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

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Develop and share a ***new health care pathway***

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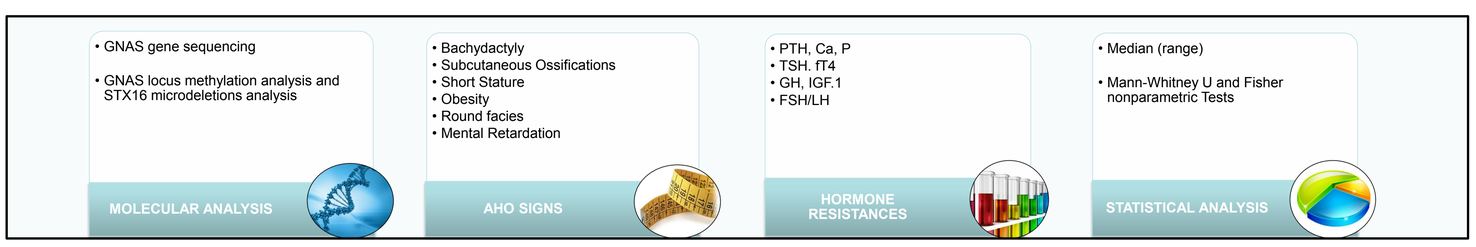
Common clinical approach to DIAGNOSIS, THERAPY and FOLLOW-UP

Materials and Methods

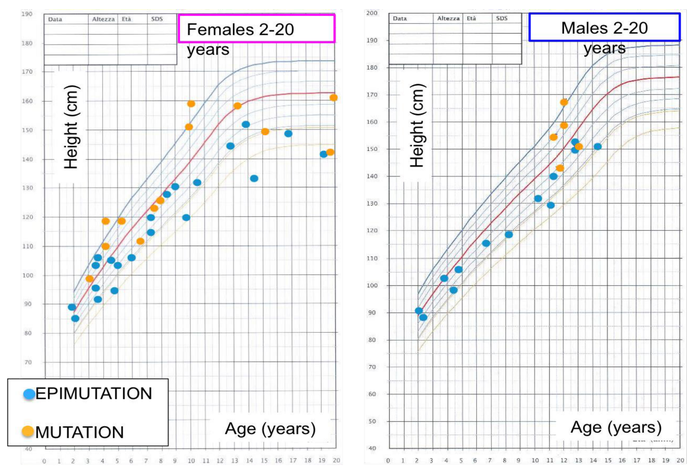


74 patients with **confirmed molecular diagnosis** from 69 unrelated families

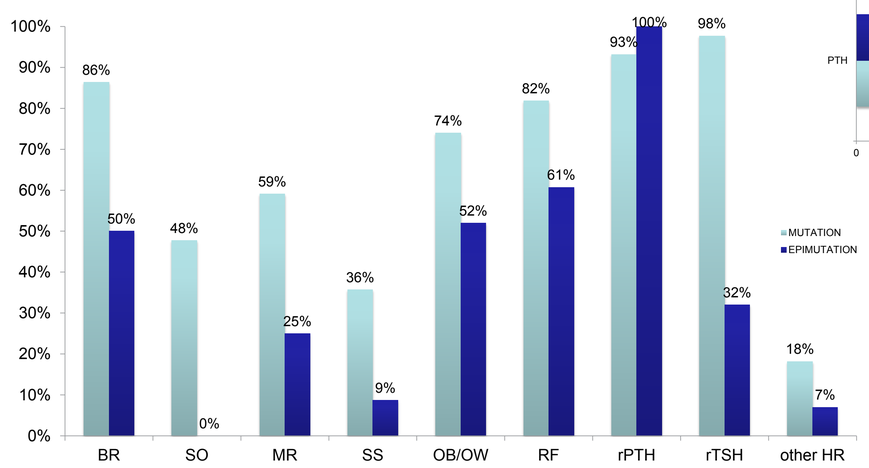
- **46** GNAS ***gene*** mutations
- **28** GNAS ***locus*** altered methylation

Results

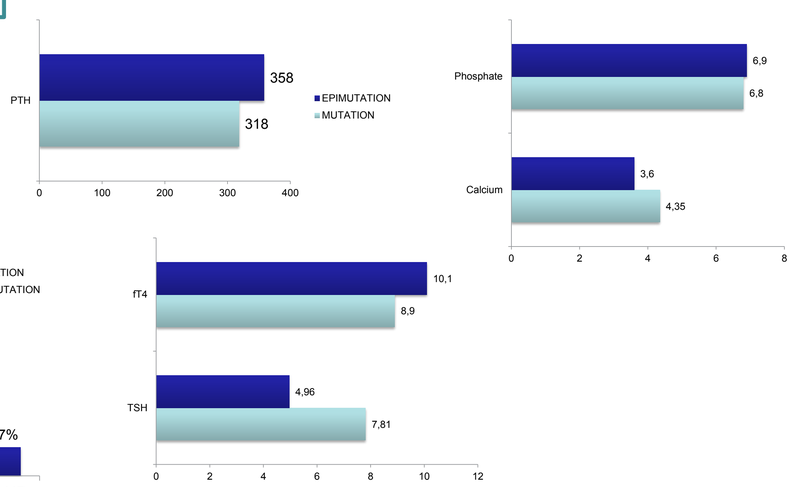
AUXOLOGICAL EVALUATION

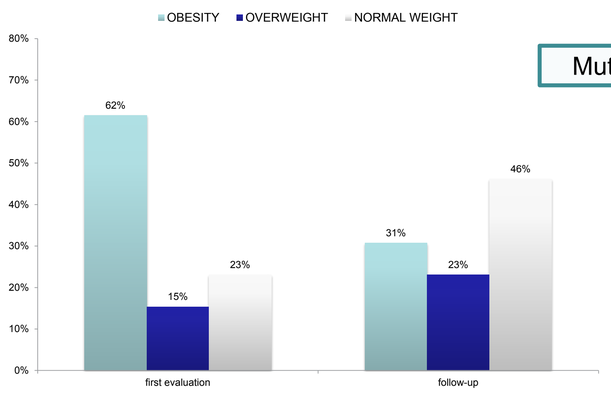


Clinical Features - Overview

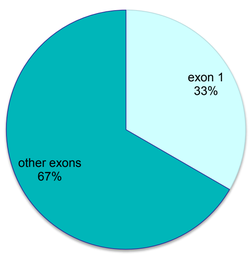


HORMONE RESISTANCES

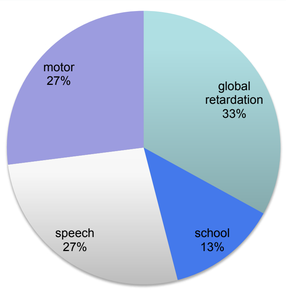




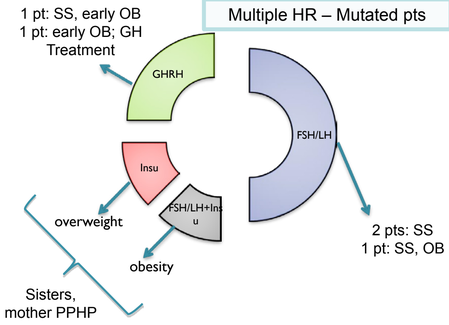
Mutation prevalence among pts with SO



Cognitive Areas involved in MR



Multiple HR – Mutated pts



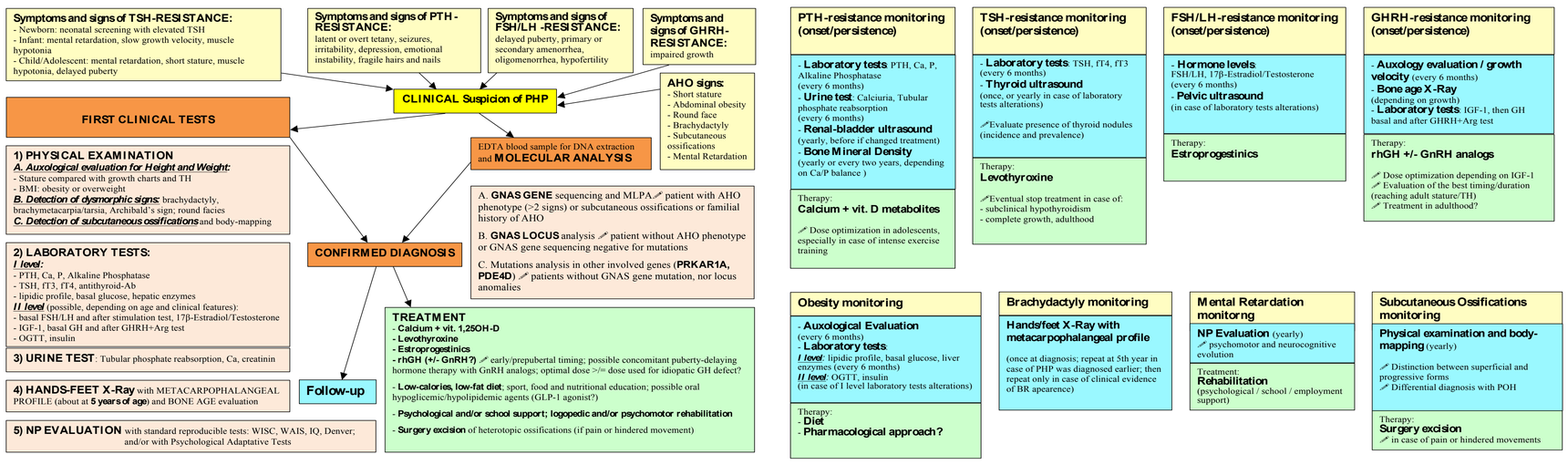
Multiple HR – Epimutated pts

XY, 33yrs, AHO: BR, OB/OW, RF → GH defect in adulthood, under rGH treatment.

XX, 65yrs, AHO: BR, OB, RF → History of hypofertility: possible FSH/LH resistance

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

ESPE 2015 210-P2

Bone, Growth Plate and Mineral Metabolism

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DOI: 10.3252/pso.eu.54espe.2015

Poster presented at: 54th Annual Meeting 7-9 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology

PosterSessionOnline.com