Clinical features:
Hypoparathyroidism is a rare condition in which the body secretes abnormally low levels of parathyroid hormone (PTH). PTH is responsible for regulation and maintenance of calcium and phosphorus in the body. The predominant clinical features of hypoparathyroidism are related to hypocalcemia. Acute episodes of hypocalcemia can lead to neuromuscular irritability, tingling and numbness of the mouth and extremities, muscle spasms and seizures. Individuals with chronic hypocalcemia may be asymptomatic. Other manifestations of hypoparathyroidism and hypocalcemia are premature cataracts, calcifications of the basal ganglia, impaired cardiac function, mental retardation and/or personality disorders. The most common cause of hypoparathyroidism is surgical resection or autoimmune destruction of the parathyroid. Iron overload of the parathyroid glands in patients with thalassaemia is another common cause of decreased parathyroid function. In rare cases, hypoparathyroidism is caused by an underlying genetic disorder. Identification of the etiology of hypoparathyroidism can aid in guiding clinical management of affected patients.

Our Hypoparathyroidism Sequencing and Deletion/Duplication Panels include analysis of all 17 genes listed below.

<table>
<thead>
<tr>
<th>Genes and Associated Disorder</th>
<th>Inheritance</th>
<th>Clinical Features/Molecular Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIRE [OMIM#607358]</td>
<td>AD/AR</td>
<td>Mutations in AIRE result in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). The most common features of APECED are chronic mucocutaneous candidiasis (CMC), hypoparathyroidism, and adrenal insufficiency. While most cases of APECED are caused by biallelic mutations in the AIRE gene, autosomal dominant inheritance has been reported (3).</td>
</tr>
<tr>
<td>Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) [OMIM#240300]</td>
<td>AD/AR</td>
<td></td>
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<tr>
<td>CASR [OMIM#601199]</td>
<td>AD</td>
<td>CASR is a plasma membrane receptor expressed in the parathyroid hormone-producing cells of the parathyroid gland, and the cells lining the kidney tubule. It is essential in regulation of mineral ion homeostasis. Heterozygous mutations in CASR can cause an autosomal dominant form of hypocalcemia with or without Bartter syndrome (4).</td>
</tr>
<tr>
<td>Hypocalcemia with or without Bartter syndrome [OMIM#601198]</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>CHD7 [OMIM#608892]</td>
<td>AD</td>
<td>Heterozygous mutations in CHD7 are associated with CHARGE syndrome, a condition characterized by a pattern of congenital anomalies including choanal atresia, malformations of the heart, inner ear, and retina. There are several reports of patients with CHARGE syndrome who are also affected with DiGeorge sequence, including hypoparathyroidism (5, 6).</td>
</tr>
<tr>
<td>CHARGE syndrome [OMIM#214800]</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>CYP24A1 [OMIM#126065]</td>
<td>AR</td>
<td>The CYP24A1 enzyme is responsible for the inactivation of vitamin D derivative 1,25-dihydroxyvitamin D₃, and controlled by levels of 1,25-dihydroxyvitamin D, serum calcium, and parathyroid hormone. Biallelic mutations in CYP24A1 are associated with idiopathic infantile onset hypercalcemia, which is characterized by severe hypercalcemia, failure to thrive, vomiting, dehydration and nephrocalcinosis. Laboratory evaluation of a cohort of infants presenting with these symptoms showed suppression of parathyroid hormone levels (7).</td>
</tr>
<tr>
<td>Infantile hypercalcemia-1 [OMIM#143880]</td>
<td>AR</td>
<td></td>
</tr>
<tr>
<td>Gene/Condition</td>
<td>Type</td>
<td>Description</td>
</tr>
<tr>
<td>---------------</td>
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</tr>
<tr>
<td>FAM111A [OMIM#615292]</td>
<td>AD</td>
<td>Kenny-Caffey syndrome and gracile bone dysplasia are allelic autosomal dominant disorders causing abnormalities of skeletal development, hypoparathyroidism and hypocalcemia. Gracile bone dysplasia is typically perinatal lethal, and is characterized by gracile bones with thin diaphysis, premature closure of the basal cranial sutures, and microphthalmia. Kenny-Caffey syndrome is less severe, and is characterized by delayed closure of the fontanelles, abnormal dentition, eye abnormalities and transient hypocalcemia. In a study by Unger, et al, 5 patients with Kenny-Caffey syndrome and 5 patients with gracile bone dysplasia were identified as heterozygous for 6 mutations in the FAM111A. For all families where parents were available, these mutations were confirmed to be de novo (8).</td>
</tr>
<tr>
<td>GATA3 [OMIM#131320]</td>
<td>AD</td>
<td>Haploinsufficiency of the GATA3 gene leads to hypoparathyroidism, sensorineural deafness and renal dysplasia (also known as HDR syndrome). In a study by Ali et al, 13 different mutations in GATA3 were identified in 13 out of 21 probands with HDR syndrome. No mutations were identified in patients with isolated hypoparathyroidism, indicating that GATA3 mutations are more likely to result in two or more phenotypic features of HDR syndrome (9).</td>
</tr>
<tr>
<td>GCM2 [OMIM#603716]</td>
<td>AD/AR</td>
<td>Isolated hypoparathyroidism can be caused by mutations in the parathyroid hormone gene (PTH) or in GCM2. While most cases of familial isolated hypoparathyroidism have been autosomal dominant in inheritance, there have been reports of autosomal recessive inheritance (10, 11).</td>
</tr>
<tr>
<td>GNAS [OMIM#139320]</td>
<td>AD</td>
<td>Heterozygous mutations in GNA11 have been identified in 5 different families with autosomal dominant hypocalcemia(12-14). In families where multiple generations were affected, these mutations segregated with disease. Nesbit, et al reported one in-frame deletion and one missense GNA11 mutation in two unrelated families with hypocalciuric hyperparathyroidism. These patients were known to be negative for mutations in CASR and AP2S1 (14).</td>
</tr>
<tr>
<td>STX16 [OMIM#603666]</td>
<td>AD</td>
<td>Pseudohypoparathyroidism (PHP) is a term that defines of group of disorders which all feature parathyroid hormone resistance. Individuals with PHP type IA, caused by maternal loss-of function mutations in GNAS, are also resistant to thyroid stimulating hormone (TSH) and gonadotropins. The GNAS gene displays tissue-specific differential expression depending on the parent of origin. Only the maternal copy of GNAS is expressed in renal tubular cells. Therefore, inactivation of the maternal allele results in no expression in these cell lines, resulting in disease. This type of PHP is also associated with Albright hereditary osteodystrophy, which is defined by skeletal abnormalities such as short stature, subcutaneous ossifications and brachydactyly. PHP type IB is also caused by maternal mutations in the differentially methylated region of GNAS, and results in a PHP phenotype without the skeletal abnormalities seen in type IA. PHP1B can also be caused by deletions in the STX16 gene, a control element of methylation of GNAS. PHP type IC is similar to type IA in cause and phenotype, with the exception of retained Gs activity in erythrocytes. Pseudopseudohypoparathyroidism (PPHP) is caused by loss-of function mutations on the paternal allele of the GNAS gene. Individuals with PPHP do not show hormone resistance, but do have clinical features consistent with a diagnosis of Albright hereditary osteodystrophy, as seen in PHP type IA(15).</td>
</tr>
</tbody>
</table>

**Pseudohypoparathyroidism, types IA [OMIM#103580], IB [OMIM#603233], IC [OMIM#612462], Pseudopseudohypoparathyroidism [OMIM#612463]**

**HADHA [OMIM#600890] HADHB [OMIM#143450]**

Mitochondrial trifunctional protein deficiency with myopathy and neuropathy [OMIM#609015]
onset skeletal myopathy. In vitro studies have indicated a genotype-
phenotype correlation, with mutations resulting in no residual protein
activity causing a more severe phenotype than those associated with
residual activity (16).

| PRKAR1A [OMIM#188830] | AD | Heterozygous mutations in PRKAR1A are associated with
acrodysostosis-1, with or without hormone resistance. This form of
skeletal dysplasia is characterized by short stature, severe
brachydactyly, facial dysostosis and nasal hypoplasia. Hormone
resistance, including PTH, is reported in a subset of affected
individuals. Acroradysostosis type 2 is caused by heterozygous mutations
in PDE4D, and is similar in phenotype to acrodysostosis type 1. Many
patients with type 2 acrodysostosis have intellectual disability and,
similar to type 1, some patients are affected with hormone resistance
(17). |
| PDE4D [OMIM#600129] |   |   |

| PRKAR1A [OMIM#188830] | AD | Heterozygous mutations in PRKAR1A are associated with
acrodysostosis-1, with or without hormone resistance. This form of
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in PDE4D, and is similar in phenotype to acrodysostosis type 1. Many
patients with type 2 acrodysostosis have intellectual disability and,
similar to type 1, some patients are affected with hormone resistance
(17). |
| PDE4D [OMIM#600129] |   |   |

| TBCE [OMIM#604934] | AR | Biallic mutations in TBCE can result in hypoparathyroidism-retardation-
dysmorphism syndrome (HRDS). This condition is characterized by
congenital hypoparathyroidism, mental retardation, facial dysmorphism
and growth failure. This condition typically affects individuals from
Middle Eastern populations, and is often caused by a known founder
mutation in the TBCE gene. Kenny-Caffey syndrome is similar in
phenotype to HRDS, but also includes the presence of osteosclerosis
and recurrent infections (18). |

| Hypoparathyroidism-retardation-
dysmorphism syndrome [OMIM#241410] |   |   |
| Kenny-Caffey syndrome, type 1 [OMIM#244460] |   |   |

| TBX1 [OMIM#602054] | AD | TBX1 is considered to be the key gene responsible for many of the
features of 22q11.2 deletion syndrome, or DiGeorge syndrome. While
this condition is most often caused by a recurrent microdeletion at the
22q11.2 locus, mutations in TBX1 have been identified in patients with
the characteristic features of DiGeorge syndrome and no identifiable
deletion. DiGeorge syndrome is associated with heart defects, cleft
palate, distinctive facial features, hearing loss, and hypocalcemia
caued by parathyroid and thymic hypoplasia (19). |

| DiGeorge syndrome [OMIM#188400] |   |   |

**Test methods:**
Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is
performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect
system. Sequencing is performed using illumina technology and reads are aligned to the reference
sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and
comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely
pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be
>99% for single nucleotide changes and insertions and deletions of less than 20 bp. Deletion/duplication analysis
of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and
rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level
mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical
phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy
number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not
detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for
the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside
laboratory.

**Hypoparathyroidism Sequencing Panel (sequence analysis of 17 genes)**

| Sample specifications: | 3 to 10 cc of blood in a purple top (EDTA) tube |
| Cost: | $2500 |
| CPT codes: | 81407 |
| Turn-around time: | 4 weeks |

**Note:** We cannot bill insurance for the above test.
Hypoparathyroidism Deletion/Duplication Panel (deletion/duplication analysis of 20 genes)

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $2500
CPT codes: 81407
Turn-around time: 4 weeks

Results:
Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References: