

Session I

## A Case of 47-Years-Old Female with Obstructive Jaundice and Weight Loss

**Huapyong Kang, Jung Hyun Jo, Hee Seung Lee, Moon Jae Chung, Jeong Youp Park, Seungmin Bang, Seung Woo Park, and Si Young Song**

*Division of Gastroenterology, Department of Internal Medicine,  
Yonsei University College of Medicine, Seoul, Korea*

### 1. Case presentation

47세 여자가 1주간의 구역, 질어진 소변 색 및 체중감소를 주소로 내원하였다. 과거 결핵으로 치료받은 병력 이외에 특이 과거력 또는 가족력이 없는 비음주, 비흡연자였다. 혈액검사에서 폐쇄성 고빌리루빈혈증 소견을 보였고, 복부 CT, MRI에서는 원위부 총담관 폐쇄를 유발하는 췌장 머리의 종괴와, 주 췌관의 확장 및 다발성 췌관석이 관찰되었다. EUS-FNA 검사에서 췌장 종괴는 췌장 선암으로 진단되었고, PET-CT에서 7번 경추에 뼈 전이 소견을 보였다. 유전자 돌연변이 검사에서 SPINK1 유전자에 이형접합형 c.194+2T>C 변이가 검출되었다.

### 2. Diagnosis

(1) 경추의 뼈 전이를 동반한 전이성 췌장암, (2) 췌장암에 의한 원위 총담관 협착, (3) 이형접합형 SPINK1 돌연변이가 있고 다발성 췌관석을 동반한 특발성 만성 췌장염

### 3. Therapy and Clinical course

담관 내 감압을 위해 ERCP를 시행하여 총담관 협착부에 금속 스텐트를 삽입하였고, 고빌리루빈혈증은 호전되었다. 전이성 췌장암의 1차 치료로 FOLFIRINOX 항암 요법 투여를 시작하여 2018.11.26 #2 FOLFIRINOX 투여까지 완료하였다. 현재까지 치료에 tolerable 하였으며, #4까지 시행 후 반응평가 시행 예정이다. 직계가족을 대상으로 유전자 돌연변이 검사를 시행하여, 가족 중 해당 돌연변이를 보유 여부를 확인할 계획이다.

### 4. Conclusion

췌장염 및 췌장암 발생의 위험 인자가 없는 비교적 젊은 나이의 환자에서 전이성 췌장암과 만성 췌장염이 진단되었고, SPINK1 유전자에 이형접합형 돌연변이가 확인된 증례를 경험하여 보고하는 바이다.

**Key words:** Pancreatic cancer, Chronic pancreatitis, Idiopathic, Hereditary, SPINK1

## Case

- F/47

- **Chief complaint**

Dark-colored urine, nausea \* 1 week

Weight loss (5 kg/6 months)



## Case

- **Past medical history**

Old pulmonary TBc (12 years ago, s/p medication)

- **Family history**

Father: Parkinson disease

Mother: Hypertension

- **Social history**

Smoking: **Never-smoker**

Alcohol: **Non-drinker**



## Case

### • Review of systems

Generalized Weakness (+)  
 Nausea (+), Abdominal discomfort (+)  
 Poor oral intake (+), Weight loss (+)  
 Fever (-), Chill (-)

**Pain: VAS 0**

### • Performance status

ECOG 1

### • Physical examination

Icteric sclera  
 Soft and flat abdomen

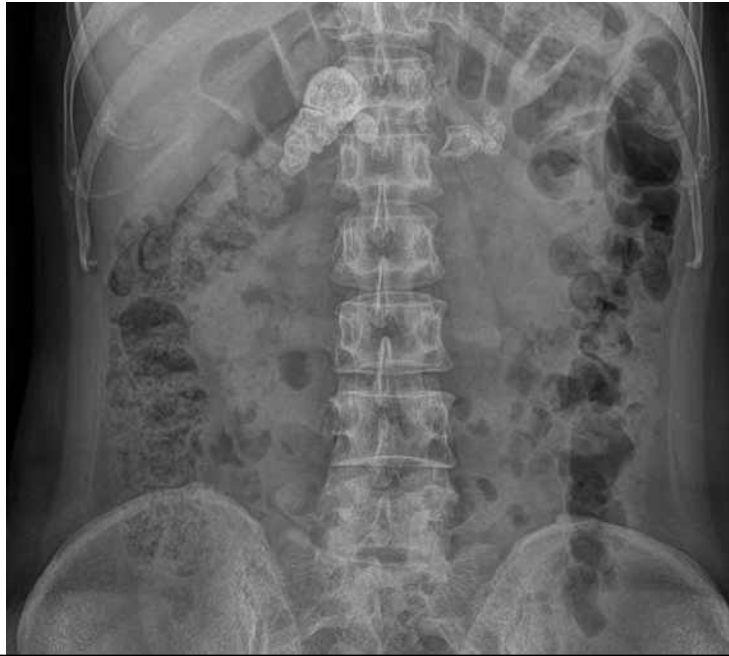
### • Vital sign

BP: 133/82 mmHg,  
 HR: 81/min,  
 RR: 18/min, BT: 36.9°C

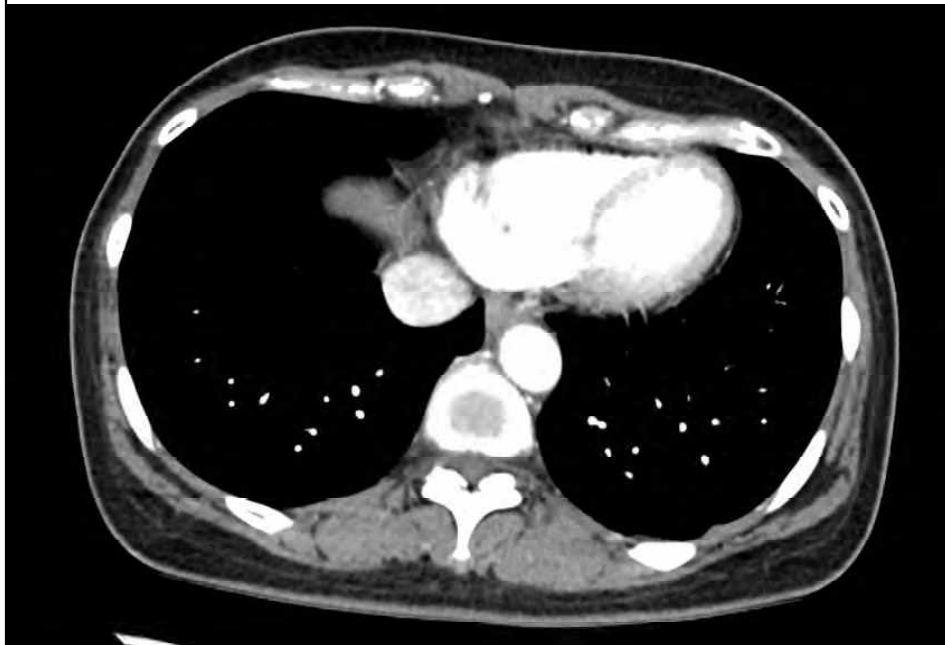
## Laboratory study

• WBC	5,410/μL	• Glucose	103 mg/dL
• ANC	4,180 /μL, 77.2%	• HbA1c	5.5%
• Hb	<b>8.5 g/dL</b>	• BUN/Creatinine	7.5/0.56 mg/dL
• Platelet count	301,000 /μL	• Amylase/Lipase	26/40 U/L
• AST/ALT	<b>207/391 IU/L</b>	• CA19-9	1.7 U/mL (Lewis a-/b+)
• Total bilirubin	<b>5.1 mg/dL</b>	• CEA	0.95 ng/mL
• Alk. Phos	<b>208 IU/L</b>		
• Gamma-GT	<b>369 IU/L</b>	<b>&lt;Urinalysis&gt;</b>	
• Albumin	3.8 g/dL	• Urobilinogen	<b>1+(1.0)</b>
• PT (INR)	1.08	• Bilirubin	<b>2+</b>
		• Color	Dark Yellow

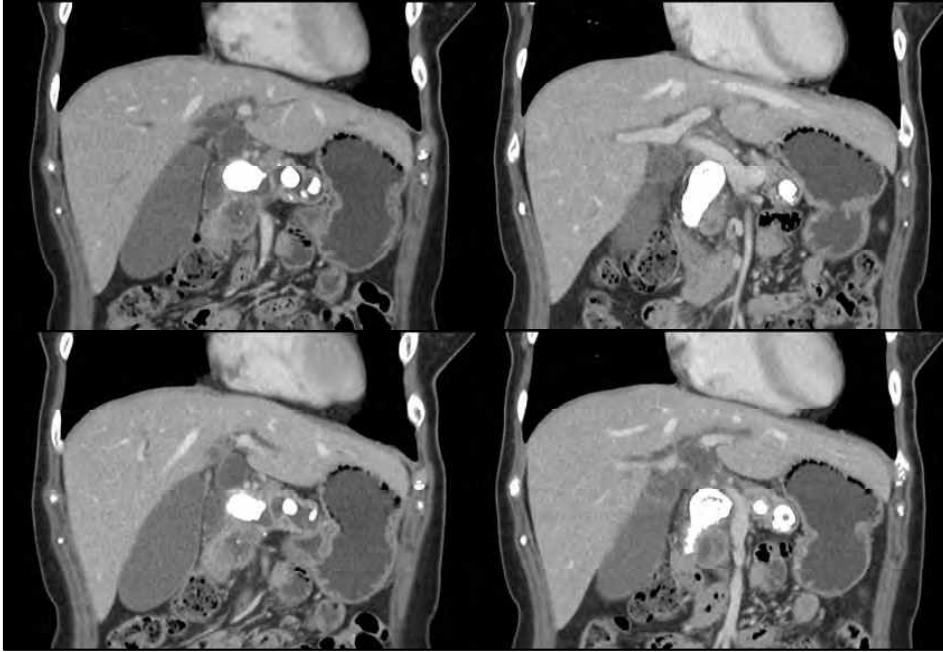
**Abdomen X-ray**



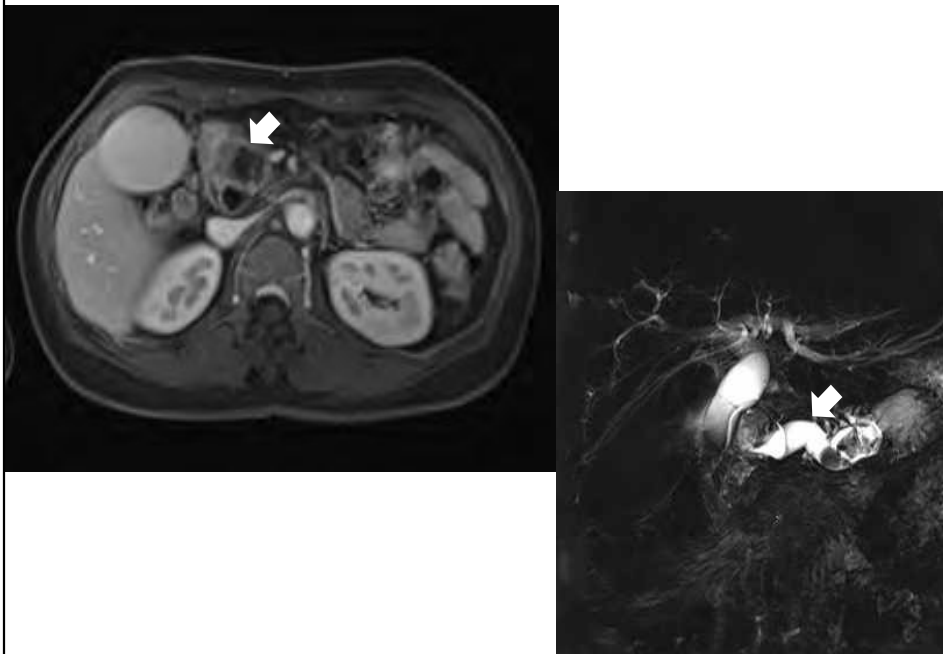
**Abdomen-pelvis CT (2018.10.20)**

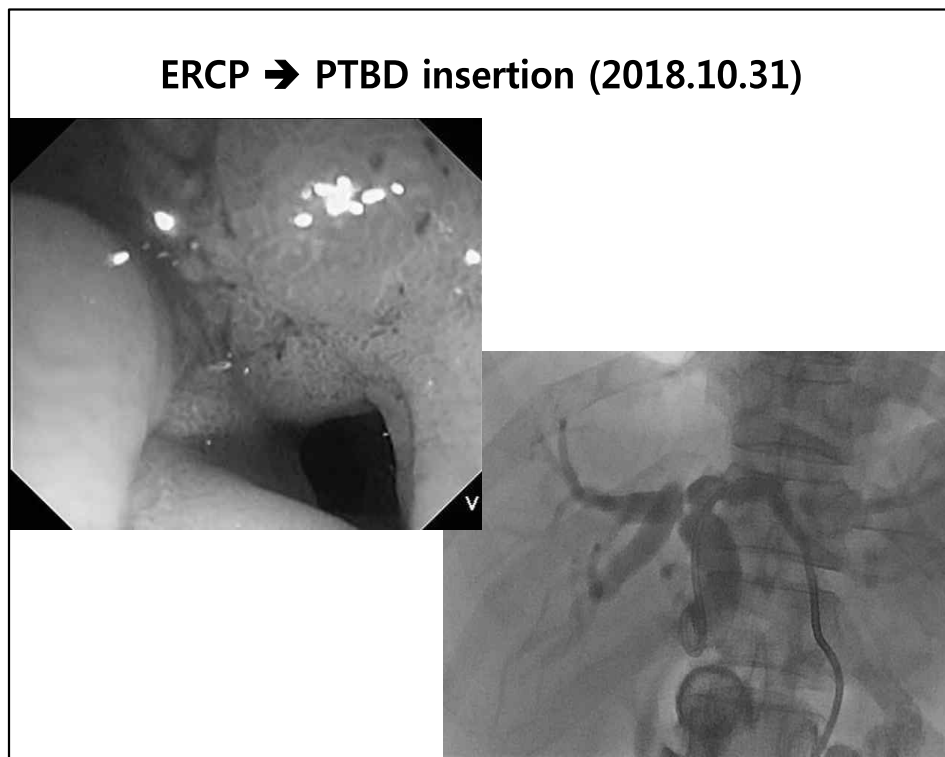
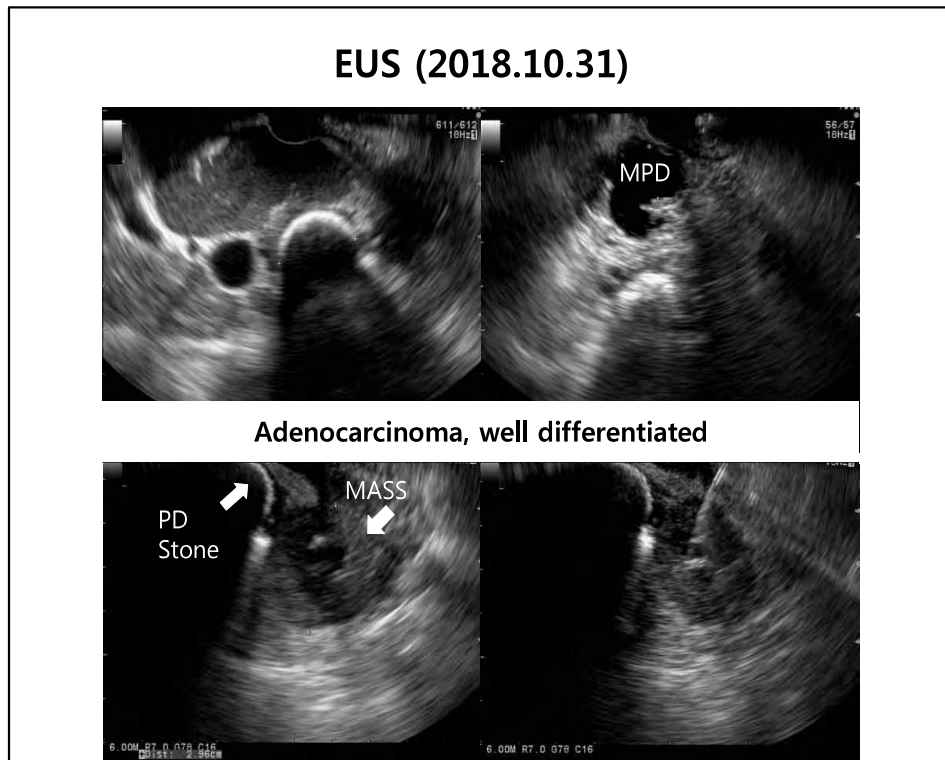


**Abdomen-pelvis CT, Coronal view (2018.10.20)**



**MRI Pancreaticobiliary+MRCP (2018.10.24)**





## Progress

- **Detailed history taking for pancreatitis/pancreatic cancer**

Never-smoker, never-drinker (religious)

NO DM history

NO obesity (BMI 20)

NO previous episode of acute/recurrent pancreatitis

NO chronic epigastric or abdominal pain

NO chronic indigestion or steatorrhea

NO family history of pancreatitis or pancreatic cancer

NO family history of other malignancy



## Progress

- **Initial diagnosis**

1) Pancreatic cancer, head, resectable, cT3N0, Stage IIA

2) Malignant biliary obstruction d/t CBD invasion of pancreatic cancer  
s/p PTBD insertion at Lt. IHD

3) Idiopathic chronic pancreatitis with multiple pancreatic duct stones

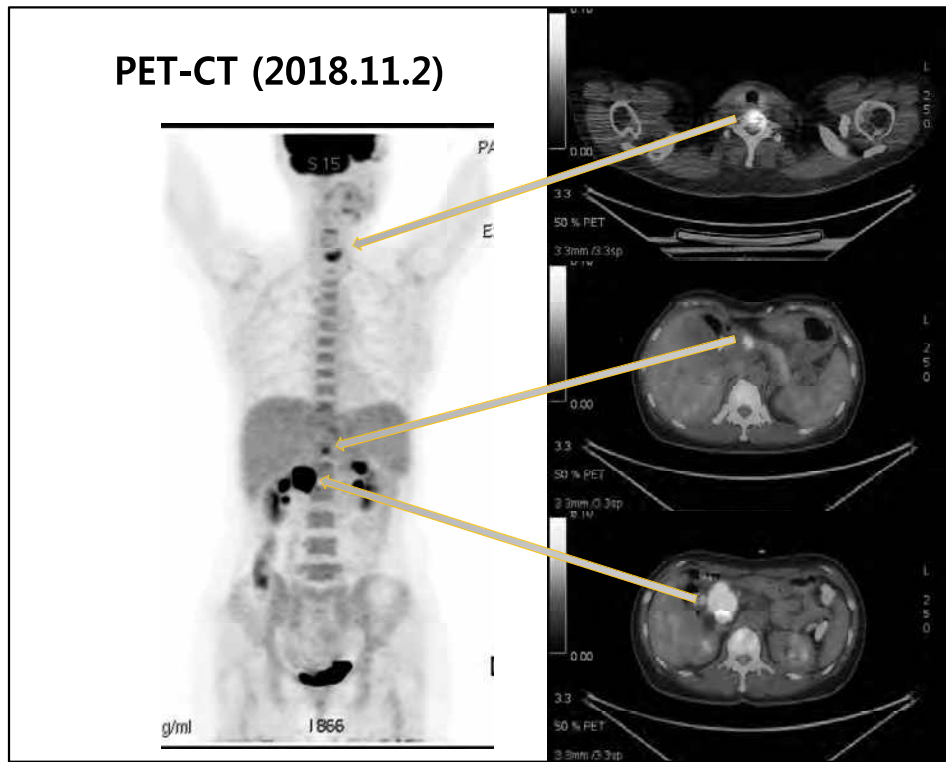
- **Plan**

Consider surgical resection

PET-CT

Gene mutation analysis for chronic pancreatitis





## Progress

- **Gene mutation analysis report**

- 검사방법: Direct sequencing
- 표적유전자: 1. PRSS1 gene (7q34)  
2. SPINK1 gene (5q32)
- 분석위치: 1. PRSS1 gene : Exon 2 & 3 & 5  
2. SPINK1 gene : Exon 4

< 결과 >

1. PRSS1 gene pathogenic variant (NM\_002769.4) :  
**Not detected**
2. SPINK1 gene pathogenic variant (NM\_003122.4) :  
**c.194+2T>C (heterozygote, rs148954387)**





## Progress

- **Final diagnosis**

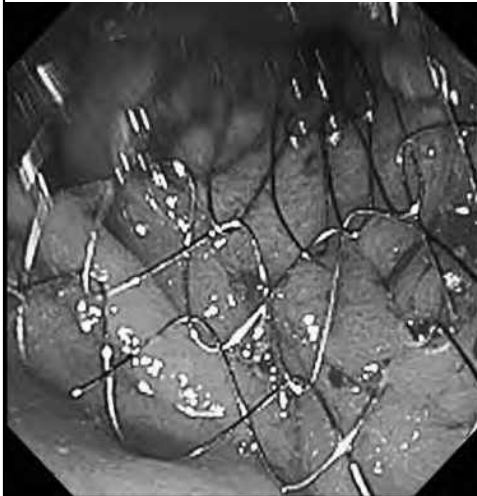
- 1) Pancreatic cancer, head, metastatic, cT3N1M1, Stage IV with bone metastasis at C7 vertebra
- 2) Malignant biliary obstruction d/t CBD invasion of pancreatic cancer s/p PTBD insertion at Lt. IHD
- 3) Idiopathic chronic pancreatitis with multiple pancreatic duct stones with heterozygous SPINK1 mutation (194+2T>C)

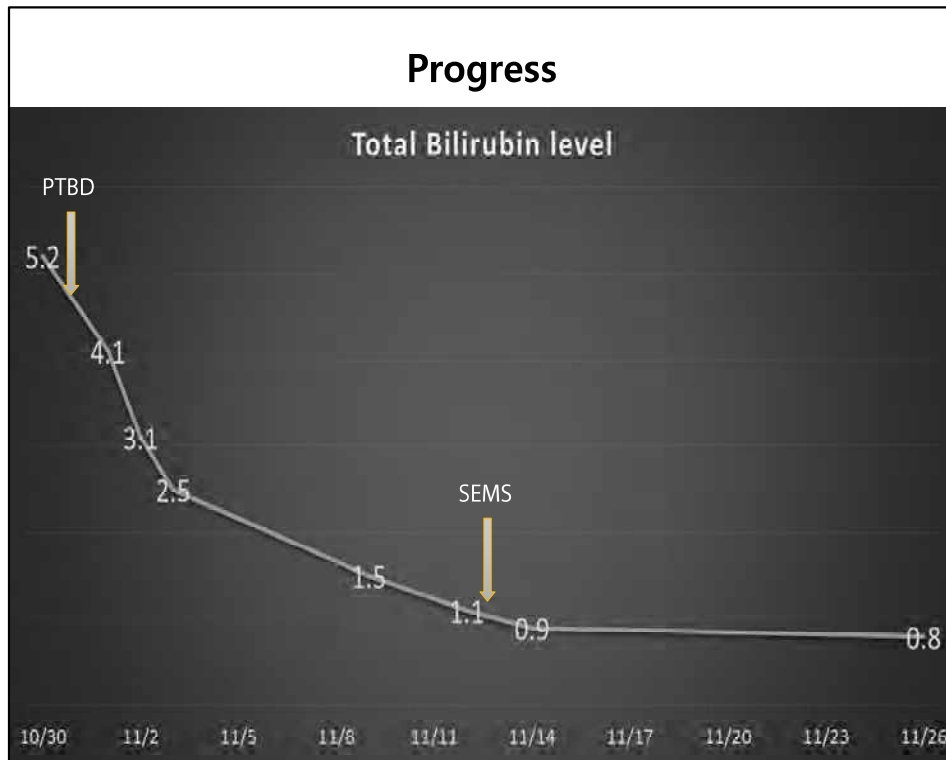
- **Plan**

- Biliary metal stent insertion
- Palliative chemotherapy
- Gene mutation analysis for family members




## ERCP (2018.11.12)





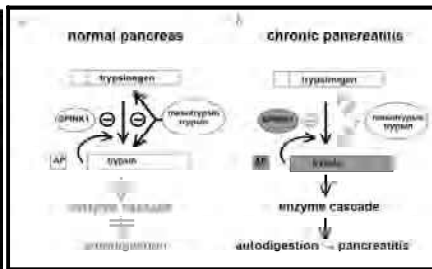
### Progress

- **Palliative chemotherapy**
  - First-line FOLFIRINOX #2 (~2018.11.26)
  - Well tolerable to chemotherapy (ECOG 0)
- **Plan**
  - Continue FOLFIRINOX and response evaluation
  - Gene mutation analysis for family members



## SPINK1 gene mutation (AR)

- Common in healthy individuals (~2%) *Witt et al. nature genetics • volume 25 • 2000*
- <1% of carriers develop pancreatitis
- Increase the risk for chronic pancreatitis (CP) (~12-fold)
- Among idiopathic CP series, 16~23% had SPINK1 mutation
- p.N34S (m/c), **c.194+2T>C (aka. IVS3+2T>C)** (common in east Asia)
- Loss of function: intrapancreatic trypsin activity inhibition
  - **Lowering the threshold for developing pancreatitis** from other genetic or environmental factors
- Heterozygote SPINK1 mutation: can be considered as benign



## Germline Variants and Risk for Pancreatic Cancer A Systematic Review and Emerging Concepts

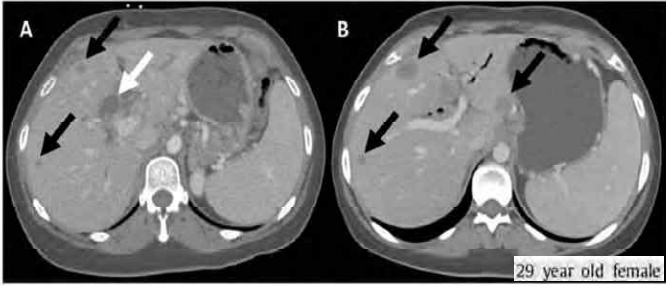
*Wei Zhan,\*† Celeste A. Shelton, MS,†‡ Phil J. Greer, MS,†  
Randall E. Brand, MD,†‡ and David C. Whitcomb, MD, PhD†‡*

*Pancreas • Volume 47, Number 8, September 2018*

TABLE 4. Pathogenic Germline Variants (Bin 1)


Gene	cDNA Nucleotide Change	rsID	Population	Reference
<i>ATM</i>	c.5932G>T	rs587779852	US, Europe	24,25
<i>ATM</i>	c.8266A>T	rs371638537	US	26
<i>BRCA1</i>	c.5263_5264insC	rs80357906	(Ashkenazi Jewish) US, Canada, Poland, Israel	27–34
<i>BRCA1</i>	c.68_69delAG*	rs386833395	(Ashkenazi Jewish) US	35,36
<i>BRCA1</i>	c.66_67delAG*	rs796856605	(Ashkenazi Jewish) US, Israel, Canada	28–30,33,34,37,38
<i>BRCA2</i>	c.5946delT	rs80359550	(Ashkenazi Jewish) US, Israel, Canada	28,29,31,33–35,37–43
<i>BRCA2</i>	c.6591_6592delTTG	rs80359605	Germany, UK	44–46
<i>BRCA2</i>	c.9227G>A	rs80359187	Germany, UK	44,46
<i>BRCA2</i>	c.10095delCinsGAATTATACT	rs276174803	Germany, UK	44,46
<i>CDKN2A</i>	c.457G>T	rs45476696	US	35,47–49
<i>CDKN2A</i>	c.377 T>A	rs104894098	US	35,47,48,50,51
<i>CDKN2A</i>	c.301G>T	rs104894094	US, Italy	35,47,48,50,52
<i>CDKN2A</i>	c.225_243del19	rs730881674	Netherlands, US	35,48,50,53–55
<i>CDKN2A</i>	c.148C>T	rs864622636	Germany, US	35,56
<i>CDKN2A</i>	c.-34G>T	rs1800586	US	35,48–50
<i>CHEK2</i>	c.1100delC	rs555607708	Germany, Poland, US	24,32,57
<i>PALB2</i>	c.509_510delGA <sup>†</sup>	rs515726124	Czech Republic, Poland, US	32,47,58
<i>PALB2</i>	c.508_509delAG <sup>†</sup>	-	Europe	59
<i>PALB2</i>	c.172_175delTTGT	rs180177143	Poland, US	27,32,60
<i>SPINK1</i>	c.194+2 T>C <sup>‡</sup>	rs148954387	Japan, Germany	61,62

Metastatic pancreatic adenocarcinoma associated with chronic calcific pancreatitis and a heterozygous *SPINK1* N34S mutation\*  
R.A. Moran et al. / *Pancreatology* 16 (2016) 869–872



29 year old female

Metastatic Pancreatic Adenocarcinoma in a Patient With Chronic Calcific Pancreatitis and a Heterozygous *SPINK1* c.194+2T>C Mutation  
*Pancreas* • Volume 47, Number 4, April 2018



41-year-old Chinese man

## Conclusion

- We experienced a case of
  - **Young** female who **do not** have any clinical risk factor of pancreatic cancer or chronic pancreatitis
  - Simultaneously diagnosed **metastatic pancreatic cancer** and **chronic pancreatitis**
  - Detected **heterozygous *SPINK1* gene mutation**

