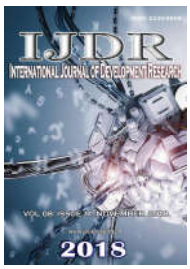
ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 08, Issue, 11, pp.24269-24271, November, 2018



ORIGINAL RESEARCH ARTICLE OPEN ACCESS

A CASE OF GENETIC ETIOLOGY OF ACUTE PANCREATITIS IN A LEBANESE PEDIATRIC PATIENT

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ARTICLE INFO

Article History:
Received 16th August, 2018
Received in revised form
19th September, 2018
Accepted 20th October, 2018
Published online 30th November, 2018

Key Words:
Genetic Etiology,
Lebanese,
Patient.

ABSTRACT

Chronic pancreatitis is an inflammatory condition that needs investigation in order to find and potentially treat the underlying cause since recurrent and chronic pancreatitis can lead to irreversible pancreatic damage or even pancreatic cancer. Hereditary pancreatitis are chronic pancreatitis or recurrent acute pancreatitis that are related to gene mutations. It is an autosomal disease, with a variable expression and a penetrance that is around 80%. (6) The mutations of gene PRSS 1 (serine protease 1) which induce activation of cationic trypsinogen gene are an example of genetic cause of pancreatitis. The most frequent mutation is the mutation that leads to the replacement of arginine with Histidine (1). Also the loss-of-function PRSS1 promoter variants seems to be a protective factor against pancreatitis. On the other side a gain of function of PRSS1 promoter variants seems to predispose to pancreatitis by increasing the expression of the gene PRSS1. So, this gene plays a role in the physiopathology of many hereditary pancreatitis. (3). CFTR (cystic fibrosis transmembrane conductance regulator), and SPINK1(the serine protease inhibitor Kazal type 1) are also other genes that seem to be implicated in the physiopathology of hereditary pancreatitis(2). A chart review has shown that mutation in those genes is seen in 33.3% of patients with acute recurrent pancreatitis or chronic pancreatitis. (4). Also the link between CFTR, PRSS1 and SPINK 1 and chronic or acute recurrent pancreatitis was shown in a pediatric Chinesestudy that has also shown a higher incidence of pancreatic stones related to the SPINK 1 mutation.(5) Hereditary pancreatitis need to be diagnosed since it can lead to pancreatic cancer several decades after the initial episode of pancreatitis. Also A paternal inheritance pattern seems to increase the risk of developing pancreatic cancer (6). There was no difference between the mutation type and the clinical or morphological characteristics of the pancreatitis. It was also seen that pancreatic adenocarcinoma is the cause of death in nearly 50% of the cases(7).Also, a study has compared the clinical course of chronic non hereditary pancreatitis and hereditary pancreatitis and the results have shown that clinical presentation of pediatric patients with hereditary pancreatitis is significantly more severe than pancreatitis due to other causes (8). Despite the fact that hereditary pancreatitis is a rare disease its prevalence seems to be higherin African American patients when compared to European patients (9). The prevalence of hereditary pancreatitis in some country like Lebanon is not clearly defined because there is lack of case reports that describe this pathology when encountered. In our case report, we described a case of pediatric hereditarypancreatitis encountered in a Lebanese hospital.

Citation: Rami George Maalouf, Chabel Habis, Cynthia Haddad, Yara Salameh and George Nicolas, 2018. "A case of genetic etiology of acute pancreatitis in a lebanese pediatric patient", *International Journal of Development Research*, 8, (11), 24269-24271.

INTRODUCTION

Case presentation: This the case of a 15-year-old girl that was born on term by a caesarian delivery. Her birth weight was 3750 g and herheight 48cm. The patient has familial dyslipidemia. Her vaccinations are up to date and her family history is significant for dyslipidemia in her 2 older brothers. There is no consanguinity between her parents. She presented to the ERwith an acute onset of epigastric pain that radiates to the interscapular area.

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The pain started 1 day ago and increased progressively in intensity. She presented to the Emergency department 24 hours after the onset of pain and described her pain as sharp pain with an intensity of 8/10. She was nauseated and vomited once in the ER. No fever, no diarrhea, no constipation and no other complaints. Her physical exam was normal except an increasedabdominal pain on palpation of the epigastric area. She is not taking any medication at home except the Lipantyl that she started taking it 3 years ago for her DLP at dose of 160 mg once daily. There was no Alcohol intake, no recent infection and no recent administration of any vaccine. In the ER her vital signs were as follow: T: 37.3CTA: 14/8mmHg Pulse: 98 bpm

Her lab results in the ER were as follow:

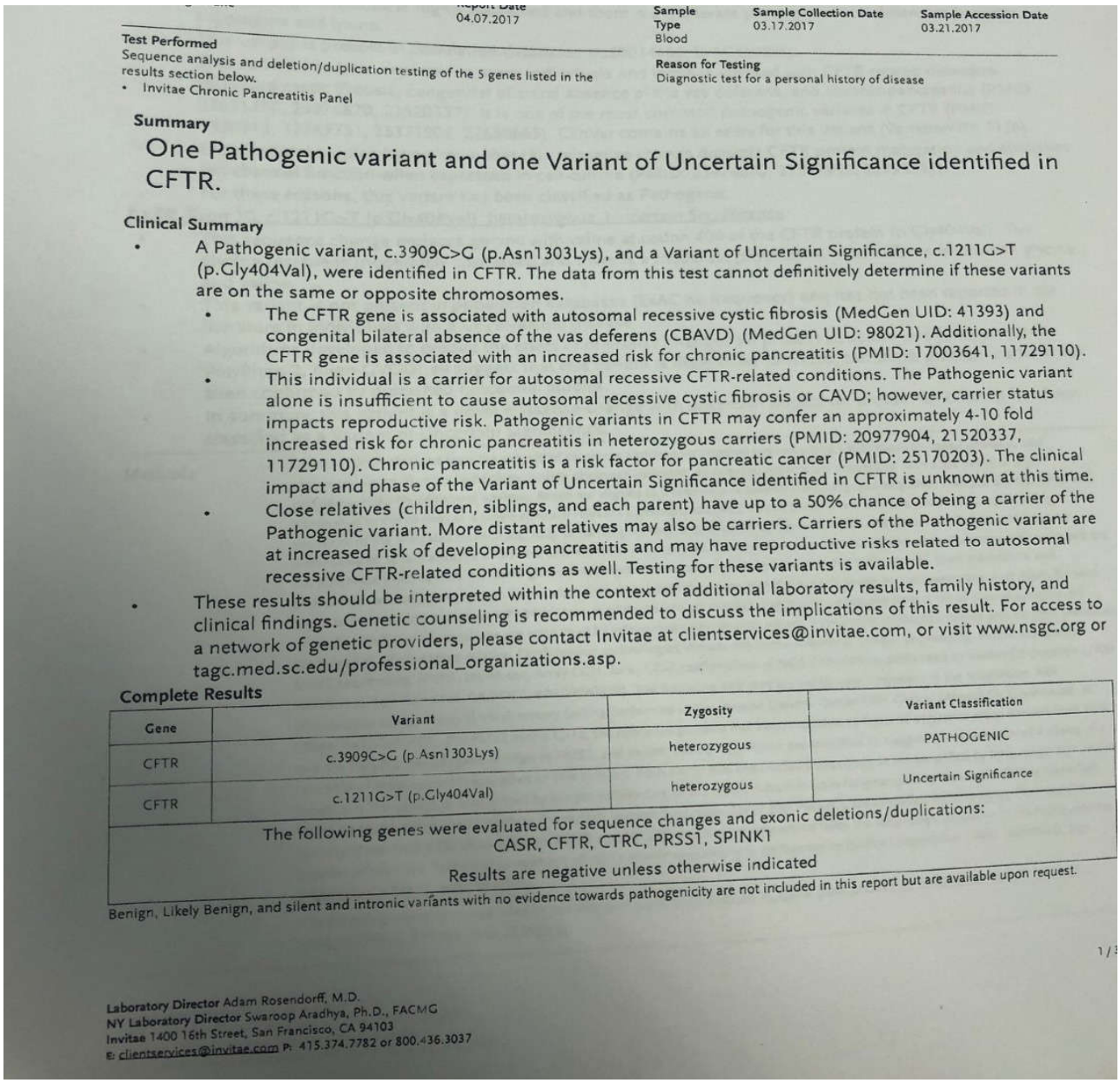
Leucocytes	13900/uL
Neutrophils	82.5%
Lymphocytes	10.9%
Monocytes	5.6%
Hemoglobine	14.1g/dL
Haematocrit	41.4%
CRP	1 mg/L

Urea	26 mg/dL
Creatinine	0.7 mg/dL
Na	136 mmol/L
K	3.6 mmol/L
Cl	94 mmol/L
Ca	10.5 mg/dL
ph	3.8 mg/dL
Mg	1.8 mg/dL
HCO3-	20 mmol/L

Ph Alk	58 U/L
GGT	11 U/L
Direct Bilirubin	0.2 mg/dL
Indirect bilirubin	0.3 mg/dL
LDH	152.5 U/L

Glycemia	101 mg/dL
Total cholesterol	204 mg/dL
HDL	74 mg/dL
LDL	141 mg/dL
Triglyceride	73 mg/dL

- IgG4:-
- Blood culture and urine culture were negative.
- Measles: IgG + IgM -
- CMV: IgG - IgM -
- Parvovirus: IgG - IgM-
- EBV: IgG + IgM -
- Varicella: IgG + IgM -
- Stool exam was negative.



04.07.2017

Sample Type: Blood
Sample Collection Date: 03.17.2017
Sample Accession Date: 03.21.2017

Test Performed
Sequence analysis and deletion/duplication testing of the 5 genes listed in the results section below.
- Invitae Chronic Pancreatitis Panel

Reason for Testing
Diagnostic test for a personal history of disease

Summary

One Pathogenic variant and one Variant of Uncertain Significance identified in CFTR.

Clinical Summary

- A Pathogenic variant, c.3909C>G (p.Asn1303Lys), and a Variant of Uncertain Significance, c.1211G>T (p.Gly404Val), were identified in CFTR. The data from this test cannot definitively determine if these variants are on the same or opposite chromosomes.
  - The CFTR gene is associated with autosomal recessive cystic fibrosis (MedGen UID: 41393) and congenital bilateral absence of the vas deferens (CBAVD) (MedGen UID: 98021). Additionally, the CFTR gene is associated with an increased risk for chronic pancreatitis (PMID: 17003641, 11729110).
  - This individual is a carrier for autosomal recessive CFTR-related conditions. The Pathogenic variant alone is insufficient to cause autosomal recessive cystic fibrosis or CAVD; however, carrier status impacts reproductive risk. Pathogenic variants in CFTR may confer an approximately 4-10 fold increased risk for chronic pancreatitis in heterozygous carriers (PMID: 20977904, 21520337, 11729110). Chronic pancreatitis is a risk factor for pancreatic cancer (PMID: 25170203). The clinical impact and phase of the Variant of Uncertain Significance identified in CFTR is unknown at this time.
  - Close relatives (children, siblings, and each parent) have up to a 50% chance of being a carrier of the Pathogenic variant. More distant relatives may also be carriers. Carriers of the Pathogenic variant are at increased risk of developing pancreatitis and may have reproductive risks related to autosomal recessive CFTR-related conditions as well. Testing for these variants is available.
- These results should be interpreted within the context of additional laboratory results, family history, and clinical findings. Genetic counseling is recommended to discuss the implications of this result. For access to a network of genetic providers, please contact Invitae at clientservices@invitae.com, or visit www.nsgc.org or tagc.med.sc.edu/professional_organizations.asp.

Complete Results

Gene	Variant	Zygosity	Variant Classification
CFTR	c.3909C>G (p.Asn1303Lys)	heterozygous	PATHOGENIC
CFTR	c.1211G>T (p.Gly404Val)	heterozygous	Uncertain Significance

The following genes were evaluated for sequence changes and exonic deletions/duplications:
CASR, CFTR, CTRC, PRSS1, SPINK1

Results are negative unless otherwise indicated

Benign, Likely Benign, and silent and intronic variants with no evidence towards pathogenicity are not included in this report but are available upon request.

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Figure 1. Genetic testing showing mutation in the CFTR gene

Amylase	1026 U/L
Lipase	3794 U/L
SGOT	20 U/L
SGPT	15 U/L

Abdominal MRI

Acute pancreatitis with peripancreatic fluid and ascitic fluid in the abdominal area. Biliary tract is normal. Since this young patient had an episode of acute pancreatitis that was not explained by any clear etiology, a genetic testing was done in order to rule out hereditary pancreatitis. The genetic testing turned out to be positive and involved the CFTR gene (Figure 1).Thus, hereditary pancreatitis was diagnosed in this patient.

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