Genetic Association Patterns are Shared Between Blood Ionized Calcium, Urinary Calcium, and Risk of Calcium Oxalate Urinary Stones in a Dog Model

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Introduction

• Our group is utilizing a spontaneous dog model to discover genetic drivers of calcium oxalate (CaOx) kidney stones.
• Most dogs with CaOx stones are hypercalciuric and have increased blood ionized calcium.
• Hypothesis: Genetic predisposition to CaOx stones may be driven by effects on calcium homeostasis.
• CaOx stones are complex, with many risk factors—this analysis focuses on calcium variables only to understand just this aspect of the condition.

OBJECTIVE: To identify patterns of genetic associations that are shared among three conditions: calcium measured in the blood, calcium measured in the urine, and CaOx stone formation in a dog model.

Methods

Dataset

• 373 Purebred Miniature Schnauzers
• Genotyped at 390,150 single nucleotide polymorphisms (SNPs)
• Measured traits:
  - Blood ionized Ca (iCa)
  - Urine calcium:creatinine (UCaCr)
  - Stone forming status (CaOx)

1) Find genotypes associated with each variable
   - Genome-wide association analysis (GWAS)
   - Linear mixed model
   - R package: ‘gastön’ (Perdry et al., 2018)
   - Separate analysis for each trait

2) Identify shared patterns of genetic associations across the traits
   - Multivariate Adaptive Shrinkage (MASH) algorithm (Urbut et al., 2019)

Results

GWAS results show shared pattern from 14.6-16.5 Mb on Chromosome 9

<table>
<thead>
<tr>
<th>Trait</th>
<th>CaOx Stone-forming Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>CaOx</td>
<td>249</td>
</tr>
<tr>
<td>iCa</td>
<td>82</td>
</tr>
<tr>
<td>UCaCr</td>
<td>92</td>
</tr>
</tbody>
</table>

Table 1. Number of dogs in each GWAS analysis. Blood ionized calcium (iCa) and urine calcium to creatinine ratio (UCaCr) were not measured in all dogs. A small number of dogs with measured iCa or UCaCr had unknown stone-forming status.

Discussion

• The identified region contained 6 genes: GNA13, SLC16A6, ARSG, ABCA9, MAP2K6, and KCNJ16.
• Of these, **KCNJ16** is the most promising candidate.
• **KCNJ16** encodes a subunit of a potassium channel highly expressed in the basolateral membrane of the distal renal tubule.
• **KCNJ16** regulates pH and electrolyte balance, and knockout mice develop a metabolic acidosis and hypercalciuria (Paulais et al., 2011).
• We plan to use whole genome sequencing data to interrogate significant regions, including **KCNJ16**, for variants within or near candidate genes.
• The approach used for this analysis will be extended to other non-calcium variables that are relevant to CaOx stones.