PHENOTYPE-GENOTYPE CORRELATIONS IN PRIMARY HYPEROXALURIA TYPE 1: THE I244T, 33_34INSC AND G190R AGXT MUTATION

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Introduction and objectives

Primary hyperoxaluria type I (PH1) caused by mutations in the AGXT gene, coding for the enzyme alanine-glyoxylate aminotransferase (AGT), resulting a wide spectrum of phenotypes ranging from renal failure in infancy to occur renal stones in late adulthood.
We aimed to investigate a possible relationship between outcome of PH1 and AGXT mutation type.

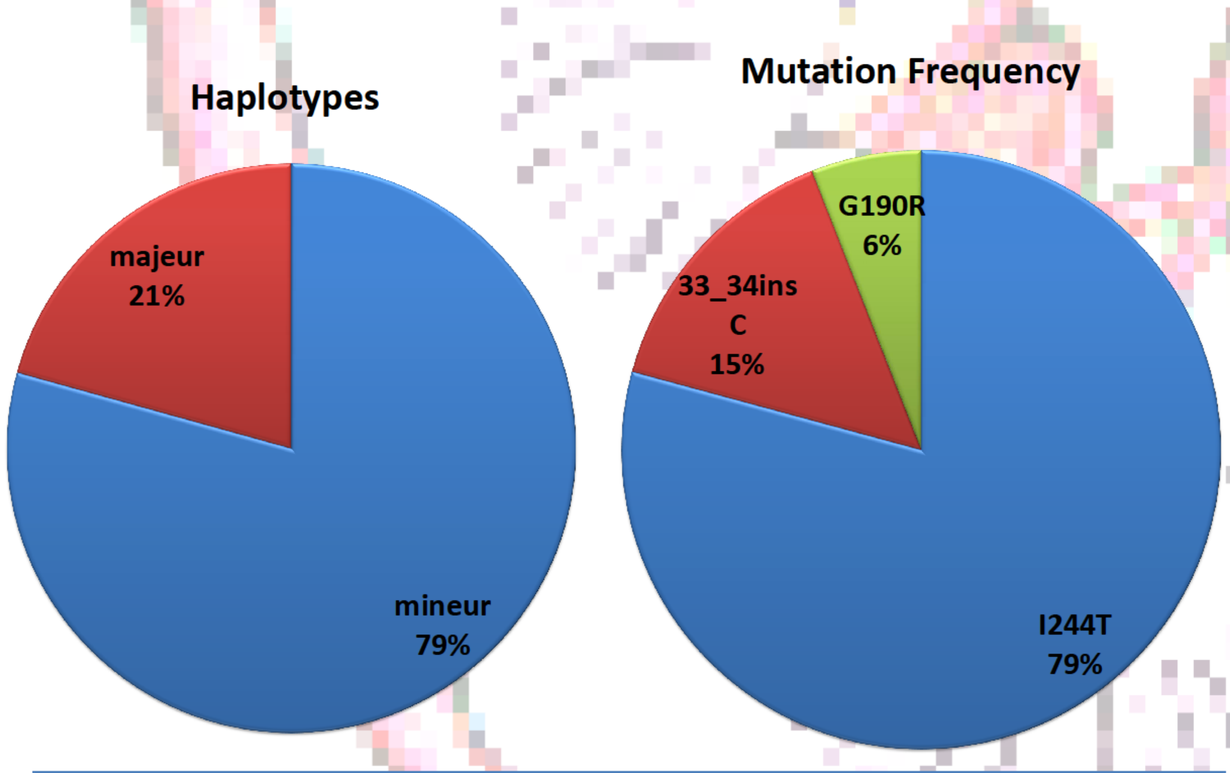
Patients and Methods

- We present a retrospective study of 53 Patients who have been diagnosed with PH1, carriers of I244T, 33_34insC and G190R AGXT mutations. Ten patients, sibling of confirmed PH1 patients were included in the analysis.
- Male to female ratio was 0, 82(24/29).
- The clinical data were compiled and genetic testing was done by determining haplotype (Minor or Major) and mutations analysis using PCR/RFLP

Results

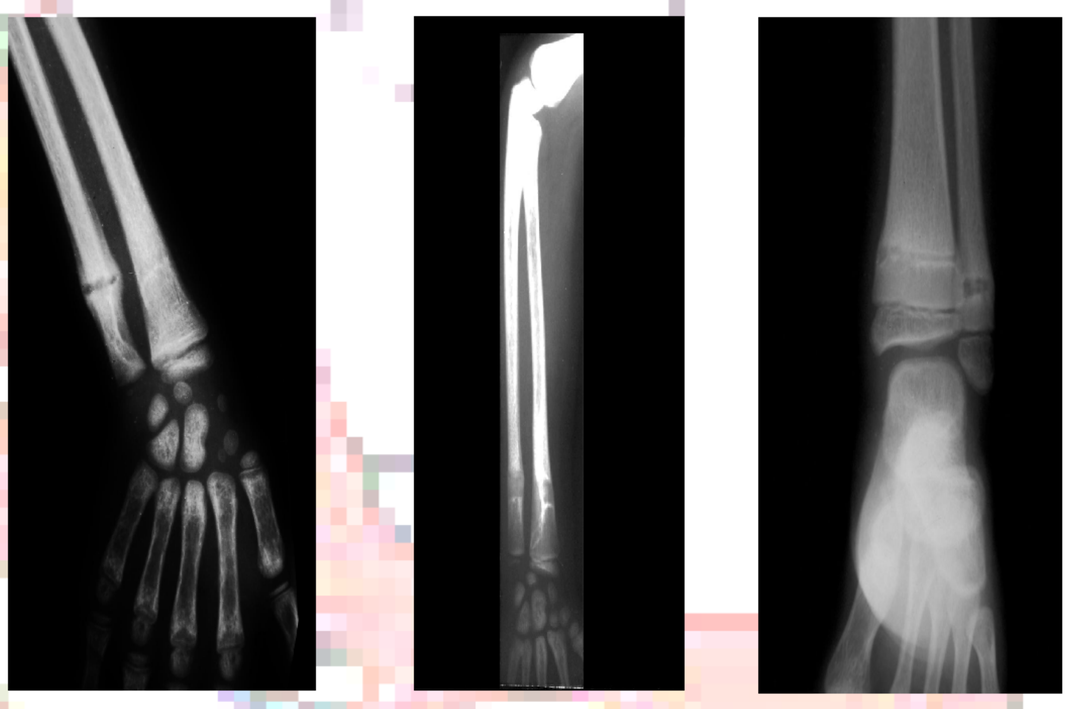
- Haplotype analysis showed that each mutation co segregates with a specific haplotype (figure1).
- The Maghrebian mutation"I244T" was most frequently involved (80%), co segregates with the Minor allele, followed by the 33_34insC mutation (15%) and the G190R (6%) which cosegregates with the Major allele.
- Differences in age at diagnosis between PH1 mutation types was higher different but the form infantile was the most frequent..

Figure1. results of molecular approach



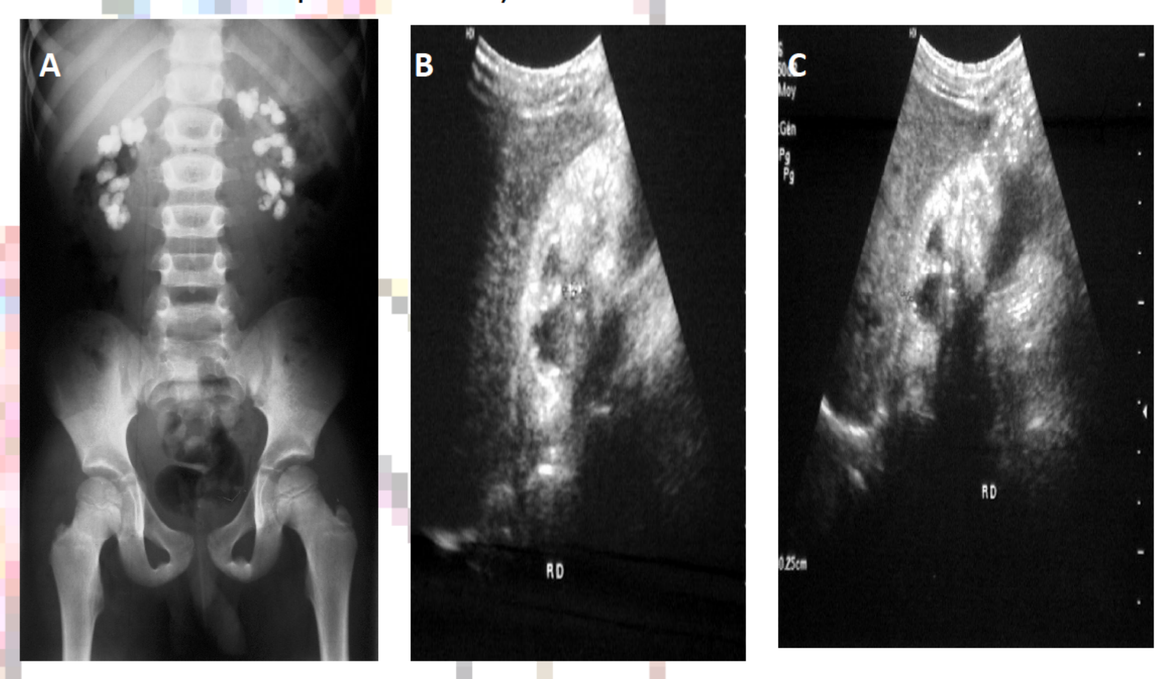
- Onset of symptoms occurred later in 33_34insC homozygotes (range: 0,2-61 years) compared with homozygote I244T (range: 0,1-40 years).
- The I244Thomozygotes were associated with slower progression to end-stage renal disease (ESRD) compared with 33_34insC homozygotes.
- Systemic manifestations were more frequently observed in the infantile form at the time of diagnosis and after evolution, in particular, ocular manifestations (11%), bone damaging (9%)(figure2), cardiovascular (7%).

Figure2. radiograph of bone oxalosis



- In the I244T group, the mutation was found in 42 patients, 15 of them were diagnosed at an adult age and 11 after family screening. The median age of disease detection was 7 years. ESRD was reached in 45% homozygous patients.
- The I244T mutation has been associated with various renal symptoms: 47% urolithiasis, 31% nephrocalocinosis (figure3).

Figure3. renal symptoms (A: nephrocalcinosis ; B: urolithiasis ; C: both urolithiasis and nephrocalcinois)



- In the 33_34insC group, a total of seven patients were homozygous, coding for a truncated protein, and 50% of them had infantile form, presented with nephrocalcinosis (60%) and five (62%) experienced ESRD.
- Three patients were carring the G190R mutation, all of them derived from the same family. It is presented with variable age at onset (range: 0,5- 16 years) and systemic manifestations at diagnosis and this especially for digestive (5%).
- No genotype phenotype correlation was seen. Most patients received chronic hemodialysis

Conclusions

The HP1 is a rare disease which has the particularity to be more frequent in Tunisia. It is characterized by a great phenotypic variability therefore no consistent relationship between mutant genotype and phenotype. It is important to make an early diagnosis to prevent the devastating effects of systemic oxalosis.

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