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# Deletions in *OPTN* gene and literature review

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### *Abstract*

Amyotrophic lateral sclerosis 12 with or without frontotemporal dementia (ALS12) is a subtype of ALS that is a neurodegenerative disorder onset in adulthood and is characterized by slowly progressive. The ALS12 is caused by a heterozygous or homozygous mutation in the *Optineurin* gene (*OPTN*) on chromosome 10p13. In this study, whole genome sequencing (WGS), utilizing next-generation sequencing techniques was performed to identify genes associated with ALS in the patient. These technologies utilize high-throughput DNA sequencing of the whole genome, representing a highly effective approach to the assessment of neurodegenerative disorders. Optical Genomic Mapping (OGM) is a new cytogenomics technics has taken the technology to the next level in the cytogenetics field by enabling the mapping of all types of structural variants (SVs) at high resolution in a single assay. It has become a prominent diagnosis method in neurogenetics and other disciplines in recent years with its ability to analyze variants that other technologies cannot detect by reaching high-resolution values that other technologies cannot reach, by using long read and specific labeling methods. In this study, we found the novel homozygous *OPTN* gene deletion by OGM in a patient with diagnosed ALS12 and confirmed and detected precise deletion breakpoints by WGS. We aimed to explore the utility of OGM and WGS as a method of characterizing the SVs associated with the Alu-mediated rearrangement.

*Keywords:* Amyotrophic Lateral Sclerosis 12 with or without Frontotemporal Dementia, ALS12, Optical Genomic Mapping, OGM, Whole Genome Sequencing, WGS, *OPTN*

## INTRODUCTION

Amyotrophic lateral sclerosis 12 with or without frontotemporal dementia (ALS12; OMIM # 613435) is a subtype of ALS that is a neurodegenerative disorder onset in adulthood and characterized by slowly progressive. ALS12 involves the upper motor neurons and initially, affects the lower limbs. The main clinical findings of ALS12 consist of dysphagia, limb muscle weakness or atrophy, dysarthria, language impairment, memory difficulties, and dementia.

ALS12 is caused by a heterozygous or homozygous mutation in the *Optineurin* gene (*OPTN*; OMIM * 602432) on chromosome 10p13.[1] Approximately 4% of familial ALS cases and 0.4% of sporadic ALS cases carry the *OPTN* mutation.[2] Also, *OPTN* mutations lead to glaucoma1, open-angle, E (primary open-angle glaucoma (POAG), OMIM # 137760), and glaucoma, normal tension, susceptibility to (OMIM # 606657). Some previous studies have stated that *OPTN* mutations may be associated with Crohn's and Paget's disease.[2]

Optineurin is a ubiquitin-binding adaptor protein encoded by *OPTN* mainly involved in regulating vesicular trafficking leading to NF-kappa-B activation, inflammatory process, and autophagy.[3,4]

Mutations in *OPTN* can disrupt these processes and decrease the efficiency of mitophagy, leading to the accumulation of damaged mitochondria and abnormal aggregation of proteins, increasing oxidative stress, affecting neuroinflammation and programmed necrosis, leading to axonal neurodegeneration in ALS pathogenesis.[5-9]

Whole genome sequencing (WGS), utilizing next-generation sequencing techniques, is performed to identify genes associated with amyotrophic lateral sclerosis (ALS) in patients. These technologies utilize high-throughput DNA sequencing of the whole genome, representing

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a highly effective approach to the assessment of neurodegenerative disorders.[10] Optical Genomic Mapping (OGM) is a new cytogenomics technics has taken the technology to the next level in the cytogenetics field by enabling the mapping of all types of structural variants (SVs) at high resolution in a single assay. It has become a prominent diagnosis method in neurogenetics and other disciplines in recent years with its ability to analyze variants that other technologies cannot detect by reaching high-resolution values that other technologies cannot reach, by using long read and specific labeling methods.[11]

In this study, we applied whole-genome analysis methods to a patient with ALS12. We found the novel homozygous *OPTN* gene deletion by OGM and confirmed and detected precise deletion breakpoints by Whole Genome Sequencing (WGS). We aimed to explore the utility of OGM as a method of characterizing the SVs associated with the Alu-mediated rearrangement.

## METHODS

We presented the case of a 46-year-old male patient with a novel homozygous variant (exon 6-exon 7 deletion) of the *OPTN* gene. A literature search of ALS12 cases associated with the *OPTN* gene copy number variants (CNVs) was performed in PubMed with the search criteria as (((ALS[Title/Abstract]) OR (amyotrophic lateral sclerosis[Title/Abstract])) AND (OPTN[Title/Abstract]) AND (Deletion[Title/Abstract])). A total of 16 publications were obtained. All cases with clinical findings and variants were summarized in published cases (Table 1). The same filtering was applied for duplication, but no articles related to *OPTN* were found. The signed informed consent has been given from the patient. Initially, we performed an OGM on the patient, after which the variant detected was confirmed by the WGS.

### *Patient*

This 46-year-old male developed muscle weakness and spasticity in his feet and lower extremities at 42 years old. The patient was followed up with previous diagnosis of spastic paraparesis. This is followed by rapidly progressive clinical features of upper and lower motor neuron dysfunction, beginning with dysarthria and weakness in the upper and lower extremities and progressing to muscle atrophy and spasticity. In the following period, the patient developed muscle spasm attacks at night and loss of sensation on the legs. The cognitive deterioration was mildly affected, and he has mild memory difficulty. There were behavioral changes manifested by crying episodes. He did not show any extrapyramidal signs in his clinical follow-up. He also described sleep disturbance, respiratory distress, and dysphagia that started in the last 2 years. The patient was currently bedridden due to weakness in the arms and legs. Muscle atrophy has increased and he was unable to speak. There was no primary open-angle glaucoma was detected in the eye examination. Family history revealed a consanguineous marriage between the patient's parents. Two siblings of the patient have similar findings. One sibling had gait disturbance, loss of balance, and vision loss. The other sibling has a speech impairment, gait loss (wheelchair use), and visual impairment. No patient in ALS clinic was identified among the 2nd-degree relatives of the patient in the pedigree examination. The 3rd-degree relatives of the patient were not provided with sufficient clinical information. His electroneuromyogram confirmed the ALS diagnosis, cranial MRIs were normal. The cerebrospinal fluid analysis did not reveal any abnormalities. The thyroid function, autoimmune antibodies, and tumor markers were normal. The patient was evaluated with OGM, and the result was confirmed with WGS. The pedigree of the family is shown in Figure 1A.

### *Optical Genome Mapping (OGM)*

The DNA isolation experiment was performed via the SP Blood and Cell Culture DNA Isolation Kit (Bionano, cat. no. 80030) using fresh blood samples from affected individuals following the manufacturer's guidelines (Bionano Prep SP Fresh Cells DNA Isolation Protocol v2, 30379, Rev B). The DNA labeling and staining experiment was performed via the Direct Label and Stain (DLS) Kit (Bionano, cat. no. 80005) following the manufacturer's guidelines (Bionano Prep Direct Label and Stain Protocol, 30206, Rev G). A volume of 8.5µL labeled gDNA solution of concentration between 4 and 12ng/ul was loaded on a Saphyr™ chip and scanned on the Saphyr™ instrument (Bionano, San Diego USA). The De Novo Assembly™ and Variant Annotation Pipeline™ were executed on Bionano Solve™ software v3.7 reporting, and direct visualization of SVs was done on Bionano Access™ v1.7.2.

**Table 1: Summary table of patients with reported deletions in the *OPTN* gene**

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Clinical diagnosis** | ALS | ALS | ALS | ALS | ALS | ALS | ALS | - | PNA- VPPA | AD | ALS |
| **Age of symptom onset** | 33 | 36 | 43 | 44 | 43 | 65 | 62 | ? | 68 | 73 | 42 |
| **Sex** | F | M | F | F | M | F | F | M | M | M | M |
| **Age of death** | 57 | 55 | ? | ? | ? | ? | ? | ? | 72 | - | - |
| **Onset symptom** | Muscle weakness of her left upper limb | Muscle weakness of his left upper limb | ? | ? | ? | ? | ? | Opaque corneas, hypoplastic irides, | CD | ? | Gait disturbance |
| **Clinical findings** | Dysphagia, difficulty of respiration, bedridden | Dysphagia, dysarthria, difficulty of respiration, fasciculation of the tongue, bedridden | S-ALS | B-ALS | S-ALS | B-ALS | B-ALS | Anterior segment dysgenesis and glaucoma | CD | Bilateral cataracts, No evidence of motor impairment reported. | Muscle weakness and spasticity, dysarthria |
| **Deletion region** | Exon 5 | Exon 5 | Exon 1-4 | Exon 3-5 | Exon 5 | Exon 3-5 | Exon 3-5 | Upstream | Exon 13-15 | Exon 5 | Exon 6-7 |
| **Pathological, imaging or other findings** | FTA | FTA | - | - | - | - | - | Bilateral retinal detachments | Fronto temporal lobar degeneration, cortical atrophy with ventricular enlargement | - | Electro neuro myogram is compatible with ALS features |
| **Size** | - | - | - | - | - | - | - | 181.5 kb | 7869 bp | 4969 bp | 6905 bp |
| **Genomic region** | - | - | - | - | - | - | - | 12.959.447-13.140.967 | 13.127.004-13.134.873 | 13.152.598-13.157.566 | 13.111.727-13.118.632 |
| **Zygosity** | HO | HO | HE | HE | HO | HE | HE | HE | HE | HE | HO |
| **References** | Maruyama *et al.*, 2010[1] | Maruyama *et al.*, 2010[1] | Iida *et al.*, 2012[25] | Iida *et al.*, 2012[25] | Iida *et al.*, 2012[25] | Iida *et al.*, 2012[25] | Iida *et al.*, 2012[25] | Schilter *et al.*, 2015[26] | Pottier *et al.*, 2015[21] | Dilliott *et al.*, 2022[27] | Present case |

(F: Female, M: Male; ?: Unknown, -: none; PNA-VPPA: Progressive nonfluent/agrammatic variant of primary progressive aphasia, AD: Alzheimer's disease, ALS: Amyotrophic Lateral Sclerosis, S-ALS: Spinal ALS, B-ALS: Bulbar ALS, CD: Cognitive difficulties, FTA: Frontotemporal atrophy, HE: Heterozygous, HO: Homozygous)

*Whole Genome Sequencing (WGS)*

The patient's DNA was extracted from the peripheral blood samples using the QIAamp DNA Mini Kit (Cat. No. / ID:51304). Then, the concentrations of samples were measured using QubitTM dsDNA HS Assay Kit (Invitrogen, Paisley, UK) and optimized as 50 ng/µl per sample. WGS was performed using the WISGEN xLIBPreP™ Enzymatics library kit and sequencing on the SURFSeq 5000 platform (GeneMind Bio, China). The created library was sequenced with an average coverage depth of 30x-40x. The raw data were subjected to quality control using the FastQC software. The adaptor sequences were then cleaned using the Cutadapt software. The cleaned sequences were aligned to the reference human genome GRCh38/hg38 using the BWA-MEM algorithm. The aligned data were converted to BAM format using the GATK software, after which the base quality scores were recalibrated using the GATK Base Quality Score Recalibration (BQSR) algorithm to enhance the accuracy of the variant calling process. The identification of variants (SNPs and INDELs) was conducted using the GATK HaplotypeCaller. The resulting variants were subjected to filtration using GATK VariantFiltration, with the requisite thresholds employed.

After base-calling and primary filtering of low-quality variants, all remaining variants (from OGM and WGS) were analyzed by using DGV (http://dgv.tcag.ca/dgv/app/home), DECIPHER (https://www.deciphergenomics.org/), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), etc., and variants with minor allele frequency (MAF) less than 1% in the gnomAD v.4.1.0 (https://gnomad.broadinstitute.org/), dbSNP (https://www.ncbi.nlm.nih.gov/snp/) databases were evaluated. The American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen) guidelines recommend that specific standard terminology be used to describe and classify the variants.[12] *OPTN* analysis was based on transcript ENST00000378748.7 in terms of consistency with the literature. Analyses were performed according to Genome Reference Consortium Human Build 38 (GRCh38).

## RESULT

For the patient, whole exome sequencing analysis (without CNV), spinocerebellar ataxias repeat test (SCA type 1, 2, 3, 6, 7, and 8), and Myotonic Dystrophy repeat test (Type 1, *DMPK* gene-CTG repeat test) were performed for muscle weakness/atrophy, dysarthria, and language impairment in the external centers. No pathogenic or likely pathogenic variants were found associated with neuromuscular diseases. OGM performed with the De Novo Assembly pipeline. The homozygous deletion found by OGM which estimated region covers the deletion is between 13,007,134 and 13,124,408 on chromosome 10 (Figure 1B). The deletion size is 6,920 bp. The deletion is at 100% VAF (Variant Allele Frequency) (compatible with homozygous zygosity). The size of the estimated region where the deletion could be 117,274 bp and the deletion size is 6,920 bp in this region. When we compared the patient and reference genome, we found that the labels located at 13.112.989 and 13.118.443 were not present in the patient genome. According to the reference genome, these missing two labels in the patient's genome were located in intron 6 and intron 7 of the *OPTN* gene. Therefore, we anticipate that the deletion may cover exon 7 of the *OPTN* gene in the estimated region. It is important to note that, polymorphic variants in label sequence may be encountered during the analysis. Therefore, the labels may not be present in the patient genome. However, the loss of two sequential labels suggests that the deletion may cover this region. In SVs analysis by OGM, the candidate region where the variant may be present is defined, but it cannot detect the breakpoints of the SVs. After the candidate regions are identified, the breakpoints need to be clarified, especially sequencing or other appropriate methods. However, we performed the WGS and detected that the homozygous deletions on the chromosome 10 location are between 13.111.727 and 13.118.632 (GRCh38/hg38). The deletion region covers with sixth and seventh exons of the *OPTN* gene (Figure 1C). Typically, the final two bases of exon 7 are fused to the initial base of exon 8. In the gene in which exons 6 and 7 have been deleted, the second codon of exon 8 becomes a stop codon due to the deletion. This premature stop codon formed by homozygous deletion has been anticipated to reduce OPTN mRNA expression through the process of nonsense-mediated decay. This is likely to result in complete or near complete loss of function of the gene product. However, expression studies are required for precise results.

With the WGS result, we both confirmed the OGM result and determined the precise

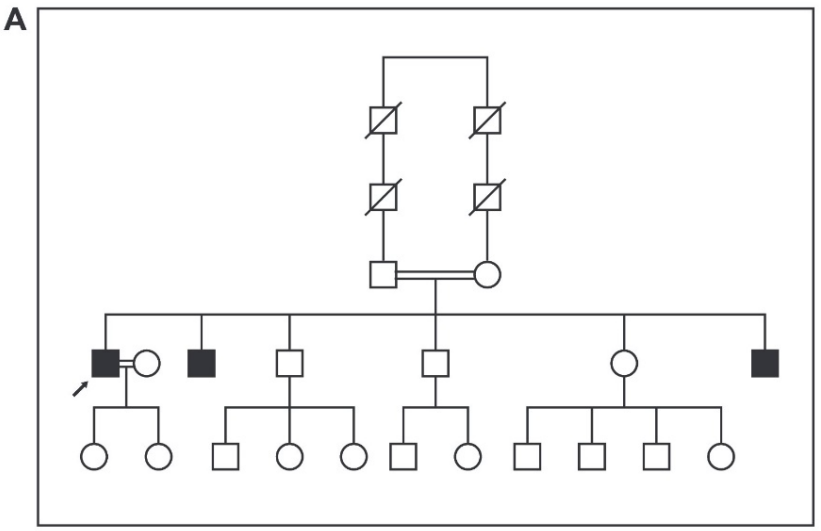


Figure 1**A**. Pedigree of the patient. The patient's parents are consanguineous and two siblings in the family have similar clinical findings. One sibling had gait disturbance, loss of balance, and vision loss. The other sibling has a speech impairment, gait loss (wheelchair use), and visual impairment.

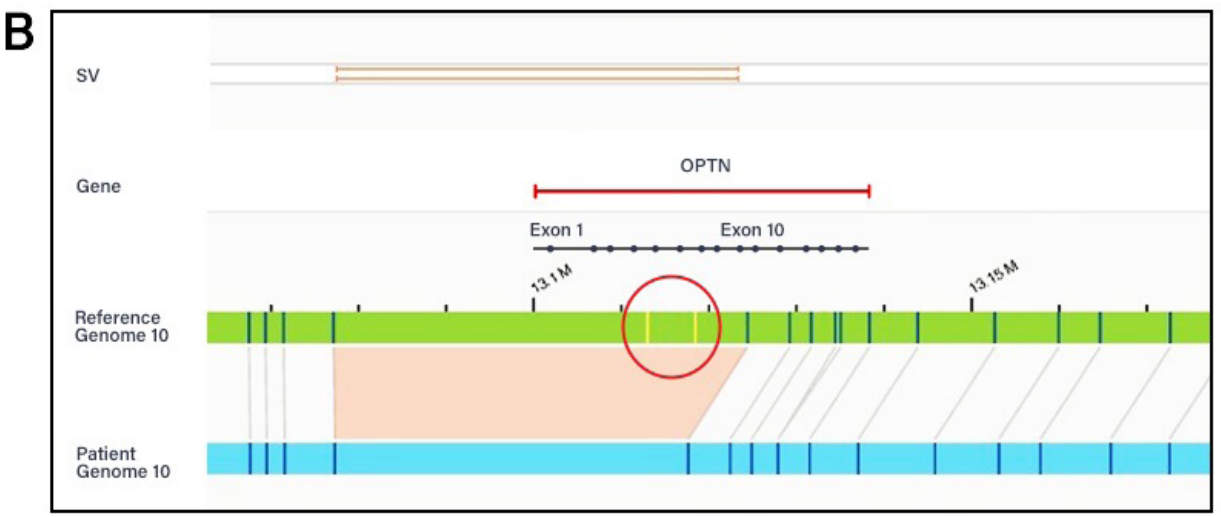


Figure 1**B**. The *OPTN* gene in estimated deletion region. Horizontal long green and blue bars are the presentation of the reference and the patient genome of chromosome 10, respectively. The black line and red line in the gene part represented the *OPTN* gene and exons-introns. Two red lines in the SV part showed the homozygous variants. The red circle showed the two missing labels in the patient's genome. Labels are in intron 6 and intron 7, respectively.

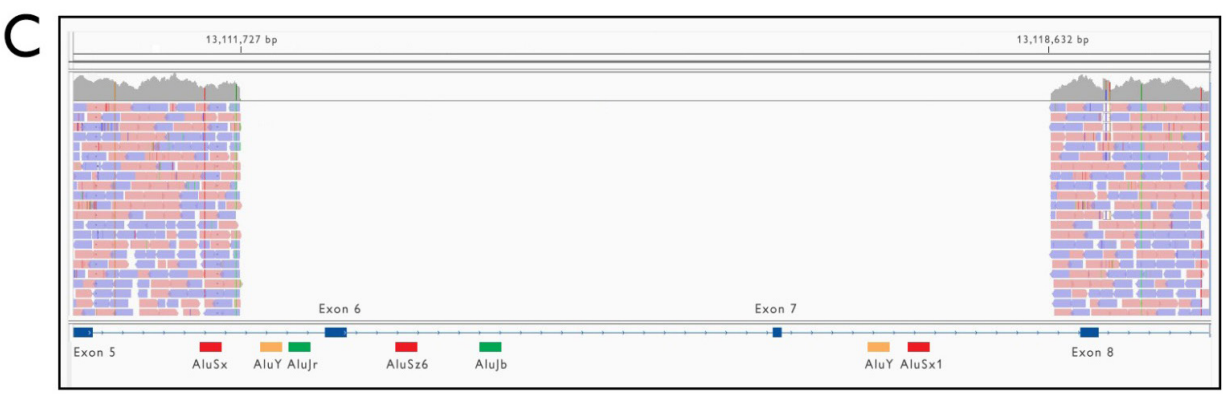


Figure 1**C**. The precise deletion breakpoints of the *OPTN* gene. The deletion region overlaps with exon 6-7 of *OPTN*. ALU repeats in the deletion region are also shown.

breakpoints. Based on the "Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen)" deletion was evaluated as pathogenic. The results of OGM and WGS are shown in Figures 1B and 1C.

## DISCUSSION

We reported an ALS patient with spastic paraplegia, dysarthria, and a new pathogenic homozygous exon 6-7 deletion in the *OPTN* gene. As far as we know, in terms of biallelic SVs causing ALS, this case is the fourth ALS patient, and this homozygous deletion is the third SV in the literature. Although *OPTN* gene mutations have been described in familial or sporadic ALS patients, the ALS and frontotemporal dementia (ALS-FTD) and parkinsonism phenotypes have also been described in the literature, albeit in a few cases.[13-15]

Other affected family members and parents have not yet been reached for genetic analysis. However, in light of the patient's homozygous mutation in the *OPTN* gene, it is hypothesized that their parents are heterozygous carriers. The recurrence of the clinic in the family also suggests this. In consideration of the novelty of the mutation and the insufficient research at the expression level, the capacity for the emergence of other *OPTN* clinics in the event of heterozygosity remains to be elucidated. In this regard, it is recommended that heterozygous patients undergo clinical follow-up, especially glaucoma until functional and clinical studies are concluded. It is important to note that carriers may have a 25% chance of having children with a genetic condition, particularly in cases of consanguineous marriages with individuals who are known to be carriers.

Pathogenic variants in *OPTN* have been found in the either heterozygous or biallelic state, suggesting that complete loss of function or haploinsufficiency of optineurin may cause ALS.[16] In the literature, most *OPTN* mutations are heterozygous and only a few homozygous mutations have been reported.[1,17-20] There are not enough case reports on whether homozygous *OPTN* carriers have earlier onset or more severe symptoms due to complete loss of function compared to heterozygous carriers. In addition, the absence of an ALS clinic in some patients despite the presence of *OPTN* mutation constitutes a limitation due to the possibility that motor neuron findings may start in the follow-up process. Also, Pottier *et al*. showed the presence of *TBK1* mutation in addition to *OPTN* mutation in the patient with FTD clinics (without an ALS clinic). They hypothesized that there may be other genes besides the *OPTN* gene (such as *TBK1*) that may affect the clinic and that the clinical picture may occur on this oligogenic basis.[21,22] In some studies, it has been shown that constitutive activation of TBK1 by mutant-OPTN leads to autophagy impairment, which causes endoplasmic stress and cell death, supporting that OPTN-TBK1 interaction may be clinically relevant.[23] However, regarding the genotype-phenotype correlation of *OPTN* especially heterozygous variants, there is not a clear relationship. Patients harboring the same mutation may present with different clinical findings.[24] However, in terms of SVs, ALS clinic was found in all patients with homozygous deletions. In heterozygous patients, Alzheimer's disease (AD), progressive non-fluent/agrammatic variant of primary progressive aphasia, anterior segment dysgenesis, and glaucoma were also reported in addition to ALS. We summarized the SVs associated with *OPTN* and phenotypes in Table 1.

In literature, exon 1-4, exon 3-5, exon 5, and exon 13-15 deletions of the *OPTN* gene were reported.[1,21,25,27] The high density of Alu repeats appears to predispose the *OPTN* to a high frequency of Alu-mediated deletions. Alu repeats in *OPTN* are three-four times higher than the average density in the human genome.[25] In the previous publications, it is seen that deletions mostly cover exon 5, suggesting that intron 5 is a hotspot region for recombination in *OPTN* due to Alu repeats.[25] In our patient, deletion is between intron 5 and intron 7, intron 5 plays a role in the variant again as in other patients. However, unlike other patients, the variant formation progressed in the 3' direction of the gene and caused a previously unrecognized exon 6-7 deletion. Alu repeats in intron 5 are AluSx, AluY, and AluJr; in intron 7 are AluY and AluSx1 (Figure 1C). We suggest that these similar Alu repeats cause deletions due to mismatches in recombination.

ALU sequences are predicted to play a role in the deletions. ALU repeats comprise approximately 11% of the human genome.[28] The high proportion of Alu repeats in the genome may lead to recombination between non-homologous loci. Such ALU-mediated recombination often

results in significant chromosomal SVs such as gene deletions, insertions, duplications, inversions, or translocations, that are responsible for the mechanism of diseases. When evaluated in terms of deletion, which is a SVs in our patient, non-allelic homology caused by Alu repeats leads to mismatches, affects double-strand break repair, and causes altered forms of genetic instability through Alu-related repeat-mediated deletion.[29,30]

OGM, a new cytogenomics technique, using the visualization of extremely long DNA molecules by unique labeling and dying the DNA. The unique labeling technique involves labeling the DNA at a specific six-base pair (bp) sequence (CTTAAG) throughout the whole genome, which leads to a specific DNA pattern and increases the sensitivity and specificity of the analysis.[31] After the labeling process, the images of the labeled DNA molecules are used to generate a genome assembly, and this labeled sample genome compared with a reference genome. The differences in the genomes described numerical variants and SVs (as deletion, insertion, duplication, balanced and unbalanced translocation, inversion, ring chromosomes, repeat expansion/contraction, copy number gain or loss (CNVs), aneuploidy, etc.). The Alu and other repeats (LINE-1, etc.,) lead to recombination between non-homologous loci and such recombination often results in deletions and other SVs as we mentioned above. These Alu or other repeats-mediated rearrangements lead to diseases such as Fanconi anemia, breast cancer, etc.[32,33] We anticipate that OGM is an ideal method for genome-wide screening for alterations mediated by Alu or other repeats. Compared to other SV analysis methods (CMA etc.), we anticipate that it is more effective than others due to its resolution values and other features such as balanced variant detection as inversion or balanced translocation. However, after scanning with OGM, a sequencing method may be required to clarify the precise breakpoints when necessary. In our patient, we used WGS for clear breakpoints in the candidate region detected by OGM. In WGS, we showed that deletion sites covering exon 6 and exon 7 were identified, compatible with the analysis performed on the missing label of OGM.

When we compare the OGM and WGS methods we used in the analysis, while OGM is capable of analyzing a multitude and complex of SVs, short-read WGS has difficulty analyzing medium or large SVs. Also, OGM analyzes the repeat number above the 500 bp, short-read WGS cannot analyze highly repetitive regions in the genome. It cannot present a high repeat number analysis based on the short-read size.

According to the long-read WGS, Oxford Nanopore Technologies continues to exhibit a high error rate and necessitates dedicated instruments for specific analyses (for high-throughput data). For both these technologies (Oxford Nanopore Technologies and Pacific Biosciences), substantial computational analyses, specific tools and custom bioinformatic pipelines are required. A further disadvantage is that they are more expensive compared to OGM. Consequently, there is a possibility that not all laboratories may have access to these technologies for routine diagnostic purposes. The reads utilized by OGM are of a significantly greater length than those employed by these technologies (short read: up to 300 bp; long read: up to 15–20 Kb; OGM: 150 Kb–2 Mb). The OGM's reads have been shown to cover the genome more clearly and with fewer gaps. Consequently, OGM has the capacity to detect SVs that may be overlooked by short and long-read sequencing technologies.[34,35]

Compared to short and long-read WGS, OGM cannot provide sequence information, the short and long-read WGS provides sequence information as well as SVs analysis. While it is impossible to assess methylation status using OGM, this is possible with the long-read sequencing platforms. OGM is unable to provide precise breakpoints, this function is provided by WGS. While the OGM is capable of detecting a multitude of SVs, its capacity to identify alterations smaller than 500 bp is limited.

In conclusion, we were able to detect and validate pathogenic, novel deletion in our patient who was diagnosed with ALS. We demonstrate the utility of OGM as a tool for the diagnosis of ALS diseases. We found WGS to be a very successful method for genome-wide screening of repeat-mediated SVs.

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## DISCLOSURE

Conflict of interest: Mehmet Burak Mutlu works for a genetic diseases evaluation company that is the distributor of OGM technology in Türkiye. The other author declares no conflict of interest.

## REFERENCES


1. Maruyama H, Morino H, Ito H, *et al*. Mutations of optineurin in amyotrophic lateral sclerosis. *Nature* 2010;465(7295):223-6. doi: 10.1038/nature08971.
2. Minegishi Y, Nakayama M, Iejima D, Kawase K, Iwata T. Significance of optineurin mutations in glaucoma and other diseases. *Prog Retin Eye Res* 2016;55:149-81. doi:10.1016/j.preteyeres.2016.08.002
3. Vaibhava V, Nagabhushana A, Chalasani ML, Sudhakar C, Kumari A, Swarup G. Optineurin mediates a negative regulation of Rab8 by the GTPase-activating protein TBC1D17. *J Cell Sci* 2012;125(Pt 21):5026-39. doi:10.1242/jcs.102327
4. Slowicka K, van Loo G. Optineurin functions for optimal immunity. *Front Immunol* 2018;9:769. doi: 10.3389/fimmu.2018.00769.
5. Kamada M, Izumi Y, Ayaki T, *et al*. Clinicopathologic features of autosomal recessive amyotrophic lateral sclerosis associated with optineurin mutation. *Neuropathology* 2014;34(1):64-70. doi:10.1111/neup.12051
6. Shen WC, Li HY, Chen GC, Chern Y, Tu PH. Mutations in the ubiquitin-binding domain of OPTN/optineurin interfere with autophagy-mediated degradation of misfolded proteins by a dominant-negative mechanism. *Autophagy* 2015;11(4):685-700. doi:10.4161/auto.36098
7. Ito Y, Ofengeim D, Najafov A, *et al.* RIPK1 mediates axonal degeneration by promoting inflammation and necroptosis in ALS. *Science* 2016;353(6299):603-8. doi:10.1126/science.aaf6803
8. Zhu M, Li A, Chen J, Zhang S, Wu J. Effects of optineurin mutants on SH-SY5Y cell survival. *Mol Cell Neurosci* 2016;74:18-24. doi:10.1016/j.mcn.2016.03.003
9. Ayaki T, Ito H, Komure O, *et al.* Multiple proteinopathies in familial ALS cases with optineurin mutations. *J Neuropathol Exp Neurol* 2018;77(2):128-38. doi:10.1093/jnen/nlx109
10. Udine E, Jain A, van Blitterswijk M. Advances in sequencing technologies for amyotrophic lateral sclerosis research. *Mol Neurodegener* 2023;18(1):4. doi:10.1186/s13024-022-00593-1
11. Barseghyan H, Eisenreich D, Lindt E, *et al*. Optical genome mapping as a potential routine clinical diagnostic method. *Genes (Basel)* 2024;15(3):342. doi:10.3390/genes15030342
12. Riggs ER, Andersen EF, Cherry AM, *et al.* Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). *Genet Med* 2020;22(2):245-57. doi:10.1038/s41436-019-0686-8
13. Dominguez J, Yu JT, Tan YJ, *et al.* Novel optineurin frameshift insertion in a family with frontotemporal dementia and parkinsonism without amyotrophic lateral sclerosis. *Front Neurol* 2021;12:645913. doi:10.3389/fneur.2021.645913
14. Kacem I, Sghaier I, Peverelli S, *et al*. Optineurin in patients with amyotrophic lateral sclerosis associated to atypical parkinsonism in Tunisian population. *Amyotroph Lateral Scler Frontotemporal Degener* 2024;25(1-2):128-34. doi:10.1080/21678421.2023.2273961
15. Nan H, Kim YJ, Chu M, *et al*. Genetic and clinical landscape of Chinese frontotemporal dementia: dominance of TBK1 and OPTN mutations. *Alzheimers Res Ther* 2024;16(1):127. doi:10.1186/s13195-024-01493-w
16. Markovinovic A, Cimbro R, Ljutic T, Kriz J, Rogelj B, Munitic I. Optineurin in amyotrophic lateral sclerosis: Multifunctional adaptor protein at the crossroads of different neuroprotective mechanisms. *Prog Neurobiol* 2017;154:1-20. doi:10.1016/j.pneurobio.2017.04.005
17. Özoğuz A, Uyan Ö, Birdal G, *et al*. The distinct genetic pattern of ALS in Turkey and novel mutations. *Neurobiol Aging* 2015;36(4):1764.e9-1764.e18. doi:10.1016/j.neurobiolaging.2014.12.032
18. Sundaramoorthy V, Walker AK, Tan V, *et al.* Defects in optineurin- and myosin VI-mediated cellular trafficking in amyotrophic lateral sclerosis. *Hum Mol Genet* 2015;24(13):3830-46. doi:10.1093/hmg/ddv126
19. Goldstein O, Nayshool O, Nefussy B, *et al.* OPTN 691_692insAG is a founder mutation causing recessive ALS and increased risk in heterozygotes. *Neurology* 2016;86(5):446-53. doi:10.1212/WNL.0000000000002334
20. Müller K, Brenner D, Weydt P, *et al*. Comprehensive analysis of the mutation spectrum in 301 German ALS families. *J Neurol Neurosurg Psychiatry* 2018;89(8):817-27. doi:10.1136/jnnp-2017-317611
21. Pottier C, Bieniek KF, Finch N, *et al*. Whole-genome sequencing reveals important role for TBK1 and OPTN mutations in frontotemporal lobar degeneration without motor neuron disease. *Acta Neuropathol* 2015;130(1):77-92. doi:10.1007/s00401-015-1436-x
22. Bury JJ, Highley JR, Cooper-Knock J, *et al.* Oligogenic inheritance of optineurin (OPTN) and C9ORF72 mutations in ALS highlights localisation of OPTN in the TDP-43-negative inclusions of C9ORF72-ALS. *Neuropathology* 2016;36(2):125-34. doi:10.1111/neup.12240
23. Medchalmi S, Tare P, Sayyad Z, Swarup G. A glaucoma- and ALS-associated mutant of OPTN induces neuronal cell death dependent on Tbk1 activity, autophagy and ER stress. *FEBS J* 2021;288(15):4576-95. doi:10.1111/febs.15752
24. Yang L, Cheng Y, Jia X, *et al.* Four novel optineurin mutations in patients with sporadic amyotrophic lateral sclerosis in Mainland China. *Neurobiol Aging* 2021;97:149.e1-149.e8. doi:10.1016/j.neurobiolaging.2020.08.002
25. Iida A, Hosono N, Sano M, *et al.* Novel deletion mutations of OPTN in amyotrophic lateral sclerosis in Japanese. *Neurobiol Aging* 2012;33(8):1843.e19-e24. doi:10.1016/j.neurobiolaging.2011.12.037
26. Schilter KF, Reis LM, Sorokina EA, Semina EV.

Identification of an Alu-repeat-mediated deletion of OPTN upstream region in a patient with a complex ocular phenotype. *Mol Genet Genomic Med* 2015;3(6):490-9. doi:10.1002/mgg3.159
27. Dilliott AA, Zhang KK, Wang J, *et al.* Targeted copy number variant identification across the neurodegenerative disease spectrum. *Mol Genet Genomic Med* 2022;10(8):e1986. doi:10.1002/mgg3.1986
28. Chénais B. Transposable elements and human diseases: Mechanisms and implication in the response to environmental pollutants. *Int J Mol Sci* 2022;23(5):2551. doi:10.3390/ijms23052551
29. Morales ME, White TB, Streva VA, DeFreece CB, Hedges DJ, Deininger PL. The contribution of alu elements to mutagenic DNA double-strand break repair. *PLoS Genet* 2015;11(3):e1005016. doi:10.1371/journal.pgen.1005016
30. Morales ME, Kaul T, Walker J, Everett C, White T, Deininger P. Altered DNA repair creates novel Alu/Alu repeat-mediated deletions. *Hum Mutat* 2021;42(5):600-13. doi:10.1002/humu.24193
31. Mantere T, Neveling K, Pebrel-Richard C, *et al*. Optical genome mapping enables constitutional chromosomal aberration detection. *Am J Hum Genet* 2021;108(8):1409-22. doi:10.1016/j.ajhg.2021.05.012
32. Levran O, Doggett NA, Auerbach AD. Identification of Alu-mediated deletions in the Fanconi anemia gene FAA. *Hum Mutat* 1998;12(3):145-52. doi:10.1002/(SICI)1098-1004(1998)12:3<145::AID-HUMU2>3.0.CO;2-G
33. Concolino P, Rizza R, Hackmann K, *et al.* Characterization of a new BRCA1 rearrangement in an Italian woman with hereditary breast and ovarian cancer syndrome. *Breast Cancer Res Treat* 2017;164(2):497-503. doi:10.1007/s10549-017-4275-8
34. Chaisson MJP, Sanders AD, Zhao X, *et al.* Multi-platform discovery of haplotype-resolved structural variation in human genomes. *Nat Commun* 2019;10(1):1784. doi:10.1038/s41467-018-08148-z
35. Ebert P, Audano PA, Zhu Q, *et al.* Haplotype-resolved diverse human genomes and integrated analysis of structural variation. *Science* 2021;372(6537):eabf7117. doi:10.1126/science.abf7117