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我眼中的生物信息学

Bioinformatics = Data + Algorithm

DTCC

2015中国数据库技术大会

DATABASE TECHNOLOGY CONFERENCE CHINA 2015

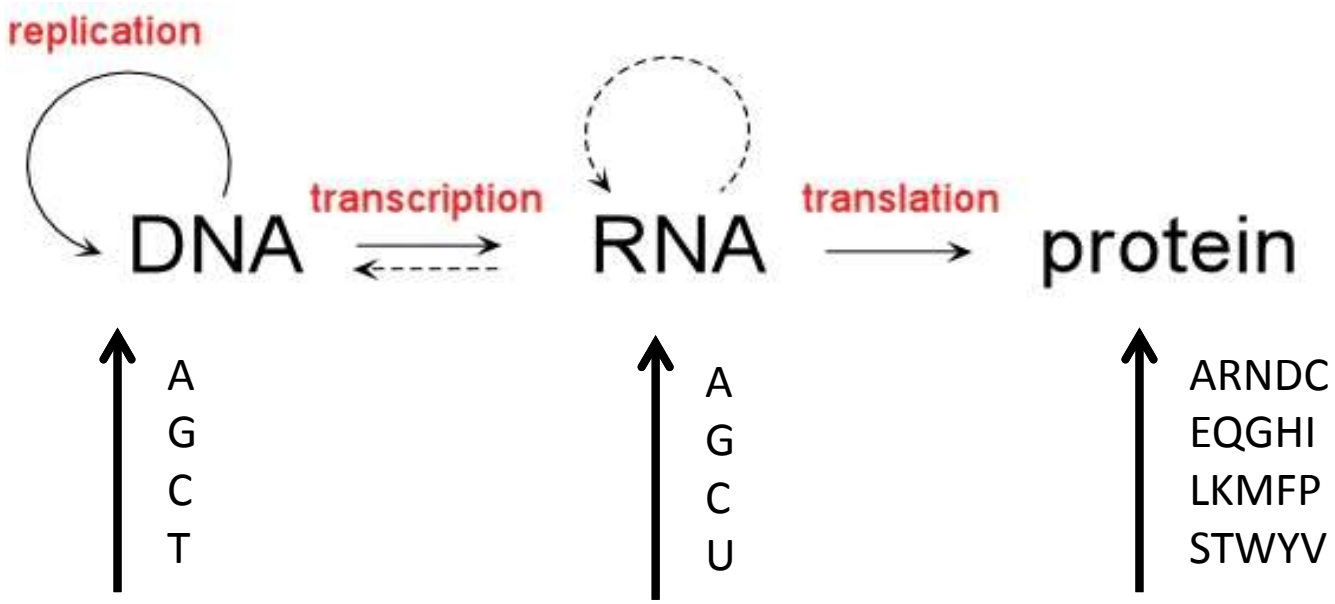
大数据技术探索和价值发现

Bioinformatics

Research, development, or application of computational tools and approaches for expanding the use of biological, medical, behavioral or health data, including those to acquire, store, organize, archive, analyze, or visualize such data.

--NIH Bioinformatics Definition Committee

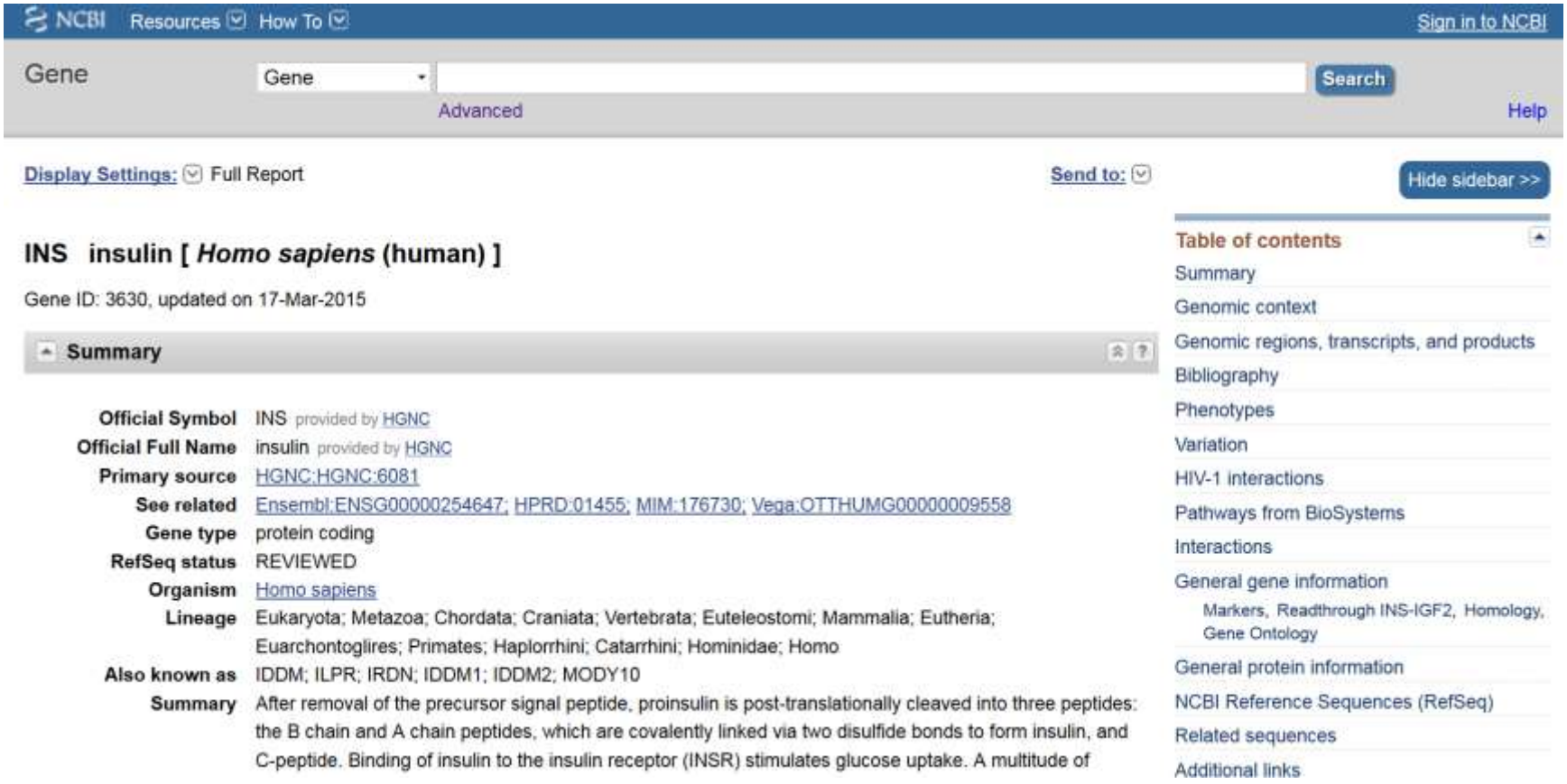
The Central dogma



Primary database

- NCBI GenBank /USA
- EMBL-EBI resource /EU
- DDBJ /Japan

NCBI Entrez interface



http://www.ncbi.nlm.nih.gov/gene/3630

>gi|631226408|ref|NP_001278826.1| insulin preproprotein [Homo sapiens]
MALWMRLLPLLALLALWGPDPAAAFVNQHLCGSHLVEALYLVCGERGFFYTPKTRREA
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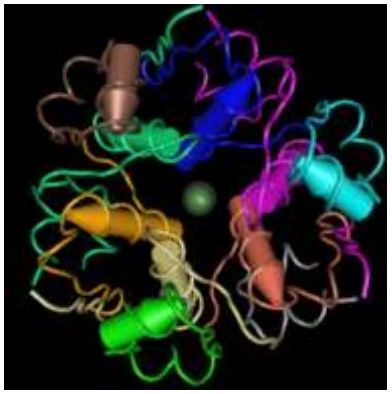
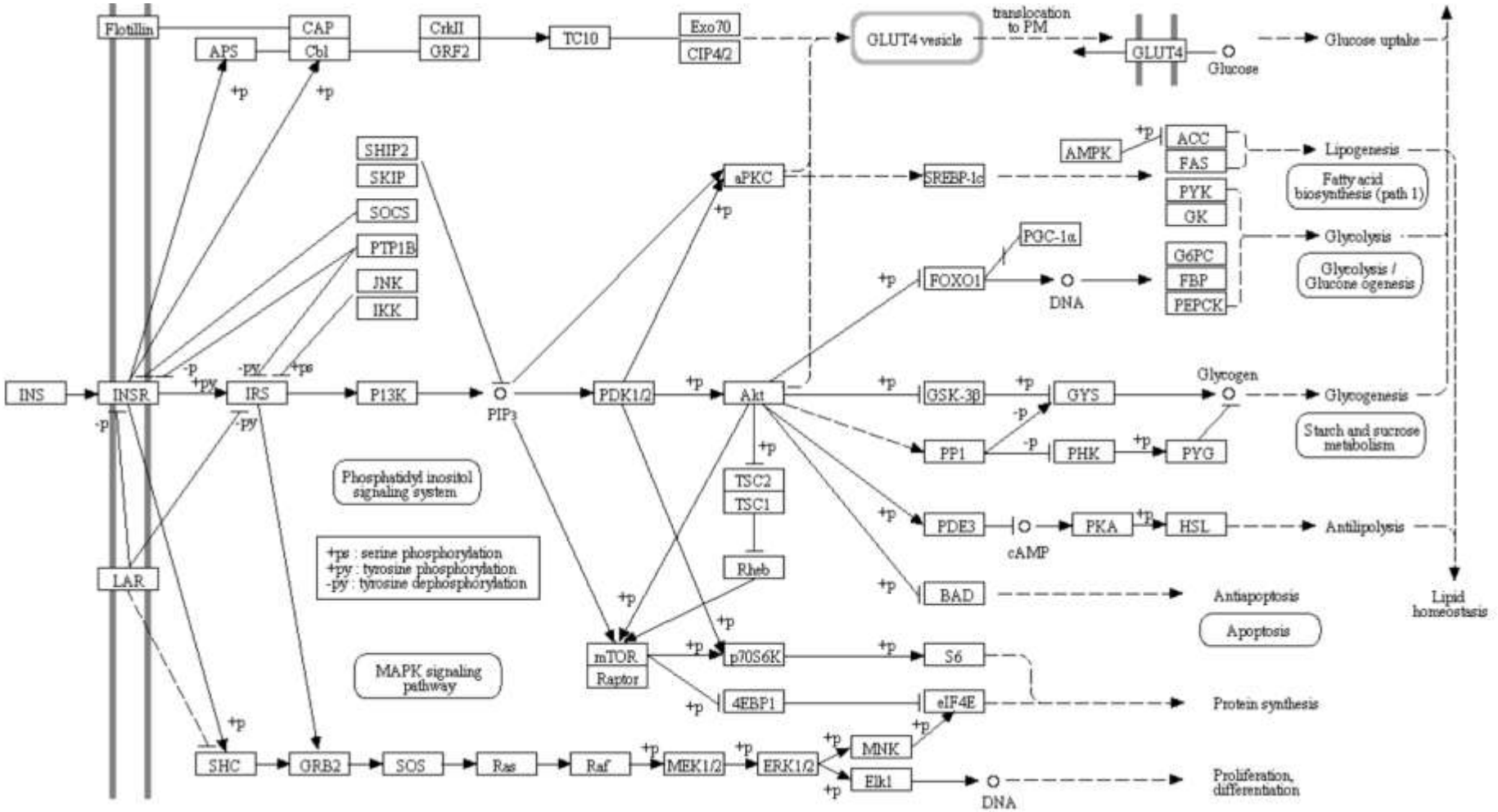
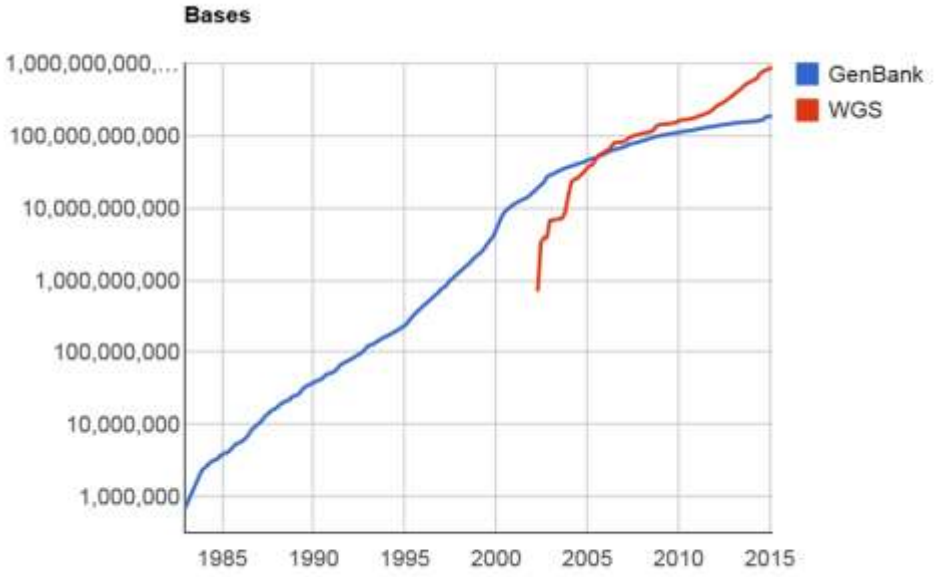




The “Big” Data

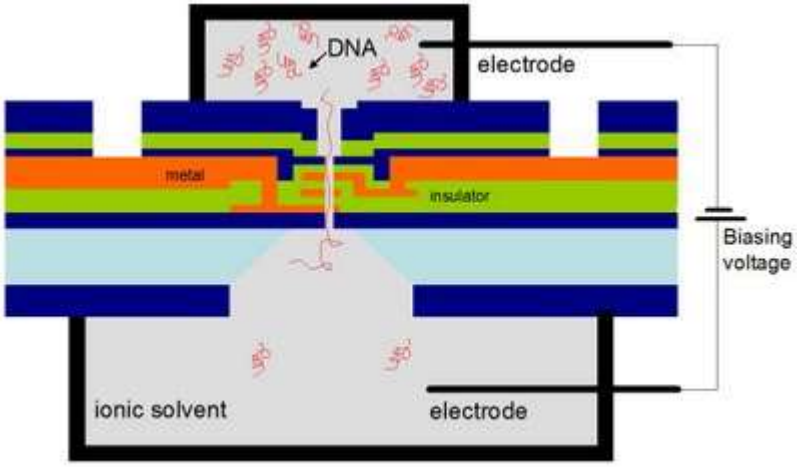
- From 1982 to the present, the number of bases in GenBank has doubled approximately every 18 months



http://www.ncbi.nlm.nih.gov/genbank/statistics

DNA Sequencer

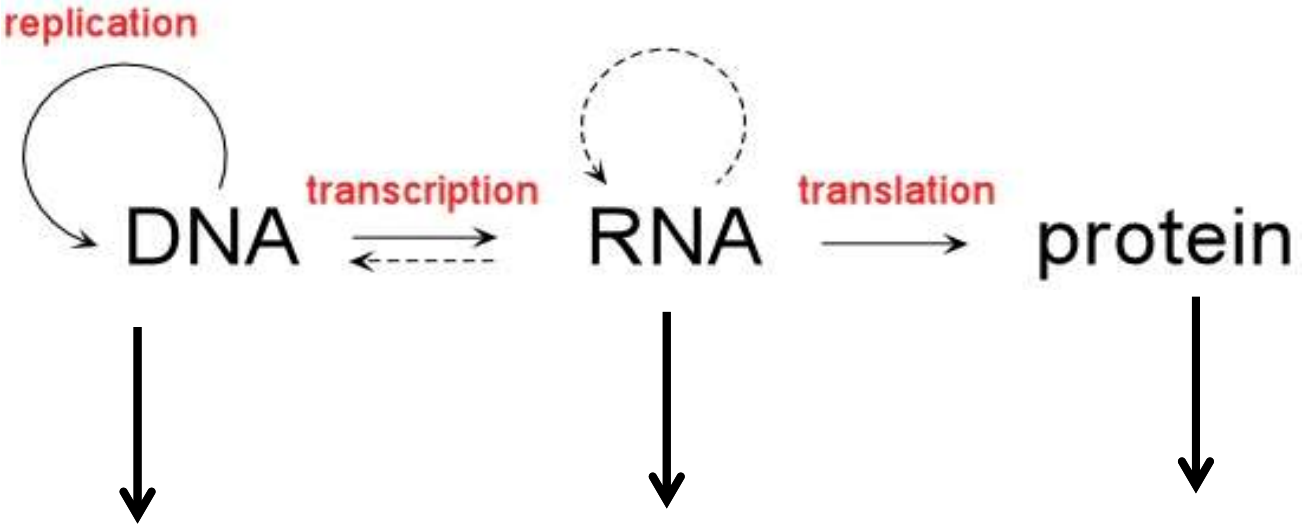
IBM transistor sequencer

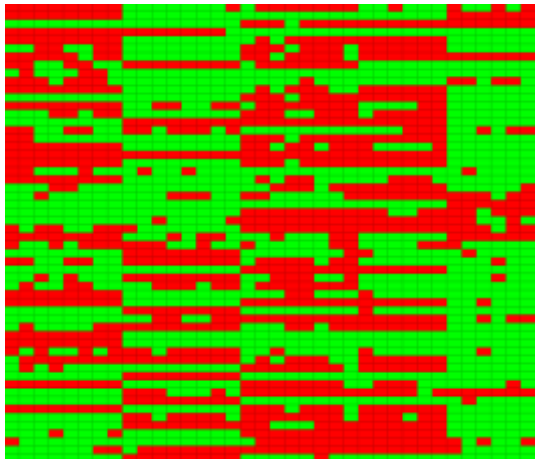


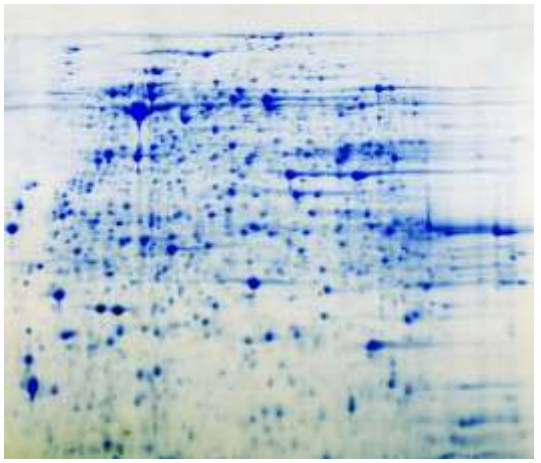
CryoEM

Mass Spec

The Central Dogma in 21st century

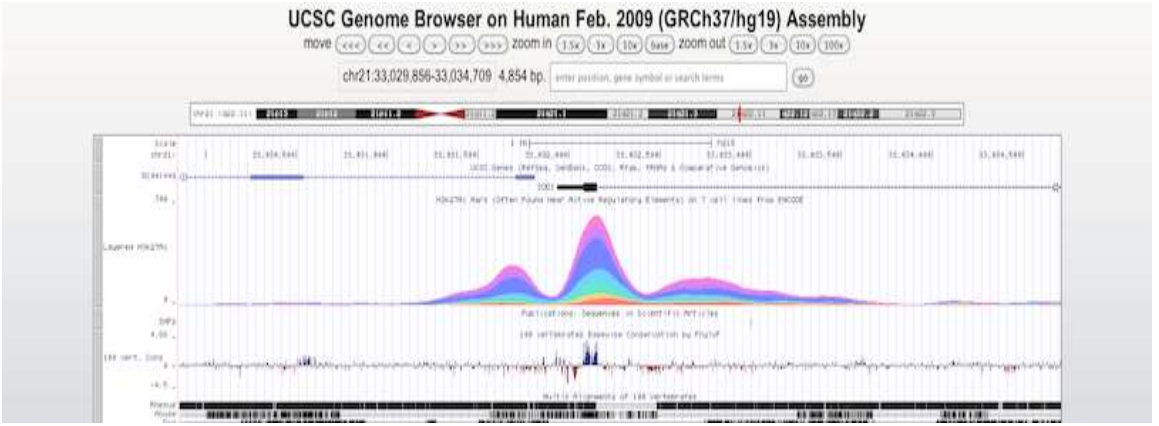




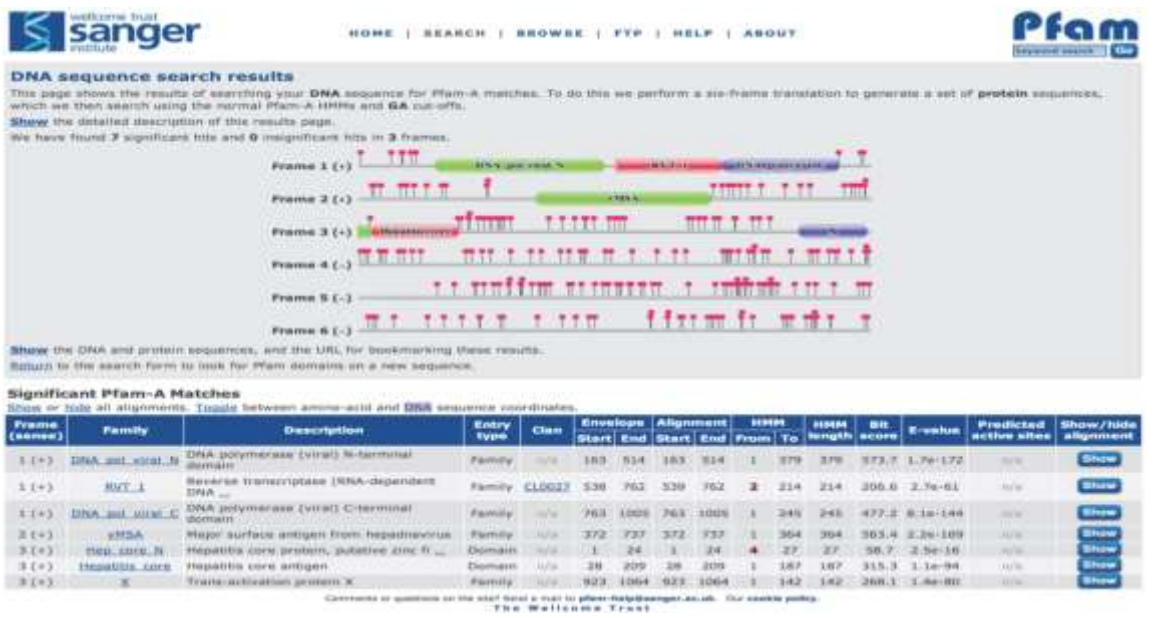


Secondary database

- UCSC database



- GPCR database



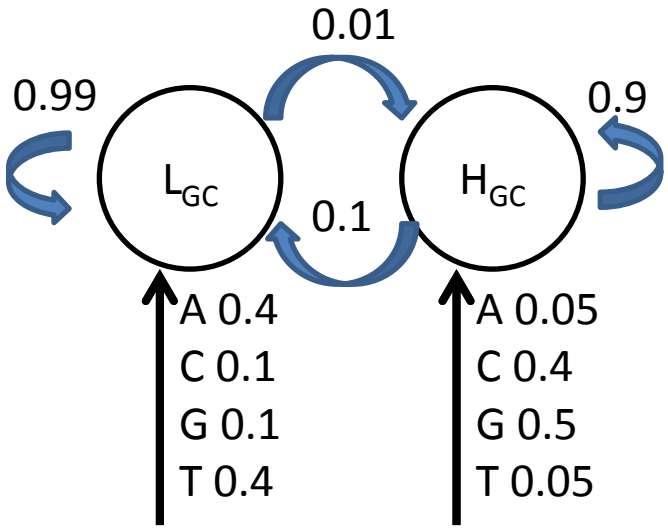
Database search "alignment"

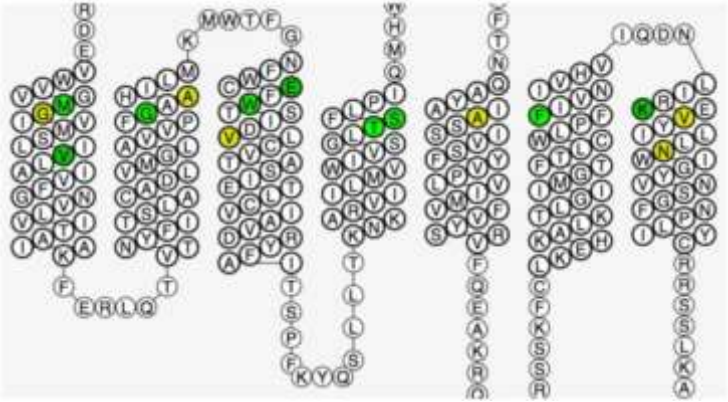
- Longest Common Subsequences
- Smith-waterman algorithm
- heuristic search (BLAST, BLAT, Burrows-Wheeler Aligner, etc)

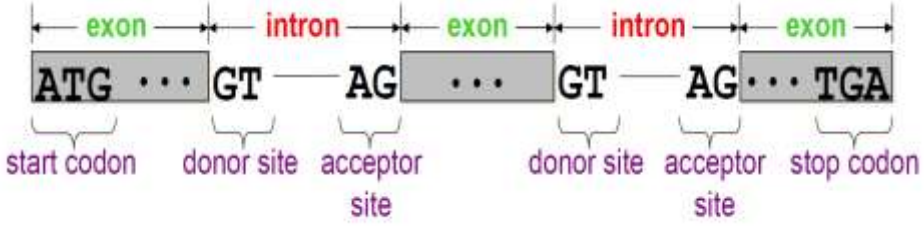
Sequence 1 = A--**CACAC**TA
Sequence 2 = AG**CACAC-**A

Hidden Markov Model

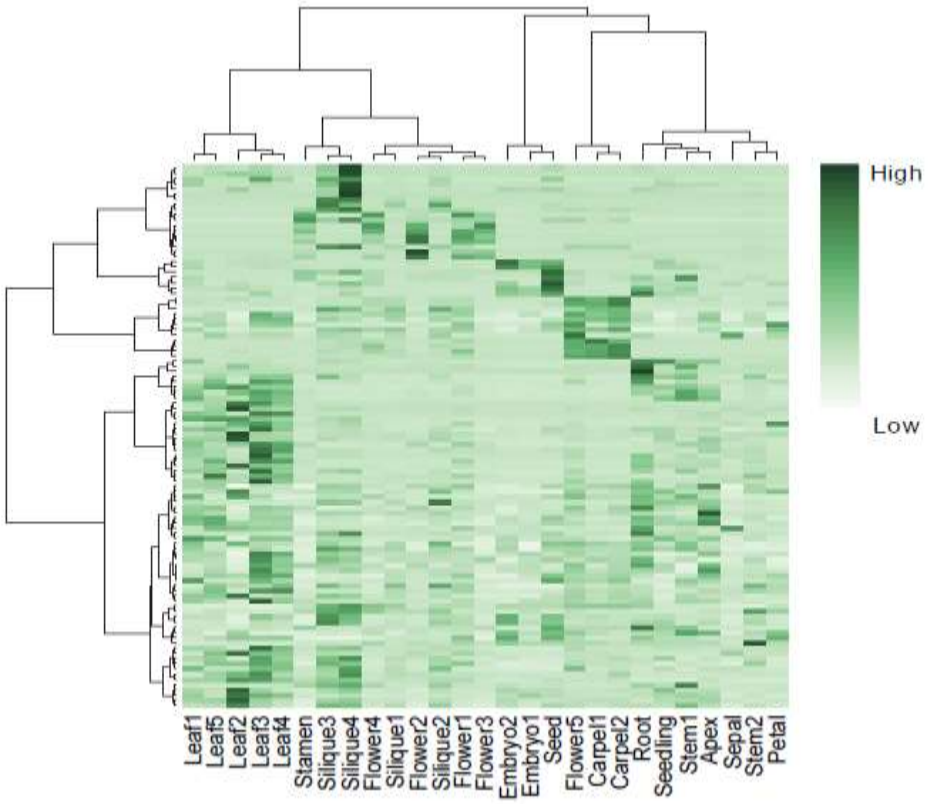
- GenScan
- Pfam/HMMER

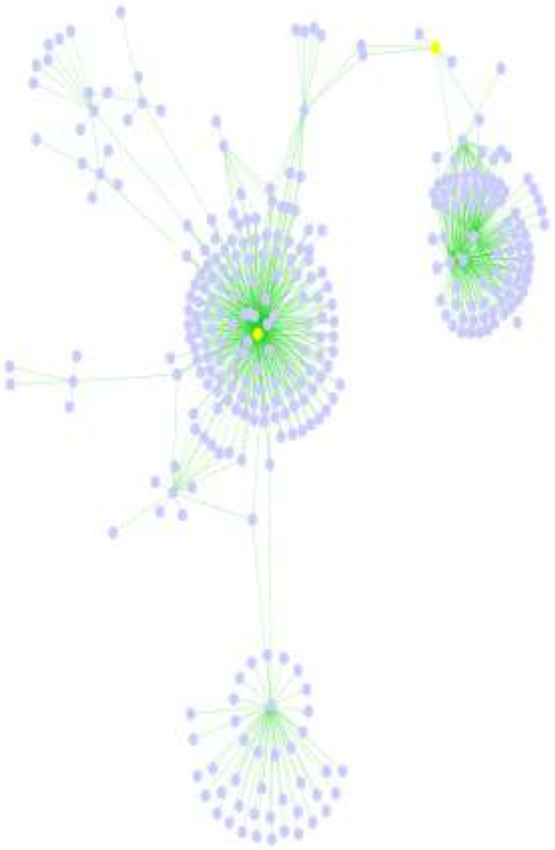






Data mining in biological data





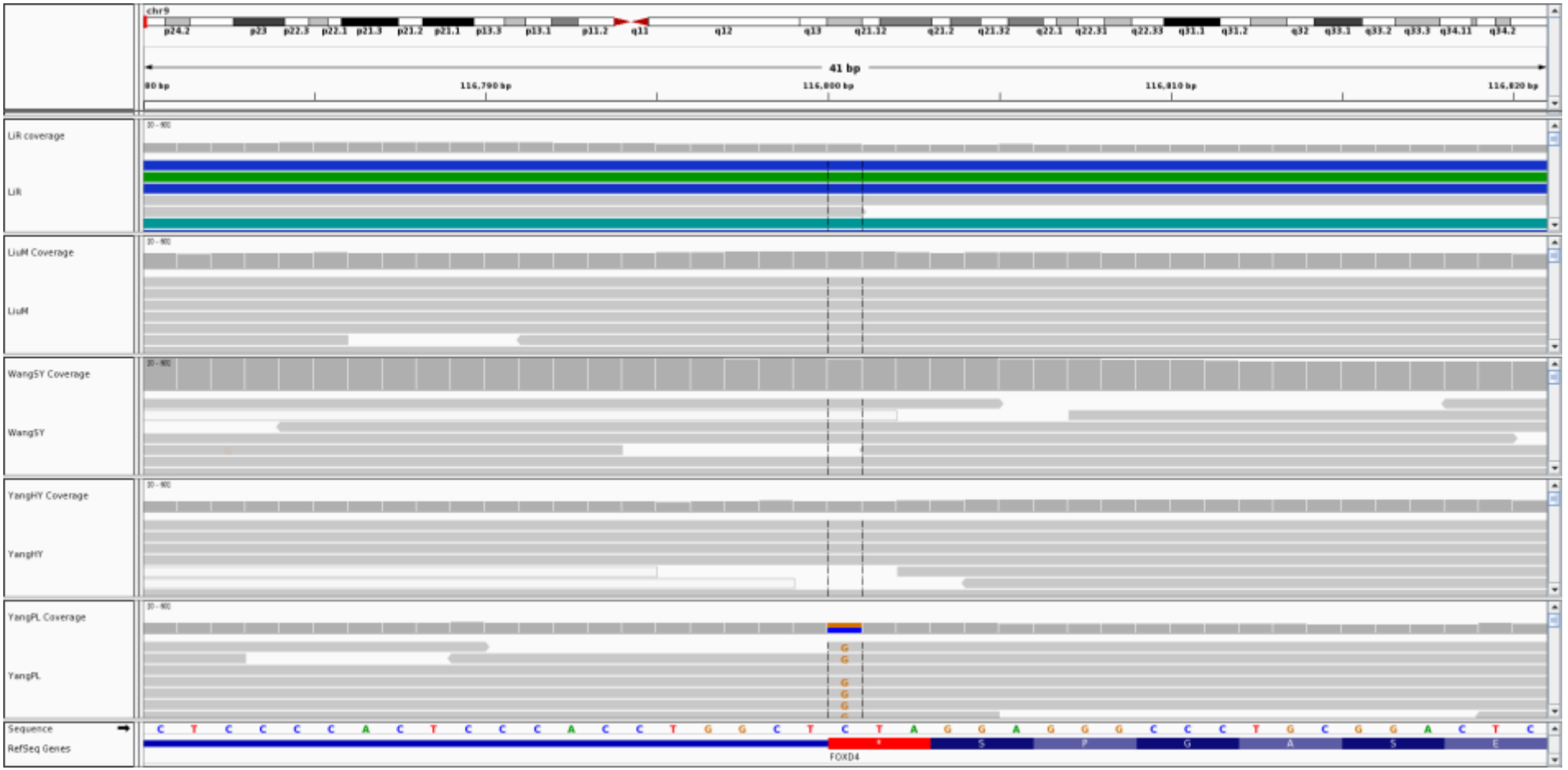
Human genetic study -- a case study

- Background
  - SNP (biomarker)
- Candidate-gene based study
  - HIV opportunistic infection
- Whole genome wide study
  - Hepatitis C

SNP (single nucleotide polymorphism)

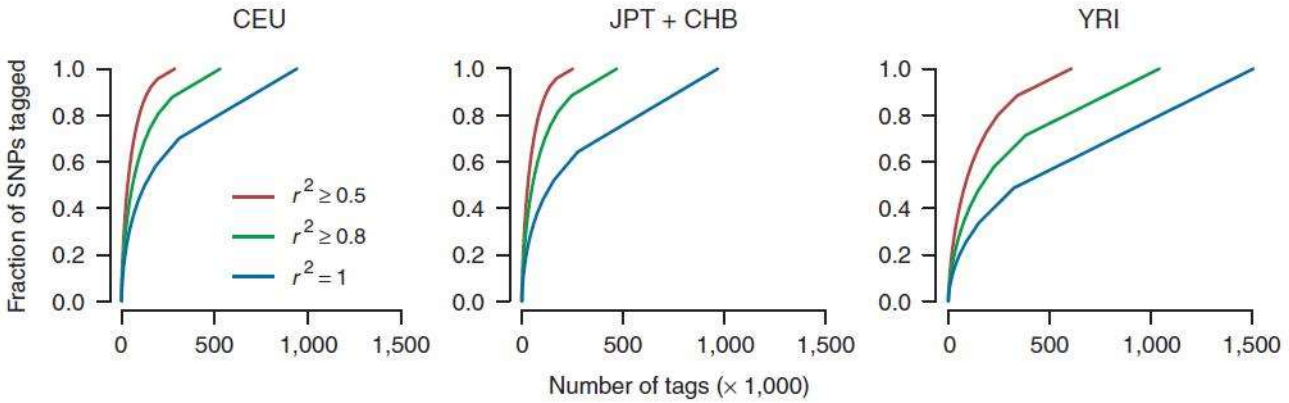
- Definition
  - DNA sequence variations that occur when a single nucleotide (A,T,C,or G) in the genome sequence is altered
- Common human variation
  - 11 million (MAF>=1%)
  - SNP frequency varies in different population
- 1000 genome project
  - Genotyped 25 population, ~2500 individuals
- Detected method
  - Sequencing
  - PCR-based methods
  - Chip (Illumina, Affy)
  - …

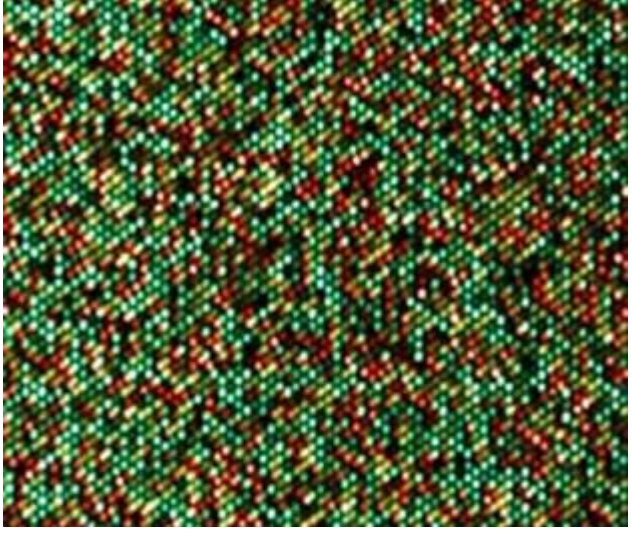
SNP detection

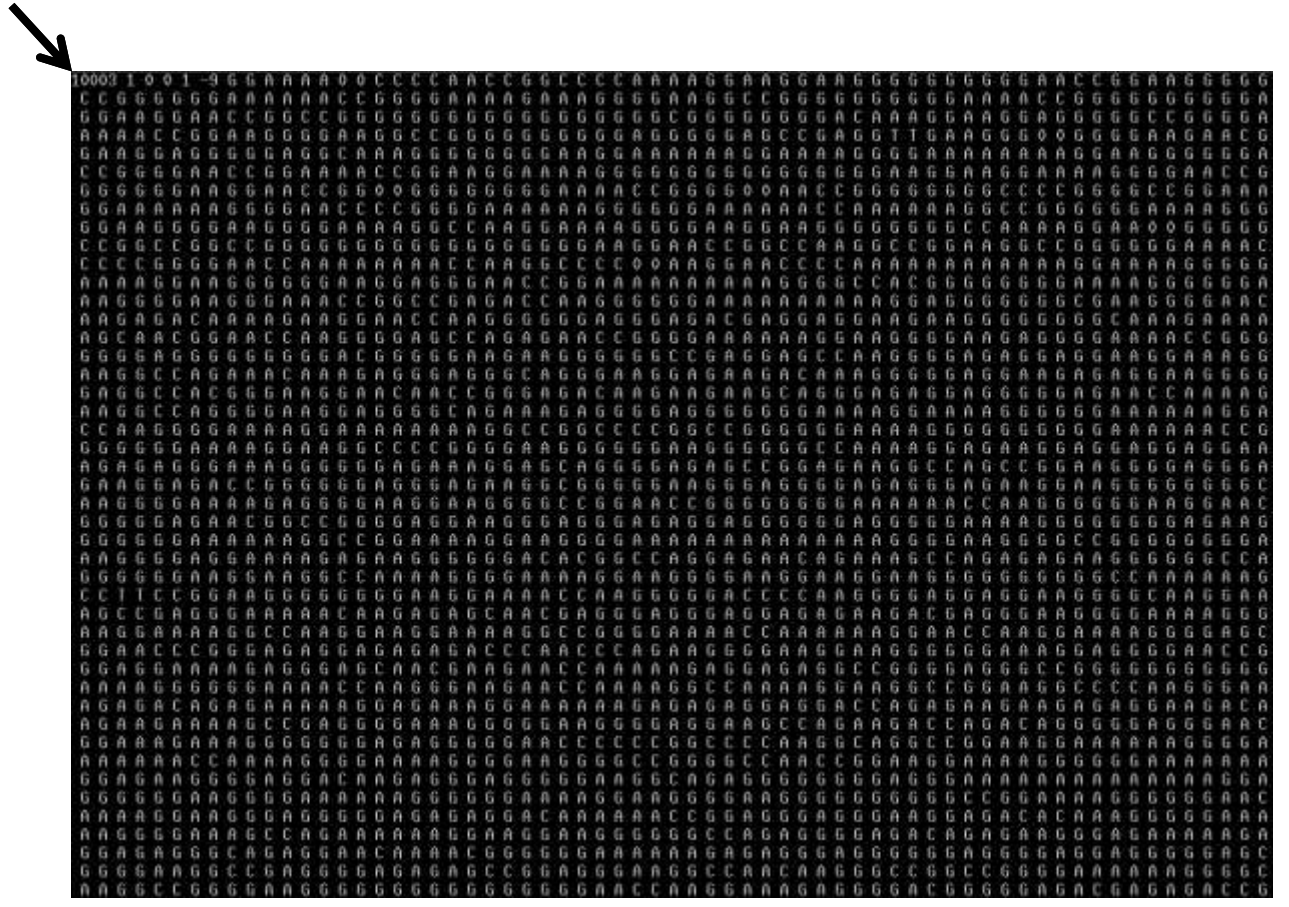


Genotyping platform on Chip

- Affy
  - Genome-wide Human SNP array 6
- Illumina
  - Human 1M-duo
- Coverage

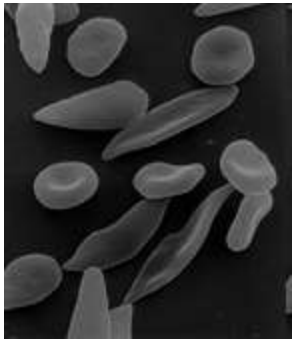






Association study in infection

- Infection disease exert evolution pressure in human population
  - Malaria and sickle-cell anaemia risk allele
- Advantage of association study
  - Linkage analysis need multiple affected and unaffected relatives
  - Family-based, case-control or cohort data
  - Fine localization and identification of causative loci with high-throughout technology



Association study methodology

- Chi-squared

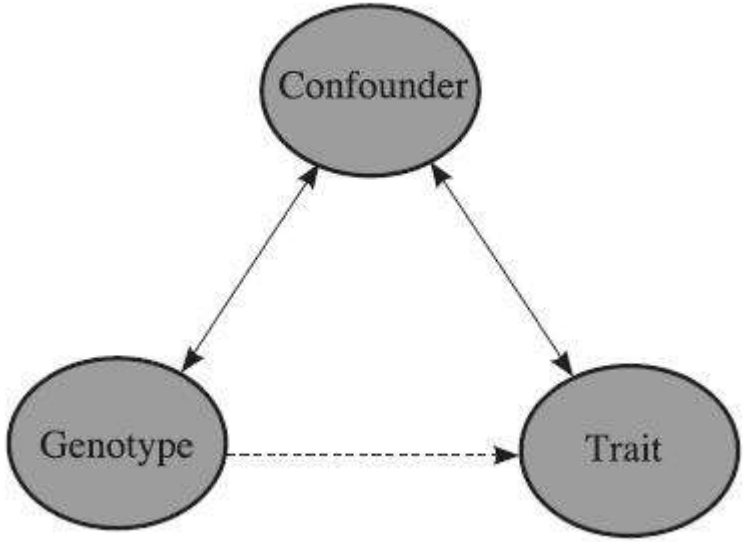
	Disease	Unaffected
Allele 1	p_{1D}	p_{1U}
Allele 2	p_{2D}	p_{2U}

- Regression

$$g(E[\mathbf{y}]) = \mathbf{X}\boldsymbol{\beta}$$

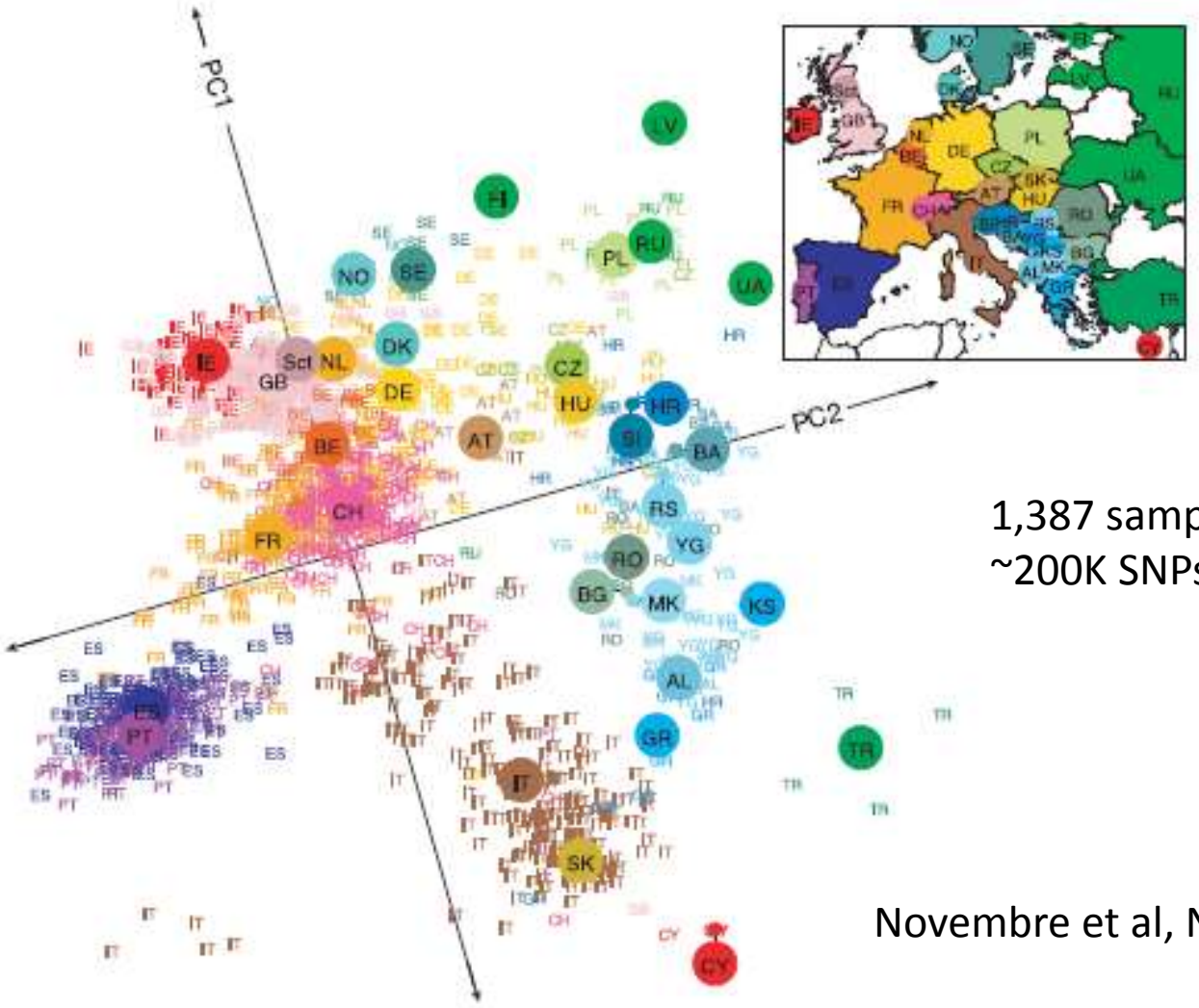
Association study methodology

- Confound factors



- Powers
  - 1-P(false negative)
  - Case-control study: genetic effect, Allele frequency …

European population structure



1,387 samples
~200K SNPs

Novembre et al, Nature, 2008

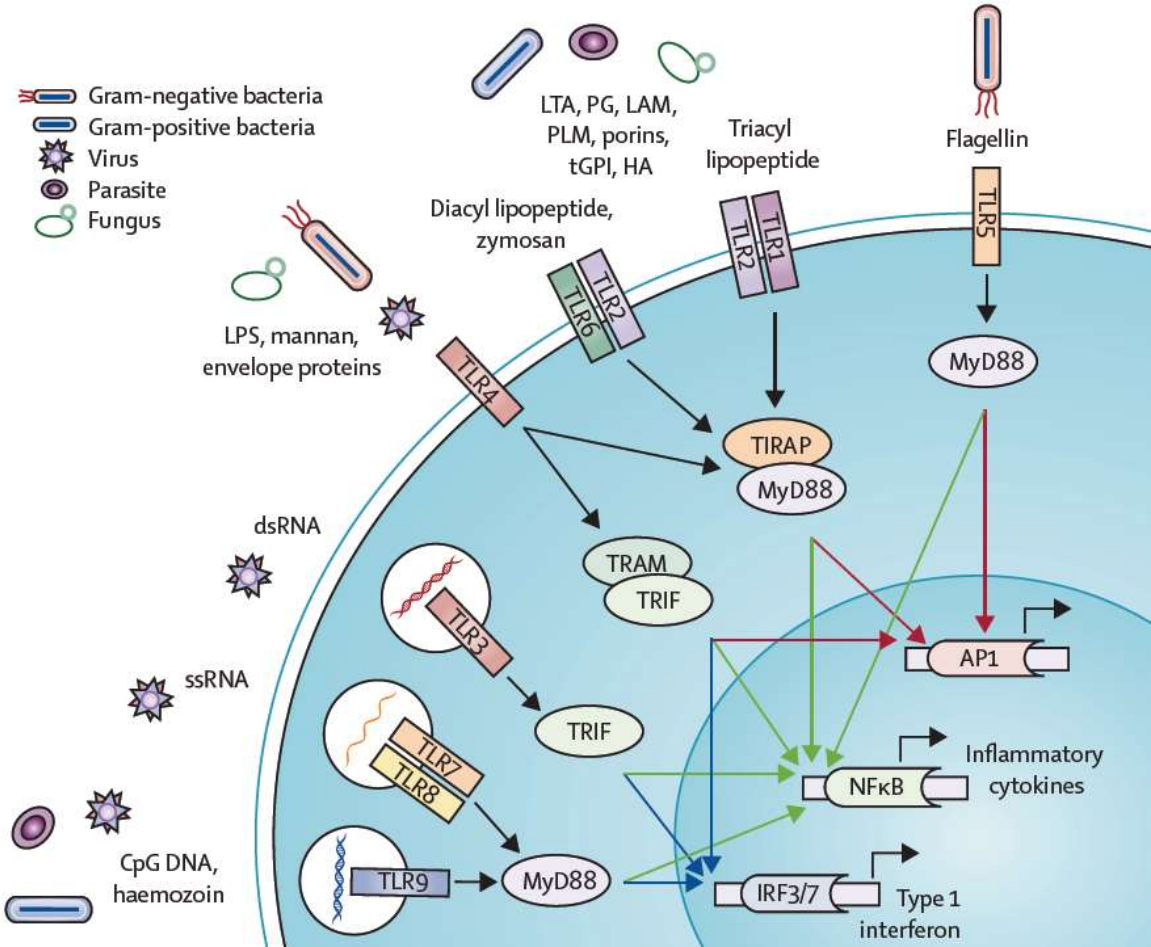
GWAS-basic analysis

- Quality control
  - MAF>0.05, HWE>0.001, GENO>0.95
  - Remove duplication or other mistakes
- Association analysis
  - Genetic model: Allelic (chisq 1df), Additive, Dominate, Recessive, Cochran-Armitage trend test, Genotypic test (chisq 2df)
  - QQplot and Manhattan plot
- Available software
  - Plink, GenABEL(R package) …

GWAS-advanced analysis

- Population stratification
  - χ^2 divided by genomic inflation
  - IBS clustering in PLINK
  - PCA in EIGENSTRAT
- Imputation
  - MACH, IMPUTE…
  - MACH cutoff(>0.9) means free genotyping
- Meta-analysis
  - Reverse variance pooling method
  - Carefully prepare the data (same population, same reference allele, same phenotype unit, etc)

TLR4 SNPs association study in HIV opportunistic infection



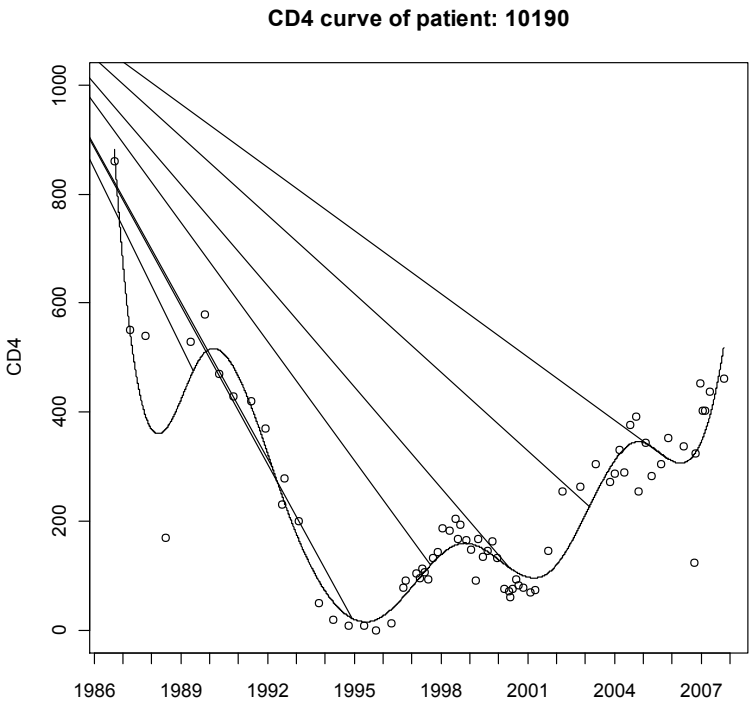
TLR (Toll-like receptors) history

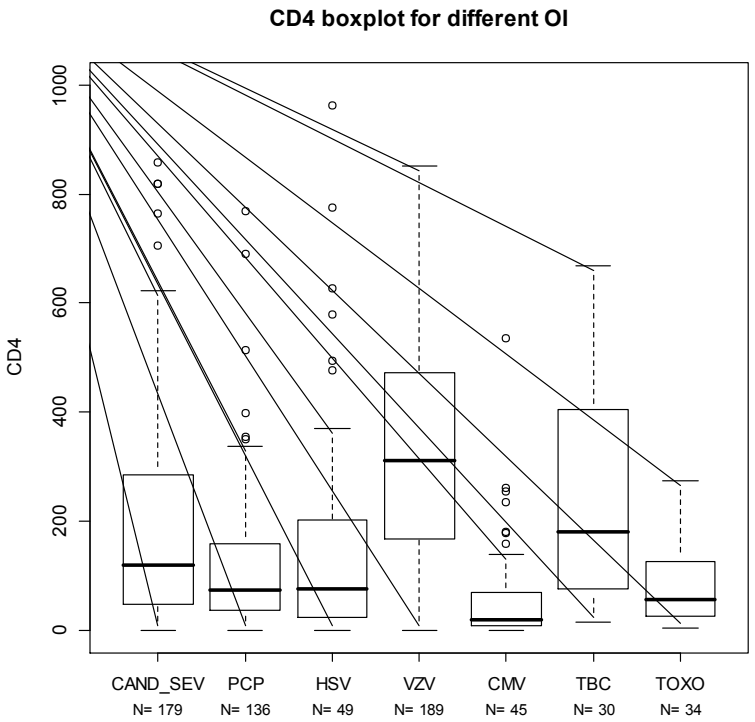
- Toll: function in the embryonic dosal-ventral development of Drosophila (1988, cell 52:269)
- Drosophila with a loss of function mutation for Toll exhibits a high susceptibility to fungal infection (1996, cell 86:973)
- TLR: the so-called Toll-like receptors, human homolog genes for Toll(1997, 1998)
- TLR4 is the LPS sensor in both mice and humans (1998, Science 282:2085)
- Inflammatory caspases are innate immune receptors for intracellular LPS (2014, Nature 514:187)

The TLR4 D299G SNP Influences Susceptibility to Opportunistic Infections in the Swiss HIV Cohort Study

- 1585 Caucasian patients are included from SHCS
- Poisson regression used to detected association
  - Neutral model
  - Additive model
    - adjusted by cofactor such as age, sex, infection risk factors and year of SHCS entry
- OIs
  - Fungal infection
    - severe candidiasis (mainly candida oesophagitis)
    - *Pneumocysitis jirovecii* pneumonia (PCP)
  - Viral infection
    - HSV infection (mucocutaneous ulceration or HSV disease)
    - VZV infection (e.g. multidermatoma or relapsing zona)
    - CMV infection (CMV disease or retinitis)
  - Mycobacterium infection
    - tuberculosis
  - Parasite infection
    - toxoplasmosis
- The permutation false discovery rate (FDR)
  - the genotyped SNPs in all the patients are randomly shuffled, and then the same poisson regression is done. We take the ratio of the cases in 1000 times shuffle in which random pvalue is less than the real one as Qvalue

CD4 distribution of OIs





Neutral model

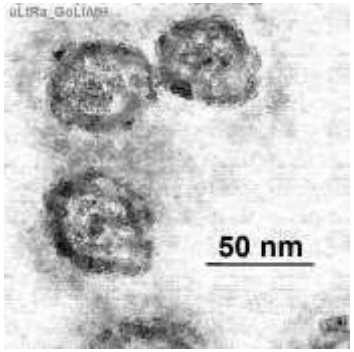
OIs	TLR_D299G	CD4+ below	Days at risk	Case of OI	Others	IR (per year)	IRR	Pvalue
CAND_SEV	0/0	300	1021865	97	711	0.0347	-	-
	0/1	300	96420	11	72	0.0417	1.2018 (1.652 0.874)	0.563
	1/1	300	3953	0	2	0	0 (Inf 0)	1
PCP	0/0	200	477977	54	403	0.0413	-	-
	0/1	200	49465	11	37	0.0812	1.9684 (2.74 1.414)	0.041
	1/1	200	2662	0	2	0	0 (Inf 0)	1
HSV	0/0	200	477977	29	428	0.0222	-	-
	0/1	200	49465	4	44	0.0295	1.3328 (2.272 0.782)	0.59
	1/1	200	2662	0	2	0	0 (Inf 0)	1
VZV	0/0	400	1841694	82	1083	0.0163	-	-
	0/1	400	190490	12	113	0.023	1.4149 (1.927 1.039)	0.262
	1/1	400	4419	0	2	0	0 (Inf 0)	1
CMV	0/0	100	193765	32	239	0.0603	-	-
	0/1	100	21441	5	20	0.0852	1.4121 (2.284 0.873)	0.473
	1/1	100	0	0	0	NaN	-	-
TBC	0/0	400	1841694	12	1153	0.0024	-	-
	0/1	400	190490	4	121	0.0077	3.2227 (5.741 1.809)	0.043
	1/1	400	4419	0	2	0	0 (Inf 0)	1
TOXO	0/0	200	477977	21	436	0.016	-	-
	0/1	200	49465	6	42	0.0443	2.7608 (4.386 1.738)	0.028
	1/1	200	2662	0	2	0	0 (Inf 0)	1

Incidence of OIs under immune suppression by TLR4 SNP

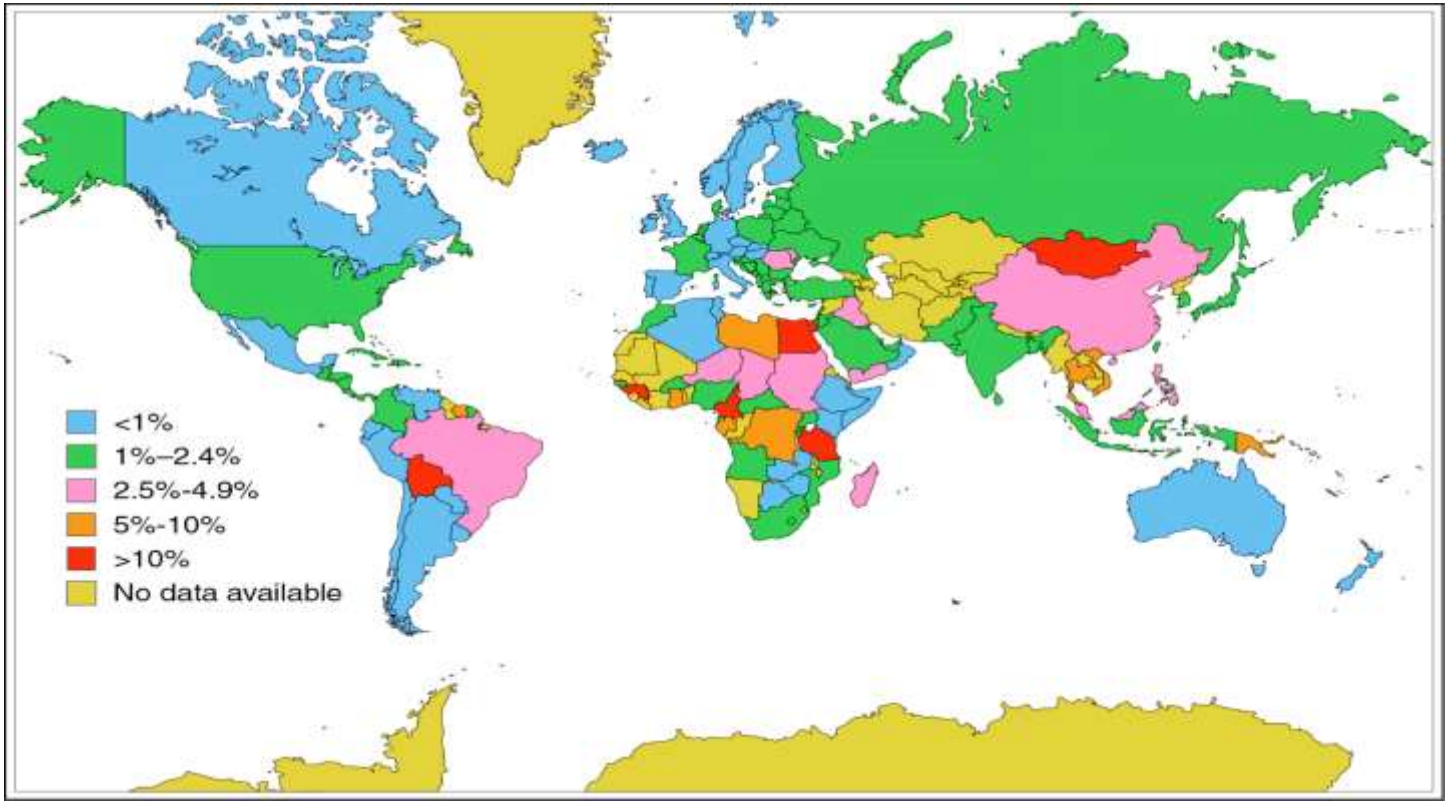
Additive model

OIs	CD4 cutoff	Incidence Rate Ratio	95% CI	Pvalue	Qvalue
CAND_SEV	300	1.1	0.8-1.5	0.7	0.7
PCP	200	2.0	1.4-2.7	0.047	0.040
HSV	200	1.3	0.8-2.2	0.6	0.6
VZV	400	1.4	1.0-1.9	0.3	0.3
CMV	100	1.4	0.9-2.2	0.3	0.3
TBC	400	2.6	1.5-4.3	0.077	0.057
TOXO	200	2.4	1.6-3.7	0.041	0.031

Genome wide association study in Hepatitis C



- **< 1%**
- **1.0-2.4%**
- **2.5-4.9%**
- **5-10%**
- **>10%**
- **NA**



Method -- clinic

- Chronic HCV infection
  - anti-HCV seropositivity (using ELISA/RIBA) and detectable HCV RNA by quantitative assays
- Spontaneous clearance
  - HCV-seropositivity and undetectable HCV RNA in patients without previous antiviral treatment
- Response to treatment
  - at least 80% of the recommended dose PEG-IFN /RBV during the first 12 weeks
  - Sustained viral response (SVR)
    - undetectable HCV RNA in serum >24 weeks after treatment termination
  - Non-response (NR)
    - Others

Method -- genotyping

- Illumina 1M-Duo chip for SCCS
- Illumina Humanhap650-Quad beadchips for SHCS study (including part of work using Illumina Humanhap550)
- Illumina Beadstudio software used for genotype calling

Method --association analysis

- Quality control
  - MAF>0.01, HWE>0.001, GENO>0.95, mind>0.95
  - Remove duplication and other cryptic relatedness
- Basic association analysis
  - Allelic based analysis or Cochran-Armitage trend test
  - Logistics regression considering covariates
  - Significance cutoff 5E-8
  - QQplot and Manhattan plot
- Applied software
  - Plink and Haploview

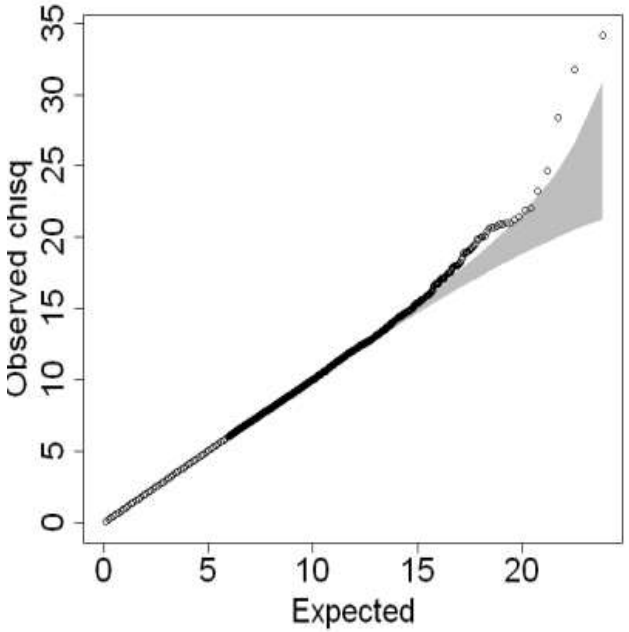
Spontaneous Clearance demographic table

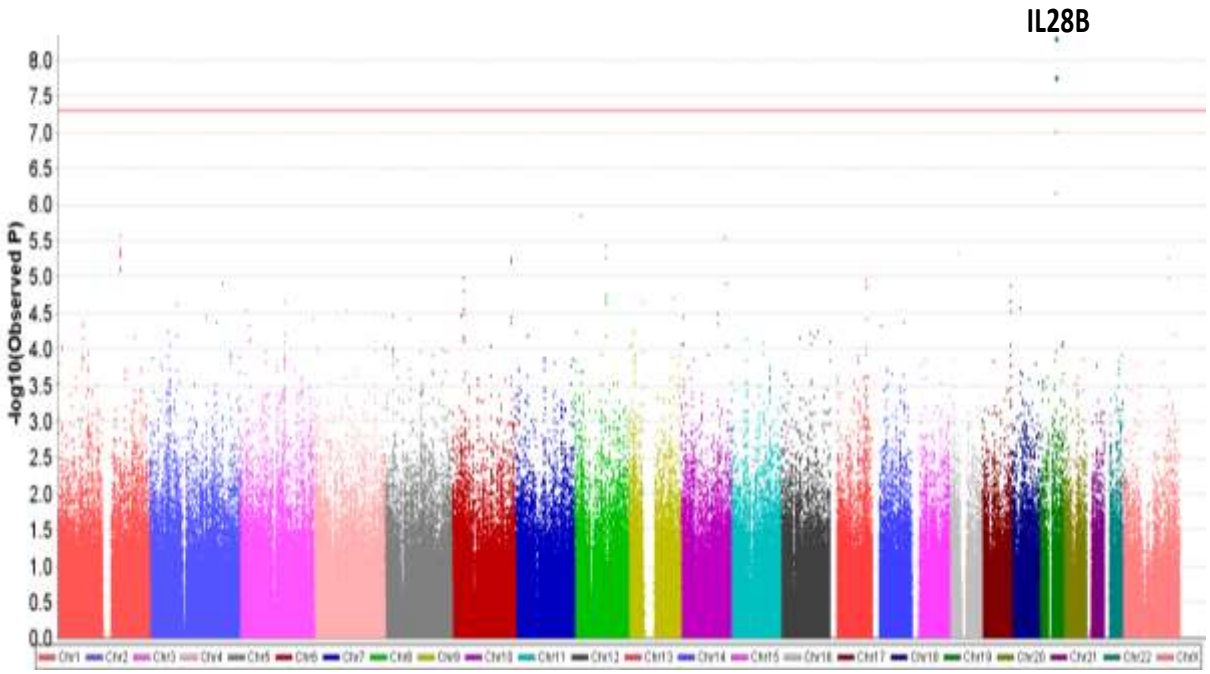
	SHCS			SCCS		
Characteristics (N, proportion)	**Chronic Infection**	**Spontaneous Clearance**	**P**	**Chronic Infection**	**Spontaneous Clearance**	**P**
N	201	199		828	87 (+73 DE)	
Age (median, IQR)	33.75 (8.93)	33.86 (9.65)	0.7	44.15 (14.03)	37.47 (8.59)	<0.001
Male sex	105 (52.2%)	136 (68.3%)	0.001	516 (62.3%)	48 (55.2%)	0.2
HBV antigen positive	21 (10.4%)	8 (4%)	0.01	8 (1%)	4 (4.6%)	0.03
Log HCV RNA (median, IQR)	6.086 (1.346)			5.877 (0.993)		
HCV genotypes						
1	78 (39.2%)			396 (47.8%)		
2	5 (2.5%)			83 (10%)		
3	60 (30.2%)			240 (29%)		
4	22 (11.1%)			70 (8.5%)		
Other/unknown	36 (18%)			39 (4.7%)		

Response to Treatment demographic table

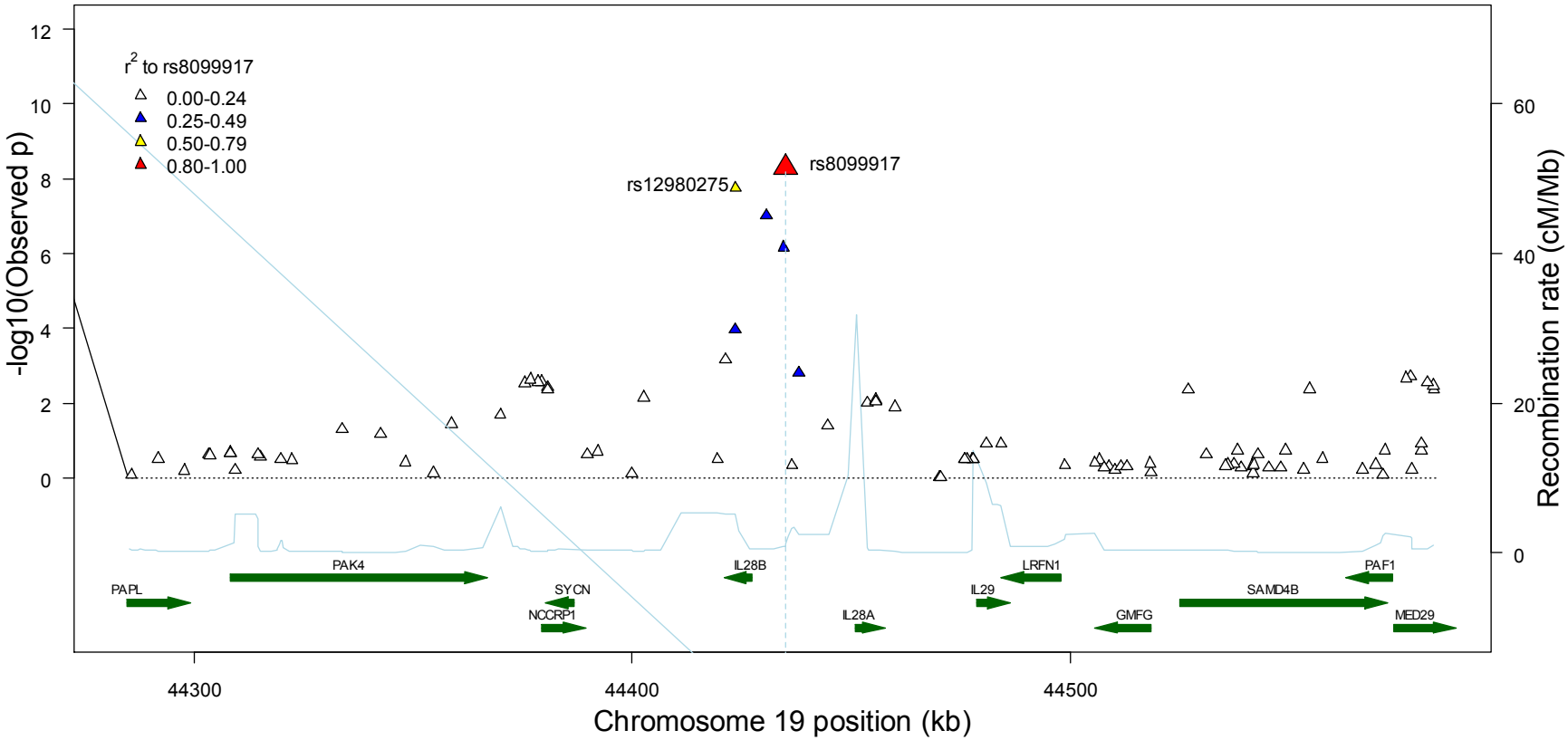
Characteristics (N, proportion)	NR	SVR	P
N	174	315	
Age (median, IQR)	19 (9)	20 (9)	0.04
Male sex	119 (68.4%)	185 (58.7%)	0.04
HBV antigen positive	2 (1.1%)	3 (1%)	0. 9
Log HCV RNA (median, IQR)	5.964 (0.844)	5.835 (1.226)	<0.001
HCV genotypes			
1	105 (60.3%)	94 (29.8%)	Ref
2	8 (4.6%)	53 (16.8%)	<0.001
3	29 (16.7%)	142 (45.1%)	<0.001
4	19 (10.9%)	17 (5.4%)	1
Other/unknown	13 (7.5%)	9 (2.9%)	0.6
Heavy drinker	31 (17.8%)	35 (11.1%)	0.03
Liver biopsy			
Inflammation	23 (13.2%)	45 (14.3%)	0.5
steatosis	85 (48.9%)	150 (47.6%)	0.5
Severe fibrosis	55 (31.6%)	59 (18.7%)	0.003

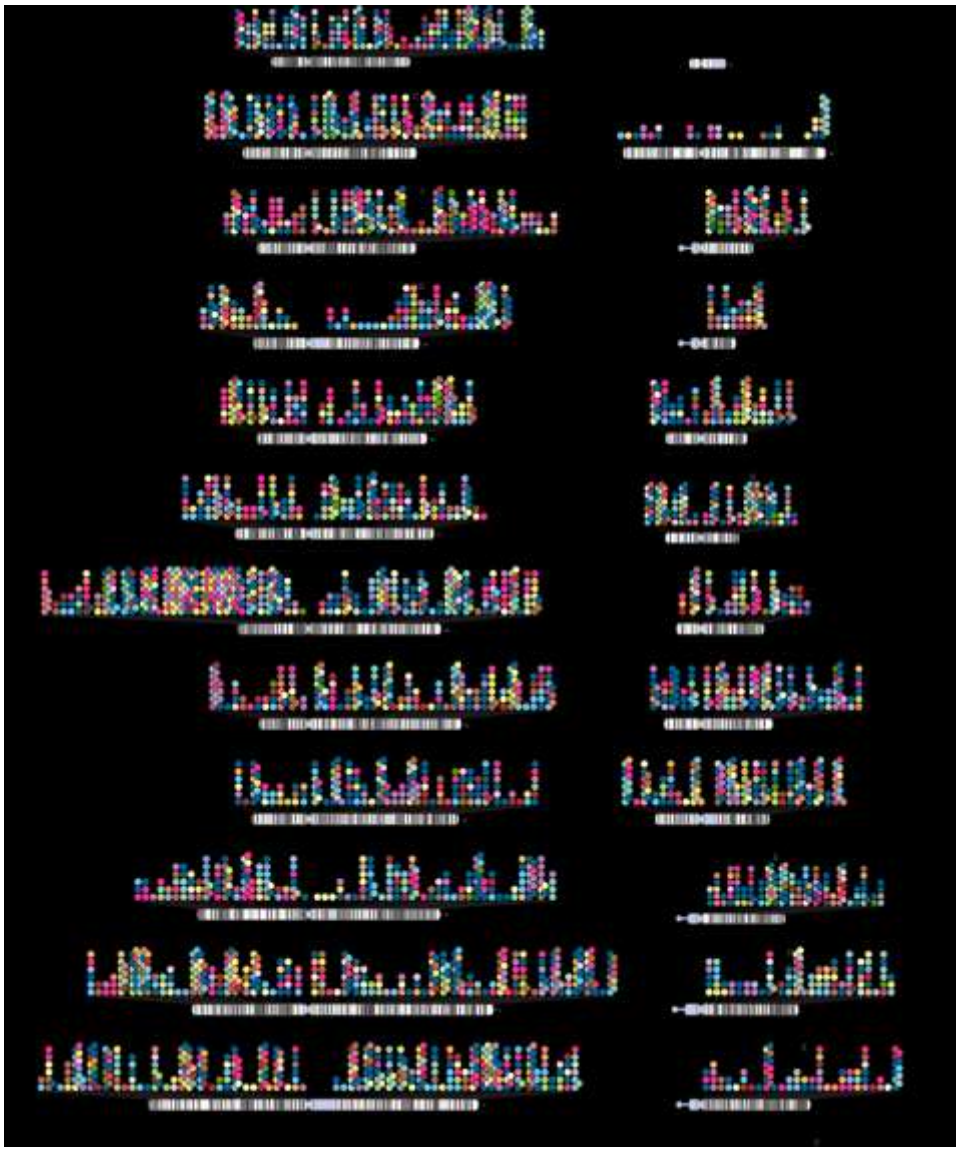
IL28B identification in the GWA for response to treatment





Region association plot of IL28B





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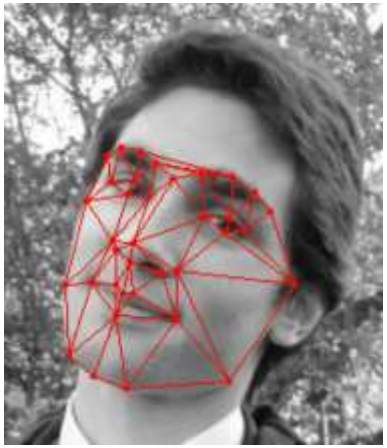
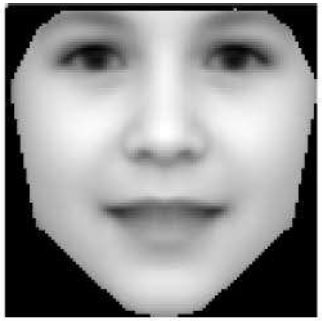
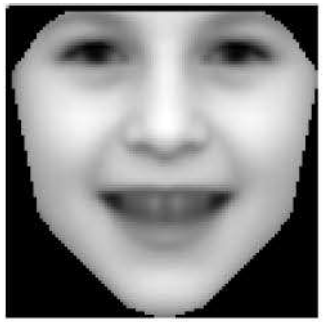
Diagnostically relevant facial gestalt information from ordinary photos



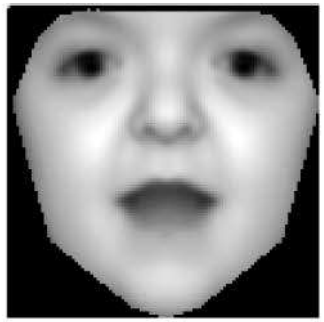
Elife, 2014



control

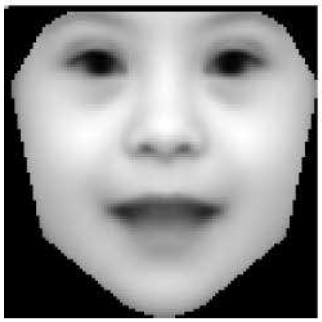


Angelman

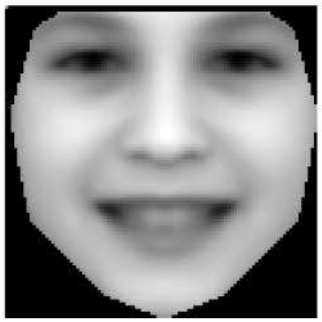


Apert

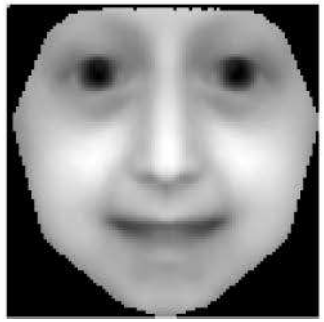
Cornelia de Lange



Down



Fragile X



Progeria

Treacher-Collins

Williams-Beuren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THANKS