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Molecular landscape of medullary nephrocalcinosis in children – a nationwide, prospective cohort study

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Research Article

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Abstract

Background

This study aimed to investigate the genetic landscape and to identify predictors of a molecular diagnosis in pediatric nephrocalcinosis.

Methods

This prospective, nationwide cohort study enrolled 79 unrelated pediatric patients with ultrasound-based medullary nephrocalcinosis of unknown etiology. Genetic evaluation was conducted using whole-exome sequencing (*n* = 75) or targeted (Sanger) sequencing (*n* = 4). Only (likely)pathogenic variants were considered diagnostic.

Results

A molecular diagnosis of Mendelian disease (MD) was established in 16% of patients, which included infantile hypercalcemia type 1 (*CYP24A1*, *n* = 3) and type 2 (*SLC34A1*, *n* = 2), familial hypomagnesemia, hypercalciuria and nephrocalcinosis (*CLDN16*, *n* = 2; *CLDN19*, *n* = 1), distal renal tubular acidosis (*ATP6V0A4*, *n* = 1; *ATP6V1B1*, *n* = 1), Bartter syndrome type 2 (*KCNJ1*, *n* = 1) and type 3 (*CLCNKB*, *n* = 1), and Dent disease type 1 (*CLCN5*, *n* = 1). Monoallelic (MA) variants, possibly predisposing to nephrocalcinosis, were found in 16% of patients, encompassing four genes, predominantly within the *SLC34A1* and *SLC34A3* (61%). In patients with MD, except for two patients with Bartter syndrome, typical phenotypes were observed, in contrast to carriers of MA variants, in whom the majority had subtle abnormalities. Clinical parameters, prematurity and family history for nephrocalcinosis/lithiasis were not associated with MD diagnoses.

Conclusions

This study clarifies the distinct genetic architecture of pediatric nephrocalcinosis. The data may possibly explain the etiology in approximately 30% of cases, when considering both MD and MA variants. Disease-specific phenotypes are associated with MD; however, the absence of typical features should not preclude a genetic diagnosis.

Introduction

Nephrocalcinosis (NC) is characterized by the aberrant deposition of calcium salts within the kidney parenchyma and serves as a critical clinical marker of underlying genetic/metabolic diseases. Although NC is frequently categorized as a rare manifestation of urolithiasis, it is distinct from nephrolithiasis (NL), and the two conditions do not invariably coexist. The precise incidence of pediatric NC remains

elusive, although it is markedly lower (~ 20 times) than that of NL [1]. Although both entities share overlapping environmental, metabolic, and genetic etiologies, including prematurity, vitamin D intoxication, and anatomical anomalies, their clinical trajectories often diverge [2]. Given that the pathophysiology of NC and NL is related but not identical, it is hypothesized that their genetic architectures are distinct; however, the exact contribution of genetic factors to NC remains unclear.

Crucially, contemporary data regarding the specific etiology of NC are sparse, and no studies have systematically investigated the molecular causes. The existing literature on children often predates the widespread integration of genetic testing into clinical practice [3, 4] or is limited to single centers or regions, leading to biased data [4–6]. In addition, certain pathologies, such as ciliopathies, may present with increased medullary echogenicity, thus phenocopying NC on ultrasonography and complicating the differential diagnosis [7].

Recent advancements in genomic medicine have significantly expanded our understanding of kidney stones. There is a growing body of evidence highlighting the role of monogenic (Mendelian) disorders (MD) [1, 8–13], and more recently of rare monoallelic (MA) variants [14–16], and common variants [16–19] that may cumulatively influence lithogenesis. Despite several landmark studies investigating Mendelian causes in pediatric populations [1, 9–12], the molecular landscape of NC remains insufficiently studied. This is largely because patients with NC have historically been analyzed as a subset of larger NL cohorts, where they represent only a small minority. Furthermore, existing data are often confounded by methodological limitations such as small sample sizes, single-center recruitment constraints, and selection biases driven by high rates of consanguinity and multiple affected families, misclassification of variants of uncertain significance (VUS) as causative [20], and lack of systematic analysis of Copy Number Variants (CNVs) [21].

Accurately determining the underlying cause of NC is paramount for its clinical management and prognosis. NC carries a significantly higher risk of progression to chronic kidney disease (CKD) than NL alone [12], with the rate of decline being highly disease-specific [22]. In this context, a definitive molecular diagnosis facilitates personalized therapeutic strategies and early interventions aimed at preserving kidney function. Thus, the present study aimed to elucidate the genetic basis of pediatric NC in a large, prospective cohort. Additionally, we sought to identify specific clinical phenotypes or parameters that were highly predictive of a positive genetic diagnosis.

Materials and methods

Patient recruitment

In this prospective, multicenter, nationwide cohort study, 79 patients with NC from 14 pediatric nephrology centers were recruited between January 2022 and December 2025. The inclusion criteria were written informed consent, age < 18 years, and an ultrasound-based diagnosis of medullary NC of unknown etiology. Patients with secondary NC due to primary hyperparathyroidism or possibly related to

medication use/treatment (e.g., corticosteroids, patients with congenital adrenal hypoplasia, X-linked hypophosphatemia on conservative treatment, or vitamin D intoxication) were not eligible. At recruitment, clinical, radiological, and laboratory data from patients were collected and analyzed in relation to their genetic status.

Molecular studies

First, we utilized targeted (Sanger) sequencing in patients with clear clinical diagnosis (*n* = 4), who were tested for 1–2 genes related to the respective diseases. In the remaining patients (*n* = 75), who required testing for a panel of genes for any reason, we applied whole-exome sequencing (WES) to analyze Single Nucleotide Variants (SNVs), small insertions and deletions, and CNVs (Fig. 1). In the two-step process, we examined a panel of 69 genes associated with NC. Next, in cases that remained negative for MD, we searched for deleterious variants in genes related to

a wide spectrum of kidney diseases (the panels are listed in Suppl. Table 1SA and S1B).

We examined rare variants with a minor allele frequency of < 1%, with the exception of a frequent variant in *SLC34A1* (c.272_292del, p.Val91_Ala97del), present in heterozygosity in 2.6% of the general population (gnomAD database). Although this variant is classified as likely benign, *in trans* with other strong *SLC34A1* pathogenic variants in the biallelic state, it may be called as a hypomorphic allele, and impact the phenotype [23–25]. Moreover, this variant in heterozygosity may also be considered a risk allele for stone disease [26]. The pathogenicity of the variants was classified using the American College of Medical Genetics and Genomics (ACMG) criteria for SNVs [27] and CNVs [28], as appropriate. Only variants classified as likely pathogenic (LP) or pathogenic (P) according to the above criteria were considered diagnostic (details in Suppl. Methods). Based on the molecular results, we separated the patients into three categories: 1/ MD (presence of LP/P biallelic variants in autosomal recessive diseases, monoallelic LP/P variants in autosomal dominant diseases, or hemizygous in X-linked disease), 2/ MA (presence of a single LP/P variant in autosomal recessive diseases, designated as predisposing variants to NC), and 3/ unsolved (the remaining cases, that is, without LP/P variant(s) in genes related to NL/NC). Following the most recent statement by the ACMG, we also report VUS and the corresponding clinical phenotypes in affected cases [29].

Clinical assessment and definitions of analyzed parameters

The analyzed data were obtained at recruitment and were provided by referring physicians from collaborating centers. For some patients, longitudinal data were available; thus, some biochemical parameters were defined as permanent or transient. Blood and urine analyses were performed locally, and the respective abnormalities were assessed according to local reference values. Medullary NC imaging by ultrasound was classified according to Hoyer's grading [30] – Suppl. Methods. The estimated glomerular filtration rate (eGFR) was calculated using Schwartz's equation [31]. The severity of CKD was

classified according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative CKD staging system, considering the physiologically lower GFR in children < 2 years of age [32]. The standard deviation scores for height and body mass index were calculated using the World Health Organization growth charts (http://www.who.int/growthref/en).

Statistical analysis

Continuous data are expressed as mean (standard deviation [SD]) or median (interquartile range [IQR]) depending on the data distribution; categorical data are presented as numbers (percentages). The chi-squared of Fisher's exact test were used to determine if there was a difference in the proportion of characteristics between the groups of patients. For continuous data, analysis of variance (one-way ANOVA) or the Kruskal-Wallis test was employed. Multinomial logistic regression analyses were used to assess the predictors of positive genetic testing results and were expressed as odd ratio (OR) and confidence intervals (CI). All *p-values* were two-sided and considered significant for $p < 0.05$.

Results

Cohort Characteristics

The study cohort comprised 79 unrelated pediatric patients with medullary NC from 79 non-consanguineous Caucasian families. Within this cohort, 59 children (74.7%) were newly diagnosed, whereas 20 (25.3%) had undergone a prior inconclusive genetic screening (Fig. 1). In the previously tested subgroup, 80% of patients (16/20) had received targeted Sanger sequencing. The remaining four patients underwent commercial next-generation sequencing panels for distal renal tubular acidosis (dRTA; patient F27), for NL/NC (patients F25, F26), and for kidney diseases (expanded renal disease panel of 401 genes; F67). Five hypercalcemic patients underwent genetic testing to exclude Williams syndrome. Crucially, in all these patients, prior genetic investigations failed to reveal any disease-causing or predisposing variants associated with NC. The comprehensive characteristics are presented in detail in Table 1.

Molecular Landscape of Nephrocalcinosis

Twenty-one causative LP/P variants in nine genes were identified, leading to a molecular diagnosis of MD in 16.4% of patients (13/79). Of these, four cases were identified by targeted (Sanger) sequencing based on highly suggestive phenotypes: familial hypomagnesemia, hypercalciuria and NC (FHHNC; *CLDN16*, *n* = 2, *CLDN19*, *n* = 1) and Dent disease type 1 (*CLCN5*; *n* = 1), while the remaining diagnoses were achieved through WES. In all these cases (8/13), except one, we detected disease-causing SNVs in other NC-related genes: *CYP24A1* (*n* = 3), *SLC34A1* (*n* = 2), *ATP6V0A4* (*n* = 1), *ATP6V1B1* (*n* = 1), and *KCNJ1* (*n* = 1). Finally, in one patient (F10), a WES-based CNV analysis disclosed a compound heterozygous deletions in *CLCNKB,* causative for Bartter syndrome (BS) type 3. The spectrum of MD

with the respective genes identified in this cohort is shown in Fig. 2. Biallelic inheritance was confirmed in 92.3% of MD cases (12/13), with one hemizygous *CLCN5* mutation. The detailed clinical and molecular profiles are summarized in Tables 2 and 3.

Beyond Mendelian causes, 16.4% of patients (13/79) harbored LP/P heterozygous variants that did not meet the stringent criteria for MD but were considered predisposing factors (MA category) – Table 4. These were identified in four genes, of which *SLC34A1* and *SLC34A3* accounted for 61.4%. Among the MA variants 85% (11/13) were enriched in our cohort compared to the general non-Finnish European population (Suppl. Table S2).

In total, ten genes were possibly implicated in the pathogenesis of NC, with four genes, that is, *CYP24A1*, *SLC34A1*, *SLC34A3*, and *CLDN16*, accounting for 77% of all identified variants (Table 3). Notably, 18.5% (5/27) of the identified diagnostic variants (in both categories) were novel variants. The details of the detected LP/P variants are presented in Suppl. Table S3.

Variants of Uncertain Significance and Incidental Findings

Several patients carried monoallelic VUS in *SLC34A3* (*n* = 3), *ATP6V1B1* (*n* = 2), *CYP24A1* (*n* = 1), *FAM20A* (*n* = 1), and *CLCNKB* (*n* = 1). Additionally, VUS were found in patients with another LP/P variant; that is, a female patient (F76) had a second variant in the same gene (*CYP24A1),* and two patients had a second *SLC34A3* variant in addition to P variants in *SLC34A1* (F31 and F35) – Table 4 and Suppl. Table S4.

Of note, the *SLC34A1* variant (p.Val91_Ala97del), a risk allele for stone disease, was identified in 10.1% (*n* = 8) of the cohort. However, the frequency of this allele (5.06%) was not significantly different from the 2.6% reported in the general population (*p* = 0.069; Suppl. Table S2).

WES also revealed incidental findings unrelated to NC, including LP/P heterozygous variants in *COL4A5* (c.1871G>A, p.Gly624Asp), *COL4A4* (c.5045G>A, p.Arg1682Gln), and *PKD1* (c.6406C>T, p.Gln2136Ter). Reverse phenotyping confirmed microhematuria in a female patient (F20) with the *COL4A5* variant, and kidney cysts in a female patient (F79) harboring the *PKD1* variant, who was also carrying a P heterozygous variant in *SLC34A3* (Table 4; Suppl. Fig. S1).

Predictors for Molecular Diagnosis

Comparative analysis revealed significant differences between MD, MA, and unsolved groups in clinical and laboratory parameters (Table 1). As expected, abnormal parathyroid hormone (PTH) levels and hypomagnesemia were more prevalent in the MD group, as was the severity of NC. However, in logistic regression analysis only low PTH (OR, 5.70; 95% CI, 1.55–21.03; $p = 0.009$) and low serum magnesium (OR, 5.44; 95% CI, 1.15–25.85; $p = 0.03$) were associated with MD.

Genotype-Phenotype Correlations and Clinical Impact

Patients with MD typically exhibited classical disease-specific phenotypes. A notable exception were two cases of BS (patient F10 and F34). Conversely, the MA group predominantly presented with isolated hypercalciuria, lacking systemic electrolyte or acid-base disturbances. Four of thirteen MA patients (30.8%) displayed intermediate phenotypes, including low PTH (patients F28 and F55) and hypomagnesemia (patient F31 and F79) – Table 4.

Molecular findings directly influenced clinical management in 30.8% of MD cases [4/13; infantile hypercalcemia (IH) type 1, *n* = 2 and BS, *n* = 2] – Table 2. Specifically, hydrochlorothiazide, previously administered to manage hypercalciuria, was discontinued due to its potential to exacerbate hypercalcemia or hypokalemia in these specific genetic contexts.

Characterization of Unsolved Cases

In 67% of the cohort (53/79), no causative or predisposing deleterious variants were identified, although five cases (5/53; 9.4%) presented with apparent *CYP24A1* phenotypes, which included hypercalcemia and low PTH (patients F30, F36, F46, F51, F52; Suppl. Table S4). Within this subgroup, seven individuals (7/53; 13.2%) had VUS, and another six patients (6/53; 11.3%) carried the *SLC34A1* allele (p.Val91_Ala97del). A portion of individuals in this category (11/53; 20.8%) had potential non-genetic or secondary causes for NC, including recurrent urinary tract infections (*n* = 4), neurofibromatosis type 1 (*n* = 3), hypothyroidism (incl. one case with Down syndrome, *n* = 3), and a history of acute kidney injury (*n* = 2) – Suppl. Fig. S2. Individuals from other categories did not present with the aforementioned conditions.

Discussion

To the best of our knowledge, this study represents the most extensive cohort-based genetic analysis of pediatric NC compiled to date. In this study we provide distinct data regarding both definitive disease-

causing variants and MA variants possibly predisposing to NC, which is the novelty of the study. Here, we employed WES, which has been proven an efficient method for genetic diagnostics in kidney diseases not only in detecting SNVs [10, 33], but also CNVs [34]. Thus, it could be regarded as the strength of this work since previous studies in patients with NL/NC did not systematically analyze CNVs [22].

Historically, patients with NL and NC have been evaluated collectively within large stone-former cohorts, wherein NC patients constitute only a small minority (Table 5). Although NL and NC share overlapping etiopathogenetic factors, they represent distinct pathophysiological entities. For instance, cystinuria serves as a primary genetic cause of NL but does not induce NC; conversely, FHHNC [35], dRTA [36] and IH type 2 [37] exhibit NC as an obligate, near-universal feature, whereas stone formation is significantly less prevalent. Evaluating these conditions collectively can obscure critical molecular distinctions. Given that, NC must be evaluated as a primary clinical entity, with or without NL.

Mendelian Landscapes

In this cohort, we identified 20 causative SNVs and one CNV across nine genes, establishing a definitive MD in ~16% of patients. This diagnostic yield is lower than the 40–50% success rates documented in several historical reports (Table 5), a discrepancy largely attributable to selection and recruitment biases in earlier cohorts. Many prior studies analyzed highly selected, small cohorts often derived from regions with elevated consanguinity rates, whereas our prospective, unselected study reflects a more representative clinical population. However, given potential regional variations driven by distinct ethnic architecture, consanguinity profile, or founder effect, these findings should be extrapolated with caution. Our data align with established national trends regarding some rare disorders. The relatively high proportion of FHHNC cases confirms previous observations of an elevated prevalence of this tubulopathy within the Polish population [35]. Conversely, no patients with primary hyperoxaluria were identified, confirming that this condition remains underrecognized or underreported locally [38]. When taking into account historical epidemiological data, this study shows that dRTA is not the leading cause of NC [4, 6], since this entity represents 15.4% of our cases with MD. Based on our findings it seems that calcium-phosphorus abnormalities due to IH type 1 and 2, found in 38.5% (5/13) of our MD cases, are currently the most common molecular causes of kidney calcifications. Intriguingly, we identified no cases of classical autosomal recessive hereditary hypophosphatemic rickets with hypercalciuria (HHRH), despite detecting a high proportion of MA heterozygous *SLC34A3* variants (4/13; 38%). This could be explained by the fact that some patients with HHRH may manifest with bone disease [37], and stay outside nephrological clinics. Furthermore, when interpreting our diagnostic yield alongside historical literature, it is evident that ultra-rare monogenic etiologies capable of presenting with medullary NC (e.g., Lowe syndrome) were not captured in this cohort. The absence or low frequency of such disorders may stem from their low prevalence (e.g., 1/500.000-1/1.000.000 for Lowe syndrome

[39]) and due to
a lower overall frequency of NC (e.g., ~50% in Lowe syndrome [39] and 40–70% in Dent disease [40]) or simply because prominent extrarenal features steer clinical management toward other subspecialties before primary renal genetics are pursued.

Monoallelic Predisposing Architecture

In light of expanding evidence characterizing non-Mendelian genetic architectures, we categorized our cohort using a framework similar to that established by Anderegg *et al*. [13]. While the prevalence of MD in pediatric stone-formers is well-documented, data regarding rare variants of intermediate effect size remain sparse. We found that 16% of the cohort carries MA variants potentially predisposing to NC. Importantly, 85% of MA variants were enriched in our cohort when compared to non-Finnish Europeans in gnomAD. Earlier pediatric studies frequently omitted MA profiling or misclassified these variants as primary causative factors (Table 5). The primary genetic driver within this category involved predominantly variants in genes encoding renal sodium–phosphate co-transporters, which accounted for 61% of the MA subgroup. Our observed frequency aligns closely with the 50% prevalence of MA variants in these genes reported by Anderegg *et al.* [13] and 40% reported by Cogal *et al.* [12] in an adult mixed NL/NC cohorts. Of note, in the latter study the authors claimed MA variants disease-causing, not predisposing. Distinguishing whether a rare heterozygous variant of intermediate effect size is causally linked to a phenotype or represents a coincidental background finding remains an ongoing challenge in genomic medicine [20]. Robust evidence from unbiased population cohorts supports a true predisposing role for *SLC34A3* [14, 15]. Similarly, genome-wide association studies have consistently linked the *SLC34A1* and *CYP24A1* loci with urolithiasis, though their individual effect sizes are modest [17-19]. Evidence supporting the predisposition to NC/NL of heterozygous *CLDN16* variants, found in 15% (2/13) of our MA cohort and in 2.5% in the entire cohort, has been provided just recently. In the large-scale dataset of adult kidney stone formers, the authors demonstrated that MA variants in *CLDN16* are significantly enriched in stone-formers compared to both non-stone-forming controls and general population datasets like gnomAD [14]. In addition to that, the most recent study of Liu IY *et al*. showed that both common and rare variants across the family of claudin genes (incl. *CLDN16*) contribute to kidney stone susceptibility in the general population [16], supporting an observation of an increased prevalence of NL in monoallelic carriers of LP/P *CLDN16* variants [41].

Here we showed that genetic architecture of NC is complex. Since genes which contribute to NC are highly penetrant, thus phenotypic characteristics are highly variable depending on allelic status. In this study we adopted the grouping of patients into MD and MA categories [13], however, some patients could be designated into either group. For example, one of the patients (F28), included into the MA group due to the stringent criteria we applied (see Material and methods section), carries two *SLC34A1* variants in biallelic state (*in trans*), of which one is P, while the second allele is likely benign (Table 4).

Although this variant has a mild or no effect on protein function [24, 42], it may be causative when accompanied by a highly damaging variant on the second allele. This hypomorphic allele may explain intermediate phenotype in our patient and/or mediate a more severe phenotype [23-25]. This phenomenon is well known in genetics, and was demonstrated in other kidney diseases (e.g., for genes *NPHS2* [43] or *PKD1* [44]).

Clinical Predictors of Monogenic Diseases

The secondary objective of this study was to identify clinical phenotypes and parameters capable of predicting
a positive monogenic diagnosis. Crucially, either clinical or structural parameters, including the sonographic severity of NC, prematurity and a family history of NC/NL were not predictive of a positive genetic diagnosis, indicating they should not be heavily weighted when determining the need for genetic testing. Aside from the patients with late-onset BS, the MD cohort exhibited classical, disease-specific clinical phenotypes. In stark contrast, patients in the MA group presented with a subtle phenotype predominantly characterized by NC and hypercalciuria without systemic electrolyte or acid-base derangements. However, lack of the classical phenotypes do not eliminate the possibility of MD as it has been shown in our two cases of BS and in many more case reports related to BS [45], and other tubular disorders. Importantly, some symptoms may develop (e.g., like hypokalemia in our case of BS; F10) or alleviate (e.g., in patients with IH type 1) with age [46, 47], making diagnosis a challenging task. Importantly, the biochemical parameters are instrumental, but should always be analyzed along with other abnormalities, typical for the respective disorders. We confirmed that low PTH and hypomagnesemia function as robust predictors of MD. These findings are expected, since these parameters reflect the dominant molecular mechanisms represented in our cohort. Hypomagnesemia is the cardinal feature of FHHNC, while suppressed PTH is a biochemical feature of IH type 1, type 2 and HHRH.

Unsolved cases and limitations

Despite utilizing high-efficiency WES, 67% of our cohort remained genetically unsolved. This diagnostic gap may be partially explained by inherent technical limitations of WES, such as an inability to systematically detect deep intronic variants or promoter-region alterations. Although we applied a WES-based CNV analysis, some large genomic rearrangements may have been missed. We may also hypothesize that some patients have translational impairment, which could only be detected by other techniques. In fact, among negative patients, there are five individuals with an apparent *CYP24A1* phenotype. As shown by others there is a small group of patients with this phenotype who have mRNA misfolding driven by the 3`UTR sequence of the gene [48]. Additionally, our data point to an equally critical clinical confounder: ultrasound-based diagnostic limitations. Medullary hyperechogenicity on

ultrasonography can easily phenocopy true NC, occurring in conditions such as underlying ciliopathies, acute kidney injury, chronic tubulointerstitial disease, or kidney scarring. Environmental and secondary non-genetic factors likely account for a significant proportion of the remaining unsolved cases. Within this subgroup, 22% of patients presented with clear medical conditions, which may pose a risk for NC (i.e., Down syndrome, hypothyroidism) or mimic NC (i.e., acute kidney injuries, recurrent urinary infections). Finally, while patients with documented vitamin D intoxication were excluded as per protocol, supplementation excess cannot be fully ruled out [49]. Prematurity,
a well-recognized independent driver of neonatal NC affecting up to 17% of preterm infants [50], occurred at
a similar frequency across all three diagnostic categories and did not serve as a distinguishing factor for unsolved cases, and consequently should not preclude molecular diagnosis.

In conclusion, this study clarifies the distinct genetic architecture underpinning pediatric medullary NC. Our data may explain the etiology of NC in approximately 30% of cases when considering MD and predisposing MA variants. Additionally, we provide evidence that disease-specific phenotypes are associated with MD, allowing for timely selection for genetic testing. However, the absence of typical features should not preclude a genetic diagnosis. No clinical parameters were found to be helpful in predicting monogenic causes.

Abbreviations

IH1
infantile hypercalcemia type 1
IH2
IH type 2
FHHNC
familial hypomagnesemia with hypercalciuria and nephrocalcinosis
dRTA
distal renal tubular acidosis
DD1
Dent disease type 1
BS2
Bartter syndrome type 2
BS3
BS type 3

Declarations

Data availability statement

The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Authors' contributions

MZ conceptualized and supervised the study, contributed to data analysis, interpretation of the results, and wrote the manuscript with support from EB-O, MKołbuc, JB, MAA, and AJ; MKołbuc, AO, PB, BB, JK-R, MM, KZ, AŻŻ, MS, PA, MSz, AW, BP, JS, JM, AŻ-C, MMW, KK-P, AB, PS collected data; JB performed statistical analyses; EB-O, MKonrad, ASS, BBB, and AJ performed molecular analyses and contributed to interpretation of the results; MAA assessed the final data, and provided feedback; All authors critically revised the content and approved the final version of the article.

Compliance with ethical standards

The study was approved by the ethics committee of our institution. Written informed consent was obtained from the legal caregivers of all participants. The study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration.

Competing interests All other authors have declared no competing interests.

Tables

Tables 1-5 are available in the Supplementary Files section.

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Figures

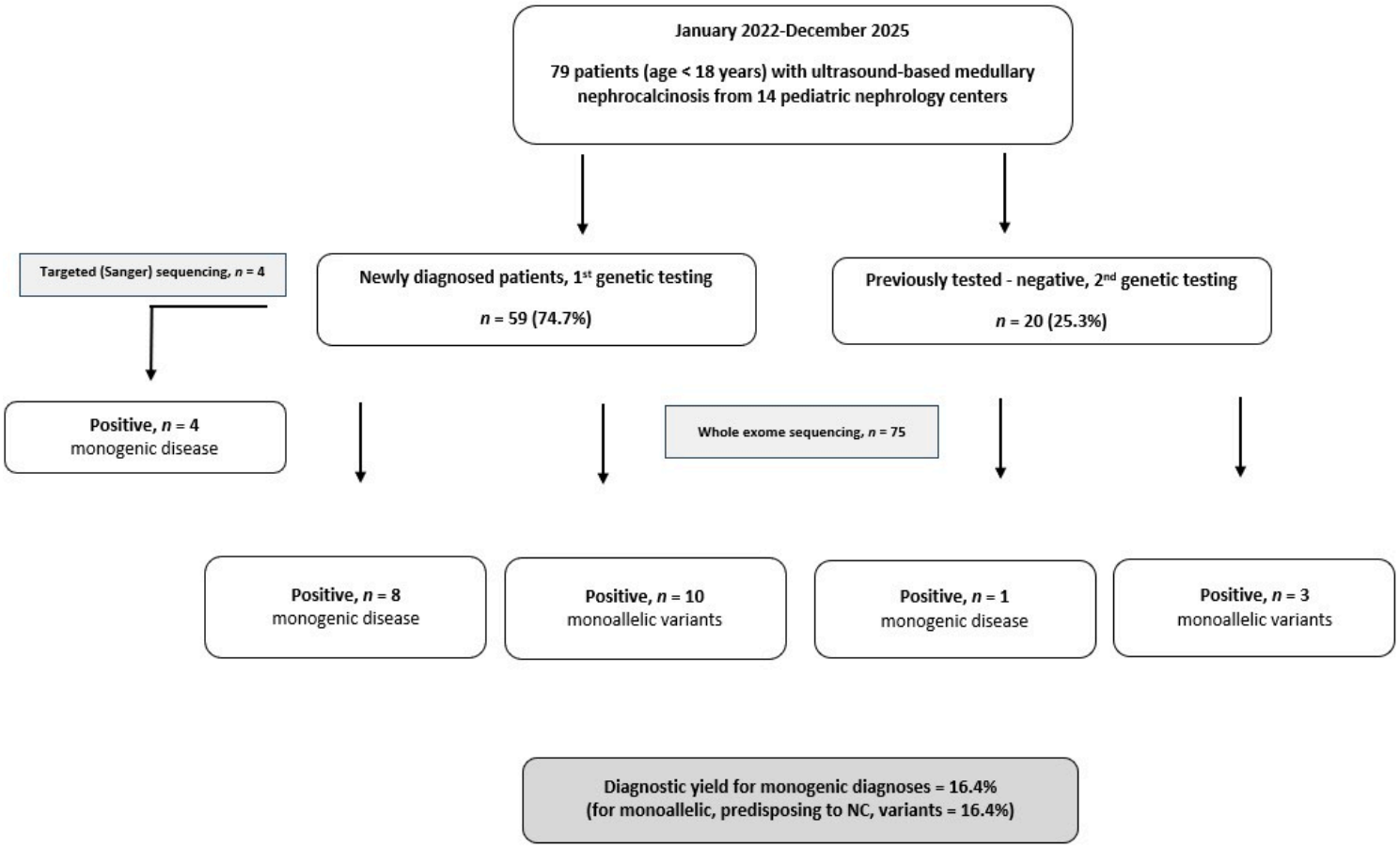


Figure 1

Flow diagram of the detection of disease-causing and predisposing (monoallelic) variants in genes related to nephrocalcinosis in a cohort of 79 children. The diagnostic yield for monogenic diagnoses in newly diagnosed, yet genetically untested patients was 20.3% compared to 5% in those with prior testing patients (p = 0.16). The overall diagnostic utility of whole-exome sequencing for monogenic causes was 12%, increasing to 29.3% when monoallelic variants were included

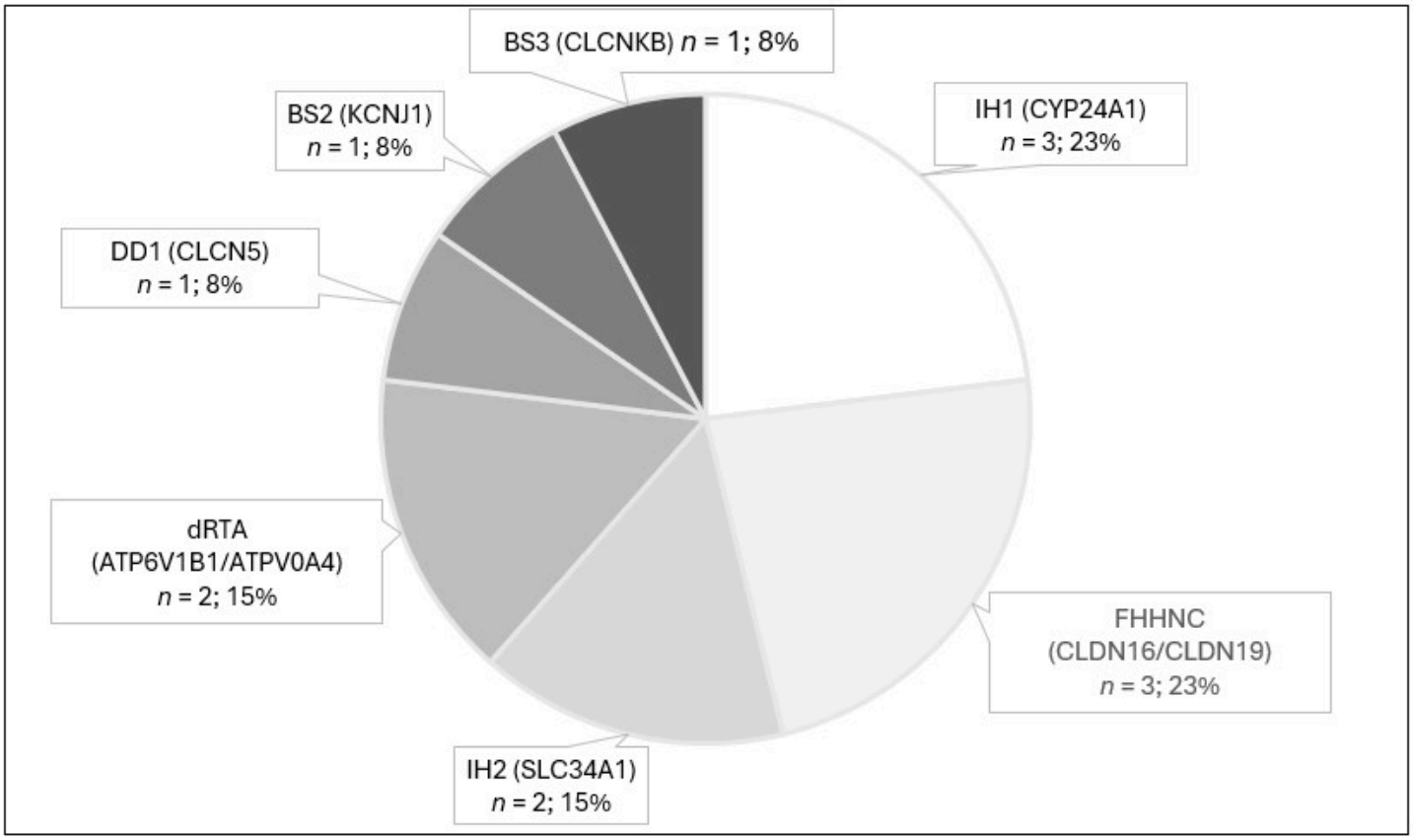


Figure 2

Spectrum of monogenic diagnoses in a cohort of children with nephrocalcinosis

Abbreviations: IH1, infantile hypercalcemia type 1; IH2, IH type 2; FHHNC, familial hypomagnesemia with hypercalciuria and nephrocalcinosis; dRTA, distal renal tubular acidosis; DD1, Dent disease type 1; BS2, Bartter syndrome type 2; BS3, BS type 3

Supplementary Files

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