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Hypoparathyroidism: Genetics and Diagnosis

Michael Mannstadt,^{1†} Luisella Cianferotti,² Rachel I Gafni,³ Francesca Giusti,⁴ Elizabeth Helen Kemp,⁵ Christian A Koch,^{6,7} Kelly L Roszko,³  Liam Yao,⁸ Gordon H Guyatt,⁸ Rajesh V Thakker,^{9,10}  Weibo Xia,¹¹  and Maria-Luisa Brandi^{12†} 

¹Endocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

²Bone Metabolic Diseases Unit, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy

³National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, USA

⁴The Bone Clinic, Casa di Cura Villa Donatello, Florence, Italy

⁵Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

⁶Department of Medicine/Endocrinology, Fox Chase Cancer Center, Philadelphia, PA, USA

⁷Department of Medicine/Endocrinology, The University of Tennessee Health Science Center, Memphis, TN, USA

⁸Department of Health Research Methods, Evidence, and Impact, and Department of Medicine, McMaster University, Hamilton, Canada

⁹Academic Endocrine Unit, Radcliffe Department of Medicine, University of Oxford, Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM), Churchill Hospital, Headington, Oxford, UK

¹⁰Oxford National Institute for Health Research (NIHR) Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford, UK

¹¹Department of Endocrinology, Peking Union Medical Collage Hospital, Beijing, China

¹²Fondazione Italiana sulla Ricerca sulle Malattie dell'Osso (F.I.R.M.O. Foundation), Florence, Italy

ABSTRACT

This narrative report summarizes diagnostic criteria for hypoparathyroidism and describes the clinical presentation and underlying genetic causes of the nonsurgical forms. We conducted a comprehensive literature search from January 2000 to January 2021 and included landmark articles before 2000, presenting a comprehensive update of these topics and suggesting a research agenda to improve diagnosis and, eventually, the prognosis of the disease. Hypoparathyroidism, which is characterized by insufficient secretion of parathyroid hormone (PTH) leading to hypocalcemia, is diagnosed on biochemical grounds. Low albumin-adjusted calcium or ionized calcium with concurrent inappropriately low serum PTH concentration are the hallmarks of the disease. In this review, we discuss the characteristics and pitfalls in measuring calcium and PTH. We also undertook a systematic review addressing the utility of measuring calcium and PTH within 24 hours after total thyroidectomy to predict long-term hypoparathyroidism. A summary of the findings is presented here; results of the detailed systematic review are published separately in this issue of *JBMR*. Several genetic disorders can present with hypoparathyroidism, either as an isolated disease or as part of a syndrome. A positive family history and, in the case of complex diseases, characteristic comorbidities raise the clinical suspicion of a genetic disorder. In addition to these disorders' phenotypic characteristics, which include autoimmune diseases, we discuss approaches for the genetic diagnosis. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: HYPOPARATHYROIDISM; CALCIUM-SENSING RECEPTOR; FAMILIAL HYPOPARATHYROIDISM; GENETIC TESTS; AUTOIMMUNE

Recommendations

Graded recommendation by systematic review: For predicting which patients who will not develop permanent post-surgical hypoparathyroidism, we recommend using parathyroid

hormone (PTH) measurements after total thyroidectomy (strong recommendation, moderate quality evidence)

Comment: The predictive value of PTH measurements was better than that of serum calcium. If PTH values are above 10 pg/mL (10 ng/L) 12 to 24 hours post-surgery, the development of

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Address correspondence to: Michael Mannstadt, MD, Endocrine Unit, Massachusetts General Hospital and Harvard Medical School, 11, 50 Blossom St, Boston, MA 02114, USA. E-mail: mannstadt@mg.harvard.edu

Additional Supporting Information may be found in the online version of this article.

[†]MM and M-LB are co-chairs of the Task Force for this narrative review.

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permanent hypoparathyroidism is very unlikely and, therefore, also the long-term need for treatment with active vitamin D and calcium supplements above the recommended daily allowance. If PTH values are lower than 10 pg/mL (10 ng/L) 12 to 24 hours post-surgery, the possibility of long-term hypoparathyroidism remains but is still less than 50%.

1. Ungraded recommendations by panel consensus:
 - a. In patients with hypoparathyroidism who have a positive family history of nonsurgical hypoparathyroidism, present with syndromic features, or are younger than 40 years, panel members undertake genetic testing.
 - b. In patients with nonsurgical hypoparathyroidism who have other clinical features of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED), panel members undertake genetic testing for *AIRE* variants.
 - c. In the absence of a definitive diagnostic test for non-monogenic autoimmune hypoparathyroidism, panel members classify patients with nonsurgical acquired disease as idiopathic hypoparathyroidism.
 - d. For research reports, panel members regard postsurgical hypoparathyroidism as permanent when it persists >12 months after surgery.

Introduction

Hypoparathyroidism is a rare endocrine disorder characterized by hypocalcemia and absent or deficient secretion of parathyroid hormone (PTH). The most frequent cause of hypoparathyroidism is the inadvertent removal or damage of parathyroid glands during neck surgery; the remaining one-fourth of cases are related to genetic or autoimmune causes, magnesium deficiency, and other rare etiologies.⁽¹⁾

The impressive recent advances in diagnostic genetics, along with new discoveries in parathyroid autoimmunity, led to new insights in the diagnosis of this disease. This article provides guidance in the diagnosis of hypoparathyroidism, an essential first step in its management.

Methods

Graded recommendations

We conducted a systematic review to develop recommendations regarding the ability to predict permanent postsurgical hypoparathyroidism from PTH measurements in the immediate postoperative period after total thyroidectomy. This study and its methods, which follow the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach, are published in a companion article. In this article, we incorporate the summary of the systematic review and its recommendation.

Nongraded recommendations

We also conducted a systematic literature search for the narrative review regarding the diagnosis and genetics of hypoparathyroidism. The literature search included articles published between January 2000 and January 2021 using Ovid Medline, Embase, and Cochrane library databases and also included landmark studies published before 2000. We limited our search to the English language and excluded letters, reviews, editorials, and

abstracts. Reviewers screened titles and abstracts and identified articles relevant to the topics, which were screened in full texts. Relevant information was incorporated in this review.

Nongraded recommendations did not follow the GRADE approach and are “expert opinions.” They were discussed and agreed upon by all authors.

Results

Diagnosis

Hypoparathyroidism occurs when the parathyroid glands produce insufficient amounts of PTH to maintain normocalcemia. Thus, the biochemical hallmark and diagnostic criteria of hypoparathyroidism is two episodes of hypocalcemia at least 2 weeks apart with concomitant inappropriately low PTH levels. Low PTH causes additional biochemical abnormalities in hypoparathyroidism that support the diagnosis: blood phosphate levels are high-normal or frankly elevated; circulating concentrations of 1,25-dihydroxy-vitamin D (active vitamin D) and bone turnover markers are low or in the low-normal range; and fractional urinary excretion of calcium is elevated, which can lead to hypercalciuria, especially when the blood calcium levels have been raised into the normal range by conventional treatment.

Hypocalcemia is defined as a free, ionized calcium (iCa^{2+}) or albumin-adjusted total calcium concentration below the normal range. About 40% of circulating calcium is bound to proteins (mainly albumin), but only the iCa^{2+} is physiologically relevant. Measurement of iCa^{2+} , however, can be cumbersome: ionized calcium is pH-dependent, and a delay in processing the blood can lead to inaccurate results because of loss of carbon dioxide or production of lactic acid by red blood cells in the specimen. Consequently, total calcium is most often measured in clinical practice. Measurement of albumin in the same specimen allows for interpretation of total calcium in the face of hypoalbuminemia (which falsely lowers total calcium measurements) and hyperalbuminemia (which falsely elevates total calcium measurements). One commonly used formula for calculating the adjusted calcium is: adjusted calcium (mg/dL) = total calcium (mg/dL) + [(4.0 – albumin (g/dL) × 0.8]. For SI units, it is adjusted calcium (mmol/L) = total calcium (mmol/L) + 0.02 × [40 g/L – patient albumin (g/L)]. This formula has limitations in certain subpopulations of patients, for example, in those with chronic kidney disease.⁽²⁾

PTH measurement helps differentiate hypoparathyroidism from other disorders of low blood calcium (see Differential Diagnosis below for details). There is no fixed threshold below which the diagnosis of hypoparathyroidism is made; even if PTH is within the laboratory normal range, the absence of an appropriate elevation in the face of hypocalcemia suggests hypoparathyroidism. The measurement of PTH is complicated by the fact that the parathyroid glands produce and secrete into the circulation full-length PTH of 84-amino acids (PTH (1–84)) as well as truncated, mostly carboxyl-terminal fragments, such as PTH (34–84) and PTH (37–84), which cannot bind and activate the common PTH receptor.^(3,4) Furthermore, proteolytic cleavage of circulating PTH, mainly by the Kupffer cells of the liver, can also result in inactive fragments. The plasma half-life of intact PTH (1–84) is only minutes. By contrast, the half-life of circulating fragments is much longer. Therefore, under normal circumstances, only about 20% of circulating PTH is intact PTH (1–84).⁽⁵⁾ In healthy parathyroid glands, the proportion of intact PTH secreted increases in hypocalcemia and decreases in hypercalcemia and

chronic kidney disease. First-generation PTH assays were radio-immunoassays using antibodies that recognize mid- to carboxyl-terminal parts of PTH, limiting their utility as they mainly detected carboxyl-terminal fragments, which are inactive at the PTH receptor (PTH1R).⁽⁶⁾ Second-generation iPTH assays, currently widely used, are two-sided immunoradiometric “sandwich” assays that use carboxyl-terminal capture antibodies linked to solid phase and amino-terminal detection antibodies.⁽⁷⁾ Although these second-generation iPTH assays still detect some PTH fragments, they can reliably help make the diagnosis of hypoparathyroidism and differentiate this disease from other conditions of hypocalcemia.

The third-generation assays use a detection antibody that recognizes the more extreme amino-terminus of PTH, reducing the proportion of fragments detected.⁽⁸⁾ This theoretical advantage has not yet translated into better clinical utility, and third-generation assays are rarely used in clinical practice.^(9,10)

High biotin intake can result in spurious results in ELISA assays that use biotinylated antibodies and streptavidin capture. For iPTH assays, falsely low values have been reported in case reports of patients taking large amounts of biotin, but this interference does not appear to be a problem with most PTH assays.⁽¹¹⁾ Spurious elevations of PTH due to interference with human anti-mouse antibodies or rheumatoid factor have been reported.^(12,13)

The clinical significance of barely detectable PTH levels in hypoparathyroidism is presently unknown. To our knowledge, large-scale purifications to determine the length and bioactivity of the circulating immunoreactive PTH molecules have never been published. If these low PTH levels indeed reflect authentic PTH, then some low, inadequate level of secretion is occurring rather than a total absence of PTH production.

Systematic review and meta-analysis to examine the utility of PTH and calcium measurements within 24 hours after total thyroidectomy in predicting chronic hypoparathyroidism after 6 to 12 months

Because neck surgery is the most frequent cause of hypoparathyroidism, in this article we present an evidence-based approach to the early recognition of this surgical complication. Currently, randomized controlled trial (RCT) data to guide the early recognition of chronic hypoparathyroidism in patients after total parathyroidectomy are missing. Therefore, our team conducted a systematic review of diagnostic accuracy studies; the complete details are published in this special issue of *JBMR*. We have included key components of this systematic review in this article.

In postsurgical patients, constituting about 75% of patients with hypoparathyroidism, the biochemical diagnosis of hypoparathyroidism is usually straightforward. When a patient presents with symptoms of hypocalcemia and low albumin-adjusted calcium and PTH levels after neck surgery, the clinician can infer hypoparathyroidism. However, most cases of postsurgical hypoparathyroidism are transient as the parathyroid function can recover after surgery. The longer the biochemical abnormalities persist, the less likely the patient will recover,⁽¹⁴⁾ and chronic hypoparathyroidism is usually diagnosed if it persists more than 12 months after surgery.

As knowledge of the likelihood of postsurgical hypoparathyroidism could minimize symptoms and complications from untreated hypocalcemia and avoid overtreatment in transient hypoparathyroidism,⁽¹⁵⁾ investigators have explored its possible prediction from early postoperative blood calcium and PTH measurements. Here, we undertook a systematic review and meta-analysis of studies evaluating the use of PTH and/or calcium levels early after total thyroidectomy to predict chronic hypoparathyroidism. A companion article provides details of the study [Complications, Symptoms, Pre-surgical Predictors in Patients with Chronic Hypoparathyroidism: A Systematic Review]. In brief, we searched PubMed, Embase, and Cochrane CENTRAL from inception to February 2021 using the following key words: “thyroidectomy,” “parathyroid hormone/PTH” and “hypoparathyroidism.” We identified 15 eligible articles reporting 16 studies with 3329 patients who were included in the analysis. In most studies, calcium and PTH were measured 12 to 24 hours after surgery ($n = 10$), used $\text{PTH} \leq 10 \text{ pg/mL}$ ($\leq 10 \text{ ng/L}$) as the threshold for predicting permanent hypoparathyroidism ($n = 10$), and chronic hypoparathyroidism defined when it persisted at 12 months after surgery ($n = 8$).

Our review found that using thresholds for early PTH measurements (12 to 24 hours after total thyroidectomy) provides higher sensitivity and specificity than blood calcium for predicting permanent hypoparathyroidism. PTH values above 10 pg/mL (10 ng/L) (a negative test) virtually excludes long-term chronic hypoparathyroidism irrespective of pre-test probability (Table 1). In these cases, the need for long-term treatment with active vitamin D and calcium supplements above the recommended daily allowance is unlikely. In patients with PTH values below 10 pg/mL (10 ng/L) (a positive test), post-test probabilities of long-term hypoparathyroidism vary widely depending on pre-test probability (Table 1) and patients and clinicians should be prepared for the possibility of long-term hypoparathyroidism and implement management strategies accordingly.

Table 1. Post-Test Probability Given Varying Pre-Test Probabilities of Chronic Hypoparathyroidism

Measurement	Pre-test probability		
	Low (1%–5%)	Intermediate (5%–10%)	High (10%–20%)
PTH (determination of chronic hypoparathyroidism at 6 months after surgery)			
Post-test probability +ve test	7–27	27–44	44–64
Post-test probability –ve test	100–100	100–100	100–100
PTH (determination of chronic hypoparathyroidism at 12 months after surgery)			
Post-test probability +ve test	3–16	16–28	28–47
Post-test probability –ve test	100–100	100–100	100–100
Calcium (determination of chronic hypoparathyroidism at 6 months after surgery)			
Post-test probability +ve test	4–19	19–33	33–52
Post-test probability –ve test	99–100	98–99	97–98

Bold indicates what we believe are the most important results in this table.

Differential diagnosis

The differentiation of hypoparathyroidism from other disorders of hypocalcemia is usually straightforward. In hypoparathyroidism, PTH is undetectable, low, or inappropriately normal for hypocalcemia. By contrast, patients with hypocalcemia secondary to vitamin D deficiency, chronic kidney disease, treatment with antiresorptive medications (eg, bisphosphonates) or calcium chelators (eg, citrated blood products) manifest appropriate compensatory secondary hyperparathyroidism with elevated PTH levels.⁽¹⁶⁾ Patients with pseudohypoparathyroidism, a rare genetic disorder of PTH resistance, have elevated PTH concentrations.⁽¹⁷⁾ Magnesium deficiency can lead to functional hypoparathyroidism and should be excluded.⁽¹⁸⁾

Many genetic forms of hypoparathyroidism are associated with unique clinical features, frequently as part of a larger syndrome. While many patients present in infancy or childhood, the onset of symptoms and timing of diagnosis can be highly variable. Thus, genetic forms of hypoparathyroidism should be considered in all patients with nonsurgical hypoparathyroidism, even when first diagnosed well into adulthood.

Genetic forms of hypoparathyroidism

Genetic forms of hypoparathyroidism include isolated hypoparathyroidism and syndromes with hypoparathyroidism as a component.^(19,20) From a mechanistic point of view, genetic forms of hypoparathyroidism comprise disorders of parathyroid gland formation, parathyroid hormone secretion, and parathyroid gland damage (Table 2). Pseudohypoparathyroidism, a genetic form of resistance to PTH, which is characterized by hypocalcemia and elevated PTH, will not be further discussed here.⁽¹⁷⁾

Diagnosis and genetic testing

A genetic or autoimmune etiology of hypoparathyroidism should be considered in patients without a history of neck surgery or other obvious causes. A positive family history of nonsurgical hypoparathyroidism is a strong predictor of an inherited disorder, but family history may be absent because pathogenic variants can occur de novo or can have varying degrees of expressivity. A thorough history and physical exam should be performed to search for signs and symptoms that may suggest a broader syndrome, such as renal disease and deafness as hallmarks of hypoparathyroidism, sensorineural deafness, and renal dysplasia (HDR) syndrome, cleft palate and cardiac abnormalities of 22q11.2 deletion syndrome, or skeletal dysplasia for hypoparathyroidism associated with pathogenic variants in *TBCE* and *FAM111A* (see below)^(19,20) (Supplemental Fig. S1). The age of onset of hypoparathyroidism can also influence the decision for genetic testing because the 22q11.2 deletion syndrome and pathogenic variants in *CASR* are relatively common in childhood-onset hypoparathyroidism.

When a genetic form of hypoparathyroidism is suspected, patients and family members can undergo genetic testing. Genetic testing helps confirm the clinical diagnosis, guide appropriate treatment, anticipate medical problems, recognize both affected and carrier family members, and exclude the variant in unaffected family members. Pre-test genetic counseling by a medical geneticist or genetic counselor is highly recommended.

Several modalities for genetic testing exist and are offered by many commercial companies for clinical diagnosis⁽²¹⁾; the choice of a test is often dictated by clinical suspicion of specific genetic disorders, availability and cost, insurance

coverage, and familiarity with the test. Some companies offer hypoparathyroidism-specific panels that include all known candidate genes and are a cost-effective method for genetic testing even in patients with sporadic “idiopathic” hypoparathyroidism (further details available in the Appendix S1 and Supplemental Table S1).

The Gene Testing Registry (<https://www.ncbi.nlm.nih.gov/gtr/>) is a useful central location for voluntary submission of genetic test information by providers.

Disorders of Parathyroid Gland Formation

Disorders of parathyroid gland formation refers to a group of disorders in which the parathyroid glands do not form properly during embryonic development, resulting in insufficient PTH production. The phenotypic spectrum of hypoparathyroidism in those harboring pathogenic variants and deletions ranges from no symptoms to severe hypocalcemia and seizures. Although hypocalcemia is often present in childhood, symptoms might not be apparent until adulthood.^(19,20) Details about mitochondrial and other rare disorders in X-linked hypoparathyroidism (Table 2) are available in the Appendix S1.

22q11.2 deletion syndrome (22q11DS)

22q11DS, also known as DiGeorge syndrome (DGS), velocardiofacial syndrome (VCFS) and conotruncal anomaly face syndrome, is the most common chromosomal microdeletion disorder, affecting 1/4000 live births.⁽²²⁾ Around 60% of patients develop hypoparathyroidism, manifesting as hypocalcemia, which may occur during the neonatal period, but can also first present in later childhood or adulthood and even wax and wane.⁽²³⁾ Occasionally, hypocalcemia is the first clinical presentation leading to the diagnosis of 22q11DS during adulthood.⁽²⁴⁾ Cleft palate, dysmorphic facies, and cardiac abnormalities, commonly manifesting as conotruncal heart defects, are often the earliest presentation; immunodeficiency, autoimmune disease, developmental delay, and psychiatric illness such as schizophrenia may appear over time.^(25,26) Genetic testing during the prenatal or neonatal period is recommended, especially when congenital heart disease is present, to determine the molecular basis of the disease.^(25,27)

Heterozygous chromosomal deletion at 22q11.2 account for more than 80% of DGS (DGS type 1 or DGS1),⁽²⁸⁾ most of which are de novo deletions likely due to low-copy repeats enriched in the two chromosomal regions prone to non-allelic homologous recombination.⁽²⁹⁾ These de novo deletions occur more frequently on the maternal allele than the paternal (1.35 times).⁽³⁰⁾ Ten percent of the deletions are inherited from maternal side and could also be mosaic.^(26,31) Although more than 100 genes are encompassed by 22q11.2 deletion, variations in the expression of *TBX1*, which encodes a T-box transcription factor necessary for mesoderm development, account for most features in DGS and underly the severity of clinical phenotypes.⁽³²⁻³⁴⁾ Altered regulation of *TBX1* expression caused by both genetic and environmental factors are also associated with DGS, including variants in DiGeorge Critical Region 6 (*DGCR6*) and *VEGF*, as well as maternal diabetes and exposure to retinoid acid.⁽³⁵⁻³⁸⁾ In addition to *TBX1*, downregulations of *CRKL*, which encodes CRK-like protooncogene adaptor protein, are related to congenital heart defects and urinary tract abnormalities in DGS.^(39,40) Epigenetic mechanisms such as histone modifications found in DGS with diabetic mothers further contribute to the various disease presentations.^(41,42) In addition, long noncoding RNAs and

Table 2. Genetic Forms of Hypoparathyroidism

	Inheritance	Chromosomal locus	Cytogenetic/genetic alteration	OMIM phenotype number (#)	Abnormalities associated with chronic hypoparathyroidism
Disorders of parathyroid gland formation					
DiGeorge syndrome type 1 (DGS1)	AD	22q11-21	del. (<i>TBX1</i>)	188400	Thymic hypoplasia with immune deficiency, conotruncal heart malformations, cleft palate, dysmorphic facies, short stature, developmental delay, gastrointestinal issues, thrombocytopenia, cognitive impairment, psychiatric disorders
DiGeorge syndrome type 2 (DGS2)	AD	10p14-p13	del. (<i>NEBL</i>)	601362	
CHARGE syndrome	AD	7q21.1 8q12.2	<i>SEMA3E</i> <i>CHD7</i>	214800	Choanal atresia and malformations of the heart, inner ear (deafness), and retina (coloboma), poor growth, genital hypoplasia
Hypoparathyroidism, sensorineural deafness and renal dysplasia (HDR)	AD	10p14	<i>GATA3</i>	146255	Deafness, renal dysplasia
Hypoparathyroidism, retardation, and dysmorphism syndrome (HRDS)/Sanjad-Sakati	AR	1q42.3	<i>TBCE</i>	241410	Growth retardation, dysmorphic facial features, developmental delay
Kenny-Caffey syndrome type 1 (KCS1)	AR	1q42.3	<i>TBCE</i>	244460	Severe proportionate short stature, cortical thickening with medullary stenosis of the tubular bones, craniofacial abnormalities, eye abnormalities
Kenny-Caffey syndrome type 2 (KCS2)	AD	11q12.1	<i>FAM111A</i>	127000	
Gracile bone dysplasia (GCLEB)	AD	11q12.1	<i>FAM111A</i>	602361	Gracile bones with thin diaphyses, premature closure of basal cranial sutures, and microphthalmia
Kearns-Sayre syndrome (KSS)	AR	2p23.3	Mt DNA	530000	Ophthalmoplegia, pigmentary degeneration of the retina, and cardiomyopathy
Pearson marrow-pancreas syndrome	AR	1p31.1	Mt DNA	540000	Bone marrow failure (altered hematopoietic precursors), diabetes, malabsorption
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes syndrome (MELAS)	AR	2p23.3	Mt DNA	557000	Myopathy, encephalopathy, lactic acidosis, stroke-like episodes, seizures, cortical blindness, hemianopsia, episodic vomiting
Mitochondrial trifunctional protein deficiency syndrome (MTPD)	AR	11q13.4	<i>HADHA</i> , <i>HADHB</i>	609015	
Medium-chain acylCoA dehydrogenase deficiency (ACADM)			<i>ACADM</i>	201450	Hypoglycemia, cardiomyopathy, myopathy with hypotonia, episodic vomiting, liver disease, peripheral neuropathy
Long-chain 3-hydroxyacylCoA dehydrogenase deficiency (LCHAD)			<i>HADHA</i>	609016	
Smith-Lemli-Opitz syndrome (SLOS)			<i>DHCR7</i>	270400	Hypoglycemia, lethargy, vomiting, seizures
Familial isolated hypoparathyroidism type 2 (FIH2)	AD, AR	6p24.2	<i>GCM2</i>	618883	Recurrent hypoglycemia, rapidly progressive myopathy, cardiomyopathy
Hypoparathyroidism X-linked recessive (HYPX)	XLR	Xq27.1	del./ins. (<i>SOX3</i>)	307700	Multiple congenital malformations (microcephaly, abnormal genitalia and nostrils), mental retardation, adrenal insufficiency

(Continues)

Table 2. Continued

	Inheritance	Chromosomal locus	Cytogenetic/genetic alteration	OMIM phenotype number (#)	Abnormalities associated with chronic hypoparathyroidism
Disorders of parathyroid hormone secretion					
Autosomal dominant hypocalcemia with hypercalciuria type 1 (ADH1)/Bartter syndrome subtype 5	AD	3q13.3-q21.1	<i>CaSR</i>	601198	Hypomagnesemia, hypercalciuria; possibly associated with Bartter syndrome
Autosomal dominant hypocalcemia with hypercalciuria type 2 (ADH2)	AD	19p13.3	<i>GNA11</i>	615361	Hypomagnesemia, hypercalciuria
Familial isolated hypoparathyroidism type 1 (FIH)	AD, AR	11p15.3	<i>PTH</i>	146200	—
Hypomagnesemia syndromes					
Hypomagnesemia 1, intestinal (HOMG1)	AR	9q21.13	<i>TRPM6</i>	602014	Hypercalciuria, nephrocalcinosis
Hypomagnesemia 2, renal (HOMG2)	AD	11q23.3	<i>FXYD2</i>	154020	Hypocalciuria
Hypomagnesemia 3, renal (HOMG3)	AR	3q28	<i>CLDN16</i>	248250	Progressive loss of kidney function, amelogenesis imperfecta
Hypomagnesemia 4, renal (HOMG4)	AR	4q25	<i>EGF</i>	611718	Mild to moderate psychomotor retardation
Hypomagnesemia 5, renal (HOMG5)	AR	1p34.2	<i>CLDN19</i>	248190	Progressive renal failure, nephrocalcinosis, and severe visual impairment, amelogenesis imperfecta
Hypomagnesemia 6, renal (HOMG6)	AD	10q24.32	<i>CNNM2</i>	613882	—
Gitelman syndrome (GTMNS)	AR	16q13	<i>SLC12A3</i>	263800	Hypokalemic metabolic alkalosis, hypocalciuria, abdominal pains, chondrocalcinosis
Episodic ataxia type 1 (EA1)	AD	12p13.32	<i>KCNA1</i>	160120	Spells of incoordination and imbalance, often associated with progressive ataxia
Hypomagnesemia, hypertension, and hypercholesterolemia syndrome	AD, AR	10q24.32	Mt DNA	500005	Hypertension, hypercholesterolemia
Hypomagnesemia, seizures, and mental retardation 1 (HOMGSMR1)		1p13.1	<i>CNNM2</i>	616418	Seizures, delayed psychomotor development
Hypomagnesemia, seizures, and mental retardation 2 (HOMGSMR2)	AD		<i>ATP1A1</i>	618314	Significantly impaired intellectual development
Damage to the parathyroid glands					
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED)	AD, AR	21q22.3	<i>AIRE</i>	240300	Adrenal insufficiency, chronic mucocutaneous candidiasis, and other possible autoimmune diseases, eg, celiac disease, vitiligo, type I diabetes, hypogonadism
Other autoimmune polyendocrine syndromes	—	—	(polygenic, HLA-related)	—	Association of organ-specific autoimmune diseases

microRNAs also play a role in the variations of clinical phenotypes, including congenital heart disease and psychiatric illness such as schizophrenia.^(34,43)

Apart from the classic 22q11.2 deletion, other chromosomal abnormalities associated with DGS include deletion at 10p13, 17p13, 4q34, and 3p12.3.^(34,44,45) DGS caused by heterozygous chromosomal microdeletion at 10p14-p13 is also referred to as DGS type 2 (DGS2) characterized by the classic DGS presentation, including cardiac defect and hypoplastic thymus. Microdeletion on a more distal locus 10p14-10pter contributes to HDR syndrome, thus interconnecting the two syndromic disorders⁽⁴⁶⁾ (see below).

CHARGE syndrome, an autosomal disorder due to pathogenic variants in *SEMAE3* (7q21.11) or *CHD7* (8q12.2), which shares some overlapping phenotypic characteristics with both DGS and HDR, has also been associated with hypocalcemia and hypoparathyroidism.^(47,48)

Fluorescence in situ hybridization (FISH) detects the presence or absence of specific regions in the genome and has historically been the most widespread method for detecting the microdeletion 22q11.2.⁽⁴⁹⁾ However, a negative FISH result does not completely exclude the diagnosis of 22q11DS.⁽²⁶⁾ Multiplex ligation-dependent probe amplification (MLPA) is a more recently developed technique, which detects both microdeletions and microduplications and is an efficient, rapid, and sensitive method for the diagnosis of 22q11DS.⁽⁵⁰⁾ Genomewide analysis has achieved considerable visibility in the field of genetics, and currently, the chromosomal microarray analysis (CMA) is the first-tier technique for the investigation of the deletion in 22q11.2.⁽⁵¹⁾ The availability and cost of these techniques can delay diagnosis, particularly in resource-poor settings.

HDR syndrome (pathogenic variants in *GATA3*)

Heterozygous pathogenic variants in *GATA3* cause the HDR syndrome.⁽⁵²⁾ *GATA3* belongs to the *GATA* family that encompasses six transcription factors, which are involved in the embryonic development of mesoderm, ectoderm, and endoderm-derived tissues.⁽⁵³⁾ *GATA3* is expressed in the inner ear, the parathyroid primordium, and the kidney. The classic triad of HDR syndrome comprises sensorineural hearing loss, hypoparathyroidism, and renal dysplasia affecting more than 90%, 80%, and 60% of cases, respectively.^(52,54) Additional features, which are less common, include female genital tract anomalies.^(55,56) Hypoparathyroidism as the sole expression of pathogenic variants in *GATA3* have not yet been reported.⁽⁵⁷⁾ Although hypoparathyroidism could be the first clinical presentation leading to HDR syndrome diagnosis,⁽⁵⁸⁾ sensorineural hearing loss is the most common one. Genetic screening for non-syndromic deafness may also uncover an early diagnosis of HDR syndrome.⁽⁵⁷⁾

The *GATA* family share two zinc finger DNA binding domains that recognize the consensus motif 5'(A/T) GATA (A/G)-3'.⁽⁵³⁾ More than 90% of *GATA3* pathogenic variants occur on the carboxy-terminal of zinc finger protein 2, leading to loss of DNA binding. The remaining variants cause either reduced DNA binding affinity due to abnormalities in the N-terminal zinc finger protein 1 or conformational changes during binding.⁽⁵⁹⁾ There are no hotspots on *GATA3*, although missense variants associated with HDR syndrome occur exclusively in the zinc finger domains. Compared with missense variants, patients with frameshift variants and gross deletions are often diagnosed at

a younger age and are therefore speculated to have more severe clinical disease.^(57,60)

Kenney-Caffey syndrome 1 and 2

Kenney-Caffey syndrome type 1 (KCS1) and hypoparathyroidism retardation and dysmorphism syndrome (HRDS), also referred to as Sanjad-Sakati syndrome, are very rare disorders, connoted by two different phenotypes (according to OMIM) but often recognized to be a single condition inherited as autosomal recessive trait, caused by homozygous inactivating variants in the gene coding for tubulin-specific chaperone E (*TBCE*), a molecular chaperone likely to have a function in parathyroid and bone development.^(61,62) In these diseases, hypoparathyroidism is associated with proportionate dwarfism and ocular abnormalities, such as corneal opacity, papilledema, recurrent infections, retinal vascular alterations, and dysmorphic facies. Skeletal features are variable and may include smaller long bones, with thicker cortices and medullary stenosis, osteosclerosis of the skull with macrocephaly, and abnormalities in dentition, such as oligodontia, microdontia, and short roots.⁽⁶¹⁾ In HRDS, as described in kindreds from the Middle East, there can be a facial dysmorphism with deep-set eyes, abnormalities in external ears, and frontal bossing, while signs of osteosclerosis are typically missing.^(61,63,64)

A most severe phenotype of KCS1 with high perinatal mortality is gracile bone dysplasia (GCLEB). Neonates with GCLEB have long, thin bones with medullary stenosis, severe osteocraniostenosis with frontal bossing, triangular face, and microphthalmia. Hypoparathyroidism can be diagnosed in the surviving infants. This disorder ensues from a heterozygous deletion in *FAM111A* (Family with Sequence Similarity 111 Member A), coding for a protein implicated in DNA replication and chromatin remodeling.⁽⁶⁵⁾

Kenney Caffey Syndrome type 2 (KCS2) is caused by heterozygous pathogenic variants of *FAM111A*, a disease with a phenotype similar to GCLEB.

Pathogenic variants in the glial cells missing transcription factor 2 gene (*GCM2*)

GCM2 encodes a transcription factor (*GCM2*) key in the development of the parathyroid glands. It is necessary for the survival and differentiation of the parathyroid precursor cells in the third pharyngeal pouch.⁽⁶⁶⁾ Mice with genetic ablation of *Gcm2* are characterized by absent parathyroid glands and develop hypocalcemia and hyperphosphatemia, whereas heterozygous mice are normal.⁽⁶⁷⁾ Continued expression of *Gcm2* in adult parathyroid cells points to a post-developmental role, especially since conditional knockout of this gene in postnatal mice showed reduced parathyroid cell number.⁽⁶⁸⁾

Both autosomal dominant and autosomal recessive modes of inheritance have been reported with *GCM2* variants. Homozygous loss-of-function variants in *GCM2* have been identified in patients with familial forms of hypoparathyroidism (also referred to as familial isolated hypoparathyroidism type 2 [FIH2]). Patients with biallelic large intragenic deletions develop hypoparathyroidism, whereas heterozygous carriers do not exhibit a phenotype.⁽⁶⁹⁾ Point substitutions may impair *GCM2* function through loss of DNA binding, failure of nuclear localization, decreased transactivation, or the complete absence of *GCM2* protein translation, all of which cause varying degrees of hypoparathyroidism.^(70,71) Surprisingly, heterozygous variants in *GCM2* have also been identified in patients with familial hypoparathyroidism;

these mutant proteins were shown to have dominant-negative properties, explaining the occasional autosomal dominant mode of inheritance.⁽⁷²⁻⁷⁵⁾

Biochemically, PTH may be detectable in some patients; the severity of the phenotype and age of presentation can be variable; thus, the diagnosis might even be delayed into adulthood.

Genetic Disorders of Parathyroid Gland Secretion

These disorders encompass diseases with diminished sensitivity of the calcium-sensing apparatus and alterations in the gene encoding PTH. Autosomal-dominant hypocalcemia (ADH) type 1 will be discussed below; details to ADH type 2 (gain-of-function variants in the *GNA11* gene) and pathogenic variants in the *PTH* gene (Table 2) are available in the Appendix S1.

Autosomal-dominant hypocalcemia type 1 (activating variants in the calcium-sensing receptor gene, *CASR*)

The calcium-sensing receptor (CaSR), a classic 7-transmembrane domain G-protein-coupled receptor, plays a dominant role in regulating systemic calcium homeostasis in response to circulating ionized calcium.^(76,77) Although the CaSR is present in numerous tissues, its expression is highest in the parathyroids and kidneys (the thick ascending limb of the loop of Henle, distal tubules, and collecting ducts of the nephron).⁽⁷⁸⁾ Increases in ionized calcium activate the CaSR on the parathyroid chief cells, leading to decreased PTH secretion, which, in turn, inhibits calcium release from bone, activation of vitamin D, and renal calcium reabsorption. In addition, activation of CaSRs in the renal tubules directly inhibits renal calcium reabsorption, further compounding the renal effects of low PTH.⁽⁷⁹⁾ Thus, heterozygous gain-of-function pathogenic variants in the gene encoding the CaSR (*CASR*) increase the receptor's sensitivity to calcium, resulting in inadequate PTH secretion and renal calcium reabsorption in the face of hypocalcemia and inappropriate suppression of PTH during eucalcemia. This disorder, termed autosomal dominant hypocalcemia type 1 (ADH1, OMIM# 601198),^(80,81) has an almost 100% biochemical penetrance⁽⁸²⁾ with de novo cases found infrequently. More than 90 different activating pathogenic variants in the *CASR* have been reported.^(83,84) The prevalence of ADH1 is unknown, but estimates range from 1 in 70,000⁽⁸⁵⁾ to 3.9 per 100,000.⁽⁸²⁾

ADH1 is characterized by variable degrees of hypocalcemia and hypomagnesemia, with abnormally low or low-normal parathyroid hormone (PTH), hyperphosphatemia, and hypercalciuria.^(81,86) Compared with other forms of hypoparathyroidism, hypercalciuria is often more severe in ADH1, as the kidney is subjected to both decreased PTH action and increased CaSR signaling.⁽⁸⁷⁾ Patients with ADH1 are at substantial risk for nephrocalcinosis, nephrolithiasis, and impaired renal function.⁽⁸⁶⁾ In particularly severe cases, some patients with activating pathogenic *CASR* variants are classified as having ADH1 with a Bartter-like syndrome (type 5), with varying findings of hypokalemia, metabolic alkalosis, hyperreninemia, and secondary hyperaldosteronism.⁽⁸⁸⁻⁹⁰⁾ Although some with ADH1 may present with severe manifestations in infancy, many affected individuals are asymptomatic or minimally symptomatic and may not be diagnosed until adulthood. This is observed even within families bearing the identical *CASR* variant, with hypocalcemia detected during routine laboratory screening or after a family member's diagnosis.

Conventional therapy for ADH1 patients requiring treatment may include calcium, magnesium, and activated vitamin D analogs (eg, calcitriol, alfacalcidol); however, raising circulating calcium further exacerbates the hypercalciuria, placing patients at increased risk of renal complications.^(86,87) Thus, current clinical practice is to maintain calcium levels near or slightly below the lower limit of normal. Despite this, some patients continue to experience neuromuscular and cognitive symptoms of hypocalcemia and sustain renal complications. Intermittent and continuous subcutaneous teriparatide (PTH (1–34)) therapy in case reports and small series that included patients with ADH1 have demonstrated improvement in hypocalcemia with variable effects on hypercalciuria.⁽⁹¹⁻⁹⁷⁾ Recombinant human parathyroid hormone PTH (1–84) was approved in 2015 for hypoparathyroidism that cannot be well-controlled with calcium and vitamin D; however, the clinical studies leading to that approval excluded patients with ADH1,^(98,99) resulting in a usage limitation labeling.⁽¹⁰⁰⁾ Three reported patients with ADH1 treated with rhPTH (1–84) had improvement in hypercalciuria compared with conventional therapy.⁽¹⁰¹⁾ Calcilytics are a class of negative allosteric modulators of the CaSR that increase PTH secretion and decrease renal calcium excretion, suggesting that they may be a promising therapy for ADH1.⁽¹⁰²⁾ Studies using several different calcilytics in ADH1 cell and animal models have demonstrated improvement in cellular signalinmineral metabolism and prevention of renal calcifications.⁽¹⁰³⁻¹⁰⁶⁾ Preliminary clinical data also support the potential utility of calcilytics to treat humans with ADH1. Briefly, intravenous exposure to the calcilytic NPSP795 in five patients with ADH1 was associated with dose-related increase in PTH and decrease in fractional calcium excretion, although without a clear increase in circulating calcium.⁽¹⁰⁷⁾

Inherited hypomagnesemia syndromes

Magnesium is a fine-regulator of PTH secretion. A group of rare genetically determined hypomagnesemia syndromes can lead to hypoparathyroidism (HOMG1-6; Gitelman syndrome; episodic ataxia type 1; hypomagnesemia, hypertension, and hypercholesterolemia syndrome; hypomagnesemia, seizures, and mental retardation 1 and 2). Hypomagnesemia, hypocalcemia, and related symptoms of neuromuscular irritability can be the sole manifestations. However, often other signs and symptoms are associated with these complex syndromes, such as nephrocalcinosis (HOMG1), progressive loss of kidney function and amelogenesis imperfecta (HOMG3 and 5), severe visual impairment (HOMG5), mild to moderate psychomotor retardation (HOMG4), hypokalemic metabolic alkalosis and chondrocalcinosis (Gitelman syndrome), progressive episodic ataxia (EA1), hypertension and hypercholesterolemia (hypomagnesemia, hypertension, and hypercholesterolemia syndrome), and psychomotor impairment (hypomagnesemia, seizures, and mental retardation 1 and 2). Many of these syndromes may manifest in adulthood.⁽¹⁰⁸⁾

Disorders of Parathyroid Gland Damage (Autoimmune Hypoparathyroidism)

Autoimmune hypoparathyroidism may occur as an acquired disease or as a component of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED) (see the companion article Etiology and Pathophysiology of Hypoparathyroidism: A Narrative Review for details of pathophysiology).

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED)

APECED (also known as autoimmune polyendocrine syndrome type 1 [APS1]) is a monogenic disease caused by biallelic inactivating variants in the *AIRE* (autoimmune regulator) gene^(109,110) presenting with chronic mucocutaneous candidiasis (75% to 85% of cases), Addison's disease (63% to 83% of cases), and hypoparathyroidism (73% to 90% of cases), although other autoimmune disorders and non-autoimmune manifestations may be observed.⁽¹¹¹⁻¹¹⁵⁾ See details about the etiology and pathophysiology of hypoparathyroidism: A narrative review in the accompanying article.

Genetic testing for *AIRE* gene mutation is offered to patients with the clinical suspicion of APECED. Conveniently, the *AIRE* gene is also part of some hypoparathyroidism genetic panels. Detection of autoantibodies against cytokines such as interferon- ω (100% of cases) and interleukin-22 (91% of cases) can serve as an alternative diagnostic tool for APECED.^(116,117) For patients with idiopathic, nonsurgical hypoparathyroidism, anti-cytokine antibodies would be most helpful to understand whether the patient might APECED.

Anti-NALP5 antibodies

For patients with the diagnosis of APECED, the presence of tissue-specific autoantibodies can predict or correlate with functional organ failure.⁽¹¹⁸⁾ Autoantibodies against the parathyroid-expressed antigen NALP5 (NACHT leucine-rich-repeat protein 5) have been associated with hypoparathyroidism in patients with APECED.⁽¹¹⁹⁾ Immunoprecipitation assays using radiolabeled ligand showed that NALP5-specific antibodies were detectable in 36 of 87 patients with APECED and were significantly associated with the presence of hypoparathyroidism.⁽¹¹⁹⁾ The association of NALP5 antibodies with APECED was confirmed in a study of 145 patients with idiopathic hypoparathyroidism, only one of whom was positive by radioimmunoprecipitation assay for NALP5 antibodies.⁽¹²⁰⁾ Further genetic and serological study revealed that this patient had APECED. In the same study, the use of immunoblotting with NALP5 expressed in bacteria proved less specific at identifying NALP5 antibodies.⁽¹²⁰⁾ Again, using a radioimmunoprecipitation assay, NALP5 antibodies were detected in a patient with acquired APECED and hypoparathyroidism because of a thymoma⁽¹²¹⁾ and in an APECED patient who originally presented with chronic hypoparathyroidism.⁽¹²²⁾

Overall, radioimmunoprecipitation is currently the best assay to detect NALP5 antibodies. When present, they occur in the context of APECED.⁽¹¹⁹⁻¹²²⁾ Although their apparent specificity for the hypoparathyroidism of APECED is striking, it is notable that less than half of all patients were positive, possibly due to disease duration or assay sensitivity.⁽¹¹⁹⁾

Anti-calcium-sensing receptor antibodies

The high expression of the CaSR on PTH-producing chief cells led to its investigation as a candidate parathyroid autoantigen that might be targeted by antibodies in cases of hypoparathyroidism.⁽¹²³⁾ Since then, many studies have investigated the presence of CaSR antibodies in patients with hypoparathyroidism phenotype; these are summarized in Table 3. However, several aspects of CaSR antibodies remain to be addressed. For example, there is variability of their prevalence in patients with idiopathic hypoparathyroidism and APECED (Table 3). This could be due to differences in the type of assay employed as currently there is no gold standard test for CaSR antibodies. Particularly, the source of

the CaSR antigen used can have a significant effect upon the frequency of CaSR antibody-positives.^(123,125,128) In addition, the study design including the size and origin of the patient and control groups and the criteria for positivity may influence the reported prevalence of CaSR antibodies. Finally, the question as to the relationship between the presence of CaSR antibodies and clinical hypoparathyroidism in APECED requires clarification.

As in other autoimmune diseases, APECED is characterized by lymphocytic infiltration of the target organs,⁽¹¹⁵⁾ although T-cell reactivity against the parathyroid glands has not been well studied.

Diagnosis of autoimmune isolated hypoparathyroidism

Idiopathic hypoparathyroidism may in some cases have an autoimmune etiology. It can be associated with other autoimmune endocrine diseases.^(131,132) The presence or personal history of other autoimmune conditions may indicate an autoimmune basis for a patient's hypoparathyroidism.

Most autoimmune diseases are associated with particular human leucocyte antigen (HLA) specificities and with a number of other gene polymorphisms that regulate various aspects of immune function; sharing of these genetic associations accounts in large part for the clustering of different autoimmune diseases within individuals and within families.^(133,134) A strong association has been reported of HLA-A*26:01 with idiopathic hypoparathyroidism, suggesting a key role in its pathogenesis for major histocompatibility complex (MHC) class I-mediated presentation of autoantigenic peptides to CD8+ cytotoxic T cells.⁽¹³⁵⁾ In another study, MHC class II HLA-DRB1*01 and HLA-DRB1*09 alleles were more frequent in idiopathic hypoparathyroidism patients than in controls.⁽¹³⁶⁾

With respect to immune responses, lymphocytic infiltration of the parathyroid gland has been reported.^(137,138) An increase in circulating activated T cells compared with controls, including those against the calcium-sensing receptor, has also been observed.^(139,140) Serum autoantibodies have been described, but their usefulness in the diagnosis of autoimmune hypoparathyroidism has not been established unequivocally (see discussion of CaSR antibodies above). Currently, there is no definitive diagnostic test for non-monogenic autoimmune hypoparathyroidism.

Knowledge gaps and research agenda

- The use of antibodies in diagnosis of hypoparathyroidism
The prospects of using antibodies to diagnose autoimmune hypoparathyroidism, idiopathic or associated with APECED, is dependent upon the development of a sensitive and specific assay, particularly regarding the detection of CaSR antibodies. Currently, there is no gold-standard assay for CaSR antibodies that has been clinically validated. It remains a key area of investigation as recent cases of hypoparathyroidism have been reported in relation to therapeutic immune checkpoint inhibitors, some of which were associated with the presence of CaSR antibodies.⁽¹⁴¹⁻¹⁴³⁾ Further research might identify novel autoantigens that might be more useful than the current antibody targets.
- Genetic diagnosis
The best use of genetic testing in hypoparathyroidism is not well elucidated. Studies should address whether genetic testing alters management and/or outcomes in diverse groups

Table 3. Detection of CaSR Antibodies in Idiopathic and APECED-Associated Hypoparathyroidism

Method of CaSR antibody detection	No. of participants with CaSR antibodies (%)		p Value ^a	p Value ^b	Reference
Radioimmunoprecipitation with in vitro translated CaSR	APECED with HP	6/17 (35)	0.004	—	(123)
	HP	8/8 (100)	<0.0001		
	Controls	0/22 (0)			
	APECED with HP	6/50 (12)	0.044	1.000	(124)
	APECED no HP	1/10 (10)	0.370		
	Controls	8/192 (4)			
	APECED with HP	0/73 (0)	—	—	(118)
	APECED no HP	0/17 (0)	—		
	Controls	0/100 (0)			
	HP	24/147 (16)		—	(125)
Immunoblotting of CaSR expressed in <i>Escherichia coli</i>	Controls	1/199 (0.5)			
	HP	3/17 (18)	0.0369	—	(126)
	Controls	0/32 (0)			
	APECED with HP	1/8 (13)	0.200	—	(126)
	HP	5/17 (29)	0.003	—	
Immunoblotting of CaSR-transfected HEK293 cells	Controls	0/32 (0)			
	HP	24/147 (16)	0.208	—	(125)
	Controls	23/199 (12)			
	APECED with HP	3/17 (18)	0.074	—	(123)
	HP	5/8 (63)	0.004		
Immunoprecipitation of CaSR expressed in HEK293 cells	Controls	0/22 (0)			
	HP	36/147 (25)	0.011	—	(125)
	Controls	27/199 (14)			
	HP Controls	2/2 (100)	0.048	—	(127)
	Controls	0/5 (0)			
CaSR stimulation assays measuring accumulation of inositol phosphate and extracellular signal-regulated kinase (ERK1/2) phosphorylation in HEK293-CaSR cells	APECED with HP	12/13 (92)	<0.0001	0.143	(128)
	APECED no HP	0/1 (0)	—		
	Controls	0/28 (0)			
	HP Controls	2/2 (100)	—	—	(127)
	Controls	0/5 (0)			
PTH-secretion inhibition assay using rat parathyroid PTH-C1 cells	APECED	2/14	—	—	(129)
	Controls	0/20 (0)			
	APECED	4/16 (25)	—	—	(130)
	Controls	0/16 (0)			
	APECED	4/16 (25)	—	—	(130)
	Controls	0/16 (0)			

CaSR = calcium-sensing receptor; APECED = autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome; HP = hypoparathyroidism; PTH = parathyroid hormone.

^aPatients compared with controls.

^bAPECED patients with hypoparathyroidism compared to those without hypoparathyroidism.

of patients with hypocalcemia suspected to have hypoparathyroidism. Additionally, further research might clarify which genetic testing modality (single gene testing, hypoparathyroidism gene panel, exome sequencing, whole-genome sequencing) is best for identifying pathogenic variants in patients with hypoparathyroidism.

- Postsurgical diagnosis
Here, we have conducted a systematic review to develop recommendations regarding the ability to predict permanent postsurgical hypoparathyroidism from PTH measurements in the immediate postoperative period after total thyroidectomy. This could be strengthened by randomized controlled trials conducted to prospectively test the utility of early predictors for permanent postsurgical hypoparathyroidism.
- Future trials
Future clinical trials should include patients with genetic

disorders to clarify the best management for these patients with specific disorders.

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Author Contributions

Michael Mannstadt: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; writing – original draft; writing – review and editing. **Luisella Cianferotti:** Data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Rachel I Gafni:** Data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Francesca Giusti:** Data curation; formal analysis; investigation; methodology; writing – review and editing. **Elizabeth Helen Kemp:** Data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Christian A. Koch:** Data curation; formal analysis; investigation; methodology; writing – review and editing. **KL Roszko:** Data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Liang Yao:** Data curation; formal analysis; investigation; methodology; writing – review and editing. **Gordon Guyatt:** Data curation; formal analysis; investigation; methodology; writing – review and editing. **Rajesh V Thakker:** Data curation; formal analysis; investigation; methodology; writing – review and editing. **Weibo Xia:** Data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Maria Luisa Brandi:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; writing – original draft; writing – review and editing.

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Data Availability Statement

The data that support the findings in this study are openly available in PubMed, MEDLINE, EMBASE, and the Cochrane databases.

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