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PARATHYROID GLAND

GNAS defects in a large PHP cohort

New research collating data on pseudohypoparathyroidism (PHP) from patients across Europe has characterized the prevalence of different genetic and epigenetic causes of this rare condition, which will aid the diagnosis and management of this disease.

PHP results from the resistance of organs to parathyroid hormone (PTH) and leads to a decrease in serum levels of calcium, an increase in serum levels of phosphate and elevated levels of PTH. The most frequent subtype of the condition, PHP1, is primarily linked to diminished expression or activity of guanine nucleotide-binding protein G(s) subunit α, encoded by *GNAS*. Patients can be classified as having PHP1A (which has features of Albright hereditary osteodystrophy (AHO), such as short stature, rounded face and shortened fingers) or PHP1B (which lacks the AHO presentation).

To quantify the prevalence of different genetic and epigenetic lesions in *GNAS* that result in PHP, investigators in the EuroPHP network used data from 407 patients with PHP who had defects in *GNAS*. Of these individuals, 48% had PHP1A and 46% had PHP1B. The remaining 6% of patients presented with rarer disease subtypes.

The team found that 41% of patients carried *GNAS* point mutations, 2% had structural rearrangement involving *GNAS* and 14% had a loss of methylation at an isolated differentially methylated region in *GNAS*. Furthermore, 38% of patients had methylation defects at all differentially methylated regions in *GNAS*. Importantly, the frequency of these lesions differed substantially between PHP subtypes.

"Our findings underline the pressing need for a novel classification of PHP owing to the major overlap between clinical and molecular forms and the risk of diagnostic errors," comments author Guiomar Perez de Nanclares.

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ORIGINAL ARTICLE Elli, F. M. *et al.* The prevalence of *GNAS* deficiency-related diseases in a large cohort of patients characterized by the EuroPHP network. *J. Clin. Endocrinol. Metab.* http://dx.doi.org/10.1210/jc.2015-4310 (2016)

FURTHER READING Mantovani, G. *et al.* Pseudohypoparathyroidism and $G_s\alpha$–cAMP-linked disorders: current view and open issues. *Nat. Rev. Endocrinol.* http://dx.doi.org/10.1038/nrendo.2016.52 (2016)