Lessel-Kreienkamp syndrome caused by an *AGO2* variant with co-existing Turner syndrome mosaicism: A case report

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Abstract. Lessel-Kreienkamp syndrome (LESKRES) is a rare neurodevelopmental disorder caused by pathogenic variants in the *AGO2* gene. The present study to the best of our knowledge, reports first case of LESKRES coexisting with mosaic Turner syndrome in a 30-year-old Korean woman who presented with lifelong developmental delay, intellectual disability, hypotonia, impaired speech development and characteristic craniofacial features. Whole-exome sequencing identified a heterozygous *de novo* in-frame deletion in *AGO2* (NM_012154.4:c.544_546del; p.Phe182del), previously reported as pathogenic for LESKRES. The variant affects a residue at the base of the L1 linker, a hinge region implicated in RNA duplex unwinding. In addition, peripheral blood karyotyping revealed mosaic Turner syndrome [45,X(7)/47,XXX(2)/46,XX(51)]. However, the patient lacked typical Turner syndrome manifestations, including short stature and characteristic somatic features, suggesting that the neurodevelopmental phenotype was primarily attributable to the *AGO2* variant. Although some minor craniofacial findings may have been influenced by Turner syndrome mosaicism, its overall clinical contribution appeared limited. In clinical genetic laboratories, even when an abnormal finding is identified through a specific genetic test, additional genetic investigations should be considered if the genotype-phenotype correlation is not consistent with the patient's clinical presentation.

Introduction

Lessel-Kreienkamp syndrome (LESKRES) is a rare neurodevelopmental disorder caused by pathogenic variants in the argonaute RNA-induced silencing complex (RISC) catalytic component 2 (*AGO2*) gene (1). The *AGO2* gene, located at chromosome 8q24.3, belongs to the argonaute protein family and spans ~122 kb. In humans, four argonaute proteins (argonaute RISC component 1, AGO2, argonaute RISC catalytic component 3 and argonaute RISC component 4) bind microRNA and small interfering RNA, and *AGO2* serves as a core component of the RISC that mediates mRNA silencing and degradation (1,2). To date, only 22 individuals have been reported in two studies (3,4), and the phenotype has been characterized by intellectual disability (100%), motor developmental delay (100%), impaired speech development (100%), impaired receptive language (100%), muscular hypotonia (57%), autistic features (56%), gait abnormalities (55%) and variable craniofacial abnormalities (14-57%), depending on the specific feature). Turner syndrome is a chromosomal disorder caused by the complete or partial absence of a second sex chromosome in females and occurs in ~1 in 2,500-3,000 live-born girls. Its clinical features include short stature, gonadal dysgenesis, congenital lymphedema and cardiovascular abnormalities. Approximately half of affected individuals have a 45,X karyotype, while others have structural sex chromosome abnormalities or mosaicism. Reduced life expectancy has been reported, primarily due to complications of heart disease and diabetes; in one clinical series of 532 patients, 30 deaths were reported, including 13 attributed to heart disease (5). Most individuals have normal intelligence, although specific neurocognitive difficulties may occur (5). Therefore, marked intellectual disability in a patient with Turner syndrome mosaicism may warrant investigation for an additional genetic disorder. The present report describes the first Korean patient with LESKRES confirmed by molecular analysis, coexisting with Turner syndrome mosaicism, which, to the best of our knowledge, has not been previously described.

Case report

A 30-year-old female Korean patient visited the outpatient rehabilitation medicine clinic of Keimyung University Dongsan Medical Center (Daegu, Republic of Korea) in October 2025, to evaluate the cause of their lifelong developmental delay and intellectual disability. The patient was the only affected individual in their family, and there was no relevant medical history in their parents or younger brother. The developmental

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history of the patient revealed delayed motor milestones and impaired speech development, including deficits in both expressive and receptive language (detailed information on the ages at which specific developmental milestones were achieved was not available). The Mini-Mental State Examination could not be performed because of her cognitive dysfunction. Neurological examination demonstrated intellectual disability, muscular hypotonia and mild strabismus. There was no history of seizures, gait abnormalities or attention deficit hyperactivity disorder. In addition, autistic features and aggressive behavior were not observed. The patient exhibited abnormal respiratory patterns during sleep, characterized by intermittent pauses in breathing and episodes of shallow breathing. Brain magnetic resonance imaging was not performed because the patient's mothor declined the examination. The craniofacial features included epicanthic folds, mild frontal bossing, a broad nasal bridge, dental anomalies and an open mouth appearance (Fig. 1). Deep-set eyes, upslanting palpebral fissures and a thin upper lip, which have been reported in some individuals with LESKRES (3), were absent in this patient. Additional findings included neonatal feeding difficulties and a history of gastro-esophageal reflux since early childhood. No cardiac or skeletal anomalies were identified. The patient's mother declined functional evaluations, such as assessments of activities of daily living and Functional Independence Measure, therefore the patient did not undergo a rehabilitation program. Since a hereditary neurodevelopmental disorder was suspected as the underlying cause of these symptoms, the patient was referred to the genetic counseling clinic at the same institution in November 2025 for further diagnostic workup.



Figure 1. Frontal and lateral views of the patient's craniofacial features. The patient exhibited epicanthic folds, mild frontal bossing, a broad nasal bridge, dental anomalies and an open mouth appearance.

Peripheral blood karyotyping was performed on the day of the patient's visit to the genetic counseling clinic in November 2025 using conventional G-banding of cultured peripheral blood lymphocytes. Analysis of 60 metaphases revealed mosaic Turner syndrome [45,X[7]/47,XXX[2]/46,XX[51]] (Fig. 2A). Given the mosaic nature and the absence of overt phenotypic features, the clinical impact of Turner syndrome in the present patient was presumed to be minimal (5). The 47,XXX(2) cell line was present at a low level and was unlikely to be clinically significant (6). Therefore, the genetic laboratory recommended additional diagnostic evaluations to investigate the possibility of other underlying disorders.

Given the syndromic presentation, whole-exome sequencing was performed to identify the genetic cause. In December 2025, genomic DNA was extracted from EDTA-anticoagulated whole blood using the QIAamp DNA Blood Mini Kit (catalogue no. 51104; QIAGEN GmbH) according to the manufacturer's instructions. DNA concentration was measured using a Qubit 3.0 fluorometer (Thermo Fisher Scientific, Inc.), and DNA integrity was assessed by agarose gel electrophoresis. Library preparation and target enrichment were performed using the xGen™ Exome Hyb Panel v2, 96 reactions (catalogue no. 10005153; Integrated DNA Technologies, Inc.). Libraries with concentrations of ≥20 ng/μl, as measured using the Qubit 3.0 fluorometer, were pooled; the mean concentration of the individual libraries before pooling was approximately 130-140 ng/μl. The pooled library was sequenced on a NovaSeq 6000Dx platform (Illumina, Inc.) to generate 150-bp paired-end reads (2x150 bp). Reads were aligned to the GRCh37/UCSC hg19 human reference genome using BWA-MEM (version 0.7.17; Broad Institute), duplicate reads were marked using biobambam2 (German Cancer Research Center), and base quality recalibration and variant calling were performed using the Genome Analysis Toolkit (version 4.1.9.0; Broad Institute). Variants were annotated using Variant Effect Predictor (version 114.0; European Molecular Biology Laboratory-European Bioinformatics Institute) and dbNSFP (University of South Florida). Evaluation focused on coding exons along with flanking ± 20 intronic bases, and sequence variants were classified based on the American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines (7). Whole-exome sequencing identified a heterozygous in-frame deletion in *AGO2* (NM_012154.4:c.544_546del; p.Phe182del; Fig. 2B), located in the L1 linker (Fig. 2C). Review of the aligned sequencing reads demonstrated the three-base deletion in reads of both forward and reverse orientation at a heterozygous allele fraction, with no evidence of strand bias or of alignment artifacts within adjacent homopolymer or repetitive sequence. The deleted residue lies at the base of the L1 linker, a hinge region implicated in RNA duplex unwinding and in the conformational movement of helix-7 and the PAZ domain upon target mRNA recognition; the same variant has been reported previously in an individual with LESKRES whose craniofacial features were consistent with those of the present patient (3). No additional pathogenic or likely pathogenic variants associated with hereditary neurodevelopmental disorder were detected.

Chromosomal microarray analysis was performed concurrently with whole-exome sequencing in December 2025 using the Applied Biosystems™ CytoScan™ Dx Assay on the CytoScan™ Dx array platform (Thermo Fisher Scientific, Inc.), according to the manufacturer's protocol. Genomic DNA was extracted from peripheral blood using the QIAamp DNA Blood Mini Kit (QIAGEN GmbH). A total of 250 ng genomic DNA was digested, amplified, purified, fragmented, labeled and hybridized to the microarray. Arrays were washed and scanned using the GeneChip™ System 3000Dx platform (Thermo Fisher Scientific, Inc.). Raw data were analyzed using the Chromosome Analysis Suite software (version 2.1.0.169; Thermo Fisher Scientific, Inc.) with the human genome reference

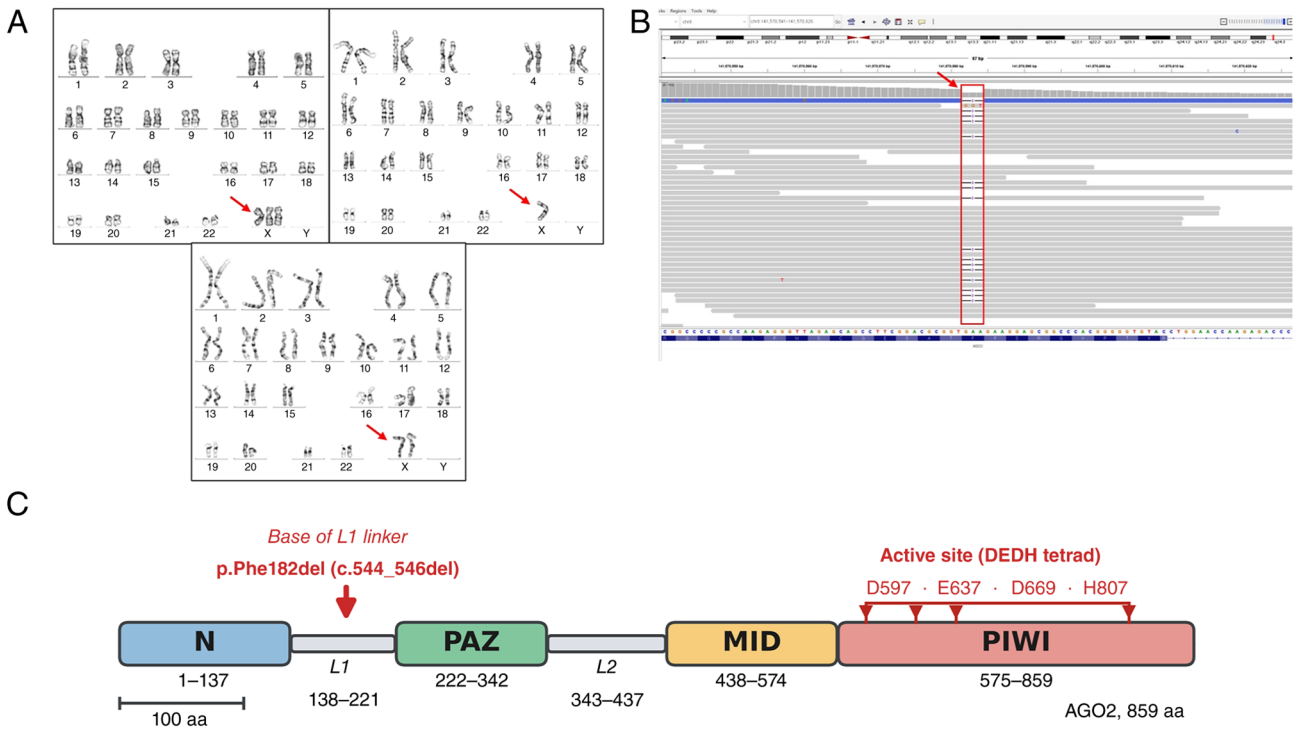


Figure 2. Peripheral blood karyotyping and whole exome sequencing findings of the patient. (A) Karyotype analysis showing mosaic Turner syndrome (45,X/47,XXX/46,XX); X chromosomes are indicated by red arrows. (B) Integrative Genomics Viewer (version 2.19.8) screenshot demonstrating a heterozygous in-frame deletion in *AGO2* (NM_012154.4: c.544_546del; p.Phe182del), with the deletion site marked by a red arrow and outlined by the red box. The deletion is present in reads of both forward and reverse orientation at a heterozygous allele fraction. (C) Schematic representation of the AGO2 protein (859 amino acids), showing the N-terminal (N), PAZ, MID and PIWI domains and the L1 and L2 linkers with their residue boundaries. The catalytic (active) site within the PIWI domain, formed by the DEDH tetrad (D597, E637, D669 and H807), is indicated. The red arrow denotes the position of the p.Phe182del variant identified in the present patient, which is located at the base of the L1 linker and is spatially distant from the catalytic site.

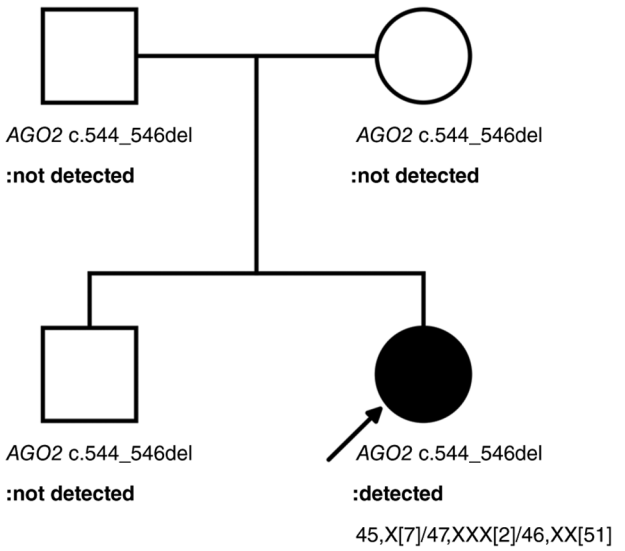


Figure 3. Pedigree chart of the patient. She was the only symptomatic individual in the family and the only carrier of the variant.

sequence GRCh37/hg19. Copy number variants and regions of homozygosity were interpreted according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines (7). Chromosomal microarray analysis revealed no clinically significant abnormalities and did not detect the mosaicism identified by peripheral blood karyotyping. This discrepancy was considered attributable to low-level mosaicism below the detection threshold of the single-nucleotide polymorphism array platform. The normal chromosomal microarray result despite mosaic karyotype findings was presumed to be due to low-grade mosaicism below the detection limit of the CytoScan Dx array platform, which generally detects mosaic chromosomal abnormalities at levels of ≥10-20% (8).

Segregation analysis confirmed that the *AGO2* variant was absent in both parents and the unaffected sibling, indicating a *de novo* origin, consistent with previous reports of LESKRES (Fig. 3) (3,4). Following the final diagnosis, the patient's mother declined all further medical care, including participation in a rehabilitation program; therefore, subsequent assessment of the patient's clinical status is not available.

Discussion

The present case expands the clinical spectrum of LESKRES and, to the best of our knowledge, represents the first reported case in Korea. When considering this variant together with previously reported LESKRES cases (3,4), intellectual disability, motor developmental delay, impaired speech development and impaired receptive language, which have been reported in all affected individuals, were also observed in the present patient. Additional findings in the present patient included muscular hypotonia, mild strabismus, abnormal respiration, epicanthic folds, mild frontal bossing,

an open-mouth appearance, a broad nasal bridge, dental anomalies, neonatal feeding difficulties and gastroesophageal reflux during early childhood. Autistic features, gait abnormalities, attention-deficit/hyperactivity disorder, seizures, visual impairment, aggressive behavior, refractive errors, skeletal anomalies and cardiac anomalies were not observed. Additionally, peripheral blood karyotyping demonstrated mosaic Turner syndrome; however, the patient did not exhibit typical phenotypic features of Turner syndrome, such as short stature, characteristic facial features or somatic stigmata and their clinical presentation was not suggestive of classic Turner syndrome (5). Some of the minor craniofacial features, such as epicanthic folds and a broad nasal bridge, may overlap with the variable facial phenotype of Turner syndrome; however, the overall clinical contribution of mosaic Turner syndrome in the present patient appeared limited, and it was difficult to completely distinguish.

In neurons, numerous mRNAs are transported into dendrites and held in a translationally silenced state within processing bodies (P-bodies) so that proteins required for synaptic remodelling can be produced locally upon synaptic stimulation, and their release from *AGO2* normally requires phosphorylation of a C-terminal serine cluster that acts as a switch terminating repression (1,3). In the reported functional analyses, this phosphorylation was markedly reduced in mutant *AGO2*, the dissociation of *AGO2* from its target mRNAs was correspondingly delayed, and the density of dendritic P-bodies was almost doubled in primary hippocampal neurons expressing p.Phe182del, p.Leu192Pro or p.Met364Thr, whereas the number of *AGO2*-containing granules in neuronal cell bodies remained unchanged. This compartment-specific pattern indicates a selective accumulation of *AGO2*-bound transcripts in dendrites rather than a general change in *AGO2* abundance, and has been interpreted as an impairment of local translation that may in turn alter plasticity in response to synaptic activity. Since dendritic P-bodies and the activity of AGO proteins in dendrites are hypothesized to contribute to synaptic activity, it is conceivable that such changes modify the complement of dendritic mRNAs available for local translation upon synaptic stimuli, although how this affects neuronal function and morphology, as well as synaptic plasticity, learning and memory, remains to be determined (3). In line with a post-transcriptional mechanism converging on the synapse, the transcripts whose *AGO2*-dependent silencing was impaired by these variants include *SHANK3* and δ-catenin (*CTNND2*), which are dose-sensitive regulators of the postsynaptic density and of dendritic spine maturation and are themselves established neurodevelopmental disease genes (9,10), although these assays employed experimentally introduced constructs rather than endogenous regulation in neural cells. Taken together, an impairment of local, activity-dependent translation in dendrites, demonstrated for the same p.Phe182del variant carried by the present patient, may plausibly contribute to the patient's intellectual disability, impaired expressive and receptive language development and muscular hypotonia, whereas the basis of the extraneurological features, including the dental anomalies, remains unclear. Although the impact of this *AGO2* variant has been demonstrated in a previous study through functional analysis, further functional studies in additional cases are needed to distinguish its contribution from that of Turner mosaicism. The present case highlights that comprehensive genetic testing increasingly uncovers additional genomic findings, including variants and karyotypic abnormalities that may not contribute to the primary clinical phenotype. Nevertheless, the present findings suggest that careful genotype-phenotype correlation and cautious clinical interpretation are essential when multiple genetic abnormalities are identified in the era of high-throughput genomic testing. From a clinical laboratory perspective, even when an abnormal result is obtained using a targeted genetic assay, further genetic investigation should be considered if the genotype-phenotype correlation is incongruent with the patient's presentation to avoid both underdiagnosis and misattribution of incidental findings to the primary disorder. Ultimately, comprehensive genetic testing should be leveraged not only to increase diagnostic yield but also to refine clinical reasoning, ensuring that incidental or secondary findings are interpreted within a robust clinical and phenotypic framework.

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Availability of data and materials

The whole-exome sequencing data generated in the present study may be found in the NCBI Sequence Read Archive under accession number SRR40522157, associated with BioProject PRJNA1523854 or at the following URL: https://www.ncbi.nlm.nih.gov/sra/SRR40522157.

Authors' contributions

DK conceptualized the study, developed the methodology, supervised the project, prepared the figures and managed the project administration. JHC collected the clinical data and reviewed the patient's medical history and clinical findings. SP and DK analyzed and interpreted the clinical and genetic data and drafted the original manuscript. DK reviewed and edited the manuscript. SP and DK confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Keimyung University Dongsan Hospital (IRB No. 2026-04-128) and conducted in accordance with the Declaration of Helsinki.

Patient consent for publication

Written informed consent for publication of this case report and any accompanying images was obtained from the patient's legal guardian.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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