Patient name: **HN:**

Patient name:
HN:
Date of birth:
Sex:

Sample type:
Specimen id:
Date of collection:
Date of receive:

Date of result:
Physician order:

RESULT : Positive

TEST INFORMATION

This test screen for the clinical information indicated below.

CLINICAL INFORMATION

Clinical information (follows HPO nomenclature):

Phenotype/Disorder: epilepsy

Consanguineous parents: No

TEST RESULTS

One Likely pathogenic variant in *CHRNE* was identified in this individual. One Likely pathogenic variant in SLC4A1 was identified in this individual. No other variants of relevance to the indication were identified. Please see below for more detailed variant information.

- **VARIANTS FINDING**

Gene	Transcript	Chromosome position	Variant	Allele State	Inheritance	Classification
SLC4A1	NM_000342.4	Chr17:42335411	p.Ala400_Ala408del	Heterozygous	Dominant	Likely pathogenic

INTERPRETATION SUMMARY

A single likely pathogenic variant (c.1199_1225del [p.Ala400_Ala408del] identified in *SLC4A1* that could explain some of the patient phenotype, but still does not account for most of her clinical problem.

RECOMMENDATIONS

The interpretation of these results should be done in the context of a patient's medical record and family history. Please note that interpretation and classification of the variants reported here may change over time. Please see a genetic counselor for services regarding the implications of these results in the context of understanding the implications of incidental findings, family planning and the informing of family members of potentially shared genetic outcomes.

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DETAILED GENETIC VARIANT INFORMATION

- ### VARIANTS FINDING

SLC4A1 NM_000342.4

Gene summary
The protein encoded by this gene is part of the anion exchanger (AE) family and is expressed in the erythrocyte plasma membrane, where it functions as a chloride/bicarbonate exchanger involved in carbon dioxide transport from tissues to lungs. The protein comprises two domains that are structurally and functionally distinct. The N-terminal 40kDa domain is located in the cytoplasm and acts as an attachment site for the red cell skeleton by binding ankyrin. The glycosylated C-terminal membrane-associated domain contains 12-14 membrane spanning segments and carries out the stilbene disulphonate-sensitive exchange transport of anions. The cytoplasmic tail at the extreme C-terminus of the membrane domain binds carbonic anhydrase II. The encoded protein associates with the red cell membrane protein glycophorin A and this association promotes the correct folding and translocation of the exchanger. This protein is predominantly dimeric but forms tetramers in the presence of ankyrin. Many mutations in this gene are known in man, and these mutations can lead to two types of disease: destabilization of red cell membrane leading to hereditary spherocytosis, and defective kidney acid secretion leading to distal renal tubular acidosis. Other mutations that do not give rise to disease result in novel blood group antigens, which form the Diego blood group system. Southeast Asian ovalocytosis (SAO, Melanesian ovalocytosis) results from the heterozygous presence of a deletion in the encoded protein and is common in areas where Plasmodium falciparum malaria is endemic. One null mutation in this gene is known, resulting in very severe anemia and nephrocalcinosis. [provided by RefSeq, Jul 2008]

Variants summary
The in-frame deletion NM_000342.4(*SLC4A1*):c.1199_1225del (p.Ala400_Ala408del) causes a change at the same amino acid residue as a previously established pathogenic variant. Additionally, the variant has been reported to ClinVar as Pathogenic/Likely pathogenic with a status of (2 stars) criteria provided, multiple submitters, no conflicts (Variation ID 17753 as of 2023-04-06). This variant results in a deletion of 9 amino acid residues starting at 400, including AlaPheSerProGlnValLeuAla. However, as this is an in-frame deletion, it is not expected to result in either a truncated protein product or loss of protein through nonsense-mediated mRNA decay. The p.Ala400_Ala408del variant is not in a repeat region. The p.Ala400_Ala408del variant results in a deletion of 27 bases that are predicted conserved by GERP++ and PhyloP. The nucleotide c.1199 in *SLC4A1* is predicted conserved by GERP++ and PhyloP across 100 vertebrates. For these reasons, this variant has been classified as Likely Pathogenic.

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METHODOLOGY

Genomic DNA is extracted from an individual at Bumrungrad Hospital. DNA sample is sent to the Macrogen, Korea to process Whole Exome Sequencing (WES). Library preparation, clustering and sequencing are processed on the Illumina platform to cover the coding regions of targeted genes ± ~10 bases of non-coding DNA flanking each exon. Raw data in an average at 6 Gb were generated. Reads from the sequence output were aligned to the human reference genome (GRCh37) using BWA. Variants are called using GATK pipeline. The tertiary analysis is performed at Bumrungrad Hospital. The variants were annotated and filtered using the Golden Helix VarSeq analysis workflow implementing the ACMG guidelines for the interpretation of sequence variants. This includes a comparison against the gnomAD population catalog of variants in 123,136 exomes, the 1000 Genomes Project Consortium's publication of 2,500 genomes, the NCBI ClinVar database of clinical assertions on variant's pathogenicity and multiple lines of computational evidence on conservation and functional impact.

Coverage Statistics for rare disease

Target region / Coverage	WES Target region
Mean depth (X)	46.3X
Mean depth ≥ 10X	94.6%

VARIANT ASSESSMENT PROCESS

The following databases and in-silico algorithms are used to annotate and evaluate the impact of the variant in the context of human disease: 1000 genomes, gnomAD, ClinVar, OMIM, dbSNP, NCIB RefSeq Genes, ExAC Gene Constraints, VS-SIFT, VS-PolyPhen2, PhyloP, GERP++, GeneSplicer, MaxEntScan, NNSplice, PWM Splice Predictor. Analysis was reported using the to HGVS nomenclature (www.hgvs.org/mutnomen) as implemented by the VarSeq transcript annotation algorithm. The reported transcript matches that used most frequently by the clinical labs submitting to ClinVar.

LIMITATIONS

It should be noted that the test result is limited to a set of genes indicated in the panel and might not cover all possible variants related to the particular condition. For some target regions, the depth covered for analysis may be variable, However, any targeted gene that fails to meet the acceptance criteria (Mean depth ≥ 10X) will be noted. Due to these limitations, ruling out the diagnosis of a genetic disorder should not be made based on negative results. An evaluation by alternative methods should be considered if a specific clinical disorder is suspected. This report only includes variants that meet a level of evidence threshold for cause or contribute to disease/condition. Reported variants are not confirmed by Sanger sequencing. Certain classes of genomic variants are also not covered using the NGS testing technology, including repeat expansions, large deletion or large duplication (≥50 kb), translocations and gene fusions or other complex structural rearrangements.

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DISCLAIMER

The result interpretation is based on the most current scientific and analytical standards. However, more evidence for disease association of genes and causal pathogenic variants are discovered every year, and it is recommended that genetic variants are re-interpreted with updated software and annotations periodically. There is also a possibility of an error in the result due to contaminants in the sample, rare technical errors, a rare genetic variant that could interfere with the analysis. This test should be used in compliance with the other diagnostic test. Note that this test cannot exclude the possibility of variants in genes not analyzed or assayed with incomplete coverage. Even though this test is not designed to distinguish between somatic and germline variants, if variant of somatic is detected, supplementary testing may be compulsory to clarify the significance of results. Genetic counseling is recommended to help understand the test result and explain the implications of this result for the patients and other family members. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.