LETTER

Human knockouts of PLA2G4A phenocopy NSAID-induced gastrointestinal and renal toxicity

We read with great interest the study by Brooke and colleagues, in which they revealed that a severe hereditary form of peptic ulcer disease known as ‘cryptogenic multifocal ulcerating stenosing enteritis’ is caused by homozygosity for a truncating mutation in PLA2G4A, causing complete loss of cytosolic phospholipase A2-α (cPLA(2)α). We describe below a family with a different truncating mutation to further delineate the PLA2G4A-related phenotype.

The family consists of healthy first cousin parents and 8-year-old triplets, two of whom had been treated for severe peptic ulcer disease since they were 2 years of age. The initial presentation was in the form of abdominal pain, anaemia and blood in stools, and multiple gastric and duodenal ulcers were diagnosed by endoscopy at 2 years of age. Gastrin and chromogranin levels were consistently normal. Response to proton pump inhibitor has been satisfactory, although a recent endoscopy revealed persistent irritation of the gastric mucosa. Occasional inadvertent skipping of medicine was always accompanied by severe bouts of abdominal pain and GI bleeding. Unexplained flank pain at

![Figure 1](A) Left: pedigree of study family. Right: autozygome analysis showing a shared run of autozygosity between the two affected members on chromosome 1, indicted by a blue asterisk. (B) Drawing of the gene and the location of the two homozygous truncating mutations identified (ours is indicated by red triangle and Brooke et al’s by blue). (C) Renal ultrasonographic images showing echogenicity of the renal pyramids in both siblings.
6 years of age in one of the two siblings prompted a renal ultrasound, which revealed echogenic foci in the renal pyramids bilaterally and these have been growing slowly in size (figure 1). This prompted a renal scan on the brother who showed identical lesions (figure 1). The renal function remains satisfactory for both despite mild increase in creatinine.

We recruited the family after obtaining informed consent in an institutional review board-approved research protocol (KFSHRC RAC# 2121053). By combining autozygome and exome sequencing, as described before,2 we identified a novel homozygous truncating mutation in PLA2G4A (NM_024420.2:c.607delG:p.(Val203Trpfs*6)) (figure 1).

PLA2G4A encodes phospholipase 2A group IV, a phospholipase enzyme that acts on membrane phospholipids to release arachidonic acid and make it available for conversion into prostaglandins through the action of cyclooxygenases COX1 and COX2. The family we describe as well as the one described by Brooke provide a rare opportunity to observe the human knockout phenotype for this gene, which phenocopies the chronic high dose use of the non-selective cyclooxygenase inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), for example, aspirin.

NSAID-induced mucosal injury is thought to stem from depletion of prostaglandins that regulate local blood flow and stimulate mucus secretion. Prostaglandins also play an important role in regulating local renal blood flow, and NSAID-induced acute and chronic kidney disease is thought to be the consequence of loss of this role. The selective involvement of the medullary pyramids in our two patients corresponds to the renal tubular damage observed experimentally when renal prostaglandin is depleted with NSAID.3 Brooke described renal failure in one of the two siblings with PLA2G4A deficiency but offered no potential link to the disease. Our observation of an evolving chronic kidney disease in the two siblings strongly argues in favour of a bona fide association between PLA2G4A deficiency and chronic kidney disease, and that loss of PLA2G4A not only phenocopies NSAID-induced mucosal injury but also NSAID-induced nephrotoxicity.

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