Autosomal Dominant Polycystic Kidney Disease

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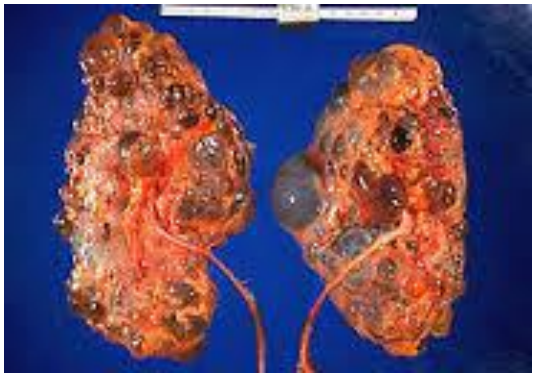
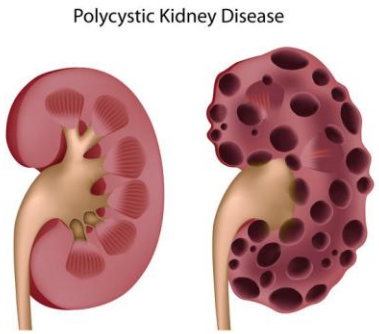
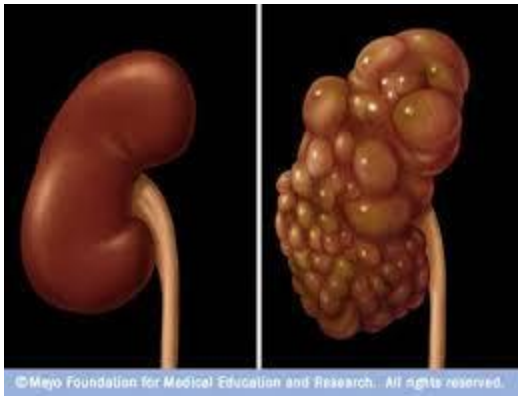
Physiology

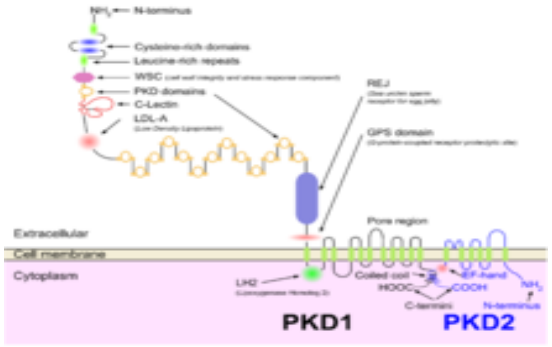


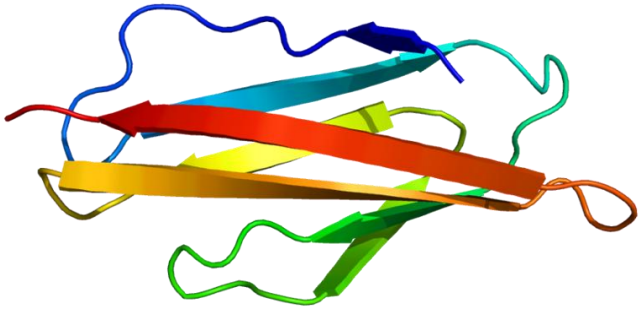




- Autosomal Dominant disorder which manifests on the autosomes and manifest in heterozygotes
- Affects primarily kidneys, but also includes the liver, pancreas, brain, and arterial blood vessels
- Possibly leads to end stage kidney disease, which an onset at about 40-60 years of age
- Manifests in about 1 in 400 to 1 in 1000 people
- Those affected with ADPKD develop cysts in the kidneys. It is unknown what causes this
- Occurs in both children and adults, although more commonly in adults. Symptoms usually discovered during middle age
- 43% of those who manifest ADPKD have a low life expectancy
- Those who survive develop end-stage renal disease or high blood pressure by 30 years old

Molecular Cause





- ADPKD manifests through the loss of function in the PKD1 to PKD2 gene
- PKD1 encodes for polycystin-1, a glycoprotein/transmembrane receptor-like protein whose function is unknown but plays a role in renal tubular development. Located on chromosome 16
- PKD2 encodes polycystin-2 which is an integral membrane protein with homology to the voltage-activated sodium and calcium a1 channels.
- Manifests through the two-hit hypothesis which states that both alleles of a single gene must lose function for the disease to manifest
- The mechanism by which each gene loses function has not been defined

Treatments

- ADPKD is a disease that has no cure; the prevention of the forming or enlargement of cysts is nonexistent
- Slowing the progression of renal disease and minimizing its symptoms
- Diuretics can be used to help urination
- A low-salt diet can be implemented to prevent more damage
- Hypertension and urinary tract infection are treated aggressively to preserve renal function
- Pain from the effect of the enlarged kidneys can be minimized by drainage and sclerosis of the cysts
- Ultimately, a kidney transplant can be performed by replacing the polycystic kidney with a normal functioning kidney, and it will not develop cysts
- A drug named Tolvaptan is under development. Tolvaptan is a vassopressin receptor antagonist which interferes with the action of vasopressin receptors
- Vassopressin is an anti diuretic hormone that increases the amount of cAMP (cyclic adenosine monophosphate) which is a molecule involved in kidney growth

Proposed Cure

- The disease is caused by the two-hit mechanism
- This mechanism, also known as the Knudson hypothesis, states that both alleles that code for a particular protein must both be affected before it manifests into the disease. If only one allele is damaged, the second one can still produce the correct protein
- The first mutation is found in all kidney tubular cells and is the mutation in the PKD gene inherited from the affected parent. The second hit is a somatic mutation in a single tubular cell that inactivated the unaffected gene from the normal parent. This second hit allows abnormal focal proliferation of renal tubular cells and cyst formation.
- It is currently unknown how either the PKD1 or PKD2 genes lose their function
- So unfortunately…
- One can undergo surgical procedures to remove cysts
- Kidney transplant
- Good dieting, low-salt diet, increased water intake, no caffeine because it interferes with cAMP decreasing

References

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Images:

Polycystic Kidney Disease

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Polycystic Kidney Disease

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- Molecular Cause
- Thompson 6th edition (2004) Polycystic Kidney Disease
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Images:

http://en.wikipedia.org/wiki/File:PKD1PKD2_en.png

http://en.wikipedia.org/wiki/File:Protein_PKD1_PDB_1b4r.png

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Treatments:

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