مرکز آموزشی و درمانی شهید هاشمی نژاد

Genetic approach of autosomal dominant polycystic kidney disease: from diagnosis to management

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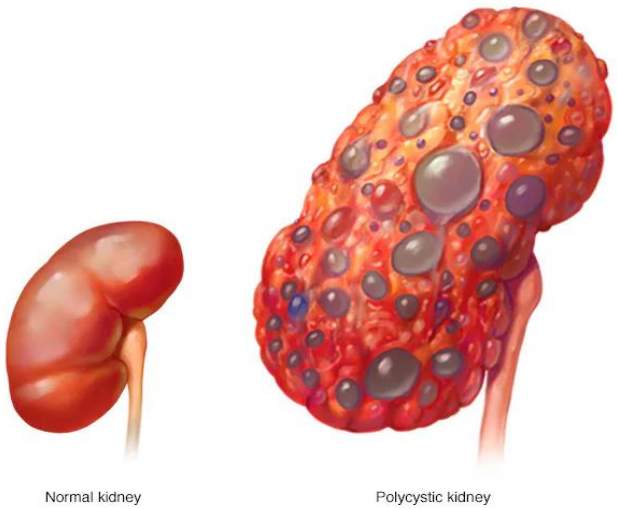
Polycystic Kidney Disease (PKD) is a genetic disorder that mainly affects the kidneys. Both cause cysts to form making the kidneys (and other organs) swell up or deform, which can lead to renal failure.

Types of Polycystic Kidney Disease

There are three types of Polycystic Kidney Disease: the infantile type, called Autosomal Recessive Polycystic Kidney Disease (ARPKD), the adult-onset type called Autosomal Dominant Polycystic Kidney Disease (ADPKD) and Acquired Cystic Kidney Disease.

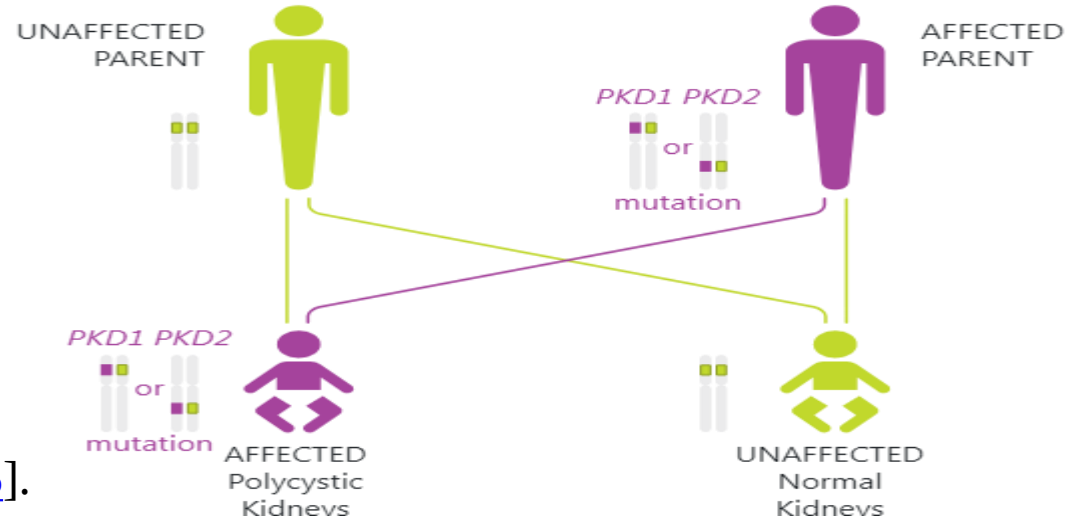


[Chapman et al 2015].

Autosomal Dominant Polycystic Kidney Disease

Autosomal Dominant Polycystic Kidney disease (ADPKD) is the cause of the most common ty pes of cysts in the kidneys that cause this disorder, accounting for **90%** of all PKD cases. It affe cts about half a million people in North America and Europe.

ADPKD occurs when a person inherits a specific mutation from just one parent.



[Chapman et al 2015].

Establishing the Diagnosis

The diagnosis of ADPKD is established in a proband with ANY of the following:

- Age-specific ultrasound criteria and an affected first-degree relative with ADPKD
- Age-specific MRI criteria and an affected first-degree relative with ADPKD
- Identification of a heterozygous pathogenic variant in one of the genes.

Molecular Genetic Testing Used in ADPKD

Gene [1]	Proportion of ADPKD Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method	
		Sequence analysis [3]	Gene-targeted deletion/duplication analysis [4]
PKD1	~78%	~97% [5]	~3%
PKD2	~15%	~97% [5]	~3%
GANAB	~0.3%	7/7	Unknown, none reported [6]
DNAJB11	~0.1%	7/7	Unknown, none reported [6]
Unknown	~7%	NA	

[Pei et al 2009]

PKD1

Pathogenic variants. About **50%-70%** of pathogenic PKD1 variants are unique to a single fam ily. The ADPKD Mutation Database lists a total of approximately 1,650 likely pathogenic PKD1 changes, accounting for about 2,450 families with PKD1-related ADPKD.

The pathogenic variants are spread throughout the gene; an estimated **65%** are predicted to truncate the protein product.

[Cornec-Le Gall et al 2013, Heyer et al 2016, Hwang et al 2016]

PKD2

Pathogenic variants. Approximately 50% of pathogenic PKD2 variants are unique to a family. According to the ADPKD Mutation Database, approximately 250 different PKD2 pathogenic variants have been described, accounting for nearly 550 families.

[Liu et al 2018] [Shen et al 2016, Grieben et al 2017]

GANAB

Pathogenic variants. To date, 11 pathogenic variants of GANAB have been described in 12 affected families. These include three frameshifting deletions , three splicing changes, three missense changes, and two nonsense changes, with pathogenic variants found in all parts of the gene.

[Porath et al 2016, Besse et al 2017]

DNAJB11

Pathogenic variants. To date, five different DNAJB11 pathogenic variants have been described in seven families with 23 affected individuals. These c onsist of two frameshifting changes, two pathogenic missense variants, and a nonsense variant.

[Cornec-Le Gall et al 2018]

Molecular Genetic Testing

Testing approaches can include a multigene panel or concurrent gene testing.

Option 1 (recommended)

A multigene panel that includes PKD1, PKD2, GANAB, DNAJB11, and other genes of interest is most likely to identify the genetic cause of the condition

Option 2

Whole Exome Sequencing (WES)

[Trujillano et al 2014, Eisenberger et al 2015]

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Rossetti et al [2007], Audrézet et al [2012], Cornec-Le Gall et al [2016], Heyer et al [2016]

Phenotype Correlations by Gene

- **PKD1.** Pathogenic variants in PKD1 are associated with more severe disease with an earlier age at diagnosis and mean age of onset of ESRD than in PKD2-related ADPKD (58.1 years for PKD1; 79.7 years for PKD2).

- **GANAB**. Pathogenic variants cause mild cystic kidney disease, usually without a decline in renal function, with the majority of affected individuals having liver cys ts. However, some affected individuals have a phenotype of autosomal dominant polycystic liver disease (ADPLD) with severe liver cystic disease and few renal c ysts.

- **DNAJB11.** The phenotype is quite consistent and results in the development of s mall, bilateral kidney cysts, usually without renal enlargement. In older individual s the kidneys become fibrotic and renal insufficiency often develops; ESRD is not ed in seven individuals between ages 59 and 89 years.

[Cornec-Le Gall et al 2018]

Genotype-Phenotype Correlations

The average age at onset of ESRD in affected individuals with truncating PKD1 v ariants is 55.6 years compared to 67.9 years for those with nontruncating PKD1 v ariants.

Family studies have identified incompletely penetrant nontruncating PKD1 varian ts that are associated with less severe disease [Rossetti et al 2009, Pei et al 2012]. One such well-studied PKD1 variant, p.Arg3277Cys, causes just a few cysts or no evidence of disease in heterozygotes

[Heyer et al 2016]

Genetic terms related to ADPKD

Mosaicism

Variable disease presentation in a family and apparent de novo disease can be due to mosaicism. Four families with ADPKD in which an individual has been found to have a somatic and/or germline PKD1 pathogenic variant have been described

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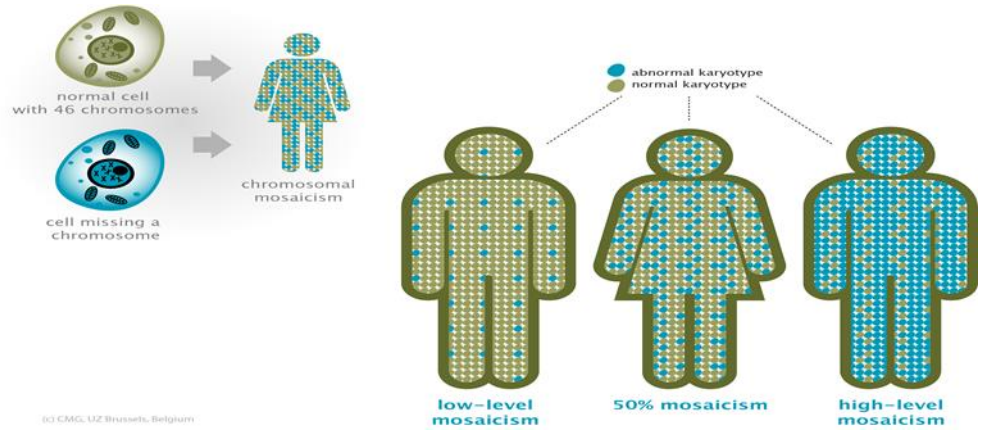

Digenic ADPKD

Individuals with pathogenic variants in both PKD1 and PKD2 have been described. Two individuals in one family were double heterozygotes for a pathogenic variant in both PKD1 and PKD2 and developed more severe renal disease than was reported in heterozygous relatives.

It has been suggested that early-onset PKD may be caused by a heterozygous pathoge nic variant in both PKD1 and HNF1B (digenic inheritance) .Variants in HNF1B are a ssociated with ADTKD.

Penetrance

Penetrance in ADPKD is age and genotype dependent. The penetrance of multiple bil ateral renal cysts in older adults is close to 100%. However, because the disease is pr ogressive, few cysts may be evident during childhood or young adulthood, especially in individuals with nontruncating PKD1 pathogenic variants or pathogenic variants in PKD2, GANAB, or DNAJB11.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with in formation on the nature, mode(s) of inheritance, and implications of genetic di sorders to help them make informed medical and personal decisions.

The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members.

Risk to Family Members

Parents of a proband

- ✓ Most individuals diagnosed with ADPKD have an affected parent.
- ✓ Some individuals diagnosed with ADPKD have the disorder as a result of a de nov o pathogenic variant. The proportion of cases caused by a de novo pathogenic vari ant is approximately 15%.

- ✓ Note: If the parent is the individual in whom the pathogenic variant first occurred, s/he may have somatic mosaicism for the variant and may be mildly/minimally aff ected.

Risk to Family Members

Sibs of a proband

The risk to sibs of the proband depends on the genetic status of the proband's parents: If a parent of the proband is affected/has the pathogenic variant, the risk to sibs of inh eriting the variant is 50%.

Offspring of a proband

A child of an individual heterozygous for an ADPKD-related pathogenic variant has a 50% chance of inheriting the pathogenic variant.

Other family members

The risk to other family members depends on the genetic status of the proband's par ents: if a parent is affected/has a pathogenic variant, his or her family members may be at risk.

Related kidney donor

At-risk relatives being considered as kidney donors need to be evaluated to determin e if they have ADPKD.
molecular genetic testing can establish the genetic status of the potential donor. If a known pathogenic variant has already been identified in an affected relative this anal ysis is straightforward.

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

Predictive testing for at-risk relatives is straightforward if the ADPKD-related pathogenic variant has been identified in an affected family member. If not, a "negative" test does not prove that they do not have ADPKD.

Potential consequences of such testing (including, but not limited to, socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result).

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals age <18 years)

For asymptomatic minors at risk for adult-onset conditions for which early treatment is not available, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. In a family with an established diagnosis of ADPKD, it is appropriate to consider testing of symptomatic individuals regardless of age.

Considerations in families with an apparent de novo pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely de novo. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

The optimal time for determination of genetic risk and discussion of the a vailability of prenatal/preimplantation genetic testing is before pregnancy. It is appropriate to offer genetic counseling (including discussion of poten tial risks to offspring and reproductive options) to young adults who are a ffected or at risk.

DNA banking

Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to b anking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown).

Banking of DNA from individuals with atypical presentation (e.g., lethal in utero on set) is particularly valuable to understanding the disease etiology and offering famil y planning choices to the family.

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision.

Preimplantation genetic testing is increasingly being employed by families at risk for ADPKD

[De Rycke et al 2005, Zeevi et al 2013].

Disorders to Consider in the Differential Diagnosis of **ADPKD**

Disorder	Gene(s)	MOI
AD tubulointerstitial kidney disease	*HNF1B*	AD
Familial juvenile hyperuricemic nephropathy type 4	*SEC61A1*	*AD*
Tuberous sclerosis complex	*TSC1* *TSC2*	AD
Von Hippel-Lindau syndrome	*VHL*	AD
Oral-facial-digital syndrome type 1	*OFD1*	AD
Hereditary angiopathy with nephropathy, aneurysms, and muscle cramp	*COL4A1*	XL
AR polycystic kidney disease	*PKHD1*	AR

[Rule et al 2012]

SUMMARY AND RECOMMENDATIONS

- ✓ **Determine the type of mutation in the affected person and then detect it in other family members**
- ✓ **Determining the prognosis of patients**
- ✓ **Kidney transplant**
- ✓ **PGD/PGS Preimplantation Genetic Diagnosis (PGD)**
- ✓ **Definitive differential diagnosis**
- ✓ **Anticipation – Atypical ADPKD Clinical Presentation**
- ✓ **Determination of new mutations in patients with no family history**

- ✓ **Coexistence of liver and kidney cysts**
- ✓ **Syndromic Presentation**

Thank you for your attention