Gain-of-Function *CASR* Variants, a Common Genetic Cause of Non-Surgical Hypoparathyroidism: Findings from a Sponsored Genetic Testing Program

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Background

- Hypoparathyroidism (HP) is a rare endocrine disorder characterized by insufficient or impaired production of parathyroid hormone (PTH), resulting in unbalanced mineral homeostasis and low levels of serum calcium
- Signs and symptoms of HP vary, and include[1]:

paresthesia	numbness	muscle stiffness	seizures
depression	ischemic heart disease	arrhythmias	tetany
basal ganglia calcifications	cataracts	infections	nephrocalcinosis/ nephrolithiasis

- Postsurgical HP is the most frequent presentation, however, genetic variants may be the second-leading cause
- Genetic forms can present as isolated HP or as part of a syndrome and include the following mechanisms:
  - Disorders of PTH secretion
  - Disorders of parathyroid gland formation
  - Interference of parathyroid gland function through autoimmunity
- The prevalence of HP due to genetic variants has not yet been well-established
- A sponsored genetic testing program using next-generation whole exome sequencing was made available at no-charge for patients with suspected genetic HP who meet the eligibility criteria
- A comprehensive genetic panel allows for parallel sequencing of all known genes involved in HP
- Genetic testing may uncover the underlying etiology of nonsurgical HP and can help confirm clinical diagnosis, guide medical management, identify affected family members, and facilitate in making informed decisions regarding the potential participation in clinical trials

Program Eligibility Criteria

The individual must reside in the US and meet any one of the following criteria:

❑ Have a diagnosis of non-surgical/idiopathic hypoparathyroidism

OR

❑ Have a diagnosis of hypocalcemia suspected to be of genetic cause

OR

❑ Have a relative with a diagnosis of genetic hypoparathyroidism

Methods

Table 1. 26-Gene Hypoparathyroidism Panel – Associated Conditions & Inheritance[2]

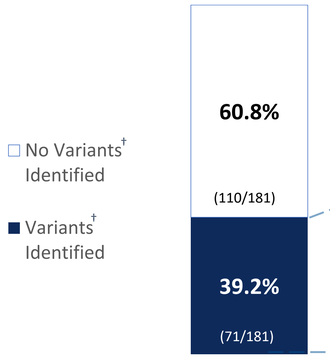
Gene	Condition(s)	Inheritance
Disorders of Parathyroid Gland Formation		
ACADM	Medium-chain acylCOA dehydrogenase deficiency (ACADMD)	AR
CHD7	CHARGE Syndrome	AD
DHCR7	Smith-Lemli-Opitz syndrome (SLOS)	AR
FAM111A	Kenny-Caffey syndrome type 2 (KCS2), Gracile bone dysplasia (GCLEB)	AD
GATA3	Hypoparathyroidism, sensorineural deafness and renal dysplasia (HDR)	AD
GCM2	Familial isolated hypoparathyroidism type 2 (FIH2)	AD, AR
HADHA	Mitochondrial trifunctional protein deficiency syndrome (MTPD), Long-chain 3-hydroxyacylCoAdehydrogenase deficiency (LCHAD)	AR
HADHB	Mitochondrial trifunctional protein deficiency syndrome (MTPD)	AR
NEBL	DiGeorge syndrome type 2 (DGS2)	AD
SEMA3E	CHARGE Syndrome	AD
SOX3	Hypoparathyroidism X-linked recessive (HYPX)	XLR
TBCE	Hypoparathyroidism, retardation, and dysmorphism syndrome (HRDS)/Sanjad-Sakati, Kenny-Caffey syndrome type 1 (KCS1)	AR
TBX1	DiGeorge syndrome type 1 (DGS1)	AD
Disorders of Parathyroid Hormone Secretion or the PTH Gene		
ATP1A1	Hypomagnesemia, seizures, and mental retardation 2 (HOMGSMR2)	AD
CASR	Autosomal dominant hypocalcemia type 1 (ADH1)	AD
CLDN16	Hypomagnesemia 3, renal (HOMG3)	AR
CLDN19	Hypomagnesemia 5, renal (HOMG5)	AR
CNNM2	Hypomagnesemia 6, renal (HOMG6), Hypomagnesemia, seizures, and mental retardation 1 (HOMGSMR1)	AD
EGF	Hypomagnesemia 4, renal (HOMG4)	AR
FXYD2	Hypomagnesemia 2, renal (HOMG2)	AD
GNA11	Autosomal dominant hypocalcemia type 2 (ADH2)	AD
KCNA1	Episodic ataxia type 1 (EA1)	AD
PTH	Familial isolated hypoparathyroidism type 1 (FIH)	AD, AR
SLC12A3	Gitelman syndrome (GTLMNS)	AR
TRPM6	Hypomagnesemia 1, intestinal (HOMG1)	AR
Damage to the Parathyroid Glands		
AIRE	Autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia (APECED)	AD, AR

AR: Autosomal Recessive, AD: Autosomal Dominant, XLR: X-Linked Recessive

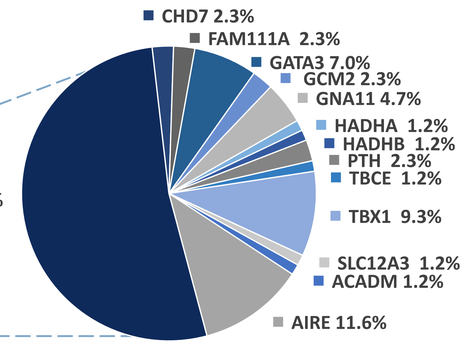
Results

- A total of 181 samples between December 2020 and March 2023 were tested from participants with a mean±SD age of 24.7±21.5 (range 0-81) who were diagnosed with nonsurgical/idiopathic HP (73.2%), hypocalcemia suspected to be of genetic cause (24.5%) or had a relative with a confirmed diagnosis of genetic HP (2.3%)
- 86 variants[†] were detected in 71 individuals with 56.3% (40/71) of variant[†] harboring individuals documented as having unknown or no family history of HP
- The most common genetic form of HP was found to be autosomal dominant hypocalcemia type 1 (22.1% of individuals tested; 40/181), caused by gain-of-function variants in the CASR gene
- *CASR* variants[†] were found in more than half of the patients with identified variants[†] (52.3%; 40/71)

Occurrence of Variants in Nonsurgical Individuals[†]



Relative Number of Individuals with Detected Variants[†]



[†] Pathogenic, Likely Pathogenic and Variants of Uncertain Significance

Conclusions

- Genetic testing identified clinically-relevant variants[†] in approximately 2 out of every 5 individuals with nonsurgical HP
- Genetic forms should be considered in all patients with HP without history of neck surgery or other obvious causes; positive results can inform management of patients and suggest further medical work-up
- Autosomal dominant hypocalcemia type 1, resulting from gain-of-function variants in the CASR gene, emerged as the prevailing genetic cause of HP; a confirmatory diagnosis may enable enrollment of eligible patients into an ongoing phase 3 clinical study [NCT05680818]
- Overall, this ongoing sponsored testing program will support the diagnosis of genetic HP, and may ultimately improve patient management

References

1. Khan AA, Bilezikian JP, Brandi ML, et al. Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop. J Bone Miner Res. 2022;37(12):2568-2585. doi:10.1002/jbmr.4691.
2. Mannstadt M, Cianferotti L, Gafni RI, et al. Hypoparathyroidism: Genetics and Diagnosis. J Bone Miner Res. 2022;37(12):2615-2629. doi:10.1002/jbmr.4667.

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