Approach to a Patient with Suspected Genetic Disorder: Case Report

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Abstract

A middle aged male known to have polycystic kidneys on ultrasound presented with features suggestive of end stage renal disease. Family history revealed presence of similar phenotype in multiple family members suggesting a genetic cause. The pedigree also determined the mode of inheritance and phenotypic expression of the disorder. Genetic testing is warranted in this family in order to anticipate and mitigate complications of the disorder. Genetic testing, though costly and not readily available locally, is an increasingly necessary armamentarium for the management and control of disorders with a genetic cause.

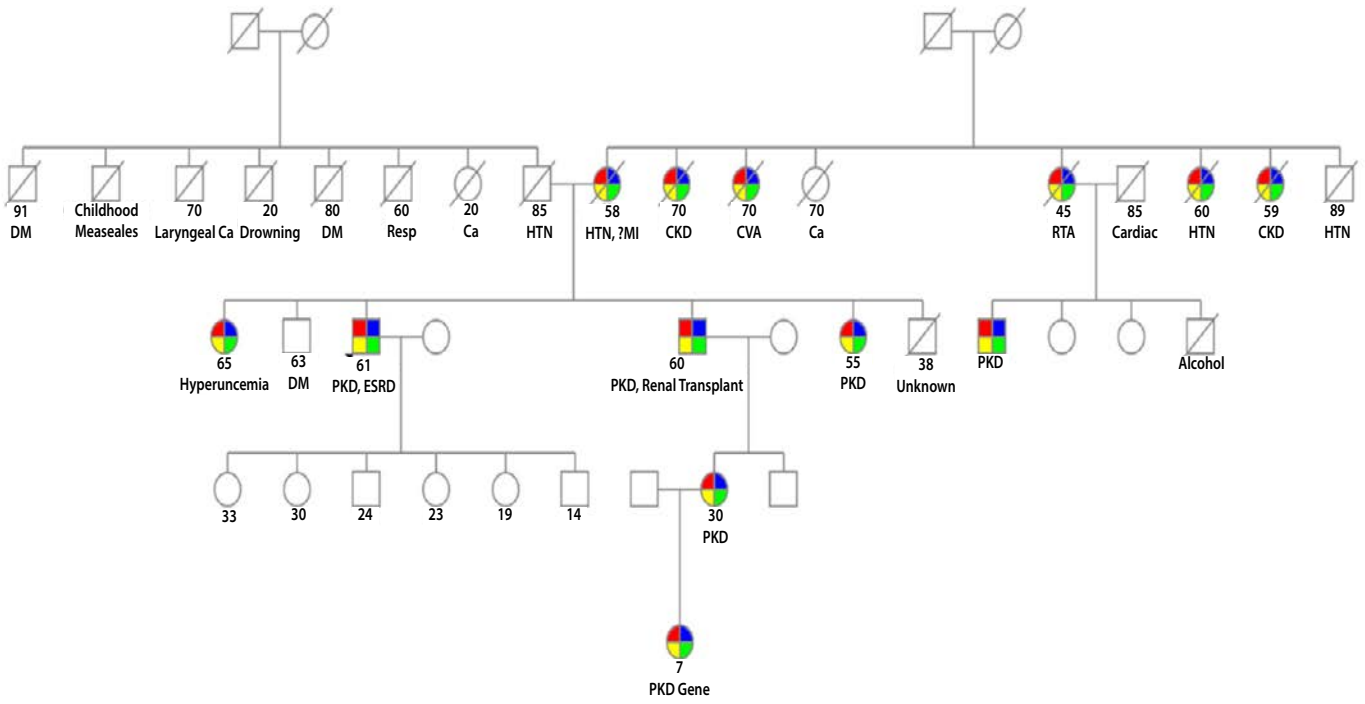
Key words: Genetic disease, Pedigree, Phenotype, Genotype

Introduction

Autosomal polycystic kidney disease is an inherited genetic disorder that manifests with cystic kidneys, pancreas liver and cerebral aneurysms. It is a highly prevalent disorder affecting 1 in 10,000 in the general population (1) and is not an uncommon disorder in the physician's practice. We highlight this case to demonstrate a systematic approach of evaluating genetic disorders and approach to genetic testing.

Case report

We present a case of a 62-year-old male who presented to our inpatient ward with signs and symptoms of End Stage Renal Disease (ESRD). Of note, five years prior, he had been found to have enlarged, polycystic kidneys on ultrasonography. His maternal lineage family history was remarkable for multiple cases of ESRD as shown in the pedigree below.



By convention, a pedigree has the following characteristics:

- Proband is the family member who brings the condition to the attention of the healthcare system member and is denoted with an arrow
- Female is denoted by a circle, male by a square
- Spousal relations are joined by a horizontal line, with the male appearing on the left of the female and their offspring as vertical offshoots
- Consanguineous relations are joined by two parallel horizontal lines
- Those with the disorder are shaded partially or wholly
- Deceased are crossed out
- Each generation is drawn along the same horizontal plane

A good pedigree aims for at least three generations where feasible. In our patient, the pedigree spans five generations and captures 38 relatives to the proband, with 24 relations from the maternal side. In evaluating the proband's paternal and maternal lineage, it is evident that the maternal lineage has the disease of concern as demonstrated in the presence of kidney disease, stroke and hypertension. In trying to decipher the mode of inheritance, the following criteria is used:

- Does it skip generations?
  - o Yes- Recessive or dominant with variable penetrance
  - o No- Dominant
- Does is affect one sex
  - o Yes- Sex-linked
  - o No- Autosomal
- Does inheritance come from maternal lineage to all her offsprings
  - o Yes- Mitochondrial
- Does inheritance come paternal lineage to only the sons- Y-linked

In our patient, the pedigree demonstrates inheritance through this maternal lineage, affecting both males and females and does not skip generations. This is in keeping with an Autosomal Dominant Disorder (ADD). This coupled with his clinical manifestation is highly suggestive of Autosomal Dominant Polycystic Kidney Disease (ADPKD). Being an autosomal dominant disorder, each individual has a 50% chance of inheriting the disorder. On the maternal lineage 13 out of 25 (52%) individuals have the gene of concern. Each affected individual having an affected parent suggests that the disorder is fully penetrant, meaning each person carrying the mutated gene manifests the phenotypic disease.

In deciphering of a pedigree, certain hypothesis may be prudent; if an offspring has a condition but their parent doesn't manifest it may mean that the condition is recessive; dominant with incomplete penetrance or a *denovo* mutation in the offspring.

In the pedigree above in the second generation, the female who died from an RTA with no phenotypic manifestation of the disorder, is denoted as having the defective gene as she passed it on to her offspring. She may not have manifested the phenotype as she died at 45 years of age whilst the age of presenting with the symptoms is in the sixth and seventh decade of life.

Regarding the phenotypic characteristics of the disorder, the following conclusions are reasonable from the pedigree;

(i) 2nd generation- phenotype results in death by the 7th and 8th decade
(ii) 3rd generation- develop end stage renal disease in the 6th and 7th decade
(iii) 4th generation- has not manifested the phenotype yet as they are still young
(iv) ADPKD1 is more likely than ADPKD2 due to the earlier onset of ESRD (54 years vs 73 years in ADPKD2)
(v) The disease expressed itself in different phenotypes (renal cysts; strokes suggesting aneurysms)
(vi) Advanced in genetic testing had led to the identification of asymptomatic persons in the 5th generation
(vii) Homogeneity in the cause of death on proband's maternal (affected) side compared to his paternal unaffected side which has a heterogeneous cause of death
(viii) In addition to screening for polycystic kidneys, there is need for surveillance for aneurysms as this seems to have been the cause of death in some of the affected persons

Genetic testing

Human Genome Project (HGP) which mapped out nucleic acid sequence in healthy persons drawn from a diverse racial and geographic populations forms the template from which normal genetic makeup is determined. Off-shoots from the HGP have been population genetics studies to determine normal variants amongst specific racial and ethnic groups under-represented in the initial HGP. Variants from the expected normal sequence are classified on a 5 point spectrum depending on whether they are identified to cause disease or not; (i) Pathogenic (ii) Likely pathogenic (iii) Variant of undetermined significant (iv) Likely benign (v) Benign. Location of pathogenic variants in gene sequences has resulted in establishment of databases for different disease entities and gene panels. A gene panel is a predetermined set of genotyping that are carried out for specific disease entities.

There are gene mutations for both autosomal dominant and autosomal recessive forms of PKD. However, given the family pedigree above, this rules

out ARPKD. Therefore, gene testing will be limited to only those mutations that are known to be autosomal dominant in nature. In ADPKD, there are two mutations; PKD1 located on chromosome 16p13.3 (short arm of chromosome 16, at locus 13.3) and PKD2 located on 4q21 (long arm of chromosome 4, locus 21). Gene panel for ADPKD would entail localization of these genes on the patient's genome at the exact locus on the chromosomes (2).

Although genotyping is not necessary to make a clinical diagnosis of ADPKD, it may be warranted in order to cascade gene testing to family members at risk. The proband's grand-niece had already had the pathogenic gene mapped out; this information if available can be used to guide of the gene testing of all the family members. If unavailable, the proband would be screened for both ADPKD1 and ADPKD2 genes. Once the exact gene mutation is established, cascading of testing to his descendants and family members at risk would entail screening for only the identified mutated gene thus ensuring cost effectiveness. Gene testing, though costly, has the potential to be cost effective as only those with the mutated gene will require follow-up for complications of ADPKD. It also has the potential of alleviating worry in those without the gene mutation and their offspring (3).

Conclusion

ADPKD, a genetic disorder commonly encountered in clinical practice requires a genetic approach in order to mop up at risk family members for screening and retarding progression to chronic kidney disease. With the lowering cost of genetic testing, and increasing number of genetic therapies, management of genetic disorders will become a mainstay of medical practice in the next decade (4,5).

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