



Review Article

GENETIC EVALUATION AND SCREENING OF DONORS IN ADPKD

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ABSTRACT

Transplantation is the treatment of choice for ESRD patients in ADPKD if there are no contraindications to Surgery or Immunosuppression. Routine pre transplant evaluation for colonic diverticula or intracranial aneurysm is not required in asymptomatic subjects. Nephrectomy is not routinely indicated in ADPKD patient. It is restricted to patients with a history of recurrent cyst infection , recurrent major bleeding ,complicated lithiasis , severe Hypertension ,or massive renal enlargement ,concomitant with renal transplantation When living related donor is considered a screening test should be done to completely eliminate the possibility that the donor will develop ADPKD in future .For potential donors aged older than 30 years ultrasound abdomen is sufficient for screening , whereas in potential donor aged younger than 30 years absence of cyst will not exclude the development of ADPKD. Computed tomography and magnetic resonance imaging may be used for such patients in renal cyst detection. Genetic linkage analysis is a highly sensitive method and is used in donor screening if imaging studies fail.

**KEY WORDS:** ADPKD, Genetic Evaluation

INTRODUCTION

**A**utosomal dominant polycystic kidney disease is generally a late onset multisystem disorder characterized by bilateral renal cysts. Cysts in other organs include the liver, seminal vesicles ,pancreas, and arachnoid membrane .Vascular abnormality include intracranial aneurysms ,dilatation of aortic root, dissection of the thoracic aorta, mitral valve prolapsed ,and abdominal wall hernias.

Renal manifestations include hypertension, renal pain, and renal insufficiency.

ADPKD is the most common potentially lethal single-gene disorder. Its prevalence at birth is between 1:400 and 1:1000[1][2].

It is the most common of all inherited renal diseases, with around 12.5 million cases worldwide. About 45% of them by age 45. In ADPKD progress to end stage renal disease by age 60 [3].

4.4% of patients requiring renal replacement therapy have ADPKD [4].

GENETICS

**ADPKD is caused by mutations in atleast two different genes, PKD1 and PKD2**

- i. PKD1
  - a. Chromosome 16
  - b. 80-90% of cases
  - c. More severe disease course
  - d. Encodes Polycystin 1



- e. Average age of ESRD onset - 53 years
- ii. PKD2
  - a. Chromosome 4
  - b. 5-10% of cases
  - c. Encodes Polycystin 2
  - d. Average age of ESRD onset - 74 years

## RENAL TRANSPLANT IN ADPKD

Renal transplant is the treatment of choice in ADPKD with end stage renal disease if there are no contraindications to surgery or immunosuppressive therapy.

### Pre Transplant Evaluation of Recipient

From routine evaluation apart, the other investigation required is Abdominal computed tomography, Cardiac Assessment including Echocardiograph, myocardial stress scintigraphy and if required coronary and aortoiliac angiography.

Routine screening for previous asymptomatic patients for diverticular disease is not recommended [5][7], but pre transplant elective colonic resection should be considered in patients with symptomatic ,severe diverticular disease.[8]

Screening for intracranial aneurysm is not recommended but patients with a previously ruptured intracranial aneurysm or with family history should be screened.[9][10]

### Pre Transplant Nephrectomy

Glassman et al [13] have suggested that bilateral nephrectomy reduces the symptoms and provides more space for the graft. Braza et al [14] observed higher graft and patient survival rates among ADPKD patients who had undergone a pre transplant unilateral nephrectomy than those without nephrectomy.

But with advancement in Antihypertensive medications, Antibiotics, painkillers and transfusion medicine, fewer kidneys have needed to be removed. Advantages in maintaining native kidneys in this disease is avoiding fluid overload, congestive heart failure, Hyperkalemia , anemia , and renal Osteodystrophy. [15]

Nephrectomy is now restricted to patients with a history of recurrent cyst infection, recurrent bleeding, complicated lithiasis , severe hypertension or massive renal enlargement .[16]

At present general consensus is pretransplant native kidneys should not be removed especially bilateral nephrectomy should be avoided [19][20]

Fuller et al have evaluated the outcome of pre transplant, concomitant and post-transplant native nephrectomy in patients with ADPKD and demonstrated that concomitant native nephrectomy compares favorably than others in terms of morbidity and hospitalization.[21]

More recently, laproscopic nephrectomy has been used in ADPKD patients who require nephrectomy prior to

transplant. The advantages of Laproscopic nephrectomy are more rapid patient recovery and shorter hospitalization.

There is no evidence for increased risk for renal cell carcinoma developing in native ADPKD kidneys after renal transplantation.

Hence pre transplant nephrectomy is not indicated as cancer prophylaxis.

### Evaluation of Donor

Living related Donor transplant has several advantages over cadaver donor by having better immunological matching, longer graft half-life, shorter cold ischemic time and avoiding hemodialysis by preemptive transplant [22][23]

However, patients with ADPKD have limited options for live related kidneys as their families are at a risk for developing ADPKD.

A screening test should be done to completely eliminate the possibility that the donor will develop ADPKD in future.

The pretest probability (prevalence) of disease in the study cohort has a significant impact on the performance of any diagnostic test.[24]

Individuals who have an affected first-degree relative have a 50% probability of ADPKD at birth, the risk for those who present later for diagnosis testing is not constant but diminishes with age.

With increasing age, more affected individuals will have received a clinical diagnosis because of their symptoms (e.g. hypertension, hematuria, flank pain from cyst rupture of passage of stone, urinary tract infection), while those who Seek diagnostic testing will be those who are affected but have clinically undiagnosed disease or are at risk but are unaffected.

The pretest probability of disease at any time point can be estimated by the ratio of those who are affected but have clinically undiagnosed disease to the total pool of at-risk individuals who seek diagnostic testing. The pretest probability of disease at birth is 50% for individuals who are at risk for PKD1 and PKD2 but begins to diverge beyond second decade of life because PKD1 is a more severe and symptomatic disease.

*For potential donors aged older than 30 years the approach is that first establish by imaging-Abdominal ultrasound, CT, or MRI of the kidneys*

### Ravine, 1994 sonographic criteria: (individuals known to be at 50% risk for the disease)

- i. <30 years: At least 2 unilateral or bilateral crystal
- ii. 30-59 years: 2 cysts in each kidney
- iii. ≥60 years: 4 cysts in each kidney Nicolau et al: 1999

- iv. The sensitivity of these criteria is nearly 100% for
  - a. All individuals with ADPKD who are age 30 years or older;
  - b. Younger individuals with PKD1 mutations.
- v. The sensitivity of these criteria is 67% for individuals with PKD2 mutations who are younger than age 30 years.

**Large echogenic kidneys without distinct macroscopic cysts in an infant/child at 50% risk for ADPKD are diagnostic.**

In an individual with a positive family history of ADPKD:

- i. The enlargement of the kidneys or liver on physical examination is highly suggestive of the diagnosis.
- ii. The presence of hypertension, mitral valve prolapsed, or abdominal wall hernia is suggestive of the diagnosis. Definite diagnosis, however, relies on imaging or molecular genetic testing.

In the absence of a family history of ADPKD, the presence of bilateral renal enlargement and cysts with/without the presence of hepatic cysts and the absence of other manifestations suggestive of a different renal cystic disease provide presumptive, but not definite, evidence for the diagnosis.

For potential donors aged older than 30 years ultrasound abdomen, which is sensitive, inexpensive and noninvasive for screening and has negative predictive value (NPV) of 100%.

In potential donor aged younger than 30 years, detection by ultrasound of single cyst in one kidney is sufficient to exclude them as donor, but absence of cyst will not exclude the development of ADPKD as there is 10% false-negative rate; negative predictive value is 90.5% and sensitivity of 88.5% in this patient group.

Thus, 1 in 25 donors aged younger than 30 years with a negative ultrasound evaluation result will subsequently develop ADPKD type1. In families with ADPKD 2, with ESRD typically occurring later than in ADPKD1, the NPV of ultrasonographic screening is only 68% for family members aged younger than 30 years[25][26]

Computed tomography and magnetic resonance imaging can also be used for renal cyst detection. Because of their increased anatomical resolution they are more sensitive than ultrasound in screening for currently detail the sensitivity, specificity, and NPV of CT and MRI in screening at-risk family members for ADPKD. [27][28]

In contrast to ultrasound, however no robust studies currently detail the sensitivity, specificity, and NPV of CT and MRI in screening at-risk family members for ADPKD [27]<sup>[28]</sup>

Heavily T2-weighted MRI (HT2MRI) may offer several advantages over ultrasound and CT as well for screening related kidney donors in families with ADPKD.

Ultrasound can detect cysts of 1.0 cm, and CT with intravenous contrast, cysts of 0.5 cm. HT2MRI can detect cysts of 0.3 cm in diameter. HT2MRI may also be more sensitive than CT [29]

HT2MRI and CT are more expensive than ultrasound when used solely for excluding the diagnosis of ADPKD. [30] HT2MRI could also have disadvantage when ultrasound, HT2MRI may have a greater false-positive rate for cyst detection. An early false positive test result may cause considerable anxiety and psychological harm to the young patient

**LINKAGE ANALYSIS**

It is used to confirm the ADPKD in pre symptomatic individual with large number of affected family members (Algorithm).

Linkage testing is not available to families with a single affected individual, and linkage testing may be complicated if a de novo mutation has occurred recently in the family.

Linkage testing is not available to families with a single affected individual, and linkage testing may be complicated if a de novo mutation has occurred recently in the family.

Testing of at least 2 or more known affected family members and 2-3 generations is required to establish is linkage.[31][32]



Parents of a Proband	Sibs of Proband	Offspring of a Proband	Other family members of the Proband
<p>i. Most of the affected individuals have one affected parent</p> <p>ii. De novo mutations occurs in 5-10%</p>	<p>i. If a parent is affected ;the risk to sibs is 50%</p> <p>ii. When renal image analysis suggests that the parents are unaffected and the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, the disease in the proband is likely caused by de novo mutation and the risk to sibs is small</p> <p>iii. Connor et al(2008) reported mosaicism</p>	<p>i. Every child has a 50% chance of inheriting the mutation</p>	<p>i. The risk to other family members depend on the genetic status of the proband's parents. If a parents is affected or has a disease-causing mutation, his or her relative are at risk</p>

**Algorithm: Proband**, what next.....? Evaluation of other member

Molecular genetic testing of younger individuals who are at risk for adult-onset disorders for which no treatment exists is not considered appropriate, because it produces psychological trauma to the individuals.

Molecular testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals

*Molecular genetic testing (sequence analysis) can be used to confirm or establish the diagnosis when it is uncertain and confirmation is required, for example potential living related kidney donor, at-risk pregnancies, early-onset disease in sibling*

Various molecular genetic methods

- i. Sequence analysis
- ii. Linkage analysis
- iii. Deletion/duplication

Various methods: DHPLC method, quantitative PCR, long-range PCR, multiplex ligation dependent probe amplification (MLPA), or array GH, SURVEYOR nuclease method

*When mutation analysis of PKD1 and PKD2 by sequencing is negative, deletion/duplication analysis of PKD2 should be considered*

In 2002, complete mutation screen of PKD1 and PKD2 was done by using DHPLC method.

Deletions /duplications are not readily detectable by sequence analysis of genomic DNA; the tests used are polymerase chain reaction (PCR)-quantitative, long-range, multiplex ligation dependent probe amplification (MLPA), or array GH.

Ying-Cai Tan et al described a novel method for genomic analysis of PKD1 and PKD2 mutations, i.e. "SURVEYOR nuclease method" that was comparable to direct sequence or detecting ADPKD mutation achieving higher

sensitivity with lower cost, proving and important tool for genetic analysis of complex genes..[33]

Molecular genetic testing is not useful in predicting age of onset severity, type of symptoms or of progression in asymptomatic individuals.

The family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

Genetic linkage analysis is a highly sensitive method of donor screening, with 99% accuracy in the diagnosis of ADPKD and an NPV of almost 100%. Unfortunately, it is both costly and time consuming. Furthermore, many individuals do not wish to be tested, preferring not to know if they are at risk for ADPKD. Recently, mosaicism in ADPKD revealed by genetic testing has been used to enable living renal transplantation.[34]

Due to the shortage of available donor kidneys, some authors have suggested the use of less than perfect organs including kidneys showing the early effects of polycystic kidney disease.[35]This is based on the estimated time for the donor kidney to fail and the graft survival period on immunosuppression. [36][37]

Selection criteria for polycystic kidney donors have been proposed which include donor age <50, normal donor creatinine at the time of retrieval, acceptable pretransplant renal biopsy, normal or only mildly enlarged kidney size (>15cm), and appropriately informed recipient who may have life expectancy of 10 years or less. [38][39]

Only 12 recipients of an ADPKD transplant kidney have been reported and Eng et al have reported the longest 15-years follow-up of ADPKD donor kidney transplantation.

The major concern with transplantation of ADPKD donor kidneys is the risk of cyst growth and, ultimately progression to renal failure.

Some authors suggested that the natural course of disease progression is slowed or arrested once the donor organ is transplanted. [37][40] Previous reports [40][41] also showed that polycystic kidneys with normal renal function and preserved renal cortical mass could be used for transplantation and disappearance of cyst may even occur as reported by Spees. [37]

Other potential risks associated with donor polycystic kidneys include bleeding and infection, particularly when renal transplant is biopsied.

Olsburgh et al have reported pyelonephritis in the setting of multiple percutaneous biopsies. 50 Considering the quality of life with a good functioning kidney and the shortage of donors, a polycystic kidney with good renal Function may be used as a donor kidney.

However, imaging every 2 to 3 years to follow cyst progression is recommended in these individuals.

## SUMMARY

- i. Transplantation is the treatment of choice for ESRD patients in ADPKD if there are no contraindications to Surgery or Immunosuppression
- ii. Routine pre transplant evaluation for colonic diverticula or intracranial aneurysm is not required in asymptomatic subjects
- iii. Nephrectomy is not routinely indicated in ADPKD patient. It is restricted to patients with a history of recurrent cyst infection, recurrent major bleeding, complicated lithiasis, severe Hypertension, or massive renal enlargement, concomitant with renal transplantation
- iv. When living related donor is considered a screening test should be done to completely eliminate the possibility that the donor will develop ADPKD in future .For potential donors aged older than 30 years ultrasound abdomen is sufficient for screening, whereas in potential donor aged younger than 30 years absence of cyst will not exclude the development of ADPKD.
- v. Computed tomography and magnetic resonance imaging may be used for such patients in renal cyst detection.
- vi. Genetic linkage analysis is a highly sensitive method and is used in donor screening if imaging studies fail.

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