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Short communication

# Idiopathic Hypoparathyroidism: New Insights into an Enigma

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**Abstract**

Calcium is a very important electrolyte - necessary for neurotransmission, cell signaling, and bone development. Hence, blood calcium levels are to be kept in a safe normal range. The parathyroid hormone has an important role in calcium metabolism at the level of the bone, kidney, or GI tract. Hypoparathyroidism is a condition of reduced formation of parathyroid hormone.

**Key words:** hypocalcemia; hyperphosphatemia; hypoparathyroidism; idiopathic; GCM2

## Introduction

Calcium is a very important electrolyte - necessary for neurotransmission, cell signaling, and bone development. Hence, blood calcium levels are to be kept in a safe normal range. The parathyroid hormone has an important role in calcium metabolism at the level of the bone, kidney, or GI tract [1]. Hypoparathyroidism is a condition of reduced formation of parathyroid hormone. It may lead to hypocalcemia, low calcitriol, and hyperphosphatemia.

Idiopathic hypoparathyroidism (IHP) is an uncommon endocrine disease, with highly variable clinical manifestations. Its incidence ranges from 0.55 to 0.88/ 100,000 in Asian populations [2]. It can occur as an isolated disease or as part of many syndromes. The etiology is labelled as idiopathic if no cause is found after excluding all possible etiologies. Idiopathic hypoparathyroidism may have a hidden genetic etiology [3]. Molecular genetic analyses over the past few decades have recognized mutations in many genes which have given us new insights into embryological development of the parathyroid glands, regulation of parathyroid hormone (PTH) synthesis and secretion, and maintenance of parathyroid gland homeostasis [4]. The quality of life (QoL) is affected in patients causing a reduced sense of well-being. But there is no conclusive evidence regarding increased mortality in patients having hypoparathyroidism [5].

Due to highly nonspecific and varied manifestations, idiopathic hypoparathyroidism often has a long lag period of diagnosis and increased risk of misdiagnosis. A serum calcium profile in patients with trivial issues like paresthesia may avoid the lengthy delay as well as misdiagnosis of patients having idiopathic hypoparathyroidism [6].

Autoantibodies against cytoplasmic parathyroid tissue may be found in up to 30–70% of patients having IHP. Treatment target is to restore calcium levels. To prevent hypocalcaemia, patients of hypoparathyroidism require lifelong calcium supplementations and calcitriol to stimulate absorption of calcium and phosphate in the gut. A diet containing high-calcium and low phosphorus is recommended.

In a previous report of two cases, we have established the critical role of GCM2 activity in human parathyroid gland development through clinical and genetic analysis of 2 patients with hypoparathyroidism. These conclusions have more immediate relevance for the diagnosis and treatment of cases having isolated hypoparathyroidism [7].

At our institution we have experience of a small but significant number of patients with IHP. Similar reports have been available from other Endocrine departments as well. Hence, with the availability of diagnostic tools like NGS being more common place, we can arrive at a definitive genetic diagnosis; proving useful in prognosticating the disease severity & requirement of therapy. In inherited cases genetic counseling of patients can also be done.

Genetic Disorders Associated with Hypoparathyroidism

| Disease | Inheritance | Gene | Locus | Prevalence | Comorbidities |
|---|---|---|---|---|---|
| **A. Disorders of parathyroid gland formation** | | | | | |
| Isolated parathyroid aplasia | AR or ADXR | GCM2<br>SOX3 | 6p23–24Xq26–27 | | |
| DiGeorge Syndrome type 1<br>DiGeorge Syndrome type 2 | Sporadic or AD<br>Sporadic or AD | TBX1<br>NEBL | 22q11.21-q11.2310p13 | 1:4,000-1:7,692 | Thymic hypoplasia with immune deficiency, conotruncal cardiac defects, cleft palate, dysmorphic facies |
| Charge Syndrome | Sporadic or AD | CHD7<br>SEMA3E | 8q12.27q21.11 | 1:8,500 | Cardiac anomalies, cleft palate, renal anomalies, ear abnormalities/ Deafness and developmental delay |
| Hypoparathyroi-dism, deafness, and renal dysplasia | AD | GATA3 | 10p14–15 | | Deafness and renal dysplasia |
| Hypoparathyroidism, retardation and dysmorphism | AR | TBCE | 1q42–43 | | Growth retardation, developmental delay, dysmorphic facies |
| Kenny-Caffey syndrome type 1<br>Kenny-Caffey syndrome type 2 | AR<br>AD | TBCE<br>FAM111A | 1q42-4311q12.1 | 1:40,000 - 1:100,000 in Saudi Arabia | Short stature, medullary stenosis, dysmorphic facies, developmental delay<br>Similar to type 1, but clinically distinguished by the absence of mental retardation |
| Mitochondrial disease Kearns-Sayre syndrome | Maternal | Mt DNA | | | Encephalomyopathy, ophthalmoplegia, retinitis pigmentosa and heart block |
| Pearson Marrow Pancreas syndrome | | Mt DNA | | | Pancreatic dysfunction, sideroblastic anemia, neutropenia, and thrombocytopenia |
| MELAS | | Mt tRNA | | | Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes |
| LCAHD | | MTP | 2p23.3 | | Impaired vision, night blindness, rhabdomyolysis, cardiomyopathy |
| **B. Disorders of parathyroid gland formation** | | | | | |
| MCADD | | ACADM | 1p31.1 | 1:17,000 | Fasting hypoglycemia, encephalopathy, hepatic dysfunction |
| **C. Disorders of parathyroid hormone synthesis or secretion** | | | | | |
| PTH gene mutations | AD or AR | PTH | 11p15.3-p15.1 | | |
| AD hypocalcemia type 1 | AD or sporadic | CASR | 3q13.3-q21.1 | | Hypercalciuria |
| AD hypocalcemia type 2 | AD or sporadic | GNA11 | 19p13.3 | | |
| D. **Disorders of parathyroid gland destruction** | | | | | |
| Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy | AR, AD or sporadic | AIRE | 21q22.3 | 1:90,000 – 1:200,000 | Mucocutaneous candidiasis, Adrenal insufficiency, and Primary hypoparathyroidism |

## Abbreviations

GI- Gastrointestinal

QOL- Quality of Life

IHP- Idiopathic Hypoparathyroidism

PTH- Parathyroid Hormone

NGS- Next Generation Sequencing

GCM2- Glial cell missing homolog 2

Mt DNA- Mitochondrial DNA

MELAS- Mitochondrial Encephalomyopathy, Lactic acidosis, Stroke-like Episodes

ACADM- Acyl CoA dehydrogenase medium chain

LCAHD- Long Chain Hydroxy-acyl CoA Dehydrogenase

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