PancreasFest: Basic Translational Research

Genetic Drivers of Epigenetic and Transcriptional Variation in Human Immune Cells

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Pittsburgh, US
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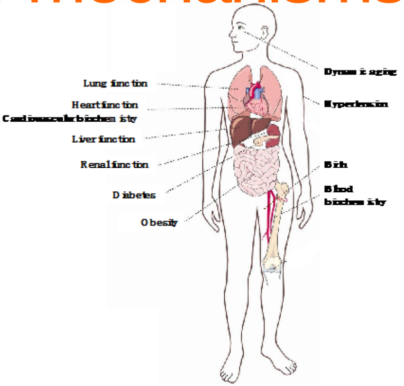
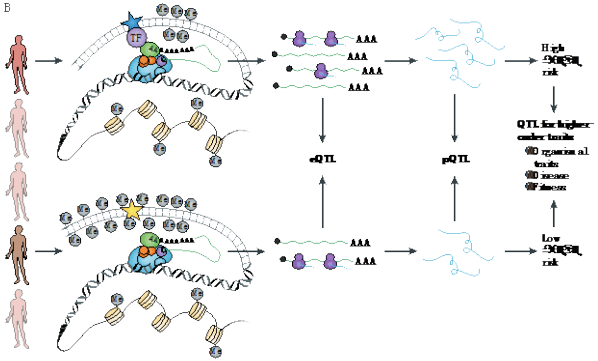
From complex disease to molecular mechanisms

Population-based variation resources
for genotype-phenotype studies

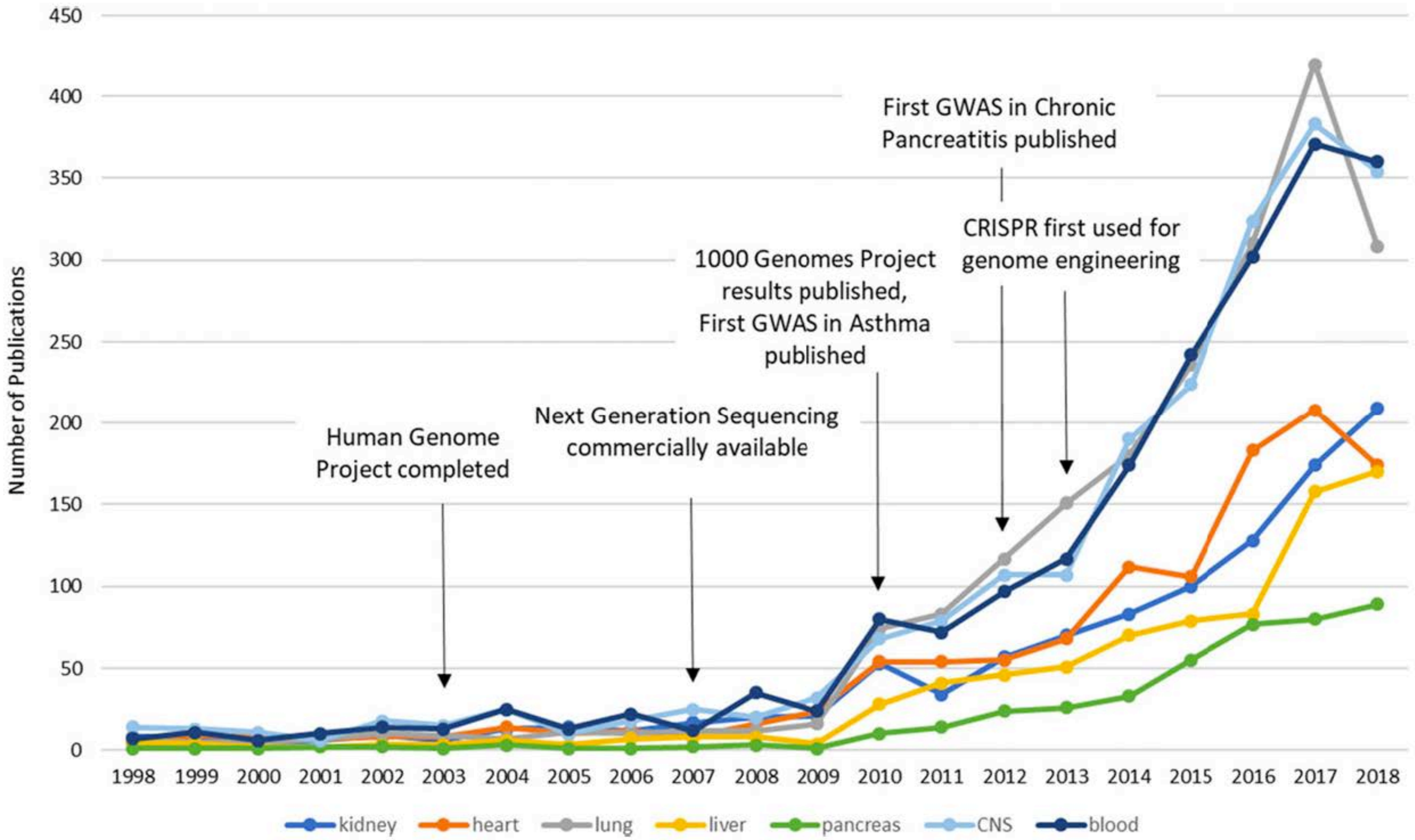


DNA
variant

Disease



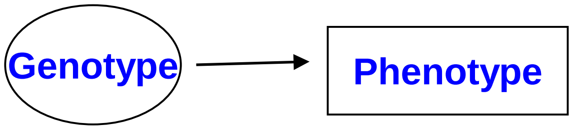
Pubmed indexed precision medicine by organs

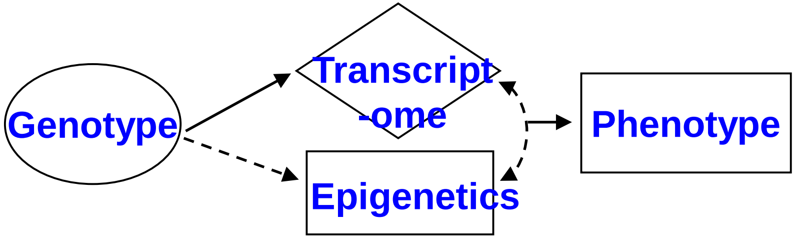


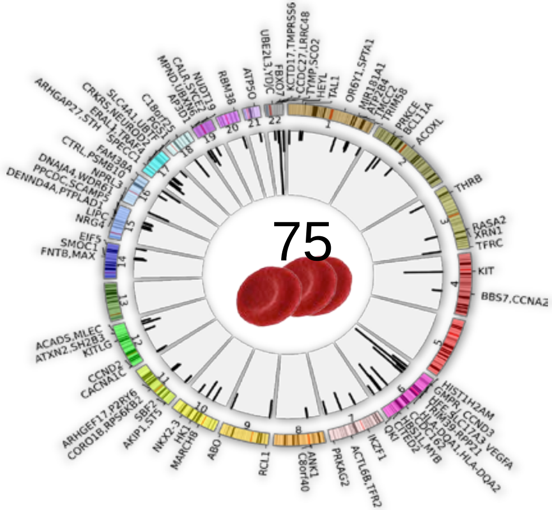
Mukherjee et al. Precision Clinical Medicine 2019

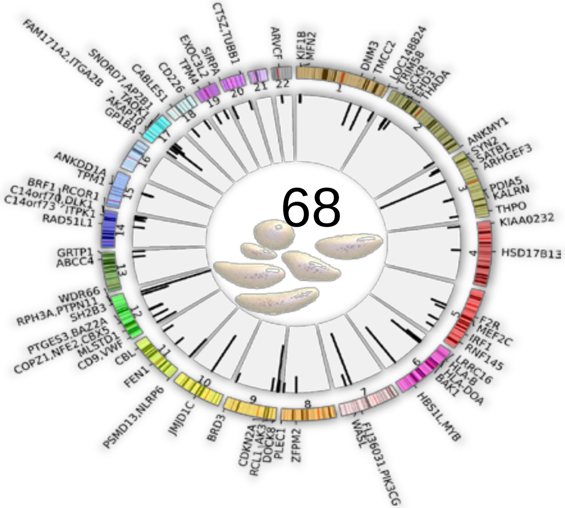
Genome wide association study

Typical GWAS









UK
10K

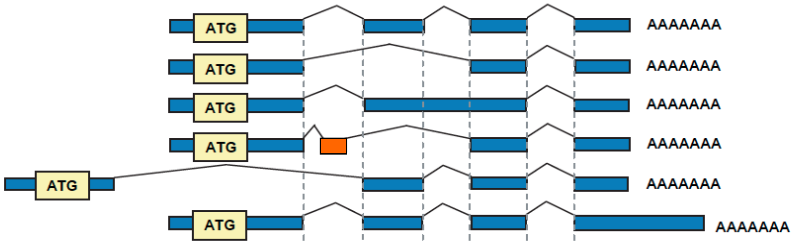
UK10K

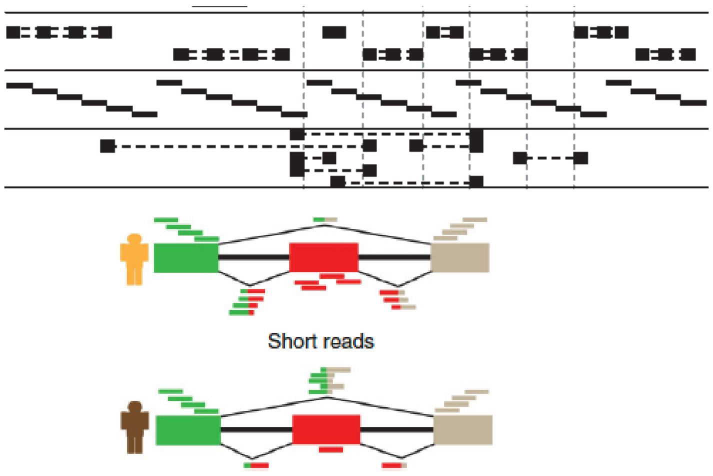
Rare Genetic Variants in Health and Disease

The UK10K Consortium, Nature 2015

Alste et al. Cell 2016

Molecular traits from RNA-seq

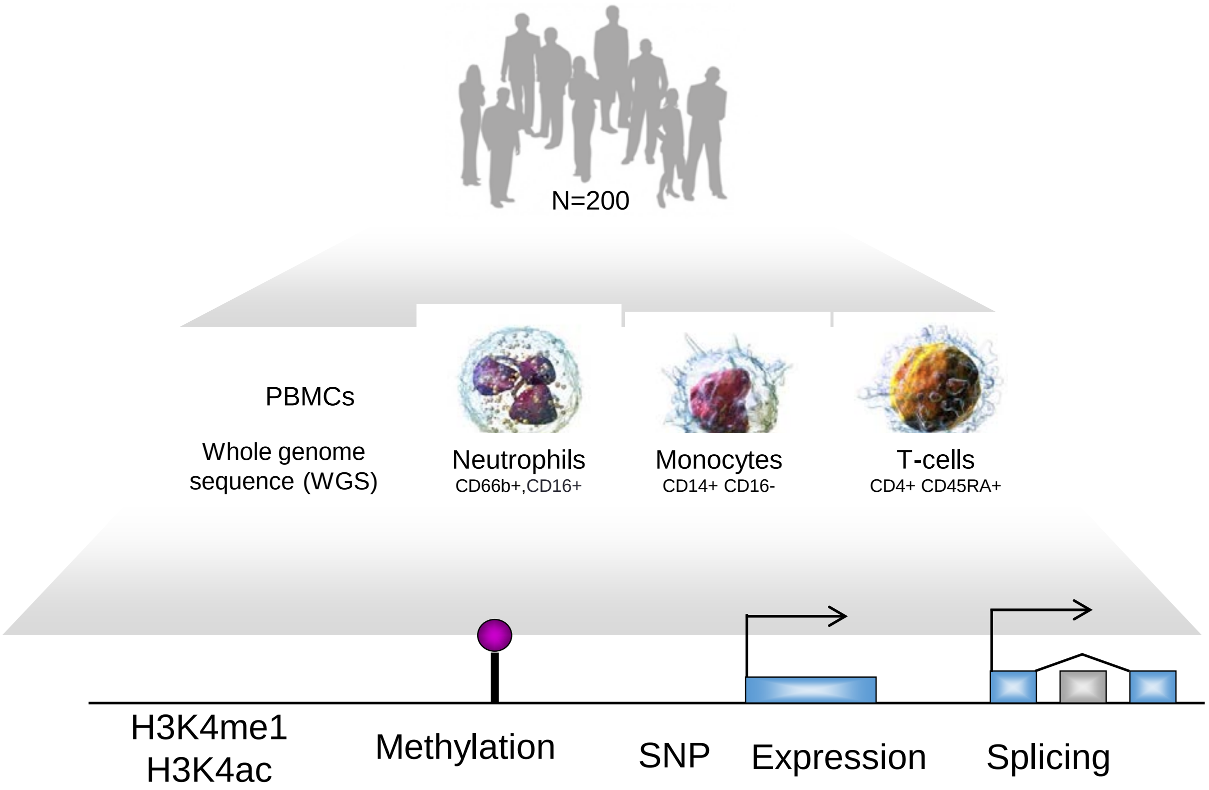




RNA expression
- Exon level — DEXSeq
- Gene level — DESeq2

RNA splicing
- Splicing junction (spliced reads) — Custom software
- Percent splice-in (PSI) — Custom software

Study design



N=200

PBMCs

Whole genome sequence (WGS)

Neutrophils
CD66b+,CD16+

Monocytes
CD14+ CD16-

T-cells
CD4+ CD45RA+

H3K4me1
H3K4ac

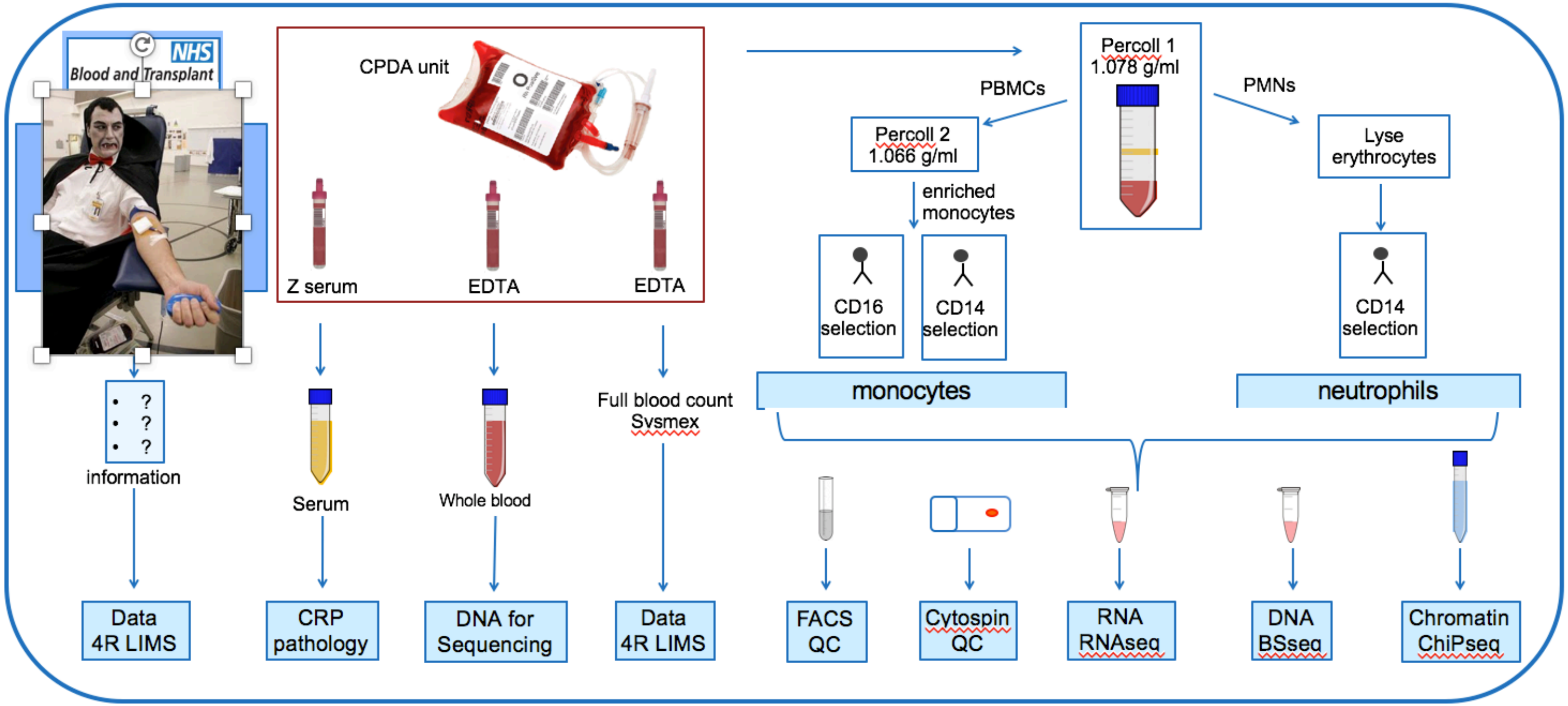
Methylation

SNP

Expression

Splicing

Chen et al. Cell 2016, 167, 1398-1414



NHS
Blood and Transplant

CPDA unit

Z serum

EDTA

EDTA

- ?
- ?
- ?

information

Serum

Whole blood

Full blood count
Sysmex

Data
4R LIMS

CRP
pathology

DNA for
Sequencing

Data
4R LIMS

Percoll 1
1.078 g/ml

PBMCs

PMNs

Percoll 2
1.066 g/ml

enriched
monocytes

Lyse
erythrocytes

CD16
selection

CD14
selection

CD14
selection

monocytes

neutrophils

FACS
QC

Cytospin
QC

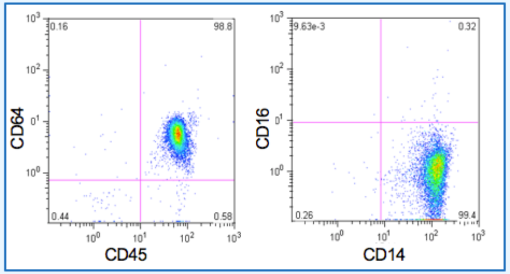
RNA
RNAseq

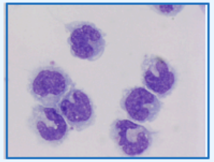
DNA
BSseq

Chromatin
ChIPseq

QC - monocytes

CD45+ CD64+ CD14+ CD16- FACS - 98% pure population

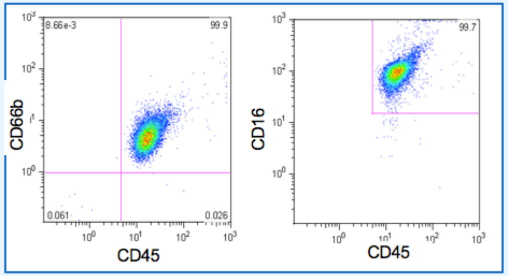


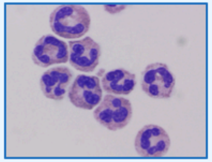


Cell morphology

QC - neutrophils

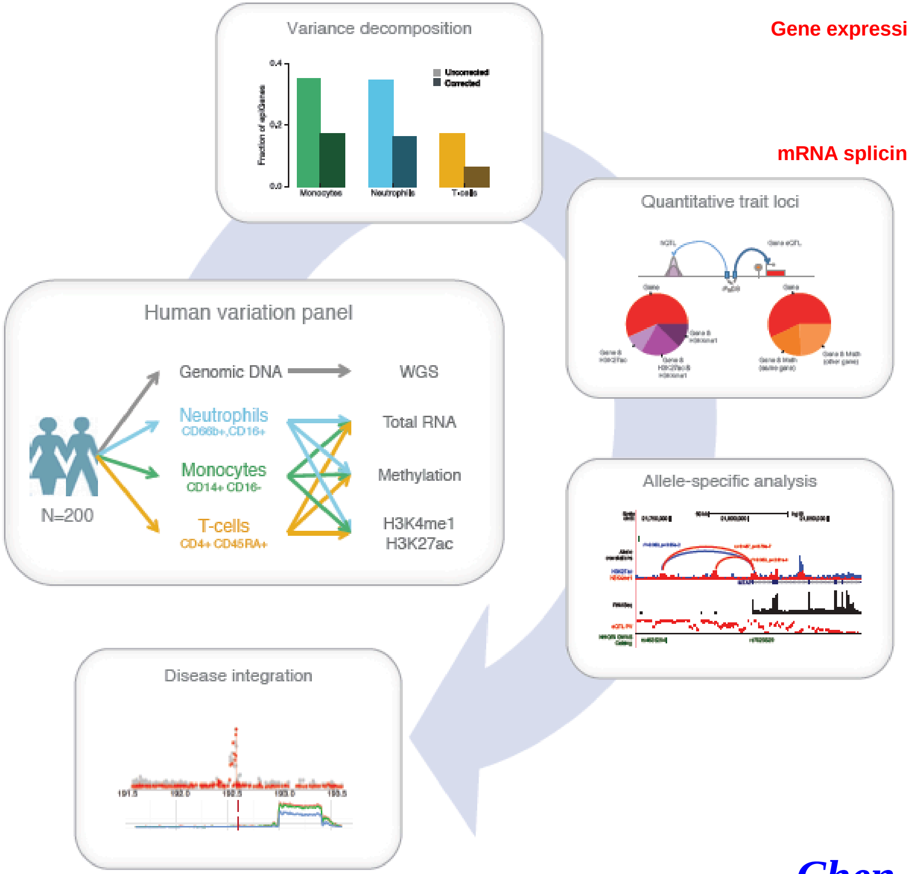
CD45+CD66b+CD16+ FACS - 99% pure population





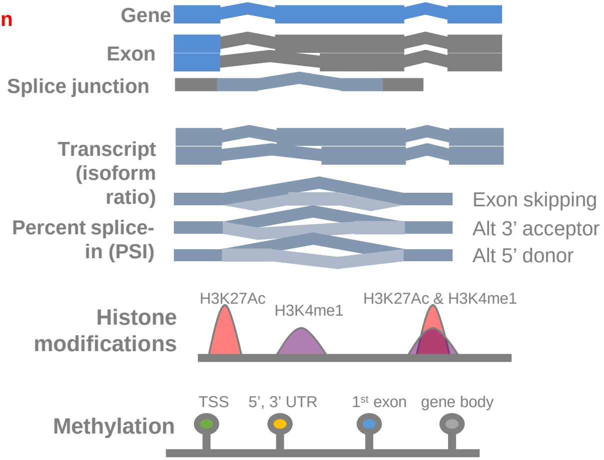
Cell morphology

Multiomics analyses



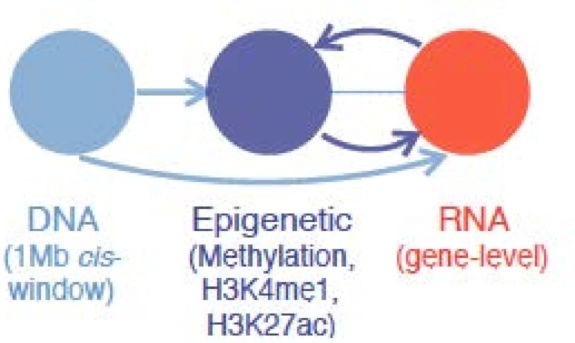
Gene expression

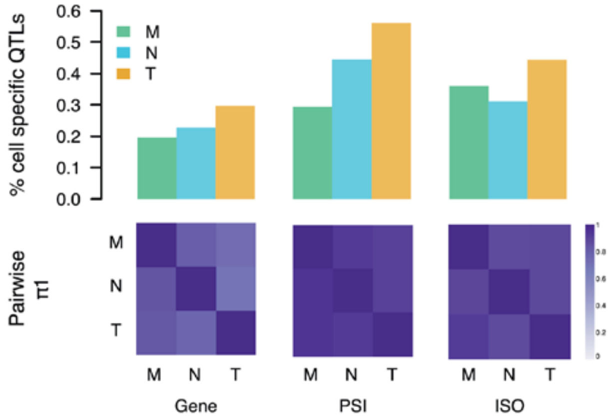
mRNA splicing



Chen et al. Cell 2016, 167, 1398-1414

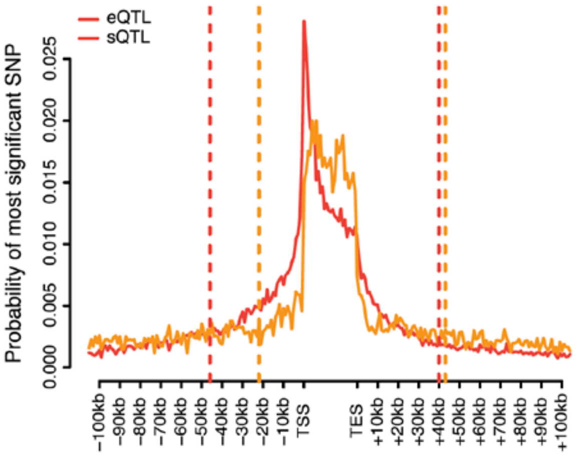
Interplay between genetics and epigenetics

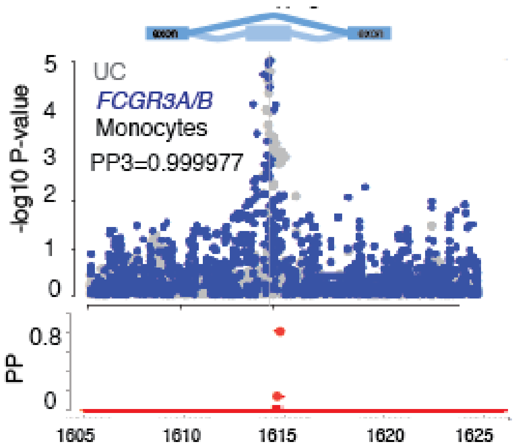




Chen et al. Cell 2016, 167, 1398-1414

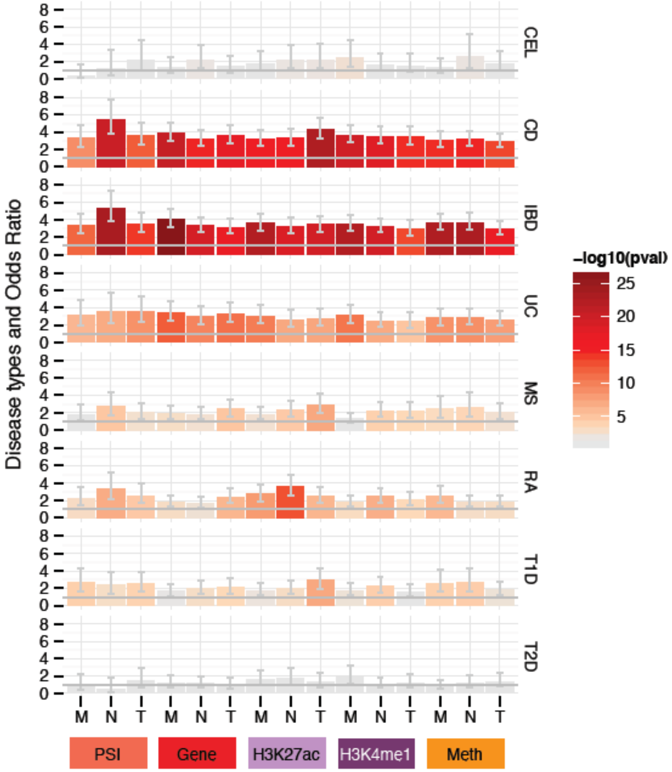
Regulatory hypothesis of SNP loci

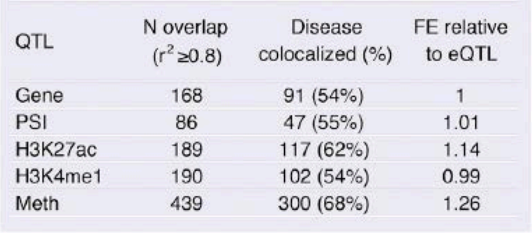




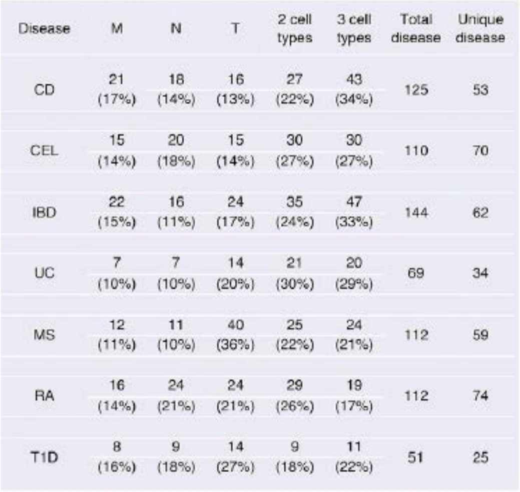
Chen et al. Cell 2016, 167, 1398-1414

Cell-type and trait specific effect





QTL	N overlap ($r^2 \geq 0.8$)	Disease colocalized (%)	FE relative to eQTL
Gene	168	91 (54%)	1
PSI	86	47 (55%)	1.01
H3K27ac	189	117 (62%)	1.14
H3K4me1	190	102 (54%)	0.99
Meth	439	300 (68%)	1.26



Disease	M	N	T	2 cell types	3 cell types	Total disease	Unique disease
CD	21 (17%)	18 (14%)	16 (13%)	27 (22%)	43 (34%)	125	53
CEL	15 (14%)	20 (18%)	15 (14%)	30 (27%)	30 (27%)	110	70
IBD	22 (15%)	16 (11%)	24 (17%)	35 (24%)	47 (33%)	144	62
UC	7 (10%)	7 (10%)	14 (20%)	21 (30%)	20 (29%)	69	34
MS	12 (11%)	11 (10%)	40 (36%)	25 (22%)	24 (21%)	112	59
RA	16 (14%)	24 (21%)	24 (21%)	29 (26%)	19 (17%)	112	74
T1D	8 (16%)	9 (18%)	14 (27%)	9 (18%)	11 (22%)	51	25

Chen et al. Cell 2016, 167, 1398-1414

West China Hospital Biobank

Capacity: 10 M
Stored: 2 M

Healthy volunteers: 300,000 with serum, plasma and buffy coat:
800,000

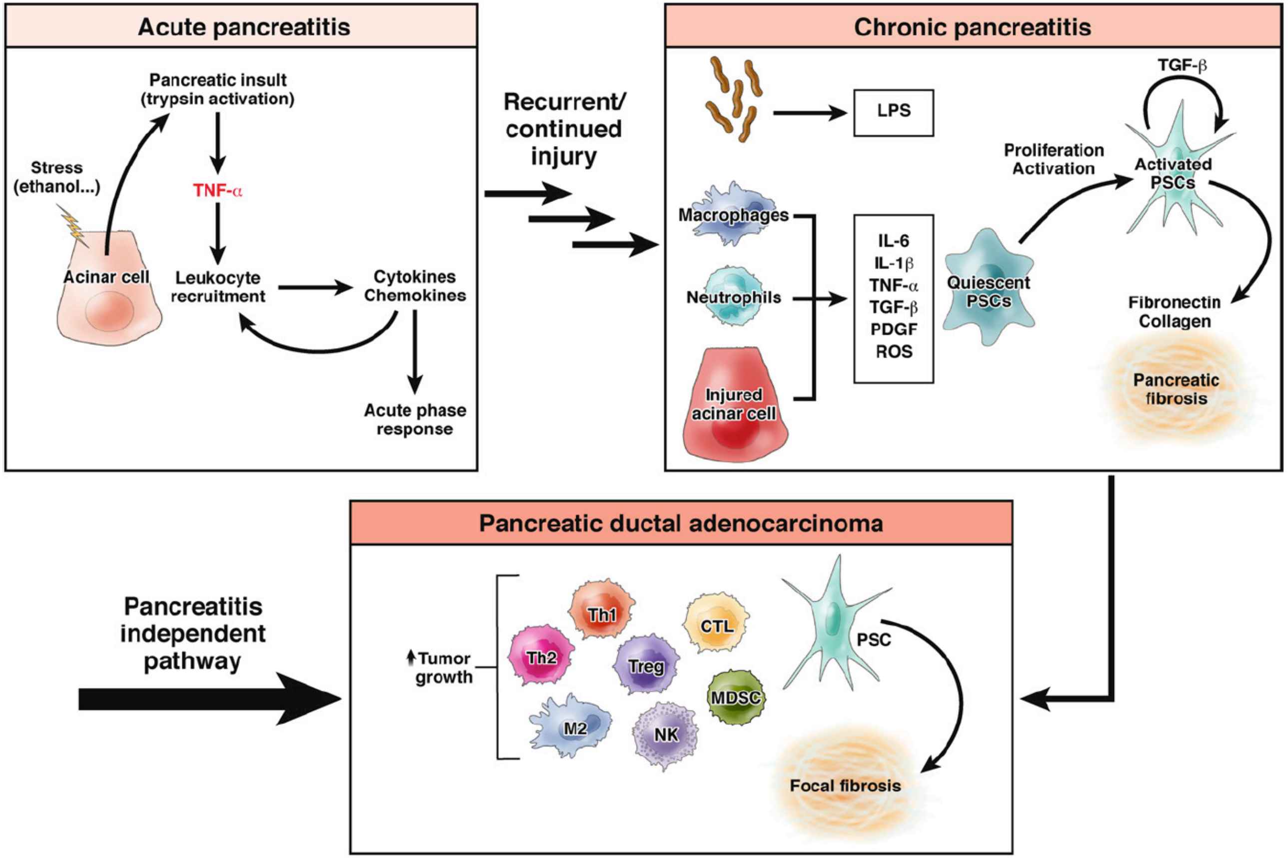
Tumour and matched blood: 200,000

Hepatitis B: 390,000

Western China geriatric cohort: 80,000

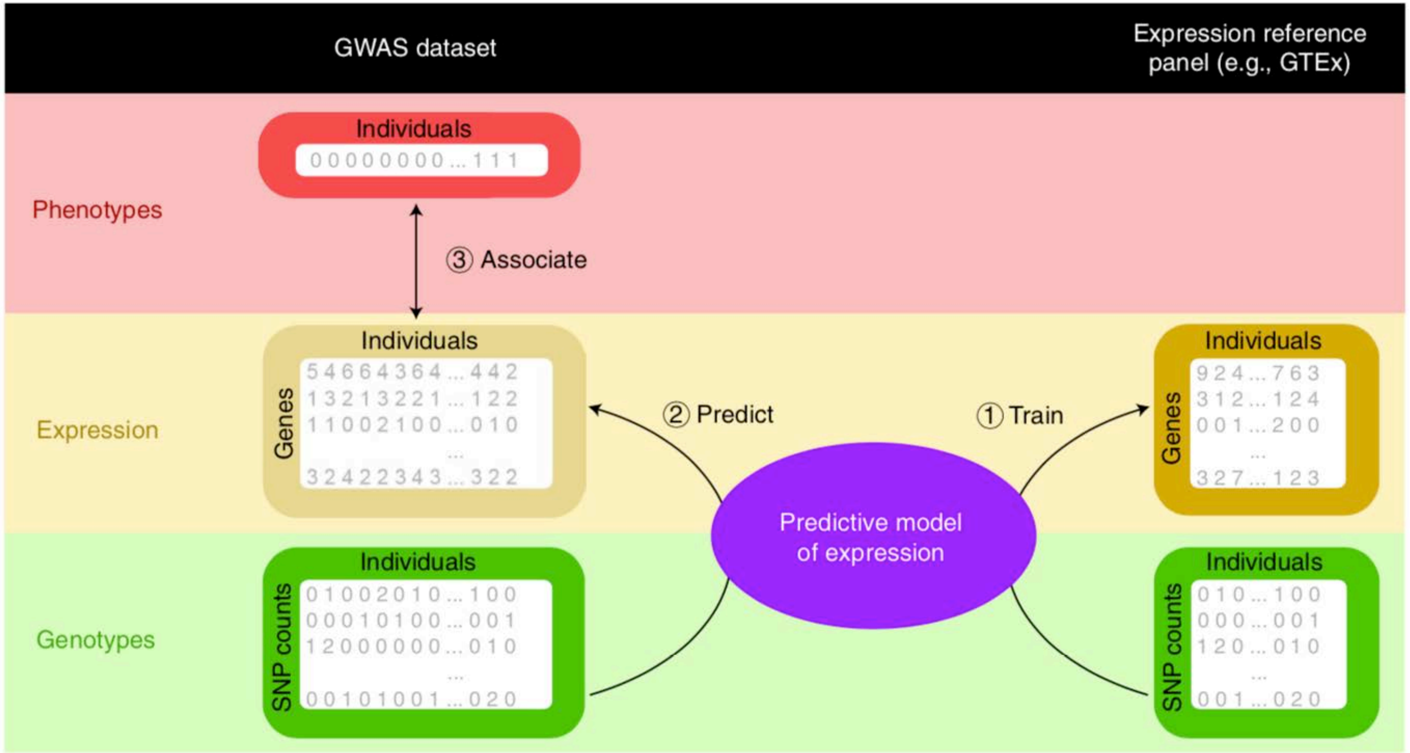
Others: 600,000

Role of immune cells in pancreatitis



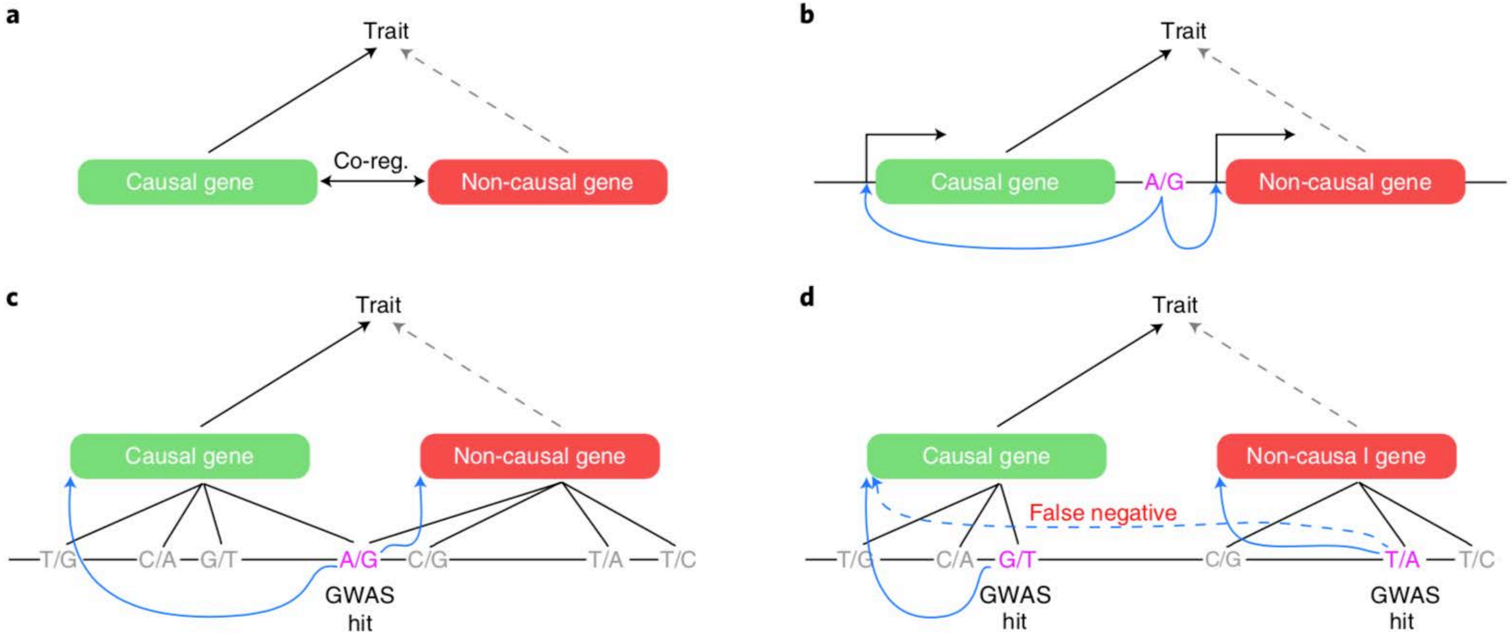
Zheng et al. Gastroenterology 2013

Transcriptome-wide association studies (TWAS)



Wainberg et al. Nature Genetics 2019

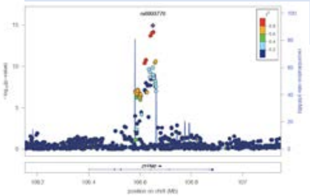
Challenges for TWAS: association is not causality



Integration of experimental and bioinformatic analyses

Genetic Mapping

QTL mapping
GWAS
EWAS
Public data

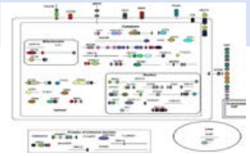


Quantitative traits
Case-control
Rare diseases

Bioinformatic prioritization

Known/novel pathways

Gene functions



ENCODE
ROADMAP
BLUEPRINT
Data

Knockdown database

Functional validation

In vitro

EMSA
Cell transfection

Coherence assay

Chip-seq
ATAC-seq
3C
DNA pull-down and MS
…

In vivo

Genetic editing:
CRISPR/Cas9
TALENS, ZNF

Model Organisms

Gene regulation/epigenetics

Stem cells

Clinical follow-up

Acknowledgements

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