Update on Hereditary Kidney Stone Disease and Introduction of a New Clinical Patient Registry in Germany

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Kidney stone disease is an increasingly prevalent condition with remarkable clinical heterogeneity, with regards to stone composition, age of manifestation, rate of recurrence, and impairment of kidney function. Calcium-based kidney stones account for the vast majority of cases, but their etiology is poorly understood, notably their genetic drivers. As recent studies indicate, hereditary conditions are most likely underestimated in prevalence, and new disease genes are constantly being identified. As a consequence, there is an urgent need of a more efficient documentation and collection of cases with underlying hereditary conditions, to better understand shared phenotypic presentation and common molecular mechanisms. By implementation of a centralized patient registry on hereditary kidney stone disease in Germany, we aim to help closing the vast knowledge gap on genetics of kidney stone disease. In this context, clinical registries are indispensable for several reasons: first, delineating better phenotype–genotype associations will allow more precise patient stratification in future clinical research studies. Second, identifying new disease genes and new mechanisms will further reduce the rate of unknown nephrolithiasis/nephrocalcinosis etiology; and third, deciphering new molecular targets will pave the way to develop drugs for recurrence prevention in severely affected families.

Keywords: nephrolithiasis, hereditary, nephrocalcinosis, kidney stone disease, monogenic, registry

Incidence and prevalence of kidney stone disease continues to rise in the general population. With a lifetime prevalence of up to 10%, nephrolithiasis (NL) and nephrocalcinosis (NC) are therefore major health burdens, especially in the Western World (1). NL and NC are associated with significant morbidity and progression to chronic kidney disease due to recurrence, repetitive surgical/endoscopic intervention, and concomitant inflammation. On a simplified level, kidney stone formation results from an imbalance of urinary inhibitors (e.g., citrate, magnesium, uromodulin, and pyrophosphate) and promoters (e.g., oxalate, calcium, phosphate, urate, and cystine) of crystalization, exceeding supersaturation with consecutive aggregation, nucleation, and stone growth at Randall’s plaque (Figure 1). This imbalance can be due to altered enteral and/or renal handling of either promoters or inhibitors, such as enteral malsecretion of oxalate or renal malreabsorption of calcium (Figure 1).

The underlying etiology of NL is thought to be multifactorial with an environmental, notable dietary, hormonal, and genetic component. In twin studies, the heritability of kidney stones has been estimated at 56% (3), and up to two-thirds of hypercalciuric stone formers have relatives with NL (4). Although calcium-containing kidney stones account for more than 80% of all, the genetic basis of such stones remains largely unknown (5). Except for variants in CLDN14, TRPV5, SLC34A1, ALPL, CASR, and UMOD, genome-wide association studies have yet to yield substantial genetic factors (6–8). However, risk alleles have been identified within genes that were also found to transmit
the disease on a Mendelian basis, such as CASR, SLC34A1, and SLC2A9 (9, 10). To date, more than 30 single genes with an Online Mendelian Inheritance in Man-defined phenotype have been identified to be implicated in NL/NC, if mutated (Table 1).

Modes of inheritance in monogenic forms include autosomal-dominant, autosomal-recessive, and X-linked transmission. Interestingly, in several of these genes, both recessive and dominant modes of inheritance have been reported: SLC7A9, SLC34A1, SLC34A3, SLC2A9, SLC22A12, and SLC4A1. While most of the syndromic and severe congenital disorders exhibit a recessive inheritance pattern (Bartter, Lowe, Dent, FHHNC, and distal renal tubular acidosis with sensorineural deafness), milder conditions are rather associated with mutations in dominant genes. The majority of encoded proteins constitute renal solute transporters (e.g., SLC34A1, SLC34A3, and SLC9A3R1), but also chloride channels (CLCN5), tight-junction proteins (e.g., CLDN16/CLDN19), and metabolizing enzymes (e.g., AGXT, APRT, and CYP24A1) have been found defective in patients with NL/NC. Hence, the underlying defect is mostly located in the tubular system of the kidney itself and can therefore be attributed as tubulopathy. Conversely, a priori extrarenal conditions, as in primary hyperoxaluria (PH) where dysfunction of liver enzymes (AGXT, GRHPR, and HOGA1) cause oxalate accumulation with secondary renal affection, are conceivable causes of NL/NC. Although each disease phenotype is thought to represent a relatively rare entity, single-gene causes may account for a significant number of patients by their broad genetic heterogeneity (42). Apart from genetic heterogeneity, there is also an allelic variation, where truncating variants rather result in a loss of function and missense variants (hypo-morphs) may cause rather subtle defects, which can be clinically overseen, especially in adult stone formers. Another recently appreciated phenomenon is about gene dosage effects in several of the aforementioned kidney stone genes. In SLC34A3 for instance, encoding one of the main phosphate transporters in the proximal tubule (NaPiIIc), it was shown that heterozygous individuals can no longer be merely regarded as healthy carriers, as they display renal calcifications and/or bone manifestation significantly more frequent than wild-type individuals; but still to a lesser degree than biallelic (homozygous and compound heterozygous) individuals (43). Similar observations were reported for families with mutations in CYP24A1 (44). The contribution of monogenic disorders to the overall prevalence of kidney stone disease has not been studied comprehensively in the past. Especially, genetic evidence based on broad screenings of a multitude of causative genes in large patient cohorts is lacking. Comprehensive genetic testing has been too costly and inefficient in the past. For most individuals with NL/NC, mutation analysis for a causative genetic defect has therefore not been accessible, despite the fact that knowledge of the molecular cause of NL/NC may have important consequences for prognosis, prophylaxis and/or treatment. Only rough estimates have been derived from clinical observation studies: based on a huge data collection of stone composition analysis, it was concluded that monogenic causes do not exceed 9.6% in children and 1.6% in adults (45). In the last decade, however, this situation has begun to change, with the advent of high-throughput sequencing techniques.
### Table 1: Genes known to cause monogenic forms of NL/NC.

| Gene symbol | Gene name |
|-------------|-----------|
| ADCY10      | Adenylate cyclase 10 |
| AGXT        | Alanine-glyoxylate aminotransferase |
| APRT        | Adenine phosphoribosyltransferase |
| ATP6V0A4    | ATPase, H+ transporting, lysosomal V0 subunit a4 |
| ATP6V1B1    | ATPase, H+ transporting, lysosomal, V1 subunit B1 |
| CA2         | Carbonic anhydrase II |
| CASR        | Calcium-sensing receptor |
| CLCN5       | Chloride channel, voltage-sensitive 5 |
| CLCNKB      | Chloride channel, voltage-sensitive Kb |
| CLDN16      | Claudin 16 |
| CLDN19      | Claudin 19 |
| CYP24A1     | Cytochrome P450, family 24, subfamily A, polypeptide 1 |
| FAM20A      | Family with sequence similarity 20, member A |
| GLRA        | Glyoxylate reductase/hydroxypruvate reductase |
| HNF4A       | Hepatocyte nuclear factor 4, alpha |
| HOGA1       | 4-Hydroxy-2-oxoglutarate aldolase 1 |
| HPRT1       | Hypoxanthine phosphoribosyltransferase 1 |
| KCNJ1       | Potassium inwardly rectifying channel, subfamily J, member 1 |
| MAGED2      | Melanoma antigen, family D, 2 |
| OCRL        | Oculocerebrorenal syndrome of Lowe |
| SLC12A1     | Solute carrier family 12, member 1 |
| SLC26A1     | Solute carrier family 26 (sulfate transporter), member 1 |
| SLC22A2     | Solute carrier family 22 (organic anion/urate transporter), member 12 |
| SLC22A9     | Solute carrier family 2 (facilitated glucose transporter), member 9 |
| SLC34A1     | Solute carrier family 34 (sodium phosphate), member 1 |
| SLC34A3     | Solute carrier family 34 (sodium phosphate), member 3 |
| SLC3A1      | Solute carrier family 3 (cystine, dibasic and neutral amino acid transporter, activator of cystine, dibasic and neutral amino acid transporter), member 1 |
| SLC4A1      | Solute carrier family 4, anion exchanger, member 1 |
| SLC7A9      | Solute carrier family 7 (glycoprotein-associated amino acid transporter light chain, bo, +system), member 9 |
| SLC9A3R1    | Solute carrier family 9, subfamily A (NHE3, cation proton antiporter 3), member 3 regulator 1 |
| VDR         | Vitamin D (1,25-dihydroxyvitamin D3) receptor |
| XDH         | Xanthine dehydrogenase |

| Disease entity                                           | MIM phenotype # | Mode | Reference |
|----------------------------------------------------------|-----------------|------|-----------|
| Idiopathic (absorptive) hypercalciuria, susceptibility   | 143870          | AD   | (11)      |
| Primary hyperoxaluria (PH), type 1, PH1                  | 259900          | AR   | (12)      |
| Adenine phosphoribosyltransferase deficiency, APRT       | 614723          | AR   | (13)      |
| dRTA                                                     | 602722          | AR   | (14)      |
| dRTA with deafness                                       | 267300          | AR   | (15)      |
| Osteopetrosis + dRTA                                     | 259730          | AR   | (16)      |
| Hypocalcemia with Bartter syndrome/hypocalcemia, AD      | 601198          | AD   | (17)      |
| Dent disease/NC, type 1                                  | 300009/310468   | XR   | (18)      |
| Bartter syndrome, type 3                                 | 607364          | AR   | (19)      |
| Familial hypomagnesaemia with hypercalcia and NC         | 248250          | AR   | (20)      |
| Familial hypomagnesaemia with hypercalcia and NC with ocular abnormalities | 248190          | AR   | (21)      |
| 1,25-(OH) D-24 hydroxylase deficiency, intantile hypercalcemia | 143880 | AR | (22) |
| Enamel renal syndrome, amelogenesis imperfert, and NC    | 204960          | AR   | (23)      |
| PH, type 2, PH2                                          | 260000          | AR   | (24)      |
| MODY + Fanconi syndrome + NC (p.R76W)                    | 125850          | AD   | (25)      |
| PKH, type 3, Ph3                                         | 613616          | AR   | (26)      |
| Ketley–Seegmiller syndrome, partial HPRT deficiency, HPRT-related gout | 300023 | XR | (27) |
| Bartter syndrome, type 2                                 | 241200          | AR   | (28)      |
| Bartter syndrome, type 5                                 | 300971          | XR   | (29)      |
| Lowe syndrome/Dent disease 2                             | 309000/300555   | XR   | (30)      |
| Bartter syndrome, type 1                                 | 601678          | AR   | (31)      |
| Ca-oxalate-NC                                            | 167030          | AR   | (32)      |
| Renal hypouricemia, RHUC1                                | 220150          | AD/AR| (33)      |
| Renal hypouricemia, RHUC2                                | 612076          | AD/AR| (34)      |
| Hypophosphatamatic NL, osteoporosis-1, NPHLOP1/Fanconi renotubular syndrome 2 | 612286/613388 | AD/AR| (35) |
| Hypophosphatametic rickets with hypercalciuria           | 241530          | AR   | (36)      |
| Hypophosphatametic rickets with hypercalciuria           | 220100          | AR   | (37)      |
| Primary dRTA, dominant/recessive                         | 179800/611590   | AD/AR| (38)      |
| Oystinuria, type A                                        | 220100          | AD/AR| (39)      |
| Hypophosphatametic NL, osteoporosis-2, NPHLOP2            | 612287          | AD   | (40)      |
| Xanthine dehydrogenase                                   | 278300          | AR   | (41)      |

*For HNF4A the MIM-phenotype number denotes MODY type 1, as occurrence of Fanconi syndrome and NC has only been shown in the presence of a specific allele: p.R76W.

AD, autosomal dominant; AR, autosomal recessive; dRTA, distal renal tubular acidosis; MODY, maturity onset diabetes of the young; NC, nephrocalcinosis; NL, nephrolithiasis; pRTA, proximal renal tubular acidosis; XR, X-chromosomal recessive.
HIGH-THROUGHPUT MUTATION ANALYSIS IN PATIENTS WITH NL/NC

To investigate patients with kidney stone disease for the presence of pathogenic mutations in known disease genes, we established a gene panel based on microfluidic multiplex-PCR and consecutive NextGen sequencing (Fluidigm™/NGS) (46, 47).

In a “pilot-study,” we consecutively recruited 268 genetically unresolved individuals from typical kidney stone clinics; 102 pediatric and 166 adult probands. As a result, we identified 50 deleterious variants in 14 out of 30 analyzed genes, leading to a molecular diagnosis in 15% of all cases. In the pediatric subgroup, we detected a causative mutation in 21%, while among adults, deleterious variants were present in 11% (Figure 2A) (48). Mutations in the cystinuria-gene SLC7A9 were found most frequently in the adult cohort (Figure 2B). Two follow-up studies were able to confirm these results. First, in an exclusively pediatric cohort of 143 NL/NC patients, 17% of cases were explained by mutations in 14 different genes (49). Second, in a cohort of 51 families with age of NL/NC manifestation before 25 years, targeted WES was used to detect a genetic cause in almost 30% (50). Not surprisingly, recessive mutations were more frequently found among neonates and in cases of congenital disease, whereas dominant conditions usually manifested later in life. These data indicate that genetic kidney stone disease is an underdiagnosed condition, despite the fact that the molecular diagnosis will potentially influence prognosis, prophylaxis, and/or treatment. A limitation worth mentioning, however, is a potential selection bias due to recruitment from specialist kidney stone clinics in all of the three aforementioned studies.

IDENTIFICATION OF NOVEL HUMAN DISEASE GENES BY CANDIDATE-GENE APPROACH

High-throughput mutation analysis is also used to screen for pathogenic variants in various candidate genes. One of the most interesting recent findings was the discovery of human mutations in SLC26A1 (32). Since the first description of Ca-oxalate (CaOx) kidney stone formation and NC in Slc26a1 (Sat1)-knockout mice by Dawson et al. in 2010, SLC26A1 has been a bona fide NL-candidate gene (51). SLC26A1 encodes an anion exchanger expressed at the basolateral membrane of proximal renal tubules, ileum, and jejunum. Consequently, by using a candidate-gene approach, pathogenic variants were identified in humans with a history of early onset CaOx-NL, namely, two unrelated individuals with biallelic missense variants (32). Functionally, pathogenicity of the identified variants was demonstrated in vitro, leading to intracellular mis-trafficking and impaired transport activity (32). Defective SLC26A1 therefore constitutes a new cause of CaOx-NL and should be considered when testing individuals for causes of recurrent CaOx-stone formation.

NEW CLINICAL PATIENT REGISTRY FOR HEREDITARY KIDNEY STONE DISEASE

Most epidemiological data on increasing prevalence in Western countries are derived from US databases. Although urgently needed, centralized European databases are not available at the time. As aforementioned genetic studies on prevalence of hereditary kidney stone disease were executed with small cohorts from specialized centers in both Europe and the US, a translation to the general situation in Europe is not valid. While in the US, the Rare Kidney Stone Consortium constitutes a platform that integrates and coordinates registry, basic science, and clinical research activities for rare conditions such as cystinuria, PH, APRT deficiency, Dent and Lowe disease, no comparable data collection on patients with hereditary kidney stone disease has been implemented neither in Europe nor in Germany today. In collaboration with the existing European PH registry, OxalEurope (Prof. Bernd Hoppe, University of Bonn), and through funding by Deutsche Forschungsgemeinschaft and Else Kröner-Fresenius Stiftung, we recently established a clinical...
patient “Registry for hereditary kidney stone disease” at the University of Leipzig. The registry is nationally supported by the German Societies of Adult Nephrology (DG/N) and Pediatric Nephrology (GPN). It is further enrolled at the German Clinical Trials Register (DRKS-ID: DRKS00012891). As a fundamental part of study recruitment, high-throughput mutation analysis for known and novel kidney stone genes is offered on a research basis for patients without an established molecular diagnosis but with a clinical picture that points to an underlying genetic susceptibility: e.g., early age of onset (<40 years), positive family history, indicative phenotypes such as NC, cystinuria, or RTA, and severely recurrent NL (>3×) (Table 2). While patients with an already established genetic diagnosis are generally enrolled, cases with secondary NL/NC causes, such as malignancy, sarcoidosis, and primary hyperparathyroidism, do not get included in genetic analysis. To actively enroll patients, a clinical center will usually need approval by the local Institutional Review Board; a process for which we offer our help and assistance by providing respective templates. Upon ethics approval, consent form and clinical data sheets (e.g., clinical questionnaire) can be downloaded from our registry website (http://www.mks-registry.net). To ensure thorough clinical phenotyping, we will be asking for substantial patient information such as ethnicity, consanguinity, family history, age of onset, recurrence (defined as every putatively new kidney stone event), daily fluid intake, surgical interventions, and extrarenal involvement among others. The documents can be filled in by the patient with the help of the enrolling physician. In addition, biochemical serum parameters, including creatinine, eGFR, PTH, vitamin D, electrolytes, uric acid, and urinalysis (pH, calcium, phosphate, magnesium, uric acid, citrate, oxalate, and cystine, preferably from 24-h urine, if not spot urine), as well as data on stone composition analysis will be requested upon enrollment. Taking into account that 24-h urine collection and stone composition analysis is not routinely performed at all institutions, we include these parameters upon availability. 2-yearly clinical follow-up visits of enrolled patients are desirable but not mandatory. After registration, recruiting clinical centers will be provided with a personalized login to enter patient data via our registry website (http://www.mks-registry.net). Alternatively, we offer entering the data electronically when sent to us on paper. Entered data will be stored on a secured server and can be accessed by participating clinical centers to view their own patient data. The following websites provide further information:

https://www.dgfn.eu/hereditaer-nierensteinleiden.html
https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00012891

In summary, kidney stone disease is an increasingly prevalent condition which is clinically heterogeneous and poorly understood, notably its genetic drivers. As a series of recent studies indicated, monogenic conditions are most likely underestimated in prevalence. By implementation of a centralized patient registry on hereditary kidney stone disease, we will contribute to overcome, at least in part, the vast knowledge gap on genetics of kidney stone disease. In this context, clinical registries are valuable sources for several reasons: first, delineating better phenotype–genotype associations will be crucial for more precise patient stratification in future clinical research studies. Second, identifying new disease genes with new disease mechanisms will diminish the gap of unknown NL/NC etiology; and third, deciphering new molecular targets helps to pave the way for developing drugs of recurrence prevention in severely affected families.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of “Ethikkommission an der Medizinischen Fakultät der Universität Leipzig” with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the “Ethikkommission an der Medizinischen Fakultät der Universität Leipzig.”

AUTHOR CONTRIBUTIONS

JH conceived and wrote the manuscript. BH, AS, LM, and RS edited the manuscript and built up the registry’s infrastructure that is introduced to the reader.

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| Table 2 | Inclusion criteria for mutation analysis in clinical patient registry. |
|---|---|
| **Clinical criteria** |  |
| Pediatric age of onset or onset during early adulthood (<40 years) plus |  |
| Positive family history or |  |
| Recurrence (>3×) or |  |
| Indicative phenotype (e.g., RTA, cystinuria, and NC) or |  |
| Established molecular genetic diagnosis |  |
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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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