

For patients with suspected or idiopathic nonsurgical hypoparathyroidism (HypoPT)

Annotated sample genetic test report

DETECTADH1

For additional questions about results, you can get in contact with the DNAvisit medical geneticist offered by Prevention Genetics via **support@preventiongenetics.com** or **715-387-0484**.

Annotated sample genetic test report

1 Confirm patient name

2 Summary of results:
positive, negative, or indeterminate

3 If the result is positive or indeterminate, a list of the abnormal genetic sequence variant(s) will be found here, including the interpretation – PATHOGENIC (positive) or UNCERTAIN (indeterminate)*

4 Detailed information of the abnormal gene sequence variant(s) is included here—including relevant journal articles, clinical features of the condition, and if genetic testing of family members is appropriate



NAME: LAST, First
PATIENT ID: ####-####-####

PATIENT INFORMATION	SPECIMEN INFORMATION	PROVIDER INFORMATION
LAST, First ID#: DOB: Month, Day, Year Sex:	Type: Collected: Month, Day, Year Received: Month, Day, Year PG ID: ####-####-#### Test Method: PGxome	Physician Genetic Counselor Institution

MOLECULAR GENETICS REPORT:
Hypoparathyroidism Panel

SUMMARY OF RESULTS: Positive

Sequence Variant(s):

Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variations, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
CASR, NM_001178065.1	AD, AR, 601199	c.2393T>G, p.Phe798Cys, Heterozygous	8336	Not Present	Damaging	PATHOGENIC

Mode of Inheritance: Autosomal Dominant=AD, Autosomal Recessive=AR, X-Linked=XL
ClinVar ID: Variant accession (www.ncbi.nlm.nih.gov/clinvar)
GnomAD: Allele Frequency registered in a large population database (gnomad.broadinstitute.org). Value listed is the highest allele frequency reported within one of seven population categories recognized in gnomAD v.2.1.1 (The "Other" population is excluded).
Missense Predictions: Summarized output (Damaging, Conflicting, or Tolerated) via PolyPhen-2, SIFT, MutationTaster, and FATHMM (PMID: 26555599).

CASR VARIANT INFORMATION:

This patient is heterozygous in the CASR gene for a sequence variant defined as c.2393T>G, which is predicted to result in the amino acid substitution p.Phe798Cys. This variant, also referred as c.2363T>G (p.Phe788Cys) in alternate transcript NM_000388, has been reported in several individuals with hypoparathyroidism (see for example: Watanabe et al. 1998. PubMed ID: 9661634; Rossi et al. 2019. PubMed ID: 31763346; Kinoshita et al. 2013. PubMed ID: 24297799; Elston et al. 2022. PubMed ID: 35402765; Ali et al. 2023. PubMed ID: 37654565). This variant was reported to have occurred *de novo* in one patient with severe hypocalcemia (Mora et al. 2006. PubMed ID: 16333828). Functional studies in HEK293 cells indicated that the p.Phe798Cys variant as an activating variant and resulted in CASR being more responsive to increases in extracellular calcium (Hu et al. 2002. PubMed ID: 12297503; Huang et al. 2007. PubMed ID: 17284438; Kinoshita et al. 2013. PubMed ID: 24297799). This variant has not been reported in a large population database (gnomAD), indicating this variant is rare and is interpreted as pathogenic in the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/variation/8336/). A different missense change that impacts the same amino acid (c.2392T>C, p.Phe798Leu) was reported to segregate in a family with hypoparathyroidism and was

Reported On: Month Day, Year
PreventionGenetics LLC, a wholly owned subsidiary of Exact Sciences Corporation.
3800 S. Business Park Ave., Marshfield, WI 54449 USA • PreventionGenetics.com
Collected On: Month, Day, Year
PAGE 1 OF 4

*In a patient with unexplained hypoparathyroidism and a calcium-sensing receptor (CASR) variant of uncertain significance (VUS), evaluate whether the clinical and biochemical phenotype is consistent with autosomal dominant hypocalcemia type 1 (ADH1). Findings that support evaluation for ADH1 include hypocalcemia, an inappropriately low or normal parathyroid hormone (PTH) level, and urine calcium that is normal or elevated despite hypocalcemia.^{1,2}

Annotated sample genetic test report

5

Copy number variant information, if positive

6

Additional notes including the availability of reflex testing and the recommendation for genetic counseling (if positive or indeterminate)

7

List of all the genes analyzed



NAME	PATIENT ID
LAST, First	#### ##

demonstrated *in vitro* to be an activating variant (Reported as F788L, Hendy et al. 2003. PubMed ID: 12915654). Taken together, the c.2393T>G (p.Phe798Cys) variant is interpreted as pathogenic.

Pathogenic variants in *CASR* have been associated with autosomal dominant familial hypocalciuric hypercalcemia, type I (HHC; OMIM #145980). Individuals with HHC are usually asymptomatic and the disorder is considered benign. However, chondrocalcinosis and pancreatitis occur in some adults. Individuals with biallelic pathogenic *CASR* variants have neonatal severe hyperparathyroidism (NSHPT). Unlike HHC, NSHPT can be fatal without parathyroidectomy (Waller et al. 2004. PubMed ID: 15241688). In addition, pathogenic variants in *CASR* have been associated with autosomal dominant hypocalcemia (OMIM #601198), autosomal dominant Bartter syndrome with hypocalcemia (OMIM #601198), and susceptibility to idiopathic generalized epilepsy 8 (OMIM #612899). Only one variant was detected in this gene. It is possible that a second causative variant is not detectable by our sequencing test. Targeted testing for this variant in biological relatives is available.

COPY NUMBER VARIANT INFORMATION:

This patient is apparently negative for copy number variants (CNVs) within the genomic regions of this test.

These results should be interpreted in the context of clinical findings, family history and other laboratory data.

All genetic tests have limitations. See limitations and other information for this test on the following page(s).

NOTES:

1) Since this test is performed using exome capture probes, a reflex to any of our exome-based tests is available (PGxome, PGxome Custom Panels).

2) Genetic counseling is recommended.

GENES ANALYZED: *ACADM, AIRE, ATP1A1, CASR, CHD7, CLDN16, CLDN19, CNNM2, DHCR7, EGF, FAM111A, FXYD2, GATA3, GCM2, GNA11, HADHA, HADHB, KCNA1, NEBL, PTH, SEMA3E, SLC12A3, SOX3, TBCE, TBX1, TRPM6*

SUMMARY STATISTICS:

Pipeline	Version	Average NGS Coverage	Fraction Bases Covered with NGS
Infinity Pipeline	5.9.1	188x	99.9%

Minimum NGS coverage is ≥20x for all coding exons and +/-10bp of flanking DNA.

Electronically signed on by:

Electronically signed and reported on by:

Reported On: Month Day, Year

Collected On: Month, Day, Year

PreventionGenetics LLC, a wholly owned subsidiary of Exact Sciences Corporation.

3800 S. Business Park Ave., Marshfield, WI 54449 USA • PreventionGenetics.com

» PAGE 2 OF 4

For patients with suspected or idiopathic nonsurgical hypoparathyroidism (HypoPT)

8

Supplemental information including: —
limitations, test procedure, reportable range,
performance, and regulatory information

NAME
LAST, First

PATIENT ID	姓姓名-姓姓名-姓姓名
------------	-------------

SUPPLEMENTAL INFORMATION

PGXOME-BASED NEXT GENERATION SEQUENCING WITH COPY NUMBER VARIANT ANALYSIS

V.25.19

Limitations: Analytical sensitivity may be impacted by complex genomic regions or variants including, but not limited to, repetitive elements, highly homologous sequence, and insertions/deletions/duplications >40bp but smaller than a full exon. Sensitivity may also be impacted by technical challenges including sample quality and probe capture efficiency.

This testing platform is not designed to detect certain types of structural rearrangements such as inversions, balanced insertions, or reciprocal translocations. Repeat expansions are not detected with this methodology. Mitochondrial genome analysis is not included in this methodology.

The ability of this testing platform to determine the absolute copy number of a genomic region is limited due to the nature of DNA capture and PCR amplification in this method.

In some cases, copy number analysis may not be available due to sample quality or technical reasons.

This testing platform is designed to detect germline variants, though decreases as read fraction becomes smaller, with findings down to 1% (Fig. 1). This platform has a limited ability to detect CNVs due to somatic mosaicism.

When sequencing does not reveal any heterozygous differences concluded that both patient alleles were sequenced.

This platform can generally not be used to determine the phase of particular, when two variants are reported in a gene associated with a disease. This is because the variants are not confirmed that they are in *trans*.

Interpretation of the test results may change based on available genetic cause of disease given that the knowledge of gene-disease is coming years. Alternatively, variants not detectable by this assay may be the clinical features.

Test Procedure: Our exome platform is whole exome sequencing technology to sequence nearly all exons, 10 bases of flanking into reported pathogenic variants in the Human Gene Mutation Database captured using a proprietary set of hybridization probes. Capture Illumina short-read platform. Data analysis and interpretation is performed and aligned to GRCh37/UCSC hg19. Results may be filtered to variants (CNV) are detected with an algorithm that compares exome matched controls. Orthogonal methods are used to confirm findings are reported using Human Genome Variation Society (HGVS) nomenclature.

CNV analysis is automatically included for the genes defined by your test. CNV analysis is included in a test such as with the PGmax™ tests or whole genome analysis is expanded to all genes in the genome. This analysis re-

PreventionGenetics LLC, a wholly owned subsidiary of Exact Sciences Corporation.
3800 S. Business Park Ave., Marshfield, WI 54449 USA • PreventionGenetics.com
Phone: (715) 387-0484 • General Fax: (715) 406-6175 • Billing Fax: (715) 207-6602 •



NAME
LAST, First

PATIENT ID	#####-####-####
------------	-----------------

meet size (deletions >250 kb or duplications >500 kb) and interpretation (uncertain, likely pathogenic, or pathogenic) criteria. In prenatal cases (including ongoing pregnancies and products of conception), this analysis reports uncertain CNVs with increased thresholds (deletions >500 kb and duplications >1 Mb). Additionally, in whole exome testing where analyzing CNVs in all genes is inherently a part of the test, these same automatic reporting size and interpretation thresholds apply.

Reportable Range: Capture and amplification based next-generation sequencing (NGS) is used to sequence the coding regions of nearly all genes and immediate flanking non-coding DNA (± 10 bp) in all available transcripts along with other non-coding regions harboring known disease-causing variants. Results are filtered to defined genes on the panel. Reportable variants include both sequence variants and NGS-detected copy number variants (CNVs). Variants not meeting our quality threshold through NGS alone are confirmed with an orthogonal method, including but not limited to Sanger and array. All variants within the analyzed genes which are classified as pathogenic, likely pathogenic, risk, or variant of uncertain significance will be reported.

Performance: The analytical sensitivity of the exome platform has been validated at >99% for single nucleotide variants, >95% for indels <49 bp, and >99% for CNV ≥3 exons in size. Sensitivity for double exon events is ~85% and single exon events is ~70%. Sensitivity is reduced in regions with repetitive elements or paralogy. Sensitivity may vary from region to region based on exon size, depth of coverage, and characteristics of the region. The average read depth of targeted regions is >100x, with >97% of targeted bases >20x. Individual gene and/or patient coverage may vary. Individual patient coverage may vary.

Regulatory Information: These results should be used in the context of available clinical findings, and should not be used as the sole basis for treatment. This test was developed and its performance characteristics determined by PreventionGenetics. US Food and Drug Administration (FDA) does not require this test to go through premarket FDA review. This laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing.

If the results of this test will be utilized as part of a clinical study in the European Union, please note this test is intended for performance evaluation only. For all other testing within the European Union, this test is intended for research use only.

References: 1. Mighton C, Abu-El-Hajja A, Aggarwal V, et al. Points to consider for the reporting of variants of uncertain significance in germline genetic and genomic testing: A statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2026;28(7):102583. doi:10.1016/j.jim.2026.102583 2. Roszko KL, Stapleton Smith LM, Sridhar AV, et al. Autosomal dominant hypocalcemia type 1: a systematic review. *J Bone Miner Res*. 2022;37(10):1926–1935. doi:10.1002/jbmr.4659



The BridgeBio Pharma, Inc corporate logo is a registered trademark of BridgeBio Pharma, Inc.
©2026 BridgeBio Pharma, Inc. All rights reserved. MAT-US-ECLTX-0168 v1