

SLC25A46: second allele hidden by head -20

Regression, seizures and optic atrophy, small-variant plus structural-variant VCFs. Required answer: **SLC25A46** compound heterozygote, chr5:110761517 T>C (p.Leu331Pro) and a 114-bp intron-3 Alu deletion at chr5:110745413, both likely pathogenic, diagnostic. The deletion is present only in the structural-variant VCF. Fable found the missense, searched for the second allele, and truncated the one query that would have shown it.

Claude Fable 5.1 (xhigh)

PARTIAL · 0.534

Required by the truth

LP + LP · diagnostic

BEFORE · EVENT 644 · REASONING

Finds the first allele and looks for a second

Found a rare heterozygous SLC25A46 missense (p.Leu331Pro), absent from gnomAD v4, in a recessive optic-atrophy gene. I'll now search for a second allele in the variant files, check ClinVar, and review raw quality for the SYNGAP1 and AHDC1 low-quality calls.

Correct gene, correct inheritance model, correct next step.

DURING · EVENTS 645, 650 · TOOL CALL AND OUTPUT

Caps the SV locus query at 20 rows

```
echo "--- SVs (any filter) overlapping SLC25A46
+/-50kb ---"
awk ... sv_all_annot.tsv | cut ... | head -20
chr5 4641408 DUP00017924 ... 115926537 ...
>5Mb_span
chr5 9384712 DEL00017959 ... 167989243 ...
>5Mb_span
... 17 more rows, all >5Mb_span ...
chr5 97021899 DUP00019624 ... 159615389 ...
>5Mb_span
```

Error: the filter matches 24 calls, sorted by start position. The first 20 are large calls that start far upstream. The local deletion is row 23 and is never displayed.

AFTER · EVENTS 727, 770 · REASONING, FINAL REPORT

Concludes there is no second allele

No deletion found in the second-allele search for SLC25A46, just common intronic variants.

```
rank 1 SLC25A46 chr5:110761517 T>C
uncertain_significance
ranks 2-3 AP3D1 (low-confidence hypothesis)
"status": "candidate_finding"
"no second rare SLC25A46 small variant or SV was
found"
```

With one allele, the missense is held at VUS and the case at candidate.

BEFORE · GRADER/TRUTH.JSON · REQUIRED VARIANTS

Two alleles in one recessive gene

```
chr5:110761517 T>C (p.Leu331Pro)
likely_pathogenic
chr5:110745413 114-bp deletion      likely_pathogenic
max_case_status: diagnostic
```

"Both variants are required for the recessive diagnosis. Identify both; a single allele is incomplete." (truth notes)

DURING · VARIANTS.STRUCTURAL.VCF.GZ · SAME FILTER, UNTRUNCATED

The deletion is a clean, local call

```
matches 24
row 23:
chr5 110745413 DEL00019738 <DEL> QUAL 205 PASS
PRECISE
END=110745528 SR=5 GT 0/1 GQ 10000 FT PASS
```

Needed at this step: read every row of the locus query, or sort it by distance and size. The call sits in intron 3, between exon 3 (ends 110,743,787) and exon 4 (starts 110,746,269), so the earlier exon-overlap SV screens could not have found it.

AFTER · GRADER/TRUTH.JSON · NOTES

Source evidence for the deletion

Deletion of 114 bases within an intron-3 Alu repeat. Whole-blood RNA sequencing demonstrated intron retention adding 1626 bases and upstream pseudoexon inclusion adding 139 bases, together affecting more than half of transcripts.

The truth classifies both alleles as likely pathogenic and allows a diagnostic case status once both are reported.

WHAT HAPPENED

File 5.1 prioritized the right gene from 5.1 million small variants and recognized that a recessive disease needs a second allele. Its genome-wide SV screens only kept calls that overlap exons, and its targeted locus query printed 20 of 24 matching rows. The four hidden rows included the causal deletion. The run then reported "no second rare SLC25A46 small variant or SV", which left the missense at VUS and the case at candidate, both below the truth. The judge's trajectory analysis identifies the same truncation.

TRAINING TARGET

When a negative result rests on a query, check that the output was complete. Truncated listings (head, pagination) cannot support "not found". For a recessive gene with one allele, review all structural calls at the locus, including intronic ones.