Understanding the origins of Type 2 Diabetes in India

Professor John Chambers
Cardiovascular Epidemiology
Imperial College London
1941 - Outbreak of neonates born with cataract
1941 - Dr McAllister Gregg (Ophthalmologist)
In 68 / 78 cases mother had Rubella in pregnancy
First recognition of Congenital Rubella Syndrome
Underpins mass immunisation vs Rubella.

When looking for mechanisms underlying a disease, try studying people with unexplained high disease risk
My clinical problem ...

- South Asians ~30% of local population
- Compared to Europeans, increased
  - MI admission rates x2
  - CVD mortality x1.7
  - T2D prevalence x3
Burden of T2D in India

• “One in four Indians has diabetes, one in four diabetics is an Indian”

• [Second] largest numbers with T2D for any country worldwide
  – 2007: 41M
  – 2025: 70M

• Accounted for ~908,000 deaths in 2007

• Huge local economic burden
  – 2005: 3.4 billion USD
  – 2025: 5.4 billion USD
Primary aim

Identify the environmental and genetic factors that contribute to cardiovascular disease, diabetes, obesity & chronic kidney disease in South Asians compared to Europeans.
LOLIPOP Study

- 2002 – 2008
- M+F, 35-75 years
- 17,606 South Asians
- 9,766 Europeans

Coronary Research Nurses

GP surgeries

5 patients / nurse / day
T2D prevalence: South Asians v European whites

OR for T2D in IA vs EW

<table>
<thead>
<tr>
<th>Age / gender</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age / gender</td>
<td>3.26 (2.93 to 3.62)</td>
<td>1.3x10^{-104}</td>
</tr>
<tr>
<td>+ BMI, WHR and physical inactivity</td>
<td>3.06 (2.73 to 3.42)</td>
<td>3.6x10^{-85}</td>
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</tbody>
</table>
Adiposity does not explain increased risk of T2D in South Asians vs Europeans

Body mass index

Waist-hip ratio
Discovery strategies: Molecular Epidemiology

Data validation
Data integration
Data use

DNA
RNA
protein
metabolites

Genomics
Transcriptomics
Proteomics
Metabolomics

Integrative/System Biology

Cell methodology bioinformatics
Heredity
Genomic hypotheses

Europeans

Shared variants

↑ Effect size

↑ Risk allele frequency

Indian Asians

Indian specific variants
Risk allele frequencies at known T2D genetic loci
Genomic hypothesis

- Europeans
- Indian Asians

- Shared variants
- $\uparrow$ Effect size
- $\uparrow$ Risk allele frequency

Indian specific variants
Discovery: Genome-wide association
Common genetic variation near \textit{MC4R} is associated with waist circumference and insulin resistance

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\~1cm increased waist circumference per allele copy
Genome-wide association study in individuals of South Asian ancestry identifies six new type 2 diabetes susceptibility loci

Jaspal S Koanova1,3,46, Danish Saleheena5,5,46, Xueling Sim6,46, Joban Sehmib1,2,46, Weihua Zhang7,46, Philippe Frossard4,46, Latonya E Bean8, Kee-Seng Chia6,9, Antigone S Dimas10,11, Neelam Hassanali12, Tazeen Jafar13,14, Jeremy BM Jowett15, Xinzong Li1, Venkatesan Radha16, Simon D Rees17,18, Fumihiro Takeuchi19, Robin Young5,6,8,20,21, Abdul Basit22, Manickam Chidambaram16, Debashish Das2, Elin Grundberg23, Åsa K Hedman11, Zafar I Hydrie22, Muhammed Islam13, Chiea-Chuen Khor6,21,24, Sudhir Kowlessur25, Malene M Kristensen15, Samuel Liju16, Wei-Yen Lim6, David R Matthews12, Jianjun Liu24, Andrew P Morris11, Alexandra C Nica10, Janani M Pindiyopathirage20, Inga Prokopenko11, Asif Rasheed4, Maria Samuel1, Nabi Shah1, A Samad Shera22, Kerrin S Small25,29, Chen Suo16, Ananda R Wickremasinghe26, Tien Yan Wong20,21,29, Mingyu Yang30, Fan Zhang30, DIAGRAM31, MuTHER32, Goncalo R Abecasis33, Anthony H Barnett17,18, Mark Caulfield34, Panos Deloukas14, Timothy M Frayling35, Philippe Froguel16, Norihiro Kato19, Prasad Katulanda12,37, M Ann Kelly17,38, Junbin Liang30, Viswanathan Mohan16,38, Dharambir K Sanghera8, James Scott1, Mark Siebold39, Paul Z Zimmet32, Paul Elliott7,80,66, Yik Ying Teo6,32,41,42,46, Mark I McCarthy11,12,43,46, John Danesh5,46, E Shyong Tai5,44,46 & John C. Chambers3,7,46.
Genomic hypothesis

Europeans

Indian Asians

Shared variants

↑ Effect size

↑ Risk allele frequency

Indian specific variants
GWA array design based on variation in Europeans, East Asians and Africans

HapMap samples
- 90 Europeans (Utah, USA)
- 90 East Asians (Beijing / Tokyo)
- 90 Yorubans (Nigeria, Africa)
DNA sequencing

• Representative sample of 316 Indian Asians

• Methods
  – x30 WGS
  – X4 WGS
  – X30 WES

• Describe 99% of SNPs with AF >0.5%
## Results

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
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<tbody>
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<td>SNPs</td>
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<td>Novel SNPs</td>
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<tr>
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<tr>
<td>Inframe / frameshift indels</td>
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<tr>
<td>Novel inframe / frameshift indels</td>
<td>3,349</td>
</tr>
</tbody>
</table>
Discovery strategy for 2016+

Whole genome sequencing

Identify South Asian specific variation

Imputation & custom arrays
EpiMigrant

Identification of epigenetic markers underlying increased risk of Type-2 diabetes in South Asians
Life course
Agouti mice

Pregnant mother fed diet supplemented with compounds rich in methyl donor groups

Pregnant mom fed regular mouse food

Offspring predominantly brown and in good health

Offspring mainly look like mother and in poorer health
Early life phenomena in T2D?

• Low-birth weight
  - Increased risk of future T2D
  - Risk may persist *across* generations.

• Relevance to India
  • Maternal nutritional status: rural Indian mothers are leaner (BMI 18) compared to Europeans.
  • South Asian neonates are up to 700g lighter, compared to Europeans.
DNA Methylation

'Structure DNA

Normal' DNA

Unmethylated CpG site

Methylated CpG site

Cancer DNA

exonA

exonB

x
Manhattan Plot

- TXNIP
- PROC
- ABCG1
- PHOSPHO1
- C7orf29
- SREBF1
- SOCS3
Effect sizes: risk of new onset Diabetes

Relative risk of T2D

- ABCG1
- TXNIP
- SREBF1
- PHOSPHO1
- SOCS3
- Q2
- Q3
- Q4

Effect sizes: risk of new onset Diabetes
Biological plausibility

- **TXNIP**: regulates glucose transport via GLUT1, central regulation of adiposity and energy expenditure.
- **ABCG1**: lipid metabolism and pancreatic beta-cell function. Null mice have beta cell failure.
- **SREBF1**: obesity, pancreatic beta-cell function, dyslipidaemia.
South Asians vs Europeans

The bar chart shows the difference in methylation (SDs) for various genes: TXNIP, PHOSPHO1, SOCS3, SREBF1, ABCG1, and MethScore. The p-values for these comparisons are as follows:

- TXNIP: P=0.16
- PHOSPHO1: P=0.04
- SOCS3: P=7.4x10^{-11}
- SREBF1: P=2.8x10^{-9}
- ABCG1: P=3.6x10^{-82}
- MethScore: P=5.2x10^{-34}
How can we reverse the epidemic of T2D?

Body mass index

Waist-hip ratio
Lifestyle modification to prevent T2D

• Intensive lifestyle modification can prevent T2D (physical activity, improved diet & weight loss)

• Limitations of current approaches
  i. Screening tools that are resource intensive (eg oral GTT) or unvalidated for prediction of incident T2D
  ii. Use intensive interventions or technologies that are not equitably available
  iii. Small scale studies limiting robustness of findings
  iv. Narrow range of geographic and Socio-economic settings.

-> New evidence based approaches are needed
iHealth-T2D Study

Ambition: Develop new approaches to T2D prevention that are effective, efficient, locally relevant and sustainable.

→ New screening strategies
→ New therapeutic strategies
→ Valid in a range of settings
Screening

**Waist**
- a free, low tech test

**HbA1c**
- a non fasting blood test

![Graph showing sensitivity of Waist circumference](image1)

![Graph showing incidence of HbA1c](image2)
Study Design

- 4 countries (India, Pakistan, Sri Lanka, UK)
- Screen >20,000 people for HbA1c / waist
- Recruit 3,600 at risk people
- Deliver Family-based lifestyle intervention
- Follow up annually for 3 years
- Launched 2015 → Complete 2019
Summary

• There is a global epidemic of diabetes, which is worst amongst South Asians
• Not explained by adiposity, or known genetic and dietary factors
• Epigenetic studies point to early life exposures, and may help identify high-risk individuals
• Our collaborative translational work includes new approaches to preventing diabetes in this high-risk population