Clinical and genetic profiles of 168 Russian patients with hypophosphatemic rickets.

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Introduction: The aim of this study was to clinically characterize and perform genetic analysis of 168 cases with HR.

Patients:
- n= 168 patients with the diagnosis of HR
- age, from 1 months to 56 years
- female n=111, male n=57
- 52 familial and 116 sporadic cases from 137 families

Methods:
1. Custom Ion AmpliSeq™ «Rickets panel» gene panel:
   - 22 genes (ALPL, ATP6V0A4, ATP6V1B1, CASR, CLCN5, CLCNKB, CYP24A1, CYP27B1, CYP2R1, DMP1, ENPP1, FGF23, GALNT3, KL, LRP5, PHEX, PTHR1, SLC2A2, SLC34A1, SLC34A3, SLC9A3R1, VDR);
   - ~83 kb, 409 amplicons, coverage 98.5%.
2. PGM semiconductor sequencer (Ion Torrent, Life Technologies).
3. Bioinformatics: Torrent Suite (Ion Torrent, Life Technologies), ANNOVAR version 2013 Feb21 (annovar.openbioinformatics.org)

Results:
- The mean age at diagnosis was 7.5 years (aged from 2 month to 17 years).

<table>
<thead>
<tr>
<th>Spectrum of mutations</th>
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<tbody>
<tr>
<td>PHEX</td>
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<tr>
<td>CLCN5</td>
</tr>
<tr>
<td>FGF23</td>
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<tr>
<td>SLC34A3</td>
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<tr>
<td>no mutations</td>
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- Mutations were identified in 92.3% of familial and 84.4% of sporadic cases.
- In 143 probands mutations were detected in PHEX, 70 of which were novel.

<table>
<thead>
<tr>
<th>Spectrum of PHEX mutations (n=117)</th>
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<tbody>
<tr>
<td>missense n=36</td>
</tr>
<tr>
<td>frameshift n=10</td>
</tr>
<tr>
<td>deletions n=15</td>
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<tr>
<td>nonsense n=25</td>
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</tbody>
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Clinical symptoms of HR
- The mean height SDS, -2.3±1.8
- The mean RSS= 4.5 points (range: 1.5-10)

Figure 1. Radiographs of wrists and knees of a 3-year-old male with severe rickets (RSS = 10 points).

Conclusion:
- This study showed the predominance of PHEX mutations among the patients with HR in Russia.
- We identified 117 PHEX mutations, including 70 unreported ones.
- Earlier diagnostic and treatment can result in less severe complications and improve the quality of life of patients with HR.

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