Case #77
NAME Educational Activities Committee
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1. A 76-year-old man was found deceased in his home from unknown causes. Autopsy revealed multicystic kidneys each weighing more than 6000 grams. What is the genetic mutation associated with this disease process?

- PKD1
- ATP7B
- WT1
- HFE
- PRSS1
Answer...
A. PKD1 (CORRECT ANSWER, 92.96% of responses)

The disease process shown was a classic example of autosomal dominant polycystic kidney disease (ADPKD). ADPKD is primarily caused by a mutation in the PKD1 gene on chromosome 16p13.3. It is also known as adult polycystic kidney disease because patients with it typically remain asymptomatic until the fourth or fifth decade of life. ADPKD is characterized by progressively developing and enlarging cysts that begin to encroach upon and eventually kill parenchymal cells, resulting in renal failure. Approximately 85% of patients with ADPKD have one or several mutations in the PKD1 gene. The remaining 15% of patients have a mutation in the PKD2 gene on chromosome 4q21.2. Mutations in the PKD1 gene are associated with a quicker progression with greater than 95% of patients developing renal failure by age 70 compared to only 45% of patients with PKD2 mutations. ADPKD can be grossly differentiated from autosomal recessive polycystic kidney disease (ARPKD) in that the outer surface of kidneys with ADPKD are irregular and covered by cysts, while the outer surface of kidneys with ARPKD are smooth. Additionally, the intraparenchymal cysts and dilated collecting ducts in ARPKD are arranged at a 90-degree angle to the cortex, while the cysts in ADPKD have no apparent organization. Other common complications of ADPKD include polycystic liver disease (up to 40% of patients) and berry aneurysms.
Histologic section of ADPKD (Photo courtesy of R. Quinton, Mayo Clinic)
Sclerotic glomeruli in residual parenchyma between cysts (Photo courtesy of R. Quinton, Mayo Clinic)
Other responses:
B. ATP7B

A loss-of-function mutation in the ATP7B gene results in Wilson disease. It is an autosomal recessive metabolic disorder that causes the accumulation of copper in hepatocytes and results in hepatocyte injury and possible necrosis. The excess copper enters the blood and spreads to other organs and tissues, with a predilection for the basal ganglia of the brain and Descemet membrane of the corneas. The accumulation of copper in the Descemet membrane leads to the classic Kayser-Fleischer rings, which are dark rings surrounding the corneas. These rings are visible on slit lamp examination in early cases and grossly in cases of severe copper overload. The outer surface of a liver with Wilson disease is generally no different from a healthy liver. However, Wilson disease can cause steatohepatitis, cirrhosis, and even acute liver failure in cases of severe damage.

C. WT1

While mutations in the WT1 gene affect the kidneys, it is not the disease process shown in our case. Mutations in the WT1 gene result in the development of a Wilms tumor, or nephroblastoma, which is an embryonal tumor that affects the kidneys and is the most common primary renal tumor in children. Wilms tumors are primarily unilateral as only approximately 10% of Wilms tumors occur bilaterally. Mutations in the WT1 gene are often accompanied by mutations in the CTNNB1 gene, which encodes β-catenin and is integral to the WNT/β-catenin signaling pathway. It was thought until recently that only WT1 and CTNNB1 mutations were responsible for the development of a Wilms tumor, however only approximately 20% of Wilms tumors have mutations in the WT1 gene. While the entirety of gene mutations responsible for Wilms tumors have not been discovered, mutations in the WTX gene have been found to account for an additional 20% of Wilms tumors. The outer surface of kidneys with Wilms tumors are significantly different from those with ADPKD. While both diseases can cause enlarged kidneys, the outer surface of kidneys with Wilms tumors are smooth with occasional dysmorphia in areas where the tumor pushes out against the renal cortex. On cut surface, Wilms tumors are often tan to gray, soft, hemorrhagic, and necrotic.
D. HFE
A loss-of-function mutation in the HFE gene is primarily responsible for causing hereditary hemochromatosis (HH). HH is an autosomal recessive metabolic disease. Other genes responsible for causing it include TFR2, HAMP, and HJV. However, mutations in the HFE gene are present in over 70% of patients with HH. These mutations cause a decrease in the synthesis of hepcidin, which is the primary regulator of iron absorption. Decreased levels of hepcidin lead to increased iron accumulation and deposition of hemosiderin in organs and tissues. HH first affects the liver where it causes hepatocyte death and subsequent cirrhosis. In the early stage there is marginal hepatomegaly. If the disease progresses without treatment the liver shrinks, and the parenchyma turns dark brown to almost black due to severe iron accumulation. It should be noted that, in severe cases, HH can cause cardiomegaly, myocardial and pancreatic fibrosis, brown myocardial discoloration, increased pancreatic pigmentation, and gray skin pigmentation.

E. PRSS1
A gain-of-function mutation in the PRSS1 gene is the most common cause of hereditary pancreatitis (HP). HP is a rare autosomal dominant disease that causes autoactivation of pancreatic enzymes within the pancreas. Patients with HP develop recurrent acute pancreatitis that can eventually progress into chronic pancreatitis with irreversible pancreatic parenchymal damage. Mutations in the SPINK1, CFTR, and CTRC genes are also known to cause HP. The PRSS1 gene encodes the regulatory regions of trypsin, which is the pancreatic enzyme responsible for activating additional pancreatic enzymes used in digestion. Mutations in PRSS1 cause elevated trypsin levels and increase the stability and rate of autoactivation of trypsin while inside the pancreas. The autoactivation causes fat necrosis and acinar cell damage and can result in fibrosis with continued cellular insult.
References


