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Mendelian and transgenerational inheritance in hypertensive renal disease

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Abstract

Familial risk in hypertensive renal disease has stimulated a search for genetic variation contributing to this risk. The current phase of population genetic studies has sought to associate genetic variation with disease in large populations by testing genotypes at a large number of common genetic variations in the genome expecting that common genetic variants contributing to renal disease risk will be identified. These genome wide association studies (GWAS) have been productive and are a clear technical success. It is also clear that narrowly-defined loci and genes containing variation contributing to disease risk have been identified. Further extension and refinement of these GWAS are likely to extend this success. However, it is also clear that few if any variants with substantial effects accounting for the greatest part of heritability will be uncovered by GWAS. This raises an interesting biological question regarding where the remaining heritable risk may be located. One result of the progress of GWAS is likely to be a renewed interest in mechanisms by which related individuals can share and transmit traits independently of Mendelian inheritance. This paper reviews current progress in this area and considers other mechanisms by which familial aggregation of risk for renal disease may arise.

Keywords

Epigenetics; Epistasis; Genome mapping; Heritability; Linkage analysis; Maternal effect; Transgenerational inheritance

Genetic mapping is an effort to associate phenotype with underlying genotype. It is an approach that can be applied to populations to seek genetic factors responsible for traits, including traits of disease susceptibility. The main requirement is evidence that the trait shows heritability. Heritability provides the main argument that genetic variation exists within the population that affects the trait. These approaches apply the principles of Mendelian genetics, as integrated with the chromosomal theory of inheritance, that have made a transformative impact on understanding of heritable disease arising from rare mutations in single genes. This success has had two relevant consequences: it has opened the promise that traits arising from the concurrent action of multiple genetic variants can yield to the same type of investigation, and; it has swept aside investigation of other mechanisms by which traits can be shared among related individuals. This paper will examine the progress of genetic studies into hypertensive renal disease and delineate the important accomplishments that have been made. In addition, it will consider whether mechanisms by which traits can be shared among related individuals that are not directly accountable by Mendelian principles may play a role in disease risk.

Heritability and renal disease in hypertension

The majority of patients with long-standing hypertension do not develop kidney disease (1). However, among those who do develop renal disease, and in whom disease advances to end-stage (ESRD), the possibility of a heritable component emerged through observation that patients often had relatives that were similarly afflicted (2). The frequency of disease among related individuals can indicate the action of genetic risk and provide an indicator of future risk. Several studies have sought to measure the frequency of concurrence of renal disease among relatives. When hypertension is the reported ESRD etiology, nearly 19% of a patient population in the southern US had a first or second-degree relative with ESRD (3). These studies recognized that familial risk might not be equal among individuals of different origins. Such a situation also suggests the possibility of heritability because the genome variation underlying genetic risk may be present at different frequencies in different populations. In the same southern US population, persons with African ancestry treated with dialysis were observed to have a higher likelihood of have a first or second degree relative with ESRD compared with Caucasians (~23% versus 14%)(3). Since the relationship between hypertension and renal disease might be cause and effect, efforts have been made to determine whether estimated risk of ESRD is confounded by the familial aggregation of hypertension. When family history of hypertension, and other potential risk aggravating factors are controlled for, ESRD risk is preserved among related individuals (4). This independence of risk for renal damage in the presence of hypertension is supported in at least one animal model of polygenic hypertension, the spontaneously hypertensive rat, in which similar susceptibility to hypertension is accompanied in distinct lines by difference in susceptibility to renal disease (5).

Many heritable renal diseases show simple Mendelian genetics. However, inheritance of risk of renal disease in hypertension may not arise from single genetic susceptibilities, but rather may reflect more than one genetic susceptibility in the population and more than one susceptibility in affected families (6). The pathogenesis of renal injury is complex and may involve diverse genetic risks including those specifically affecting glomerular structure, those that may produce proteinuria without initial structural damage to the glomerulus, those that may specifically damage tubular structure or function, those that can be associated with more or less inflammatory injury and those which can determine whether disease terminates by replacement of functional renal epithelium with fibrotic scar or with recovery of epithelial function. Conceivably, in hypertensive patients with declining renal function all of these outcomes might arise from a single genetic cause. Alternatively genetic variation may shape the role of more than one of these factors in the progression of injury and the ultimate destruction of renal clearance. Pathogenetic complexity with underlying genetic complexity poses a challenge to investigation. That challenge can be met, partially, by the disintegration of the disease outcome of reduced renal clearance into intermediate phenotypes such as albumin excretion and increased serum creatinine concentration. Many of the desirable intermediate phenotypes can best be obtained by sampling and histological analysis of renal tissue. However, this is a risk-accruing procedure not possible in the context of a population genetics study. This is a limitation that has an important impact on genetic studies of hypertensive renal disease.

Mapping the genome for renal disease risk

Initial efforts to map genetic loci influencing renal parameters focused on creatinine clearance and proteinuria. These traits were shown to be heritable with the effect of genes on the trait estimated to range from 17% for creatinine clearance in African Americans (AA) (7), to 49% for urinary albumin excretion (Mixed Caucasian and AA, (8)). These heritability estimates provide a reasonable foundation for a mapping study. Analysis of the populations

used to estimate heritability was performed by linkage analysis (in which transmission of genetic variants and traits in related individuals is examined to identify chromosomal regions that might influence trait values). However, linkage studies generally failed to find loci with statistically significant trait effects on creatinine clearance (7) or urinary albumin excretion (8), though a further refinement, adding more genotype data, did identify one locus for creatinine clearance (Chr 3p) with statistical significance (9).

Further studies sought to improve mapping in a number of ways. For example, Turner and colleagues extended studies of creatinine clearance and albumin excretion originally reported by others after new data was collected. New estimates of heritability indicated strong heritability (approximately 50%) of serum creatinine and creatinine clearance in AA, somewhat less heritability in Caucasians, lower heritability of albumin excretion in AAs (30%), but found no evidence of heritability of albuminuria in Caucasians (10). A chromosome 7 locus was mapped affecting serum creatinine levels in AAs. Several other linkage studies in different populations examining similar traits have been reported. However, the depth of discovery obtained has been rather limited (11, 12). A similar outcome in linkage mapping of other complex traits prompted consideration of other mapping methodologies. The rapid emergence of single nucleotide polymorphism (SNP) data from diverse human populations as well as technical advances allowing low-cost high-throughput genotyping of these polymorphisms in large numbers of subjects provided the rationale for a new effort in population genetics, genome-wide association studies (GWAS).

Genome-wide Association Studies

In contrast to linkage analysis performed in pedigrees of related individuals, GWAS is a population-based approach whose foundation is the availability of a large number of stable polymorphisms, the relative frequency of whose alleles is known in the study population and which are selected because they are common. Since recombination breaks down linkage between adjacent markers and trait variants in a population, a large number (typically 500,000 or more) of such markers, densely spaced across the genome, is required to test the hypothesis that a given marker is associated with a trait in the population. Marker density can be increased by imputation, a process that uses linkage disequilibrium to predict the likely allelic state of adjacent untyped markers (13, 14). This high marker density offers fine scale resolution, even down to the level of the causative gene, though only rarely to the causative variant. One important cost of the approach is the statistical impediment created by the fact that such studies test a unique hypothesis for essentially every SNP genotyped. This requires adjustment of significance thresholds for the large numbers of markers tested so that a p value of 5×10^{-8} is the typical significance threshold. To achieve sufficient levels of power, a large study population is needed. This is reflected in the current practice of combining several study populations (that may have different structure and composition as well as different sampling methodology) to increase statistical power (15, 16).

GWAS studies have advanced sufficiently to be able to assess both their technical performance and their capacity to yield insight into the genetic variation underlying traits. These studies are remarkable for their scale and for the vast amount of data they generate. They are also remarkable for the extraordinary degree of scientific cooperation needed both within the large groups that possess data and DNA samples from specific populations as well as among the groups forming the study consortia. The results are in general a stunning tribute to the capacity of large-scale scientific investigation to produce robust answers to challenging questions. The answer to the question: “are GWAS in large human populations able to reveal genes containing variation that contributes to population variance in traits related to declining renal function and albuminuria?” is a clear and affirmative yes (17–20).

Because renal tissue sampling is not possible in cross-sectional, large-scale population studies, other indicators of reduced renal function and renal disease have been measured. These include creatinine clearance calculated from serum and urinary creatinine, estimated glomerular filtration rate (eGFR) calculated from serum creatinine or from serum cystatin c levels and renal protein (or specifically albumin) excretion. To achieve the requisite power to overcome the multiple testing limitations of GWAS, it has been necessary to study large populations. Such populations are generally not selected on a case:control basis for renal disease and are therefore not generally segregated into individuals in which the presence of hypertension has been a specific investigational criterion. These populations include individuals with and without diminished renal function, with and without hypertension and with and without diabetes, or other major sources of renal injury. Thus, with a few exceptions GWAS has targeted principally declining renal function through extra-renal indicators in large and diverse populations. A typical study design has been to examine one or more populations to discover associated genetic variants (discovery phase) and to then test selectively those variants in an independent population to ensure that discoveries are reproducible (replication phase). This type of design is suitable to eliminate false positives, however, it does so at some risk of eliminating from further investigation true positives that fail to replicate in the smaller follow up study, a fact that must be considered when the failure of GWAS to account for all the population variance in renal disease risk is addressed.

A brief summary of reported renal function GWAS studies is provided in Table 1.

There are several important features that have emerged from these studies. The first is that they have generated evidence of their own success at the technical level. This is an important accomplishment because the large scale of these studies means that technical failures arising from sample handling errors, inconsistent DNA quality, and persistent inaccuracies in genotype assay, all provide real pitfalls. Technical success is attested by the discovery that several of the variants identified as associated with renal traits (CST3, GATM, CPS1, SLC22A2, TMEM60, WDR37, SLC6A13, WDR72 and TBX2) are likely to have been identified because they directly affect the intermediate phenotype being measured rather than because they affect renal function (18, 19). For example, variation in CST3 which encodes cystatin c probably affects serum levels of cystatin c directly, rather than through any effect on renal function. Similarly, several associated genes were inferred to be involved in creatinine synthesis or secretion because they were associated with eGFR estimated from serum creatinine levels, but not eGFR estimated from serum cystatin levels. Among genes not implicated in the turnover of GFR markers, the mechanism of action is often indistinct. ANXA9 encodes an annexin that is expressed in the kidney, differs in its calcium-dependent binding properties of phospholipid-containing lysosomes compared to other annexins, but its explicit function is not well defined. Stanniocalcin 1 (STC1) may be involved in regulation of mitochondrial anti-oxidant pathways and may have other anti-inflammatory properties (21, 22). Uromodulin (UMOD) links adaptive and innate immunity in the urinary tract via the Toll-like receptor, suggesting defense from Gram-negative bacterial infection (23).

In summary, GWAS studies have made important contributions. They have provided clarity to the genetic architecture of heritable risk of loss of renal function. They have shown that this risk is real, they have identified genes through which this risk may be manifest and they have shown that the effects associated with individual common alleles are remarkably small, much smaller than expected and sufficiently small as to produce few results that are likely to impact the clinical approach to this disease. Genes containing variants with moderate to large effects have not been identified. This was not the expected finding and is a risk that was not well articulated in the rationale for these large-scale studies. While it is not yet clear whether the set of alleles creating susceptibility to hypertension and the set of alleles

creating susceptibility to renal injury in hypertension are overlapping, existing GWAS studies addressing these two areas have yield only limited support for this with UMOD (19, 24, 25) and ATXN2 (19, 26). The disappointment resulting from the failure of GWAS to identify common alleles with large effects is somewhat balanced by the fact that GWAS studies have led to substantial clarification that the genetic architecture of common disease risk is not as simple as initially hypothesized. One consequence is to redirect the focus research effort to other hypotheses that may account for sharing of disease risk within families.

Admixture Mapping and Renal Disease in Hypertensive African-Americans

Risk of hypertensive renal disease is notably high among African-Americans (2) and the heritability of indicators of renal injury is higher in this sub-population than in Caucasians in the same population (3, 10). Admixture mapping uses populations containing individuals of recently mixed ancestries. Genomic regions causing differences in heritable disease susceptibility present in the unmixed ancestral populations may be identified in individuals in the admixed population. This identification seeks to locate genomic regions present in affected individuals in the admixed population that are consistently acquired in the haplotype present in the ancestral population at risk for the disease (27).

Genome-wide admixture mapping has been used successfully to identify a major genetic locus affecting risk of reduced renal function in African-Americans. The risk appears to be dissociated from diabetic renal injury, but not from renal injury attributable to hypertension or HIV infection, and appears to produce a histological phenotype resembling focal segmental glomerulosclerosis. The region localized contains two possibly important genes, MYH9 and APOL1, an unconventional myosin and an apolipoprotein (28, 29). While MYH9 variation is most strongly associated with risk, variation in the adjacent APOL1 gene appears to provide resistance to trypanosome infection (30, 31). This presents the possibility that selection has acted on this locus to increase the frequency of an adaptive allele of APOL1 in geographic regions with endemic trypanosome infection. Renal risk-enhancing alleles of MYH9 (in linkage disequilibrium with the APOL1) may have increased in frequency in this population secondary to selection acting on the adaptive APOL1 variation. However, the mechanism of the nephropathy associated with variation in African alleles in this region remains a complex and incompletely resolved question. Evidence of Mendelian glomerular disease associated with MYH9 mutation (32, 33) and proteinuria in MYH9 knockout mice treated with nephrotoxins (34) suggest the importance of MYH9 in development of the disease phenotype. However, the evidence implicating MYH9 variation in humans is incomplete and is complicated by the fact that APOL1 variants have the stronger association with disease (30, 35).

GWAS and the uncharted discovery space

While there is strong evidence to support a role for variation in the genes listed in Table 1 to affect renal function, GWAS studies often encounter a shortfall in their capacity to account for all of the heritable effects. Thus, efforts are underway to reassess the underlying presumptions that have motivated GWAS and consideration is being given to other means to account for the gap between what GWAS set out to achieve and what has been accomplished. GWAS has been tremendously successful and has produced highly reliable, rigorously proven results. However, the motivating hypothesis for these studies (acknowledging that all such hypothesis are necessarily generalizations whose value comes not from the completeness of their success, but their reasonableness to address a problem) was that common genetic variation would explain the heritability of common disease susceptibility. Alternative explanations that may account for the incomplete success of

GWAS include the possibility that heritability is attributable to a much larger number of rare variants in the population that have large effects, but in relatively few individuals. Another possibility is that interactions between multiple susceptibility variants, each possessing only limited effects and possibly operating in the same functional pathway, combine to produce more than additive effects on traits, a situation called epistasis. Since the main effects of each variant are likely to be small, interactions among alleles may not be detected. The problem of detecting epistasis is increased by the high dimensionality of the task. This arises from: the large number of possible pairwise interactions that occur when hundreds of thousands of SNPs have been genotyped; the large number of multiple interaction combinations that could be tested (i.e., interactions that depend on interaction of multiple, rather than pairs of SNPs); and the power diluting effect that arises because SNPs tested in GWAS generally are surrogates for the causal SNP which dilutes the relationship between genotype and trait. Nonetheless, the potential importance of such interactions cannot be overlooked. Some progress is being made in the development of tools for the computationally intensive task of testing for epistasis and may accelerate progress in this challenging area.

Another type of interaction with genetic variation that may be important in GWAS is interaction between gene variants and the environment. These are also very challenging to uncover, especially in human population studies in which there is no capacity to control environmental exposures which can only be partially accounted for by extensive subject profiling and that in any case require combination of different populations (and likely environmental exposures) to identify main effects. Another possibility that is unaccounted for is that the GWAS gap is attributable to forms of genetic variation that differ from single nucleotide polymorphisms, such as deletions, insertions and chromosomal inversions, which are not always tested by high throughput genotyping platforms. However, this explanation and the possibility that common disease traits are broadly attributable to regions of the genome with insufficient SNP representation seem unlikely.

Is there more to familial aggregation of traits than Mendelian inheritance?

GWAS studies represent the incremental application of the principles of Mendelian genetics to the challenging task of deciphering the mechanisms by which heritable disease risk is transmitted across generations. It builds upon the extraordinary success that has been accomplished by applying Mendelian principles to understand single gene traits. However, single gene traits are typically characterized by having high heritability, moderate to high penetrance and usually create distinct phenotypes. One intriguing possibility left on the table by GWAS is that unaccounted heritability may be transmitted through mechanisms other than Mendelian chromosomal inheritance. It is important to consider this possibility because heritability estimates for complex disease traits are typically made in nuclear families. However, GWAS studies are population, not family studies. Thus, the heritability gap might result from mechanisms of trait sharing that operate among closely-related individuals, but that may not be similarly discernable across populations.

The broad term for such phenomena is “epigenetics”. However, this word provides an umbrella of definitions that has undergone substantial change since the original notion of epigenesis was introduced by Conrad Waddington as the process by which phenotypes develop from genotypes (36). More recently, Riggs has re-defined epigenetics, liberating it from the genomic DNA sequence as: “the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence.” (37) A more recent twist has emerged from the impact of increased understanding of DNA methylation and histone influenced mechanisms of epigenetic inheritance on gene expression to redefine it as “the sum of the alterations to the chromatin template that

collectively establish and propagate different patterns of gene expression (transcription) and silencing from the same genome” (38).

One mechanism of epigenetic inheritance is recently evolved and present only in marsupials and placental mammals, perhaps reflecting the role of the mother in the pre-and post-natal provisioning of offspring with resources (39, 40). This is the mechanism of imprinting in which certain genes are expressed in a parent-of-origin specific manner and which depends on germ-line methylation of progeny DNA, notably in the cytosine and guanine rich promoter regions of certain genes, that subsequently affects the expression of one or other parental alleles of the imprinted gene. This ultimately gives greater control over progeny phenotype (and therefore maternal resource consumption) through the action of maternally-directed imprinting mechanisms, apportioning the maternal interest to preserve resources for future progeny that may have different paternity over the paternal interest to deplete maternal resources for the benefit of the current progeny (40). Imprinting is a durable, but transitory process, requiring erasure and reestablishment at each generation (during gametogenesis and in the early embryo), and perhaps thereby permitting some scope for adaptive responses driven by environmental inputs, such as nutrition, an epigenetic mechanisms with origins as ancient as insects (41).

Another important mechanism for transferring maternal resources to progeny is the transmission of pre-formed immunological competence to progeny whose immune systems are immature. This process provides another method by which progeny phenotype can be shaped independently of its DNA. Trans-generational immune molecule transfer appears to have a more ancient evolutionary history than genetic imprinting, occurring prior to the development of immunoglobulins, even in insects (42). Its occurrence in birds and mammals through the transfer of immunoglobulins either via the yolk, the placenta and lactation is well understood (43–45). This understanding leads to two implications. The most obvious is that this is a resource transfer that provides temporary passive immunity to the progeny until their own immune systems are able to react to interaction with antigens. However, there are secondary implications that can shape progeny traits over longer time frames. This is illustrated well by experiments in inbred rodent models where maternal immunoglobulin transmission to progeny has a strong impact on the penetrance of traits involving autoimmune diseases such as type 1 diabetes and atherosclerosis(46, 47). These effects appear to endure beyond the period of passive immunization, indeed may persist over more than one generation (48), suggesting that maternal immunoglobulin shapes the future reactivity of the progeny immune system (49–51).

Immunoglobulin transfer between mother and progeny can have significant effects beyond passive immunization. Antibodies generated to an antigen are the result of B cell response and clonal selection that includes both differential usage of many exons encoding structural elements of immunoglobulin (52) followed by recombination that generates novel somatic DNA sequence to optimize antigen recognition (53). The resulting antibodies are called idiotypic antibodies. The recombination of variable regions of immunoglobulin results in the production of immunoglobulins that are themselves immunogenic because they contain amino acid sequences different from those in the animal’s germ line. Thus a network of antibody responses may result from exposure to a single antigen to include idiotypic antibodies as well as anti-idiotypic antibodies produced in response to the idiotypic antibodies (and anti-anti-idiotypic antibodies, etc). Remarkably, progeny immune responses can be shaped over long time periods by exposure to maternally transmitted idiotypic antibodies, and also to anti-idiotypic antibodies (51). Thus, the whole network of immunoglobulins produced in response to maternal antigen exposure has the capacity to convey information to progeny that shapes the progeny’s immune response to subsequent antigen exposure. This may be highly relevant to genetic studies of autoimmune diseases.

For example, asthma has substantial heritability and involves IgE-mediated responses to allergens (54, 55). The genotype:phenotype relationship of the asthma trait may be disrupted by non-genetic mechanisms arising from maternal immunoglobulin transfer where progeny response to asthma-inducing allergen can be heavily modified by maternally transferred immunoglobulin (51).

Work in the rat SHR model of hypertension indicates that blood pressure traits are strongly influenced by exposure both to the maternal uterine environment, as shown by SHR embryo transfer experiments into normotensive recipients, and by changes in the neonatal environment such as fostering of pups to normotensive surrogate mothers (56–58). Furthermore, there is extensive sequence variation in the immunoglobulin heavy chain locus that appears to affect susceptibility to end organ disease in this model of hypertension (59). Similar allotypic germ line variation occurs in human immunoglobulins, having the potential to affect traits in a number of human diseases that have an inflammatory component (60–64). Unfortunately this germ line variation is not represented on the genotypic arrays used in GWAS because they are absent from the HapMap collection upon which these arrays are based (65). Thus, while such germ line variants are heritable, their effect in GWAS studies is not directly assessed. Furthermore, if this variation is, as suggested by the SHR rat, capable of altering immunological responses affecting cardiovascular diseases, the effect of such genetic variation on disease risk will be disrupted by the concurrent presence in individuals of parental immunoglobulin exposure that may direct immune and inflammatory responses contrary to the direction encoded by the progeny genome.

Conclusion

GWAS studies have begun to reveal genetic variants that can influence risk of renal disease in hypertension. It can be expected that this approach will be pursued further to maximize the capacity of this approach to uncover such variants by extending them across larger study populations. However, it also appears that there are other factors at work that may contribute to familial aggregation of risk of hypertensive renal disease. These factors include rare (compared to the common variants studied by GWAS) genetic variants, gene:gene interactions, gene:environment interactions and mechanisms of transgenerational inheritance that may depend on modification of expression of genes by histone modification and DNA methylation as well as transgenerational transmission of proteins from parent to progeny.

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Abbreviations

eGFR	estimated glomerular filtration rate
GWAS	genome-wide association study
SHR	spontaneously hypertensive rat
SNP	single nucleotide polymorphism

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Key Messages

1. Genome-wide association studies have begun to uncover common genetic variation in the population that impacts several measures of declining renal function.
2. A gap appears to be emerging between the hoped for capacity of these studies to explain heritable risk for loss of renal function in association with diseases such as hypertension and what may be achieved by them.
3. Other mechanisms, including non-Mendelian mechanisms, by which trait aggregation in families may occur are now under consideration and investigation.

Table 1

Identification of SNPs associated with renal function traits in GWAS

Chr	Position (base)	SNP ID	Gene(s)	Trait	Note	References
1	149,218,101	rs267734	ANXA9	eGFR serum creatinine		17–20
2	27,584,444	rs1260326	GCKR	eGFR serum creatinine		19
2	73,721,836	rs13538	NAT8/ALMS1	eGFR serum creatinine		17, 19
2	143,289,827	rs347685	TFDP2	eGFR serum creatinine		19
2	211,248,752	rs7422339	CPS1	eGFR serum creatinine	#	19
4	77,587,871	rs17319721	SHROOM3	eGFR serum creatinine		18–20
5	39,432,889	rs11959928	DAB2	eGFR serum creatinine		19
5	176,750,242	rs6420094	SLC34A1	eGFR serum creatinine		19
6	43,914,587	rs881858	VEGFA	eGFR serum creatinine		19
6	90,089,661	rs2064831	GABRR2	serum creatinine		20
6	160,588,379	rs2279463	SLC22A2	eGFR serum creatinine	#	17, 19
7	77,254,375	rs6465825	TMEM60	eGFR serum creatinine	#	19
7	151,038,734	rs7805747	PRKAG2	eGFR serum creatinine		19
8	23,822,264	rs1731274	STC1	eGFR serum cystatin		18, 19
8	139,815,390	rs4588898	COL22A2	serum creatinine		20
9	70,624,527	rs4744712	PIP5K1B, FAM122A	eGFR serum creatinine		19
10	1,146,165	rs10794720	WDR37	eGFR serum creatinine	#	19
12	219,559	rs10774021	SLC6A13	eGFR serum creatinine	#	19
12	78,005,502	rs12300068	SYT1	serum creatinine		20
12	110,492,139	rs653178	ATXN2	eGFR serum cystatin		19
13	71,245,697	rs626277	DACH1	eGFR serum creatinine		19
15	43,486,085	rs2467853	GATM	eGFR serum creatinine	#	17–20
15	51,733,885	rs491567	WDR72	eGFR serum creatinine	#	19
15	73,946,038	rs1394125	UBE2Q2, FBXO22	eGFR serum creatinine		19
16	20,275,191	rs12917707	UMOD	eGFR serum creatinine		17–20
17	56,811,371	rs9895661	TBX2, BCAS3	eGFR serum creatinine	#	17, 19
19	38,048,731	rs12460876	SLC7A9	eGFR serum creatinine		17, 19
20	23,558,262	rs13038305	CST3	eGFR serum cystatin	*	18, 19
22	35,025,888	rs4821481	MYH9/APOL1	FSGS, ESRD		22–24

#likely involved in creatinine metabolism
*likely involved in cystatin c metabolism