TITLE:
PHENOTYPIC AND GENOTYPIC RELATIONSHIP OF CALCIUM STONE FOMERS

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RESEARCH PROJECT DESCRIPTION:
Background Rationale: Urinary lithiasis will affect 1 in 11 people in the United States(1). Hereditability of nephrolithiasis is estimated to be approximately 50% in related studies (2). Phenotype of kidney stone disease could be a summation of hereditary traits or gene interaction with our environment, epigenetics. Family studies suggest that stone transmission is not typical Mendelian type, but more of a complex polygenic pattern (3,4,5). **Working Hypothesis:** Certain types of patient patterns of stone disease have been associated with specific genotypes: 1. Calcium-Oxalate stones with hypocitraturia associate with Vitamin D receptor abnormalities (5,6,7). 2. Calcium-phosphate stone formers with normal citrate levels associated with calcium sensitive receptor abnormalities (8.9,10). 3. Osteopontin gene abnormalities are associated with diverse types of kidney stone formation (11,12,13) 4. Calcium-Oxalate stones with hypercalciuria associate with Claudin 14 receptor abnormalities (14). NPT2a, AQP1 and DGHK (15) channels, have recently been associated with nephrolithiasis via GWAS*. We endeavor to group patients in our database by identifying stone type, serum, and urine laboratory parameters to identify patterns of disease and couple phenotyping with genotyping. **Methods:** Continuous variables will be compared using independent t−test. Categorical variables will be examined using chi−squared or fisher exact test (SAS 9.4 Cary, NC). Our larger aim is to perform group phenotyping and obtain blood samples from these patients for GWAS*. **Role of MD student:** To analyze our database**.** **Impact:** This represents and innovative strategy for tailoring evaluation and management of kidney stones by using a comprehensive approach including genetic and clinical testing. Funding: none

*GWAS: Genome-wide association studies

References:
1. C.D. Scales Jr., A.C. Smith, J.M. Hanley, C.S. Saigal, Urologic Diseases in America Project, Prevalence of kidney stones in the United States; Eur Urol, 62 (2012), pp. 160–165
2. Kidney Int. 2011 Sep;80(6):587-93. doi: 10.1038/ki.2010.430. Epub 2010 Oct 20. Genetics and calcium nephrolithiasis. Vezzoli G1, Terranegra A, Arcidiacono T, Soldati L.
3. World J Urol. 1997;15(3):186-94.Genes in idiopathic calcium oxalate stone disease. Goodman HO1, Brommage R, Assimos DG, Holmes RP.
4. J Urol. 1995 Feb;153(2):301-7. Genetic factors in calcium oxalate stone disease. Goodman HO1, Holmes RP, Assimos DG.
5. Nephrol Dial Transplant. 2004 Sep;19(9):2259-65. Epub 2004 Jun 22. The relationship of 3' vitamin D receptor haplotypes to urinary supersaturation of calcium oxalate salts and to age at onset and familial prevalence of nephrolithiasis. Mossetti G1, Rendina D, Viceconti R, Manno G, Guadagno V, Strazzullo P, Nunziata V.

6. J. Endourol. 2005 Jan-Feb;19(1):111-5. Association of vitamin D receptor-gene (FokI) polymorphism with calcium oxalate nephrolithiasis. Bid HK1, Kumar A, Kapoor R, Mittal RD.
7. BJU Int. 2007 Jun;99(6):1534-8. Epub 2007 Apr 5. Association of vitamin D receptor (Fok-I) polymorphism with the clinical presentation of calcium urolithiasis. Liu CC1, Huang CH, Wu WJ, Huang SP, Chou YH, Li CC, Chai CY, Wu MT.
8. Curr Pharm Biotechnol. 2009 Apr;10(3):302-10. Roles of calcium-sensing receptor (CaSR) in renal mineral ion transport. Vezzoli G1, Soldati L, Gambaro G.
9. Nephrol Dial Transplant. 2010 Jul;25(7):2245-52. doi: 10.1093/ndt/gfp760. Epub 2010 Jan 12. Calcium kidney stones are associated with a haplotype of the calcium-sensing receptor gene regulatory region. Vezzoli G1, Terranegra A, Arcidiacono T, Gambaro G, Milanesi L, Mosca E, Soldati L; GENIAL network (Genetics and Environment in Nephrolithiasis Italian Alliance).
10. Ann Hum Genet. 2009 Mar;73(2):176-83. doi: 10.1111/j.1469-1809.2008.00492.x. Epub 2008 Dec 23. Heterogeneous disease modeling for Hardy-Weinberg disequilibrium in case-control studies: application to renal stones and calcium-sensing receptor polymorphisms. Hamilton DC1, Grover VK, Smith CA, Cole DE.
11. Urolithiasis. 2013 Aug;41(4):303-13. doi: 10.1007/s00240-013-0582-7. Epub 2013 Jun 20. Association between polymorphisms in osteopontin gene (SPP1) and first episode calcium oxalate urolithiasis. Safarinejad MR1, Shafiei N, Safarinejad S.
12. Kidney Int. 2007 Sep;72(5):592-8. Epub 2007 May 23. Association of osteopontin gene haplotypes with nephrolithiasis. Gao B1, Yasui T, Itoh Y, Li Z, Okada A, Tozawa K, Hayashi Y, Kohri K.
13. Clin Chim Acta. 2010 May 2;411(9-10):739-43. doi: 10.1016/j.cca.2010.02.007. Epub 2010 Feb 6. The impact of osteopontin promoter polymorphisms on the risk of calcium urolithiasis. Liu CC1, Huang SP, Tsai LY, Wu WJ, Juo SH, Chou YH, Huang CH, Wu MT.
14. Nat Genet. 2009 Aug;41(8):926-30. doi: 10.1038/ng.404. Epub 2009 Jun 28. Sequence variants in the CLDN14 gene associate with kidney stones and bone mineral density.
Thorleifsson G1, Holm H, Edvardsson V, Walters GB, Styrkarsdottir U, Gudbjartsson DF, Sulem P, Halldorsson BV, de Vegt F, d'Ancona FC, den Heijer M, Franzson L, Christiansen C, Alexandersen P, Rafnar T, Kristjansson K, Sigurdsson G, Kiemeney LA, Bodvarsson M, Indridason OS, Palsson R, Kong A, Thorsteinsdottir U, Stefansson K.
15. J Hum Genet. 2013 Sep;58(9):588-93. doi: 10.1038/jhg.2013.59. Epub 2013 May 30. A replication study for three nephrolithiasis loci at 5q35.3, 7p14.3 and 13q14.1 in the Japanese population. Yasui T1, Okada A, Urabe Y, Usami M, Mizuno K, Kubota Y, Tozawa K, Sasaki S, Higashi Y, Sato Y, Kubo M, Nakamura Y, Matsuda K, Kohri K.