

# Paternal isodisomy is a frequent cause of sporadic pseudohypoparathyroidism Ib

C. Colson, N. Richard, N. Gruchy, M. Decamp, ML. Kottler

kottler-ml@chu-caen.fr

Department of Genetic, University Hospital Caen, France; Reference center for rare diseases of phospho-calcium metabolism. Caen Basse Normandie University

Pseudohypoparathyroidism type Ib (PHP-Ib) is an imprinting disorder characterized by the presence of end-organ resistance to parathyroid hormone (PTH) leading hypocalcemia and hypophosphatemia, and, sometimes, TSH-resistance. Unlike in patients with PHP-Ia, in most cases, there are no signs of Albright's hereditary osteodystrophy. PHP-Ib is associated with methylation changes at one or several differentially methylated regions (DMRs) within the *GNAS* locus. *GNAS* is a complex imprinted locus on chromosome 20q13.2-13.3 that encodes the  $\alpha$ -subunit of the stimulatory G protein (*Gsa*) and gives rise different transcripts according to parental origin of the allele. Derived exclusively from the paternal allele are *XLas*, *A/B* and *AS*, and from the maternal allele is *NESP55*. Consistent with this imprinted expression pattern, the promoters of these imprinted transcripts are methylated on the silenced allele

PHP-Ib familial form (AD-PHP-Ib) is defined by an isolated loss of methylation of *GNAS* A/B DMR, secondary to deletions in *STX16* gene, which is located ~ 200 kb centromeric of *GNAS*. However, the cause of the *GNAS* diffuse imprinting defects in sporadic PHP-Ib : a loss of methylation at *GNAS* A/B DMR combined with loss of methylation at *XL* and *AS*, and with gain of methylation at *NESP55*, remains understood.

Epigenetic changes from sporadic PHPI-b mimic the paternal-specific methylation pattern. The transmission of both homologous chromosomes, or segments thereof, from a single parent to its offspring is described as uniparental disomy (UPD). Thus, loss of maternal allele or paternal UPD of chromosome 20 (patUPD20) without maternal contribution is a plausible cause of sporadic PHP-Ib.

## METHODS AND RESULTS

We screened a cohort of 53 patients presenting with sporadic PHP-Ib to evaluate the frequency of patUPD20.

Comparative Genomic Hybridation combined with Single Nucleotide polymorphism arrays (CGH+SNP-array) was used to identify copy neutral (absence of copy number variant CNV) with loss of heterozygosity (cnLOH) (fig.1).

Comparison of short tandem repeats along chromosome 20 between the proband and his parents were used to confirm cnLOH and patUPD20.

Because CGH+SNP-array required high quality DNA, only 20 samples were tested (fig.2).

We found 5 patients (25%) with patUPD20 : 3 complete patUPD20 (fig. 3), 1 patUPD of the long arm of chromosome 20 (fig. 4) and 1 with an interstitial UPD including *GNAS* locus (fig. 5). We found no difference between patients with patUPD20 and patients without patUPD20 about clinical findings and methylation defects

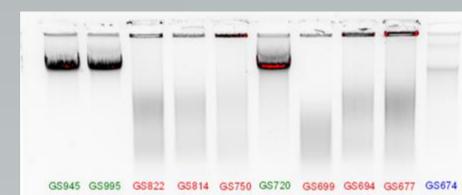


Figure 2 : DNA gel electrophoresis

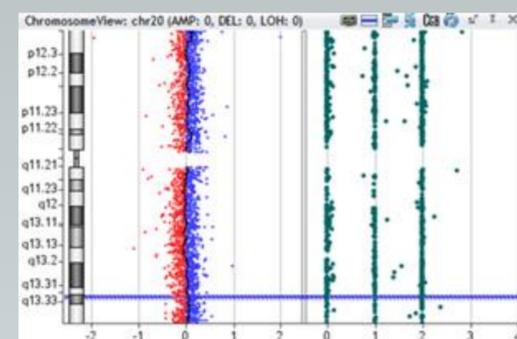


Figure 1 : control patient : no CNV and no LOH : no cnLOH

Figure 3 : complete patUPD20

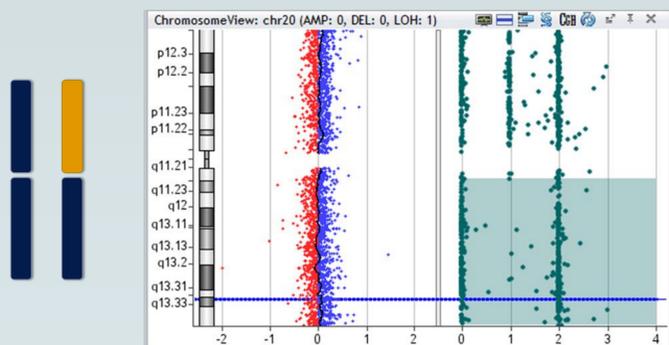
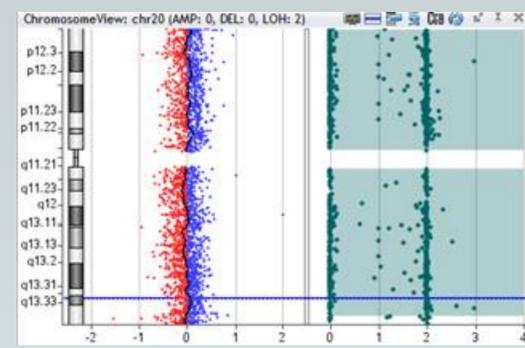
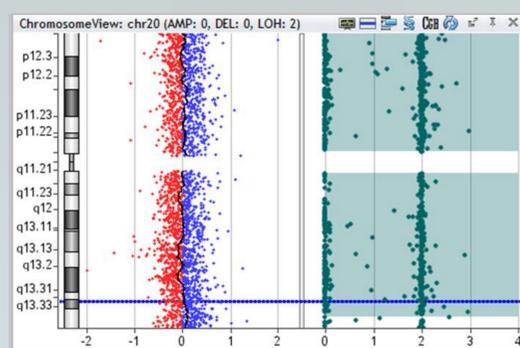
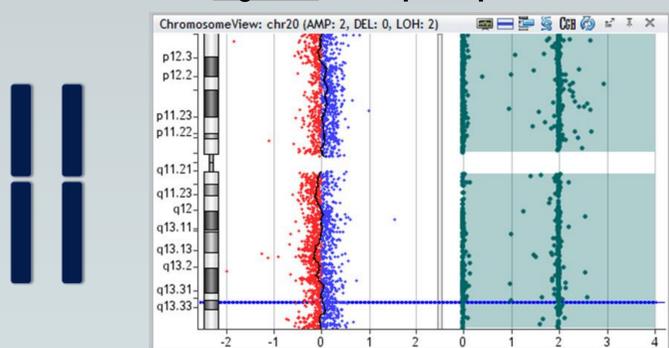
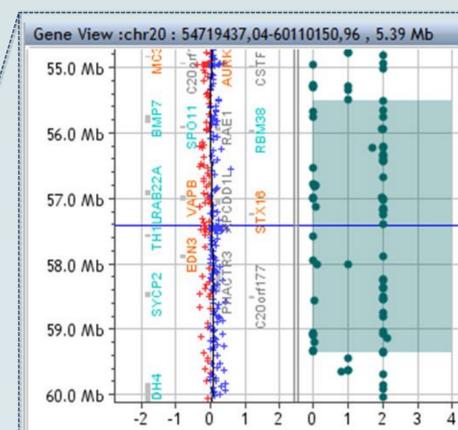
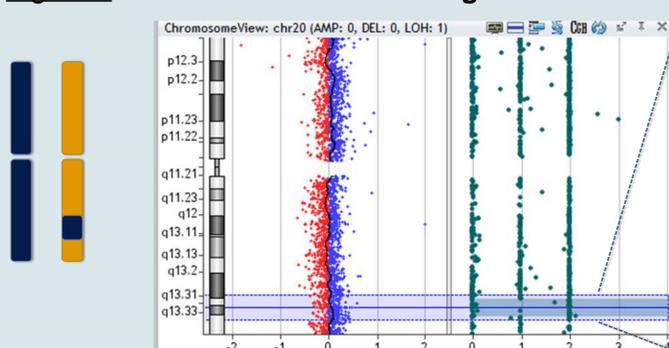


Figure 4 : patUPD of the long arm of chromosome 20 (patUPD20q)

Figure 5 : interstitial UPD including *GNAS* locus



## Conclusions

Up to day, six patients with sporadic PHP-Ib and patUPD20 have been reported.

Using CGH+SNP-array, we found 5/20 (25%) patients presenting patUPD20 suggesting that **patUPD20 is a frequent cause of sporadic PHP-Ib**,

However our method identifies only isodisomy not heterodisomy and thus underestimate the frequency of unidisomy. The mechanism could be the nondisjunction in paternal meiose II for complete patUPD20 and others, postzygotic mitotic recombinations.

The risk of recurrence for another pregnancy is very low < 1% when **sporadic PHP-Ib is due to patUPD20**.

We suggest to test sporadic PHP-Ib for patUPD20.