Novel frameshift mutation in LIS1 gene is a probable cause of lissencephaly: a case report

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Abstract

Background: Lissencephaly (LIS) is a cortical malformation, characterized by smooth or nearly smooth cerebral surface and a shortage of gyral and sulcal development, which is caused by deficient neuronal migration during embryogenesis. Neuronal migration involves many gene products, among which is the product of the PAFAH1B1 gene, associated with this disease. LIS is a rare disease, characterized by low population frequency, and with non-specific clinical symptoms such as early epilepsy, developmental delay or cerebral palsy-like motor problems. Given that high-throughput sequencing techniques have been improving diagnosis, we have chosen this technique for addressing this patient.

Case presentation: We present the case of a seven years old male patient with an undiagnosed rare disease, with non-specific clinical symptoms possibly compatible with lissencephaly. The patient was enrolled in a study that included the sequencing of his whole genome. Sequence data was analyzed following a bioinformatic pipeline. The variants obtained were annotated and then subjected to different filters for prioritization. Also mitochondrial genome was analyzed. A novel candidate frameshift insertion in known PAFAH1B1 gene was found, explaining the index case phenotype. The assessment through in silico tools reported that it causes nonsense mediated mechanisms and that it is damaging with high confidence scores. The insertion causes a change in the reading frame, and produces a premature stop codon, severely affecting the protein function and probably the silencing of one allele. The healthy mother did not carry the mutation, and the unaffected father was not available for analysis.

Conclusions: Through this work we found a novel de novo mutation in LIS1/PAFAH1B1 gene, as a likely cause of a rare disease in a young boy with non-specific clinical symptoms. The mutation found correlates with the phenotype studied since the loss of function in the gene product has already been described in this condition. Since there are no other variants in the PAFAH1B1 gene with low population frequency and due to family history, a de novo disease mechanism is proposed.

Keywords: Lissencephaly, PAFAH1B1, Whole-genome sequencing, Rare disease, Novel mutation, Case report

Background

Lissencephaly (LIS) is a subtype of malformations of cortical development (MCD), which are a heterogeneous group of disorders with diverse phenotypic and genotypic presentations. Patients with LIS may present different...
degrees of developmental delays, seizures, severe psychomotor impairment, muscle spasticity or hypotonia [1].

Lissencephaly is a disorder caused by a defect in neuronal migration, which occurs between 12 and 24 weeks of gestation and results in a lack of development of brain folds (gyri) and grooves (sulci) [2]. Neuronal migration is a complex process, which requires the coordination of many gene products.

*LIS1* and *DCX* were the first genes that were associated with LIS, discovered in 1993 and 1998, respectively [3, 4]. In the past years with the advent of new molecular genomics technologies, many additional genes were found. These LIS-related genes include *ACTB, ACTG1, ARX, CDKS, CRADD, DYNCH1I, KIF2A, KIF5C, NDE1/NDELI, TUBA1A, TUBA8, TUBB, TUBB2B, TUBB3, TUBG1, RELN and VLDLR*. Many of these 19 LIS-associated genes are related to microtubule structural proteins (tubulin) or microtubule-associated proteins [5].

The *PAFAH1B1* gene (Genbank accession number: NM_000430), located at chromosome 17p13.3, encodes the alpha subunit of the 1B isoform of the platelet-activation factor acetylhydrolase regulatory, a highly conserved protein of 410 amino acids, known as LIS1 or PAFAH1B1 [6]. It has two protein coding transcripts and several non-coding ones. LIS1/PAFAH1B1 forms the non-catalytic subunit of the G protein-like heterotrimeric cytosolic platelet-activating factor acetylhydrolase (PAF-AH) brain isoform Ib (PAFAH1B1) [7]. Along with two other subunits, PAFAH1B2 and PAFAH1B3, LIS1/PAFAH1B1 forms a trimeric complex which regulates the level of platelet activating factor (PAF) in the brain, by catalyzing the removal of the acetyl group at the SN-2 position of platelet-activating factor [8, 9]. The regulation of optimal concentrations of PAF in the brain may be critical for correct neuronal migration, essential for normal brain development and function. LIS1/PAFAH1B1 has also been shown to play a central role in the organization of the cytoskeleton, which in turn affects neuronal proliferation and migration [6]. Mutations in this gene have previously been associated with cortical brain malformation in children (Table 1).

Here, we comment on the case of a seven years old boy with an undiagnosed rare disease, with non-specific symptoms that could be compatible with LIS, but with an unclear presentation. Whole genome sequencing (WGS) of the patient was performed in the context of a genomics project (urugenomes.org) and sequence data was analyzed following a bioinformatics pipeline which concluded with a set of annotated and prioritized variants. A novel candidate frameshift variant was found that fits with the boy’s phenotype. To support the pathogenicity of the variant we used computational prediction tools and made segregation analysis with Sanger sequencing.

To the best of our knowledge this is the first time this variant is reported [11] and it is the most likely cause of the patient’s disease.

**Case presentation**

The index case is a seven years old boy with perinatal clinical records of poorly controlled pregnancy, homelessness and multiple drugs abuse through all gestation. Both parents are healthy and non-consanguineous. Early term delivery, low birthweight with microcephaly at birth with a head circumference of 32 cm (Z score -3).

The patient develops a spastic bilateral cerebral palsy, Gross Motor Function Classification System (GMFCS) IV, Bimanual fine motor function (BFMf) IVa, Communication Function Classification System (CFCS) IV. Associated with a profound intellectual disability, visual and auditory sensory deficit, pharmacoresistant epilepsy with generalized tonic clonic seizures, and congenital microcephaly with a head circumference growth always under -3 standard deviations. No dysmorphic signs were detected.

Cerebral magnetic resonance imaging (MRI) shows a diffuse lissencephaly-pachygyria spectrum with main affection at posterior brain areas (Fig. 1).

**Genetic and evolutionary analysis**

Whole genome sequencing (WGS) of the patient was performed and sequence data was analyzed following a bio-informatic pipeline which included analysis of the quality of reads [12], mapping onto human reference genome (hg19) [13], mark of duplicates, sorting and variant calling [14]. The variants obtained were annotated [15] and then subjected to different sets of filters to detect potentially causative mutations (see Supplementary Material). After these filters were applied, we obtained 40 homozygous or hemizygous variants with population frequency less than 1% located at splicing sites or coding regions, 458 heterozygous variants with population frequency less than 1% and 439 heterozygous variants with population frequency less than 0.5% and located at splicing sites or coding regions.

Among these prioritized variants we found a potential causative mutation in heterozygous state in the *LIS1/PAFAH1B1* gene. This gene was previously associated with the phenotype (LIS), especially with an autosomal dominant mechanism of inheritance. The potential causative mutation found is a frameshift insertion of a single nucleotide in exon 8 (PAFAH1B1:NM_000430:exon8:c.681dupG:p.(Lys228Glufs*28)), that lies between the first 23% to 55% of the protein depending on the transcript, according to the SIFT Indel tool [16]. The frameshift indel was reported as damaging with a confidence score of 0.858, and causing a nonsense mediated decay (NMD).
Table 1 Mutations in \textit{LIS1/PAFAH1B1} gene associated with cortical brain malformation available in ClinVar [10]. All mutations are associated with lissencephaly phenotype but two that are marked with * (associated with Subcortical band heterotopia) and ** (associated with abnormal cortical gyration).

| Name | Protein change | Mutation type | Accession | GRCh37Location | dbSNP ID |
|------|----------------|---------------|-----------|----------------|----------|
| Likely Pathogenic | | | | | |
| c.1142A > G (p.His381Arg) | H381R | missense | VCV000931583 | 2,583,597 | rs2069361452 |
| c.967 T > A (p.Trp323Arg) | W323R | missense | VCV000812182 | 2,579,865 | rs2069271269 |
| c.900G > C (p.Glu300Asp) | E300D | missense | VCV000436141 | 2,577,582 | rs857784291 |
| c.121G > A (p.Glu141Lys) | E41K | missense | VCV000159503 | 2,569,313 | rs857784250 |
| c.503G > A (p.Cys168Tyr) | C168Y | missense | VCV000159525 | 2,573,560 | rs200390886 |
| c.569-3del | non coding | | VCV000211827 | 2,575,943 | rs79045863 |
| c.671+4A > G | non coding | | VCV000159537 | 2,576,056 | rs857784279 |
| c.671+5G > A | non coding | | VCV000159536 | 2,576,055 | rs857784279 |
| c.900G > A (p.Glu300Arg) | E300D | missense | VCV000159545 | 2,577,583 | rs857784287 |
| c.938C > T (p.Ser313Phe) | S313F | missense | VCV000159552 | 2,579,836 | rs857784293 |
| c.965 T > G (p.Met322Arg) | M322R | missense | VCV000159553 | 2,579,863 | rs857784294 |
| c.1193G > A (p.Gly398Asp) | G398D | missense | VCV000159500 | 2,585,056 | rs587784247 |
| NC_000017.11:g.(?_2638238)_(2638345_?)del | large deletion | | VCV000495279 | 2,541,532—2,541,639 |
| NC_000017.11:g.(?_2680139)_(2681852_?)del | large deletion | | VCV000495278 | 2,583,433—2,585,146 |
| c.899A > G (p.Glu300Gly) | E300G | missense | VCV000436140 | 2,577,581 | rs1555527149 |
| c.400-1G > A | splicing acceptor | | VCV001526061 | 2,573,456 | |
| c.661G > A (p.Val221Met) | V221M | missense | VCV000931348 | 2,577,582 | rs1262666760 |
| c.1009C > G (p.His337Asp) | H337D | missense | VCV000159488 | 2,583,464 | rs587784236 |
| c.1190C > T (p.Thr397Ile) | T397I | missense | VCV000429277 | 2,585,053 | rs1131691295 |
| c.722G > C (p.Arg241Pro) | R241P | missense | VCV000159545 | 2,577,583 | rs1555527149 |
| Pathogenic | | | | | |
| c.441dup (p.Gly148fs) | G148fs | frame shift | VCV000211825 | 2,573,495—2,573,496 | rs79045861 |
| c.162dup (p.Trp55fs) | W55fs | frame shift | VCV000211828 | 2,569,346—2,569,347 | rs113994198 |
| c.716dup (p.Met239fs) | M239fs | frame shift | VCV000159542 | 2,577,397—2,577,398 | rs857784284 |
| c.1050del (p.Lys315fs) | K315fs | frame shift | VCV00021176 | 2,583,500 | rs113994200 |
| c.703_704del (p.Glu235fs) | E235fs | frame shift | VCV000211829 | 2,577,382—2,577,383 | rs79045865 |
| c.3G > A (p.Met1Ile) | M1I | missense | VCV000159503 | 2,541,585 | rs857784265 |
| c.33-3C > T | non coding | | VCV000159514 | 2,568,663 | rs857784260 |
| c.37C > T (p.Arg12Ter) | R12* | stop gain | VCV000159516 | 2,568,670 | rs857784262 |
| c.56T > G (p.Leu19Arg) | L19R | missense | VCV000159529 | 2,568,689 | rs79045861 |
| c.71_72dup (p.Glu25fs) | E25fs | frame shift | VCV000211830 | 2,568,702—2,568,703 | rs79045866 |
| c.72 T > G (p.Tyr24Ter) | Y24* | stop gain | VCV000159543 | 2,568,705 | rs857784285 |
| c.84 T > G (p.Tyr28Ter) | Y28* | stop gain | VCV000159547 | 2,568,717 | rs859295961 |
| c.136_137del (p.Lys46fs) | K46fs | frame shift | VCV000159505 | 2,569,325—2,569,326 | rs79045865 |
| c.152del (p.Leu51fs) | L51fs | frame shift | VCV000159506 | 2,569,341 | rs857784253 |
| c.190_192 + 5dup | | | VCV000211820 | 2,569,381—2,569,382 | rs79045857 |
| c.192G > A (p.Lys64Asn) | K64N | missense | VCV000159511 | 2,569,384 | rs857784257 |
| c.192 + 1G > T | | | VCV000159510 | 2,569,385 | rs857784256 |
| c.288_289dup (p.Arg97fs) | R97fs | frame shift | VCV000211821 | 2,570,378—2,570,379 | rs79045858 |
| c.371 T > A (p.Val124Asp) | V124D | missense | VCV000159515 | 2,570,464 | rs857784261 |
| c.386A > T (p.Asp129Val) | D129V | missense | VCV000159517 | 2,570,479 | rs857784263 |
| c.399 + 1G > A | | | VCV000159519 | 2,570,493 | rs857784264 |
| c.405G > A (p.Trp135Ter) | W135* | stop gain | VCV000159521 | 2,573,462 | rs857784266 |
| c.455_456del (p.Ser152fs) | S152fs | frame shift | VCV000159523 | 2,573,510—2,573,511 | rs857784268 |
## Table 1 (continued)

| Name                  | Protein change       | Mutation type | Accession   | GRCh37Location | dbSNP ID      |
|-----------------------|----------------------|---------------|-------------|----------------|---------------|
| c.460C > T (p.Gln154Ter) | Q154*                | stop gain     | VCV00159524 | 2,573,517      | rs587784269   |
| c.484G > A (p.Gly162Ser) | G162S               | missense      | VCV000008079 | 2,573,541      | rs121434487   |
| c.524_528del (p.Lys175fs) | K175fs              | frame shift  | VCV00159526 | 2,573,579—2,573,583 | rs587784270   |
| c.537dup (p.Gln180fs) | Q180fs              | frame shift  | VCV00211826 | 2,573,590—2,573,591 | rs587784271   |
| c.537del (p.Gln180fs) | Q180fs              | frame shift  | VCV00159527 | 2,573,591      | rs587784271   |
| c.623C > G (p.Ser211Ter) | S211*               | stop gain     | VCV00159530 | 2,576,012       | rs587784273   |
| c.644_651del (p.Thr215fs) | T215fs             | frame shift  | VCV00159531 | 2,576,018—2,576,025 | rs587784274   |
| c.647_648del (p.Ile216fs) | I216fs              | frame shift  | VCV00159532 | 2,576,025—2,576,026 | rs587784275   |
| c.658del (p.Cys161fs) | E220fs              | frame shift  | VCV00159534 | 2,576,036      | rs587784277   |
| c.657G > A (p.Trp219Ter) | W219*               | stop gain     | VCV00159533 | 2,576,037      | rs587784276   |
| c.664C > T (p.Gln222Ter) | Q222*               | stop gain     | VCV00159535 | 2,576,044—2,576,045 | rs797045864   |
| c.667dup (p.Glu222fs) | E220fs              | frame shift  | VCV00159536 | 2,576,050—2,576,051 | rs587784278   |
| c.671G > A (p.Gly224Asp) | G224D               | missense      | VCV00159538 | 2,576,051      | rs587784281   |
| c.675C > G (p.Tyr225Ter) | Y225*               | stop gain     | VCV00159539 | 2,577,357       | rs587784282   |
| c.728_732dup (p.Asp245fs) | D245fs             | frame shift  | VCV00211831 | 2,577,406—2,577,407 | rs587784286   |
| c.730C > T (p.Glu244Asp) | G224D               | missense      | VCV00159540 | 2,577,412       | rs587784286   |
| c.743T > A (p.Phe248Ser) | F248S               | non coding    | VCV00159545 | 2,577,423—2,577,424 | rs587784286   |
| c.1002 + 1G > A splice donor |                     |               | VCV00159486 | 2,579,905—2,579,906 | rs587784235   |
| c.1003-30_1032del               |                     | splice acceptor | VCV00211817 | 2,583,426—2,583,427 | rs155527743   |
| c.1009C > T (p.His377Tyr) | H377Y               | missense      | VCV00159489 | 2,583,464       | rs587784236   |
| c.1018dup (p.Trp284Ter) | W824*               | stop gain     | VCV00159490 | 2,583,555—2,583,556 | rs587784240   |
| c.1024_1031del (p.Arg342fs) | R342fs              | frame shift  | VCV00159491 | 2,583,558—2,583,559 | rs587784238   |
| c.1050dup (p.Arg355fs) | S355fs              | frame shift  | VCV00159492 | 2,583,519       | rs587784239   |
| c.1111C > T (p.Arg371Ter) | R371*               | stop gain     | VCV00159493 | 2,583,555       | rs587784240   |
| c.1135C > T (p.His377Tyr) | H377Y               | missense      | VCV00159495 | 2,583,590       | rs587784242   |
| c.1159G > T (p.Asp377Tyr) | D387Y               | missense      | VCV00159497 | 2,583,614       | rs587784244   |
| c.1165C > T (p.His379Tyr) | H389Y               | missense      | VCV00159498 | 2,583,028       | rs587784245   |
| c.1174G > C (p.Ser399Thr) | S399T               | missense      | VCV00159500 | 2,583,059       | rs587784248   |
| c.1198C > G (p.Trp401His) | D401H               | missense      | VCV00159501 | 2,585,064       | rs587784249   |
| c.1233A > G (p.Thr411Cys) | R411C               | stop lost     | VCV00159504 | 2,585,096       | rs587784251   |
| c.1311C > T (p.Arg403Ter) | R403*               | stop gain     | VCV00159495 | 2,583,555       | rs587784241   |
| c.568 + 1G > A splice donor |                     |               | VCV00436137 | 2,573,626—2,573,627 | rs155527733   |
| c.162del (p.Lys54fs) | K54fs               | frame shift  | VCV000211180 | 2,569,347      | rs133994198   |
| c.265C > T (p.Arg89Ter) | R89*                | stop gain     | VCV00159512 | 2,570,358       | rs587784258   |
| c.817C > T (p.Arg273Ter) | R273*               | stop gain     | VCV00008074 | 2,577,499       | rs121434483   |
| c.305dup (p.Tyr102Ter) | Y102*               | stop gain     | VCV00159513 | 2,570,397—2,570,398 | rs587784259   |
| c.347dup (p.His117fs) | H117fs              | frame shift  | VCV00211823 | 2,570,436—2,570,437 | rs587784589   |
| c.368T > A (p.Met123Lys)** | M123K               | missense      | VCV001077134 | 2,570,461       | rs587784251   |
| c.523A > T (p.Lys175Ter) | K175*               | stop gain     | VCV00209180 | 2,573,580       | rs5877045061  |
| c.910del (p.Ser304fs) | S304fs              | frame shift  | VCV00159515 | 2,579,802       | rs587784292   |
| c.911del (p.Ser304fs) | S304fs              | frame shift  | VCV00211835 | 2,579,809       | rs5877045871   |
response. It generates a premature stop codon 27 amino acids later, causing the loss of 156 amino acids.

If the mutated gene evaded NMD and led to a final product, this would be a 254 amino acids protein instead of the wild type 410 residues. A crystal structure has been described for LIS1 complexed to the brain cytosolic PAF-AH [17]. The complex shows that LIS1 folds into a beta propeller and interacts as a homodimer with a PAF-AH homodimer. From 14 reported surface interacting residues with PAF-AH, 8 are missing from our patient’s hypothetical protein. We predict that the mutated LIS1 could have self-aggregation tendencies, as the 27 new residues composing the shorter C-terminal region, not only would not allow the correct folding into a complete beta-propeller, but in addition would be highly disordered. As a qualitative indicator for this, the homology model in this C-terminal region has very low quality, in particular for the ‘HRTQRMGTY’ amino acid stretch, according to QMEANDiscO scoring function [18]. Even without aggregation and assuming the protein could fold into a ‘half propeller’, this protein would be unable to productively interact with PAF-AH as well as its additional molecular partners, notably dynein and a number of dynein-associated proteins. Indeed, LIS1 has been described as a molecular hub at a crossroad of several pathways, coupling PAF signaling to dynein regulation [17]. We expect all these functions to be hampered or inexistent in the protein product coded by this allelet.

The unaffected mother was sequenced at the proposed variant position and no mutation was detected. This is considered to support the hypothesis of a de novo mutation in the patient. Unfortunately the father of the patient (also unaffected) was not available for analysis.

Figure 2 A shows an IGV view of the candidate position. 37 reads are covering that location with a good quality. Additionally, the variant was confirmed with Sanger Sequencing in the patient (Fig. 2B, top) and was not seen in the mother (Fig. 2B, bottom)

Discussion and conclusion
We found a novel probably causative frameshift variant in a patient with a previously undiagnosed rare disease using WGS. Previous genetic tests (sequencing of MECP2 and ARX genes, and methylation analysis for Angelman syndrome) were performed with inconclusive results. This is expected since Lissencephaly and

| Name | Protein change | Mutation type | Accession | GRCh37Location | dbSNP ID |
|------|----------------|---------------|-----------|----------------|----------|
| c.852G > A (p.Trp284Ter) | W284* | stop gain | VCV000561072 | 2,577,534 | rs1567559851 |
| c.514dup (p.Met172fs) | M172fs | frame shift | VCV000436136 | 2,573,570—2,573,571 | rs1555526718 |
| c.430C > T (p.Arg144Ter) | R144* | stop gain | VCV000159522 | 2,573,487 | rs387784267 |
| c.1159 + 1G > A | splice donor | VCV000379162 | 2,583,615 | rs1057520515 |
| c.1159 + 2T > A | splice donor | VCV000159496 | 2,583,616 | rs587784243 |
| c.569-10 T > C | non coding | VCV000021182 | 2,575,939 | rs113994202 |
| c.681dupG | L228Glufs | frame shift | this paper | |
epileptic encephalopathy are highly heterogeneous genetic disorders in their etiology: ie. different genes are associated with several presentations of this pathology. For example, \textit{RELN} gene is affected in the Norman-Roberts syndrome (LIS2) \cite{19}, heterozygous mutations in \textit{TUBA1A} are responsible for the LIS3 syndrome \cite{20}, homozygous mutations in the \textit{NDE1} gene are associated to LIS4 \cite{21}, among many others (\textit{LAMB1} to LIS5 \cite{22}, \textit{KATNB1} to LIS6 \cite{23}, \textit{CDK5} to LIS7 \cite{24}, \textit{TMTC} to LIS8 \cite{25}, \textit{MACF1} LIS9 \cite{26}, \textit{CEP85L} LIS10 \cite{27}). Additionally X-linked forms of Lissencephaly are caused by \textit{DCX} and \textit{ARX} genes \cite{28}. Hence, usually WGS or WES are accurate strategies for assessing patients with epileptic encephalopathy. However, in this case if we had had the MRI results (fairly consistent with LIS) before we had done the NGS sequencing, we might have end up doing a targeted sequencing approach, such as the \textit{PAFAH1B1} gene or at least a subset of genes or WES, instead of...
doing the complete genome. This being a matter of costs and resources and not crucial for the patient’s diagnosis.

The variant we detected was an insertion of one nucleotide (G) in the coding sequence of LIS1 gene, causing a change in the reading frame. The localization of the variant corresponds to the first 23% to 55% of the protein (depending on the transcript) and as a consequence a premature stop codon is produced causing the loss of the last 156 amino acids of the protein. Therefore, a severe affection of the protein function is expected and probably a silencing of this allele either by encoding a truncated protein or by the mechanism of degradation of messenger RNA mediated by terminator mutations (NMD).

This variant has not been previously described and does not appear in the population frequency databases. It corresponds to the phenotype of the patient and the loss of function in the gene product is a mechanism already described in this condition (truncating mutations were described in other patients and being the gene involved in the microdeletion of Miller-Dieker lissencephaly syndrome). Since there are no other variants in the LIS1/PAFAH1B1 gene with less than 1% population frequency and due to family history, we proposed a de novo mechanism for this case. This was (partially) confirmed by Sanger sequencing of the mother who doesn’t have the mutation. Father was unavailable for analysis, so this aspect remains unknown. Nevertheless, we consider that there is sufficient evidence that supports the pathogenic classification of the novel variant.

According to ACMG (American College of Medical Genetics and Genomics) variant interpretation guidelines [29] the frameshift variant found corresponds to the PVS1 (pathogenicity very strong) rule. It is a null variant (frameshift) in a gene where loss of function (LOF) is a known mechanism of disease (in ExAC database PAFAH1B1 gene has a maximal probability of being LOF intolerant, pLI = 1 [30]). The frameshift mutation is also classified as a PM2 (moderate evidence of pathogenicity) since it was absent in population databases (1000 Genomes Project, GnomAD, etc.). We also consider applying rule PP4 (Patient’s phenotype is highly specific for a disease with a single genetic etiology), since the MRI findings are very specific for PAFAH1B1-related LIS. According to ACMG rules, the variant is classified as pathogenic, as it belongs to one very strong (PVS1), one moderate (PM2) and one supporting category (PP4).

We could also consider applying PP3 (supporting evidence of pathogenicity) since the pathogenic computational verdict is based on one pathogenic prediction from SIFT Indel Tool, one pathogenic prediction from the conservation score GERP [31] and no benign predictions. However, some studies avoid [32] applying PP3 in LoF variants when PVS1 is valid.

Furthermore there are other disruptive (frameshift or stop codon) variants in the same gene region reported as pathogenic [33], supporting the importance of the region for proper gene product function.

Through this work we were able to find a molecular diagnosis of a rare disease in a seven years old boy with severe and heterogeneous neurological symptoms. We found a de novo novel frameshift mutation in the LIS1/PAFAH1B1 gene that most likely causes a silencing of one allele. This finding shows the benefit of the use of NGS as a diagnosis tool of rare diseases.

Abbreviations
LIS: Lissencephaly; MCD: Malformations of cortical development; PAFAH1B1: Platelet-activating factor acetylhydrolase brain isoform Ib; PAF: Platelet activating factor; PAF-AH: Platelet-activating factor acetylhydrolase; WGS: Whole Genome Sequencing; GMFSC: Gross Motor Function Classification System; BFMF: Bimanual fine motor function; CFCS: Communication Function Classification System; MRI: Magnetic Resonance Imaging; ARX: Aristaless Related Homeobox; MECP2: Methyl-GpG binding protein 2; NGS: Next Generation Sequencing; NMD: Nonsense Mediated Decay.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12887-022-03595-6.

Additional file 1.

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Authors’ contributions
CS: Bioinformatic Analysis (Methodology), data analysis and interpretation, wrote the manuscript. MG: Evolutionary and protein structure prediction analysis. Read and edit the manuscript. SR: Genetic diagnosis, data interpretation, wrote the manuscript. AT: Genetic diagnosis, data interpretation, read the manuscript. CS: Bioinformatic Analysis (Methodology), data analysis and interpretation, wrote the manuscript. AT: Genetic diagnosis, data interpretation, read the manuscript. VN: Clinical evaluation and diagnosis, supervision of patients, data collection, data interpretation, reviewed the manuscript. JS: Bioinformatic Analysis (Methodology), supervision, conceptualization, coordination of data collection and interpretation, wrote the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials
The variant found in this study is available in ClinVar, ID: SUB9799916 [11]. The bam files generated and analyzed during the current study are only available from the corresponding author upon reasonable request.
Declarations

Ethics approval and consent to participate
The patient and his family accepted to participate in the study, and granted permission for the publication of the results involved. This study was approved by the ethics committee of Institut Pasteur de Montevideo (IP011-17/CE/AC-MB).

Consent for publication
The patient and his family granted permission for the publication of the results involved. Written informed consent was obtained from the patient’s family to the submission of the case report.

Competing interests
The authors declare that they have no competing interests.

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