



# Genetics of Chronic Pancreatitis: Lessons Learned

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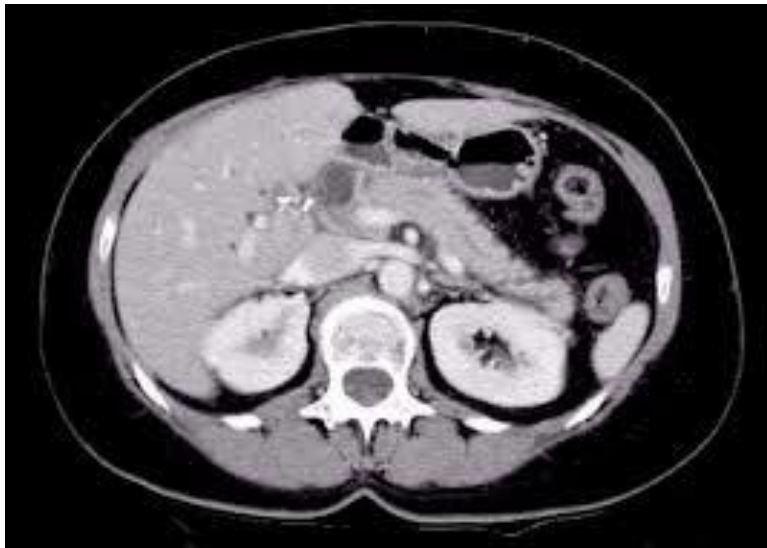
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All India Institute of Medical Sciences,  
New Delhi, India

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?

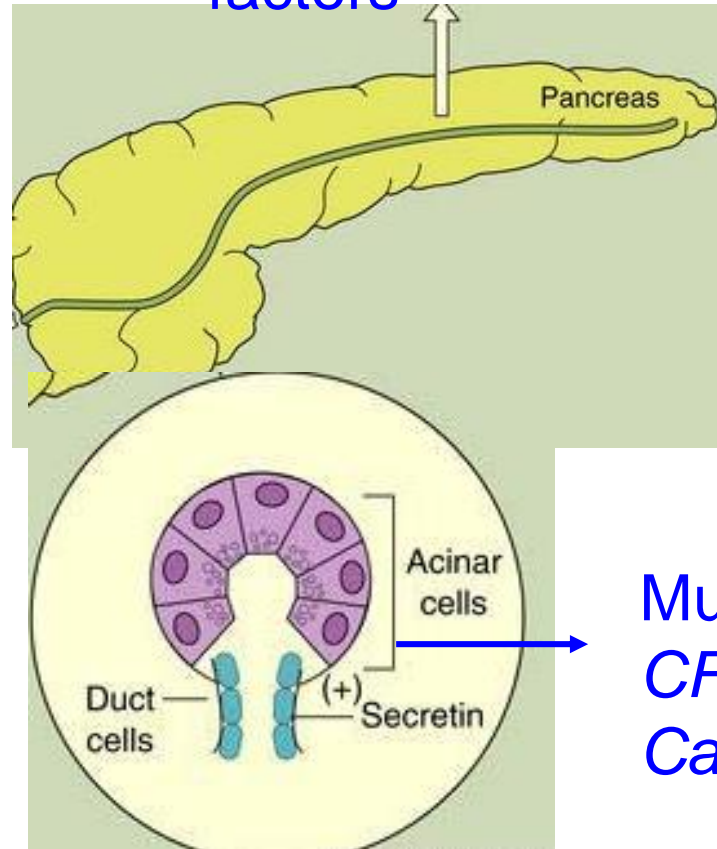
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# CP: Etiopathogenesis

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Environmental  
factors



Mutations (*SPINK1*,  
*CFTR*, *PRSS1*,  
*Cathepsin B*, *CTRC*)

# CP in India: Genetic mutations

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## 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

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# CP in India: Genetic mutations

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

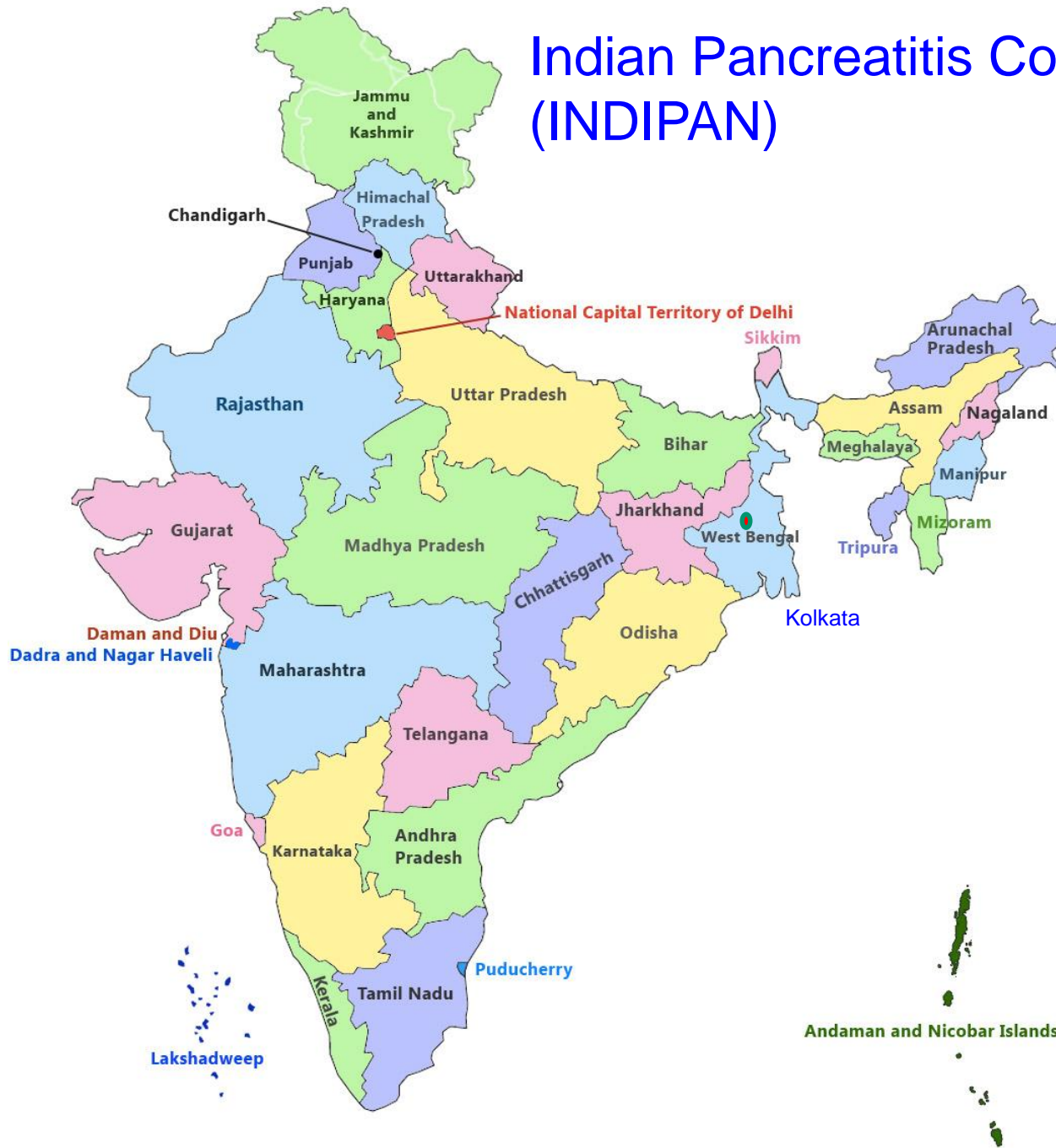
Shallu Midha,<sup>1</sup> Rajni Khajuria,<sup>1</sup> Shivaram Shastri,<sup>1</sup> Madhulika Kabra,<sup>2</sup>  
Pramod Kumar Garg<sup>1</sup>  
*Gut* 2010;59:800-807

# CP: Genetic mutations

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- 2 genes implicated in our patients:
  - *SPINK 1*: 42%
  - *CFTR*: 9%
- *PRSS1* mutation not seen

# Indian Pancreatitis Consortium (INDIPAN)





# CP: Genetic mutations

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- 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,  $P= 4.04 \times 10^{-05}$ )

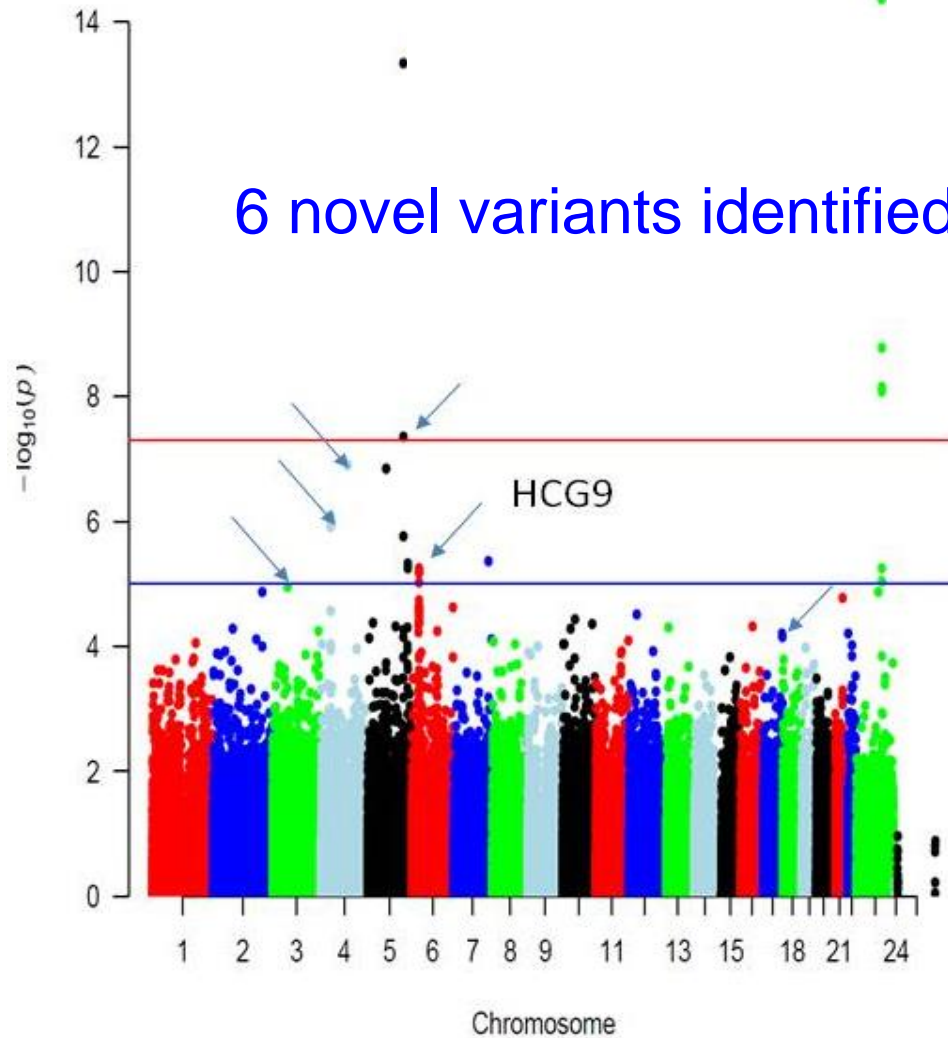
(Giri et al. PLoS One 2016)

# GWAS in CP: Indian Patients

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- 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



# CP: Is it only Genetic?

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- Genetic mutations: Not the whole story

# CP and Genetics

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

# CP and Genetics

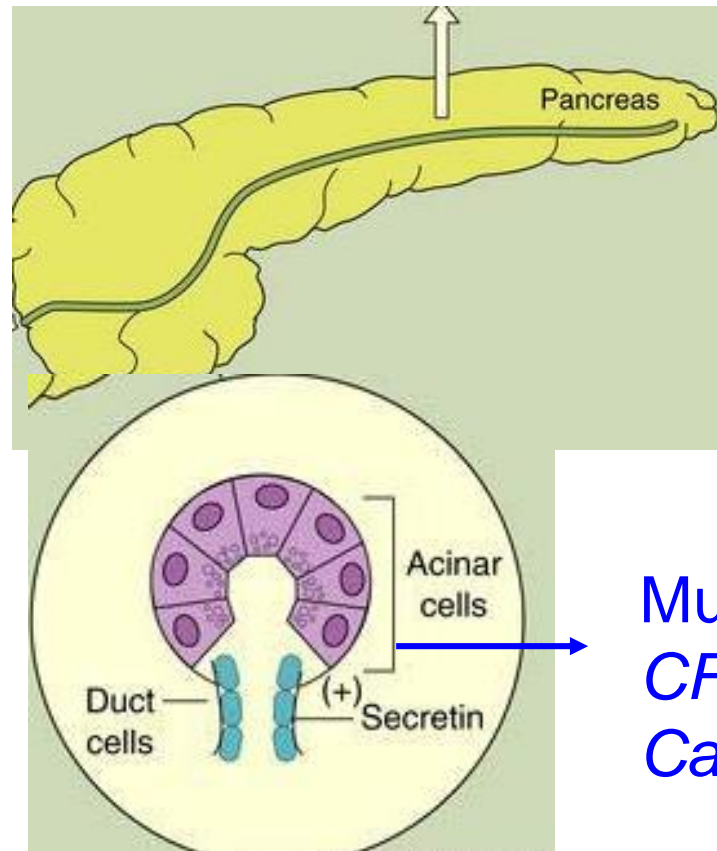
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- Many unanswered questions about genetics

# CP: Etiopathogenesis

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Environmental factors ✓



Mutations (*SPINK1*,  
*CFTR*, *PRSS1*,  
*Cathepsin B*, *CTRC*)

# CP in India

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- Changing phenotype and
- Implications for pathophysiology





# Chronic Pancreatitis in India

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



Died early

# “Tropical Pancreatitis”

The name still carries on

*Geevarghese 1968, 1971*

- Is it true any more?

# AIIMS Study

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- 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\*\*

\*(*Gut* 2010) \*\**Bhasin et al Clin Gastro Hepatol* 2009)

<b>Variable</b>	<b>Patients (n=242)</b>
Age at onset (mean $\pm$ SD) (yrs)	24.7 $\pm$ 11.7
Residence - Northern India	61.2%

Kerala\* (n=220)

30.6 yrs.

Chandigarh\*\* (n=64)

33 years

*\*(Balakrishnan. Ind J Gastro 2006)*

*\*\* (Bhasin et al. Clin Gastro Hepatol 2009)*

# CP in India

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



# AIIMS study: Nutrition

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- 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

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

# CP: Etiopathogenesis

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

\**(Narendranathan et al. J Gastroenterol Hepatol 1994; 9:282-5)*

\*\* *(Mathangi et al. Int J Pancreatol. 2000;27:203-8)*

# CP in India

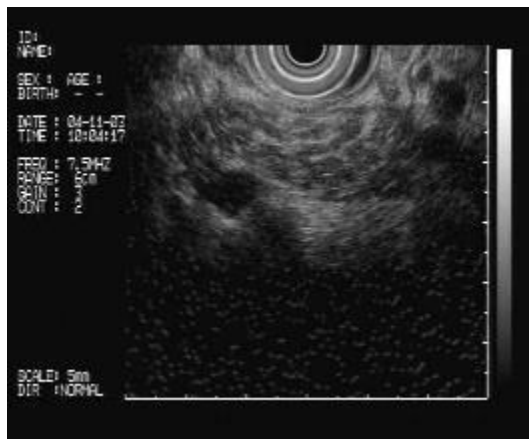
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- Etiology
- Young age of onset
- Malnutrition
- Cassava
- **Severe disease, Large calculi**
- Diabetes
- Die early

# Disease severity

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- AIIMS study:
- Both early and advanced CP
- Chandigarh: 53% non-calcific CP



# CP in India

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

# AIIMS study: Diabetes

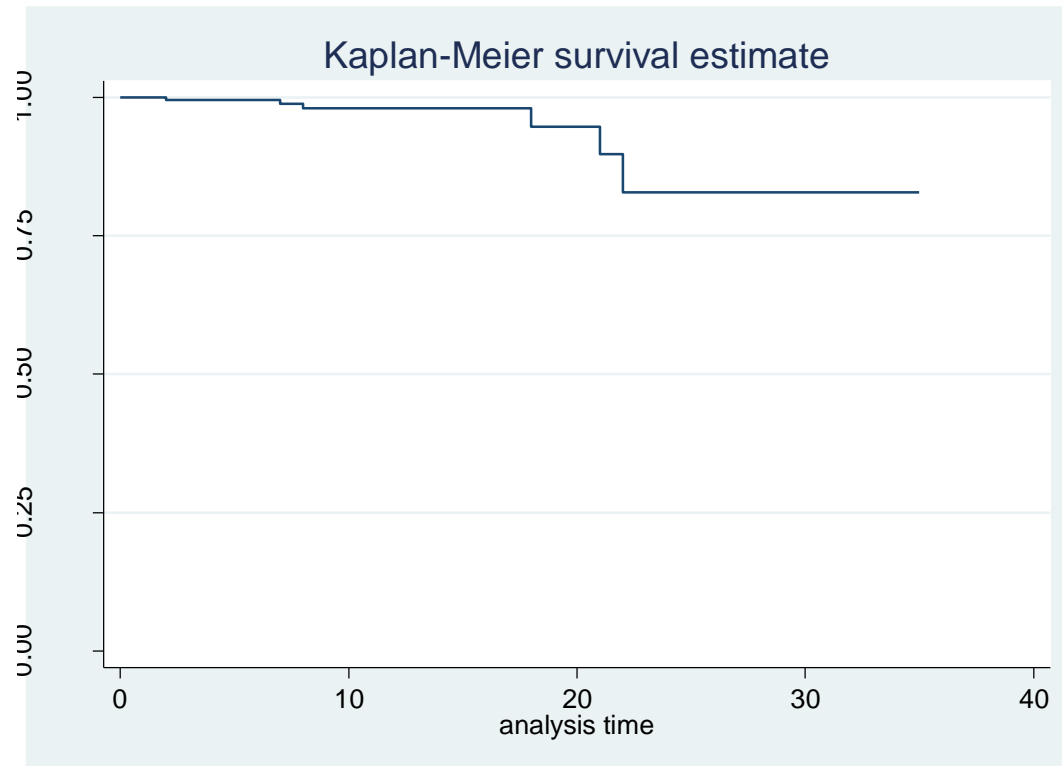
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- Diabetes: 86 (35.53%)
  - Mean age:  $30.45 \pm 9.80$  years
- Kochi: 59%
- Chandigarh: 23%
- Rx for diabetes:
  - Insulin ~50%

# CP: Survival and life expectancy

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- The probability of surviving for 35 years (age 60 years) after onset of CP was 83%





# CP in India: Changing profile

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- Data from Kerala:

	1984	2004
• Mean age at onset	20.7	30.6
• BMI	15.9	20.4
• SE status	Poor	Middle
• Diabetes (%)	77	59

*(Balakrishnan. Ind J Gastro 2006)*

# CP in India

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

\* (*Balakrishnan et al. J Pancreas 2008*)

# Perceptions vs. Reality

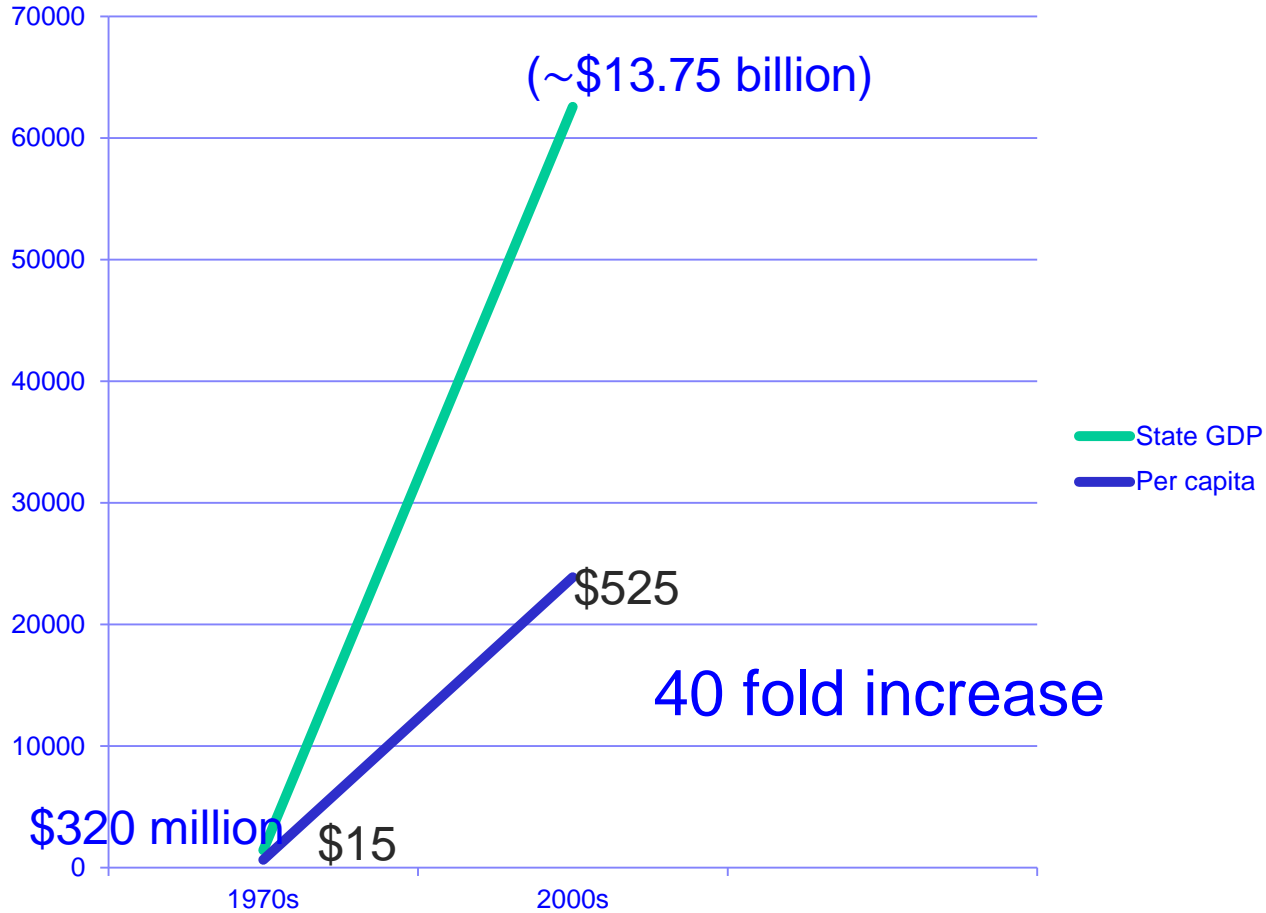
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- Tropical Pancreatitis
  - Special CP in India
  - Young age of onset
  - Cassava
  - Severe disease
  - Malnutrition
  - Diabetes 90%
  - Early death
- CP:
  - Alcoholic CP: 1/3<sup>rd</sup>
  - Genetic strong risk
  - No cassava
  - Early, advanced
  - Malnutrition X
  - Diabetes: 35%
  - Good prognosis

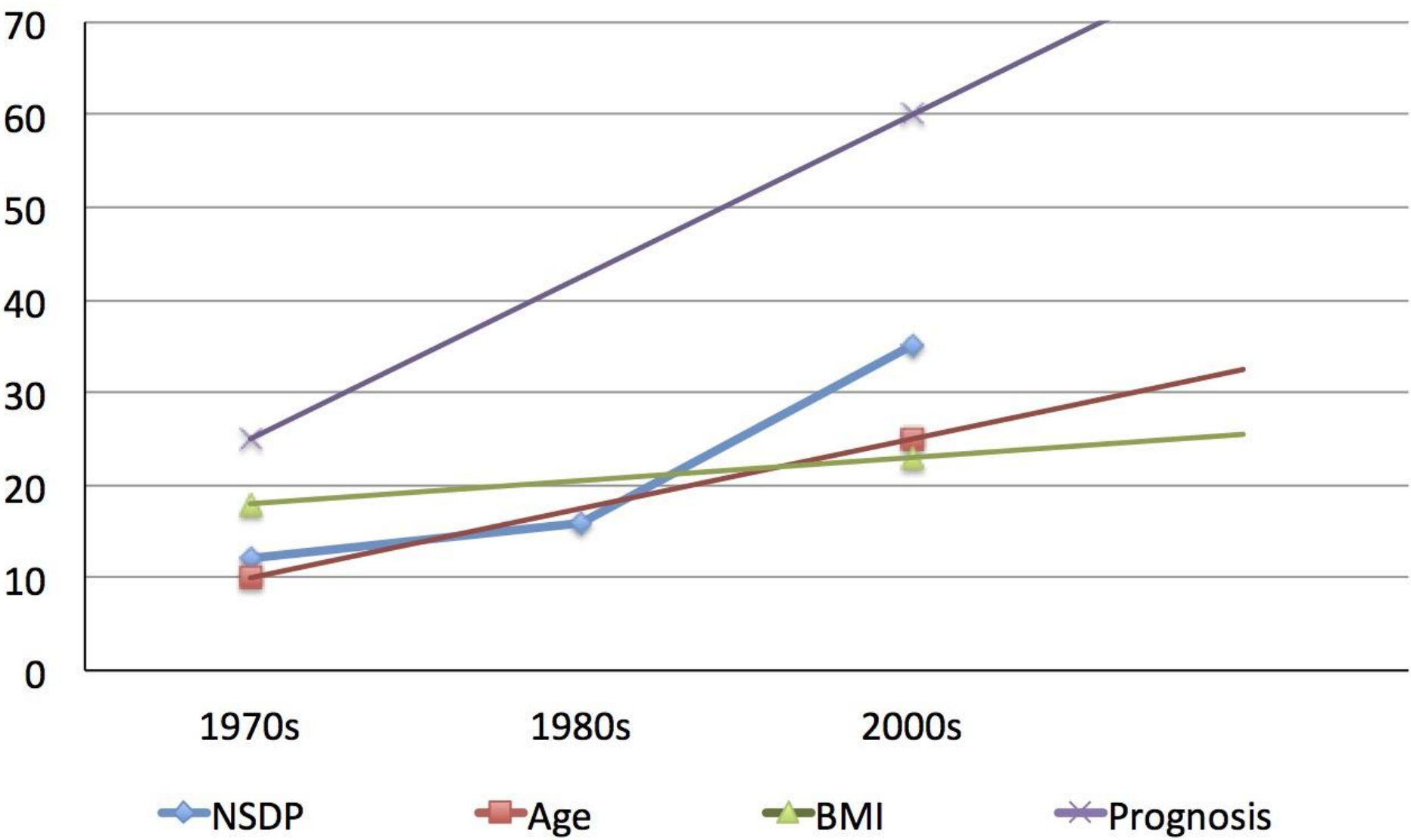
# CP in India: Changing profile

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- 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





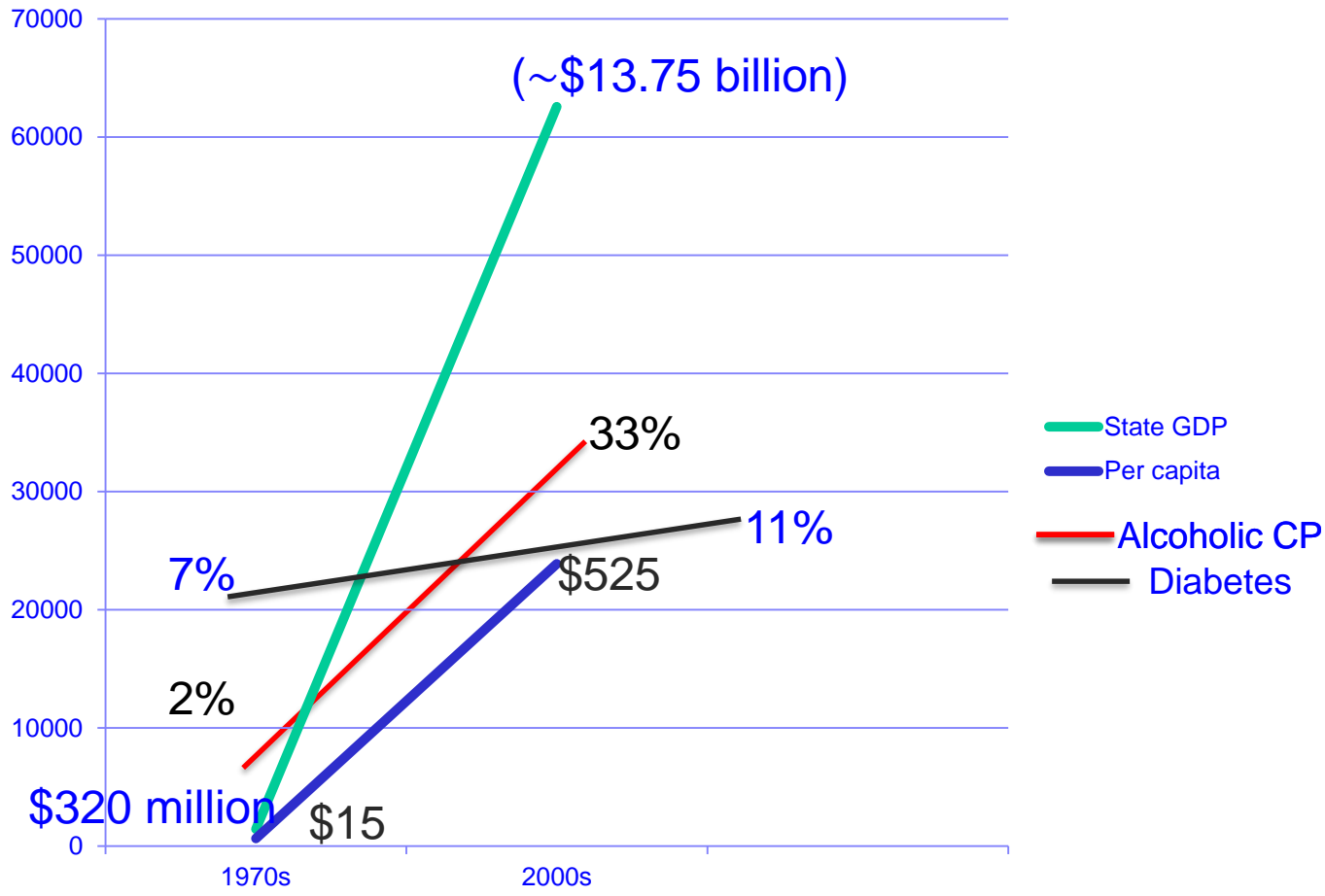
# Flip side of development

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- 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

# CP: Genes & Environment

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Genetics



CP



Environmental factors

Environmental factors



CP



Genetic risk factors

# CP: Summary

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

# Acknowledgement

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## AIIMS:

- Payal Bhardwaj
- Shallu Midha
- Madhulika Kabra
- Tony Jacob George
- Peush Sahni
- Kajal Jain
- Samagra Agrawal
- John George

## Collaborators:

- Dwaipayan Bharadwaj, IGIB
- Lalit Garg, NII
- Kausik Chakravarty, IGIB
- Aparna Dixit, JNU
- Surindra Rana, PGI, Chandigarh
- Kshaunish Das, IGIMS, Kolkata
- Samir Mohindra, SGPGI, Lucknow

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