HHS Public Access

Author manuscript

Nat Rev Nephrol. Author manuscript; available in PMC 2016 December 29.

Published in final edited form as:

Nat Rev Nephrol. 2015 November ; 11(11): 635–636. doi:10.1038/nrneph.2015.148.

Decade in review–genetics of kidney diseases: Genetic dissection of kidney disorders

F Hildebrandt[1]

[1]Boston Children's Hospital, Division of Nephrology, 300 Longwood Avenue, Enders 561, Boston, MA 02115, United States

A DECADE IN REVIEW

A surprisingly high fraction of chronic kidney disease is caused by monogenic mutations

Next generation sequencing identifies monogenic causes of disease—The advent of next-generation sequencing techniques, including whole exome sequencing (WES), has led to the discovery that a surprisingly high fraction of early-onset chronic kidney diseases (CKD) are caused by mutations in a monogenic gene (also known 'single-gene disorder' or 'Mendelian' disorder). In a monogenic gene the occurrence of disease in the affected individual is explained by a mutation in a single gene only. In different patients a mutation in one of many alternative genes may cause a similar-appearing disease (known as 'gene locus heterogeneity').

A revolution in diagnostics of early-onset CKD—A striking discovery was made when a world wide cohort of 1,780 individuals with steroid-resistant nephrotic syndrome (SRNS) manifesting before 25 years of age, was studied by mutation analysis of the 27 genes that are currently known to cause SRNS if mutated.[1] It was found that in almost 30% of these individuals the causative mutation was detected, fully explaining why these individuals develop SRNS. The fraction of families, in whom a single-gene cause was identified, correlated with early onset of disease, being 70% in newborns and 12% in young adults. This surprisingly high fraction of monogenic causation of SRNS has been confirmed by other groups (Giglio et al. *JASN* 26, 230–236, 2015; Trautman et al. *CJASN* 10:592–600, 2015).

Similarly high percentages of monogenic causation were detected in individuals manifesting with CKD before age 25 due to other causes, that included cystic kidney diseases (>50%) (Halbritter et al. *Hum Genet* 132, 865–884, 2013), urinary stone disease (21%) (Halbritter et al. *JASN* 26:543–51, 2015, editorial Goldfarb pp.507–10), congenital anomalies of the kidneys and urinary tract (CAKUT) (17%) (Kohl et al. *JASN* 25: 1917–1922, 2014; Hwang et al. *Kidney Internat* 85, 1429–1433, 2014), and nephritis (15%) (Lovric, unpublished). Already, ~25% of all cases with CKD under 25 years of age can be explained by monogenic mutations in about 250 recessive or dominant genes. These findings are currently

Correspondence should be addressed to: Friedhelm Hildebrandt, M.D., Division of Nephrology, Department of Medicine, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, Phone: +1 617-355-6129, Fax: +1 617-730-0365, friedhelm.hildebrandt@childrens.harvard.edu.

revolutionizing our practice of diagnosing and understanding early-onset chronic kidney disease.

Many clinical consequences result from gene identification—The recent findings on monogenic causation of CKD will have important practical consequences. They will: i) provide patients and families with an unequivocal molecular genetic diagnosis, ii) generate new insights into disease mechanisms, and iii) have consequences for personalized treatment and prevention of CKD. The number of genes that cause monogenic forms of PKD will keep rising in the near future, as a novel monogenic gene causative for CKD is discovered virtually every month.

Monogenic causes of adult-onset CKD—A very interesting observation was made recently regarding the question if an increasing percentage of *adult-onset* CKD may also be attributed to monogenic causation: Tory et al. found that the *NPHS2* (*podocin*) gene variant R229Q, which has been considered a 'variant of unknown significance' for many years, is in fact disease-causing, but only if combined in the compound heterozygous state with one of a few very distinct other *NPHS2* mutations.[2] The combination of both alleles will then lead to adult onset of SRNS. This finding is of great significance, because it indicates that in the near future we may be able to perform functional studies for the many genetic variants of recessive and dominant CKD-causing genes, for which there is currently not enough evidence of their deleteriousness. Such "mild" genetic variants/mutations will most likely cause late-onset forms of disease and thereby may explain a significant proportion of adult-onset CKD. Providing functional information on the deleteriousness of variants in monogenic CKD genes will be one of the most important and rewarding contributions to the understanding renal pathogenesis over the next 10 years.

Discovery of monogenic genes revealed pathogenic pathways

Proteins encoded by monogenic disease genes converge onto functional pathways—The discovery of ~30 genes that, if mutated, cause monogenic forms of SRNS genes has revealed that their related gene products are part of protein-protein interaction complexes critical for glomerular podocyte function. These protein-protein interaction complexes are currently noted to converge onto specific pathways of glomerular function. For example, identification of mutations in the gene *ARHGDIA* (*Rho-GDI alpha*) demonstrated that proper regulation of the small GTPases Rho/Rac/Cdc42 is essential for the integrity of the glomerular filter.[3] This finding may open inroads into developing Rho/Rac inhibitors and activators to treat SRNS, for which currently no efficient treatment exists (Shibata et al. *Nat Med* 14: 1370–1376, 2008).

A mechanism for renal fibrosis—Cystic kidney diseases have also been termed "renal ciliopathies" because they are due to dysfunction of primary cilia and centrosomes. Recent discoveries of mutations in the centrosomal protein CEP164[4] and in the *FAN1* gene[5] have implicated DNA damage response signaling (DDR) in the pathogenesis of renal ciliopathies. This led to the concept that accumulation of DNA damage with consecutive premature cellular senescence may play a significant role in the development of renal fibrosis, which is

central to all CKD independent of primary cause (Lans & Hoeijmakers *Nat Genet* 44: 836–838, 2012).

Genetic disease models offer inroads into treatment approaches for CKD

Loss of function mutations in recessive monogenic kidney disease genes can easily be transferred into animal models of knockdown and knockout, e.g. in mice or zebrafish. Using mouse models, first successful treatment approaches for renal cystic ciliopathies have been implemented in mouse models. Specifically, Bukanov et al. addressed impaired cell cycle dysregulation as a potential cause of cystogenesis. They showed that treatment with the cyclin-dependent kinase (CDK) inhibitor roscovitine™ efficiently arrested cystic disease in jck and cpk mouse models of polycystic kidney disease. The mechanism of action revealed effective cell-cycle arrest, transcriptional inhibition, and attenuation of apoptosis.[6]

Treatment of SRNS with coenzyme Q_{10}—In SRNS the detection of mutations in novel disease-causing genes has begun to reveal the availability of treatment options. For instance, it was discovered that mutations in the genes *COQ6*[7] and *ADCK4* (Ashraf et al. JCI 123: 5179–5189, 2013), which regulate coenzyme Q_{10} biosynthesis, may cause SRNS. These finding uncovered the possibility of treating individuals with this specific variants of SRNS with the innocuous food supplement coenzyme Q_{10}.

Genome-wide association studies define genetic risk alleles

Mutations in monogenic rare disease genes have a very strong effect on disease causation and are thereby on positioned the ‘full penetrance’ end of the spectrum of genetic causality. Monogenic mutations are usually discovered by WES. On the other end of the spectrum of genetic causality are polygenic disorders, which are more common, exert weak causality on the disease phenotype, and are usually referred to a ‘risk alleles’. Polygenic diseases manifest later in life, are commonly associated with environmental effects, and are usually detected by genome-wide asso-ciation studies (GWAS). Risk alleles usually account for only a small proportion of the variance of the disease phenotype, and the assignment of an associated marker allele mechanistically to loss of gene function is difficult to attain.

A breakthrough regarding a risk allele for CKD was achieved by the discovery of an association between *APOL1* variants and chronic kidney disease. The variants G1 and G2 were found to be strongly associated with an increased risk of focal segmental glomerulosclerosis and chronic kidney disease in African-American individuals.[8] About 60% of African-Americans in the USA (compared with 4% of European Americans) carry both recessive risk alleles, increasing the risk of developing focal segmental glomerulosclerosis 5–30 fold, thereby likely explaining the known racial disparities in nondiabetic nephropathy seen in African Americans.[9] The G1 and G2 *APOL1* risk alleles always occur on different homologous chromosomes and thereby behave like recessive “mutations”.

Another important association of genetic variants with disease was identified by Koettgen and colleagues in a single nucleotide polymorphism that was strongly associated with chronic kidney disease. This polymorphism (rs12917707) is located near the *UMOD* gene,

which if mutated, causes autosomal dominant medullary cystic kidney disease type 2.[10] These results were recently confirmed in a large worldwide cohort (Fox *Kidney Internat* 87:1017–29, 2015).

Ten Featured References

1. Sadowski CE, et al. A Single-Gene Cause in 29.5% of Cases of Steroid-Resistant Nephrotic Syndrome. Journal of the American Society of Nephrology: JASN. 2014; 26:1279–1289. [PubMed: 25349199]
2. Tory K, et al. Mutation-dependent recessive inheritance of NPHS2-associated steroid-resistant nephrotic syndrome. Nature genetics. 2014; 46:299–304. [PubMed: 24509478]
3. Gee HY, et al. ARHGDIA mutations cause nephrotic syndrome via defective RHO GTPase signaling. The Journal of clinical investigation. 2013; 123:3243–3253. [PubMed: 23867502]
4. Chaki M, et al. Exome capture reveals ZNF423 and CEP164 mutations, linking renal ciliopathies to DNA damage response signaling. Cell. 2012; 150:533–548. [PubMed: 22863007]
5. Zhou W, et al. FAN1 mutations cause karyomegalic interstitial nephritis, linking chronic kidney failure to defective DNA damage repair. Nature genetics. 2012; 44:910–915. [PubMed: 22772369]
6. Bukanov NO, Smith LA, Klinger KW, Ledbetter SR, Ibraghimov-Beskrovnaya O. Long-lasting arrest of murine polycystic kidney disease with CDK inhibitor roscovitine. Nature. 2006; 444:949–952. [PubMed: 17122773]
7. Heeringa SF, et al. COQ6 mutations in human patients produce nephrotic syndrome with sensorineural deafness. The Journal of clinical investigation. 2011; 121:2013–2024. [PubMed: 21540551]
8. Genovese G, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. 2010; 329:841–845. [PubMed: 20647424]
9. Freedman BI, et al. The apolipoprotein L1 (APOL1) gene and nondiabetic nephropathy in African Americans. Journal of the American Society of Nephrology: JASN. 2010; 21:1422–1426. [PubMed: 20688934]
10. Kottgen A, et al. Multiple loci associated with indices of renal function and chronic kidney disease. Nature genetics. 2009; 41:712–717. [PubMed: 19430482]