# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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**SUPPLEMENTARY APPENDIX**

# Diagnostic utility of exome sequencing for kidney disease

*Emily E. Groopman, B.A.[1], Maddalena Marasa, M.D.[1], Sophia Cameron-Christie, Ph.D.[2], Slavé Petrovski, Ph.D.[2], Vimla S. Aggarwal, M.B., B.S.[3], Hila Milo-Rasouly, Ph.D.[1], Yifu Li, M.D.[1], Junying Zhang, B.S.[1], Jordan Nestor, M.D.[1], Priya Krithivasan, M.Sc.[1], Wan Yee Lam, B.S.[1], Adele Mitrotti, M.D.[1], Stacy Piva, B.A.[1], Byum Hee Kil, B.A.[1], Debanjana Chatterjee, Ph.D.[1], Rachel Reingold, B.S.[1], Drew Bradbury, B.S.[1], Michael DiVecchia, L.P.N.[1], Holly Snyder, N.P.[1], Xueru Mu, M.D., Ph.D.[1], Karla Mehl, M.D.[1], Olivia Balderes, B.A.[1], David A. Fasel, B.S.[4], Chunhua Weng, Ph.D.[4], Jai Radhakrishnan, M.D.[1], Pietro Canetta, M.D.[1], Gerald B. Appel, M.D.[1], Andrew S. Bomback, M.D., M.P.H.[1], Wooin Ahn, M.D.[1], Natalie S. Uy, M.D.[5], Shumyle Alam, M.D.[6], David J. Cohen, M.D.[1], Russell J. Crew, M.D.[1], Geoffrey K. Dube, M.D.[1], Maya K. Rao, M.D.[1], Sitharthan Kamalakaran, Ph.D.[7], Brett Copeland, B.S.[7], Zhong Ren, M.S.[7], Joshua Bridgers, M.S.[7], Colin D. Malone, Ph.D.[7], Caroline M. Mebane, M.S.[7], Neha Dagaonkar, M.S.[7], Bengt C. Fellström, M.D.[9], Ph.D.[8], Carolina Haefliger, M.D.[2], Sumit Mohan, M.D.[1,10], Simone Sanna-Cherchi, M.D.[1], Krzysztof Kiryluk, M.D., M.S.[1], Jan Fleckner, Ph.D.[2], Ruth March, Ph.D.[2], Adam Platt, Ph.D.[2], David B. Goldstein, Ph.D.[7,8], and Ali G. Gharavi, M.D.[1,7]*

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**SECTION S1**

**Supplementary Methods**

**Study design and protocol.** The study was designed by Dr. Gharavi, Emily Groopman, Dr. Goldstein, and Dr. Platt and was sponsored by the Columbia Institute for Genomic Medicine (IGM) and Astrazeneca. The study was approved by the Columbia University Institutional Review Board and local ethics committees and performed in accordance with the policy on bioethics and human biologic samples of the AURORA study sponsor, AstraZeneca. The sponsors, their representatives, and the authors collected and analyzed the data. All authors had full access to the data and vouch for the accuracy and completeness of the data. Emily Groopman and Dr. Gharavi wrote the first draft of the paper. All authors decided to submit the manuscript for publication.

**Cohorts.** We performed proband-only exome sequencing and diagnostic analysis among 3,315 individuals representing two independent cohorts of patients with kidney disease. 1,128 individuals were drawn from the AURORA study and 2,187 individuals were drawn from patients seen at Columbia University Medical Center (CUMC). The study was approved by the Columbia University Institutional Review Board and local ethics committees and performed in accordance with the policy on bioethics and human biologic samples of the AURORA study sponsor, AstraZeneca.

***AURORA***

The AURORA study and its inclusion and exclusion criteria have been previously described.[1-3] The AURORA study recruited males and females from 280 centers in 25 countries, with the majority of individuals from the United Kingdom and European Union.[2] Inclusion criteria were: 1) age between 50 and 80 years; and 2) all-cause end-stage renal disease (ESRD) undergoing hemodialysis for at least 3 months. The study did not select for or exclude patients based on the primary cause of ESRD. The exclusion criteria were: 1) having received statin therapy within the past 6 months or having a clear

indication or contraindication for use of a lipid-altering drug; 2) expected kidney transplantation within one year; 3) major hematological, neoplastic, metabolic (excluding diabetes), gastrointestinal, or infectious disease predicted to limit life expectancy to less than one year; 4) history of malignancy; 5) active liver disease (as indicated by an alanine aminotransferase level more than three times the upper limit of normal range); 6) history of statin-induced myopathy; 7) uncontrolled hypothyroidism; 8) unexplained creatine kinase more than three times the upper limit of the normal range; and 9) serious hypersensitivity to statins.

The AURORA study participants consented to genetic research; the consent defined that results would not be provided back to patients. As of May 2018, Global Data Protection Regulation (GDPR) in the European Union provides study participants with the right to request data. **Table S2** shows the clinical features of the exome sequenced AURORA participants versus all patients participating in the AURORA study.

***Columbia University Medical Center (CUMC) Genetic Studies of Chronic Kidney Disease (CKD)***

Columbia University Medical Center (CUMC) is a tertiary care medical center with a Nephrology Division providing care for all aspects of kidney disease, including both inherited and acquired forms of chronic kidney disease (CKD), hypertension and renovascular disease, and ESRD (dialysis and transplantation). Among the Division's areas of specialty care are glomerulopathies and inherited kidney diseases.

The CUMC Genetic Studies of Chronic Kidney Disease (IRB #AAAC7385) is a genetic research and biobanking protocol recruiting patients seen by the CUMC Nephrology Division for the evaluation and management of kidney disease, with the aim of elucidating the genetic basis of CKD. Inclusion criteria are a clinical diagnosis of CKD, the criteria for which include: the presence of renal failure requiring dialysis or transplantation; creatinine >1.5 mg/dL in men or >1.3 mg/dL in women with or without proteinuria; and/or the presence of significant proteinuria or hematuria indicative of

active glomerular disease. All patients with a clinical diagnosis of CKD are eligible, irrespective of age, sex/gender, and/or race/ethnicity.

Patients are recruited mainly through office visits; additional entry points include perinatal care (e.g., detection of congenital anomalies of the kidney and urinary tract on prenatal imaging and enrollment of the neonate after birth) and events held by nonprofit organizations for patients with various forms of CKD (e.g., National Kidney Foundation, IGA Nephropathy Foundation, NephCure Kidney International). Recruitment tools include an informational brochure, flyer, and consent forms, all of which are available in both English and Spanish and have been approved by the Columbia Institutional Review Board. Recruitment rate is approximately 80%.

Enrollment is achieved using a team of bilingual study coordinators who are in close contact with physicians. The physicians introduce the study to the participants. Once the potential participant indicates willingness to consider enrollment, then a study coordinator meets with the potential participant, reviews eligibility, explains the study in clear, easy-to-understand language, and provides a copy of the consent form for the participant to read. The study coordinator answers any questions from a participant regarding the study.

All individuals provide informed consent. For enrollment of minors, the signature of the parent/guardian is required. Minors 6 and under are explained the study in age-appropriate language but no assent is required. Minors between the ages of 7-11 with decision-making capability are explained the study in age-appropriate language, and verbal assent is obtained. Minors 12 and older with decision-making capability are explained the study in age-appropriate language, and written assent is documented on the consent form. At each step, individuals are reminded that their responses are confidential and that they may refuse to participate in the project or withdraw at any time without explanation, and further, that such an action will in no way affect their future interactions with their health care provider, or by CUMC. The consent includes: usage of the biosamples collected for genetic studies, including microarray and exome sequencing; and the request to be re-contacted if

a clinically actionable finding is identified, which as a research-level finding is first validated using a second sample collected from the individual at the time of re-contact in a clinically certified (CLIA) laboratory environment prior to being formally returned. The associated risks of CLIA validation are discussed with the individual, enabling he or she to make an informed choice regarding validation of the genetic findings.

Following the above consent process to participate in the study, individuals provide a single venous blood sample or buccal swab, from which DNA is extracted using standard protocols. As noted above, the DNA is used for genetic studies including microarray and exome sequencing. In the case of neonates, samples are obtained from umbilical cord blood, residual blood from clinical samples, buccal swabs, or from a single venous blood sample, in that order of preference. All data collected is stored in a secure computerized database, and all patient samples are stored using a unique, anonymized numerical identifier, with the relation of this identifier to patient names maintained in the locked computer file in the centralized database. Electronic data complies with all HIPAA and other privacy and security regulations, and resides on a firewall server maintained by the CUMC IT department.

The 2,187 probands in the present study were selected as broadly representative subset of the 3,122 patients recruited between October 2013 and September 2017 for the Genetic Studies of CKD protocol (**Table S3**). Importantly, the major clinical diagnostic categories seen in the general patient population seen by the CUMC Nephrology Division (**Table S4**) are represented among both the 2,187 exome-sequenced individuals and the 3,122 individuals recruited for the Genetic Studies of CKD.

**Diagnostic analysis pipeline.** We developed an in-house pipeline to analyze sequence data for diagnostic variants for patients' renal disease. The major steps, including exome sequencing, bioinformatics processing, variant annotation, and sequence interpretation, are detailed below:

### *Exome sequencing*

Genomic DNA was isolated from patient samples using standard protocols, and sequenced at the Columbia Institute for Genomic Medicine (IGM). Peripheral blood samples were provided for the majority of patients, although other sources of DNA were accepted. Sequence capture was performed using either the Roche NimbleGen SeqCap Exome EZ v3.0 kit or the IDT xGen Exome Research Panel v1.0 kit. Paired-end sequencing was performed on the Illumina 2500 HiSeq platform or the Illumina NovaSeq 6000 platform, using 125bp and 150bp reads, respectively. Mean sequence coverage was 111x, with on average 97% of the target bases in a given sample achieving at least 10x coverage.

### *Bioinformatics processing*

Exome sequence data was processed as previously described.[4] Briefly, reads were aligned to the reference genome (Genome Reference Consortium build 37, human genome 19) using Burrows-Wheeler Alignment Tool (BWA), followed by duplicate removal using Picard tools. Variant and genotype calling were performed using GATK v3.6 best practices.[5]

### *Variant annotation*

Variants were annotated using the Analysis Tool for Annotated Variants[6] (https://redmine.igm.cumc.columbia.edu/projects/atav) and ANNOVAR[7] (http://annovar.openbioinformatics.org/).

Key resources used for variant annotation are listed below:

| Purpose | Resource | URL |
|---|---|---|
| Predict effect of DNA sequence variant on function of the encoded protein | ANNOVAR | http://annovar.openbioinformatics.org/ |
| | SnpEff | http://snpeff.sourceforge.net/ |
| Assess variant frequency (minor allele frequency; MAF) in the general population | Genome Aggregation Database (gnomAD) | http://gnomad.broadinstitute.org/ |
| | Exome Aggregation Consortium (ExAC) | http://exac.broadinstitute.org/ |
| | dbSNP | https://www.ncbi.nlm.nih.gov/SNP/ |
| | 1000 Genomes Project | http://www.internationalgenome.org/ |
| | DiscovEHR | http://www.discovehrshare.com/ |
| In-silico prediction of deleteriousness of variant | dbNSFP (version 3.3a) | https://sites.google.com/site/jpopgen/dbNSFP |
| Identify prior reports of variant in disease cases | Human Gene Mutation Database (HGMD, v. 2017.2) | http://www.hgmd.cf.ac.uk/ac/index.php |
| | ClinVar (release 08/15/2017) | https://www.ncbi.nlm.nih.gov/clinvar/ |
| | Leiden Open Variant Database (LOVD) | http://www.lovd.nl/ |
| | Autosomal Dominant Polycystic Kidney Disease Mutation Database (PKDB) | http://pkdb.mayo.edu/ |

In addition, to facilitate identification of variants potentially causal for nephropathy we utilized a manually curated list of 625 genes associated with Mendelian forms of genitourinary disease. This list was generated by querying the Online Mendelian Inheritance in Man (OMIM)[8] and Orpha.net[9] databases for genes associated with Mendelian forms of genitourinary disease, followed by manual review of the primary literature to assess the strength of evidence supporting each gene-disease association and characterize the relevant molecular genetic and clinical attributes of the gene-disease pairs.

Our research group created this list in May 2016 and have made it publicly available via our website (http://www.columbiamedicine.org/divisions/gharavi/resources.php; uploaded 07/31/2018).

The genes, associated conditions, and number of exons uncaptured by the exome sequencing capture kits used in this study are given in **Table S5**.

### *Variant interpretation*

#### Primary findings for Mendelian forms of nephropathy

We prioritized rare (MAF ≤1%) nonsynonymous variants and canonical splice site variants occurring in the above 625 nephropathy-associated genes (**Table S5**), and also evaluated such rare, predicted deleterious variants in other genes associated with Mendelian disorders using the OMIM database. In addition, we analyzed sequence data for more common (MAF > 1%) Mendelian nephropathy-associated alleles, such as the *NPHS2* p.R229Q allele. The *NPHS2* p.R229Q allele is known to be causal for steroid-resistant nephrotic syndrome when found in trans with certain variants in the more distal exons[10,11]; thus, for the purposes of diagnostic analysis, we noted only the patients who harbored it with another such pathogenic allele (see **Table S7**).

To identify diagnostic variants, we assessed 1) the pathogenicity of the variant per American College of Medical Genetics (ACMG) guidelines for diagnostic sequence interpretation[12] and 2) whether it was explicative for the individual's renal disease, based on the clinical information available. Only alleles that both were classified as Pathogenic or Likely Pathogenic per ACMG criteria and were judged to be explicative for the individual's renal disease were deemed diagnostic. Diagnostic variants were manually reviewed using the Integrative Genomics Viewer[13]; those which were also suspect of being artefactual variant calls based on variant type (e.g., small indels) or sequencing quality metrics (single nucleotide variants with a genotype quality score ≤30) were confirmed by Sanger sequencing.

*Variant-level assessment*

As noted above, we classified variants according to the ACMG guidelines for diagnostic sequence interpretation.[12] Supporting criteria for alleles classified as Pathogenic or Likely Pathogenic at the variant level are provided in the relevant tables (**Table S7 and Table S14**).

Per this framework, variants for which 1) not all criteria were met to qualify as Pathogenic or Likely Pathogenic or 2) the criteria for benign and pathogenic were contradictory were classified as variants of uncertain significance (VUS). We identified on average 6.6 VUS per individual (range 3-8), with 85.9% of individuals having at least one VUS. Novel, rare missense variants in autosomal dominant nephropathy-associated genes accounted for the majority of these cases, with 77.6% of individuals with VUS harboring at least one such variant. The majority of recurrent VUS were previously reported variants listed as disease causal in clinical variant databases (i.e., classified as "Pathogenic" or "Likely Pathogenic" in ClinVar and/or "Disease Mutation (DM)" in the Human Gene Mutation Database) whose allele frequencies exceeded that expected for the associated disorder, based on known disease prevalence and allelic heterogeneity.

We then applied stringent filtering criteria to the observed VUS to assess the minimal burden of these variants (see **Supplementary Table S6**). We considered individuals with heterozygous genotypes under a dominant model and those with biallelic (i.e., hemizygous, homozygous, and compound heterozygous) genotypes under a recessive model; filtering criteria for each model are summarized below:

| **Model** | **Dominant** | **Recessive** |
|---|---|---|
| Genotypes | Heterozygous | Biallelic (homozygous, hemizygous, or compound heterozygous) |
| Population allele frequency cutoff‡ | Zero (absent) | ≤ 0.05% and zero homozygotes |
| Variant types | Nonsense, frameshift, splice-site, in-frame insertion/deletion, missense | |
| Predicted deleteriousness# | CADD[14] ≥ 20; Missense variants – predicted damaging by 3 out of 3 missense meta-predictors: MetaSVM,[15] M-CAP,[16] REVEL[17] | |

‡Population allele frequency cutoff was evaluated using the global frequency in the Genome Aggregation Database (gnomAD), a database including exome sequence data from 123,136 unrelated population controls. The 0.05% frequency cutoff was calculated using a previously published formula to derive frequencies for causal variants for monogenic disorders,[18] using the following parameters: prevalence ≤ 1/10,000, corresponding to the maximal estimated prevalence of common recessive monogenic renal disorders[19]; full penetrance; and each causal variant accounting for no more than 5% of disease cases.

#CADD ≥ 20: top 1% deleteriousness percentile of variants, relative to all possible single-nucleotide substitutions of the human genome. (Not applicable for insertion/deletion variants.)

Missense score cutoffs were: MetaSVM – D (Damaging); M-CAP – D (Damaging); REVEL ≥ 0.7 (corresponding to exclusion of 95% of benign variants).

The resultant stringently filtered list (see **Supplementary Table S6**) consists of 1,088 heterozygous genotypes and 29 biallelic genotypes; altogether, 927 (28.0%) of the 3,315 individuals in the AURORA-CUMC cohort harbored at least one such stringently filtered VUS.

These findings highlight the challenges of diagnostic exome sequence analysis, including interpreting the many sufficiently rare, previously unreported protein-altering alleles that are present in a given individual's exome and the need to stringently review alleles listed as disease causal in clinical variant databases.

*Case-level assessment*

Following identification of putatively pathogenic variants (classified as Pathogenic or Likely Pathogenic per ACMG guidelines), we assessed whether the genetic findings were explicative for the individual's renal disease via reviewing their available clinical data. For CUMC patients, we had access to individuals' electronic health records, which we manually reviewed to assess whether the genetic findings were explicative for the patient's observed clinical presentation. For AURORA cases, we had more limited information, which included the primary cause of renal disease, as classified by broad etiologic subtype, and the major medical problems, given as clinical diagnostic codes, for each individual. The individuals for which the variants found were explicative of their known clinical presentation were deemed diagnostic cases (**Table S7**).

For an additional 30 patients (**Table S14**), the putatively pathogenic variants found remained inexplicative of their known clinical presentation following review. These alleles may in fact be contributory, but nonetheless were not deemed diagnostic due to insufficient phenotypic concordance based on the clinical information available.

**Additional findings of renal relevance.** In addition to assessing sequence data for variants in genes associated with Mendelian forms of nephropathy, we annotated for the *APOL1* risk genotypes (two copies of the *APOL1* G1 (rs73885139 and rs60910145) and G2 (rs71785313) risk alleles; i.e., G1/G1, G1/G2, or G2/G2), as they have been reported to influence disease risk, prognosis, and transplant outcomes across different forms of nephropathy.[20,21] However, the presence of the *APOL1* risk genotype was considered independently of the findings diagnostic for Mendelian forms of nephropathy, and thus not counted towards the yield of such diagnostic variants.

**Secondary findings.** We assessed CUMC patients' sequence data for pathogenic variants in the 59 genes recommended by the ACMG for return as medically actionable secondary findings for individuals undergoing genome-wide sequencing.[22] As the AURORA study protocol and consent did not permit analysis of the cohort for secondary findings, we did not perform this analysis for AURORA patients. Per ACMG recommendations for analysis of secondary findings,[22] we noted only variants classified as known pathogenic (KP) or expected pathogenic (EP).

EP variants were noted only among the genes for which reporting EP as well as KP variants has been recommended,[22] and, per current ACMG recommendations for secondary findings,[22] were limited to previously unreported loss-of-function variants (LOFs; defined as nonsense, frameshift, and canonical splice site) occurring in genes for which LOF is a known mechanism of disease. To identify (KP) missense variants, we rigorously curated missense variants previously reported pathogenic (i.e., classified as "Pathogenic" or "Likely Pathogenic" in ClinVar and/or "Disease Mutation (DM)" in the

Human Gene Mutation Database). The missense variants included here thus represent variants meeting the criteria to be classified as Known Pathogenic, which include multiple independent case occurrences, with segregation amongst the families assessed and experimental evidence using well-established assays supporting that the variant impairs the function of the gene or encoded protein.

**Comparison of the diagnostic yield of exome sequencing versus that using more targeted genetic testing**

To further examine the diagnostic utility of exome sequencing for patients with kidney disease, we evaluated the diagnostic yield found in our study to the yield which may result from applying more targeted approaches. To this aim, we compared the diagnostic yield observed using exome sequencing in the combined AURORA-CUMC cohort to that potentially obtained used the more targeted modality of phenotype-driven gene panels.

Given that clinicians may vary in how they classify patients' phenotypes and which gene panels they choose to order for that phenotype, we evaluated the yield of targeted panels for congenital or cystic renal disease, glomerulopathy (including the subtypes of Alport syndrome and thin basement membrane disease and focal segmental glomerulosclerosis), and tubulointerstitial disease across major clinical diagnostic categories of kidney disease, represented in the AURORA-CUMC cohort (see **Table 1**). The phenotypes targeted by these panels are among the leading indications for genetic testing among patients suspected to have monogenic forms of nephropathy.[23,24] Moreover, these panels include the most prevalent monogenic forms of nephropathy detected in our cohort (see **Figure 1**): autosomal dominant polycystic kidney disease due to mutations in *PKD1* and *PKD2* (cystic renal disease panels); glomerulopathy due to mutations in *COL4A3*, *COL4A4*, and *COL4A5* (glomerulopathy panels); and *UMOD*-associated tubulointerstitial disease (tubulointerstitial disease panels).

As the panels for these phenotypes can also vary between different genetic testing providers, we assessed offerings from three different clinical laboratories. When evaluating diagnostic yield of targeted testing for each phenotype, we assessed panels from these three different clinical genetic testing providers, and conservatively used the union of the panels assessed – i.e., we defined positive cases as those for which the causal gene detected via exome sequencing was included on *any* of the three targeted panels included for the given phenotype. Similarly, for the comparison, we assumed equivalent technical sensitivity and specificity for each testing modality. Gene panels were

identified via querying the National Institutes of Health Genetic Testing Registry (GTR; see https://www.ncbi.nlm.nih.gov/gtr/) for gene panels associated with each of the above broad phenotypes.

The panels used, along with the provider, number of genes tested, and GTR test identification number, are provided in **Table S18.** The results of the comparison are shown in **Table S19**.

## SECTION S2

### Clinical characteristics of the patients with diagnostic *PKD1* and *PKD2* variants

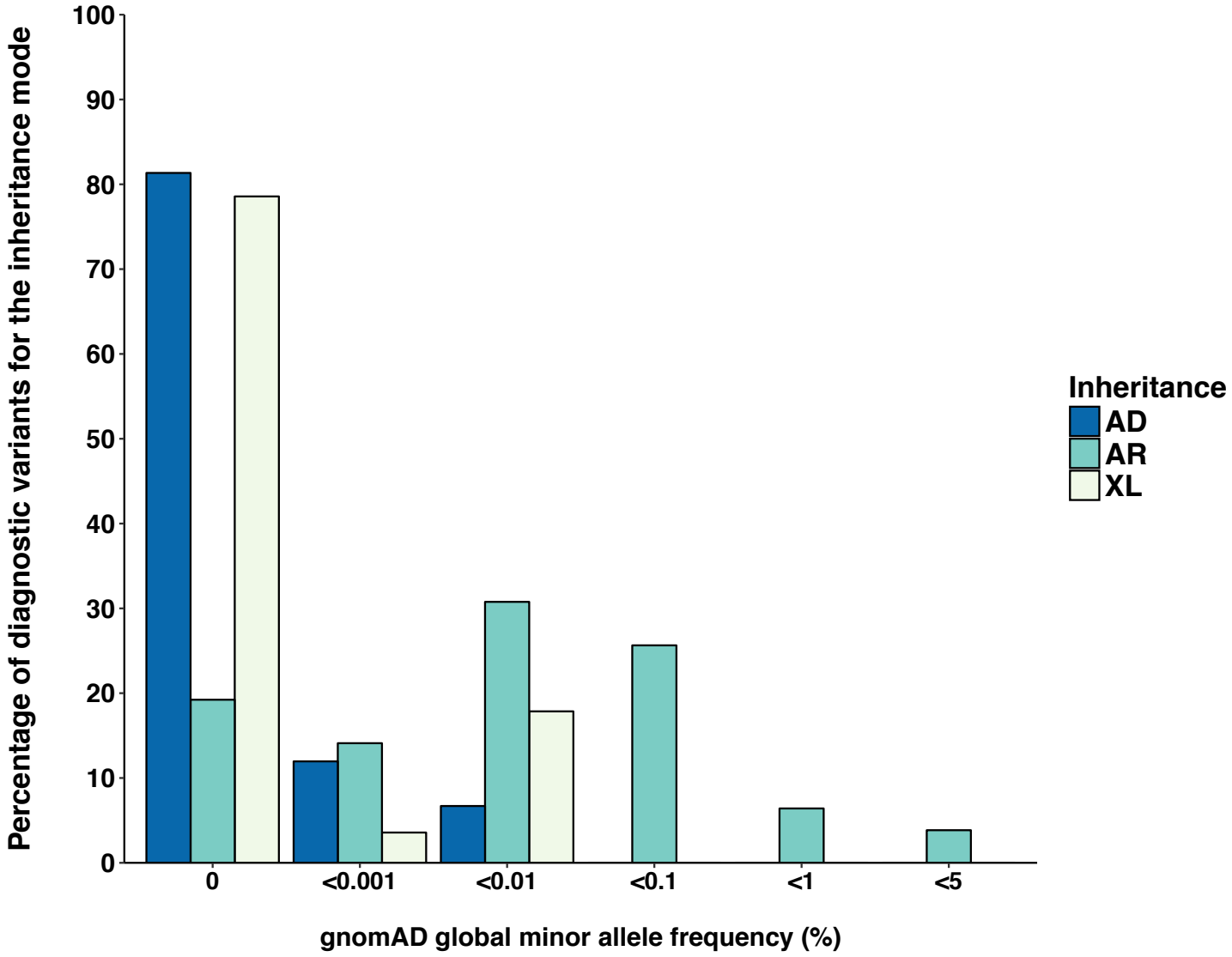
In total, we detected diagnostic variants for ADPKD in 97 cases: 75 patients harbored variants in *PKD1*, and 22 patients had variants in *PKD2* (see **Figure 1** and **Table S7 and Table S8**). Review of the available clinical data supports that single-gene testing of *PKD1* and *PKD2* would have been a viable option for the majority of these patients, but it is important to recognize that for a minority, the primary cause of disease was uncertain based on clinical findings alone, favoring broader genetic workup. Moreover, recent of discoveries of additional genes producing ADPKD-spectrum phenotypes, such as *GANAB*[25] and *DNAJB11*[26] suggest that such that genome-wide testing may still be useful, e.g., for cases with such phenotypes null for diagnostic variants in *PKD1* or *PKD2*. We did not detect diagnostic variants in such newly discovered genes among the cases in our cohort, which may reflect that, as noted in reviews of the studies to date of large ADPKD cohorts, the overwhelming majority of ADPKD patients have variants in *PKD1* (~78%) and *PKD2* (~15%).[27,28]

The patients with diagnostic genetic findings in *PKD1* and *PKD2* overwhelmingly consisted of individuals clinically diagnosed with “congenital or cystic renal disease” (94/97; 96.9%). The 5 CUMC cases within this clinical diagnostic category had a specific diagnosis of the associated disease, autosomal dominant polycystic kidney disease (ADPKD). The 89 AURORA cases with *PKD1* and *PKD2* alterations all had clinical diagnoses of “congenital or cystic renal disease” and strongly supportive features based on the available clinical data, such as a history of polycystic liver disease, prior nephrectomy, and/or prior cerebrovascular accident.

The remaining 3/97 cases (3.1%) in whom *PKD1/2* alterations were found harbored clinical diagnoses of nephropathy of unknown origin. As these patients were from CUMC, we were able to review their electronic health records. These individuals showed more atypical presentations (e.g., age over 40 years at presentation, asymmetric or focal PKD on renal imaging, no reported family history of renal disease) such that the primary cause of disease was deemed to be uncertain by the

referring clinician (i.e., a clinical diagnosis of nephropathy of unknown origin). Genetic analysis has been recommended to resolve such atypical cases, as mutations in other genes can yield overlapping clinical phenotypes.[27,29] Hence, broader genetic testing approaches, such as an expanded renal cystic disease gene panel or exome sequencing, may still be useful in this subset of individuals.

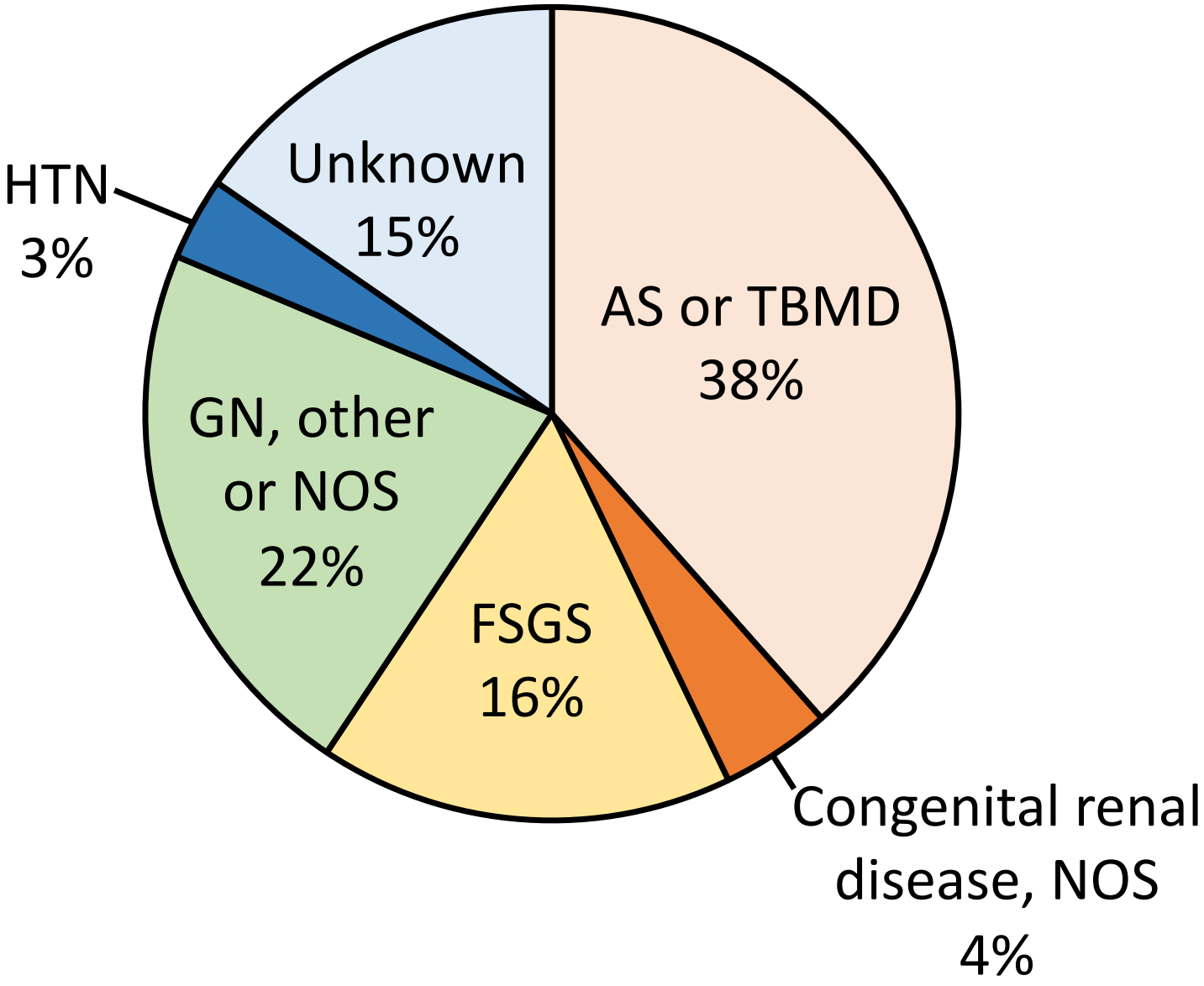
**Figure S1. Allele frequency distribution of the 343 diagnostic variants**




The frequency distribution of the 343 diagnostic variants is shown above. The x-axis shows the frequency of the variant (minor allele frequency; MAF) in the Genome Aggregation Database (gnomAD), a database including exome sequence data from 123,136 unrelated population controls, using the following frequency thresholds: zero (absent in gnomAD), <0.001%, <0.01%, <0.1%, <1%, and <5%. The y-axis shows the percent of diagnostic variants for a given inheritance mode – autosomal dominant (AD); autosomal recessive (AR); or X-linked (XL) – within this frequency bin. The frequencies of the diagnostic variants largely fell well below 1%, a commonly used threshold for "rare variants," with 228 (66%) of the 343 variants altogether absent in gnomAD. The maximum MAF

observed across all variants and inheritance modes was 3.1%, corresponding to the *NPHS2* p.R229Q allele, a common variant causal for steroid-resistant nephrotic syndrome when found in trans with certain variants in the more distal exons, including the p.A284V and p.R291W alleles (also observed here)[10,11]. Excluding the *NPHS2* p.R229Q allele, the maximum MAF observed, across all variants and inheritance modes, was 0.38%.

**Figure S2. Clinical diagnostic spectrum of patients with diagnostic variants in *COL4A3-5***




The clinical diagnostic spectrum of the patients with diagnostic variants in the *COL4A3, COL4A4,* and *COL4A5* genes is shown above. In total, variants in these genes accounted for 92 genetic diagnoses in 91 patients: as a single trait in 90 patients and as a dual molecular diagnosis in one patient, who had diagnostic variants in both *COL4A4* and *COL4A5* (see **Table S10**).

The clinical diagnoses of these 91 cases are summarized below. Notably, the majority of patients with *COL4A3-5* variants did not have the clinical diagnosis of the associated hereditary nephropathies, Alport syndrome or Thin Basement Membrane Disease (AS or TBMD, a subtype of glomerulopathy).

| **Clinical diagnosis** | **No. of patients** | **Proportion of all patients with diagnostic *COL4A3-5* variants (%)** |
|---|---|---|
| Glomerulopathy | 70 | 77 |
| *Alport syndrome or thin basement membrane disease* | *35* | *38* |
| *Focal segmental glomerulosclerosis* | *15* | *16* |
| *Other or not otherwise specified glomerulopathy* | *20* | *22* |
| Non-Glomerulopathy | 21 | 23 |
| *Congenital renal disease (not otherwise specified)* | *4* | *4* |
| *Hypertensive nephropathy* | *3* | *3* |
| *Nephropathy of unknown origin* | *14* | *15* |
| **Total** | **91** | **100** |

Note that percentages may not sum to 100 due to rounding.

Clinical diagnoses are abbreviated in **Figure S2** as follows: GN: glomerulopathy; AS or TBMD: Alport syndrome or thin basement membrane disease, a subtype of glomerulopathy; FSGS: focal segmental glomerulosclerosis, a subtype of glomerulopathy; HTN: hypertensive nephropathy; NOS: not otherwise specified; Unknown: nephropathy of unknown origin.

**Table S1. Stages of Chronic Kidney Disease (CKD)**

Under current guidelines,[30] chronic kidney disease (CKD) is defined as "abnormalities of kidney structure or function present for >3 months, with implications for health." It is recommended that CKD be classified based on the cause and two indices of renal function: the estimated glomerular filtration rate (eGFR) and albuminuria (a metric of urinary protein excretion), the latter which can be used to further subdivide each stage. The stages of CKD, along with the associated eGFR, level of disease severity, and presence of clinical symptoms, are listed below.

| CKD Stage | eGFR[#] | eGFR category | Level of Disease Severity[†] | Clinical Symptoms[‡] |
|---|---|---|---|---|
| Stage 1 | ≥90 | Normal or high | Normal renal function without proteinuria but increased CKD risk | Patients are often asymptomatic, but may show symptoms resulting from the underlying etiology of kidney disease. |
| Stage 2 | 60-89 | Mildly decreased | Normal renal function without proteinuria but increased CKD risk | Patients are often asymptomatic, but may show symptoms resulting from the underlying etiology of kidney disease. |
| Stage 3a | 45-59 | Mildly to moderately decreased | Mild to moderate CKD without substantial proteinuria | Patients can be asymptomatic; some report symptoms. |
| Stage 3b | 30-44 | Moderately to severely decreased | Mild to moderate CKD without substantial proteinuria | Patients can be asymptomatic; some report symptoms. |
| Stage 4 | 15-29 | Severely decreased | Advanced CKD or any CKD with substantial proteinuria | Patients often show worsening symptoms. |
| Stage 5 | <15 | Kidney failure | Advanced CKD or any CKD with substantial proteinuria | Patients often show worsening symptoms. |

[#]eGFR: estimated glomerular filtration rate, an index of renal function (units: ml/min per 1.73 $m^2$ body surface area).
[†]The categories of proteinuria (measured via assessment of urinary albumin excretion, i.e., albuminuria) are: A1 (albuminuria <30 mg/g), A2 (30-300 mg/g) and A3 (>300 mg/g), respectively corresponding to normal to mildly increased, moderately increased, and severely increased. Here, "substantial proteinuria" is defined as albuminuria >300 mg/g.[31]
See Kalantar-Zadeh and Fouque[31] for a detailed list of the clinical symptoms associated with the different severity levels and stages of CKD.

**Table S2. Clinical features of the exome sequenced AURORA participants versus all AURORA study participants**

| Cohort | Exome sequenced | | All participants | |
|---|---|---|---|---|
| **No. of Patients** | **1,128** | | **2,773** | |
| **Characteristic** | **N** | **%** | **N** | **%** |
| ***Age at time of study entry (yr)*** | | | | |
| <50 | 1 | 0.1 | 3 | 0.1 |
| 50-59 | 387 | 34.3 | 968 | 34.9 |
| 60-69 | 367 | 32.5 | 899 | 32.4 |
| 70+ | 373 | 33.1 | 903 | 32.6 |
| ***Sex*** | | | | |
| Female | 427 | 37.9 | 1050 | 37.9 |
| Male | 701 | 62.1 | 1723 | 62.1 |
| ***Race/Ethnicity*** | | | | |
| White European | 1023 | 90.7 | 2354 | 84.9 |
| Hispanic | 50 | 4.4 | 113 | 4.1 |
| Black/African American | 18 | 1.6 | 98 | 3.5 |
| Asian | 20 | 1.8 | 139 | 5.0 |
| Other/Unspecified | 17 | 1.5 | 69 | 2.5 |
| ***Clinical diagnosis*** | | | | |
| Congenital or cystic renal disease | 159 | 14.1 | 356 | 12.8 |
| Glomerulopathy | 231 | 20.5 | 512 | 18.5 |
| Diabetic nephropathy | 184 | 16.3 | 535 | 19.3 |
| Hypertensive nephropathy | 193 | 17.1 | 554 | 20.0 |
| Tubulointerstitial disease | 212 | 18.8 | 399 | 14.4 |
| Other | 50 | 4.4 | 129 | 4.7 |
| Nephropathy of unknown origin | 99 | 8.8 | 288 | 10.4 |

[#]For the full AURORA cohort, only the age categories above were available; thus, the ages of the AURORA patients exome sequenced were binned into these categories, to facilitate direct comparison between them and all participants.

Per the AURORA study design (see **Section S1, Cohorts**), all patients included had reached end-stage renal disease and were on dialysis.

**Table S3. Clinical features of the exome sequenced Columbia University Medical Center (CUMC) Genetic Studies of Chronic Kidney Disease (CKD) participants versus all Genetic Studies of CKD study participants**

| **Cohort** | **Exome sequenced** | | **All participants** | |
|---|---|---|---|---|
| **No. of Patients** | **2,187** | | **3,122** | |
| **Characteristic** | **N** | **%** | **N** | **%** |
| ***Age at time of study entry (yr)*** | | | | |
| 0-21 | 278 | 12.7 | 460 | 14.7 |
| 22-44 | 713 | 32.6 | 953 | 30.5 |
| 45-64 | 800 | 36.6 | 1034 | 33.1 |
| 65+ | 396 | 18.1 | 675 | 21.6 |
| ***Sex*** | | | | |
| Female | 945 | 43.2 | 1355 | 43.4 |
| Male | 1242 | 56.8 | 1767 | 56.6 |
| ***Race/Ethnicity*** | | | | |
| White European | 1113 | 50.9 | 1752 | 56.1 |
| Hispanic | 435 | 19.9 | 538 | 17.2 |
| Black/African American | 330 | 15.1 | 430 | 13.8 |
| Asian | 224 | 10.2 | 286 | 9.2 |
| Other/Unspecified | 85 | 3.9 | 116 | 3.7 |
| ***Clinical diagnosis*** | | | | |
| Congenital or cystic renal disease | 372 | 17.0 | 678 | 21.7 |
| Glomerulopathy | 1180 | 54.0 | 1592 | 51.0 |
| Diabetic nephropathy | 186 | 8.5 | 199 | 6.4 |
| Hypertensive nephropathy | 126 | 5.8 | 157 | 5.0 |
| Tubulointerstitial disease | 32 | 1.5 | 38 | 1.2 |
| Other | 109 | 5.0 | 127 | 4.1 |
| Nephropathy of unknown origin | 182 | 8.3 | 331 | 10.6 |
| ***Reached ESRD*** | 1016 | 46.5 | 1167 | 37.4 |
| ***Positive family history for kidney disease*** | 619 | 28.3 | 1032 | 33.1 |

ESRD: End-stage renal disease (including both patients on dialysis and renal transplant recipients).

**Table S4. Clinical diagnostic composition of the Columbia University Medical Center (CUMC) Nephrology outpatient population versus the Genetic Studies of Chronic Kidney Disease (CKD) patients**

| | All CUMC Nephrology Outpatients in 2017 | | CUMC Genetic Studies of CKD | | | |
|---|---|---|---|---|---|---|
| | | | Exome sequenced | | All recruited | |
| **Total no. of patients** | **5,819** | | **2,187** | | **3,122** | |
| Clinical Diagnosis | N | % | N | % | N | % |
| Congenital or cystic renal disease | 256 | 4.4 | 372 | 17.0 | 678 | 21.7 |
| Glomerulopathy | 739 | 12.7 | 1180 | 54.0 | 1592 | 51.0 |
| Diabetic nephropathy | 659 | 11.3 | 186 | 8.5 | 199 | 6.4 |
| Hypertensive nephropathy | 2220 | 38.2 | 126 | 5.8 | 157 | 5.0 |
| Tubulointerstitial disease | 38 | 0.7 | 32 | 1.5 | 38 | 1.2 |
| Other | 590 | 10.1 | 109 | 5.0 | 127 | 4.1 |
| Nephropathy of unknown origin | 1317 | 22.6 | 182 | 8.3 | 331 | 10.6 |

CKD: Chronic kidney disease; CUMC: Columbia University Medical Center.

**Table S5. 625 genes associated with Mendelian forms of kidney and genitourinary disease†**

| Gene Name | Cytogenetic Location | OMIM Gene MIM Number | Associated Mendelian Kidney/Genitourinary Disorder | No. of exons not targeted by exome sequencing capture kit | | |
|---|---|---|---|---|---|---|
| | | | | Roche | IDT | Both |
| *ABCC6* | 16p13.11 | 603234 | Pseudoxanthoma elasticum arterial calcification, generalized, of infancy, 2 | 0 | 0 | 0 |
| *ABCD4* | 14q24.3 | 603214 | Methylmalonic aciduria and homocystinuria, cblJ type | 0 | 0 | 0 |
| *ACE* | 17q23 | 106180 | Renal tubular dysgenesis | 0 | 0 | 0 |
| *ACP5* | 19p13.2 | 171640 | Spondyloenchondrodysplasia with immune dysregulation | 0 | 0 | 0 |
| *ACTA2* | 10q23.31 | 102620 | Multisystemic smooth muscle dysfunction syndrome | 0 | 0 | 0 |
| *ACTB* | 7p22.1 | 102630 | Baraitser-Winter syndrome 1 | 0 | 0 | 0 |
| *ACTG2* | 2p13.1 | 102545 | Megacystis-microcolon-intestinal hypoperistalsis syndrome, Visceral myopathy | 0 | 0 | 0 |
| *ACTN4* | 19q13 | 604638 | Focal Segmental Glomerulosclerosis 1 | 0 | 0 | 0 |
| *ACVRL1* | 12q13.13 | 601284 | Hereditary hemorrhagic telangiectasia | 0 | 0 | 0 |
| *ADAMTS13* | 9q34.2 | 604134 | Thrombotic thrombocytopenic purpura, familial | 0 | 0 | 0 |
| *AFF4* | 5q31.1 | 604417 | CHOPS syndrome | 0 | 0 | 0 |
| *AGPAT2* | 9q34.3 | 603100 | Lipodystrophy congenital generalized, type 1 | 0 | 0 | 0 |
| *AGT* | 1q42-43 | 106150 | Renal tubular dysgenesis | 0 | 0 | 0 |
| *AGTR1* | 3q24 | 106165 | Renal tubular dysgenesis | 0 | 0 | 0 |
| *AGXT* | 2q37.3 | 604285 | Hyperoxaluria, primary, type 1 | 0 | 0 | 0 |
| *AHI1* | 6q23.3 | 608894 | Joubert Syndrome 3 | 0 | 0 | 0 |
| *ALG8* | 11q14.1 | 608103 | Polycystic liver disease 3 with or without kidney cysts | 0 | 0 | 0 |
| *ALG9* | 11q23 | 606941 | Gillessen-Kaesbach-Nishimura sundrome (GIKANIS), Congenital disorder of glycosylation, type 2 | 0 | 0 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *ALMS1* | 2p13.1 | 606844 | Alstrom syndrome | 0 | 1 | 0 |
| *ALPL* | 1p36.12 | 171760 | Hypophosphatasia, infantile | 0 | 0 | 0 |
| *AMER1* | Xq11.2 | 300647 | Osteopathia striata with cranial sclerosis | 0 | 0 | 0 |
| *AMN* | 14q3232 | 605799 | Megaloblasticanemia1-norwegian_type | 0 | 0 | 0 |
| *ANKS6* | 9q22.33 | 615370 | Nephronophthisis 16 | 0 | 0 | 0 |
| *ANLN* | 7p14.2 | 616027 | Focal Segmental Glomerulosclerosis 8 | 0 | 0 | 0 |
| *ANOS1* | Xp22.31 | 300836 | Hypogonadotropic hypogonadism 1 with or without anosmia (Kallmann syndrome 1) | 0 | 0 | 0 |
| *AP2S1* | 19q13.32 | 602242 | Hypocalciuric hypercalcemia, familial type 3 | 0 | 0 | 0 |
| *APC2* | 19p13.3 | 612034 | Sotos syndrome | 0 | 0 | 0 |
| *APOA1* | 11q23.3 | 107680 | Amyloidosis, familial visceral, 3 or more types | 0 | 0 | 0 |
| *APOPT1* | 14q32.33 | 616003 | Mitochondrial Complex 4 deficiency | 0 | 0 | 0 |
| *APRT* | 16q24.3 | 102600 | Adenine phosphoribosyltransferase deficiency | 0 | 0 | 0 |
| *AQP2* | 12q12-q13 | 107777 | Diabetes insipidus, nephrogenic | 0 | 0 | 0 |
| *ARHGDIA* | 17q25.3 | 601925 | Nephrotic syndrome type 8 | 0 | 0 | 0 |
| *ARID1A* | 1p36.11 | 603024 | Coffin-Siris syndrome | 0 | 0 | 0 |
| *ARID1B* | 6q25.3 | 614556 | Coffin-Siris syndrome | 0 | 0 | 0 |
| *ARL13B* | 3q111 | 608922 | Nephronophtisis, Joubert syndrome 8 | 0 | 0 | 0 |
| *ARL6* | 3q11.2 | 608845 | Bardet-biedl syndrome 3 | 0 | 0 | 0 |
| *ARMC5* | 16p11.2 | 615549 | Cushing syndrome due to macronodular adrenal hyperplasia | 0 | 0 | 0 |
| *ARNT2* | 15q25.1 | 606036 | Webb-Dattani syndrome | 0 | 0 | 0 |
| *ARX* | Xp21.3 | 300382 | Proud syndrome | 0 | 0 | 0 |
| *ASXL1* | 20q11.21 | 612990 | Bohring-Opitz syndrome | 0 | 0 | 0 |
| *ATP6V0A4* | 7q34 | 605239 | Renal tubular acidosis, distal | 0 | 0 | 0 |
| *ATP6V1B1* | 2p13.3 | 192132 | Renal tubular acidosis with deafness | 0 | 0 | 0 |
| *ATP7A* | Xq21.1 | 300011 | Occipital horn syndrome | 0 | 0 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *ATP7B* | 13q14.3 | 606882 | Wilson Disease | 0 | 0 | 0 |
| *AUH* | 9q22.31 | 600529 | 3-methylglutaconic aciduria, type I | 0 | 0 | 0 |
| *AVP* | 20p13 | 192340 | Diabetes insipidus, neurohypophyseal | 0 | 0 | 0 |
| *AVPR2* | Xq28 | 300538 | Nephrogenic syndrome of inappropriate diuresis Diabetes insipidus, nephrogenic | 0 | 0 | 0 |
| *B2M* | 15q21.1 | 109700 | Amyloidosis, familial visceral | 0 | 0 | 0 |
| *B3GLCT* | 13q12.3 | 610308 | Peters-plus syndrome | 0 | 0 | 0 |
| *B4GAT1* | 11q13.2 | 605517 | Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 13 | 0 | 0 | 0 |
| *B9D1* | 17p11.2 | 614144 | Meckel syndrome; Meckel-Gruber syndrome type 9 | 0 | 0 | 0 |
| *B9D2* | 19q13.2 | 611951 | Meckel syndrome type 10 | 0 | 0 | 0 |
| *BBIP1* | 10q25.2 | 613605 | Bardet-Biedl syndrome 18 | 0 | 0 | 0 |
| *BBS1* | 11q13.2 | 209901 | Bardet-Biedl syndrome 1 | 0 | 0 | 0 |
| *BBS10* | 12q21.2 | 610148 | Bardet-Biedl syndrome 10 | 0 | 0 | 0 |
| *BBS12* | 4q27 | 610683 | Bardet-Biedl syndrome 12 | 0 | 0 | 0 |
| *BBS2* | 16q12.2 | 606151 | Bardet-Biedl syndrome 2 | 0 | 0 | 0 |
| *BBS4* | 15q24.1 | 600374 | Bardet-Biedl Syndrome 4 | 0 | 0 | 0 |
| *BBS5* | 2q31.1 | 603650 | Bardet-Biedl Syndrome 5 | 0 | 0 | 0 |
| *BBS7* | 4q27 | 607590 | Bardet-Biedl syndrome 7 | 0 | 0 | 0 |
| *BBS9* | 7p14.3 | 607968 | Bardet-Biedl syndrome 9 | 0 | 0 | 0 |
| *BCOR* | Xp11.4 | 300485 | Microphthalmia, Lenz type; Microphthalmia, syndromic 2 | 0 | 0 | 0 |
| *BCS1L* | 2q35 | 603647 | Mitochondrial complex 3 deficiency, nuclear type 1 | 0 | 0 | 0 |
| *BMP4* | 14q22-23 | 112262 | Microphthalmia, syndromic 6 | 0 | 0 | 0 |
| *BMPER* | 7p14.3 | 608699 | Diaphanospondylodysostosis | 0 | 0 | 0 |
| *BRAF* | 7q34 | 164757 | Noonan syndrome with multiple lentigines, Cardiofaciocutaneous syndrome | 0 | 1 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *BRIP1* | 16p11.2 | 605882 | Fanconi anemia | 0 | 0 | 0 |
| *BSCL2* | 11q12.3 | 606158 | Lipodystrophy congenital generalized, type 2 | 0 | 0 | 0 |
| *BSND* | 1p32.1 | 606412 | Bartter Syndrome, Type 4a, neonatal | 0 | 0 | 0 |
| *BUB1B* | 15q15.1 | 602860 | Mosaic variegated aneuploidy syndrome 1 | 0 | 0 | 0 |
| *C1QA* | 1p36.12 | 120550 | C1q Deficiency | 0 | 0 | 0 |
| *C1QB* | 1p36.12 | 120570 | C1q Deficiency | 0 | 0 | 0 |
| *C1QC* | 1p36.12 | 120575 | C1q Deficiency | 0 | 0 | 0 |
| *C2* | 6p21.33 | 613927 | C2 Deficiency | 0 | 0 | 0 |
| *C3* | 19p13.3 | 120700 | Complement component 3 deficiency | 0 | 0 | 0 |
| *C4A* | 6p21.33 | 120810 | Complement component 4A deficiency | 0 | 0 | 0 |
| *C5orf42* | 5p13.2 | 614571 | Orofaciodigital syndrome 6 | 0 | 0 | 0 |
| *CA2* | 8q21.2 | 611492 | Osteopetrosis with renal tubular acidosis | 0 | 0 | 0 |
| *CACNA1S* | 1q321 | 114208 | Hypokalemic periodic paralysis, hokpp | 0 | 0 | 0 |
| *CAD* | 2p23.3 | 114010 | Congenital disorder of glycosylation, type Iz | 0 | 0 | 0 |
| *CASP10* | 2q33.1 | 601762 | Autoimmune Lymhoproliferative syndrome type 2A | 0 | 0 | 0 |
| *CASR* | 3q13 | 601199 | Neonatal severe primary hyperparathyroidism; Hypocalcemia with Bartter syndrome | 0 | 0 | 0 |
| *CC2D2A* | 4p15.32 | 612013 | Joubert syndrome with hepatic defect, Joubert syndrome with oculorenal defect, Meckel Syndrome 6, Jouber syndrome 9, COACH syndrome | 0 | 0 | 0 |
| *CCBE1* | 18q21.32 | 612753 | Hennekam Lymphangiectasia-Lymphedema Syndrome | 0 | 0 | 0 |
| *CCDC22* | Xp11.23 | 300859 | 3C syndrome | 0 | 0 | 0 |
| *CD151* | 11p15.5 | 602243 | Nephropathy with pretibial epidermolysis bullosa and deafness | 0 | 0 | 0 |
| *CD19* | 16p11.2 | 107265 | Immunodeficiency, common variable, 3 | 0 | 0 | 0 |
| *CD81* | 11p15.5 | 186845 | Immunodeficiency, common variable, 6 | 0 | 0 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *CD96* | 3q13.1-q13.2 | 606037 | C syndrome | 0 | 0 | 0 |
| *CDC5L* | 6p21 | 602868 | Congenital Anomalies of the Kidney and the Urinary Tract | 0 | 0 | 0 |
| *CDC73* | 1q31.2 | 607393 | Hyperparathyroidism 2 | 0 | 0 | 0 |
| *CDKN1B* | 12p13.1 | 600778 | Multiple endocrine neoplasia, type 4 | 0 | 0 | 0 |
| *CDKN1C* | 11p15.5 | 600856 | Beckwith-wiedemann syndrome; IMAGE syndrome | 0 | 0 | 0 |
| *CECR1* | 22q11.1 | 607575 | Sneddon syndrome Polyarteritis nodosa, childhood-onset | 0 | 0 | 0 |
| *CENPF* | 1q41 | 600236 | Stromme syndrome | 0 | 0 | 0 |
| *CEP104* | 1p36.32 | 616690 | Joubert syndrome 25 | 0 | 0 | 0 |
| *CEP120* | 5q23.2 | 613446 | Short-rib thoracic dysplasia 13 with or without polydactyly | 0 | 0 | 0 |
| *CEP164* | 11q23.3 | 614848 | Senior-Loken syndrome, Nephronopthisis 15 | 0 | 0 | 0 |
| *CEP290* | 12q21.32 | 610142 | Joubert syndrome with oculorenal defect, Bardet-biedl syndrome 14, Joubert Syndrome 5, Meckel syndrome 4, Senior-Loken Syndrome 6 | 0 | 0 | 0 |
| *CEP41* | 7q32.2 | 610523 | Joubert's syndrome type 15 | 0 | 0 | 0 |
| *CEP83* | 12q22 | 615847 | Nephronophthisis 18 | 0 | 0 | 0 |
| *CFH* | 1q31.3 | 134370 | Complement factor h deficiency | 0 | 0 | 0 |
| *CFHR5* | 1q31.3 | 608593 | Nephropathy due to CFHR5 deficiency | 0 | 0 | 0 |
| *CFI* | 4q25 | 217030 | Complement factor I deficiency | 0 | 0 | 0 |
| *CHD7* | 8q12.2 | 608892 | CHARGE syndrome | 0 | 0 | 0 |
| *CHRM3* | 1q43 | 118494 | Prune belly syndrome, Eagle-barrett syndrome | 0 | 0 | 0 |
| *CHST14* | 15q15.1 | 608429 | Ehlers-Danlos syndrome, musculocontractural type 1 | 0 | 0 | 0 |
| *CISD2* | 4q24 | 611507 | Wolfram syndrome 2 | 0 | 0 | 0 |
| *CLCN5* | Xp11.23 | 300008 | Dent disease nephrolithiasis type 1 hypophosphatemic Rickets | 0 | 0 | 0 |
| *CLCNKA* | 1p36.13 | 602024 | Bartter's Syndrome Type 4b, Neonatal | 0 | 0 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *CLCNKB* | 1p36.13 | 602023 | Bartter syndrome, type 3 and type 4b | 0 | 0 | 0 |
| *CLDN16* | 3q28 | 603959 | Hypomagnesemia 3, renal | 0 | 0 | 0 |
| *CLDN19* | 1p34.2 | 610036 | Familial primary hypomagnesemia with hypercalciuria and nephrocalcinosis with severe ocular involvement; Hypomagnesemia 5, renal, with ocular involvement | 0 | 0 | 0 |
| *CNNM2* | 10q24.32 | 607803 | Hypomagnesemia type 6 Hypomagnesemia, seizures, and mental retardation | 0 | 0 | 0 |
| *COL18A1* | 21q22.3 | 120328 | Knobloch syndrome | 0 | 0 | 0 |
| *COL4A1* | 13q34 | 120130 | Hereditary angiopathy with nephropathy, aneurysms and Msucle cramps (HANAC) | 0 | 0 | 0 |
| *COL4A3* | 2q36-q37 | 120070 | Alport syndrome | 0 | 0 | 0 |
| *COL4A4* | 2q35-q37 | 120131 | Alport syndrome; nephrotic syndrome (FSGS 1) | 0 | 0 | 0 |
| *COL4A5* | Xq22.3 | 303630 | Alport syndrome | 0 | 0 | 0 |
| *COL5A1* | 9q34.3 | 120215 | Ehlers-Danlos syndrome, classic type | 0 | 0 | 0 |
| *COPA* | 1q23.2 | 601924 | Autoimmune interstitial lung, joint, and kidney disease | 0 | 0 | 0 |
| *COQ2* | 4q21.23 | 609825 | Coenzyme q10 deficiency | 0 | 0 | 0 |
| *COQ6* | 14q24.3 | 614647 | Coenzyme Q10 deficiency, primary, 6 | 0 | 0 | 0 |
| *COQ7* | 16p12.3 | 601683 | Coenzyme Q10 deficiency, primary, 8 | 0 | 0 | 0 |
| *COQ8B* | 19q13.1 | 615567 | Nephrotic syndrome, type 9 | 0 | 0 | 0 |
| *COQ9* | 16q21 | 612837 | Coenzyme Q10 deficiency, primary, 5 | 0 | 0 | 0 |
| *COX10* | 17p12 | 602125 | Mitochondrial Complex  4 deficiency | 0 | 0 | 0 |
| *COX14* | 12q13.12 | 614478 | Mitochondrial Complex 4 deficiency | 0 | 0 | 0 |
| *COX20* | 1q44 | 614698 | Mitochondrial Complex 4 deficiency | 0 | 0 | 0 |
| *COX6B1* | 19p13.12 | 124089 | Mitochondrial Complex 4 deficiency | 0 | 0 | 0 |
| *COX7B* | Xp21.1 | 300885 | Linear skin defects with multiple congenital anomalies 2 | 0 | 0 | 0 |
| *COX8A* | 11q13.1 | 123870 | Mitochondrial Complex 4 deficiency | 0 | 0 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *CPT1A* | 11q13.3 | 600528 | Carnitine palmitoyl transferase 1A deficiency | 0 | 0 | 0 |
| *CPT2* | 1p32 | 600650 | Lethal neonatal carnitine palmitoyltransferase 2 deficiency | 0 | 0 | 0 |
| *CRB2* | 9q33.3 | 609720 | FSGS 9 Ventriculomegaly with cystic kidney disease | 0 | 0 | 0 |
| *CREBBP* | 16p133 | 600140 | Rubinstein Taybi syndrome type 1 | 0 | 0 | 0 |
| *CRTAP* | 3p22.3 | 605497 | Osteogenesis imperfecta, type 7 | 0 | 0 | 0 |
| *CSPP1* | 8q13.1-q13.2 | 611654 | Meckel syndrome, Joubert syndrome 21 | 0 | 0 | 0 |
| *CTC1* | 17p13.1 | 613129 | Dyskeratosis congenita | 0 | 0 | 0 |
| *CTNS* | 17p13 | 606272 | Cystinosis, nephropathic cystinosis, late-onset juvenile or adolescent nephropathic | 0 | 0 | 0 |
| *CUBN* | 10p13 | 602997 | Megaloblastic anemia 1-finnish type | 0 | 0 | 0 |
| *CUL3* | 2q36.2 | 603136 | Pseudohypoaldosteronism, type 2e | 0 | 0 | 0 |
| *CYP11A1* | 15q24.1 | 118485 | 46,XY disorder of sex development-adrenal insufficiency due to CYP11A1 deficiency syndrome; Inherited isolated adrenal insufficiency due to CYP11A1 deficiency | 0 | 0 | 0 |
| *CYP11B1* | 8q24.3 | 610613 | Congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency | 0 | 0 | 0 |
| *CYP17A1* | 10q243 | 609300 | 17-alpha-hydroxylase17,20-lyasedeficiency | 0 | 0 | 0 |
| *CYP21A2* | 6p21.33 | 613815 | Adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency; Hyperandrogenism, nonclassic type, due to 21-hydroxylase deficiency | 0 | 0 | 0 |
| *CYP24A1* | 20q13.2 | 126065 | Hypercalcemia infantile, 1 | 0 | 0 | 0 |
| *DCDC2* | 6p22.3 | 605755 | Nephronophthisis 19 | 0 | 0 | 0 |
| *DCHS1* | 11p15.4 | 603057 | Van Maldergem syndrome 1 | 0 | 0 | 0 |
| *DDX59* | 1q32.1 | 615464 | Orofaciodigital syndrome V | 0 | 0 | 0 |
| *DGKE* | 17q22 | 601440 | Nephrotic syndrome type 7 | 0 | 0 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *DHCR7* | 11q13.4 | 602858 | Smith-Lemli-Opitz Syndrome | 0 | 0 | 0 |
| *DIS3L2* | 2q37.1 | 614184 | Perlman's syndrome (nephroblastomatosis, gigantism) | 0 | 0 | 0 |
| *DKC1* | Xq28 | 300126 | Dyskeratosis Congenita, X-linked | 0 | 0 | 0 |
| *DLG3* | Xq13.1 | 300189 | Mental retardation, x-linked 90 | 0 | 0 | 0 |
| *DLL3* | 19q13.2 | 602768 | Autosomal recessive spondylocostal dysostosis | 0 | 0 | 0 |
| *DLL4* | 15q15.1 | 605185 | Adams-Oliver syndrome 6 | 0 | 0 | 0 |
| *DLX4* | 17q21.33 | 601911 | Orofacial cleft 15 | 0 | 0 | 0 |
| *DMP1* | 4q22.1 | 600980 | Hypophosphataemic rickets | 0 | 0 | 0 |
| *DNA2* | 10q21.3 | 601810 | Seckel syndrome 8 | 0 | 0 | 0 |
| *DNAAF1* | 16q24.1 | 613190 | Ciliary dyskinesia, primary, 13 | 0 | 0 | 0 |
| *DNASE1L3* | 3p14.3 | 602244 | Systemic Lupus Erythematosus 16 | 0 | 0 | 0 |
| *DNMT3B* | 20q1121 | 602900 | Immunodeficiency-centromeric instability, facial anomalies syndrome 1, icf1 | 0 | 0 | 0 |
| *DPH1* | 17p13.3 | 603527 | Developmental delay with short stature, dysmorphic features, and sparse hair | 0 | 0 | 0 |
| *DSTYK* | 1q321 | 612666 | Congenital Anomalies of the Kidney and the Urinary Tract | 0 | 0 | 0 |
| *DYNC2H1* | 11q22.3 | 603297 | Short rib-polydactyly syndrome, Verma-Naumoff type, Short rib-polydactyly syndrome (Jeune's syndrome) type 3 | 0 | 0 | 0 |
| *EBP* | Xp11.23 | 300205 | Chondrodysplasia punctata | 0 | 0 | 0 |
| *EDNRA* | 4q31.22-q31.23 | 131243 | Mandibulfacial dysostosis with alopecia | 0 | 0 | 0 |
| *EFEMP2* | 11q13.1 | 604633 | Cutis laxa type 1 | 0 | 0 | 0 |
| *EGF* | 4q25 | 131530 | Hypomagnesemia 4, renal | 0 | 0 | 0 |
| *EHHADH* | 3q27.2 | 607037 | Fanconi renotubular syndrome 3 | 0 | 0 | 0 |
| *EIF2AK3* | 2p12 | 604032 | Wolcott-Rallison Syndrome | 0 | 0 | 0 |
| *EIF2B4* | 2p23.3 | 606687 | Ovarioleukodystrophy, leukoencelpaly with vanishing white | 0 | 0 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | matter | | | |
| *EMP2* | 16p13.13 | 602334 | Nephrotic syndrome type 10 | 0 | 0 | 0 |
| *ENG* | 9q34.11 | 131195 | Hereditary hemorrhagic telangiectasia | 0 | 0 | 0 |
| *ENPP1* | 6q23.2 | 173335 | Hypophosphataemicrickets | 0 | 0 | 0 |
| *EPG5* | 18q12.3-q21.1 | 615068 | Vici syndrome | 0 | 0 | 0 |
| *ERBB3* | 12q13.2 | 190151 | Lethal congenital contracture syndrome 2 | 0 | 0 | 0 |
| *ERCC4* | 16p13.12 | 133520 | Fanconi anemia, Xeroderma pigmentosum, type f, Cockayne syndrome | 0 | 0 | 0 |
| *ERCC6* | 10q11.23 | 609413 | Cockayne syndrome, type B | 0 | 0 | 0 |
| *ERCC8* | 5q12.1 | 609412 | Cockayne Syndrome, Type A | 0 | 0 | 0 |
| *ESCO2* | 8p21.1 | 609353 | Roberts syndrome | 0 | 0 | 0 |
| *ETFA* | 15q23-q25 | 608053 | Glutaric aciduria 2a | 0 | 0 | 0 |
| *ETFB* | 19q13.3 | 130410 | Glutaric acidemia 2b | 0 | 0 | 0 |
| *ETFDH* | 4q32.1 | 231675 | Glutaric acidemia 2c | 0 | 0 | 0 |
| *EVC* | 4p16.2 | 604831 | Ellis Van Creveld syndrome | 0 | 0 | 0 |
| *EVC2* | 4p16.2 | 607261 | Ellis Van Creveld syndrome | 0 | 0 | 0 |
| *EYA1* | 8q13.3 | 601653 | Branchio-oto-renal syndrome 1 | 0 | 0 | 0 |
| *FAH* | 15q25.1 | 613871 | tyrosinemia, type 1 | 0 | 0 | 0 |
| *FAM20A* | 17q24.2 | 611062 | Amelogenesis imperfecta-nephrocalcinosis syndrome; Amelogenesis imperfecta type IG (enamel-renal syndrome) | 0 | 0 | 0 |
| *FAM20C* | 7p22.3 | 611061 | Raine syndrome | 0 | 0 | 0 |
| *FAM58A* | Xq28 | 300708 | STAR (toe Syndactyly, Telecanthus, and Anogenital and Renal Malformations) | 0 | 0 | 0 |
| *FAN1* | 15q13.2-q13.3 | 613534 | Interstitial nephritis, karyomegalic | 0 | 0 | 0 |

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|---|---|---|---|---|---|---|
| *FANCA* | 16q24.3 | 607139 | Fanconi anemia, complementation group a | 0 | 0 | 0 |
| *FANCB* | Xp22.2 | 300515 | Fanconi anemia, complementation group b | 0 | 0 | 0 |
| *FANCC* | 9q22.32 | 613899 | Fanconi anemia, complementation group c | 0 | 0 | 0 |
| *FANCD2* | 3p26 | 613984 | Fanconi anemia, Complementation group d2 | 0 | 0 | 0 |
| *FANCE* | 6p22-p21 | 613976 | Fanconi anemia, complementation group e | 0 | 0 | 0 |
| *FANCF* | 11p14.3 | 613897 | Fanconi anemia | 0 | 0 | 0 |
| *FANCG* | 9p13.3 | 602956 | Fanconi anemia | 0 | 0 | 0 |
| *FANCI* | 15q26.1 | 611360 | Fanconi anemia, complementation group I | 0 | 0 | 0 |
| *FANCL* | 2p16.1 | 608111 | Fanconi anemia, complementation group L | 0 | 0 | 0 |
| *FANCM* | 14q21.2 | 609644 | Fanconi anemia | 0 | 0 | 0 |
| *FASTKD2* | 2q33.3 | 612322 | Mitochondrial Complex 4 deficiency | 0 | 0 | 0 |
| *FAT4* | 4q28.1 | 612411 | Van Maldergem Syndrome 2 Hennekam lymphangiectasia-lymphedema syndrome 2 | 0 | 0 | 0 |
| *FBLN5* | 14q32.12 | 604580 | Cutis laxa type IA | 0 | 0 | 0 |
| *FBXL4* | 6q16.1-q16.2 | 605654 | Mitochondrial DNA depletion syndrome 13 | 0 | 0 | 0 |
| *FGA* | 4q31.3 | 134820 | Amyloidosis, familial visceral, hereditary renal | 0 | 0 | 0 |
| *FGF10* | 5p13-p12 | 602115 | Lacrimoauriculodentodigital syndrome | 0 | 0 | 0 |
| *FGF20* | 8p22 | 605558 | Renal hypodysplasiaaplasia 2 | 0 | 0 | 0 |
| *FGF23* | 12p13.3 | 605380 | Hypophosphatemic Rickets, autosomal dominant Tumoral Calcinosis, hyperphosphatemic, familial | 0 | 0 | 0 |
| *FGFR1* | 8p12 | 136350 | Encephalocraniocutaneous Lipomatosis, Kallmann syndrome 2, kal2 | 0 | 0 | 0 |
| *FGFR2* | 10q26 | 176943 | Pfeiffer syndrome type 3, Antley-Bixler syndrome, Apert syndrome, LADD syndrome | 0 | 0 | 0 |
| *FGFR3* | 4p16.3 | 134934 | Thanatophoric dysplasia type 1, Thanatophoric dysplasia type | 0 | 0 | 0 |

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|---|---|---|---|---|---|---|
| | | | 2,Lacrimoauriculodentodigital syndrome | | | |
| *FKBP14* | 7p14.3 | 614505 | Ehlers-Danlos syndrome with progressive kyphoscoliosis, myopathy, and hearing loss | 0 | 0 | 0 |
| *FLCN* | 17p11 | 607273 | Birt-Hogg-Dube Syndrome | 0 | 0 | 0 |
| *FLNA* | Xq28 | 300017 | Congenital short bowel syndrome Melnick-Needles syndrome Otopalatodigital syndrome, type 2; Frontometaphyseal Dysplasia | 0 | 0 | 0 |
| *FLNB* | 3p14.3 | 603381 | Spondylocarpotarsal synostosis syndrome | 0 | 0 | 0 |
| *FLT4* | 5q35.3 | 136352 | Lymphedema, hereditary, IA | 0 | 0 | 0 |
| *FN1* | 2q34 | 135600 | Glomerulopathy with fibronectin deposits 2 | 0 | 0 | 0 |
| *FOXC1* | 6p25 | 601090 | Axenfeld-Rieger syndrome, Type 3 | 0 | 0 | 0 |
| *FOXC2* | 16q24.1 | 602402 | Lymphedema-distichiasis syndrome with renal disease and diabetes mellitus | 0 | 0 | 0 |
| *FOXF1* | 16q24.1 | 601089 | Alveolar capillary dysplasia with misalignment of pulmonary veins, acdmpv | 0 | 0 | 0 |
| *FRAS1* | 4q21.21 | 607830 | Fraser syndrome | 0 | 0 | 0 |
| *FREM1* | 9p22.3 | 608944 | Bifid nose with or without anorectal and renal anomalies | 0 | 0 | 0 |
| *FREM2* | 13q13.3 | 608945 | Fraser syndrome | 0 | 0 | 0 |
| *FUZ* | 19q13.33 | 610622 | Caudal regression sequence | 0 | 0 | 0 |
| *FXYD2* | 11q23.3 | 601814 | Hypomagnesemia 2, renal | 0 | 0 | 0 |
| *G6PC* | 17q21.31 | 613742 | Glycogen storage disease Ia | 0 | 0 | 0 |
| *GALNT3* | 2q24.3 | 601756 | Tumoral calcinosis, hyperphosphatemic, familial, hftc | 0 | 0 | 0 |
| *GATA3* | 10p14 | 131320 | Hypoparathyroidism, deafness, renal disease syndrome | 0 | 0 | 0 |
| *GATA6* | 18q11.2 | 601656 | Pancreatic agenesis and congenital heart defects | 0 | 0 | 0 |
| *GBA* | 1q22 | 606463 | Gaucher disease | 0 | 0 | 0 |
| *GCDH* | 19p13.13 | 608801 | Glutaricaciduria, type I | 0 | 0 | 0 |

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|---|---|---|---|---|---|---|
| *GCM2* | 6p24.2 | 603716 | Hypoparathyroidism, familial isolated | 0 | 0 | 0 |
| *GDF2* | 10q11.22 | 605120 | Hereditary hemorrhagic telangiectasia | 0 | 1 | 0 |
| *GDNF* | 5p131-p12 | 600837 | Congenital Anomalies of the Kidney and the Urinary Tract | 0 | 0 | 0 |
| *GLA* | Xq22.1 | 300644 | Fabry Disease | 0 | 0 | 0 |
| *GLB1* | 3p22.3 | 611458 | GM1-gangliosidosis, type 1, type 2 | 0 | 0 | 0 |
| *GLI3* | 6p14.1 | 165240 | Pallister-Hall syndrome | 0 | 1 | 0 |
| *GLIS2* | 16p13.3 | 608539 | Nephronophthisis 7 | 0 | 0 | 0 |
| *GLIS3* | 9p24.2 | 610192 | Diabetes Mellitus, Neonatal, With Congenital Hypothyroidism | 0 | 0 | 0 |
| *GNA11* | 19p13.3 | 139313 | Hypocalciuric hypercalcemia, type 2 | 0 | 0 | 0 |
| *GNAS* | 20q13.32 | 139320 | pseudohypoparathyroidism, type 1B | 0 | 0 | 0 |
| *GNAS-AS1* | 20q13.32 | 610540 | pseudohypoparathyroidism, type 1B | 1 | All | 1 |
| *GNB1* | 1p36.33 | 139380 | Mental retardation, autosomal dominant 42 | 0 | 0 | 0 |
| *GPC3* | Xq26.2 | 300037 | Simpson golabi behmel syndrome type 1 | 0 | 0 | 0 |
| *GRHPR* | 9p13.2 | 604296 | Hyperoxaluria, primary, type 2 | 0 | 0 | 0 |
| *GRIP1* | 12q14.3 | 604597 | Fraser syndrome | 0 | 0 | 0 |
| *GSN* | 9q33.2 | 137350 | Amyloidosis, Finnish type cerebral amyloid angiopathy, GSN-related | 0 | 0 | 0 |
| *HBB* | 11p15.4 | 141900 | Sickle Cell Anemia beta-thalassemia, dominant inclusion body type | 0 | 0 | 0 |
| *HDAC8* | Xq13.1 | 300269 | Cornelia de Lange syndrome | 0 | 0 | 0 |
| *HES7* | 17p13.1 | 608059 | Autosomal recessive spondylocostal dysostosis | 0 | 0 | 0 |
| *HGD* | 3q13.33 | 607474 | Alkaptonuria | 0 | 0 | 0 |
| *HNF1A* | 12q24.31 | 142410 | Diabetes mellitus, insulin-dependent, 20; MODY, type 3; Renal cell carcinoma | 0 | 0 | 0 |
| *HNF1B* | 17q12 | 189907 | Renal Cysts and Diabetes Syndrome | 0 | 0 | 0 |
| *HNF4A* | 20q13.12 | 600281 | Renal cysts and diabetes syndrome; Hyperinsulinism due to | 0 | 0 | 0 |

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|---|---|---|---|---|---|---|
| | | | HNF4A deficiency; Fanconi renotubular syndrome 4, with maturity-onset diabetes of the young | | | |
| *HOGA1* | 10q24.2 | 613597 | Primary hyperoxaluria type 3 | 0 | 0 | 0 |
| *HOXA13* | 7p15.2 | 142959 | Hand-foot-uterus syndrome | 0 | 0 | 0 |
| *HOXD13* | 2q311 | 142989 | Vacterl association with hydrocephalus | 0 | 0 | 0 |
| *HPRT1* | Xq26.2-q26.3 | 308000 | Kelley-Seegmiller Syndrome Lesch-Nyhan Syndrome | 0 | 0 | 0 |
| *HPS1* | 10q24.2 | 604982 | Hermansky-Pudlak syndrome 1 | 0 | 0 | 0 |
| *HPSE2* | 10q24.2 | 613469 | Ochoa syndrome; Urofacial syndrome 1 | 0 | 0 | 0 |
| *HRAS* | 11p15.5 | 190020 | Costello syndrome | 0 | 0 | 0 |
| *HSD11B2* | 16q22.1 | 614232 | Apparent mineralocorticoid excess | 0 | 0 | 0 |
| *HSD17B3* | 9q22.32 | 605573 | 46,XY disorder of sex development due to 17-beta-hydroxysteroid dehydrogenase 3 deficiency | 0 | 0 | 0 |
| *HSD17B4* | 5q21 | 601860 | D-bifunctional protein deficiency | 0 | 0 | 0 |
| *HSD3B2* | 1p12 | 613890 | Congenital adrenal hyperplasia due to 3-beta-hydroxysteroid dehydrogenase deficiency | 0 | 0 | 0 |
| *HSPA9* | 5q31.2 | 600548 | Even-plus syndrome | 0 | 0 | 0 |
| *HSPG2* | 1p36.12 | 142461 | Schwartz-Jampel syndrome | 0 | 0 | 0 |
| *HYLS1* | 11q24.2 | 610693 | Hydrolethalus syndrome | 0 | 0 | 0 |
| *ICK* | 6p12.1 | 612325 | Endocrine-cerebroosteodysplasia | 0 | 0 | 0 |
| *IFT122* | 3q21.3-q22.1 | 606045 | Cranioectodermal dysplasia type 1 | 0 | 0 | 0 |
| *IFT140* | 16p13.3 | 614620 | Short rib-polydactyly syndrome (Jeune's syndrome) type 9 | 0 | 0 | 0 |
| *IFT172* | 2p23.3 | 607386 | Bardet-Biedl syndrome, Short rib-polydactyly syndrome (Jeune's syndrome) type 10 | 0 | 0 | 0 |
| *IFT27* | 22q12.3 | 615870 | Bardet-Biedl syndrome 19 | 0 | 0 | 0 |

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| *IFT43* | 14q24.3 | 614068 | Cranioectodermal dysplasia type 3 | 0 | 0 | 0 |
| *IFT80* | 3q25.33 | 611177 | Short rib-polydactyly syndrome, Verma-Naumoff type | 0 | 1 | 0 |
| *IKBKAP* | 9q31 | 603722 | Familial dysautonomia, Hereditary sensory and autonomic neuropathy type 3, hsan3 | 0 | 0 | 0 |
| *INF2* | 14q32.33 | 610982 | Focal Segmental Glomerulosclerosis 5 Charcot-Marie-Tooth disease E | 0 | 0 | 0 |
| *INPP5E* | 9q34.3 | 613037 | Joubert syndrome with hepatic defectJoubert Syndrome 1 | 0 | 0 | 0 |
| *INPPL1* | 11q13.4 | 600829 | Opsismodysplasia | 0 | 0 | 0 |
| *INSR* | 19p13.2 | 147670 | Rabson-Mendenhall syndrome | 0 | 0 | 0 |
| *INVS* | 9q31.1 | 243305 | Senior-Loken syndrome, Nephronophthisis 2, infantile | 0 | 0 | 0 |
| *IQCB1* | 3q13.33; 3q21.1 | 609237 | Senior-loken syndrome 5 | 0 | 0 | 0 |
| *IRF6* | 1q32.2 | 607199 | Popliteal pterygium syndrome 1 | 0 | 0 | 0 |
| *ITGA3* | 17q21.33 | 605025 | Interstitial lung disease, nephrotic syndrome, and epidermolysis bullosa, congenital | 0 | 0 | 0 |
| *ITGA6* | 2q31.1 | 147556 | Junctional epidermolysis bullosa-pyloric atresia syndrome, Epidermolysis bullosa, junctional, with pyloric stenosis | 0 | 0 | 0 |
| *ITGA8* | 10p13 | 604063 | Renal hypodysplasia-aplasia 1 | 0 | 0 | 0 |
| *ITGB4* | 17q25.1 | 147557 | Epidermolysis bullosa, junctional, with pyloric atresia | 0 | 0 | 0 |
| *JAG1* | 20p12.2 | 601920 | Alagille syndrome type 1 | 0 | 0 | 0 |
| *JAM3* | 11q25 | 606871 | Hemorrhagic destruction of the brain, subependymal calcification, and cataracts | 0 | 0 | 0 |
| *KANK1* | 9p24.3 | 607704 | Nephroticsyndrome | 0 | 0 | 0 |
| *KANK2* | 19p13.2 | 614610 | Palmoplantar keratoderma and woolly hair | 0 | 0 | 0 |
| *KANK4* | 1p31.3 | 614612 | Nephrotic syndrome | 0 | 0 | 0 |
| *KANSL1* | 17q21.31 | 612452 | Koolen-De Vries Syndrome | 0 | 0 | 0 |

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|---|---|---|---|---|---|---|
| *KAT6B* | 10q22.2 | 605880 | Genitopatellar syndrome | 0 | 0 | 0 |
| *KCNA1* | 12p13.32 | 176260 | Hypomagnesemia associated with myokymia | 0 | 0 | 0 |
| *KCNH1* | 1q32.2 | 603305 | Zimmermann-Laband syndrome 1 | 0 | 0 | 0 |
| *KCNJ1* | 11q24.3 | 600359 | Bartter's syndrome, type 2 | 0 | 0 | 0 |
| *KCNJ10* | 1q23.2 | 602208 | Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (sesame syndrome) | 0 | 0 | 0 |
| *KCNJ5* | 11q243 | 600734 | Hyperaldosteronism,familial,type 3 | 0 | 0 | 0 |
| *KCTD1* | 18q11.2 | 613420 | Scalp-Ear-Nipple Syndrome | 0 | 0 | 0 |
| *KDM1A* | 1p36.12 | 609132 | Cleft palate, psychomotor retardation, and distinctive facial features | 0 | 0 | 0 |
| *KDM6A* | Xp11.3 | 300128 | Kabuki syndrome | 0 | 0 | 0 |
| *KIF14* | 1q32.1 | 611279 | Meckel syndrome 12 | 0 | 0 | 0 |
| *KIF7* | 15q26.1 | 611254 | Acrocallosal syndrome | 0 | 0 | 0 |
| *KL* | 13q13.1 | 604824 | Tumoral calcinosis, hyperphosphatemic | 0 | 0 | 0 |
| *KLHL3* | 5q31.2 | 605775 | Pseudohypoaldosteronism, type 2d | 0 | 0 | 0 |
| *KMT2D* | 12q13.12 | 602113 | Kabuki syndrome 1 | 0 | 0 | 0 |
| *KRAS* | 12p12.1 | 190070 | Cardiofaciocutaneous syndrome | 0 | 0 | 0 |
| *KYNU* | 2q22.2 | 605197 | Hydroxykynureninuria | 0 | 0 | 0 |
| *LAMB2* | 3p21.31 | 150325 | Nephrotic syndrome, type 5, with or without ocular abnormalities Pierson Syndrome | 0 | 0 | 0 |
| *LAMB3* | 1q32.2 | 150310 | Amelogenesis imperfecta, type IA; Epidermolysis bullosa, junctional, Herlitz type; Epidermolysis bullosa, junctional, non-Herlitz type | 0 | 0 | 0 |
| *LAMC2* | 1q25.3 | 150292 | Epidermolysis bullosa, junctional, Herlitz type; Epidermolysis bullosa, junctional, non-Herlitz type | 0 | 0 | 0 |
| *LARS* | 5q32 | 151350 | Infantile liver failure syndrome 1 | 0 | 0 | 0 |

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|---|---|---|---|---|---|---|
| *LCAT* | 16q22.1 | 606967 | Norum disease | 0 | 1 | 0 |
| *LDHA* | 11p15.1 | 150000 | Glycogen storage disease XI | 0 | 0 | 0 |
| *LFNG* | 7q22.3 | 602576 | Autosomal recessive spondylocostal dysostosis | 0 | 0 | 0 |
| *LMBRD1* | 6q13 | 612625 | Methylmalonic aciduria and homocystinuria, cblF type | 0 | 0 | 0 |
| *LMNA* | 1q22 | 150330 | Atypical Werner syndrome Laminopathy type Decaudain-Vigouroux LMNA-related cardiocutaneous progeria syndrome, Restrictive Dermopathy, Lethal | 0 | 0 | 0 |
| *LMX1B* | 9q33.3 | 602575 | Nail-patella syndrome | 0 | 0 | 0 |
| *LONP1* | 19p13.3 | 605490 | CODAS syndrome | 0 | 0 | 0 |
| *LPIN1* | 2p25.1 | 605518 | Myoglobinuria, acute recurrent | 0 | 0 | 0 |
| *LRIG2* | 1p13.1 | 608869 | Ochoa syndrome, Urofacial Syndrome 2 | 0 | 0 | 0 |
| *LRP2* | 2q31.1 | 600073 | Donnai-barrow syndrome | 0 | 1 | 0 |
| *LRP4* | 11p11.2 | 604270 | Cenani-lenz syndactyly syndrome | 0 | 0 | 0 |
| *LTBP4* | 19q13.2 | 604710 | Cutis laxa, autosomal recessive, type IC | 0 | 0 | 0 |
| *LYZ* | 12q15 | 153450 | Amyloidosis, familial visceral, renal | 0 | 0 | 0 |
| *LZTFL1* | 3p21.31 | 606568 | Bardet Biedl syndrome type 17 | 0 | 0 | 0 |
| *MAFB* | 20q12 | 608968 | Multicentric carpo-tarsal osteolysis with or without nephropathy | 0 | 0 | 0 |
| *MAGED2* | Xp11.21 | 300470 | Bartter syndrome, type 5, antenatal, transient | 0 | 0 | 0 |
| *MAP2K1* | 15q22.31 | 176872 | Cardiofaciocutaneous syndrome | 0 | 0 | 0 |
| *MAP2K2* | 19p13.3 | 601263 | Cardiofaciocutaneous syndrome | 0 | 0 | 0 |
| *MAPRE2* | 18q12.1-q12.2 | 605789 | Symmetric circumferential skin creases congenital, 2 | 0 | 0 | 0 |
| *MBTPS2* | xp22.12 | 300294 | IFAP Syndrome with or without Bresheck Syndrome | 0 | 0 | 0 |
| *MEFV* | 16p13.3 | 608107 | Familial Mediterranean fever | 0 | 0 | 0 |
| *MESP2* | 15q26.1 | 605195 | Autosomal recessive spondylocostal dysostosis | 0 | 0 | 0 |

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|---|---|---|---|---|---|---|
| *MIR17HG* | 13q31.3 | 609415 | Feingold syndrome 2; Brachydactyly with short stature and microcephaly | 2 | All | 2 |
| *MKKS* | 20p12.2 | 604896 | Bardet-biedl syndrome 6, McKusick-Kaufman syndrome | 0 | 0 | 0 |
| *MKS1* | 17q22 | 609883 | Meckel syndrome 1, Bardet-Biedl syndrome 13 | 0 | 0 | 0 |
| *MLH1* | 3p22.2 | 120436 | Muir-Torre syndrome | 0 | 0 | 0 |
| *MMACHC* | 1p34.1 | 609831 | Methylmalonic aciduria and homocystinuria, cblc type | 0 | 0 | 0 |
| *MNX1* | 7q36.3 | 142994 | Currarino syndrome | 0 | 0 | 0 |
| *MRPS22* | 3q23 | 605810 | Combined oxidative phosphorylation deficiency 5 | 0 | 0 | 0 |
| *MSH2* | 2p21-p16 | 609309 | Muir-Torre syndrome colorectal cancer, hereditary, nonpolyposis, type 1 | 0 | 0 | 0 |
| *MSH6* | 2p16.3 | 600678 | Muir-Torre syndrome | 0 | 0 | 0 |
| *MTM1* | Xq29 | 300415 | Myotubular myopathy | 0 | 0 | 0 |
| *MUC1* | 1q22 | 158340 | Medullary cystic kidney disease 1 | 0 | 0 | 0 |
| *MUT* | 6p12.3 | 609058 | Vitamin B12-unresponsive methylmalonic acidemia type mut0 | 0 | 0 | 0 |
| *MVK* | 12q2411 | 251170 | Mevalonic aciduria | 0 | 0 | 0 |
| *MYCN* | 2p24.3 | 164840 | Feingold syndrome | 0 | 0 | 0 |
| *MYH9* | 22q13.1 | 160775 | Fechtner syndrome; Epstein Syndrome | 0 | 0 | 0 |
| *MYO1E* | 15q21-q22 | 601479 | Glomerulosclerosis, focal segmental, 6 | 0 | 0 | 0 |
| *NAA10* | Xq28 | 300013 | Microphthalmia, Lenz type, Microphthalmia, syndromic 1 | 0 | 0 | 0 |
| *NARS2* | 11q14.1 | 612803 | Combined oxidative phosphorylation deficiency 24 | 0 | 0 | 0 |
| *NBN* | 8q21.3 | 602667 | Nijmegen breakage syndrome | 0 | 0 | 0 |
| *NECTIN1* | 11q23.3 | 600644 | Cleft lip,palate-ectodermal dysplasia syndrome | 0 | 0 | 0 |
| *NEK1* | 4q33 | 604588 | Short rib-polydactyly syndrome (Jeune's syndrome) type 6 | 0 | 0 | 0 |
| *NEK8* | 17q11.1 | 609799 | Nephronophthisis 9 Renal-heaptic-pancreatic dysplasia 2 | 0 | 0 | 0 |
| *NEXMIF* | Xq13.3 | 300524 | Mental retardation, X-linked 98 | 0 | 0 | 0 |
| *NF1* | 17q11.2 | 613113 | Neurofibromatosis, type I | 0 | 0 | 0 |

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| *NHP2* | 5q35.3 | 606470 | Dyskeratosis congenita | 0 | 0 | 0 |
| *NIPBL* | 5p13.2 | 608667 | Cornelia de lange syndrome type 1 | 0 | 0 | 0 |
| *NLRP3* | 1q44 | 606416 | Muckle-wells syndrome Familial cold-induced inflammatory syndrome 1 | 0 | 0 | 0 |
| *NOTCH2* | 1p12 | 600275 | Acroosteolysis dominant type, Alagille syndrome 2, Hajdu-Cheney Syndrome | 0 | 0 | 0 |
| *NOTCH3* | 19p13.12 | 600276 | Infantile myofibromatosis, Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy 1, Lateral meningocele syndrome | 0 | 0 | 0 |
| *NPHP1* | 2q13 | 607100 | Bardet-Biedl syndrome, Nephronophthisis 1 (juvenile), Senior-Loken syndrome, Joubert syndrome 4 | 0 | 0 | 0 |
| *NPHP3* | 3q22.1 | 608002 | Senior-Loken syndrome, Nephronophthisis 3 (adolescent), Meckel syndrome 7, Renal-hepatic-pancreatic dysplasia | 0 | 0 | 0 |
| *NPHP4* | 1p36 | 607215 | Nephronophthisis 4 Senior-Loken syndrome 4 | 0 | 0 | 0 |
| *NPHS1* | 19q13.12 | 602716 | Congenital nephrotic syndrome, Finnish type | 0 | 0 | 0 |
| *NPHS2* | 1q25.2 | 604766 | Nephrotic syndrome type 2 | 0 | 0 | 0 |
| *NR0B1* | Xp21.2 | 300473 | Adrenal hypoplasia, congenital, with hypogonadotropic hypogonadism | 0 | 0 | 0 |
| *NR3C2* | 4q31.1 | 600983 | Pseudohypoaldosteronism Type I, autosomal dominant Hypertension, Early-Onset, Autosomal Dominant, With Exacerbation in Pregnancy | 0 | 0 | 0 |
| *NSD1* | 5q35 | 606681 | Sotos syndrome 1; Beckwith-Wiedemann syndrome, BWS | 0 | 0 | 0 |
| *NSDHL* | Xq28 | 300275 | CHILD syndrome | 0 | 0 | 0 |
| *NUP107* | 12q15 | 607617 | Nephrotic syndrome, type 11 | 0 | 0 | 0 |
| *NUP205* | 7q33 | 614352 | Nephrotic syndrome, type 13 | 0 | 0 | 0 |
| *NUP93* | 16q13 | 614351 | Nephrotic Syndrome, Type 12 | | 0 | 0 |

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| *OCLN* | 5q13.2 | 602876 | Band-like calcification with simplified gyration and polymicogyria | 0 | 0 | 0 |
| *OCRL* | Xq25 | 300535 | Dent disease 2 Lowe syndrome | 0 | 0 | 0 |
| *OFD1* | Xp22.2 | 300170 | Joubert syndrome type 10, Orofaciodigital syndrome I, Golabi-Behmel syndrome, type 2 | 0 | 0 | 0 |
| *OPLAH* | 8q24.3 | 614243 | 5-oxoprolinase deficiency | 0 | 0 | 0 |
| *PAF1* | 19q131 | 610506 | Zellweger syndrome 3 | 0 | 0 | 0 |
| *PALB2* | 16p12.2 | 610355 | Fanconi Anemia, Complementation Group N | 0 | 0 | 0 |
| *PAX2* | 10q24.31 | 167409 | Renal coloboma syndrome, FSGS 7, Papillorenal Syndrome, PAPRS | 0 | 0 | 0 |
| *PC* | 11q13.2 | 608786 | Pyruvate carboxylase deficiency | 0 | 0 | 0 |
| *PDE6D* | 2q37.1 | 602676 | Joubert's syndrome type 22 | 0 | 0 | 0 |
| *PDSS1* | 10p12.1 | 607429 | Coenzyme Q10 deficiency, primary, 2 | 0 | 0 | 0 |
| *PDSS2* | 6q21 | 610564 | Coenzyme q10 deficiency, primary, 3 | 0 | 0 | 0 |
| *PET100* | 19p13.2 | 614770 | Mitochondrial Complex 4 deficiency | 0 | 0 | 0 |
| *PEX1* | 7q21.2 | 602136 | Zellweger syndrome | 0 | 0 | 0 |
| *PEX10* | 1p36.32 | 602859 | Zellweger syndrome | 0 | 0 | 0 |
| *PEX11B* | 1q21.1 | 603867 | Zellweger syndrome | 0 | 0 | 0 |
| *PEX12* | 17q12 | 601758 | Zellweger syndrome | 0 | 0 | 0 |
| *PEX13* | 2p15 | 601789 | Zellweger syndrome | 0 | 0 | 0 |
| *PEX14* | 1p36.22 | 601791 | Zellweger syndrome | 0 | 0 | 0 |
| *PEX16* | 11p11.2 | 603360 | Zellweger syndrome | 0 | 0 | 0 |
| *PEX19* | 1q23.2 | 600279 | Zellweger syndrome | 0 | 0 | 0 |
| *PEX2* | 8q21.11 | 170993 | Zellweger syndrome | 0 | 0 | 0 |
| *PEX26* | 22q11.21 | 608666 | Zellweger syndrome | 0 | 0 | 0 |
| *PEX3* | 6q24.2 | 603164 | Zellweger syndrome | 0 | 0 | 0 |

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|---|---|---|---|---|---|---|
| *PEX5* | 3q26.33 | 600414 | Zellweger syndrome | 0 | 0 | 0 |
| *PEX6* | 6p21.1 | 601498 | Zellweger syndrome | 0 | 0 | 0 |
| *PGK1* | Xq21.1 | 311800 | Phosphoglycerate kinase 1 deficiency | 0 | 0 | 0 |
| *PGM3* | 6q14.1 | 172100 | Immunodeficiency 23 | 0 | 0 | 0 |
| *PHEX* | Xp22.2-p22.1 | 300550 | Hypophosphatemic rickets | 0 | 0 | 0 |
| *PHGDH* | 1p12 | 606879 | Neu-Laxova syndrome 1 | 0 | 0 | 0 |
| *PIEZO2* | 18p11.22-p11.21 | 613629 | Marden-Walker Syndrome | 0 | 0 | 0 |
| *PIGA* | X22.2 | 311770 | Multiple Congenital anomalies-hypotonia-seizures syndrome 2 | 0 | 0 | 0 |
| *PIGL* | 17p11.2 | 605947 | CHIME syndrome | 0 | 0 | 0 |
| *PIGN* | 18q21.33 | 606097 | Multiple congenital anomalies-hypotonia-seizures syndrome 1 | 0 | 0 | 0 |
| *PIGT* | 20q13.12 | 610272 | Multiple congenital anomalies-hypotonia-seizures syndrome 3 | 0 | 0 | 0 |
| *PIK3CA* | 3q26.32 | 171834 | Cowden syndrome | 0 | 0 | 0 |
| *PIK3R2* | 19p13.11 | 603157 | Megalencephaly-polymicogyria-polydactyly-hyodrcephalus syndrome 1 | 0 | 0 | 0 |
| *PITX2* | 4q25 | 601542 | Axenfeld-Rieger syndrome, type 1; Iridogoniodysgenesis, type 2; Peters anomaly; Ring dermoid of cornea | 0 | 0 | 0 |
| *PKD1* | 16p13.3 | 601313 | Polycystic kidney disease 1 | 0 | 0 | 0 |
| *PKD2* | 4q22.1 | 173910 | Polycystic kidney disease 2 | 0 | 0 | 0 |
| *PKHD1* | 6p12.3-p12.2 | 606702 | Autosomal recessive polycystic kidney disease, Polycystic and hepatic disease | 0 | 0 | 0 |
| *PLCE1* | 10q23.3 | 608414 | Nephrotic syndrome type 3 | 0 | 0 | 0 |
| *PLG* | 6q26 | 173350 | Plasminogen deficiency, Type I | 0 | 0 | 0 |
| *PLOD1* | 1p36.22 | 153454 | Ehlers-Danlos syndrome, type 6 | 0 | 0 | 0 |

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| *PMM2* | 16p13.2 | 601785 | Congenital disorder of glycosylation, type Ia | 0 | 0 | 0 |
| *PNPLA6* | 19p13.2 | 603197 | Laurence-Moon syndrome | 0 | 0 | 0 |
| *POMC* | 2p23.3 | 176830 | Obesity, adrenal insufficiency, and red hair due to POMC deficiency | 0 | 0 | 0 |
| *POMT1* | 9q34.13 | 607423 | Muscular dystrophy-dystroglycanopathy, type A, 1 | 0 | 0 | 0 |
| *POR* | 7q11.23 | 124015 | Congenital adrenal hyperplasia due to cytochrome P450 oxidoreductase deficiency, Antley-Bixler Syndrome with Genital Anomalies and Disordered Steroidogenesis | 0 | 0 | 0 |
| *PORCN* | Xp11.23 | 300651 | Focal dermal hypoplasia | 0 | 0 | 0 |
| *PPP1R15B* | 1q32.1 | 613257 | Microcephaly, short stature, and impaired glucose metabolism 2 | 0 | 0 | 0 |
| *PQBP1* | Xp11.23 | 300463 | Renpenning Syndrome 1 | 0 | 0 | 0 |
| *PRKCD* | 3p21.1 | 176977 | Autoimmune lymphoproliferative syndrome, type 2 | 0 | 0 | 0 |
| *PRODH* | 22q11.21 | 606810 | Hyperprolinemia, type I | 0 | 0 | 0 |
| *PROKR2* | 20p123 | 607123 | Kallmann syndrome 3, kal3 (hypogonadotropic hypogonadism 3 with or without anosmia) | 0 | 0 | 0 |
| *PRPS1* | Xq22.3 | 311850 | Phosphoribosylpyrophosphate Synthetase Syperactivity | 0 | 0 | 0 |
| *PSAP* | 10q22.1 | 176801 | Metachromatic leukodystrophy due to SAP-b deficiency | 0 | 0 | 0 |
| *PTEN* | 10q23.31 | 601728 | Cowden syndrome, VATER association with macrocephaly and ventriculomegaly | 0 | 0 | 0 |
| *PTH* | 11p15.3 | 168450 | Hypoparathyroidism | 0 | 0 | 0 |
| *PTH1R* | 3p21.31 | 168468 | Metaphyseal chondrodysplasia, Murk Jansen type | 0 | 0 | 0 |
| *PTPN11* | 12q24.13 | 176876 | Noonan syndrome with multiple lentiginesLeopard syndrome 1 | 0 | 0 | 0 |
| *PTPRO* | 12p13.3-p13.2; | 600579 | Nephrotic syndrome, type 6 | 0 | 0 | 0 |

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|---|---|---|---|---|---|---|
| | 12p13-p12 | | | | | |
| *PUF60* | 8q24.3 | 604819 | Verheij syndrome | 0 | 0 | 0 |
| *PYGM* | 11q13.1 | 608455 | McArdle Disease | 0 | 0 | 0 |
| *RAB18* | 10p12.1 | 602207 | Micro syndrome | 0 | 0 | 0 |
| *RAB23* | 6p12.1-p11.2 | 606144 | Carpenter syndrome | 0 | 0 | 0 |
| *RAB3GAP1* | 2q21.3 | 602536 | Micro syndrome | 0 | 0 | 0 |
| *RAB3GAP2* | 1q41 | 609275 | Micro syndrome | 0 | 0 | 0 |
| *RAD51C* | 17q22 | 602774 | Fanconi anemia, complementation group O | 0 | 0 | 0 |
| *RAI1* | 17p11.2 | 607642 | Smith-Magenis syndrome Yuan-Harel-Lupski syndrome | 0 | 0 | 0 |
| *RAP1A* | 1p13.2 | 179520 | Kabuki syndrome | 0 | 0 | 0 |
| *RAP1B* | 12q15 | 179530 | Kabuki syndrome | 0 | 0 | 0 |
| *RBBP8* | 18q11.2 | 604124 | Seckel Syndrome 2 | 0 | 0 | 0 |
| *RBM10* | Xp11.3 | 300080 | TARP syndrome | 0 | 0 | 0 |
| *RBM8A* | 1q21.1 | 605313 | Thrombocytopenia-absent radius syndrome | 0 | 0 | 0 |
| *RECQL4* | 8q24.3 | 603780 | Baller-gerold syndrome | 0 | 0 | 0 |
| *REN* | 1q32.1 | 179820 | Renal tubular dysgenesis hyperuricemic nephropathy, familial juvenile 2 | 0 | 0 | 0 |
| *RERE* | 1p36.23 | 605226 | Neurodevelopmental disorder with or without anomalies of the brain, eye, or heart | 0 | 0 | 0 |
| *RET* | 10q11.21 | 164761 | Renal agenesis, bilateral | 0 | 0 | 0 |
| *RIN2* | 20p11.23 | 610222 | Macrocephaly, alopecia, cutis laxa, and scoliosis | 0 | 0 | 0 |
| *RIPK4* | 21q22.3 | 605706 | Popliteal pterygium syndrome, Bartsocas-Papas type | 0 | 0 | 0 |
| *RIPPLY2* | 6q14.2 | 609891 | Autosomal recessive spondylocostal dysostosis | 0 | 0 | 0 |
| *RMND1* | 6q25.1 | 614917 | Combined oxidative phosphorylation deficiency 11 | 0 | 0 | 0 |
| *RNU4ATAC* | 2q14.2 | 601428 | Microcephalic osteodysplastic primordial dwarfism, type I | All | All | All |

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|---|---|---|---|---|---|---|
| *ROBO2* | 3p12.3 | 602431 | Vesicoureteral reflux 2 | 0 | 0 | 0 |
| *ROR2* | 9q22.31 | 602337 | Robinow syndrome | 0 | 0 | 0 |
| *RPGRIP1L* | 16q12.2 | 610937 | Meckel syndrome 5, Joubert syndrome 7, COACH syndrome | 0 | 0 | 0 |
| *RPL11* | 1p36.11 | 604175 | Diamond-Blackfan anemia 7 | 0 | 0 | 0 |
| *RPL26* | 17p13.1 | 603704 | Diamond-Blackfan anemia 11 | 0 | 0 | 0 |
| *RPL35A* | 3q29 | 180468 | Blackfan-Diamond anemia | 0 | 0 | 0 |
| *RPL5* | 1p22.1 | 603634 | Blackfan-Diamond anemia | 0 | 0 | 0 |
| *RPS10* | 6p21.31 | 603632 | Blackfan-Diamond anemia | 0 | 0 | 0 |
| *RPS17* | 15q25.2 | 180472 | Blackfan-Diamond anemia | 0 | 0 | 0 |
| *RPS19* | 19q13.2 | 603474 | Diamond-Blackfan anemia 1 | 0 | 0 | 0 |
| *RPS24* | 10q22.3 | 602412 | Blackfan-Diamond anemia | 0 | 0 | 0 |
| *RPS26* | 12q13.2 | 603701 | Diamond-Blackfan anemia 10 | 0 | 0 | 0 |
| *RPS28* | 19p13.2 | 603685 | Blackfan-Diamond anemia | 0 | 0 | 0 |
| *RPS29* | 14q21.3 | 603633 | Blackfan-Diamond anemia | 0 | 0 | 0 |
| *RPS7* | 2p25.3 | 603658 | Blackfan-Diamond anemia | 0 | 0 | 0 |
| *RRM2B* | 8q22.3 | 604712 | Mitochondrial DNA depletion syndrome 8A | 0 | 0 | 0 |
| *RTTN* | 18q22.2 | 610436 | Microsephaly, short stature, and polymicogyria with or without seizures | 0 | 0 | 0 |
| *SALL1* | 16q12.1 | 602218 | Townes-Brocks Branchiootorenal-like Syndrome | 0 | 0 | 0 |
| *SALL4* | 20q13.2 | 607343 | Acro-renal-ocular syndrome, Duane-Radial Ray Syndrome IVIC Syndrome | 0 | 0 | 0 |
| *SARS2* | 19q13.2 | 612804 | Hyperuricemia, pulmonary hypertension, renal failure and alkalosis | 0 | 0 | 0 |
| *SBDS* | 7q11.21 | 607444 | Shwachman-Diamond syndrome | 0 | 0 | 0 |
| *SC5D* | 11q23.3-q24.1 | 602286 | Lathosterolosis | 0 | 0 | 0 |

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| *SCARB2* | 4q21.1 | 602257 | Epilepsy, Progressive Myoclonic, 4 with or without Renal Failure | 0 | 0 | 0 |
| *SCN4A* | 17q233 | 603967 | Hypokalemic periodic paralysis, hokpp type2 | 0 | 0 | 0 |
| *SCNN1A* | 12p13.31 | 600228 | Pseudohypoaldosteronism, Type I | 0 | 0 | 0 |
| *SCNN1B* | 16p12.2 | 600760 | Liddle syndrome | 0 | 0 | 0 |
| *SCNN1G* | 16p12 | 600761 | Pseudohypoaldosteronism, type 1; Liddle Syndrome | 0 | 0 | 0 |
| *SCO1* | 17p13.1 | 603644 | Mitochondrial Complex 4 deficiency | 0 | 0 | 0 |
| *SDCCAG8* | 1q43 | 613524 | Senior loken syndrome type 7, Bardet-Biedl Syndrome 16 | 0 | 0 | 0 |
| *SDHB* | 1p36.1-p35 | 185470 | Cowden Syndrome 2, Pheochormocytoma Paragangliomas 4 | 0 | 0 | 0 |
| *SDHC* | 1q23.3 | 602413 | Cowden syndrome | 0 | 0 | 0 |
| *SDHD* | 11q23.1 | 602690 | Pheochromocytoma Cowden syndrome 3 | 0 | 0 | 0 |
| *SEMA3E* | 7q21.11 | 608166 | Charge syndrome | 0 | 0 | 0 |
| *SERPINH1* | 11q13.5 | 600943 | Osteogenesis imperfecta, type X | 0 | 0 | 0 |
| *SETBP1* | 18q12.3 | 611060 | Schinzel-Giedion Midface Retraction Syndrome | 0 | 0 | 0 |
| *SF3B4* | 1q21.2 | 605593 | Nager syndrome, Acrofacial dysostosis 1, Nager type | 0 | 0 | 0 |
| *SHH* | 7q36.3 | 600725 | Single median maxillary central incisor holoprosencephaly 3 | 0 | 0 | 0 |
| *SI* | 3q26.1 | 609845 | Sucrase-isomaltase deficiency, congenital | 0 | 0 | 0 |
| *SIX1* | 14q23.1 | 601205 | Branchio-oto-renal syndrome | 0 | 0 | 0 |
| *SIX2* | 2p21 | 604994 | Renal hypodysplasia | 0 | 0 | 0 |
| *SIX5* | 19q13.32 | 600963 | Branchio-oto-renal syndrome 2 | 0 | 0 | 0 |
| *SLC12A1* | 15q21.1 | 600839 | Bartter syndrome, type 1, antenatal | 0 | 0 | 0 |
| *SLC12A3* | 16q13 | 600968 | Gitelman syndrome | 0 | 0 | 0 |
| *SLC16A12* | 10q23.31 | 611910 | Cataract, juvenile, with microcornea and glucosuria | 0 | 0 | 0 |
| *SLC1A1* | 9p24.2 | 133550 | Dicarboylic aminoaciduria | 0 | 0 | 0 |
| *SLC22A12* | 11q13.1 | 607096 | Hypouricemia, renal, 1, rhuc1 | 0 | 0 | 0 |
| *SLC25A1* | 4p16.3 | 190315 | Combined D-2- and L-2-hydroxyglutaric aciduria | 0 | 0 | 0 |

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| *SLC26A4* | 7q223 | 605646 | Pendred syndrome | 0 | 0 | 0 |
| *SLC2A10* | 20q1312 | 606145 | Arterial tortuosity syndrome,ats | 0 | 0 | 0 |
| *SLC2A2* | 3q26.2 | 138160 | Fanconi-Bickel syndrome | 0 | 0 | 0 |
| *SLC2A9* | 4p16.1 | 606142 | Hypouricemia, renal, 2 | 0 | 0 | 0 |
| *SLC34A1* | 5q35.3 | 182309 | Fanconi renotubular syndrome 2 hypercalcemia, infantile, 2 nephrolithiasis,osteoporosis, hypophosphatemic, 1 | 0 | 0 | 0 |
| *SLC34A3* | 9q34.3 | 609826 | Hypophosphatemic rickets with hypercalciuria, hereditary | 0 | 0 | 0 |
| *SLC36A2* | 5q33.1 | 608331 | Hyperglycinuria | 0 | 0 | 0 |
| *SLC37A4* | 11q23.3 | 602671 | Glycogen storage disease Ib Ic | 0 | 0 | 0 |
| *SLC3A1* | 2p21 | 104614 | Cystinuria | 0 | 0 | 0 |
| *SLC4A1* | 17q21.31 | 109270 | Renal tubular acidosis, distal | 0 | 0 | 0 |
| *SLC4A4* | 4q13.3 | 603345 | Renal tubular acidosis, proximal, with ocular abnormalities and mental retardation | 0 | 0 | 0 |
| *SLC5A2* | 16p11.2 | 182381 | Renal glucosuria | 0 | 0 | 0 |
| *SLC6A19* | 5p15.33 | 608893 | Hartnup Disorder Hyperglycinuria | 0 | 0 | 0 |
| *SLC6A20* | 3p21.31 | 605616 | Hyperglycinuria | 0 | 0 | 0 |
| *SLC7A7* | 14q11.2 | 603593 | Lysinuric protein intolerance | 0 | 0 | 0 |
| *SLC7A9* | 19q13.1 | 604144 | Cystinuria | 0 | 0 | 0 |
| *SLC9A3R1* | 17q25.1 | 604990 | Nephrolithiasis,osteoporosis, hypophosphatemic, 2 | 0 | 0 | 0 |
| *SLIT2* | 4p152 | 603746 | Congenital Anomalies of the Kidney and the Urinary Tract | 0 | 0 | 0 |
| *SLX4* | 16p13.3 | 613278 | Fanconi anemia, complementation group P | 0 | 0 | 0 |
| *SMAD3* | 15q22.33 | 603109 | Loeys-Dietz syndrome 3 | 0 | 0 | 0 |
| *SMARCAL1* | 2q35 | 606622 | Schimke immuno-osseous dysplasiaSchimke's immunoosseous dystrophy | 0 | 0 | 0 |
| *SMARCE1* | 17q21.2 | 603111 | Coffin-Siris syndrome | 0 | 1 | 0 |
| *SMC1A* | Xp11.22 | 300040 | Cornelia de Lange syndrome | 0 | 0 | 0 |

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| *SMOC1* | 14q24.2 | 608488 | Microphthalmia with limb anomalies | 0 | 0 | 0 |
| *SNRPB* | 20p13 | 182282 | Cerebrocostomandibular syndrome | 0 | 0 | 0 |
| *SOX11* | 2p25.2 | 600898 | Mental retardation, autosomal dominant, 27 | 0 | 0 | 0 |
| *SOX17* | 8q11.23 | 610928 | Vesicoureteral Reflux 3 | 0 | 0 | 0 |
| *SOX18* | 20q13.33 | 601618 | Hypotrichosis-lymphedema-telangiectasia-renal defect syndrome | 0 | 0 | 0 |
| *SOX9* | 17q24.3 | 608160 | Campomelic dysplasia | 0 | 0 | 0 |
| *SPECC1L* | 22q11.23 | 614140 | Opitz GBBB syndrome, type 2 | 0 | 0 | 0 |
| *SPINT2* | 19q13.2 | 605124 | Diarrhea 3, secretory sodium, congenital, syndromic | 0 | 0 | 0 |
| *SRCAP* | 16p11.2 | 611421 | Floating-Harbor syndrome | 0 | 0 | 0 |
| *STAR* | 8p11.23 | 600617 | Lipoid adrenal hyperplasia | 0 | 0 | 0 |
| *STK11* | 19p13.3 | 602216 | Peutz-Jeghers syndrome | 0 | 0 | 0 |
| *STRA6* | 15q24.1 | 610745 | Microphthalmia, syndromic 9, mcops9 | 0 | 0 | 0 |
| *STRADA* | 17q23.3 | 608626 | Polyhydramnios, megalencephaly, and symptomatic epilepsy | 0 | 0 | 0 |
| *STUB1* | 16p13.3 | 607207 | Spinocerebellar ataxia, autosomal recessive 16 | 0 | 0 | 0 |
| *STX16* | 20q13.32 | 603666 | Pseudohypoparathyroidism, type 1B | 0 | 0 | 0 |
| *SUCLA2* | 13q14.2 | 603921 | Mitochondrial dna depletion syndrome, encephalomyopathic form, with methylmalonic aciduria | 0 | 0 | 0 |
| *SUGCT* | 7p14.1 | 609187 | Glutaric aciduria 3 | 0 | 0 | 0 |
| *TACO1* | 17q23.3 | 612958 | Mitochondrial Complex 4 deficiency | 0 | 0 | 0 |
| *TAPT1* | 4p15.32 | 612758 | Osteochondrodysplasia, complex lethal, Symoens-Barnes-Gistelinck type | 0 | 0 | 0 |
| *TBC1D20* | 20q13 | 611663 | Micro syndrome | 0 | 0 | 0 |
| *TBC1D24* | 16p13.3 | 613577 | DOOR syndrome | 0 | 0 | 0 |
| *TBCE* | 1q42.3 | 604934 | Hypoparathyroidism-retardation-dysmorphism syndrome; Kenny-Caffey syndrome, type 1 | 0 | 0 | 0 |

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| *TBX18* | 6q14.3 | 604613 | Congenital hydronephrosisCongenital anomalies of Kidney and Urinary Tract 2 | 0 | 0 | 0 |
| *TCTN2* | 12q24.31 | 613846 | Meckel-gruber syndrome type 8, Joubert syndrome 24 | 0 | 0 | 0 |
| *TCTN3* | 10q24.1 | 613847 | Joubert syndrome 18, Orofaciodigital syndrome 4 | 0 | 0 | 0 |
| *TERC* | 3q26.2 | 602322 | Dyskeratosis congenita | 0 | All | 0 |
| *TFAP2A* | 6p24.3 | 107580 | Branchiooculofacial Syndrome | 0 | 0 | 0 |
| *THOC6* | 16p13.3 | 615403 | Beaulieu-Boycott-Innes Syndrome | 0 | 0 | 0 |
| *TMCO1* | 1q24.1 | 614123 | Craniofacial dysmorphism, skeletal anomalies, and mental retardation syndrome | 0 | 0 | 0 |
| *TMEM138* | qq112.2 | 614459 | Joubert syndrome 16 | 0 | 0 | 0 |
| *TMEM216* | 11q12.2 | 613277 | Joubert syndrome 2, Meckel syndrome | 0 | 0 | 0 |
| *TMEM231* | 16q23.1 | 614949 | Joubert syndrome type 20, meckel-gruber syndrome type 11 | 0 | 0 | 0 |
| *TMEM237* | 2q33.1 | 614423 | Joubert syndrome type 14 | 0 | 0 | 0 |
| *TMEM67* | 8q22.1 | 609884 | Nephronophtisis 11, Meckel Syndrome 3, Joubert syndrome 6, COACH syndrome | 0 | 0 | 0 |
| *TMEM70* | 8q21.11 | 612418 | TMEM70-related mitochondrial encephalo-cardio-myopathy | 0 | 0 | 0 |
| *TNFRSF1A* | 12p1331 | 191190 | Autosomal dominant periodic fever syndrome | 0 | 0 | 0 |
| *TNXB* | 6p21.33-p21.32 | 600985 | Vesicoureteral Reflux 8 Ehlers-Danlos syndrome due to tenascin-X deficiency | 0 | 0 | 0 |
| *TP63* | 3q28 | 603273 | EEC syndrome, Ectrodactyly, ectodermal dysplasia, and cleft lip,palate syndrome 3 | 0 | 0 | 0 |
| *TRAF3IP1* | 2q37.3 | 607380 | Senior-Loken syndrome 9 | 0 | 0 | 0 |
| *TRAIP* | 3p21.31 | 605958 | Seckel syndrome 9 | 0 | 0 | 0 |
| *TRAP1* | 16p133 | 606219 | Congenital Anomalies of the Kidney and the Urinary Tract | 0 | 0 | 0 |
| *TREX1* | 3p21.31 | 606609 | HERNS syndrome; Vasculopathy, retinal, with cerebral leukodystrophy | 0 | 0 | 0 |

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| *TRIM32* | 9q33.1 | 602290 | Bardet-biedl syndrome 11 | 0 | 0 | 0 |
| *TRMT5* | 14q23.1 | 611023 | Combined oxidative phosphorylation deficiency 26 | 0 | 0 | 0 |
| *TRNT1* | 3p26.2 | 612907 | Sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay | 0 | 0 | 0 |
| *TRPC6* | 11q22.1 | 603652 | Focal Segmental Glomerulosclerosis 2 | 0 | 0 | 0 |
| *TRPM6* | 9q21.13 | 607009 | Hypomagnesemia 1, intestinal | 0 | 0 | 0 |
| *TSC1* | 9q34 | 605284 | Tuberous Sclerosis-1 | 0 | 0 | 0 |
| *TSC2* | 16p13.3 | 191092 | Tuberous sclerosis-2 | 0 | 0 | 0 |
| *TSR2* | Xp11.22 | 300945 | Blackfan-Diamond anemia | 0 | 0 | 0 |
| *TTC21B* | 2q24.3 | 612014 | Nephronophthisis 12 | 0 | 0 | 0 |
| *TTC37* | 5q15 | 614589 | Trichohepatonenteric syndrome 1 | 0 | 0 | 0 |
| *TTC8* | 14q31.3 | 608132 | Bardet-Biedl Syndrome 8 | 0 | 0 | 0 |
| *TTR* | 18q12.1 | 176300 | Amyloidosis, hereditary, transthyretin-related | 0 | 0 | 0 |
| *TWIST2* | 2q37.3 | 607556 | Focal facial dermal dysplasia type 3 | 0 | 0 | 0 |
| *TXNL4A* | 18q23 | 611595 | Burn-McKeown syndrome | 0 | 0 | 0 |
| *UBE2T* | 1q32.1 | 610538 | Fanconi anemia | 0 | 0 | 0 |
| *UBR1* | 15q15.2 | 605981 | Johanson-Blizzard syndrome | 0 | 0 | 0 |
| *UMOD* | 16p12.3 | 191845 | Medullary cystic kidney disease 2 hyperuricemic nephropathy glomerulocystic kidney disease | 0 | 0 | 0 |
| *UMPS* | 3q21.2 | 613891 | Hereditary orotic aciduria | 0 | 0 | 0 |
| *UPB1* | 22q11.23 | 606673 | Beta-ureidopropionase deficiency | 0 | 0 | 0 |
| *UPK3A* | 22q1331 | 611559 | Renal hypodysplasia, urogenital dysplasia | 0 | 0 | 0 |
| *UQCC2* | 6p21.31 | 614461 | Mitochondrial complex 3 deficiency, nuclear type 7 | 0 | 0 | 0 |
| *USP9X* | Xp11.4 | 300072 | Mental retardation, X-linked 99, syndromic, female-restricted | 0 | 0 | 0 |
| *VANGL1* | 1p13.1 | 610132 | Caudal regression syndrome | 0 | 0 | 0 |
| *VHL* | 3p25.3 | 608537 | Von Hippel-Lindau Syndrome | 0 | 0 | 0 |

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| *VIPAS39* | 14q24.3 | 613401 | Arthrogryposis, renal dysfunction, and cholestasis 2; arcs2 | 0 | 0 | 0 |
| *VPS33B* | 15q26.1 | 608552 | Arthrogryposis, renal dysfunction, and cholestasis 1; arcs1 | 0 | 0 | 0 |
| *WAS* | Xp11.23 | 300392 | Wiskott-Aldrich syndrome | 0 | 0 | 0 |
| *WDPCP* | 2p15 | 613580 | Bardet-Biedl syndrome | 0 | 0 | 0 |
| *WDR19* | 4p14 | 608151 | Senior-Loken syndrome, Short-rib thoracic dysplasia 5, Nephronophthisis type 13, Cranioectodermal dysplasia | 0 | 0 | 0 |
| *WDR34* | 9q34.11 | 613363 | Short rib-polydactyly syndrome, Verma-Naumoff typeShort-rib thoracic dysplasia 11 with or without polydactyly | 0 | 0 | 0 |
| *WDR35* | 2p24.1 | 613602 | Short rib-polydactyly syndrome, Verma-Naumoff type, Short rib-polydactyly syndrome (Jeune's syndrome) type 7, Cranioectodermal dysplasia type 2 | 0 | 0 | 0 |
| *WDR60* | 7q36.3 | 615462 | Short rib-polydactyly syndrome, Verma-Naumoff type, Short rib-polydactyly syndrome (Jeune's syndrome) type 8 | 0 | 0 | 0 |
| *WDR73* | 15q25.2 | 616144 | Galloway-Mowat syndrome | 0 | 0 | 0 |
| *WFS1* | 4p16.1 | 606201 | Wolfram syndrome type 1 | 0 | 0 | 0 |
| *WNK1* | 12p13.33 | 605232 | Pseudohypoaldosteronism, type 2c | 0 | 0 | 0 |
| *WNK4* | 17q21.2 | 601844 | Pseudohypoaldosteronism, type 2b | 0 | 0 | 0 |
| *WNT3* | 7q21.31 | 165330 | Tetraamelia-multiple malformations syndrome | 0 | 0 | 0 |
| *WNT4* | 1p36.12 | 603490 | SERKAL syndrome Mullerian aplasia and hyperandrogenism | 0 | 0 | 0 |
| *WNT5A* | 3p14.3 | 164975 | Robinow syndrome, autosomal dominant 1 | 0 | 0 | 0 |
| *WNT7A* | 3p25.1 | 601570 | Ulna and fibula, absense of, with severe limb deficiency | 0 | 0 | 0 |
| *WT1* | 11p13 | 607102 | Denys-Drash syndrome, Frasier syndrome, Nephrotic syndrome type 4, Wilms tumor type 1 | 0 | 0 | 0 |
| *XDH* | 2p23.1 | 607633 | Xanthinuria, type i | 0 | 0 | 0 |
| *XPNPEP3* | 22q13.2 | 613553 | Nephronophthisis-like nephropathy 1 | 0 | 0 | 0 |
| *XRCC4* | 5q14.2 | 194363 | Short stature, microcephaly, and endocrine dysfunction | 0 | 0 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *XYLT2* | 17q21.33 | 608125 | Spondylocular syndrome | 0 | 0 | 0 |
| *YAP1* | 11q22.1 | 606608 | Coloboma, ocular; Coloboma, ocular, with or without hearing impairment, cleft lip palate, and or mental retardation | 0 | 0 | 0 |
| *ZAP70* | 2q11.2 | 176947 | Autoimmune Disease, multisystem, infantile-onset, 2 | 0 | 0 | 0 |
| *ZIC3* | Xq26.3 | 300265 | VACTERL association, X-linked Heterotaxy, visceral, 1 | 0 | 0 | 0 |
| *ZMPSTE24* | 1p34.2 | 606480 | Restrictive Dermopathy, Lethal | 0 | 0 | 0 |
| *ZNF423* | 16q12.1 | 604557 | Nephronophthisis-14 Joubert syndrome 16 | 0 | 0 | 0 |
| *ZNF687* | 1q21.3 | 610568 | Paget disease of bone 6 | 0 | 0 | 0 |

†The list was established May 2016; thus, we encourage readers to also examine gene-disease databases such as Online Mendelian Inheritance in Man (OMIM; see **Section S1, Diagnostic analysis pipeline, Variant annotation**) to incorporate more recently identified Mendelian genitourinary-disease associated genes, using their judgement of the validity of gene-disease association.[32]

**Table S6. Stringently filtered variants of uncertain significance (VUS) in the 625 genes associated with Mendelian forms of kidney and genitourinary disease.**

See **Supplementary Appendix 2** on NEJM.org: sheet "**TableS6**".

Models and associated filtering parameters are detailed in **Section S1, Supplementary Methods**.

Age is age at time of study entry (yr).

For AURORA patients, study consent protocols permitted providing only the broad clinical diagnosis for patient information.

Family history data was available only for CUMC patients.

Zygosity: heterozygous (Het); homozygous (Hom); or hemizygous (Hemi).

MAF: Minor allele frequency.

**Table S7. Diagnostic genetic findings and clinical implications**

See **Supplementary Appendix 2** on NEJM.org: sheet "**TableS7**".

Age is age at time of study entry (yr).

For AURORA patients, study consent protocols permitted providing only the broad clinical diagnosis for patient information.

Family history data was available only for CUMC patients.

Zygosity: heterozygous (Het); homozygous (Hom); or hemizygous (Hemi).

Inheritance: autosomal dominant (AD); autosomal recessive (AR); or X-linked.

For the 167 CUMC patients with a genetic diagnosis, we utilized the additional medical data available to assess the diagnostic utility and clinical implications of the genetic findings. We categorized the diagnostic utility of a genetic diagnosis into one of four groups: 1) confirm the clinically suspected hereditary etiology of renal disease; 2) discern a specific sub-etiology within a broader category of clinically suspected disease; 3) reclassify disease; and 4) identify a molecular etiology, for undiagnosed cases with nephropathy of unknown origin. We evaluated the clinical implications of the genetic diagnosis by assessing whether the genetic diagnosis had the potential to: 1) inform prognosis (e.g., regarding disease severity and/or renal transplantation); 2) initiate referral for subspecialty care (and, if so, which other, non-nephrologic specialties would be involved); and/or 3) advise choice of therapy, including use or avoidance of agents and/or referral to clinical trials for therapies targeted to the associated genetic disease.

## Table S8. Genetic and clinical phenotypic spectrum of the 312 genetic diagnoses found in the 307 positive patients

| Gene | Disease | OMIM Phenotype MIM No. | Clinical diagnosis | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Congenital or cystic renal disease | Glomerulopathy | Diabetic nephropathy | Hypertensive nephropathy | Tubulointerstitial disease | Other | Nephropathy of unknown origin | Total |
| | | | No. of patients in whom diagnostic variants were detected | | | | | | | |
| *PKD1* | Polycystic kidney disease 1 | 173900 | 72 | 0 | 0 | 0 | 0 | 0 | 3 | 75 |
| *COL4A5* | Alport syndrome, X-linked | 301050 | 1 | 34 | 0 | 0 | 0 | 0 | 9 | 44 |
| *COL4A3* | Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease | 104200, 203780; 141200 | 2 | 20 | 0 | 1 | 0 | 0 | 4 | 27 |
| *PKD2* | Polycystic kidney disease 2 | 613095 | 22 | 0 | 0 | 0 | 0 | 0 | 0 | 22 |
| *COL4A4* | Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease | 203780; 141200 | 1 | 16 | 0 | 2 | 0 | 0 | 2 | 21 |
| *UMOD* | Autosomal dominant tubulointerstitial kidney disease, *UMOD*-associated | 609886; 162000; 603860 | 2 | 1 | 0 | 2 | 1 | 0 | 3 | 9 |
| *TRPC6* | Glomerulosclerosis focal segmental 2 | 603965 | 0 | 6 | 0 | 0 | 0 | 0 | 2 | 8 |
| *INF2* | Glomerulosclerosis focal segmental 5 | 613237 | 0 | 3 | 0 | 1 | 0 | 0 | 2 | 6 |
| *NPHS2* | Nephrotic syndrome type 2 | 600995 | 0 | 4 | 0 | 1 | 0 | 0 | 1 | 6 |
| *EYA1* | Branchiootorenal syndrome 1 with or without cataracts | 113650 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 5 |
| *HNF1A* | MODY type III | 600496 | 0 | 0 | 4 | 0 | 0 | 0 | 1 | 5 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *PAX2* | Glomerulosclerosis focal segmental 7; Papillorenal syndrome | 616002; 120330 | 2 | 1 | 0 | 0 | 0 | 0 | 2 | 5 |
| *CLCN5* | Dent disease | 300009 | 0 | 1 | 0 | 0 | 1 | 0 | 2 | 4 |
| *CREBBP* | Rubinstein-Taybi syndrome 1 | 180849 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 3 |
| *DHCR7* | Smith-Lemli-Opitz syndrome | 270400 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 3 |
| *GLA* | Fabry disease | 301500 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 3 |
| *HBB* | Sickle cell disease | 603903 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 3 |
| *NPHP3* | Nephronophthisis 3 | 604387 | 0 | 2 | 0 | 0 | 0 | 0 | 1 | 3 |
| *NPHP4* | Nephronophthisis 4 | 606966 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 |
| *PKHD1* | Polycystic kidney disease, autosomal recessive | 263200 | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 3 |
| *SLC12A3* | Gitelman syndrome | 263800 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 3 |
| *AVP* | Diabetes insipidus, neurohypophyseal | 125700 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| *CRB2* | Focal segmental glomerulosclerosis 9 | 616220 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 2 |
| *NF1* | Neurofibromatosis type 1 | 162200 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| *NPHS1* | Nephrotic syndrome type 1 | 256300 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 2 |
| *PTPN11* | Noonan syndrome 1 | 163950 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 2 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *SLC3A1* | Cystinuria | 220100 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 2 |
| *ACTG2* | Visceral myopathy | 155310 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *APOA1* | Amyloidosis, renal | 105200 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| *ATP6V1B1* | Renal tubular acidosis with deafness | 267300 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| *CDKN1C* | Beckwith-Wiedemann syndrome | 130650 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| *COL11A1* | Stickler syndrome type II | 604841 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *FANCB* | Fanconi anemia complementation group B | 300514 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *FGFR2* | Pfeiffer syndrome | 101600 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| *HNF1B* | Renal cysts and diabetes syndrome | 137920 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *HNF4A* | MODY type I | 125850 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| *IQCB1* | Senior-Loken syndrome 5 | 609254 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *JAG1* | Alagille syndrome 1 | 118450 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *KAL1* | Hypogonadotropic hypogonadism 1 with or without anosmia (Kallmann syndrome 1) | 308700 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| *KANSL1* | Koolen-De Vries syndrome | 610443 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *KLHL3* | Pseudohypoaldosteronism type IID | 614495 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *KRAS* | Noonan syndrome 3 | 609942 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| *LMX1B* | Nail-patella syndrome | 161200 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| *LRIG2* | Urofacial syndrome 2 | 615112 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *MC4R* | Obesity autosomal dominant | 601665 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| *MKKS* | Bardet-Biedl syndrome 6 | 605231 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| *MYCN* | Feingold syndrome 1 | 164280 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| *MYH9* | Epstein syndrome; Fechtner syndrome | 153650; 153640 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| *OCRL* | Dent disease 2 | 300555 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| *PLCE1* | Nephrotic syndrome type 3 | 610725 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| *REN* | Autosomal dominant tubulointerstitial kidney disease, *REN*-associated | 613092 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| *RERE* | Neurodevelopmental disorder with or without anomalies of the brain eye or heart | 616975 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *ROBO2* | Vesicoureteral reflux 2 | 610878 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *SALL1* | Townes-Brocks syndrome 1 | 107480 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| *SEC61A1* | Hyperuricemic nephropathy familial juvenile 4 | 617056 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *SLC16A12* | Cataract 47 juvenile with microcornea | 612018 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *SLC26A1* | Nephrolithiasis calcium oxalate | 167030 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| *SLC34A3* | Hypophosphatemic rickets with hypercalciuria | 241530 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| *SLC4A1* | Renal tubular acidosis distal, autosomal dominant | 179800 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| *SLC7A9* | Cystinuria | 220100 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| *SMARCAL1* | Schimke immunoosseous dysplasia | 242900 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| *SMC1A* | Cornelia de Lange syndrome 2 | 300590 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *TSC2* | Tuberous sclerosis 2 | 613254 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| *TTC21B* | Nephronophthisis 12 | 613820 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| *WDR19* | Nephronophthisis 13 | 614377 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *WT1* | Nephrotic syndrome type 4 | 256370 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Total no. of genetic diagnoses** | | | **127** | **103[#]** | **6** | **8** | **11** | **6** | **51[#]** | **312[#]** |
| **Total no. of positive patients** | | | **127** | **101[#]** | **6** | **8** | **11** | **6** | **48[#]** | **307[#]** |

[#]Of the five patients with dual molecular diagnoses in nephropathy-associated genes (see **Table S10**), two had a clinical diagnosis of glomerulopathy and three had a clinical diagnosis of nephropathy of unknown origin. Thus, altogether we detected 312 genetic diagnoses in the 307 positive patients.

**Table S9. Summary of the 343 diagnostic variants found in the 307 positive patients**

| **All positive patients, N=307** | | |
|---|---|---|
| **Inheritance** | **No. of patients** | **%** |
| Autosomal dominant | 206 | 67 |
| Autosomal recessive | 42 | 14 |
| X-linked | 54 | 18 |
| Dual | 5 | 2 |
| | | |
| **All diagnostic variants, N=343** | | |
| | **No. of variants** | **%** |
| **Variant effect** | | |
| Protein-truncating | 167 | 49 |
| *Frameshift* | *66* | *19* |
| *Nonsense* | *63* | *18* |
| *Splice-site* | *38* | *11* |
| Non-truncating | 176 | 51 |
| *In-frame insertion or deletion* | *5* | *1* |
| *Missense* | *171* | *50* |
| **Variant type** | | |
| Previously reported | 202 | 59 |
| Novel[#] | 141 | 41 |
| **ACMG Classification** | | |
| Pathogenic | 169 | 49 |
| Likely Pathogenic | 174 | 51 |

[#]Novel: not present in the clinical variant databases assessed (see **Section S1, Supplementary Methods**) at the time of analysis.

ACMG: American College of Medical Genetics and Genomics

**Table S10. Dual molecular diagnoses in nephropathy-associated genes**

| Patient ID | Sex | Age | Race/ Ethnicity | Positive family history for kidney disease | Clinical Diagnosis | Gene | Genetic Diagnosis | OMIM Phenotype MIM No. |
|---|---|---|---|---|---|---|---|---|
| CKD118[#] | - | - | - | - | Glomerulopathy | *COL4A4* | Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease | 203780; 141200 |
| | | | | | | *KRAS* | Noonan syndrome 3 | 609942 |
| CKD178 | F | 32 | White European | No | Nephropathy of unknown origin | *NPHP4* | Nephronophthisis 4 | 606966 |
| | | | | | | *SLC34A3* | Hypophosphatemic rickets with hypercalciuria | 241530 |
| CKD194 | F | 43 | Hispanic | Yes | Glomerulopathy | *COL4A4* | Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease | 203780; 141200 |
| | | | | | | *COL4A5* | Alport syndrome, X-linked | 301050 |
| CKD250 | M | 52 | Hispanic | Yes | Nephropathy of unknown origin | *INF2* | Glomerulosclerosis focal segmental 5 | 613237 |
| | | | | | | *SLC26A1* | Nephrolithiasis, calcium oxalate | 167030 |
| CKD302 | M | 29 | Hispanic | No | Nephropathy of unknown origin | *COL4A5* | Alport syndrome, X-linked | 301050 |
| | | | | | | *NPHP3* | Nephronophthisis 3 | 604387 |

[#]For AURORA patients, study consent protocols permitted providing only the broad clinical diagnosis for patient information.

Age is age at time of study entry (yr).

Variant-level data, including variant classifications and supporting ACMG criteria, are in **Table S7**.

**Table S11. Genetic and clinical heterogeneity of diagnostic genetic findings in the AURORA, CUMC, and AURORA-CUMC cohorts**

| Cohort | No. of distinct monogenic disorders detected | No. of singleton genetic diagnoses | No. of recurrent genetic diagnoses | No. of recurrent genetic diagnoses found across different clinical diagnostic subgroups |
|---|---|---|---|---|
| AURORA | 24 | 13 | 11 | 8 |
| CUMC | 55 | 35 | 20 | 15 |
| AURORA-CUMC | 66 | 39 | 27 | 21 |

**Table S12. Comparison of diagnostic yield between the AURORA and CUMC cohorts**

In this study, we aimed to evaluate the utility of exome sequencing across the different categories of the kidney and genitourinary disorders encountered in clinical practice. Combined, the patients from the AURORA and CUMC cohorts represent the major causes of kidney disease (see main text, **Table 1**). Individually, the AURORA and CUMC cohorts represent two distinct populations differing in their setting, recruitment goals, and clinical features (see **Section S1, Supplementary Methods, Cohorts;** and **Tables S2, S3, and S4**). The AURORA study recruited patients with end-stage renal disease (ESRD) aged 50-80 years, predominantly from Europe and South America. The CUMC cohort represents a multiethnic population with chronic kidney disease (CKD) or ESRD served at a tertiary care medical center in New York City. Unsurprisingly, comparison of diagnostic yield between the two cohorts showed differences (see below, **Table S12**). The overall diagnostic yield was higher in the AURORA cohort; however, detailed examination revealed that this was driven by the enrichment for autosomal dominant polycystic kidney disease (ADPKD) cases in AURORA. The age entry criteria of age >50 years in AURORA may have resulted in this enrichment for ADPKD cases, owing to the lower mortality rate for ADPKD patients on dialysis.[33] As shown below, after removing patients with ADPKD (from both cohorts), the overall diagnostic yield did not vary significantly between the two cohorts.

The only other clinical category for which the two cohorts significantly differed was among patients with tubulointerstitial disease. This likely results from the relatively small sample size and absence of patients with pyelonephritis, an acquired etiology of renal disease, among the CUMC tubulointerstitial disease cases. The difference reflects the fact that the CUMC is a primary referral center for glomerular disease and physicians are highly selective in coding a diagnosis of tubulointerstitial disease. Thus, patients with tubulointerstitial disease account for a small fraction (generally, <1%) of the total CUMC outpatient population (see **Table S4**), and

these few individuals are enriched for patients referred for suspected hereditary forms of tubulointerstitial disease. In contrast, the AURORA tubulointerstitial disease group represents a broader sample of patients with all-cause tubulointerstitial disease: in particular, nearly 50% of cases have the acquired etiology of pyelonephritis as cause of their ESRD. In contrast, there were no cases of pyelonephritis in the CUMC tubulointerstitial disease cohort.

| Clinical Diagnosis | AURORA | | CUMC | | Comparison | |
|---|---|---|---|---|---|---|
| | N/N Total | Yield (%) | N/N Total | Yield (%) | OR (95% CI) | P-value[†] |
| Congenital or cystic renal disease | 96/159 | 60.4 | 31/372 | 8.3 | 16.6 (10.0, 28.1) | $< 2.2 \times 10^{-15}$ |
| *Congenital or cystic renal disease, excluding ADPKD cases* | *7/70* | *10.0* | *26/365* | *7.1* | *1.4 (0.51, 3.62)* | *1.00* |
| Glomerulopathy | 24/231 | 10.4 | 77/1180 | 6.5 | 1.7 (0.98, 2.7) | 0.50 |
| Diabetic nephropathy | 1/184 | 0.5 | 5/186 | 2.7 | 0.19 (0.004, 1.8) | 1.00 |
| Hypertensive nephropathy | 6/193 | 3.1 | 2/126 | 1.6 | 2.0 (0.35, 20.4) | 1.00 |
| Tubulointerstitial disease[‡] | 3/212 | 1.4 | 8/32 | 25 | 0.04 (0.01, 0.20) | $4.7 \times 10^{-5}$ |
| Other | 1/50 | 2.0 | 5/109 | 4.6 | 0.43 (0.01, 4.0) | 1.00 |
| Nephropathy of unknown origin | 9/99 | 9.1 | 39/182 | 21.4 | 0.37 (0.15, 0.82) | 0.08 |
| Total | 140/1128 | 12.4 | 167/2187 | 7.6 | 1.7 (1.3, 2.2) | $1.2 \times 10^{-4}$ |
| *Total, excluding ADPKD cases* | *51/1039* | *4.9* | *162/2180* | *7.4* | *0.64 (0.46, 0.89)* | *0.08* |

[†]Bonferroni-adjusted p-value, for 10 independent comparisons.

[‡]50% of the AURORA patients with tubulointerstitial disease have the acquired etiology of pyelonephritis. In contrast, there were no cases of pyelonephritis in the CUMC tubulointerstitial disease cohort.

ADPKD: Autosomal Dominant Polycystic Kidney Disease; ADPKD cases were individuals with diagnostic *PKD1* or *PKD2* variants and/or clinically diagnosed with ADPKD based on the established imaging criteria.[29]

**Table S13. Adjusted models for comparison of diagnostic yield by clinical indication**

| | AURORA[†] | | CUMC[‡] | | AURORA-CUMC[#] | |
|---|---|---|---|---|---|---|
| | **OR (95% CI)** | **P-value** | **OR (95% CI)** | **P-value** | **OR (95% CI)** | **P-value** |
| **Female gender** | 1.0 (0.66, 1.6) | 0.85 | 0.79 (0.56, 1.1) | 0.17 | 0.95 (0.74, 1.2) | 0.71 |
| **Self-identified non-white European ethnicity** | 0.51 (0.17, 0.51) | 0.22 | 0.75 (0.54, 1.1) | 0.10 | 0.78 (0.57, 1.1) | 0.11 |
| **Age at time of study entry (yr)** | 0.99 (0.97, 1.0) | 0.62 | 0.99 (0.98, 1.0) | 0.64 | 1.0 (0.99, 1.01) | 0.16 |
| **Positive family history for kidney disease** | - | - | 3.4 (2.5, 4.7) | $2.7 \times 10^{-13}$ | - | - |
| **Clinical Diagnosis** | | | | | | |
| Diabetic nephropathy | (ref) | - | (ref) | - | (ref) | - |
| Congenital or cystic renal disease | 241.6 (32.8, 1781.2) | $7.3 \times 10^{-8}$ | 2.1 (1.05, 5.3) | 0.02 | 25.9 (11.0, 60.7) | $7.7 \times 10^{-14}$ |
| Nephropathy of unknown origin | 16.8 (2.1, 135.2) | $7.1 \times 10^{-3}$ | 6.9 (2.6, 18.2) | $1.0 \times 10^{-4}$ | 13.6 (5.7, 32.5) | $3.9 \times 10^{-8}$ |
| Glomerulopathy | 18.6 (2.5, 139.7) | $4.5 \times 10^{-3}$ | 2.0 (0.78, 0.15) | 0.15 | 6.5 (2.8, 15.0) | $1.4 \times 10^{-5}$ |
| Hypertensive nephropathy | 5.4 (0.64, 45.3) | 0.12 | 0.49 (0.09, 2.6) | 0.80 | 1.4 (0.47, 4.0) | 0.55 |
| Tubulointerstitial disease | 2.3 (0.24, 22.6) | 0.47 | 8.3 (2.4, 28.5) | $7.3 \times 10^{-4}$ | 2.1 (0.76, 5.8) | 0.15 |
| Other | 3.4 (0.21, 54.8) | 0.40 | 1.6 (0.45, 5.9) | 0.46 | 2.8 (0.88, 8.8) | 0.08 |

[†]Adjusted for sex, race (self-identified non-white European versus white European), and age at time of study entry; family history data was unavailable for patients from the AURORA cohort.

[‡]Adjusted for sex, race (self-identified non-white European versus white European), age at time of study entry, and positive family history for kidney disease.

[#]Adjusted for cohort, sex, race (self-identified non-white European versus white European), and age at time of study entry.

**Table S14. Putatively diagnostic variants requiring further clinical follow up**

See **Supplementary Appendix 2** on NEJM.org: sheet "**TableS14**".

Age is age at time of study entry (yr).

For AURORA patients, study consent protocols permitted providing only the broad clinical diagnosis for patient information.

Family history data was available only for CUMC patients.

Zygosity: heterozygous (Het); homozygous (Hom); or hemizygous (Hemi).

Inheritance: autosomal dominant (AD); autosomal recessive (AR); or X-linked.

**Table S15. Clinical diagnostic spectrum of patients with the *APOL1* risk genotypes**

| Clinical Diagnosis | Black/African American | | Hispanic | | Total | |
|---|---|---|---|---|---|---|
| | N/N total | % | N/N total | % | N/N total | % |
| Control | 173/1219 | 14 | 14/511 | 3 | 187/1730 | 11 |
| **All kidney disease cases** | **100/348** | **29** | **36/485** | **7** | **136/833** | **16** |
| Glomerulopathy | 53/159 | 33 | 26/204 | 13 | 79/363 | 22 |
| *Focal segmental glomerulosclerosis*† | *34/63* | *54* | *22/53* | *42* | *56/116* | *48* |
| Hypertensive nephropathy | 13/47 | 28 | 6/34 | 18 | 19/81 | 23 |
| Diabetic nephropathy | 9/43 | 21 | 1/98 | 1 | 10/141 | 7 |
| Congenital or cystic renal disease | 4/43 | 9 | 0/81 | 0 | 4/124 | 3 |
| Other | 5/20 | 25 | 0/26 | 0 | 5/46 | 2 |
| Nephropathy of unknown origin | 16/36 | 44 | 3/42 | 7 | 19/78 | 24 |

N/N total = Number of individuals with the *APOL1* risk genotypes divided by the total number of individuals in the given clinical diagnostic subgroup

†Among the patients clinically diagnosed with glomerulopathy, no AURORA cases carried clinical diagnostic codes for focal segmental glomerulosclerosis, a subtype of glomerulopathy; thus, the frequencies for patients with focal segmental glomerulosclerosis are with respect to the CUMC cohort.

**Table S16. Diagnostic findings in Mendelian nephropathy-associated genes among individuals with *APOL1* risk genotypes**

| Patient ID | Sex | Age | Race/Ethnicity | Positive family history for kidney disease | Clinical Diagnosis | Gene | Genetic Diagnosis | OMIM Phenotype MIM No. |
|---|---|---|---|---|---|---|---|---|
| CKD189 | M | 28 | Black/African American | No | Nephropathy of unknown origin | *HBB* | Sickle cell disease | 603903 |
| CKD195 | M | 55 | Black/African American | Yes | Nephropathy of unknown origin | *TRPC6* | Glomerulosclerosis focal segmental 2 | 603965 |
| CKD210 | M | 56 | Hispanic | Yes | Glomerulopathy | *INF2* | Glomerulosclerosis focal segmental 5 | 613237 |
| CKD265 | M | 49 | Black/African American | No | Other | *HBB* | Sickle cell disease | 603903 |
| CKD281 | F | 44 | Black/African American | Yes | Nephropathy of unknown origin | *COL4A4* | Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease | 203780; 141200 |
| CKD291 | M | 45 | Black/African American | No | Glomerulopathy | *CREBBP* | Rubinstein-Taybi syndrome 1 | 180849 |

Age is age at time of study entry (yr).

Variant-level data, including variant classifications and supporting ACMG criteria, are in **Table S7**.

**Table S17. Findings in the ACMG 59 medically actionable genes and implications for clinical care**

See **Supplementary Appendix 2** on NEJM.org: sheet "**TableS17**".

Age is age at time of study entry (yr).

Zygosity: heterozygous (Het); homozygous (Hom).

Inheritance: autosomal dominant (AD); autosomal recessive (AR).

As the AURORA study protocol did not permit analysis of genetic data for secondary findings, we analyzed only data from CUMC patients for the ACMG 59 genes. Among the 34 cases in whom ACMG 59 gene findings were detected, we assessed: 1) the extent of known phenotypic concordance (the column, "Known Clinical Features Consistent With the ACMG 59 Gene Disorder") and 2) the greater implications of these genetic findings, including the subspecialty referrals and initial evaluation prompted (in the columns, "Resultant Subspecialty Referrals" and "Associated Targeted Evaluations/Workup", respectively) and the implications for nephrologic care (in the column, "Implications for Nephrologic Care").

For these CUMC patients, we had access to their electronic health records, and found that 26/34 (76%) individuals had a personal and/or family history of clinical features consistent with the associated ACMG 59 syndrome. We found 5 of the 34 (14.7%) individuals had diagnoses that were highly specific for the associated ACMG 59 genetic diagnosis (e.g., early-onset colon and endometrial cancer in the context of an *MSH2* variant; familial hypercholesterolemia with *LDLR* mutation) and 14 (41%) had suggestive clinical features potentially consistent with the associated ACMG 59 diagnosis (e.g., prolonged QT interval in the context of an *SCN5A* mutation; prostate cancer in a male with a *BRCA2* mutation). Of these 19 individuals, 6 (31%) had a concordant family history.

We note that as many of the ACMG 59 disorders have late onset and may not have yet manifested in the proband, we also checked for a compatible family history of disease. An additional 7 (21%) individuals who did not personally manifest signs of the associated ACMG 59 gene condition had a positive family history (e.g., multiple relatives with early-onset breast cancer in the context of a *BRCA2* mutation). All of these 7 individuals had variants in genes associated with hereditary cancer predisposition (*BRCA2*: N=4; *PMS2*: N=2; *MSH6*: N=1); importantly, 6 of these 7 individuals were aged 40y or under, such that the associated disease may still manifest.

The remaining 8 (24%) of individuals had no documented clinical features supportive of the ACMG 59 condition; however, 4 of these 8 individuals had not undergone the relevant diagnostic studies (e.g., no record of cardiac ECG and/or echocardiography in the context of mutations for hereditary cardiomyopathy).

These findings are summarized below, and detailed in further depth in **Table S17**.

| **Concordance of Known Clinical Features with ACMG 59 Genetic Diagnosis** | **No. of individuals** | **Rate (%)** |
|---|---|---|
| **Consistent personal features** | 19 | 56 |
| Highly specific clinical diagnosis | 5 | 15 |
| Suggestive clinical features | 14 | 41 |
| *Consistent clinical features and positive family history* | *6* | *32‡* |
| **Positive family history only** | 7 | 21 |
| ***Consistent personal features and/or family history*** | ***26*** | ***76*** |
| **No known supportive clinical features** | **8** | **24** |
| **Total** | **34** | **-** |

‡Percentage with respect to the total number of individuals with consistent personal features, N=19.

**Table S18. Targeted phenotype-driven gene panels evaluated for comparison of the diagnostic yield of exome sequencing versus that of more targeted genetic testing**

| Clinical Indication | Panel | Provider | No. of Genes Tested[†] | GTR Test ID |
|---|---|---|---|---|
| Congenital or cystic renal disease | Polycystic kidney disease and related disorders Comprehensive panel | Connective Tissue Gene Tests | 22 | GTR000559426.2 |
| Congenital or cystic renal disease | ExomePLUS - Cystic & Dysplasia/Agenesis | Laboratory for Molecular Medicine | 22 | GTR000552070.4 |
| Congenital or cystic renal disease | Hereditary Cystic Kidney Diseases Sequencing Panel | Prevention Genetics | 41 | GTR000561677.1 |
| Glomerulopathy | Nephrotic syndrome and related disorders | Connective Tissue Gene Tests | 42 | GTR000560987.2 |
| Glomerulopathy | Exome PLUS Proteinuria/FSGS & Hematuria | Laboratory for Molecular Medicine | 32 | GTR000552068.4 |
| Glomerulopathy | Nephrotic Syndrome (NS)/Focal Segmental Glomerulosclerosis (FSGS) Sequencing Panel | Prevention Genetics | 49 | GTR000509600.18 |
| Tubulointerstitial disease | Hyperuricemic nephropathy, familial juvenile NGS panel | Connective Tissue Gene Tests | 3 | GTR000561327.1 |
| Tubulointerstitial disease | Nephrolithiasis and Nephrocalcinosis Sequencing Panel | Prevention Genetics | 30 | GTR000551609.7 |
| Tubulointerstitial disease | ExomePLUS - Electrolyte & Kidney Stone | Laboratory for Molecular Medicine | 49 | GTR000552069.4 |

[†]Number of genes tested is with respect to at the time of analysis (9/22/2018).

**Table S19. Comparison of diagnostic yield of exome sequencing versus that of targeted testing**

To further assessed the diagnostic utility of exome sequencing for patients with kidney disease, we compared the diagnostic yield observed using exome sequencing in the combined AURORA-CUMC cohort versus that potentially obtained using more targeted testing. The methodology for this analysis is detailed in **Section S1 (Supplementary Methods, Comparison of the diagnostic yield of exome sequencing versus targeted testing);** the results are shown in the **Table** below.

| | | ES | | Cystic Kidney Disease Panels | | | Glomerulopathy Panels | | | Tubulointerstitial Disease Panels | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Clinical Diagnosis** | **Total No. of Cases Sequenced** | **No. of Positive Cases** | **Yield (%)** | **No. of Positive Cases** | **Yield (%)** | **Proportion of Positive ES Cases (%)** | **No. of Positive Cases** | **Yield (%)** | **Proportion of Positive ES Cases (%)** | **No. of Positive Cases** | **Yield (%)** | **Proportion of Positive ES Cases (%)** |
| Congenital or cystic renal disease | 531 | 127 | 23.9 | 109 | 20.5 | 85.8 | 6 | 1.1 | 4.7 | 4 | 0.8 | 3.1 |
| Glomerulopathy | 1411 | 101 | 7.2 | 7 | 0.5 | 6.9 | 92 | 6.5 | 91.1 | 1 | 0.1 | 1.0 |
| Diabetic nephropathy | 370 | 6 | 1.6 | 0 | 0.0 | 0.0 | 0 | 0.0 | 0.0 | 0 | 0.0 | 0.0 |
| Hypertensive nephropathy | 319 | 8 | 2.5 | 2 | 0.6 | 25.0 | 5 | 1.6 | 62.5 | 3 | 0.9 | 37.5 |
| Tubulointerstitial disease | 244 | 11 | 4.5 | 2 | 0.8 | 18.2 | 2 | 0.8 | 18.2 | 8 | 3.3 | 72.7 |
| Other | 159 | 6 | 3.8 | 1 | 0.6 | 16.7 | 2 | 1.3 | 33.3 | 1 | 0.6 | 16.7 |
| Nephropathy of unknown origin | 281 | 48 | 17.1 | 15 | 5.3 | 31.3 | 26 | 9.3 | 54.2 | 8 | 2.8 | 16.7 |
| **Total** | **3315** | **307** | **9.3** | **136** | **4.1** | **44.3** | **133** | **4.0** | **43.3** | **25** | **0.8** | **8.1** |

ES: Exome sequencing. Yield was calculated by dividing as the number of positive cases by the given modality divided by the total number of cases sequenced. The proportion of positive ES cases was calculated by dividing the number of positive cases by the given panel by the total number of positive WES cases.

When evaluating diagnostic yield of targeted testing for each phenotype, we assessed panels from three different clinical genetic testing providers, and conservatively used the union of the panels assessed – i.e., we defined positive cases as those for which the causal gene detected via exome sequencing was included on *any* of the three targeted panels included for that phenotype. The panels used for each phenotype are listed in **Table S18.**

As noted above and in **Section S1 (Supplementary Methods, Comparison of the diagnostic yield of exome sequencing versus targeted testing)**, we conservatively took the union of the targeted panels offered by three different clinical laboratories for each phenotype in order to account for variability between genetic testing providers. In our comparison, we also assumed equivalent technical sensitivity and specificity for each testing modality, although they may likewise vary in practice.

As expected, the yield of the targeted panels varied substantially by clinical diagnostic category, with the high rates for certain subtypes (e.g., cystic disease panel for congenital or cystic renal disease) supporting their utility for patients with more specific clinical presentations. Nonetheless, we found that none of the resulting unified phenotype-driven panels would achieve greater than 45% of the diagnostic yield of exome sequencing when considering all the nephropathies represented in the AURORA-CUMC cohort. Furthermore, their yield was less than that of exome sequencing across the different clinical diagnostic categories. In addition, the yield of a targeted panel would depend on the clinician correctly classifying the patient into the relevant phenotypic subcategory, which may not always occur. Moreover, for patients with nephropathy of unknown origin, for whom exome sequencing demonstrated high diagnostic yield, clinicians would struggle to select one phenotype-driven panel as a first-line diagnostic test.

These analyses reinforce the high genetic and phenotypic heterogeneity observed in the general kidney disease patient population and highlight the limitations of targeted, phenotype-driven testing as a first-line diagnostic test in this context. Moreover, for a

substantial proportion of patients, such targeted approaches could delay achieving a diagnosis, as clinicians would need to order additional testing following the negative results observed on the first panel chosen, and, for patients whose disease resulted from genes not included on any of the panels selected, could still eventually need to proceed to exome sequencing.

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