this was soon deemed less likely based on the evolution of his clinical presentation. He stayed in the hospital for 5 days, and during that time he had a heart murmur which resolved spontaneously. Echocardiogram was reportedly normal. He had bilateral club feet, right more affected than left, which have undergone casting with some correction. To our knowledge, he has not had trouble with other systems.

His development has been delayed: he rolled at 6 months, sat at 1 year, and stood and walked at 4 years.

At 6 years of age, he had six nonspecific words and could follow simple two-step directions. He has never had a period of regression. He currently has physical therapy once or twice per month, which the parents feel is helping.

He has no paternal siblings, and he has three maternal half-brothers (all different fathers), who are healthy at 9 years, 7 years, and 7 months (Figure 1). Both of his parents are healthy. His maternal family history is significant for eight maternal aunts and two maternal uncles. One maternal aunt (now deceased) was said to have an intellectual disability (ID), but she was never clinically evaluated. Two other maternal aunts reportedly had unexplained primary infertility, which was thought to be difficulty conceiving and not multiple miscarriages. Records documenting the infertility were not available, and they were not evaluated. The maternal grandparents are alive and well. Consanguinity was denied.

On examination, the affected individual appeared short for his age, but exact height and weight measurements were not obtained. He interacted nonverbally with his parents but did not speak. He walked with an unstable gait for short distances. He had a high frontal hairline with a prominent widow's peak, mild frontal bossing, a very flat and broad nasal bridge with wide up-slanting palpebral fissures, and apparent hypertelorism. He had anteverted nares with mildly hypoplastic alae nasi, midfacial hypoplasia, a normal chin, and a normal palate although he had substantial dental caries. His posterior hairline and neck were normal, as were his nipples and chest. He had mild camptodactyly of the fingers, but no contractures.

His feet were both internally rotated, the right was much worse than the left. The right foot could be stretched to the neutral position, but not the left. Bearing of weight on the left foot appeared to be supported by the lateral surface of the foot and ankle. Of note, he did not have low-set or small ears. He did not have single palmar creases, and

he did not have open helical fields bilaterally (Figure 2). Due to his multiple congenital abnormalities, the reported maternal family history of two aunts with primary infertility, and one aunt with uncharacterized ID, we pursued a karyotype for this patient.

3 | GENETIC INVESTIGATIONS

The results of a standard GTG-banded karyotype at 550 band resolution were 46,XY,add(18)(q21.3), demonstrating that there was additional, but unidentifiable, material on chromosome 18q. A highlight of the translocation and the sex chromosomes is shown in Figure 3a. Subsequent chromosome microarray analysis (CMA) with an Illumina Infinium Global Screening Array showed an approximate 6.4 Mb deletion from chromosome 18q and an approximate 32 Mb duplication of material from chromosome 5p in the proband (Figure 3b). The CMA probes allowed an estimation of the approximate breakpoints with the following chromosomal coordinates: deletion of chromosome 18q arr[hg19] 18q22.3-q23(71,518,518-77,943,115) x1 and a 32 Mb duplication of chromosome 5p, arr[hg19] 5p13.3-p15.33(51,045-32,062,984)x3.

Fluorescent *in situ* hybridization (FISH) was used to confirm that the unbalanced translocation resulted in the partial trisomy of chromosome 5p and that the duplicated material on chromosome 18q was derived from chromosome 5p (Figure 3c). The combined data from the karyotype and the CMA allowed identification of the karyotype [46,XY,der(18)t(5,18)(p13.3;q22.3)]. An ideogram (Figure 3d) was constructed with an online chromosome annotation tool (<http://www.cydas.org/OnlineAnalysis/>; accessed September 15, 2019) to show the translocation between chromosomes 5 and 18 (Hiller et al., 2005). The karyotypes and the CMAs for both parents were normal.

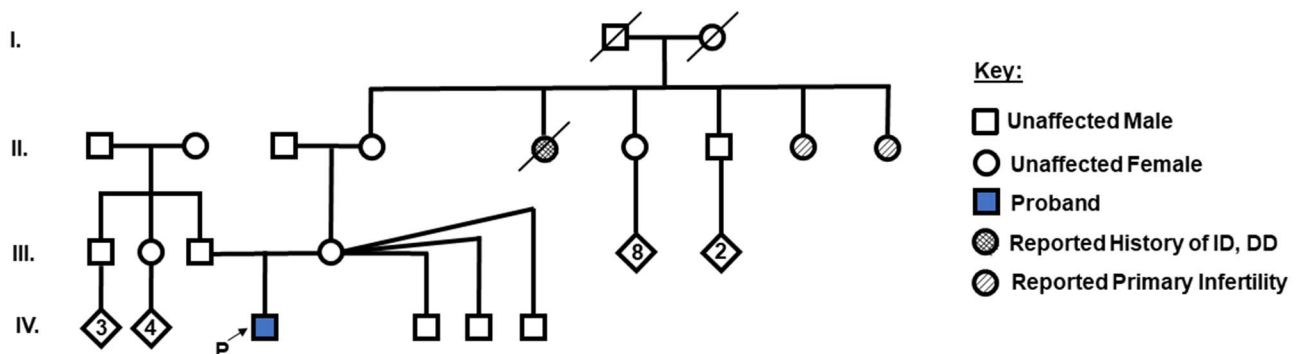


FIGURE 1 Pedigree of the family. There is a maternal history of two individuals with infertility and one individual with uncharacterized ID



FIGURE 2 Photos of the affected individual. The top panel shows him at 1 year of age, and the lower panel shows him at 4 years old

4 | DISCUSSION

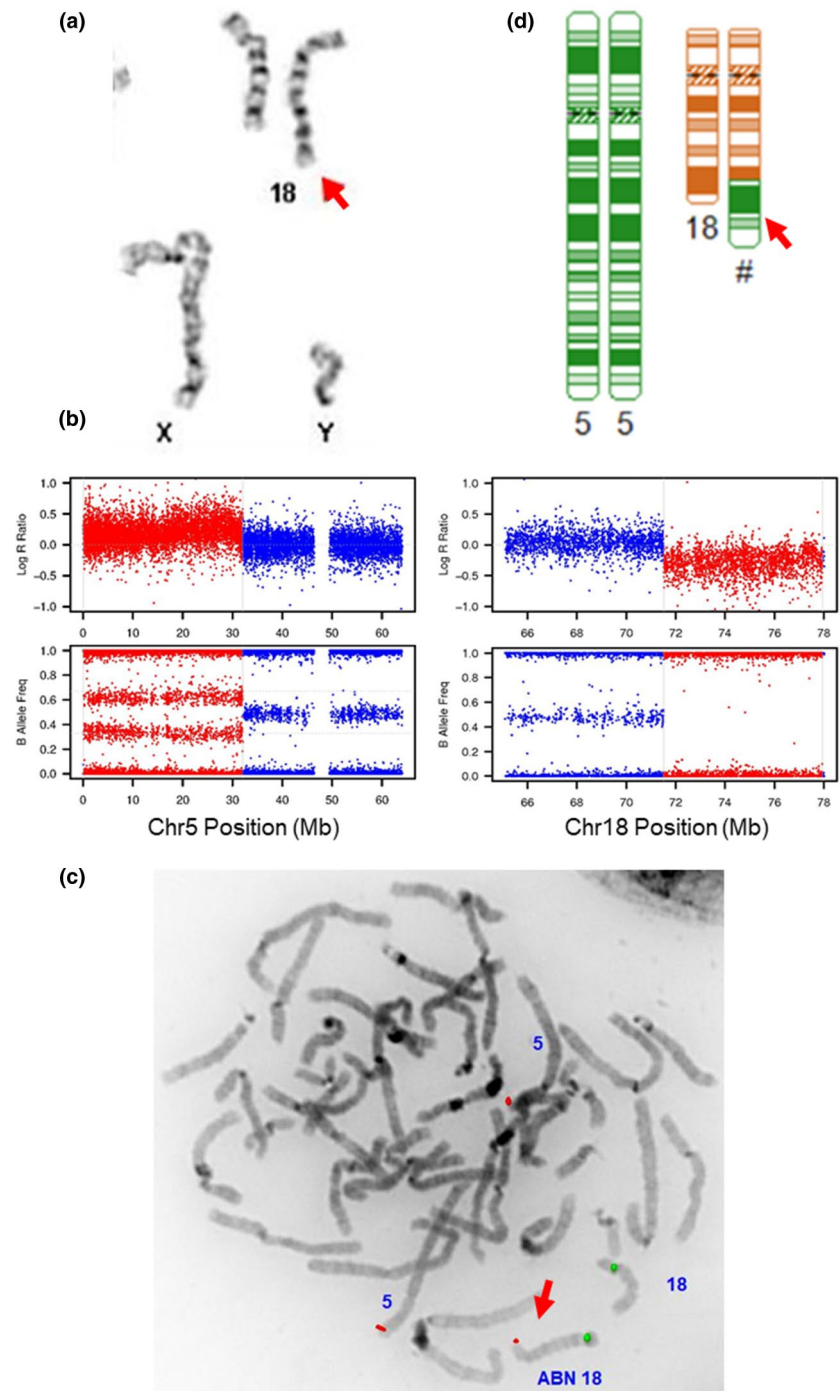
Here, we present an individual who has an unbalanced translocation caused by duplication of the terminal region of chromosome 5p encompassing 32 Mb coupled with a 6.4 Mb deletion of the terminal region of chromosome 18q. The partial monosomy in the individual we present includes the 18q22.3-q23 region. Deletions within this region contain a critical region for the “typical” distal 18q deletion syndrome and are associated with short stature, delayed myelination, white matter disorders, growth hormone insufficiency, and congenital aural atresia. Developmental delay is often severe in patients with deletions proximal to 18q21.31 and mild when deletions were found to be distal to 18q21.33 (Feenstra et al., 2007). For example, a deletion in the 18q23 terminal band in a 4-year-old child showed only a few of the typical clinical features known in 18q deletion syndrome, which were transient hypotonia, developmental delay, decreased growth, mid-face hypoplasia, and increased whorls on the fingers (Kohonen-Corish et al., 1996).

Individuals with chromosome 5p terminal duplications have been described with diverse phenotypes. Effects of duplications are varied and include developmental delay with failure to thrive, behavioral problems, poor muscle

tone, respiratory problems, short neck, arachnodactyly, hypoplasia of the abdominal muscles, and variable facial dysmorphism. Distinctive facial features might include dolichocephaly, macrocephaly, large anterior fontanelle, epicanthal folds, low-set ears, and proximally placed haluces (Cervera et al., 2005). As expected, the size of the duplication and the genes involved determine the range and the severity of the presenting features (Khodr et al., 1982). It has been suggested that duplications involving 5p13.3 or larger define a critical size for manifestation of a severe phenotype (Loscalzo et al., 2008).

The duplication in the individual we describe includes the 5p13.3 region, suggesting that some of his features are caused by this chromosomal aberration. He has upslanting palpebral fissures, hypertelorism, a heart defect, club feet, and a broad nasal bridge, which are consistent with the 5p13 duplication. Unlike other descriptions of the 5p duplication syndrome, our patient did not have low-set or small ears, whereas abnormal ears were described in individuals with both partial and complete chromosome 5p duplications (Avansino et al., 1999; Reichenbach et al., 1999). Another individual with complete trisomy of chromosome 5p had triventricular hydrocephalus (Grosso et al., 2002); however, we were unable to obtain

FIGURE 3 Cytogenetic analysis. (a) Karyotype shows the addition of unknown content on chromosome 18 with karyotype 46,XY,add(18)(q21.3). (b) Chromosome microarray analysis (hg19) shows an approximate 6.4 Mb deletion from chromosome 18q and an approximate 32 Mb duplication on chromosome 5p. (c) FISH confirms that the duplicated material originates from chromosome 5. (d) An ideogram constructed from the breakpoints estimated by CMA and the appropriate karyotype description [46,XY,der(18)t(5;18)(p13.3;q22.3)] shows the involvement of chromosome 5 (<http://www.cydas.org/>)



neuroradiological imaging for the individual we present due to difficulty in accessing these services. The hypotonia, midfacial hypoplasia, and foot deformity of the individual presented in this report are also consistent with the 18q22 terminal deletion. A comparison of the clinical features of 18q22.3 terminal deletions, 5p13.3 terminal duplications, and the individual we present is shown in Table 1.

The parental karyotypes were normal for both the mother and the father suggesting a *de novo* translocation in the proband. These findings were surprising given the reported family history of a maternal relative (now

deceased) with undefined ID, and two maternal relatives with infertility as we expected that the mother would be a carrier of a balanced translocation. However, a diagnosis in a child will not always explain other family histories.

Most island nations in the Caribbean region do not have access to physicians trained in genetics. The island where the affected individual described in this report resides is no exception. Our involvement with the management of this patient has had a positive impact on the family and the community in at least three ways. First, the family now has a medical explanation for the disorder in their child. Diagnosis

TABLE 1 Comparison of features between chromosome 5p duplication syndrome (5p13.3-terminus), 18q deletion syndrome (18q22.3-terminus), and the individual we present in this study

Manifestations	5p duplication syndrome (5p13.3-ter)	18q deletion syndrome (18q22.3-ter)	This study
Broad nasal bridge	✓		✓
Clubfoot	✓		✓
Congenital aural atresia		✓	
Developmental delay	✓	✓	✓
Epicanthal folds	✓		
Frontal bossing			✓
Heart defect	✓		✓
Hypertelorism	✓		✓
Hypotonia		✓	✓
Intellectual disability	✓	✓	✓
Low-set or small ears	✓		
Mid-face hypoplasia		✓	✓
Short stature		✓	✓
Upslanting palpebral fissures	✓		✓

matters, and the parents were appreciative of the insight we gave them toward understanding the disorder. The parental karyotyping also allowed us to inform the parents of the likelihood that the disorder in their child occurred *de novo*, and that neither parent has the very high risk associated with a balanced chromosomal translocation. Second, the medical community benefited from our involvement as we were able to provide a teaching session for the physicians of the pediatric ward based on this case presentation. We used this case to help the physicians within the Department of Pediatrics to develop an approach to a child with dysmorphology. Without a visiting pediatric geneticist, this training session would have not been available. Finally, we believe that the overall community also benefits from our program. We obtained an unambiguous molecular diagnosis for a child with congenital abnormalities and provided examples from the literature to explain how this type of disorder might be caused by (1) a parent who is a carrier of a balanced translocation, (2) a parent who has gonadal mosaicism, or (3), a *de novo* event. We believe that providing rational explanations is an important step toward engendering general acceptance that these types of disorders exist in all populations and helps other members of the community support families who are caring for individuals affected with genetic disorders.

5 | METHODS

5.1 | Ethical compliance

Clinical evaluations were performed at a *pro bono* pediatric genetics clinic at the request of a locally registered

consulting pediatrician. Both parents of the affected individual provided written informed consent for genetic testing, release of clinical history, and publication of photos. Due to the small population size of most Caribbean islands, our institutional review board (IRB) has requested that we do not reveal the precise nationality or geographic location of the family in this study.

5.2 | Chromosomal analysis

Blood in sodium heparin vacutainer tubes was sent in an insulated box at ambient temperature by express shipping to Baylor Genetics Laboratories (Houston, TX) for karyotype and FISH analysis using standard protocols. DNA was isolated from whole blood by Qiagen Puregene (Venlo, Netherlands) and shipped to The Children's Hospital of Philadelphia for CMA. An Illumina Infinium Global Screening Array (Illumina, San Diego, California) was used to obtain research CMA for the affected individual and unaffected parents. The PennCNV algorithm was used for CNV calls based on hg19 (Wang et al., 2007).

An alpha satellite probe, D18Z1, which hybridizes to the centromere and pericentromeric region of chromosome 18 labeled with FITC (green) was obtained from Oxford Gene Technology. The BAC clone, RP11-20B3, which hybridizes to chromosome 5p at coordinates 3,002,343-3,160,642 [GRCh37/hg19] was labeled by a standard nick translation procedure using Spectrumorange™ dUTP (from Abbott Molecular) for verification of the unbalanced translocation by FISH.

ACKNOWLEDGMENT

We thank the patient and his family for participating in this study.

ETHICS STATEMENT

This study was performed in accordance with the ethical standards detailed in the Declaration of Helsinki.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

GV, SU, and AKS wrote the first draft of this manuscript. BN, KRY, and EJB provided clinical care, support, and clinical characterizations. Molecular and karyotype analysis was provided by DL, JLS, SHE, EJB, and HH. SG assisted with the presentation of the figures. AKS coordinated and supervised this project from its inception. All authors approved the final manuscript. The relatively large number of authors for this piece is due to the international collaborative aspect of the project.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Verdi, G., Li, D., Elsea, S. H., Nelson, B., Bhoj, E. J., Hakonarson, H., Yearwood, K. R., Upadhya, S., Gluschitz, S., Smith, J. L. & Sobering, A. K. (2022). A novel unbalanced translocation between chromosomes 5p and 18q leading to dysmorphology and global developmental delay. *Molecular Genetics & Genomic Medicine*, *10*, e1900. <https://doi.org/10.1002/mgg3.1900>