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Case Report

Utility Of Optical Genome Mapping For Accurate Detection And Fine-Mapping Of Structural Variants In Elusive Rare Diseases.

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Abstract

Though up to 50% of cases cannot be identified by standard diagnostic techniques, rare diseases (RDs) frequently have a genetic foundation. Balanced rearrangements are among the structural variants (SVs) that often avoid identification by exome sequencing, microarray, and karyotyping. In this investigation, optical genome mapping was used.
(OGM) to look into two RD patients whose genetic cause was still unknown after earlier genomic testing. The BCL11A gene was disrupted by a balanced reciprocal translocation in Patient 1, which is linked to Dias-Logan syndrome.Patient 2's ectopic enhancer-promoter interactions and polydactyly, which mirrored characteristics seen in rodent models and comparable human instances, were caused by a mosaic 682 kb deletion close to the IHH gene.
These results demonstrate the effectiveness of OGM in detecting intricate SVs and highlight new pathogenic processes in uncommon genetic illnesses. As a result, adding OGM to standard diagnostic processes will improve genetic identification, identify novel syndromes with unclear causes, and ultimately better the clinical care of many patients with uncommon diseases

Keywords: *optical genome mapping; structural variants; balanced translocation; enhancer–promoter interactions; congenital malformations; IHH; BCL11A.*

INTRODUCTION

Conditions commonly linked to hereditary factors are included in the category of rare diseases (RDs).
Whole exome sequencing and array analysis have gained popularity in the past ten years for the genetic identification of people with RDs. But the diagnostic output of these Depending on the clinical group and the strategy employed, even when combined, approaches only attain a maximum of 30% to 50% [1]. The family and doctors experience emotional distress when an etiological diagnosis cannot be made, which makes it difficult to provide suitable, well-known genetic counseling. It is thought that the fact that certain causative genetic variants are still difficult to detect using these methods contributes to this low diagnostic yield. The genetic etiology of these RDs may be caused by disruption in important genes or regulatory areas [2,3].For example, with an estimated frequency of 0.25%, balanced reciprocal translocations are rather common [5]. Healthy carriers run the risk of giving birth to children with unbalanced translocations, even though the majority of balanced translocations do not directly cause disease.
In many instances, the offspring suffers from severe phenotypic repercussions or non-viable problems. But occasionally, there can be notable phenotypic repercussions when a crucial gene is disrupted at the breakpoint regions.Determining the breakpoints involved in structural rearrangements is therefore essential, at least in de novo rearrangements, to ascertain whether a gene's coding sequence has been altered or whether the important location of distant
The correct expression of a nearby gene may be deregulated as a result of changed regulatory elements, such as enhancers, repressors, or insulator sequences. First introduced in 2009, optical genome mapping (OGM) is a potent method for high-resolution visualization and analysis of the complete genome's structure. Large-scale structural differences in DNA

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and mosaic alterations that conventional genetic analysis methods can miss can be found with OGM.

Two individuals whose genetic status was still unknown after previous genomic methods were unable to detect harmful mutations underwent OGM. The purpose of this study was to adopt a more thorough perspective on the OGM-derived genomic landscape of uncommon variations linked to RDs. This method may uncover new pathways involving intricate SVs that conventional genomic methods frequently overlook.

DETAILED CASE DESCRIPTION

Patient 1 is a 5-year-old boy who has no family history of neurodevelopmental issues and is the only child in a single-parent household. In vitro fertilization with donor sperm injected intracytoplasmically produced the pregnancy. Mild polyhydramniosis and right renal pelvic dilatation were found during pregnancy. At 41 weeks of pregnancy, the patient was born. birth weight of 4.540 g, length of 55 cm, and head circumference of 37 cm, all of which surpass the 97th percentile according to the International Standards for Newborn Weight, indicate macrosomia during cesarean section gestation [6]. A large forehead, bilateral strabismus, flattened nasal bridge, right kidney hydronephrosis, and left kidney dysplasia were further clinical findings.

Significant language and psychomotor delays were noted at the follow-up, followed by a moderate intellectual handicap. No abnormal results were seen in the brain MRI examination. The patient's blood karyotyping showed a reciprocal translocation that was not seen in the mother's or the sperm donor's blood cells (46,XY,t(2;11)(p11.2;p13)dn). A balanced translocation without any loss or gain of genetic material was shown by array comparative genomic hybridization (CGH-array) study, which revealed no anomalies (array CGH 180 K Agilent Technologies, Santa Clara, CA, USA). There were no noteworthy results from the clinical exome sequencing (New Focused Exome v2; Agilent Technologies, Santa Clara, CA, USA).

The breakpoint sites were more accurately defined by OGM analysis, which verified the translocation between chromosomes 2 and 11, changing them from 46,XY,t(2;11)(p11.2;p13), as determined by Karyotyping, to 46,XY,t(2;11)(p16.1;p15.4) (Figure 1b). Although no gene with a well-established function was included in the breakpoint region found on chromosome 11, this chromosomal rearrangement resulted in the interference with the chromosome 2 BCL11A gene. Hemoglobin electrophoresis and quantification were carried out in light of the known function of the BCL11A gene in hemoglobin switching and fetal hemoglobin (HbF) silencing [7]. Without any other hematological abnormalities, the study showed increased HbF at 5% (normal < 0.5%) (Hb: 12.3 g/dL).

By integrating clinical information, molecular studies, cytogenetics, and HbF monitoring, this De novo translocation was deemed harmful, indicating that the patient had Dias-Logan syndrome as a result of BCL11A haploinsufficiency.The third kid of healthy non-consanguineous parents is patient number two. She had complex polysyndactyly (mirror image of hands and feet), slight facial dysmorphism, and agenesis of the corpus callosum when she was born in 1983 with a polymalformative syndrome.

It has 33 fingers and toes in all, no thumbs, femoral shortening, and several joint problems. A new kind of acrocallosal syndrome was proposed in 1985 when a thorough description of the clinical phenomenology was published [8]. The second patient is the third child of non-consanguineous, healthy parents. Agenesis of the corpus callosum, mild facial dysmorphism, complex polysyndactyly (mirror image of hands and feet), various joint abnormalities, femoral shortening, and a total of 33 fingers and toes without thumbs were all features of her 1983 birth with a polymalformative syndrome. In 1985, a thorough description of the clinical phenomenology was provided, indicating the possibility of a novel acrocallosal condition [8]. Although she is unable to stand or walk, she has rhizomelic shortening of the lower limbs, normal muscle tone, and mobility in her limbs. She has a severe intellectual disability and requires assistance with meals and personal hygiene. She nevertheless exhibits social engagement with limited language, using echolalia and single words and basic sentences. Night terrors, phobias, and tantrums are examples of behavioral issues. To determine the cause of the deformities, numerous genetic investigations have been conducted on this patient over the years.

Two distinct methods are used in cytogenetic analysis, which includes high resolution karyotyping and genomic array studies: a high-density oligo array (Affymetrix CytoScan HD SNP array, Life CGH-array 160 K (Nimgenetics) & Technologies, Carlsbad, CA, USA) did not identify any genetic anomalies in the patient. Similarly, after family segregation analysis, whole exome sequencing was ruled out as the cause of the BHLHA9 gene's variant NM_001164405.2:c.305 C > A; p.(Ser102 Tyr), which had no known clinical significance.All prior genetic analyses, including genomic array investigations, have failed to identify this mosaic change, which has a variation allelic frequency of 0.27.A visual examination of the area in the array from the back, however, verified a minor decline.without going over the manufacturer-set threshold value for variant calling in the signal strength for each probe in the impacted area. (b) Findings from the Affymetrix CytoScan HD SNP array, a high-resolution genomic array. The chromosome 2 image only reveals a modest drop in probes in the deletion region, falling short of statistically significant levels. (c) Rao et al.'s Hi-C data [9] (10 kb) GM12878 cell line resolution). Several topologically associated domains (TADs) are included in this region; blue arrows indicate the projected TAD unions. The

deleted region in Patient 2 is represented by the horizontal black bar at the bottom, which indicates that one of the TAD junctions or insulators in that area may be eliminated as a result of the deletion. The image was acquired using a converted genomic coordinate (chr2:219997044-220691125) from the UCSC Genome Browser on Human (GRCh37/hg19).

(d) The genomic regions impacted in other documented cases with a comparable phenotype are displayed in the genomic overview of the deleted region on chromosome 2q35 [10–12]. Deletions are shown by the red bars, and the blue Duplication is represented by a bar. While the deletions have breakpoints that affect various sections of the NHEJ1 gene, located distally but very close to IHH, the vertical dashed line, which represents the 5′ end of the IHH gene, demonstrates that only the duplication described by Yuksel-Apak [10] directly impacts the IHH gene.The population control databases (DGV) do not include any information about this deletion. It should be mentioned that the Indian Hedgehog (IHH) gene is rather close to one of the deleted region's breakpoints. Based on data from comparable studies, this deletion was deemed harmful. deletions or duplications close to the IHH gene that have been linked to a very similar phenotype in the past. The population control databases (DGV) do not include any information about this deletion. It should be mentioned that the Indian Hedgehog (IHH) gene is rather close to one of the deleted region's breakpoints. Based on data from comparable studies, this deletion was deemed harmful. The deletions or duplications close to the IHH gene that have been linked to a very similar phenotype in the past.

DISCUSSION

This study offers a more thorough evaluation of OGM's ability to identify SVs linked to uncommon diseases that were previously overlooked by conventional genetic methods like exome sequencing and microarray analysis. Additionally, even in cases where SVs are known to exist, OGM offers a higher resolution of the breakpoint and permits a deeper comprehension of the chemical mechanism at play. In Patient 1, a balanced chromosomal translocation t(2;11) interrupted the BCL11A gene. The BAF SWI/SNF chromatin remodeling complex is linked to the C2H2-type zinc-finger protein BCL11A [13].This gene is essential for controlling both brain growth and the developmental transition from gamma to beta globin, which indirectly suppresses HbF levels [14]. Whether this gene's haploinsufficiency is caused by heterozygous truncating Dialogan syndrome has been shown to be caused by mutations or missense variants in the N-terminal region [OMIM #617101]. Intellectual disability, linguistic delay, persistence of HbF, and various dysmorphic characteristics, such as microcephaly, are the hallmarks of this condition [7]. It is confirmed that the translocation causes a functional impairment of the BCL11A gene by the intellectual developmental problem linked to the persistence of HbF in our patient.

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However, it is quite possible that two novel fusion transcripts could be created as a result of the chromosomal transfer. These could be harmful through a variety of mechanisms, such as the presence of a novel polypeptide that combines functional domains from two distinct genes and/or a putative dominant-negative effect because functional domains in partially truncated proteins are preserved [15]. The genes Exons 3 and 4 of the ZNF195 gene begin in the same reading frame as exon 3 of the BCL11A gene, which is translated in the same sense at the breakpoints in Patient 1.However, a frameshift would take place if the breakpoint was inside intron 1.We cannot completely rule out the possibility that one or both fusion transcripts contributed to the phenotype, which could account for the clinical manifestations in our patient—macrosomia and renal abnormalities—that have not been previously documented in Dias-Logan syndrome. However, there is still uncertainty regarding the synthesis of these unique chimeric proteins, their ability to translocate, and their quick degradation within the cell.from the cytoplasm into the nucleus, or even if they cause a harmful disruption. As a result, it is now very unlikely that the chimeric genes contributed to the phenotype. Regardless, the deletion of BCL11A exons 1 and 2 Since it suggests the loss of both the NuRD-interacting domain and a C2HC zinc-finger domain involved in protein–protein interaction, the gene (replaced by exons 1-3 of ZNF195) is anticipated to cause a loss of function [14]. It is important to remember that missense mutations in these domains result in transcriptional activity, dimerization, and localization defects that are clinically identical to those brought on by truncating variants [7].A mosaic microdeletion of 682 kb in the chromosomal region 2q35, which impacts 30 genes and is situated very near the IHH gene, was discovered by OGM in Patient 2. All previous genetic study methods failed to discover this mosaic change, which is estimated to be 27% methods.

The capacity of array-based methods, which are thought to be the best for identifying copy number variations, to detect low-grade mosaicisms is restricted, especially when it comes to tiny segmental aneusomies (less than 30%) [16]. On the other hand, OGM is more effective at identifying large-scale SVs because it relies on the identification and counting of

individual DNA molecules rather than relative quantification. OGM functions regardless of coverage or sequencing issues, exhibits great sensitivity for low-frequency changes, and makes complex changes easier to explain.

using NGS and arrays. Because of this, OGM is a useful technique, particularly for evaluating mosaics and SVs that are challenging to detect using other technologies. The loss modifies the genomic structure, which may result in ectopic connections between enhancers and promoters and, as previously proposed, abnormal gene expression patterns, even if it has no direct effect on the IHH gene (Figure 2c). In the Doublefoot (Dbf) mouse model, a remarkably identical loss was found in the adjacent distal region of the IHH gene [11].

The morphological characteristics of this mutant mouse are very comparable to those of our Patient 2, including tibial hypoplasia, enlarged digits on all four limbs, and preaxial polydactyly with 6–9 triphalangeal digits.thickened curled tail, hydrocephalus, and skull. Another similar instance in humans was a female baby whose centromeric breakpoint, which is situated 429 base pairs downstream of the IHH gene's transcription start site [12], had a microdeletion that overlapped Patient 2's [Figure 2d]. Significant polydactyly, with eight fingers on each hand that were mirror images of the right hand, seven fingers on the left foot, and six fingers on the right foot with an enlarged hallux, were among the clinical findings.Furthermore, Patient 2's clinical characteristics are very comparable to those of other people who exhibit symptoms of acrocallosal syndrome. This person had severe hand and foot polysyndactyly, anomalies of the craniofacial structure, including macrocephaly,severe hypertelorism, low-set and dysplastic ears, agenesis of the corpus callosum, and substantial psychomotor delay due to a massive duplication involving the IHH locus [10] (Figure 2d).None of the genes in the deletion have been directly associated with polydactyly, and none of them exhibit constraint scores that would indicate that they are haploinsufficient (LOEUF < 0.3), making them susceptible to heterozygous deletions, even though haploinsufficiency of some of the genes may partially contribute to the patient's phenotype [17]. It is noteworthy that the IHH gene is extremely near to the proximal breakpoint of the deletion in Patient 2. A crucial secreted signaling component of the Hedgehog protein family is encoded by this gene. compounds that control several developmental processes, such as morphogenesis, pattern creation, and growth. A particular function of the protein that the IHH gene encodes is related to bone growth and differentiation. Brachydactyly type A1 is caused by mutations in this gene and is typified by acrocapitofemoral dysplasia and shortened or deformed fingers and toes. Additionally, Lupiañez et al. [18] showed that CRISPR/Cas genome editing and expression evaluations in mouse limb tissue and patient-derived fibroblasts Pathogenic phenotypes can arise from the rewiring of long-range regulatory architecture caused by disruption of TADs (Topologically Associated Domains). According to their research, specific human limb deformities are brought on by deletions, inversions, or duplications that change the organization of the WNT6/IHH/EPHA4/PAX3 locus, which spans TAD. A number of disease-related A cluster of limb enhancers typically linked to EPHA4 is positioned incorrectly in relation to TAD boundaries, resulting in ectopic interactions between promoters and non-coding DNA. This leads to ectopic limb expression of another gene within the locus. Only when the variation interfered with a boundary domain linked to CTCF did this rewiring take place.Their results highlight the crucial role that TADs play in coordinating gene expression through genomic architecture and provide standards for assessing a human's propensity for disease. structural variations, especially in the human genome's non-coding areas. Strong experimental evidence has shown that certain SVs can cause pathogenic phenotypes by disrupting higher level genomic organization, depending on their size and location.It is extremely significant that, although having somatic mosaicism, Patient 2's clinical characteristics closely reflect the acrocallosal-like condition brought on by IHH duplication and the phenotype of the Dbf mice model, which is produced by a comparable loss.Specifically, the female fetus's polydactyly, as reported by Trimouille et al. [12], is identical to Patient 2's, with fingers arranged in a mirror pattern. Consequently, we speculate that Despite the patient's mosaicism, the primary pathophysiological consequence of the deletion is the same: an ectopic connection between the IHH gene and enhancers in the EPHA4 chromatin domain as a result of a reconfiguration of the TAD borders. Our findings support the idea that ectopic enhancer–promoter interactions leading to ectopic/dysregulated genic expression as a result of the removal of specified boundaries are the cause of the toxicity of some deletions linked to human diseases [19].OGM has a lot of potential to help diagnose unsolved genetic illnesses, particularly when it comes to identifying complicated SVs or mosaic alterations that are hard to find with conventional methods. But at the moment, its applicability is restricted by high

expenses, the requirement for specific tools and skilled workers, and the need to combine it with other technologies in order to have a comprehensive picture of the genome. Additionally, accessibility in environments with low resources continues to be a major obstacle, which may short-term prevent its inclusion into standard clinical practice.

MATERIALS AND METHODS

DNA from peripheral blood samples was extracted, digested, and tagged in accordance with the manufacturer's instructions

for OGM ultra-high molecular weight (Bionano Genomics, Inc., San Diego, CA, USA). A Saphyr chip was loaded with labeled DNA, and a Saphyr Bionano Genomics, Inc., San Diego, CA, USA, is the instrument. SVs were compared to the human reference GRCh37 assembly during the de novo genome map construction process, which was carried out using BionanoSolve. Bionano Access and Bionano Tools were used to examine the data on Saphyr Compute Servers (Bionano Genomics, Inc., San Diego, CA, USA). For every data set, a molecular quality report was produced that contained three essential metrics for assessing sample QC: map rate, effective coverage, and molecule N50 (≥150 kbp).Molecule N50, which is used to evaluate the size distribution of DNA ≥ 150 kbp, is a weighted average of all molecules based on their sequence length. The measure for map rate is computed as the GRCh38-aligned DNA molecules as a proportion. The coverage depth of molecules matched to the reference genome (GRCh38) is used to compute the effective coverage. 230 kbp of molecule N50 (≥150 kbp), a 70% map rate, and at least 160X effective genome coverage were the analytical QC goals.Using conventional techniques, peripheral blood leukocytes were used to extract the genomic DNA of the patient and their parents. The SureSelect Human All Exon V8 (Agilent Technologies, Santa Clara, CA, USA) was used for exome sequencing, and the Illumina NextSeq500 platform was used in accordance with the manufacturer's instructions to get a minimum reading. 100X depth. The Alissa Interpret platform (Agilent Technologies) was used for read alignments, variant calling, and annotations. Analysis was done on potential genes found in several databases as well as disease-causing genes linked to neurodevelopmental disorders.

The clinical impact and pathogenicity of the variations were assessed using previously published criteria [20,21]. The revolutionary potential of OGM in addressing enigmatic genetic etiologies in congenital uncommon illnesses is highlighted in this study. OGM accurately identified a translocation that disrupted BCL11A in Patient 1, connecting it to Dias-Logan syndrome and expanding our knowledge of its clinical range. OGM discovered a mosaic deletion close to the IHH gene in Patient 2, which resulted in ectopic regulatory interactions and a phenotype.These findings validate the utility of OGM in detecting SVs overlooked by conventional methods, providing crucial insights into the complex genomic architecture underlying rare disorders. Based on these illustrative examples, we propose that integrating OGM into routine diagnostic workflows will significantly enhance genetic diagnosis, facilitate the discovery of previously unidentified syndromes, and eventually improve the clinical management of patients with rare diseases through advanced personalized medicine.

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