The Role of Genetics in Pancreatitis

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KEYWORDS

• Hereditary pancreatitis • Familial pancreatitis • Genetic evaluation
• Genetic variants associated with pancreatitis • *PRSS1* • *SPINK1* • *CFTR*

KEY POINTS

- Genetic risk assessment for individuals with suspected hereditary and familial pancreatitis provides an opportunity to discover a causative cause for disease.
- Early identification of hereditary pancreatitis, through genetic evaluation and testing, and proper management in gene mutation carriers requires a multidisciplinary approach in order to be complete and most effective.
- Continued advances in genomic technologies with complete genotyping can establish additional associations between complex genetic causes and environment interactions that may provide personalized management and preventive strategies for pancreatitis in the future.

INTRODUCTION

Individuals with recurrent acute and chronic pancreatitis (CP) may have an inherited predisposition to the development of the disease. Pancreatitis in the setting of a significant family history of the disease can be classified as hereditary or familial pancreatitis. Hereditary pancreatitis (HP) has been defined as either 2 or more individuals within a family exhibiting pancreatitis for 2 or more generations or pancreatitis linked to the inheritance of a pathogenic mutation in the cationic trypsinogen *PRSS1* (protease serine 1) gene.[1] Most HP cases are related to acute pancreatitis or CP in an autosomal dominant pattern of inheritance, although additional cases have been attributed to autosomal recessive inheritance.[2,3] On the other hand, familial pancreatitis (FP) is a broader term used to describe families in which pancreatitis occurs with a greater

Disclosure Statement: No disclosures.
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Gastrointest Endoscopy Clin N Am 28 (2018) 587–603
https://doi.org/10.1016/j.giec.2018.06.001
giendo.theclinics.com
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incidence than expected by chance alone in the general population.[4–6] Familial pancreatitis may or may not be caused by a genetic defect.

In 1952, Comfort and Steinberg were the first to describe HP as recurrent acute pancreatitis (RAP) and CP that tends to run in families.[7] In 1996, facilitated by advancements in molecular genetics, Whitcomb and colleagues[8–10] discovered that HP was caused by a gain-of-function mutation in the cationic trypsinogen gene, which consequently revolutionized the understanding of the mechanism of disease. This finding supported the trypsin-dependent theory where gain-of-function mutations result in trypsinogen or trypsin that is degradation resistant. In addition, premature trypsin activation may provide an alternate mechanism leading to RAP, with a subset of these patients then progressing to CP. Additional genes have been identified in those individuals with personal and family history of pancreatitis, and genetic testing is a useful risk assessment tool to determine whether an individual has an underlying pathogenic variant and increased risk of developing pancreatitis.[11,12] It is important to also recognize and consider relevant environmental factors and exposures and their potential impact on the clinical manifestations in individuals with a genetic predisposition to the development of pancreatitis.

In this chapter, the authors closely examine the specific genes implicated in pancreatitis, investigate the role of genetic testing for diagnosis, and describe the impact of genetic testing results on clinical management.

GERMLINE VARIANTS ASSOCIATED WITH PANCREATITIS

There are several germline genetic alterations that have been associated with the development of pancreatitis. Since its discovery in 1996, *PRSS1* and additional genes have been implicated in HP as either disease causing or modifiers of disease. These include serine protease inhibitor Kazal type 1 (*SPINK 1*) and cystic fibrosis transmembrane conductance regulator (*CFTR*) genes. Both carry a 1% penetrance in comparison to 80% or higher penetrance reported with *PRSS1* gene mutations.[2,3] In addition, many HP cases seem to have a complex multigene and multifactorial cause, including gene–environment interactions between various pathogenic gene variants that affect trypsin regulation, such as calcium-sensing receptor (*CASR*), chymotrypsin C (*CTRC*), and claudin-2 (*CLDN2*) (**Fig. 1**, **Table 1**).[1,4–6,13]

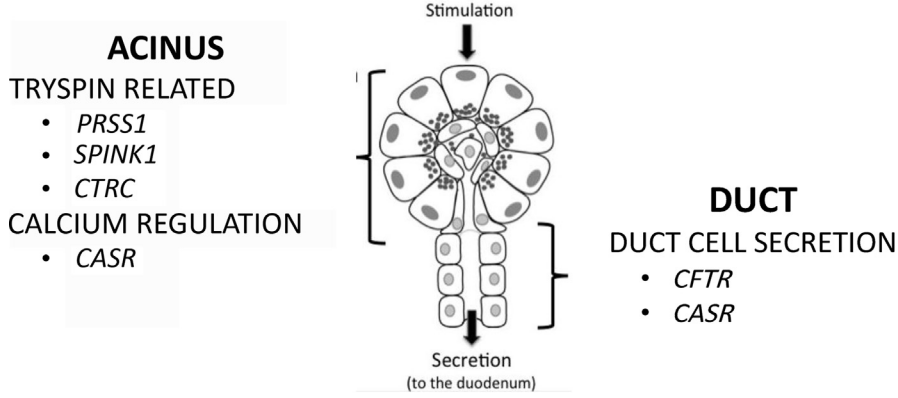

Fig. 1. Genetic variants that affect trypsinogen activation in pancreatic acinar cells and ducts. (*Adapted from* Solomon S, Whitcomb DC. Genetics of pancreatitis: an update for clinicians and genetic counselors. Curr Gastroenterol Rep 2012;14(2):112–7; with permission.)

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