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Genetic disorders of parathyroid development and function

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Abstract/summary

Hypoparathyroidism is characterized by hypocalcemia and hyperphosphatemia and is due to insufficient levels of circulating parathyroid hormone. Hypoparathyroidism may be an isolated condition or a component of a complex syndrome. Although genetic disorders are not the most common cause of hypoparathyroidism, molecular analyses have identified a growing number of genes that when defective result in impaired formation of the parathyroid glands, disordered synthesis or secretion of parathyroid hormone, or postnatal destruction of the parathyroid glands.

Keywords

hypoparathyroidism; parathyroid hormone; genetics; etiologies

Introduction

Hypoparathyroidism may occur as an isolated endocrine disorder or as a component of a complex developmental, metabolic, or endocrinologic syndrome. Molecular genetic analyses over the past twenty years have identified mutations in a growing number of genes that have provided novel insights into embryological development of the parathyroid glands, regulation of parathyroid hormone (PTH) synthesis and secretion, and maintenance of parathyroid gland homeostasis (see Table 1). In the interest of taxonomy, pseudohypoparathyroidism, in which the biochemical manifestations of hypoparathyroidism are due to resistance to PTH rather than to deficiency of PTH, will be separately addressed (please see Muriel Babey, Maria-Luisa Brandi and Dolores Shoback's article "Conventional Treatment of Hypoparathyroidism," in this issue).

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Disorders of parathyroid gland formation

Isolated parathyroid aplasia – *GCM2*, *SOX3*

Some genetic defects will affect embryological development of only the parathyroid glands, and thereby lead to isolated hypoparathyroidism. The most common cause of isolated hypoparathyroidism is loss of function mutation in the *GCM2* (previously *GCMB*) gene at 6p23–24¹. *GCM2* is a member of a small family of transcription factors that were first identified in *Drosophila melanogaster* and which conservation that is limited to the N-terminal region that contains a unique GCM DNA binding domain.

GCM2 is related to the *Drosophila* glial cells missing gene, which likely acts as a binary switch that determines cell fate between neuronal and glial cells. There are two mammalian homologs: *GCM1*, which is primarily expressed in the thymus and placenta, and regulates placental branching and vasculogenesis; and *GCM2*, which is principally if not exclusively expressed in the developing and mature parathyroid gland². *GCM2* is a master regulator of parathyroid gland development. Most cases of isolated hypoparathyroidism are due to autosomal recessive mutations that inactivate *GCM2*^{1, 3}, but in some cases *GCM2* mutations produce an abnormal *GCM2* protein with dominant-negative effects^{4, 5}.

In mice, *Gcm2* is specifically expressed in the developing second and third pharyngeal pouches beginning at E9.5 days⁶ and studies with *Gcm2* null mutant mice suggest that *Gcm2* is not required for organogenesis, but is necessary for subsequent differentiation and survival of parathyroid cells with null mutant mice undergoing apoptosis by E12.5⁷. *GCM2* is part of a network of transcription factors that are required for normal development of the parathyroid glands. The transcription factor GATA binding protein-3 (*GATA3*) is also necessary for development and survival of parathyroid glands, and is highly expressed in parathyroid cell precursors in the pharyngeal pouch as well as in other tissues (see below). *GATA3* contains a carboxy-terminal zinc-finger that is essential for DNA binding, and it induces *GCM2* transcription by binding to specific *GATA3* sites that are present in the promoter of the human *GCM2* gene⁸. Remarkably, gain of function mutations of *GCM2* are a cause of parathyroid hyperplasia⁹ and familial isolated hyperparathyroidism¹⁰.

Another cause of isolated hypoparathyroidism shows X-linked recessive inheritance. Affected patients present with infantile hypocalcemic seizures, while heterozygous females are unaffected. The cause of hypoparathyroidism is complete agenesis of the parathyroid glands. Linkage analysis has localized the underlying mutation to a 1.5 Mb region on Xq26–27, in which there is a deletion-insertion involving Chromosomes 2p25.3 and Xq27.1, near Sry-box 3 (*SOX3*), presumed to impact embryonic development of the parathyroid glands¹¹.

DiGeorge Sequence - 22q11, *TBX1*, 10p13

DiGeorge Sequence (DGS) refers to a well-characterized and yet highly variable constellation of developmental anomalies that can include parathyroid dysplasia. Typical features of DGS include thymic aplasia with impaired T-cell mediated immunity, conotruncal cardiac defects, cleft palate, and dysmorphic facies with mid-face hypoplasia, hypertelorism and external ear anomalies (see Figure 1). Additionally, patients with DGS

may have feeding difficulties, poor growth, and cognitive impairment. Notably, there is a range of DGS disease presentation, and various developmental syndromes with limited features of DGS have been described (e.g. Shprintzen syndrome, velocardiofacial syndrome and conotruncal anomaly face syndrome) that represent different manifestations of the same molecular defect, typically a large deletion at 22q11^{12, 13, 14}. Not all patients with DGS have clinical hypoparathyroidism¹², and several series have shown that hypoparathyroidism is present in only about 20% of older patients with DGS¹⁴. By contrast, up to 50% of patients in infancy can have hypoparathyroidism, which can vary from severe and symptomatic early-onset hypocalcemia associated with neonatal seizures, to mild and asymptomatic hypocalcemia that may only be discovered later in adulthood. Hypocalcemia can wax and wane during infancy and childhood, with some DGS patients even demonstrating complete resolution of hypocalcemia after 1 year of age. Nevertheless, the tendency for hypocalcemia to recur during times of stress (e.g. surgery or severe illness) suggests that parathyroid hypoplasia is more common in DGS than is widely appreciated^{15, 16, 17}. Under this proposition, it is likely that many subjects are able to produce sufficient PTH to maintain normal mineral homeostasis during ordinary conditions.

Most patients with DGS have hemizygous microdeletions within chromosome 22q11.2123¹⁸; these microdeletions usually arise *de novo* but can also be inherited from a parent (5–10%). 22q11 deletions are common, and occur with an incidence of approximately 1 in 2,000–5,000 live births, and are the most common human contiguous gene deletion¹⁹. The relatively high frequency of spontaneous deletions is related to the presence of four distinct highly homologous blocks of low copy number repeats (LCRs) that flank the deletion region, which can lead to mispairing of the LCRs during meiosis and unequal meiotic exchange, leading to the microdeletion. The majority of affected individuals have a 3-Mb deletion of the chromosome 22q11.2 region (about 90% of cases), while a smaller 1.5-Mb deletion is present in about 7%. The 3 Mb deletion encompasses approximately 40 genes, but it is likely that loss of the *TBX1* gene, which encodes the Tbox transcription factor gene 1, is responsible for most of the clinical findings in DGS.

Patients with point mutations in *TBX1* will manifest several of the phenotypic findings of 22q11 syndrome including hypocalcemia, cardiac defects, cleft palate and facial anomalies, but notably not learning disabilities²⁰.

A less common cause of DGS is a deletion at Chromosome 10p13, termed the DiGeorge locus type II (DGS2)^{21, 22, 23}. The critical region for DGS2 has been mapped within a 1cM interval in 10p13. DGS type 2 is likely caused by mutations in the nebulin (*NEBL*) gene, which is abundantly expressed in cardiac muscle^{24, 25}.

CHARGE Syndrome – *CHD7*, *SEMA3E*

Hypoparathyroidism can be a component of the CHARGE (Coloboma, Heart defects, Atresia choanae, Retarded growth and development, Genital hypoplasia and Ear anomalies/deafness) syndrome. CHARGE syndrome occurs with an incidence of 1 in 8,500–10,000 live births and in over 75% of cases is due to a heterozygous loss-of-function mutation within the coding region of the *CHD7* gene at Chromosome 8q12.2^{26, 27}. *CHD7* is a member of the chromodomain helicase DNA binding protein (CHD) family of ATP-dependent chromatin

remodelers, which catalyze nucleosome movement on DNA. Mutations are usually *de novo* mutation, but the syndrome can also be inherited in an autosomal dominant manner. A less common cause is due to abnormalities involving semaphorin 3E (*SEMA3E*), that controls cell positioning during embryonic development on Chromosome 7q21.11²⁸.

There is significant clinical overlap between DGS and CHARGE syndrome, with both having hypoparathyroidism, cardiac anomalies, cleft palate, renal anomalies, ear abnormalities/deafness and developmental delay. Hypocalcemia, attributed to hypoparathyroidism, is more common in CHARGE syndrome newborns (72%) compared to DGS newborns (26%)²⁹.

Hypoparathyroidism, deafness and renal dysplasia (HDR)/Barakat syndrome – *GATA3*

Hypoparathyroidism, sensorineural deafness and renal dysplasia syndrome (HDR), also known as Barakat syndrome, is an autosomal dominant inherited disorder³⁰ caused by haplo-insufficiency of the GATA binding protein-3 (*GATA3*) gene, on Chromosome 10p14–15, distal to the DGS2^{31, 32, 33}. The *GATA3* protein is a transcription factor with a carboxy-terminal zinc-finger that is essential for DNA binding, and is expressed in the developing parathyroid gland, thymus, kidney, inner ear and central nervous system. *GATA3* interacts with *GCM2* (see above, isolated parathyroid aplasia) and *MafB*, two known transcriptional regulators of parathyroid development, and synergistically stimulates the PTH promoter, activating PTH gene transcription and serving as a critical regulator of PTH gene expression³⁴.

There is wide phenotypic variability, and hypoparathyroidism ranges from asymptomatic and transient neonatal hypocalcemia that resolves in infancy to severe, symptomatic hypocalcemia with seizures and tetany from infancy that persists through adulthood. The sensorineural hearing loss is usually bilateral and is the most penetrant of the three HDR features. Deafness is present in over 95% of HDR patients and is typically discovered during infancy or childhood³⁵. Renal abnormalities are the least penetrant feature, present in 60% of patients, and are extremely variable, with only a minority (9%) of patients progressing to end stage renal disease³⁶. Notably, there are no cardiac, immunologic or palatal abnormalities.

Hypoparathyroidism, retardation and dysmorphism (HRD) – *TBCE*, *FAM111A*

Hypoparathyroidism, retardation and dysmorphism syndrome (HRD), also known as Sanjad-Sakati Syndrome, consists of permanent hypoparathyroidism, severe pre- and post-natal growth retardation, reduced T-cell subsets and developmental delay³⁷. Dysmorphic features include microcephaly, microphthalmia, micrognathia, ear abnormalities, depressed nasal bridge, thin upper lip, hooked small nose, and small hands and feet³⁷. It is an autosomal recessive inherited disorder, and usually due to mutations in the *TBCE* gene located on Chromosome 1q42–43, that primarily affects patients of Arabic descent³⁸.

Kenny-Caffey syndrome (KCS) is a clinically similar allelic syndrome, which includes hypocalcemia due to hypoparathyroidism, short stature, thickening of the long bones, thin marrow cavities (medullary stenosis), developmental delay and facial abnormalities, including small eyes with hypermetropia and frontal bossing with triangular facies³⁹. It may

be inherited as an autosomal recessive⁴⁰ or autosomal dominant disorder. The autosomal recessive form has been mapped to the same locus (1q42-q43) as the HRD syndrome and both are caused by mutations in the tubulin folding cofactor E (*TBCE*) gene and thus are allelic disorders due to a common founder mutation³⁹. Mutations in the *TBCE* gene affect the synthesis of chaperone proteins that are involved in the normal folding of beta-tubulin, with abnormal tubulin formation affecting the Golgi apparatus and endosomes, suggesting a possible connection between tubulin physiology and development of the parathyroid gland. The autosomal dominant form of KCS, which is clinically distinguished from the autosomal recessive form of KCS by the absence of mental retardation, is due to a heterozygous mutation of the *FAM111A* gene (family with sequence similarity 111 member A), which is a chromatin-associated protein involved in DNA replication⁴¹.

Mitochondrial disease - Kearns-Sayre syndrome, Pearson Marrow-pancreas syndrome, MELAS, LCHAD, MCADD

Several mitochondrial syndromes are associated with hypoparathyroidism. KearnsSayre syndrome is characterized by encephalomyopathy, ophthalmoplegia, retinitis pigmentosa and heart block⁴². Pearson Marrow-Pancreas syndrome is characterized by pancreatic dysfunction, sideroblastic anemia, neutropenia and thrombocytopenia⁴³. The mitochondrial DNA deletion is identical in Kearns-Sayre syndrome and Pearson Marrow-pancreas syndrome. They have different ages of disease onset, with Pearson Marrow-pancreas syndrome presenting in infancy, while Kearns-Sayre syndrome presents later. Pearson Marrow-pancreas syndrome frequently evolves into KearnsSayre syndrome. It is not uncommon to have hypoparathyroidism, with variable age of onset.

Other mitochondrial disorders associated with hypoparathyroidism include mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) due to point mutations in mitochondrial tRNA⁴⁴; long-chain 3-hydroxyacyl-CoA dehydrogenase (LCAHD) or combined mitochondrial trifunctional protein (MTP) deficiency due to mutations in MTP^{45, 46, 47}; medium-chain acyl-CoA dehydrogenase deficiency (MCADD) due to mutations in the *ACADM* gene⁴⁸. The mechanism by which these mitochondrial defects affect parathyroid gland development or function is unknown.

Disorders of parathyroid hormone synthesis or secretion

***PTH* gene mutation**

Isolated hypoparathyroidism can result from mutations in the *PTH* gene located on Chromosome 11p15.3-p15.1 that impair synthesis of PTH. The *PTH* gene contains 3 exons which encode the 115-amino acid preproPTH protein. Two proteolytic cleavages are required to produce the biologically active 84-amino acid PTH molecule. The first cleavage occurs cotranslationally in the endoplasmic reticulum (ER) by the signalase enzyme, which removes the amino-terminal 25-amino-acid signal or pre-peptide that directs the nascent preproPTH protein into the ER. The 6-amino-acid pro-peptide is subsequently removed by proprotein convertases, after trafficking to the Golgi apparatus, to generate the mature 84-amino-acid PTH polypeptide. In a few instances, autosomal dominant isolated hypoparathyroidism has been associated with heterozygous mutations in the *PTH* gene. In

two families, PTH gene missense mutations were identified in exon 2, either p.C18R^{49, 50} or p.M14K⁵¹, that replace key amino acids in the hydrophobic core of the leader sequence. The mutations prevent normal removal of the leader sequence and impair translocation of the abnormal protein across the ER. The dominant negative mechanism is thought to be induction of an ER stress response that leads to apoptosis of the parathyroid cells^{52, 51}. In another hypoparathyroid patient, a heterozygous initiator codon mutation (M1T) was identified, predicting abnormal initiation of translation of the preproPTH mRNA at the +7 Met codon, thereby producing an n-terminally truncated protein with an abnormal leader sequence⁵³.

Autosomal recessive forms of familial isolated hypoparathyroidism due to *PTH* gene mutations have also been described. Remarkably, in most cases these mutations also affect the leader sequence of the preproPTH molecule. In two instances, different mutations at codon 23 (p.S23P and p.S23X)^{54, 55} predict generation of a non-secreted PTH molecule due to a defective or truncated leader sequence. In a third case, a donor splice site mutation at the exon 2–intron 2 junction of the *PTH* gene leads to exon skipping, with loss of the initiator methionine and the signal sequence encoded by exon 2^{56, 54}. And in a most exceptional case, a bioinactive form of PTH was produced by an arginine-to-cysteine substitution at position 25 of the mature PTH(1–84) polypeptide that impairs recognition of the PTH molecule in some assays for intact PTH⁵⁷.

Autosomal Dominant hypocalcemia type 1 and type 2 – mutations in *CASR* (ADH1) and *GNA11* (ADH2)

Gain of function mutations in the genes encoding the calcium-sensing receptor (*CASR*)^{58, 59}, or the alpha subunit of the G protein, Gα11 (*GNA11*)^{60, 61, 62}, that couples the *CASR* to activation of intracellular signaling pathways in the parathyroid cell, result in autosomal dominant hypocalcemic types 1 (ADH1) and 2 (ADH2), respectively⁶³.

In ADH1 heterozygous mutations in the *CASR* increase the sensitivity of the calcium sensing receptor to extracellular ionized calcium. Consequently, PTH synthesis and secretion are suppressed at normal ionized calcium concentrations. Patients present with hypocalcemia, hyperphosphatemia, low magnesium levels, and low or low-normal levels of PTH. There is a wide range of clinical presentation, ranging from seizures in infancy to asymptomatic mild hypocalcemia in adulthood. Urinary calcium is usually elevated, as renal excretion of calcium is increased due to both the decrease in circulating PTH concentrations and the activation of calcium-sensing receptor in the distal renal tubule. Most activating mutations in the *CASR* gene on Chromosome 3q13.3-q21.1 are familial^{58, 64, 59, 65, 66, 67}, but there have been a few sporadic cases due to *de novo* mutations^{64, 68}.

Increased sensitivity of the parathyroid cell to extracellular ionized calcium has also been proposed as the mechanism for hypoparathyroidism in patients with ADH2, but in this disorder the enhanced sensitivity to calcium is due to a gain-of-function in Gα11, which couples the calcium-sensing receptor to intracellular signal generators such as phospholipase C⁶⁹. Patients with ADH2 do not appear to have increased fractional excretion of calcium by the kidney⁶¹, presumably because Gα11 is not the key transmembrane coupling protein for the calcium-sensing receptor in the distal renal tubule. By contrast, patients with ADH2 have

short stature⁶¹, which may be a consequence of activated Gα11 signaling in the growth plates of long bones. Somatic missense mutations in *GNA11* are considered proto-oncogenic and have been identified in some blue nevi, primary uveal melanomas and uveal melanoma metastases⁷⁰. However, *GNA11* mutations in ADH2 are less activating than oncogenic *GNA11* mutations⁶¹. These familial activating mutations in the *GNA11* gene occur at Chromosome 19p13.

As opposed to these gain-of-function mutations, mutations that inactivate the *CASR* and *GNA11* genes reduce sensitivity of parathyroid cells to extracellular ionized calcium and are associated with the contrasting endocrine disorder Familial Hypocalciuric Hypercalcemia^{71, 60}. All *CASR* mutations, as well as polymorphisms, are cataloged in a calcium-sensing receptor online database⁷², which is regularly updated and provides a highly useful resource.

Knowledge of the shared pathophysiology of hypoparathyroidism (i.e. increased sensitivity to extracellular ionized calcium) in these two disorders, ADH1 and ADH2, has led to the development of calciolytic agents that reduce calcium sensitivity of the calcium-sensing receptor and which can reduce PTH secretion in animal models. To date, there has been one phase 2 study in adults with ADH treated with a calcium-sensing receptor antagonist ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02204579) Identifier: NCT02204579). Novel treatment therapies will be covered in greater detail in Gaia Tabacco and John P. Bilezikian's article "New Directions in Treatment of Hypoparathyroidism," in this issue.

Disorders of parathyroid gland destruction

Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) - *AIRE*

Autoimmune destruction of the parathyroids occurs most commonly in association with autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), also known as Autoimmune Polyglandular Syndrome type 1 (APS1). The classic triad consists of mucocutaneous candidiasis, hypoparathyroidism and adrenal insufficiency, and these features typically manifest in a corresponding chronological order. There are many additional autoimmune features that may develop, including additional endocrinopathies such as ovarian failure, hypothyroidism, insulin dependent diabetes and hypophysitis. Non-endocrine manifestations include hepatitis, malabsorption, pernicious anemia, vitiligo, alopecia, nail and dental dystrophy⁷³. There is wide variability in the clinical expression, with no significant correlation between genotype and phenotype⁷⁴. This is exemplified by significant intrafamilial differences between siblings carrying the same mutation.

More than 100 different mutations of the autoimmune regulator (*AIRE*) gene⁷⁵ have been identified in patients with APECED⁷⁶. *AIRE* encodes a transcription factor that functions as an important regulator in thymic epithelial cells. *AIRE* induces expression of important "self" identity proteins and T cells that respond to those proteins are eliminated in the thymus through apoptosis, thereby avoiding autoimmune disorders^{77, 78}. It is typically an autosomal recessive disorder caused by various different mutations in the *AIRE* gene, on Chromosome 21q22.3^{79, 80}. It is most prevalent in Finns (prevalence 1/25,000)^{79, 81}, Sardinians (1/14,400)⁸¹ and Iranian Jews (1/6,500 to 1/9000)⁸², suggesting significant

founder effects⁸³. It is less commonly caused by autosomal dominant inheritance⁸⁴ and sporadic *de novo* mutations⁸⁵. Interestingly, biallelic mutations in *AIRE* can cause isolated hypoparathyroidism, without additional clinical features of APECED⁸⁶.

Summary

Hypoparathyroidism consists of a heterogeneous group of disorders, with a broad phenotypic spectrum, that presents across the lifespan. Although genetic disorders are not a common cause of hypoparathyroidism, accurate diagnosis of the underlying genetic etiology is essential, affecting treatment goals, screening for comorbidities and family planning. Research has brought us closer to understanding the molecular mechanisms underlying the development of the parathyroid glands, disordered synthesis and secretion of PTH and postnatal destruction of the parathyroid glands. However, further research is needed to elucidate the exact function of several genes that are known to result in hypoparathyroidism.

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Key points:

- Hypoparathyroidism can be an isolated endocrine disorder or part of a complex syndrome.
- Genetic defects account for disorders of parathyroid gland formation, dysregulation of parathyroid hormone synthesis or secretion, and autoimmune destruction of the parathyroid glands.
- Genetic hypoparathyroidism may be sporadic or exhibit autosomal dominant, autosomal recessive, or X-linked recessive inheritance.

Patient 1

Patient 2

Figure 1- DiGeorge Sequence

Patient 1: Relatively non-dysmorphic 1 year old male with DiGeorge Sequence. Note, bitemporal narrowing, malar flatness, squared helices with a prominent antitragus, attached lobes, a prominent blue tinged vessel over the nasal root, bulbous nasal tip with hypoplastic alae nasi, small mouth and mild micrognathia. Patient 2: 19-year-old male with DiGeorge Sequence. Note, malar flatness, mild upslanting palpebral fissures, unilateral helical protuberance, attached lobes, a broad nasal root and bulbous tip with hypoplastic alae nasi.

Table 1-

Genetic Disorders Associated with Hypoparathyroidism

Disease	Inheritance	Gene	Locus	OMIM	Prevalence (if know Associated comorbidities)
Disorders of parathyroid gland formation					
Isolated parathyroid aplasia	AR or AD XR	<i>GCM2</i> <i>SOX3</i>	6p23–24 Xq26–27	*603716 *307700	
DiGeorge Syndrome DiGeorge Syndrome type 1 DiGeorge Syndrome type 2	sporadic or AD sporadic or AD	<i>TBX1</i> <i>NEBL</i>	22q11.21-q11.23 10p13	#188400 %601362	1:4,000 – 1:7,692 thymic hypoplasia with immune deficiency, conotruncal cardiac defects, cleft palate, dysmorphic facies
Charge Syndrome	sporadic or AD	<i>CHD7</i> <i>SEMA3E</i>	8q12.2 7q21.11	#214800 #214800	1:8,500 Cardiac anomalies, cleft palate, renal anomalies, ear abnormalities/deafness and developmental delay
Hypoparathyroidism, deafness and renal dysplasia	AD	<i>GATA3</i>	10p14–15	#146255	Deafness and renal dysplasia
Hypoparathyroidism, retardation and dysmorphism	AR	<i>TBCE</i>	1q42–43	#241410	growth retardation, developmental delay, dysmorphic facies
Kenny-Caffey syndrome type 1 Kenny-Caffey syndrome type 2	AR AD	<i>TBCE</i> <i>FAM111A</i>	1q42–43 11q12.1	#244460 #127000	1:40,000 – 1:100,000 in Saudi Arabia short stature, medullary stenosis, dysmorphic facies, developmental delay similar to type 1, but clinically distinguished by the absence of mental retardation
Mitochondrial disease Kearns-Sayre syndrome	maternal		mtDNA	#530000	encephalomyopathy, ophthalmoplegia, retinitis pigmentosa and heart block
Pearson Marrow-Pancreas syndrome			mtDNA	#557000	pancreatic dysfunction, sideroblastic anemia, neutropenia and thrombocytopenia
MELAS			mt tRNA	#540000	mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes
LCAHD		<i>MTP</i>	2p23.3	#609016	

Disease	Inheritance	Gene	Locus	OMIM	Prevalence (if know Associated comorbidities)
Disorders of parathyroid gland formation					
MCADD		<i>ACADM</i>	1p31.1	#201450	1:17,000
Disorders of parathyroid hormone synthesis or secretion					
PTH gene mutations	AD or AR	<i>PTH</i>	11p15.3-p15.1	*168450	
AD hypocalcemia type 1	AD or sporadi	<i>CASR</i>	3q13.3-q21.1	#601198	hypercalciuria
AD hypocalcemia type 2	AD or sporadic	<i>GNA11</i>	19p13.3	#615361	
Disorders of parathyroid gland destruction					
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy	AR, AD or sporadic	<i>AIRE</i>	21q22.3	#240300	1:90,000 – 1:200,000 mucocutaneous candidiasis and adrenal insufficiency

OMIM, Online Mendelian Inheritance in Man; AR, autosomal recessive; AD, autosomal dominant; XR, X-linked recessive; mtDNA, mitochondrial DNA; mt tRNA, mitochondrial tRNA