Genetic and epigenetic alterations of GNAS locus and clinical consequences in Pseudohypoparathyroidism: a new health care pathway

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Background

Genetic and epigenetic alterations at the GNAS locus are responsible for the Gsα protein dysfunctions causing Pseudohypoparathyroidism (PHP), a heterogeneous disease characterized by multiple hormone resistances and AHO signs (short stature, obesity, round face, brachydactyly, subcutaneous ossifications and mental retardation). A clinical overlap among molecular subtypes of the disease (Ia, Ib, Ic and II) makes the current classification inadequate; furthermore a common clinical approach still needs to be defined.

- Lack of knowledge about some clinical features and their evolution
- No common standards in clinical management
- New Classification required

Aims and Objective

In the largest Italian case series of (epi)genetically characterized PHP patients, this work attempts to review and update the clinical data, correlating them to the molecular diagnosis, and to develop a healthcare pathway for patients with AHO/PHP.

Cooperating Network of ISPED Centers - Study Group Endocrine diseases due to altered function of Gsα protein

Review of clinical data of patients with confirmed molecular diagnosis
Collection of new follow-up data

Develop and share a new health care pathway

Common clinical approach to DIAGNOSIS, THERAPY and FOLLOW-UP

Materials and Methods

- GNAS gene sequencing
- CMOS locus methylation analysis and 27K methylation analysis
- Mutations in other exons
- Risk Factors
- Clinical Manifestations
- Multiple Hormones/Endocrine Laboratory Tests
- Clinical Evaluation

Results

AUXOLOGICAL EVALUATION

Clinical Features - Overview

HORMONE RESISTANCES

Mutation prevalence among pts with SO

Cognitive Areas involved in MR

Conclusions

A dedicated healthcare pathway addressing all the PHP’s aspects in a systematic way would improve the management of the disease, allowing an earlier diagnosis of hormonal resistances, which is fundamental to optimize the medical treatment (i.e. rGH therapy). On the other hand, the different prevalence and features of some AHO signs need to be confirmed by follow-up data, leading thus to a better clinical-oriented molecular analysis.

The authors have nothing to disclose

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Objectives

- 74 patients with confirmed molecular diagnosis from 69 unrelated families
- 46 GNAS gene mutations
- 28 GNAS locus altered methylation