Phenotype-genotype correlation in a series of 131 patients studied for calcium-sensing receptor gene (CASR)

1Vahe C*, 2Odou MF, 3Desailloud R, 1Leroy C, 1Bauters C, 3Sherpeerel A, 4Pattou F, 4Carnaille B, 1Wemeau JL, 1Vantyghem MC

1Endocrinology and Metabolism Department, 2Genetic Department, 3Pneumology Department, 4Endocrine Surgery Department, Lille University Hospital, 1Endocrinology Department Amiens University Hospital, FRANCE

Correspondance: Hôpital Huriez, rue Michel Polonovski, 59000 Lille, France; mc-vantyghem@chru-lille.fr

INTRODUCTION

CASR loss-of-function mutations lead to
- familial hypocalciuric hypercalcemia (FHH)
- neonatal severe hyperparathyroidism
- and primary hyperparathyroidism.

FHH is characterized by mild hypercalcemia, hypocalciuria, calcium clearance/creatinine clearance (CaCl/CrCl)<0.01, normal or high PTH level. Nevertheless the phenotype may vary (Thakker 2012).

The aim of this work was to compare the phenotypes of patients bearing or not a pathogenic CASR-mutation.

METHODS

Patients included (n=131; 96 female, median(IQR) age 63(40-77)) referred for a calcium disorder not explained by sporadic hyperparathyroidism, were sequenced for CASR gene after written informed consent.

Patients taking diuretics, diphosphonates, lithium, with kidney failure, CaSR-antibodies or gain-of-function CASR-mutations had been excluded.

A healthy group of control patients from Pneumology Department was compared to patients with calcemia disease.

Gender, age, nephrolithiasis, bone absorptiometry, blood calcium, phosphate, creatinine, 25-hydroxyvitaminD and PTH levels, 24-H calcium, and CaCl/CrCl were compared according to the level of calcium <100, 100-105 or >105 mg/L and the presence of a pathogenic CASR mutation.

RESULTS

The CASR-mutated group (n= 21) showed higher calcemia and lower PTH levels than the non-mutated group (n=110), with no difference for other parameters (Table 1).

The non-mutated group included 51 normal CASR, 50 heterozygous and 9 homozygous or composite heterozygous variants. The comparison of these 3 sub-groups with the CASR-mutated group also differed for calcemia and PTH (p<0.01) (Table 2).

CaSR-mutations and CASR-variants were identified respectively in none and 15 (53%) of the 28 patients with calcemia=100mg/L, 4 (14%) and 14 (50%) of the 28 patients with calcemia between 100-105mg/L, and 17 (22%) and 30 (40%) of the 75 patients with calcemia>105mg/L (Table 3).

Seven of 13 (53%) patients tested without any calcium disorder bore CASR-variants.

<table>
<thead>
<tr>
<th>Table 1: Comparison of biological parameters between mutated and non-mutated groups</th>
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<tbody>
<tr>
<td><strong>Non mutated</strong></td>
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<tr>
<td>Ca (mg/L)</td>
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<tr>
<td>PTH (pg/mL)</td>
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<tr>
<td>25OHTdD(ng/mL)</td>
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<tr>
<td>CaU(mg/24h)</td>
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<td>CaCl/CrCL</td>
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<th>Table 2: Biochemical parameters according to genotype</th>
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<tr>
<td><strong>Normal</strong></td>
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<tr>
<td>Ca (mg/L)</td>
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<tr>
<td>CaCl/CrCl</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
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<tr>
<td>25OHTdD (ng/mL)</td>
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<td>Ca/PTH</td>
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<th>Table 3: Genotype according to blood calcium level</th>
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<tr>
<td><strong>Normal</strong></td>
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<tr>
<td>Healthy and Ca&lt;100ng/mL</td>
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<tr>
<td>Ca= 100mg/L and calcium disorder</td>
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<td>Ca 100-105 mg/L</td>
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<td>Ca&gt;105</td>
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CONCLUSION

50% of patients with calcemia<105mg/L showed a CASR-variant, whereas 40% with calcemia>105mg/L showed a CASR-mutation, with lower PTH levels, but no difference in terms of calciuria or (CaCl/CrCl) despite similar vitaminD status. Calcemia/PTH ratio>2 could be a better marker of pathogenic CASR-mutation than (CaCl/CrCl)<0.01.