Genetics of Chronic Pancreatitis: Lessons Learned

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Genetics is the basis of all diseases except perhaps trauma but in that case also I have my doubts!
What is Chronic Pancreatitis & How does it develop?
CP: Etiopathogenesis

Environmental factors

Mutations (SPINK1, CFTR, PRSS1, Cathepsin B, CTRC)
CP in India: Genetic mutations

Tropical Calcific Pancreatitis: Strong Association With $SPINK1$ Trypsin Inhibitor Mutations

EESH BHATIA,* GOURDAS CHoudhuri,† SADIQ S. SIKORA,§ OLFERT LANDT,¶ ANDREAS KAGE,‖ MICHAEL BECKER,# and HEIKO WITT#

Gastroenterology 2002

Mutations in the pancreatic secretory trypsin inhibitor gene ($PSTI/SPINK1$) rather than the cationic trypsinogen gene ($PRSS1$) are significantly associated with tropical calcific pancreatitis.

G R Chandak, M M Idris, D N Reddy, S Bhaskar, P V J Sriram, L Singh
CP in India: Genetic mutations

Idiopathic chronic pancreatitis in India: phenotypic characterisation and strong genetic susceptibility due to SPINK1 and CFTR gene mutations

Shallu Midha,¹ Rajni Khajuria,¹ Shivaram Shastri,¹ Madhulika Kabra,² Pramod Kumar Garg¹
Gut 2010;59:800-807
CP: Genetic mutations

- 2 genes implicated in our patients:
  - SPINK 1: 42%
  - CFTR: 9%

- PRSS1 mutation not seen
Indian Pancreatitis Consortium (INDIPAN)
CP: Genetic mutations

- Replication study in Indian patients with CP:
  - 2 variants in *CLDN2* gene (rs4409525 - OR 1.71, \( P = 1.38 \times 10^{-09} \); rs12008279 - OR 1.56, \( P = 1.53 \times 10^{-04} \))
  - 2 variants in *MORC4* gene (rs12688220 - OR 1.72, \( P = 9.20 \times 10^{-09} \); rs6622126 - OR 1.75, \( P = 4.04 \times 10^{-05} \))

*(Giri et al. PLoS One 2016)*
GWAS in CP: Indian Patients

- 4354 individuals studied
- Discovery cohort: 1643 individuals
  (498 cases and 1145 control)
- Validation: 2711 individuals
  (902 cases and 1809 control)
GWAS in CP: Indian Patients

6 novel variants identified
CP: Is it only Genetic?

- Genetic mutations: Not the whole story
CP and Genetics

- \textit{SPINK1} (N34S): Unanswered Questions
- Prevalence of CP: 100/100,000
  - CP: 100 (40 - alcohol, 60 - idiopathic)
  - 60 idiopathic: 20 \textit{SPINK1} mutation +
- \textit{SPINK1} mutation in general population: 2%
  - \textit{SPINK1} in general population: 2000/100,000
- Odds of developing CP in \textit{SPINK1} mutation: 20/2000 i.e. 1%; 99% don’t develop CP
CP and Genetics

• Many unanswered questions about genetics
CP: Etiopathogenesis

Environmental factors ✓

Mutations (SPINK1, CFTR, PRSS1, Cathepsin B, CTRC)
CP in India

- Changing phenotype and
- Implications for pathophysiology
Chronic Pancreatitis in India

- Large series from Kerala: >1000 patients
  - Young patients
  - Malnourished
  - 90% Diabetes
  - Large pancreatic stones
“Tropical Pancreatitis”

The name still carries on

Geevarghese 1968, 1971
• Is it true any more?
• A total of 411 patients

• Causes:
  – alcohol - 157 (38.2%),
  – idiopathic - 242 (58.9%),
  – hereditary - 10 (2.4%)
  – Others - 2 patients

Chandigarh: 38.1% alcohol related**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n=242)</th>
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<tbody>
<tr>
<td>Age at onset (mean ±SD) (yrs)</td>
<td>24.7±11.7</td>
</tr>
<tr>
<td>Residence - Northern India</td>
<td>61.2%</td>
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<tr>
<td>Kerala* (n=220)</td>
<td>30.6 yrs.</td>
</tr>
<tr>
<td>Chandigarh** (n=64)</td>
<td>33 years</td>
</tr>
</tbody>
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*Balakrishnan. *Ind J Gastro* 2006*

**Bhasin et al. *Clin Gastro Hepatol* 2009**
CP in India

- Etiology
- Young age of onset
- Malnutrition
- Cassava
- Severe disease
- Large calculi
- Diabetes
- Die early
AIIMS study: Nutrition

- 224 patients with CP*:
- 75% were either normally nourished (n=131, 58.5%) or overweight (n=37, 16.5%)
- However, 35.7% of patients lost weight after disease

Malnutrition effect of CP and not a cause

*(Midha et al, J Gastro Hepatol 2006)*
CP in India

- Etiology
- Young age of onset
- Malnutrition
- **Cassava**
- Severe disease
- Large calculi
- Diabetes
- Die early
CP: Etiopathogenesis

• AIIMS study: cassava none
• Kerala: No association*
• Animal study: rat model fed cassava but no CP**

CP in India

- Etiology
- Young age of onset
- Malnutrition
- Cassava
- Severe disease, Large calculi
- Diabetes
- Die early
Disease severity

- AllIMS study:
- Both early and advanced CP
- Chandigarh: 53% non-calcific CP
CP in India

– Etiology
– Young age of onset
– Malnutrition
– Cassava, Severe disease
– Large calculi
– Diabetes
– Die early
AIIMS study: Diabetes

- Diabetes: 86 (35.53%)
  - Mean age: 30.45±9.80 years
- Kochi: 59%
- Chandigarh: 23%
- Rx for diabetes:
  - Insulin ~50%
CP: Survival and life expectancy

• The probability of surviving for 35 years (age 60 years) after onset of CP was 83%
CP in India: Changing profile

- Data from Kerala:
  - Mean age at onset: 1984 - 20.7, 2004 - 30.6
  - BMI: 1984 - 15.9, 2004 - 20.4
  - SE status: 1984 - Poor, 2004 - Middle
  - Diabetes (%): 1984 - 77, 2004 - 59

(Balakrishnan. Ind J Gastro 2006)
CP in India

- IPANS: multicentre study*
- 1086 patients with CP
  - 3.8% satisfied criteria for tropical pancreatitis

* (Balakrishnan et al. J Pancreas 2008)
Perceptions vs. Reality

- Tropical Pancreatitis
  - Special CP in India
  - Young age of onset
  - Cassava
  - Severe disease
  - Malnutrition
  - Diabetes 90%
  - Early death

- CP:
  - Alcoholic CP: 1/3rd
  - Genetic strong risk
  - No cassava
  - Early, advanced
  - Malnutrition X
  - Diabetes: 35%
  - Good prognosis
CP in India: Changing profile

- Why has there been a significant change in age of onset, nutritional status, diabetes, prognosis?

- Rapid economic development
Kerala State GDP and per capita income

40 fold increase

State GDP: $320 million (≈$13.75 billion)
Per capita: $15

1970s: $320 million
2000s: $525

Kerala State GDP and per capita income
Kerala State GDP and per capita income

Flip side of development
Flip side of development

• With increase in socio-economic status:

  • Alcohol consumption
    – National average/capita alcohol - 4 litres
    – Kerala stands first at 8.3 litres

• Urbanization increased
Flip side of development

Kerala State GDP and per capita income

Garg, Narayan. GEGH 2017
CP: Summary

- Environmental factors: cause/modify disease phenotype/behavior
- A complex disease with strong Gene-Environment interaction
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