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Genetics and imaging of hereditary pancreatitis– a pictorial essay.

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Learning objectives

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- To review the imaging of patients with hereditary pancreatitis from the National Surgical Centre for Pancreatic Cancer (NSCPC) and Tallaght Hospital, Dublin.
- To identify common imaging findings in this cohort
- To establish whether specific genotypes have specific imaging features.

Background

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- Pancreatitis is the most common pancreatic disease in children and adults in the world. Over half the presentations of acute pancreatitis occur secondary to alcohol or cholelithiasis.
- Alcohol accounts for 80% of chronic pancreatitis in the developed world while malnutrition is the most common cause worldwide.
- Chronic pancreatitis in children and young adults is a debilitating illness secondary to exocrine and endocrine dysfunction.
- Chronic pancreatitis is young adults and children may be due to hereditary pancreatitis, 'tropical pancreatitis' (nutritional and/ or genetic aetiology) or idiopathic.

Background

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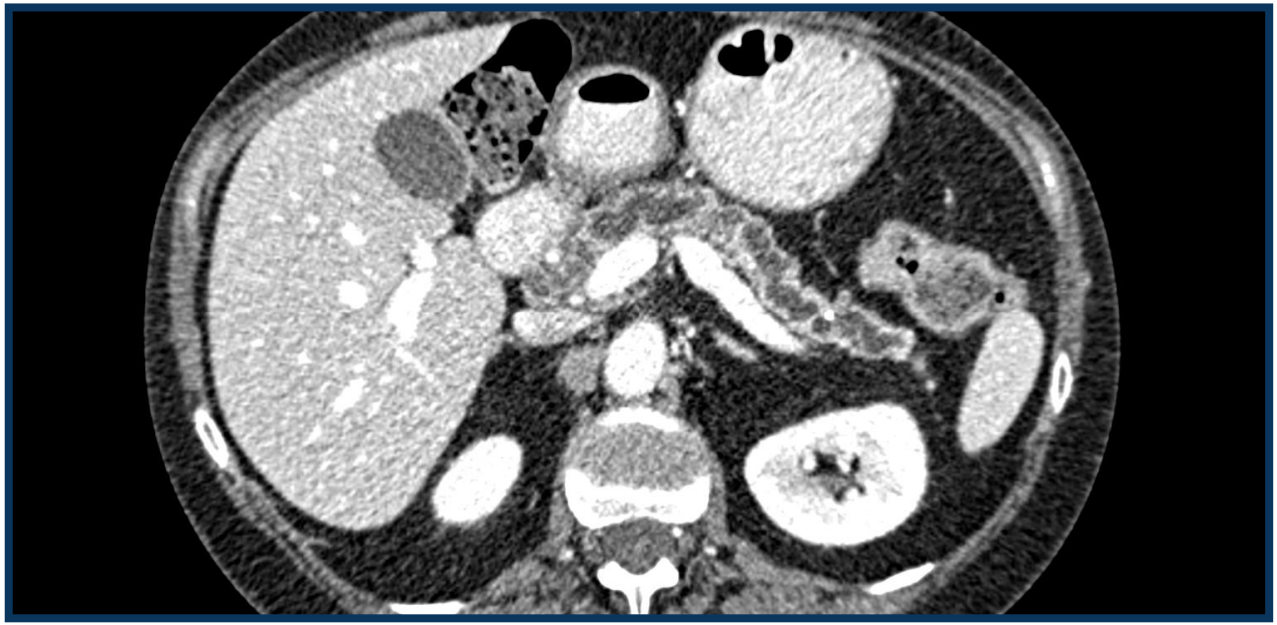

Axial post contrast CT of the pancreas demonstrating the imaging features of chronic pancreatitis. The pancreatic parenchyma is atrophic and the main pancreatic duct is dilated and tortuous. There are parenchymal and ductal pancreatic calcifications.

Backround - HP Genotypes

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1. Autosomal Dominant (AD) hereditary pancreatitis (HP). The PRSS1 gene is associated with AD HP. This leads to acute, recurrent or chronic pancreatitis associated with an autosomal dominant (AD) pattern of inheritance. Symptoms are similar to alcoholic pancreatitis but typically begin in adolescence.
2. Autosomal Recessive (AR) hereditary pancreatitis (HP). The SPINK1 gene is associated autosomal recessive pancreatitis. Familial recurrent pancreatitis is linked to heterozygous SPINK1 mutations.
3. Cystic Fibrosis: The CFTR gene mutation with an R117H mutation is associated with pancreatitis in cystic fibrosis patients.

Imaging Findings / Procedure details

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- Cross-sectional imaging plays a roll in determining the severity of disease, to detect complications and determine interventional and surgical treatment options.

- In this exhibit we will discuss hereditary pancreatitis (HP) and the specific imaging features seen in patients with HP. We will examine the different genetic mutations that give rise to HP and discuss their imaging differences.

Imaging Findings / Procedure details

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- We carried out a retrospective search of all patients presented at the NSCPC MDT with benign disease (699 patients). There were 10 patients with genetically proven hereditary pancreatitis.
- We also carried out a retrospective search of the SVHG cystic fibrosis patient population (352 patients). Four of these patients had the R117H gene mutation with associated chronic pancreatitis.
- The baseline and follow-up cross-sectional imaging of these patients was reviewed and correlated with their underlying genotype.

Imaging Findings / Procedure details

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Patient number	Age	Gender	Family	Gene Mutation
1	33	F	Family 1	PRSS1
2	46	F	Family 1	PRSS1
3	25	M	Family 1	PRSS1
4	66	M	-	SPINK1
5	21	M	Family 2	PRSS1
6	27	M	Family 2	PRSS1
7	44	F	-	PRSS1
8	47	F	-	PRSS1
9	20	F	-	SPINK1
10	31	M	-	SPINK1

Demographics of the patients with hereditary pancreatitis ranging in age from 20 to 66. This cohort includes two families with 1st degree relatives diagnosed with HP. The SPINK1 mutations are less common and without a familial link in our patient population. Both genotypes have a M:F ratio of 1:1

Imaging Findings / Procedure details
Autosomal Dominant HP

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- PRSS1, the encoding cationic trypsinogen mutation, is inherited in an autosomal dominant manner.
- Penetrance is determined by genetic, epigenetic, and/or environmental factors.
- On average, patients with this mutation will have had their first episode of acute pancreatitis by 10 years of age and have imaging features of chronic pancreatitis by 20 years of age.
- Our patient population contained 2 families with > 2 first degree relatives with HP and a PRSS1 gene mutation. All of these patients had pancreatic atrophy and most patients had associated main pancreatic duct dilatation and calcification.

Imaging Findings / Procedure details
Autosomal Dominant HP

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- PRSS1 imaging features:

1/7 patient had a normal pancreas on CT and MRI.

6/7 patients had pancreatic atrophy

6/7 patients had pancreatic ductal and parenchymal calcification

6/7 patients had main pancreatic duct (MPD) dilatation.

All patients with the PRSS1 gene mutation with imaging features of chronic pancreatitis had the triad of pancreatic atrophy, calcification and MPD dilatation.

Imaging Findings / Procedure details

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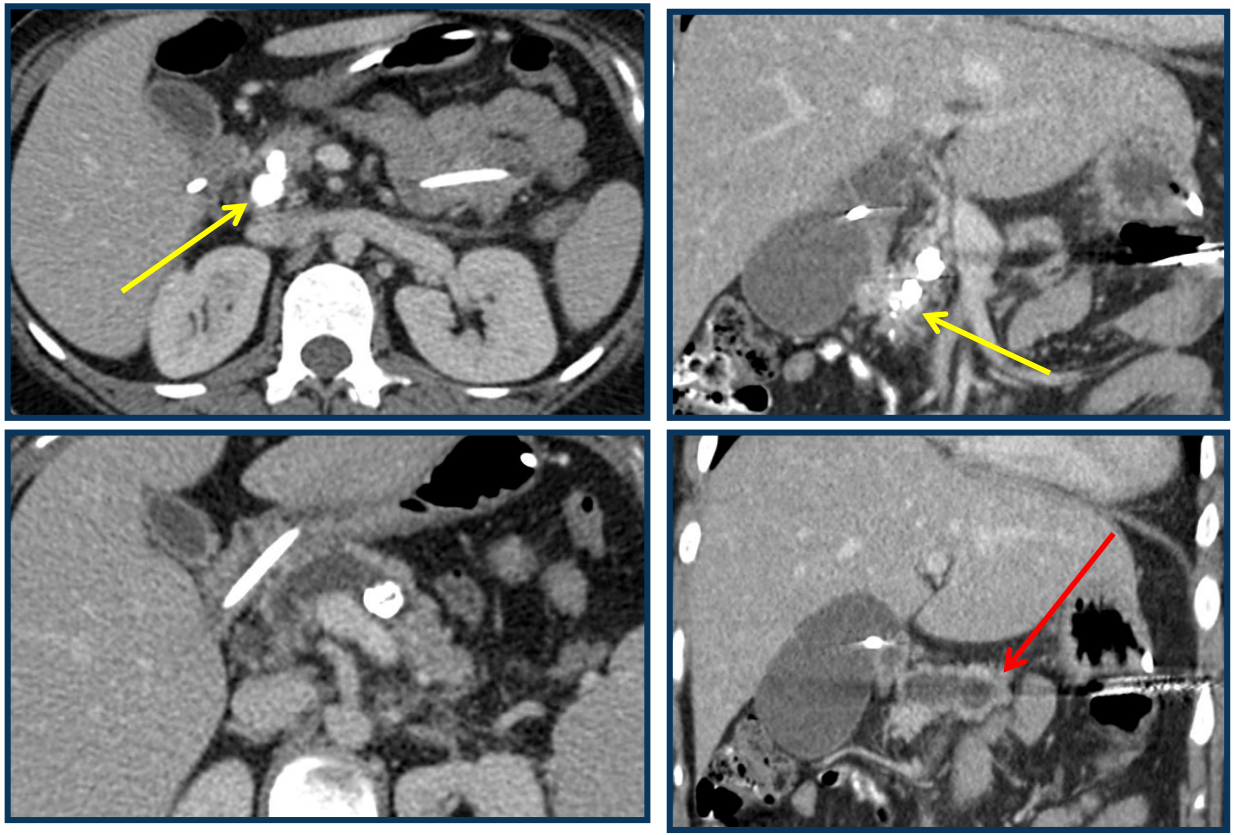

PRSS1 – 33 year old female from family 1.

Axial and Coronal CT images showing marked MPD dilatation secondary to an obstructing intra-ductal calculus (yellow arrows). There is atrophy of the upstream pancreatic parenchyma (red arrows)

Imaging Findings / Procedure details

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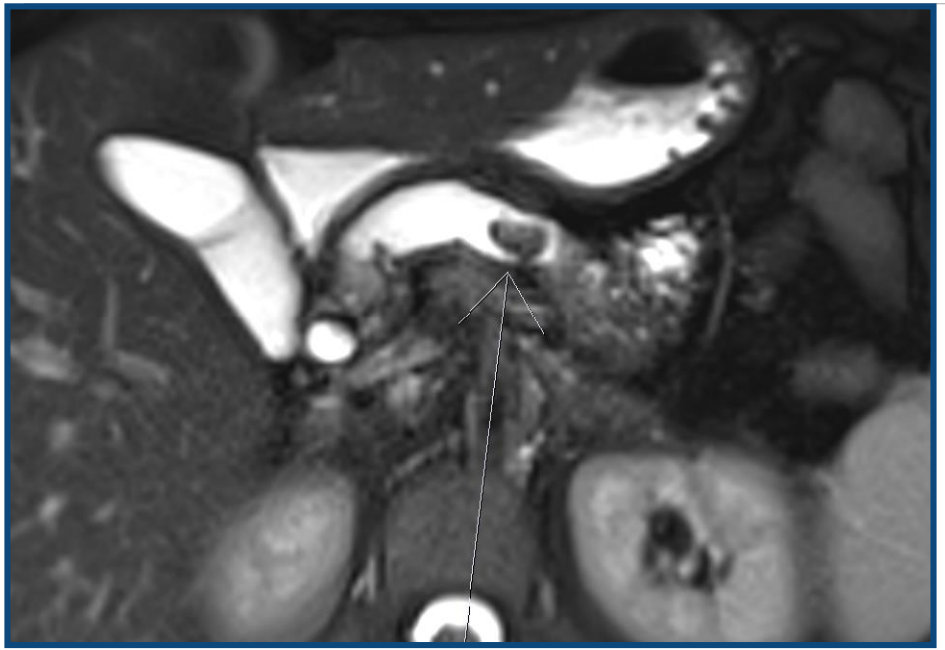

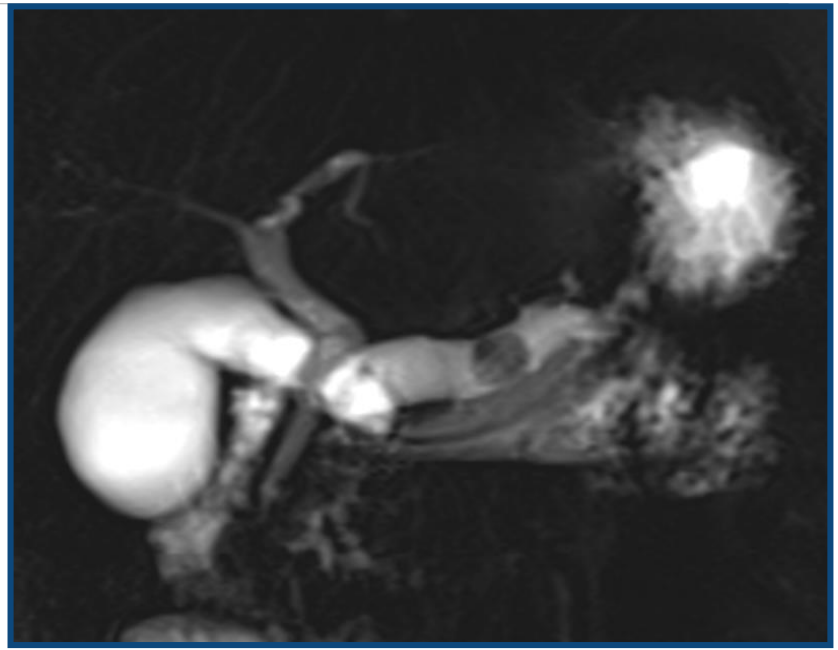

PRSS1 – 33 year old female from family 1.
Axial and Coronal MRI (MRCP) shows a large intra-ductal calculus (white arrow) with associated MPD dilatation.

Imaging Findings / Procedure details

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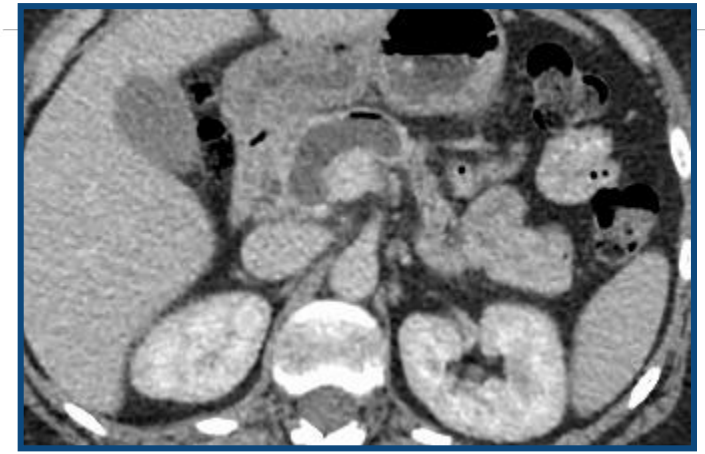

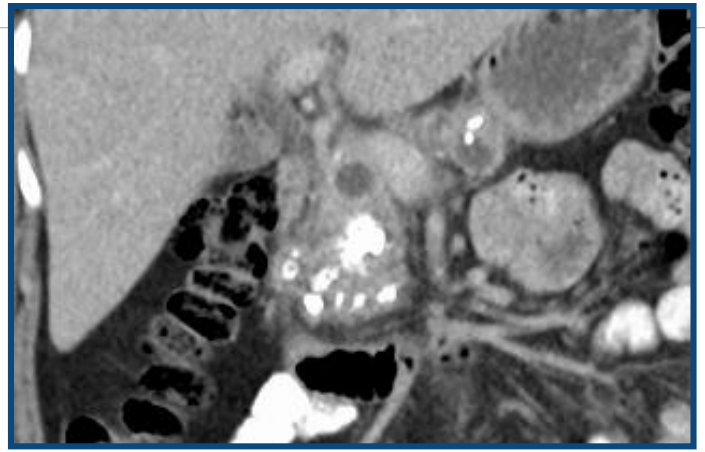

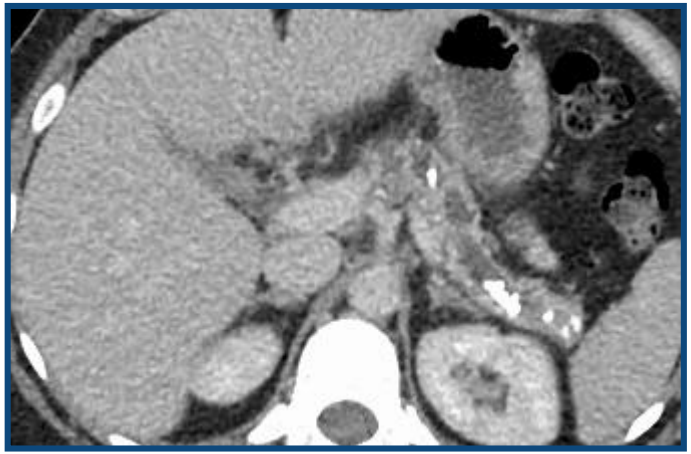

PRSS1 – 45 year old female from family 1. Axial and Coronal CT images demonstrating diffuse MPD dilatation with parenchymal and ductal calcifications.

Imaging Findings / Procedure details

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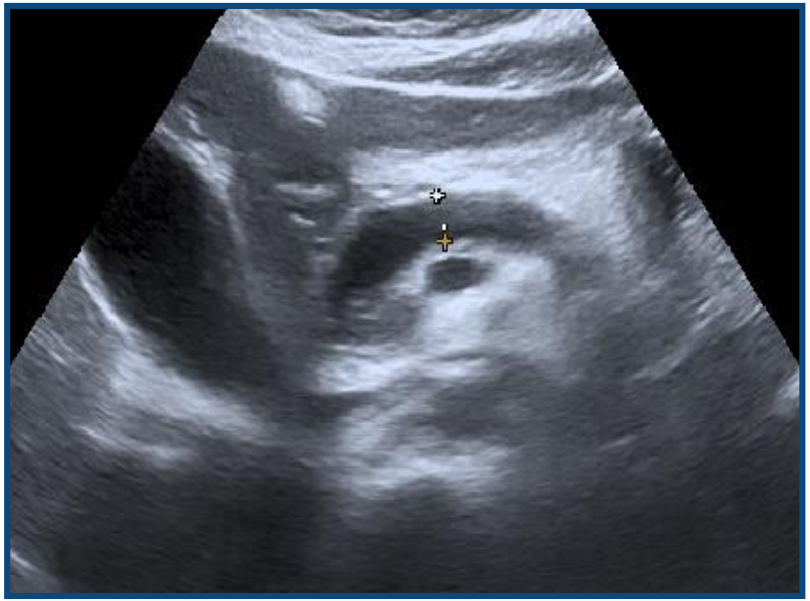

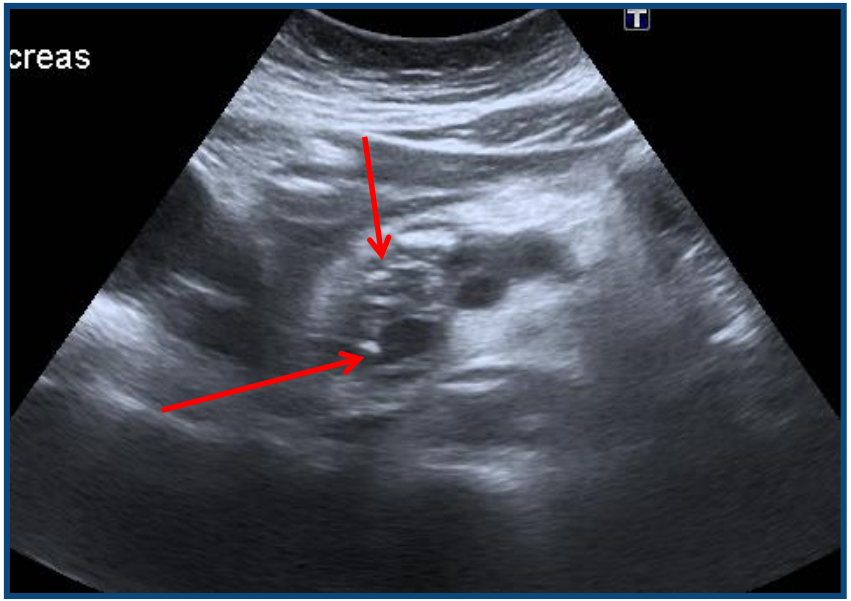

PRSS1 – 45 year old female from family 1.
Axial Ultrasound evaluation of the pancreas demonstrating MPD dilatation, pancreatic atrophy and intra-ductal calculi (red arrows).

Imaging Findings / Procedure details

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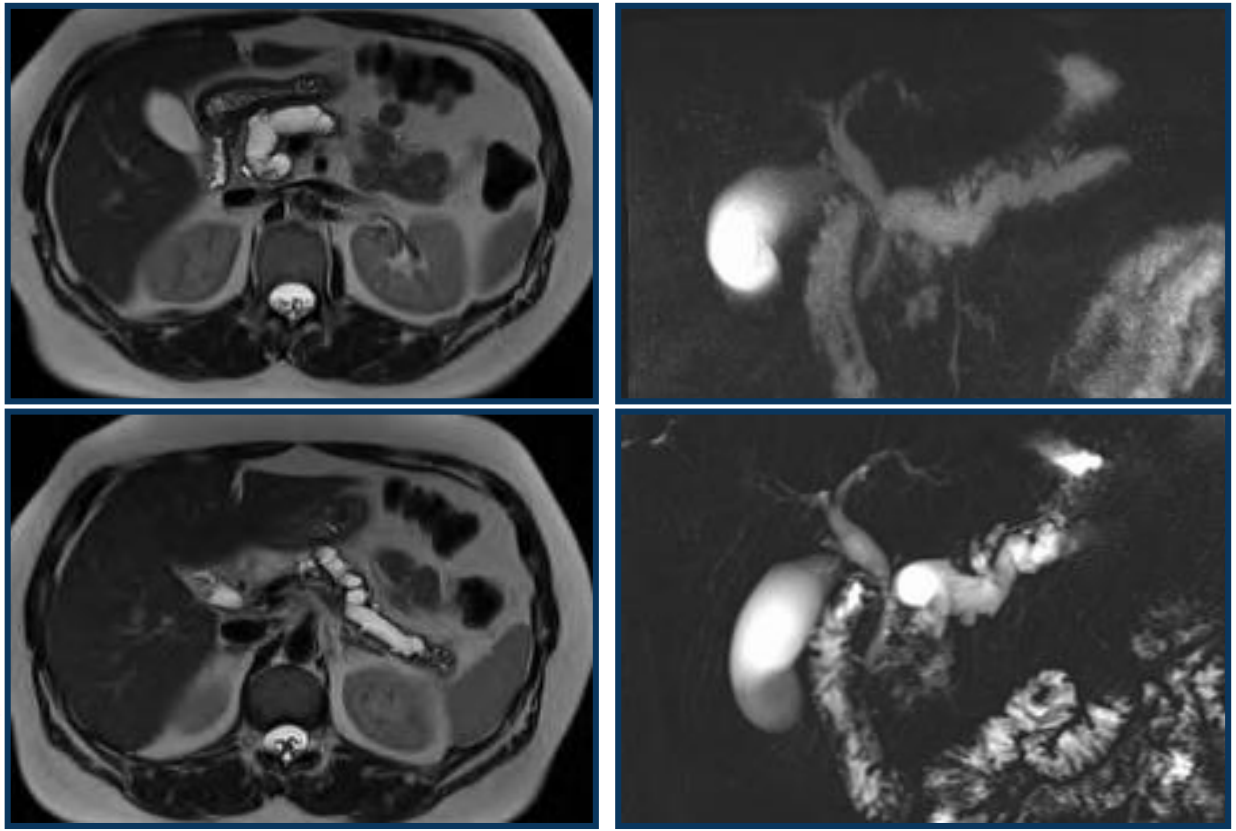

PRSS1 – 45 year old female from family 1. Axial and Coronal MIP from an MRCP.

These images demonstrate gross MPD dilatation with upstream branch ductal dilatation. There is atrophy of the pancreatic parenchyma.

Imaging Findings / Procedure details

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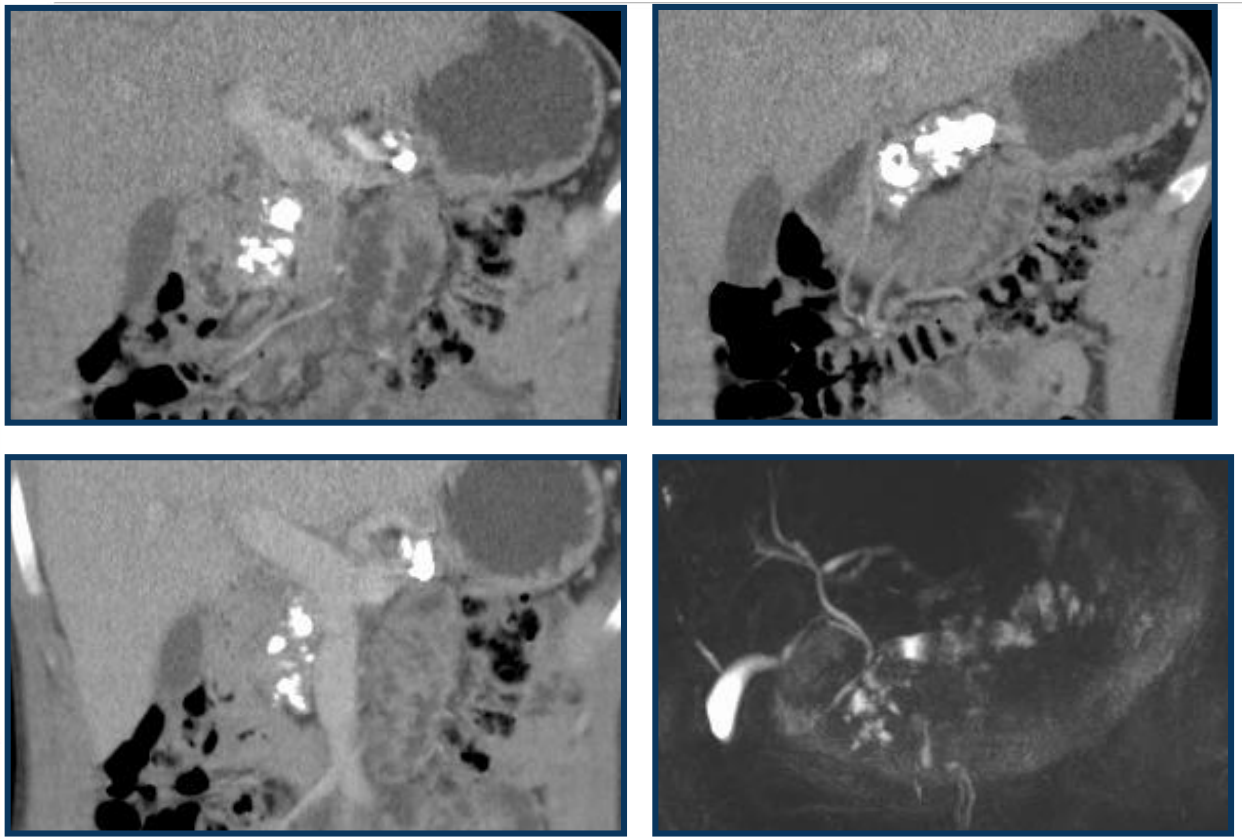

PRSS1 – 24 year old male from family 1.

Coronal CT and MIP from an MRCP.

These images demonstrate gross parenchymal calcification with intra-ductal calculi in the MPD causing marked dilatation (MIP).

Imaging Findings / Procedure details

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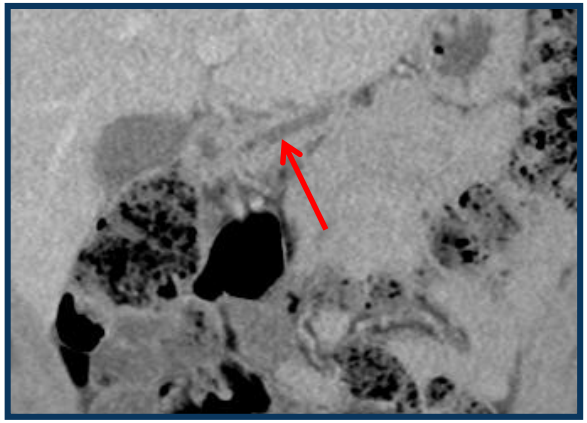

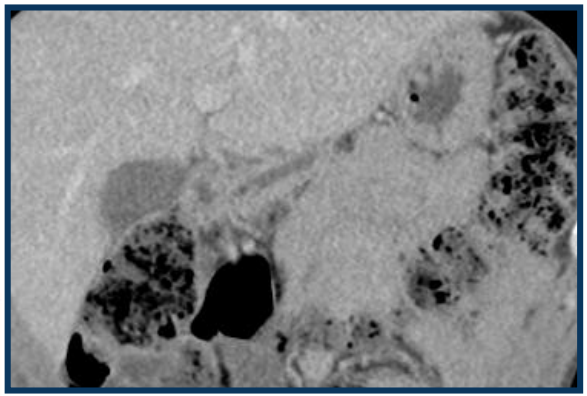

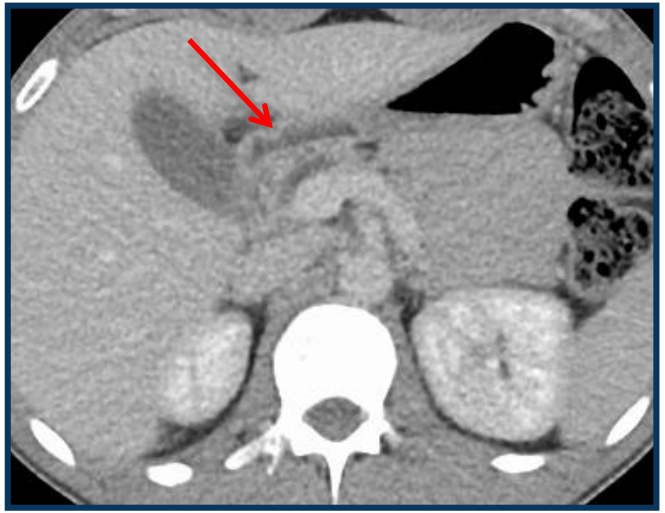

PRSS1 – 25 year old male non-familial. Coronal and axial CT images.

These images demonstrate MPD dilatation with associated atrophy of the pancreatic parenchyma.

Imaging Findings / Procedure details

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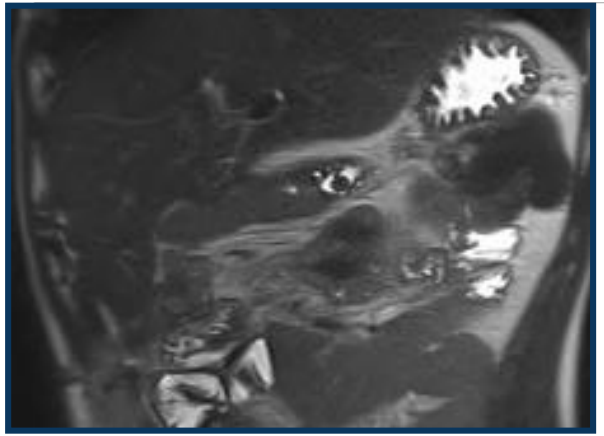

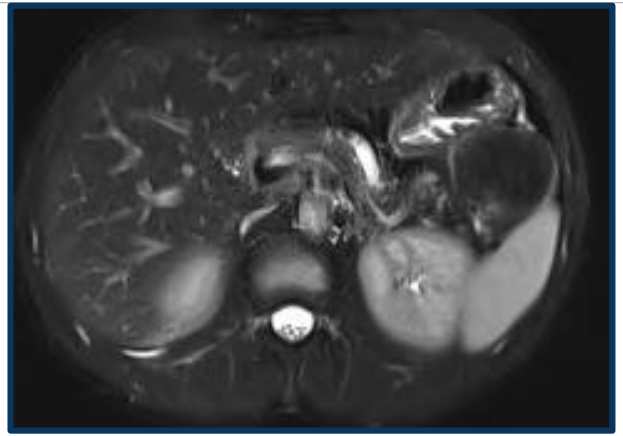

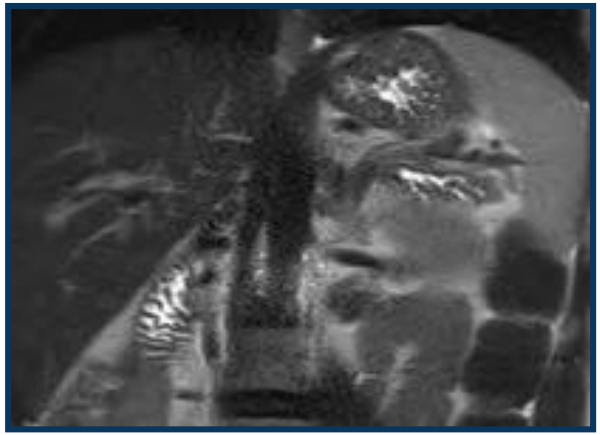

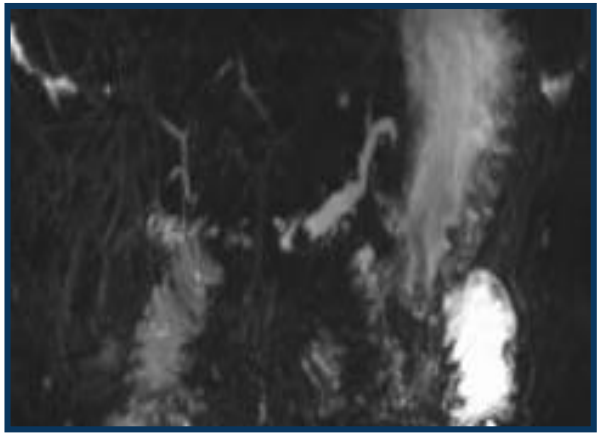

PRSS1 – 25 year old male non-familial. Axial and Coronal MIP from an MRCP.

These images demonstrate MPD and branch ductal dilatation secondary to an obstructing intra-ductal calculus. There is also atrophy of the pancreatic parenchyma.

Imaging Findings / Procedure details
Autosomal recessive HP

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- SPINK 1 imaging features:

3/10 had a SPINK 1 gene mutation.

1/3 patients had pancreatic atrophy

1/3 patients had parenchymal calcification

1/3 patients had main pancreatic duct (MPD) dilatation.

Imaging of patients with the SPINK1 gene mutation demonstrated less significant features of chronic pancreatitis than those with a PRSS1 mutation. 1 patient had pancreatic atrophy and a different patient had pancreatic calcification. None of these patients had the imaging triad described in the PRSS1 patients.

Imaging Findings / Procedure details
Autosomal recessive HP

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- SPINK1- serine protease inhibitor, Kazal type 1 gene.
- SPINK1 is most commonly reported as having autosomal recessive inheritance pattern however, the literature also describes mendelian inheritance patterns associated with SPINK1 HP.
- Patients with SPINK1 HP also typically present in adolescence with acute pancreatitis.
- The imaging features in our patient population are less severe than those seen in patients with PRSS1 hereditary pancreatitis.

Imaging Findings / Procedure details

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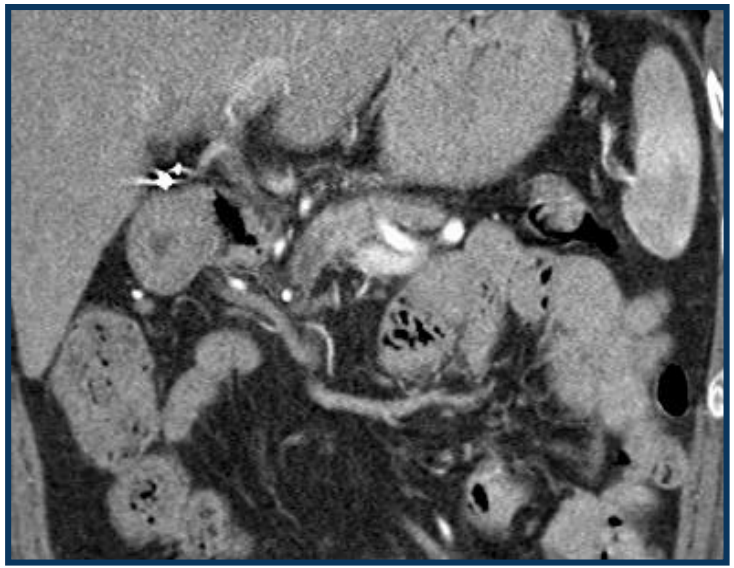

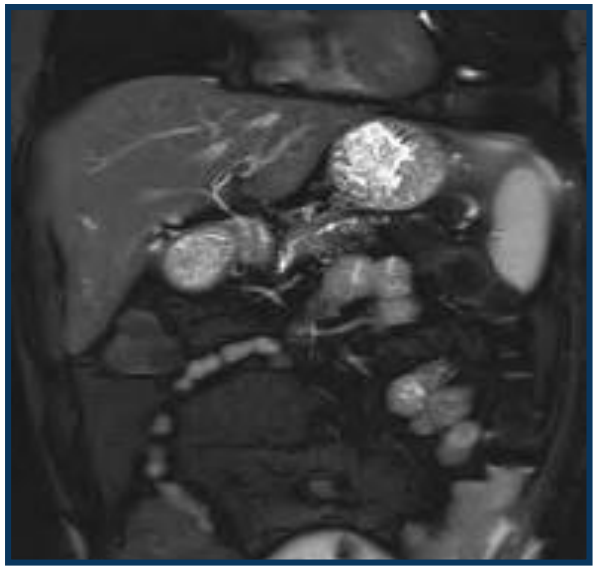

56 year old male with the SPINK1. Coronal contrast enhanced CT and T2 MRI. There is pancreatic atrophy without MPD dilatation or parenchymal calcification.

Imaging Findings / Procedure details

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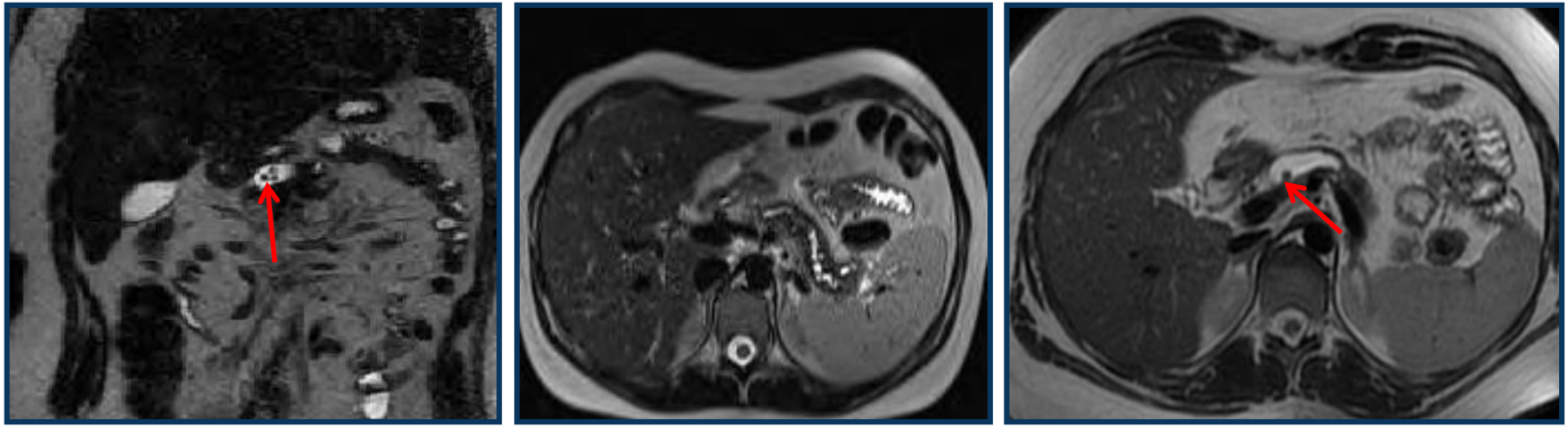

21 year old female with the SPINK1gene mutation. Coronal and axial T2 weighted MRI sequences. There is MPD dilatation with intra-ductal calculi (red arrows). There is no associated calcification with little atrophy.

Imaging Findings / Procedure details
Cystic fibrosis – HP

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- In patients with cystic fibrosis the Cystic fibrosis trans-membrane conductance regulator gene (CFTR) is affected.
- There are 9 variants of the CFTR gene mutation which are associated with pancreatitis.
- These variants include CFTR – R117H, R74Q, R75Q, R170H, L967S, L997F, D1152H, S1235R and D1270N.
- There are 352 patients with cystic fibrosis attending our centre.
- 46/352 have the R117H mutation and 1/352 had the D1152H mutation.
- 4/46 patients had imaging features of pancreatitis, the patient with the D1152H mutation did not.

Imaging Findings / Procedure details
Cystic fibrosis – HP

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- CFTR – R117H Mutation.
- 3/46 patients had features of chronic pancreatitis (CP).
- 3/3 had pancreatic atrophy.
- 1/3 had MPD dilatation.
- 0/3 had intra-ductal or parenchymal calcification.

- 1/46 had features of acute pancreatitis without imaging follow-up for the evaluation of chronic pancreatitis.

None of these patients had the imaging triad seen in the group with the PRSS1 gene mutation. All patients with features of CP had pancreatic atrophy.

Imaging Findings / Procedure details

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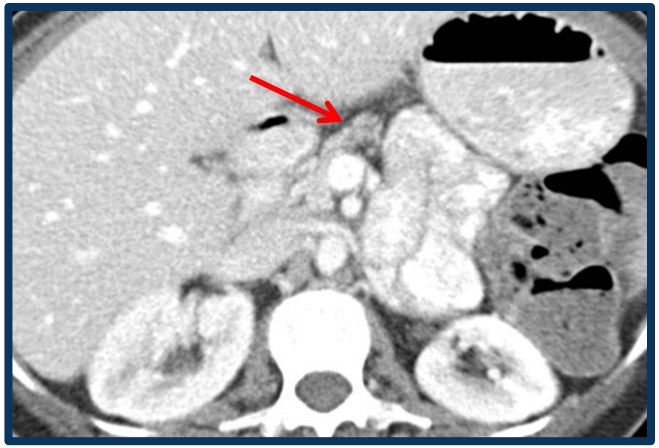

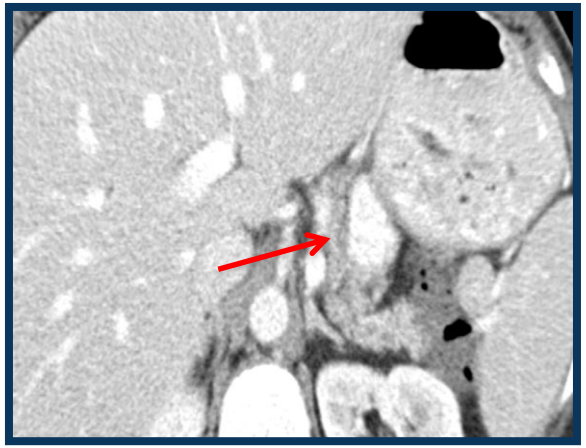

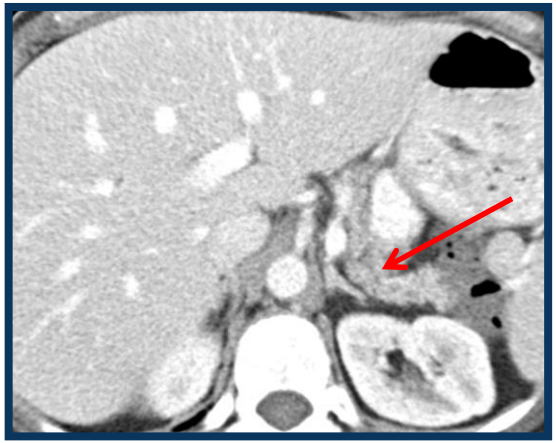

44 year old female with cystic fibrosis, CFTR – R117H gene mutation. Axial and coronal images from a contrast enhanced CT. The is diffuse atrophy (red arrows) of the pancreatic parenchyma without associated MPD dilatation or calcification.

Imaging Findings / Procedure details

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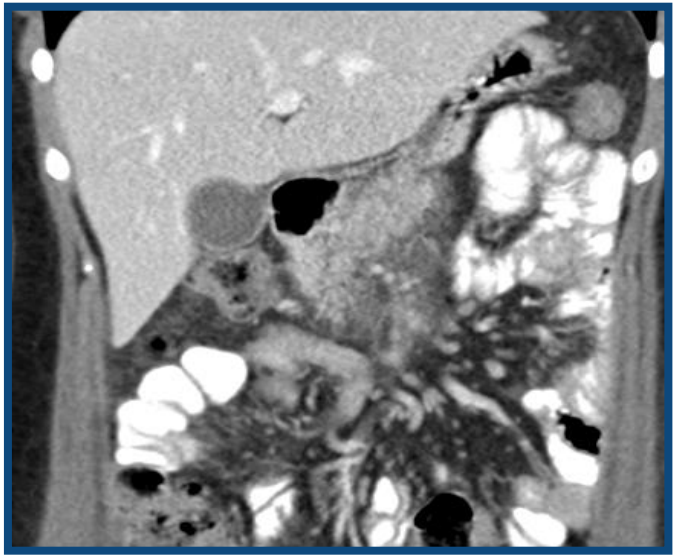

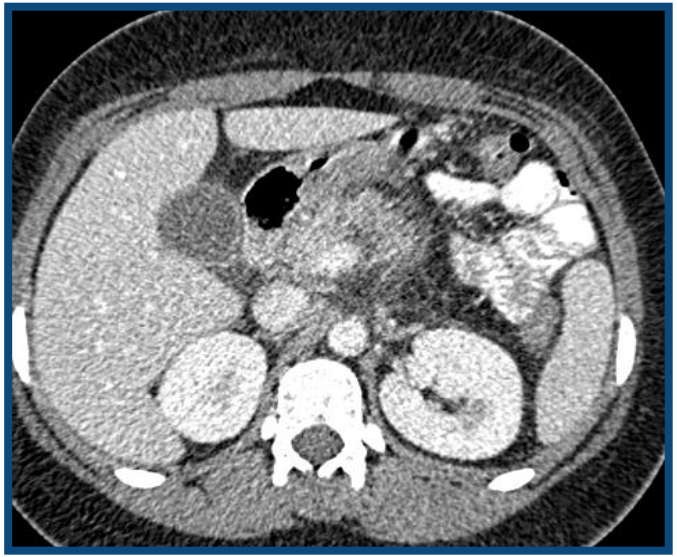

20 year old female with cystic fibrosis, CFTR – R117H gene mutation. Axial and coronal images from a contrast enhanced CT. There is acute pancreatitis with peri-pancreatic inflammation and free fluid without evidence of pancreatic necrosis.

Conclusion

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- Hereditary pancreatitis is a rare genetic disease.
- There are 3 known genotypes
  - Autosomal Dominant PRSS1. The imaging features (triad of pancreatic atrophy, calcification and MPD dilatation) are indistinguishable from chronic alcoholic pancreatitis and included duct dilatation and intra-ductal calculi. In this series the familial and non-familial cases had identical imaging features.
  - Autosomal Recessive SPINK. In this series these patients had pancreatic atrophy and calcification without duct dilatation or calculi.
  - Cystic Fibrosis CFTR. In this series these patients had pancreatic atrophy without parenchymal or intra-ductal calcifications, one had main pancreatic duct dilatation. There were other features of cystic fibrosis.

Conclusion

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- Patients with hereditary pancreatitis present in adolescence and develop pancreatic atrophy and main pancreatic duct dilatation in early adulthood.
- Hereditary pancreatitis patients
  - Are at risk of pancreatic insufficiency
  - Have, regardless of genotype, a reported 40% increased lifetime risk for developing pancreatic adenocarcinoma.
- Radiologists should consider hereditary pancreatitis when 'chronic pancreatitis' is found on CT in non-alcoholic younger patients. Patients should be referred to specialist endocrinologists/ pancreatologists for genetic testing and, if proven to have HP, lifelong surveillance.

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