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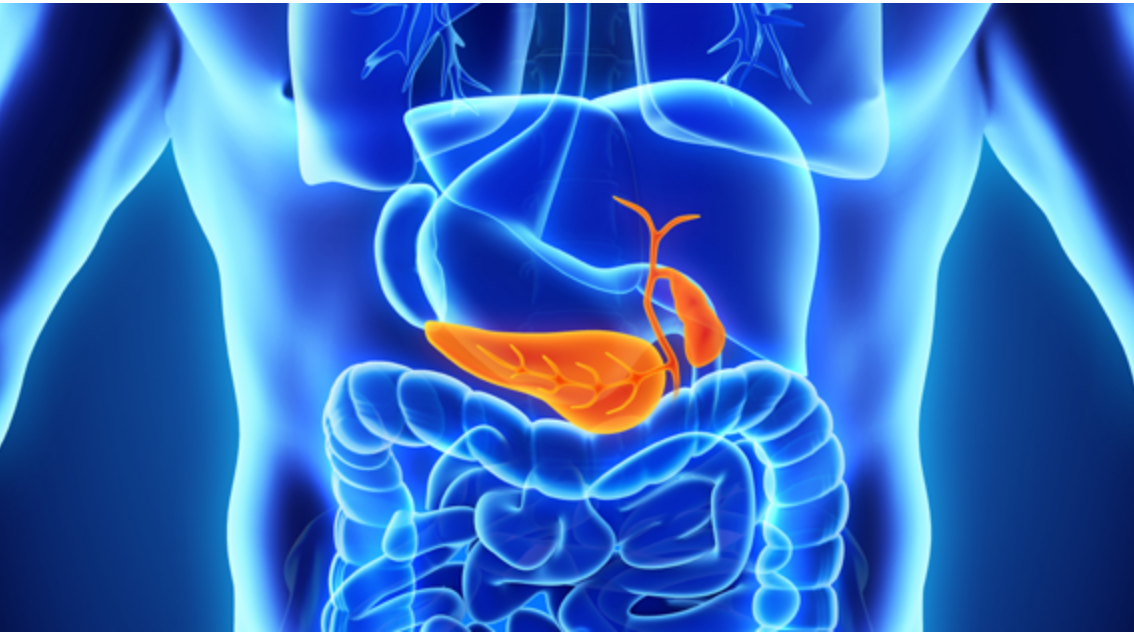

Gene panel *SPINK1, PRSS1, CTRC, CPA1, CFTR* et *CASR* for the diagnosis of hereditary pancreatitis

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Hereditary pancreatitis is defined as inflammation of the pancreas, characterised by recurrent episodes of acute pancreatitis and/or chronic pancreatitis, whereby these pathologies are observed in at least two first-degree relatives or at least three second-degree relatives, and are present in two or more generations.

Globally, the prevalence of hereditary pancreatitis is estimated at 6.115/100,000[1].

Research criteria and characteristics of hereditary pancreatitis[2]

- Family history of acute recurrent pancreatitis, chronic pancreatitis, pancreatitis in childhood
- Relative, who is a carrier of the genes associated with hereditary pancreatitis
- Onset of the first episodes of pancreatitis in the first two decades of life, often before age of 15:
  - unexplained pancreatitis in a child
  - chronic idiopathic pancreatitis in a patient under 25
- Recurrent acute pancreatitis of unknown aetiology

Pathophysiology of hereditary pancreatitis

The acinar cells of the pancreas produce substances essential for the digestion of food: pancreatic enzymes, in the form of inactive pro-enzymes, as well as inhibitors of these enzymes. After they are transported in the pancreatic juice which mixes with the bile in the intestine, enzymes become activated in the digestive tract to break down the ingested food.

The clinical signs of hereditary pancreatitis are thought to result from an imbalance between the normally secreted proteases and their inhibitors, leading to autodigestion of the pancreatic parenchyma.

Some mutated genes found in hereditary pancreatitis encode abnormal proteins that activate proteases or inhibit protease inhibitors and thus are the ultimate cause of pancreatic tissue damage.

Some examples are listed below:

Gene	Encoded protein	Deleterious effects of mutated protein
PRSS1	Cationic trypsin	▸ Conversion of inactive trypsinogen to trypsin prior to its excretion from the pancreas ▸ Inappropriate self-activation of trypsin ▸ Increased stability of trypsin ▸ Elevated intra-pancreatic levels of trypsin
SPINK1	Trypsin inhibitor protein	Low concentrations of inhibitory protein
CTRC	CTRC protein	Loss of trypsin and trypsinogen degradation function
CASR	*Calcium-sensing receptor gene*	Calcium metabolism dysfunction
CPA1	Cathepsin A1	Structural abnormalities of trypsin
CFTR	CFTR protein	▸ Transmembrane hydro-electrolyte flow anomaly ▸ Changes in the characteristics of the exocrine secretions

Diagnosis of hereditary pancreatitis by Eurofins Biomnis

The Eurofins Biomnis panel includes 6 genes: *SPINK1, PRSS1, CTRC, CPA1, CFTR* and *CASR*.

These genes can be assigned to two categories:

- **genes responsible for pancreatitis:** *PRSS1* and *SPINK1* (except the N34S mutation)
- **susceptibility genes:** *CTRC, CPA1, CFTR* et *CASR* and the N34S mutation of *SPINK1*.

Details of the "hereditary pancreatitis" gene panel

Genes	Chr	Transmission mode	Variants described in databases		Detection rate (%)	Most frequent variants
			ClinVar	HGMD® Pro		
PRSS1*	7	AD	23	70	5%	p.Ala16Val p.Asn29Ile p.Arg122Hi p.Arg122Cys
SPINK1	5	AD	14	48	10-15%	p.Asn34Ser p.Pro55Ser
CTRC	1	AD/AR**	11	52	5%	p.R254W and p.K247_R254del
CPA1	7	AD/AR		41	Very rare	p.Gly225Ser
CASR	3	AD**		3	Very rare	p.P682L)
CFTR	7	AD/AR**	518	1918	20-30%	>1300

AD = autosomal dominant; AR = autosomal recessive
** Some regions of the genome are duplicated (pseudogenes)*
***polygenic and / or multifactorial*

Methodology

All of the coding regions of the genes in the panel are analysed by next-generation sequencing (NGS) on an Illumina NextSeq2000 sequencer. The data from the sequencing is then analysed and interpreted via the SeqOne bioinformatics pipeline.

Results

- Mutations in the PRSS1 gene are detected in **60-80% cases of hereditary pancreatitis.**
- Pathogenic variations in genes such as CFTR and SPINK1 are factors in the onset of apparently idiopathic pancreatitis.
- In about 10% of cases, mutations in two genes can be identified; these are termed “trans-heterozygous” genes.

Benefits of the “hereditary pancreatitis” gene panel

- Explains the symptoms of a patient,
- Distinguishes hereditary pancreatitis from pancreatitis of another origin,
- Enables the diagnosis of hereditary pancreatitis in a child and thus avoid additional investigations,
- Assesses the risk for related parties,
- Identifies an atypical form of cystic fibrosis in the case of mutations in the *CFTR* gene and therefore offer appropriate treatment as early as possible, in particular by referring male patients to an andrologist to assess the risk of infertility,
- Defines strategies for managing and preventing complications,
- Offers the possibility of genetic counselling in the event of severe mutations in the *CFTR* or *PRRS1* gene.

For the present, in the absence of preventive treatment for acute episodes and of specific management, there is no therapeutic benefit in the identification of a genetic cause in pancreatitis.

References

1. *Ouyang, G., Pan, G., Liu, Q. et al. The global, regional, and national burden of pancreatitis in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. BMC Med 18, 388 (2020)*
2. *Raphael KL, Willingham FFClin Exp Gastroenterol. 2016 Jul 26;9:197-207:*
3. *Shelton CA, Umapathy C, Stello K, Yadav D, Whitcomb DC. Hereditary pancreatitis in the United States: survival and rates of pancreatic cancer. Am J Gastroenterol. 2018;113:1376. PubMed PMID: 30018304.*

Practical details

Test	Panel of 6 “hereditary pancreatitis” genes
Analysis code	**EXOME**
Turnaround	**6 weeks** Extended period if additional examinations required
Sample	**Solo:** 5 mL EDTA whole blood or DNA sample **Duo/Trio:** 5mL EDTA whole blood or DNA sample from relative
Storage and transport	Room temperature
Technique	Exome sequencing
Cost	Contact us at international@eurofins-biomnis.com
Required documents	B59-INTGB analysis order form available on **www.eurofins-biomnis.com** > Test guide > Analysis code **EXOME**
Complementary test	Study of relative persons by Sanger sequencing: 5 mL EDTA whole blood or DNA sample from relative
To learn more about exome sequencing by Eurofins Biomnis, see our dedicated information brochure at **www.eurofins-biomnis.com > Resources > Focus on > Whole exome sequencing**	

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