

Is It Hereditary Pancreatitis?

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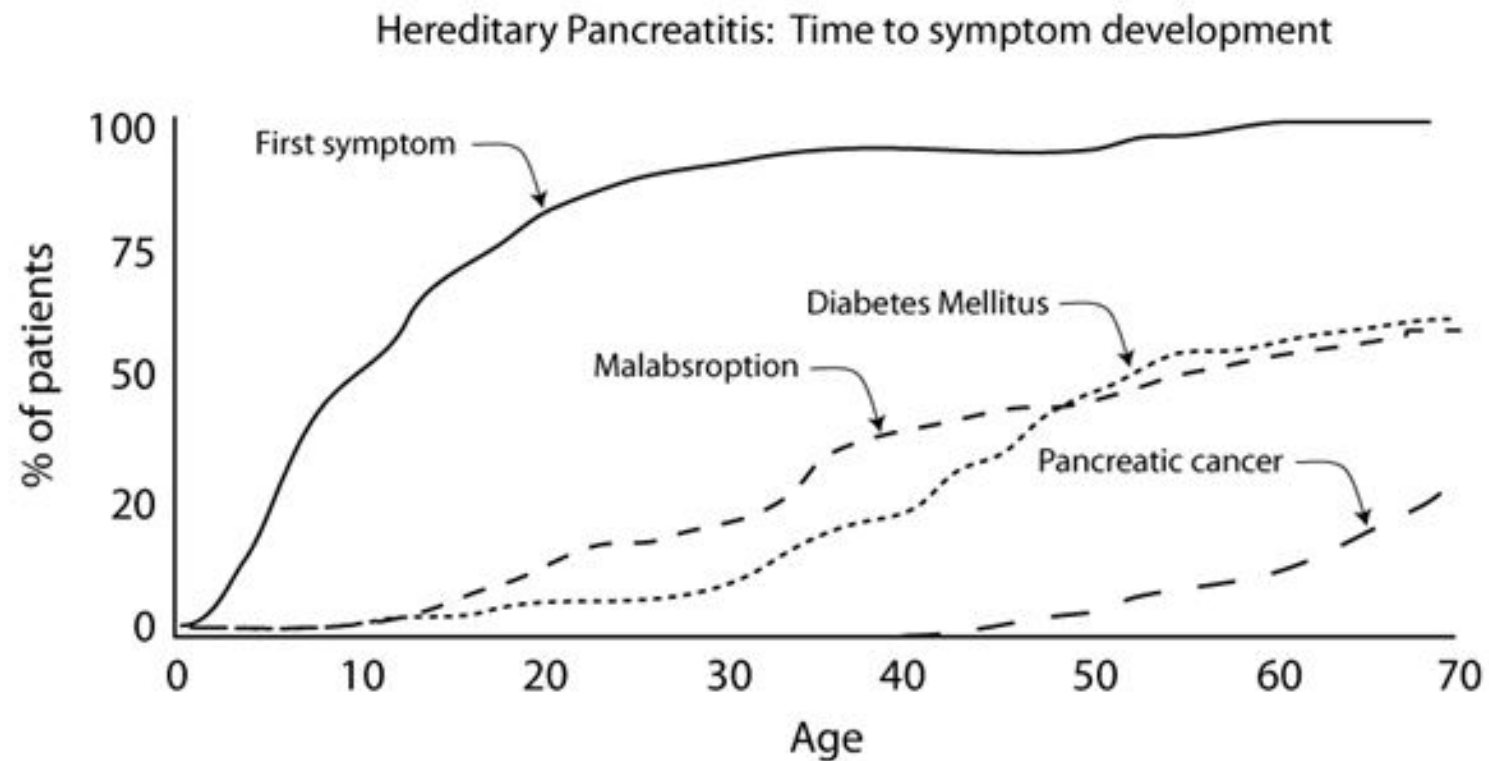
Disclosures

Employee of Ariel Precision Medicine

Clinical Presentation

Clinical Definition: *Two or more individuals with RAP or CP in two or more generations of a family OR pancreatitis in the presence of a known pathogenic PRSS1 variant*

Age of onset (acute attack): 10-12 years (range <1 to >70 years)



Epidemiology

Primarily Caucasian (USA and Europe)

Prevalence: 0.3/100,000 in France

Rare cause of CP:

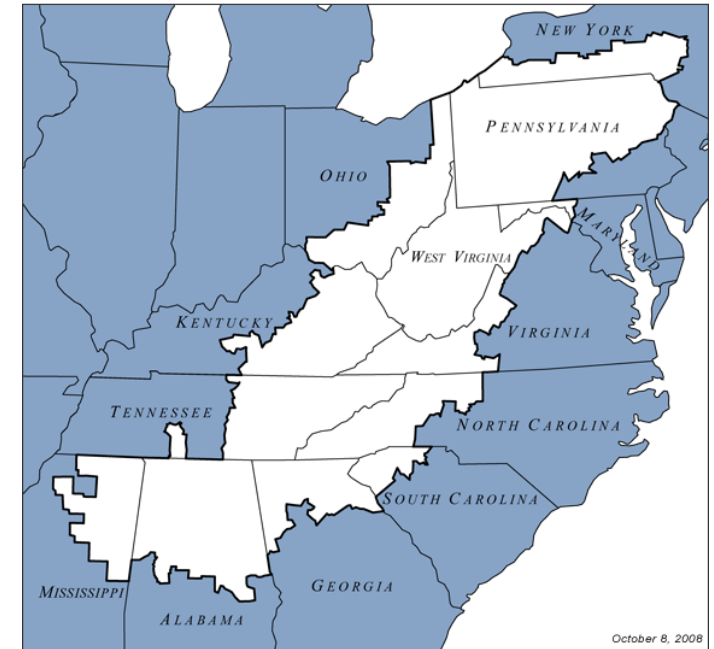
~10% of CP is attributed to a genetic etiology (NAPS)

PRSS1 variants are overrepresented in adolescents (INSPPIRE):

17% with ARP

46% with CP

The Appalachian Region



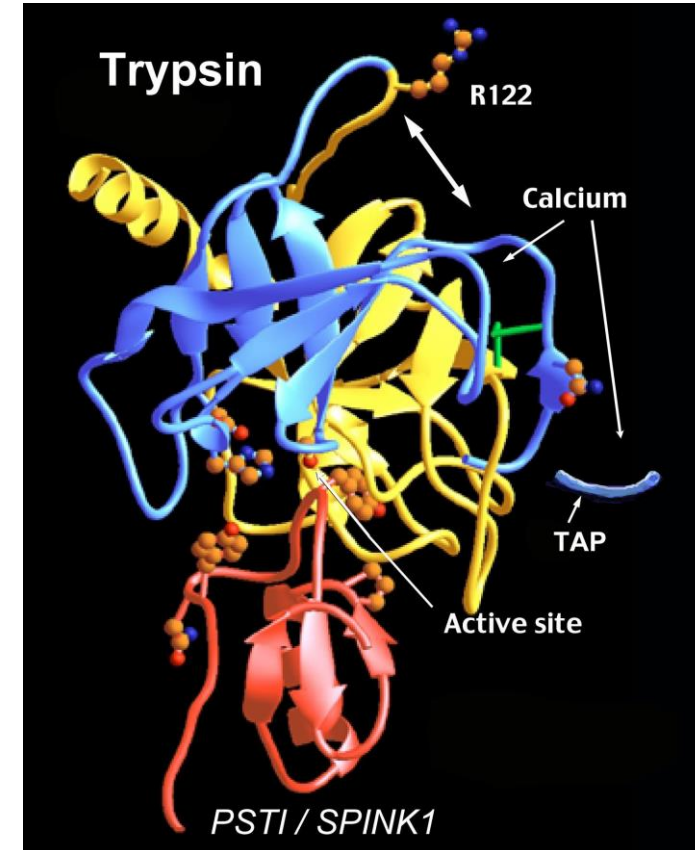
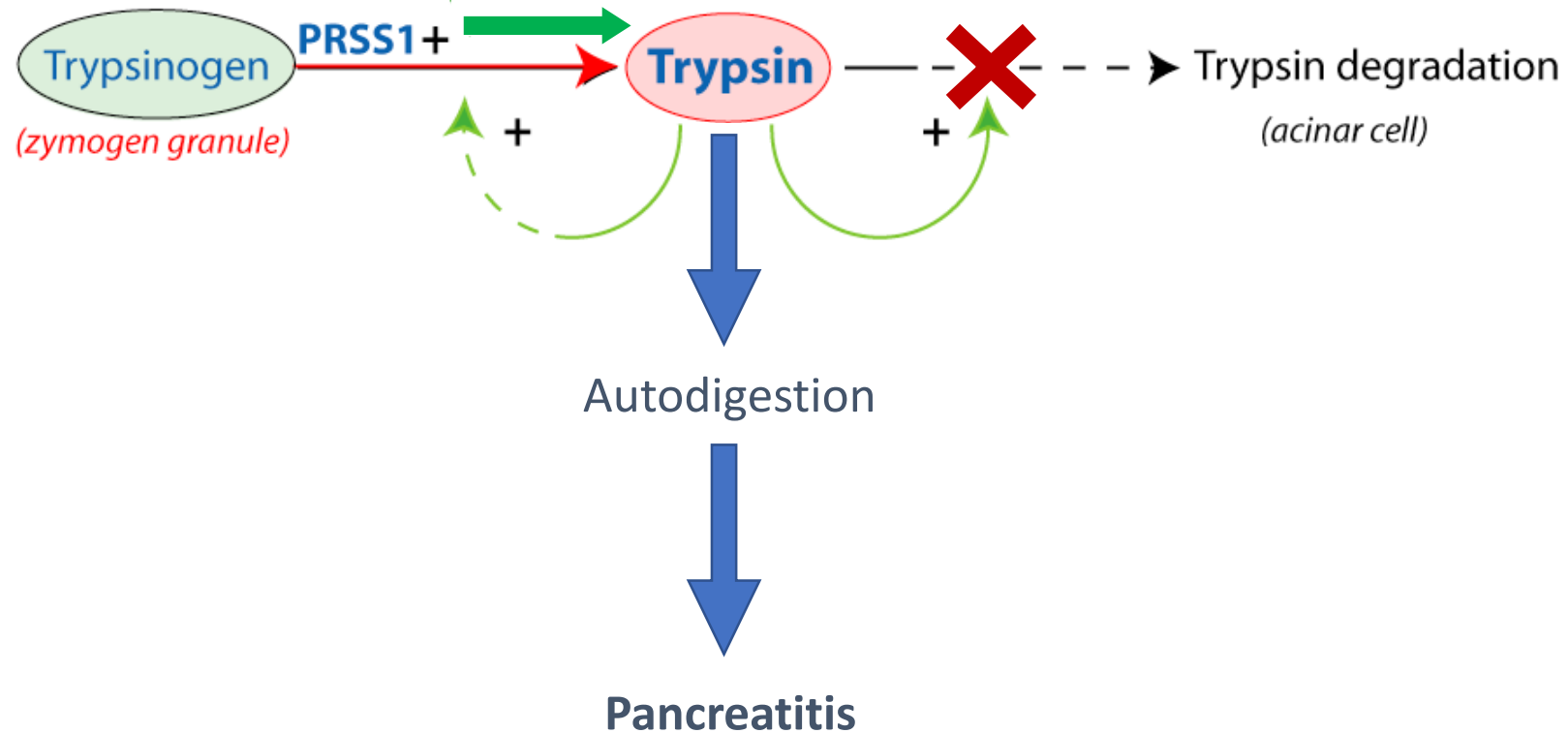
Kumar S, et al. Risk Factors Associated With Pediatric Acute Recurrent and Chronic Pancreatitis: Lessons From INSPPIRE. *JAMA Pediatr.* 2016;170(6):562-9.

Conwell DL, et al. Validation of Demographics, Etiology, and Risk Factors for Chronic Pancreatitis in the USA: A Report of the North American Pancreas Study (NAPS) Group. *Dig Dis Sci.* 2017;62(8):2133-2140.

Genetics of HP

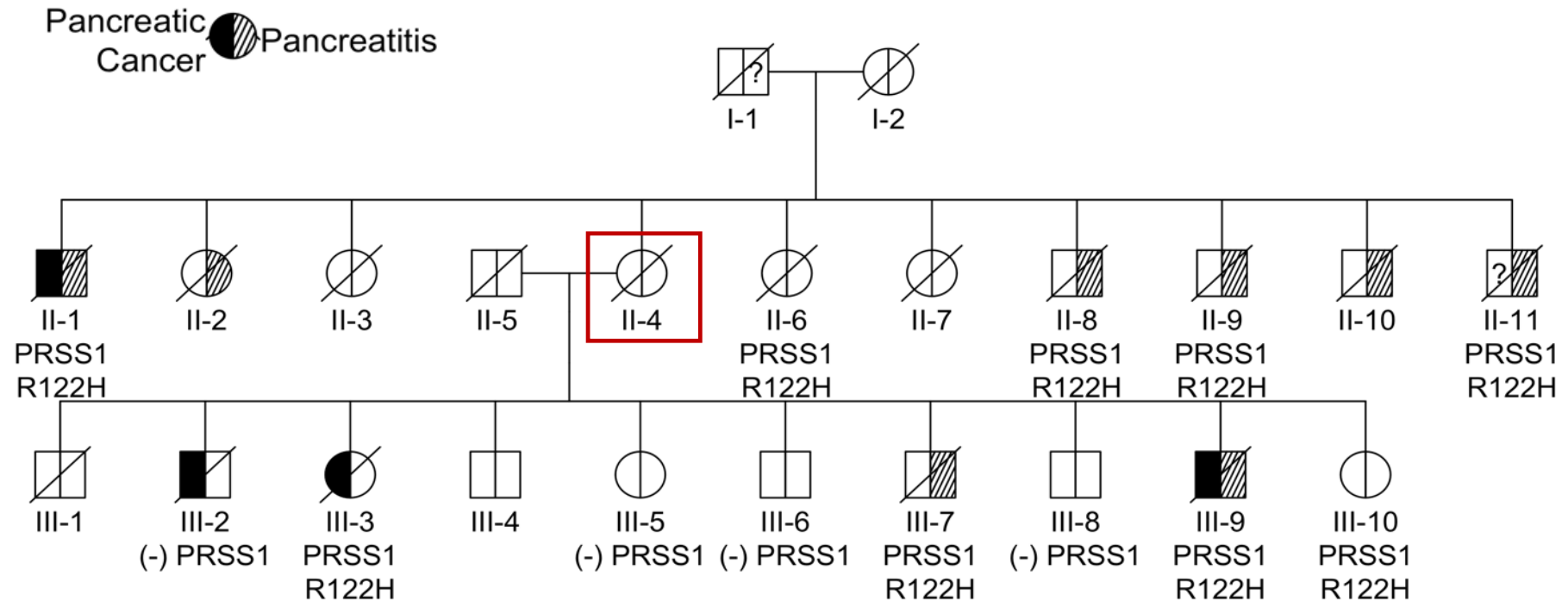
Gain-of-function variants in *PRSS1* (cationic trypsinogen)

> 90% are p.R122H or p.N29I



PRSS1-HP in Families

Autosomal dominant, reduced (80%) penetrance, variable expressivity



Additional Genes

***SPINK1* loss-of-function** – suicide inhibitor of trypsin

Common modifier

***CFTR* loss-of-function** – secretion of bicarbonate

***CTRC* loss-of-function** – regulation of trypsin activity

Moderate risk in presence of other variants

Among other genes

Genetic Testing & Counseling

When to suspect HP	Idiopathic and/or early onset pancreatitis Pancreatitis in an individual with a family history				
Utility of testing	<table border="0"> <tr> <td>Diagnosis</td> <td>Risk prediction</td> </tr> <tr> <td>Management</td> <td>Risk to family</td> </tr> </table>	Diagnosis	Risk prediction	Management	Risk to family
Diagnosis	Risk prediction				
Management	Risk to family				
Results	<p>Testing of affected individual</p> <p>Positive – counsel accordingly (e.g. 50% inheritance)</p> <p>Negative/VUS – does not rule out HP</p>				
Predictive Testing	<p>Not generally recommended, particularly <16 years of age</p> <p>Lack of preventative therapies</p> <p>Penetrance is unpredictable</p> <p>Family planning</p>				
Risk Counseling	<p>Consider:</p> <table border="0"> <tr> <td>Family presentation</td> <td>Environmental exposure</td> </tr> <tr> <td>Genotype</td> <td></td> </tr> </table>	Family presentation	Environmental exposure	Genotype	
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