



The Genomics of Calcium Nephrolithiasis

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Nephrolithiasis is the process of forming stones in the kidneys from the crystal aggregation of the minerals contained in urine. Calcium of stone is mostly (80%) from calcium oxalate or calcium phosphate, causing kidney diseases and obstruction of the urinary tract, and have a high reoccurrence risk [1]. It is well established that calcium nephrolithiasis is the most prevalent form of kidney stones, and is a worldwide health problem affected by genes, the environment, diet and lifestyle [2]. To manage calcium nephrolithiasis, diet and medical treatment should be considered. Dogliotti et al. [3] stated that greater citrate and water consumption can reduce the formation of calcium crystals in the kidneys by binding free calcium ions and help excretion of calcium. Xu et al. [4] suggested that thiazide treatment is the standard therapy for calcium stone patients with idiopathic hypercalciuria. However, the functional role of genetic factors in calcium nephrolithiasis formation is still unclear.

Genetic analysis approaches provide powerful molecular detection and interpretation in the mechanism of calcium nephrolithiasis. For example, scientists discovered many genes that are related to calcium nephrolithiasis, such as vitamin D receptor (*VDR*) [5], fibroblast growth factor 23 (*FGF23*) [6] and claudin 14 (*CLDN14*) [7]. In 1999, Ruggiero et al. [8] firstly reported that *VDR* polymorphism was associated with a higher urinary calcium excretion. Further experiments supported the involvement of vitamin D receptor in calcium nephrolithiasis by investigating *FGF23*. *FGF23* can influence vitamin D metabolism and phosphate reabsorption [6]. Overexpression of *FGF23* was observed in calcium nephrolithiasis patients [9]. In 2009, genome-wide association study (GWAS) was conducted to identify the potential genes as biomarkers for calcium nephrolithiasis [7]; *CLDN14* was detected to be an important one. Collectively, evidence has accumulated to suggest that genetic polymorphism plays a role in susceptibility to calcium nephrolithiasis.

Recent genetic association studies indicated the importance of calcium channels in pathogenesis of calcium nephrolithiasis [10]. The candidate genes include transient receptor potential channels subtype V (*TRPV*) [11], calcium release-activated calcium channel protein 1 (*ORAI1*) [12], and the calcium sensing receptor (*CaSR*) gene [13]. In 2008, Suzuki et al. [11] reported that haplotypes of epithelial calcium channel *TRPV6* are risk factors for renal calcium stone formation. The haplotypes may increase the calcium entry and further cause hypercalciuria. In 2010, store-operated calcium channel was reported to associate with calcium nephrolithiasis. Chou et al. [12] discovered genetic polymorphisms of *ORAI1*, a subunit of the store-operated calcium channel, that associated with calcium nephrolithiasis. In addition, calcium-sensing receptor has been considered as a critical target for calcium nephrolithiasis [13]. The activation of *CaSR* gene can inhibit parathyroid hormone secretion and tubular calcium reabsorption, which controls serum calcium levels [14]. A SNP (rs17251221) in *CaSR* was found to associate with stone multiplicity in calcium nephrolithiasis [13]. In 2013, Vezzoli et al. [15] further indicated another SNP rs6776158 in *CaSR* gene promoter that associated with calcium nephrolithiasis. These observations imply that *CaSR*-mediated calcium signaling is a crucial mediator of calcium nephrolithiasis.

In conclusion, genetic polymorphism plays a critical role in

calcium nephrolithiasis. In light of the fact that genome sequencing is a very powerful tool and has been used in clinical application, pharmacogenomics is a rational therapeutic approach aimed at treating such disorders.

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Received November 28, 2013; Accepted November 28, 2013; Published December 06, 2013

Citation: Wang ET, Chou YH, Chang WC (2013) The Genomics of Calcium Nephrolithiasis. *J Pharmacogenom Pharmacoproteomics* 4: e136. doi:10.4172/2153-0645.1000e136

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Citation: Wang ET, Chou YH, Chang WC (2013) The Genomics of Calcium Nephrolithiasis. J Pharmacogenom Pharmacoproteomics 4: e136.
doi:[10.4172/2153-0645.1000e136](https://doi.org/10.4172/2153-0645.1000e136)

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