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1 GWAS检测平台介绍

2 GWAS技术路线介绍

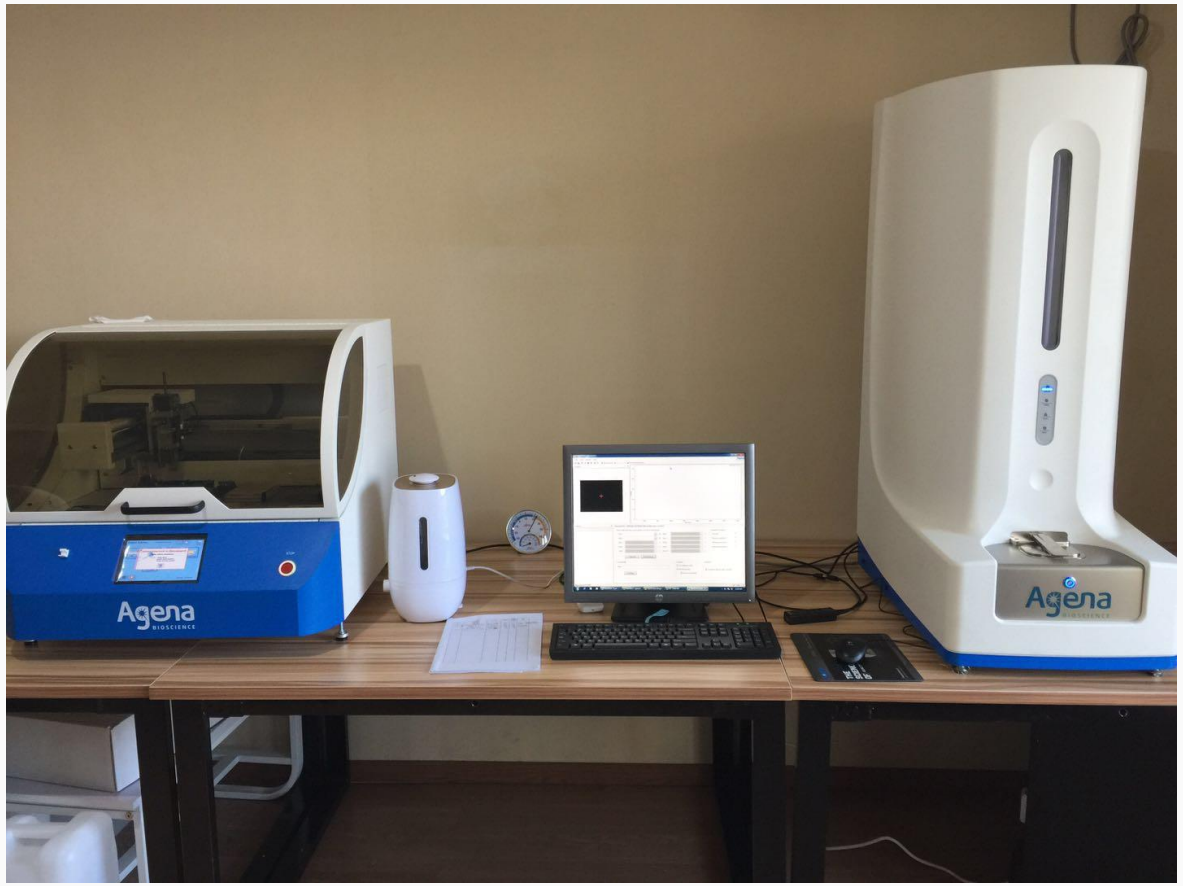
3 GWAS芯片介绍

4 GWAS数据分析介绍

iScan芯片技术服务

GWAS芯片	中华芯片 ASA芯片
甲基化芯片	850K芯片

Massarray技术服务



候选SNP位点分型

候选甲基化位点定量检测

GWAS技术路线

全基因组关联研究（Genome-wide Association Studies，GWAS）是指在全基因组层面上开展多中心、大样本、反复验证的基因与疾病的关联研究，全面揭示疾病发生、发展与治疗相关的遗传基因。GWAS为全面系统研究复杂疾病的遗传因素掀开了新的一页，为我们了解人类复杂疾病的发病机制提供了更多的线索。

GWAS技术路线

GWAS技术路线——群体散发样本

GWAS芯片检测

Illumina zhonghua8、ASA

候选SNP位点二期样本验证

Massarray Genotype

GWAS生物信息学分析

人群分层分析
单点分析
显著性注释
Fine mapping分析等

生物信息学分析

关联分析
单倍体型分析等

GWAS技术路线——家系样本

外显子/全基因组重测序

SNP/Indel等数据分析

GWAS基因芯片检测

连锁分析确定候选区域

候选突变位点

家系所有样本候选突变检测

突变与表型共分离分析

致病基因突变

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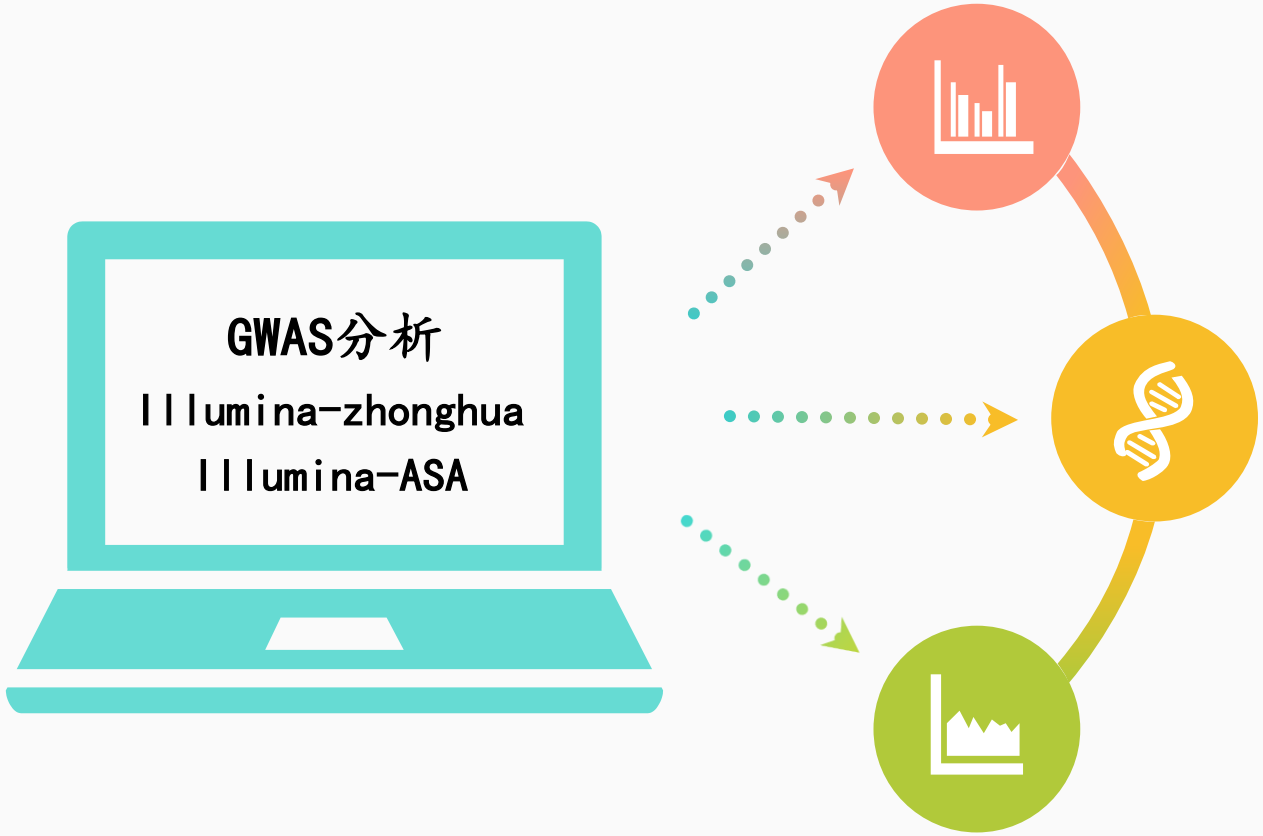
GWAS技术路线——eQTL、mQTL研究



转录组分析

Expression quantitative trait loci

表达谱芯片/转录组NGS

表观遗传学分析

Methylation quantitative trait loci

Illumina 850K array

代谢组分析

Metabolomic quantitative trait loci

GC/LC mass, NMR

GWAS技术路线——eQTL、mQTL研究

PLoS Genet. 2015 Nov 5;11(11):e1005553. doi: 10.1371/journal.pgen.1005553. eCollection 2015.

Metabolomic Quantitative Trait Loci (mQTL) Mapping Implicates the Ubiquitin Proteasome System in Cardiovascular Disease Pathogenesis.

Kraus WE[1,2], Muoio DM[2,3], Stevens R[2], Craig D[2], [illegible] ER[2,4], Gregory SG[2], Newgard CB[2], Shah SH[1,2].

Author information

Abstract

Levels of certain circulating short-chain dicar
acylcarnitine (MCA) metabolites are heritable
pathways that influence levels of most of thes
metabolomics in samples from a large CVD c
metabolites in CVD pathogenesis. Using gen
several metabolites with genetic loci. Our stro
components of endoplasmic reticulum (ER) s
a second cohort of CATHGEN subjects (N = 2
independently predicted CVD events. Associ
genes as differentially methylated (BRSK2 ar
variants and SCDA metabolites corroborated
Moreover, culture of human kidney cells in th
induced accumulation of SCDA metabolites ir
implicates the UPS arm of the ER stress path
risk.

Mol Psychiatry. 2013 Mar;18(3):340-6. doi: 10.1038/mp.2011.174. Epub 2012 Jan 3.

Enrichment of cis-regulatory gene expression SNPs and methylation quantitative trait loci among bipolar disorder susceptibility variants.

Gamazon ER[1], Badner JA, Cheng L, Zhang C, Zhang D, Cox NJ, Gershon ES, Schork NJ, Smith EN, Bloss CS, Nurnberger JI, Edenberg HJ, Foroud T, Koller Byerley W, McMahon FJ, Schulze TG, Berrettini WH, Potash JB, Zandi PP, Mahe C.

Author information

Abstract

We conducted a systematic study of top susceptibility variants from
gain insight into the functional consequences of genetic variation in
explore the effects of these susceptibility variants on DNA methylati
the top susceptibility variants, we identified an enrichment of cis reg
of quantitative trait loci for DNA CpG methylation, hereafter referrec
susceptibility variants that cis regulate both cerebellar expression a
bipolar disorder susceptibility variants. This finding suggests that m
annotating genetic variation within the context of studies of pathoph
suggesting that mQTL enrichment was specific to the cerebellum, ir
information to restrict the number of single-nucleotide polymorphisn
With this restriction a priori informed by the observed functional enr
P(bonferroni)<0.05) from two other GWA studies (TGen+GAIN; 219
in an independent GWA study (WTCCC). Collectively, our findings
genetic variants for gene expression and DNA methylation to advar

Schizophr Bull. 2015 Nov;41(6):1294-308. doi: 10.1093/schbul/sbv017. Epub 2015 Mar 10.

Systematic Integration of Brain eQTL and GWAS Identifies ZNF323 as a Novel Schizophrenia Risk Gene and Suggests Recent Positive Selection Based on Compensatory Advantage on Pulmonary Function.

Luo XJ[1], Mattheisen M[2], Li M[3], Huang L[4], Rietschel M[5], Børglum AD[6], Als TD[7], van den Oord EJ[8], Aberg KA[8], Mors O[9], Mortensen PB[10], Luo Z[11], Degenhardt F[12], Cichon S[13], Schulze TG[14], Nöthen MM[12], iPSYCH-GEMS SCZ working group; MooDS SCZ Consortium, Su B[15], Zhao Z[16], Gan L[16], Yao YG[17].

Collaborators (33)

Author information

Abstract

Genome-wide association studies have identified multiple risk variants and loci that show robust association with schizophrenia. Nevertheless, it remains unclear how these variants confer risk to schizophrenia. In addition, the driving force that maintains the schizophrenia risk variants in human gene pool is poorly understood. To investigate whether expression-associated genetic variants contribute to schizophrenia susceptibility, we systematically integrated brain expression quantitative trait loci and genome-wide association data of schizophrenia using Sherlock, a Bayesian statistical framework. Our analyses identified ZNF323 as a schizophrenia risk gene (P = 2.22×10(-6)). Subsequent analyses confirmed the association of the ZNF323 and its expression-associated single nucleotide polymorphism rs1150711 in independent samples (gene-expression: P = 1.40×10(-6); single-marker meta-analysis in the combined discovery and replication sample comprising 44123 individuals: P = 6.85×10(-10)). We found that the ZNF323 was significantly downregulated in hippocampus and frontal cortex of schizophrenia patients (P = .0038 and P = .0233, respectively). Evidence for pleiotropic effects was detected (association of rs1150711 with lung function and gene expression of ZNF323 in lung: P = 6.62×10(-5) and P = 9.00×10(-5), respectively) with the risk allele (T allele) for schizophrenia acting as protective allele for lung function. Subsequent population genetics analyses suggest that the risk allele (T) of rs1150711 might have undergone recent positive selection in human population. Our findings suggest that the ZNF323 is a schizophrenia susceptibility gene whose expression may influence schizophrenia risk. Our study also illustrates a possible mechanism for maintaining schizophrenia risk variants in the human gene pool.

中华芯片

HumanOmniZhongHua

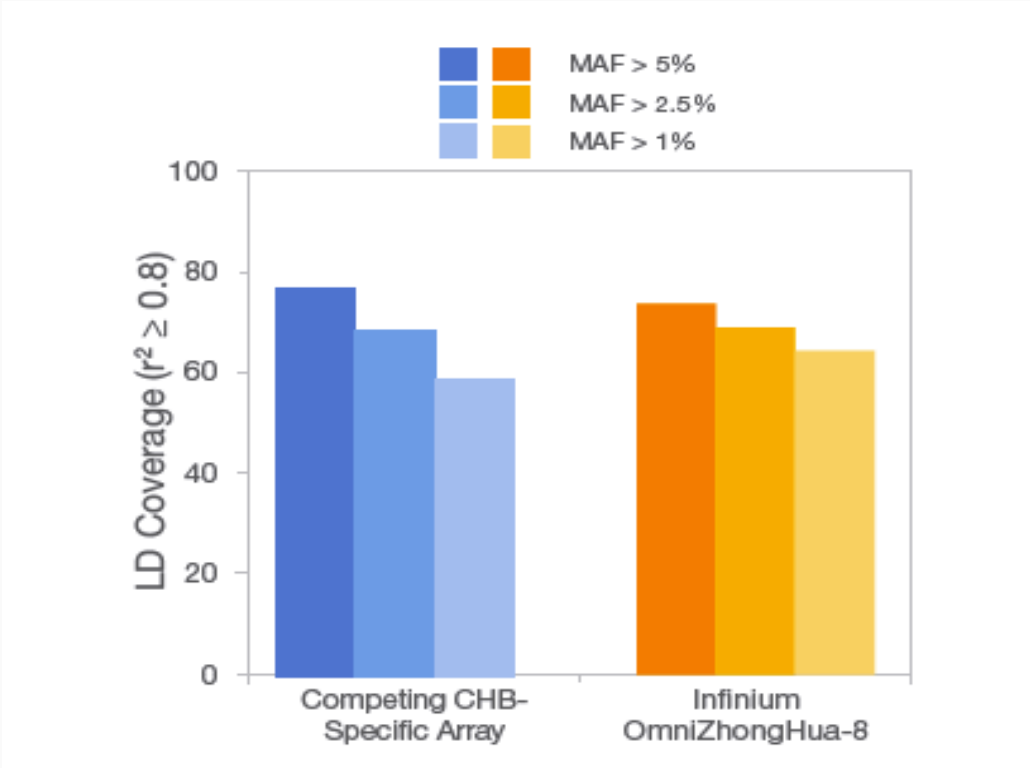
最大程度覆盖了在中国人群体中发现的常见和稀有变异，优化的标签SNP内容来自HapMap所有三个阶段以及千人基因组计划。

优势：针对中国人群位点设计，覆盖率很高，属于中国人群GWAS研究的首选。

GWAS芯片介绍

- SNP位点数量：878,291个；

- MAF>5%的覆盖率为77%，MAF>2.5%的覆盖率为73%，MAF>1%的覆盖率为65%，关联参数r2>0.8；



GWAS芯片介绍

Marker Categories	Number of Markersa
In RefSeqb Genes	387,986 (469,862)
In RefSeq Exons	44,577
In RefSeq Promoter Regions	20,420
In ADME Genes	9883 (12,592)
In ADME Exons	973
MHC (Extended MHC)	7770 (12,049)
Overlap with Genes in COSMIC	352,213
Overlap with Genes in Gene Ontology	93,823
Nonsense Markers	88
Missense Markers	10,485
Synonymous Markers	11,512
Silent Markers	22,489
Mitochondrial Markers	107
Indels	24
Sex Chromosomes	X Y 20,46 1772

Asian Screening array芯片

迄今为止对东亚地区(CHB JPT等为主）的低频突变体（MAF为1-5%）覆盖度最佳的芯片；
最新的明确临床意义位点、药物疗效相关位点、HLA区域位点、GWAS易感位点等共计12万个；
质控位点共计1.6万个；
每张芯片24个样本。

优势：价格低廉、包含明确意义位点

GWAS芯片介绍

Genome-Wide Backbone ~ 660,000

- Maximized imputation Accuracy and Genomic Coverage
- 9000 Asian Whole Genomes 15x/30x coverage

Clinical Research ~ 120,000

- Known clinical information
- Pharmacogenomics
- HLA
- Loss of Function Exome
- ASA KOL submissions

Asian Discovery Panel ~ 50,000

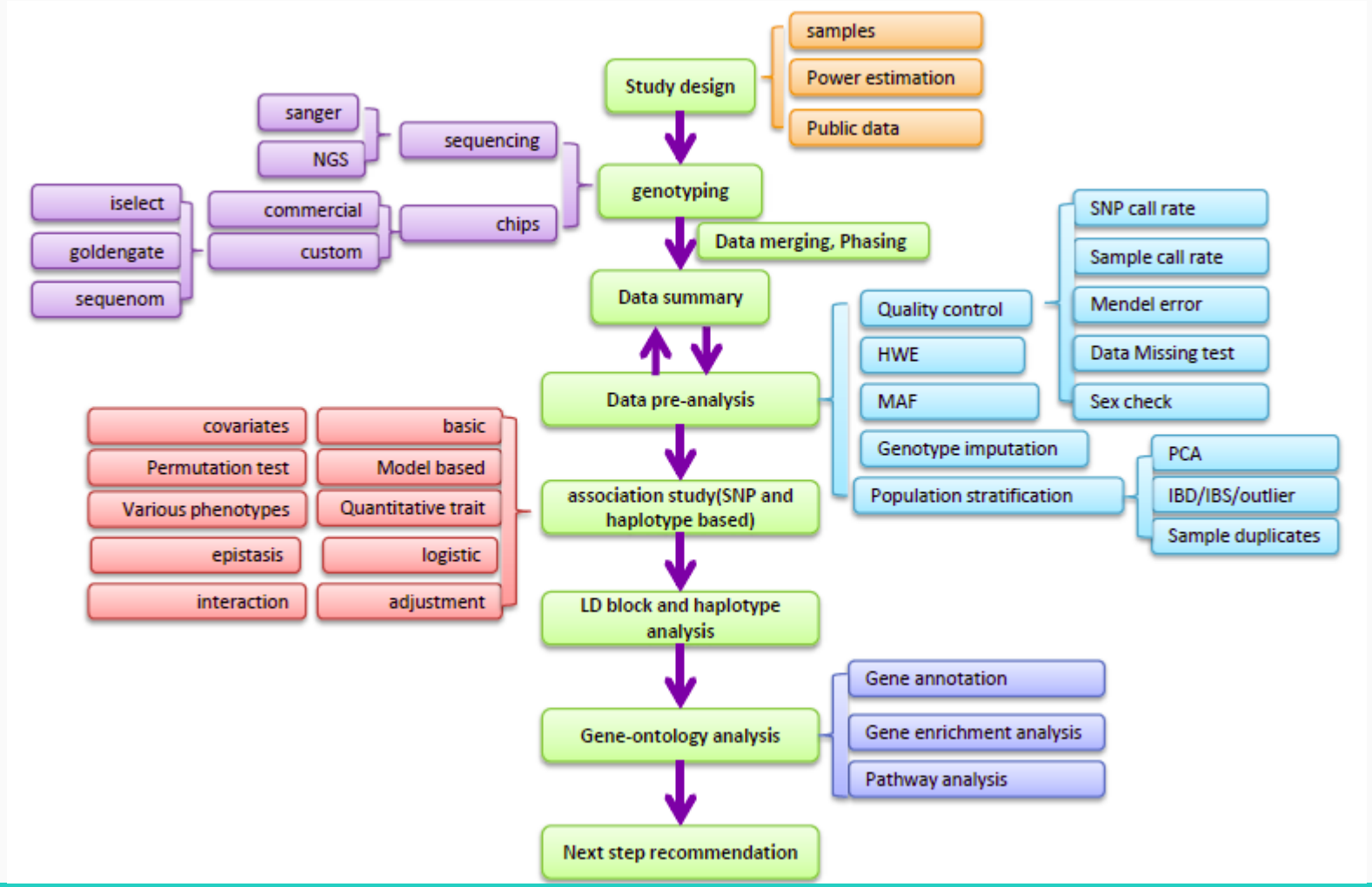
- Novel genes/alleles associated with clinical phenotypes (phenotype agnostics)
- Asian specific LOF Exome

Quality Control ~ 16,000

- Sample tracking and stratification
- Asian focused panel of AIMS

GWAS数据分析介绍

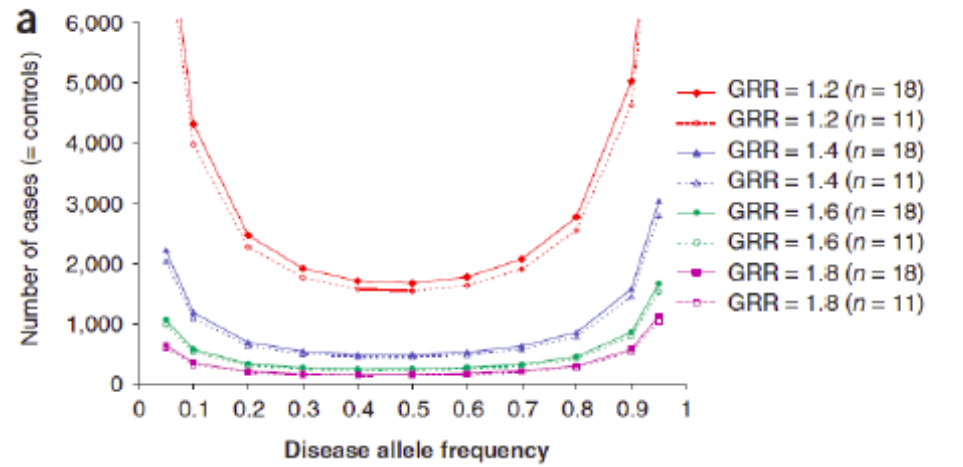
Association study flow



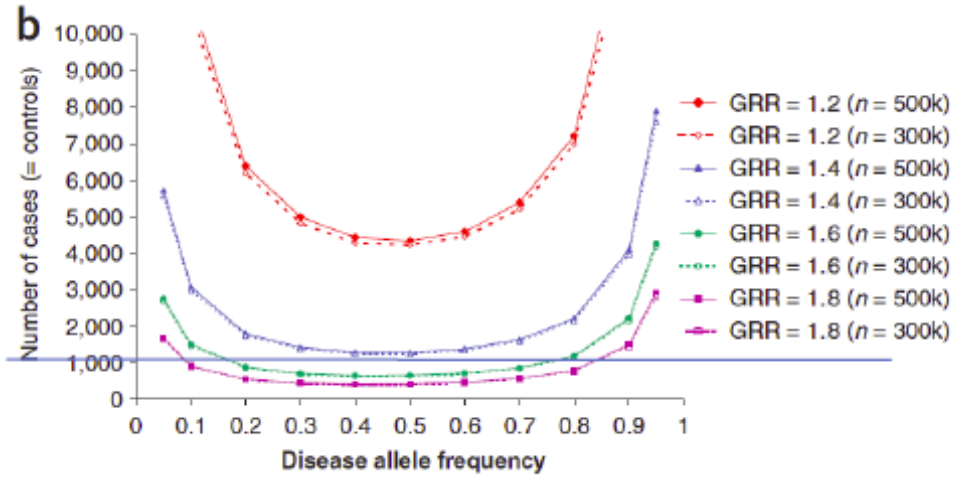
GWAS数据分析介绍

Case size

Candidate



GWAS

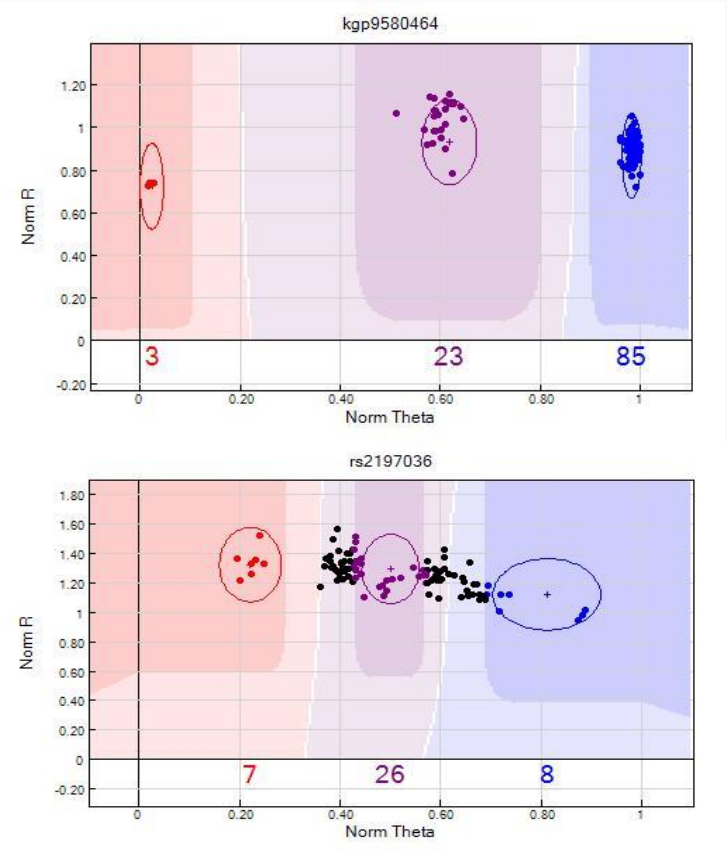


80% Power

- 预处理
  - Sample Call rate
  - SNP call Frequence
  - HWE
  - MAF

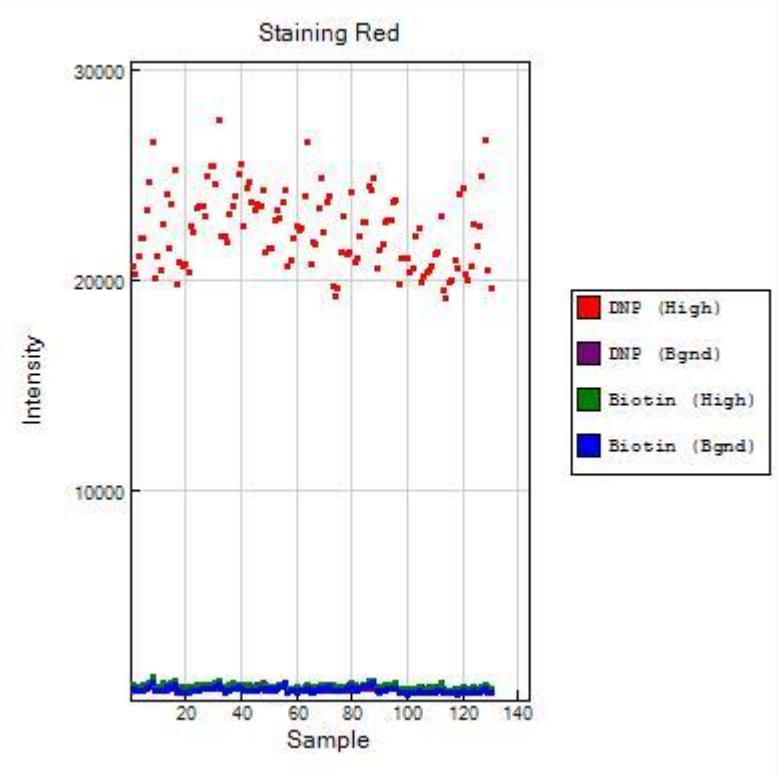
GWAS数据分析介绍

- Genotyping
  - Genomestudio V2011 genotype module V1.9.4
    - Manifest file
    - Cluster file



Internal control analysis

- Internal control
  - Staining
  - Extension
  - Hybridization
  - Target Removal
  - Stringency
  - Non-specific binding
  - Non polymorphic



Imputation analysis

- Imputation

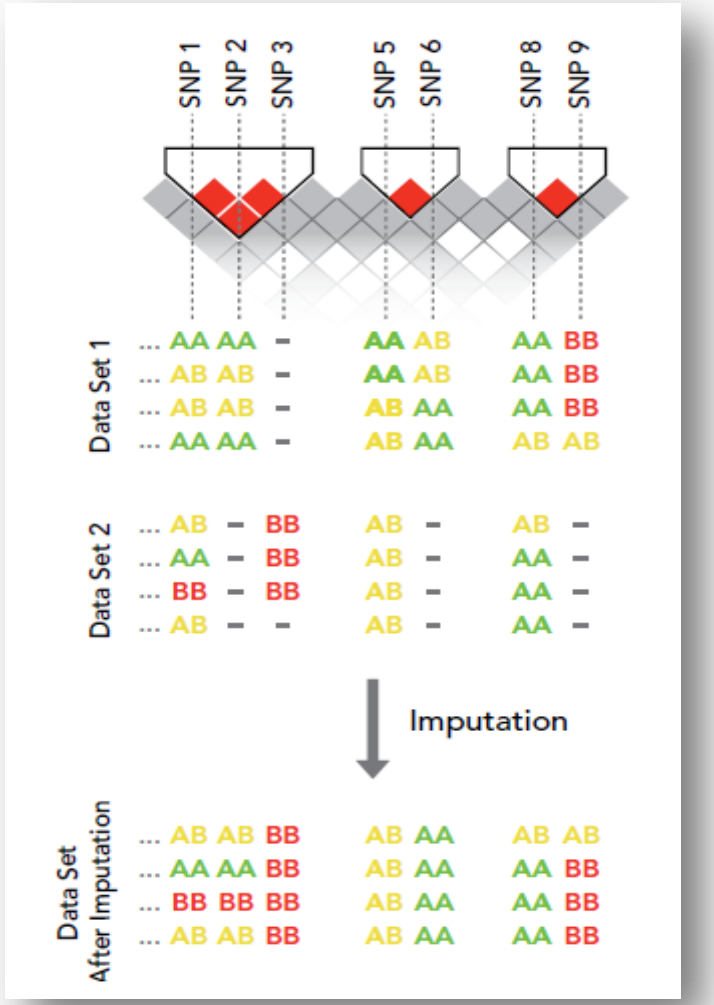
> Imputation exploits "available information about patterns of correlation among typed and untyped SNPs in a reference panel …(e.g. HapMap samples) to explicitly predict, or impute, the genotypes at untyped SNPs in a study sample".
>
> --Guan et al., *PLoS Genetics*

Benefits of Imputation:

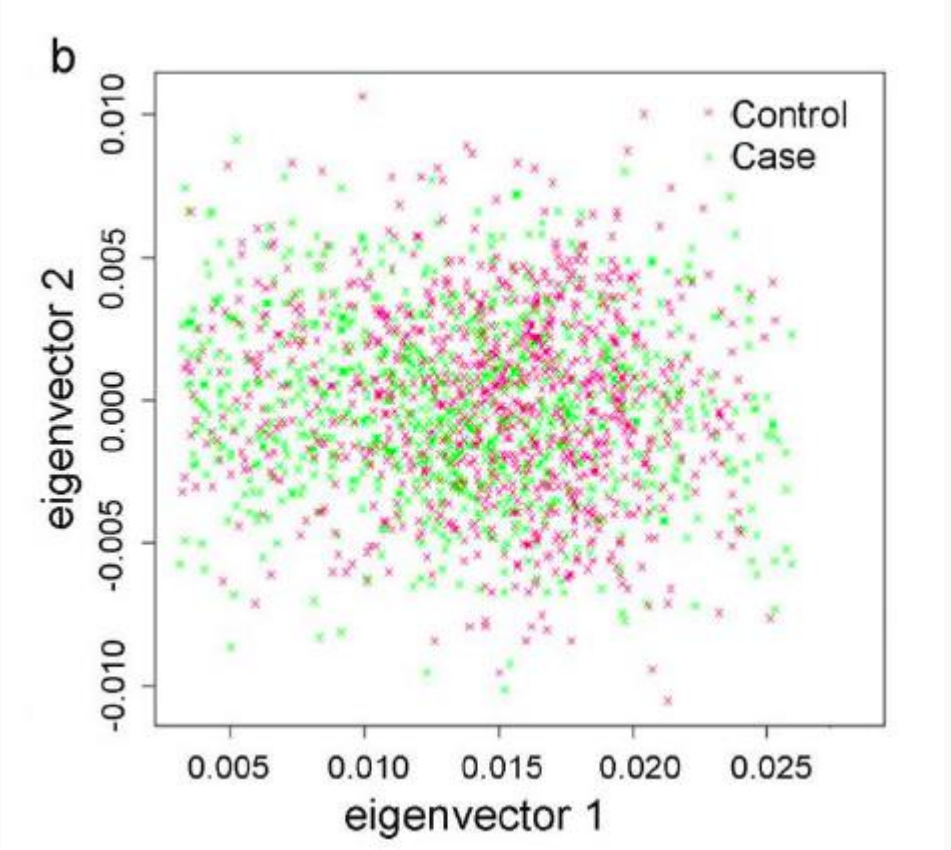
1. Increases "power" to detect associations
2. Provides improved explanation for detected associations
   - helps to localize causal variant
3. Powerful framework for combining data collected across different genotyping platforms

GWAS数据分析介绍

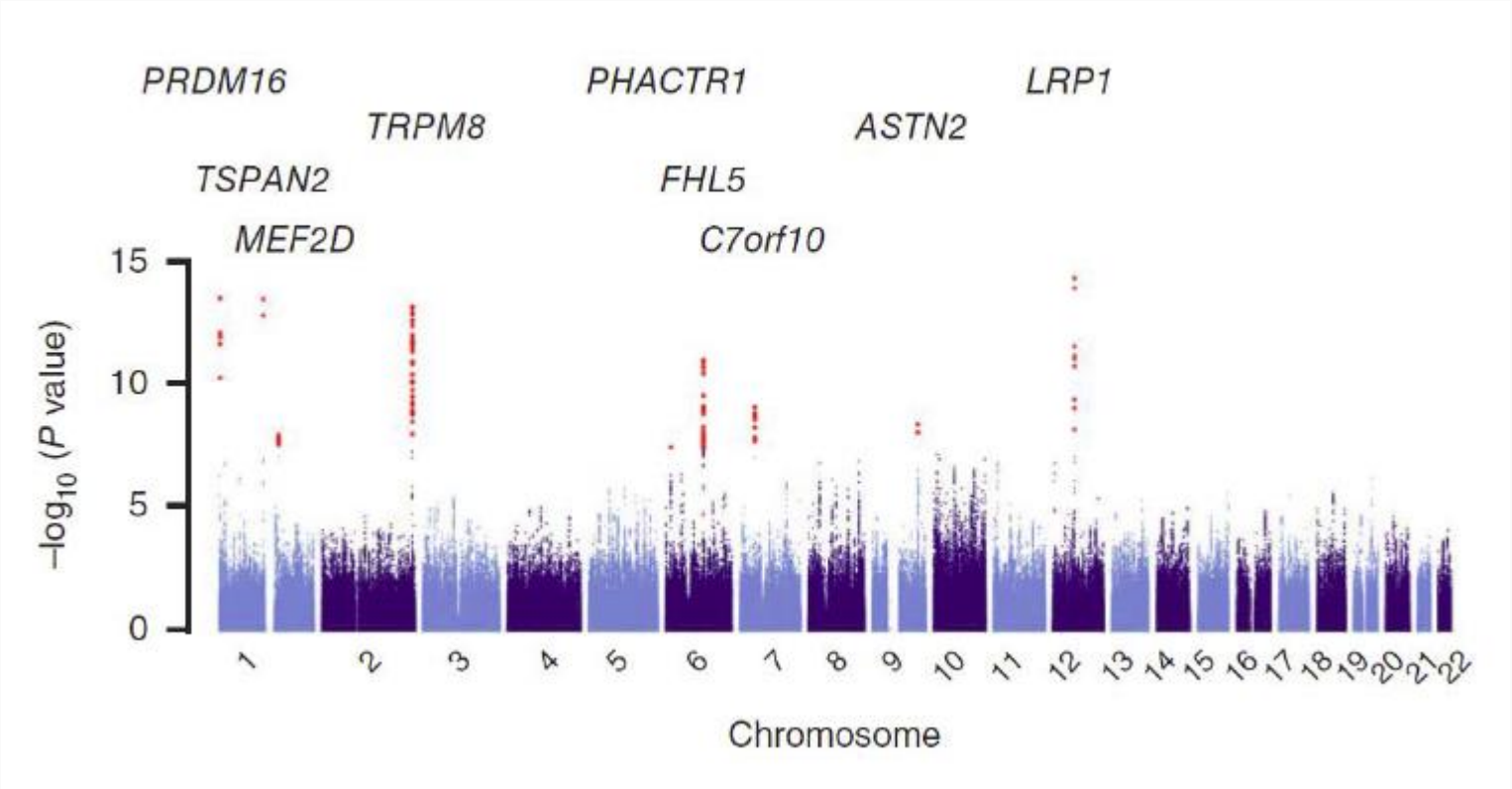
- SNPs 1－9 form three blocks of high LD
- Data Sets 1 and 2 represent a total of eight individuals genotyped using two different arrays at SNPs 1－9.
- SNP 2 is genotyped in Data Set 1 but not Data Set 2.
- Due to strong LD between SNPs 1－3, the individual genotypes for SNP 2 can be inferred in Data Set 2 based on those present in Data Set 1.



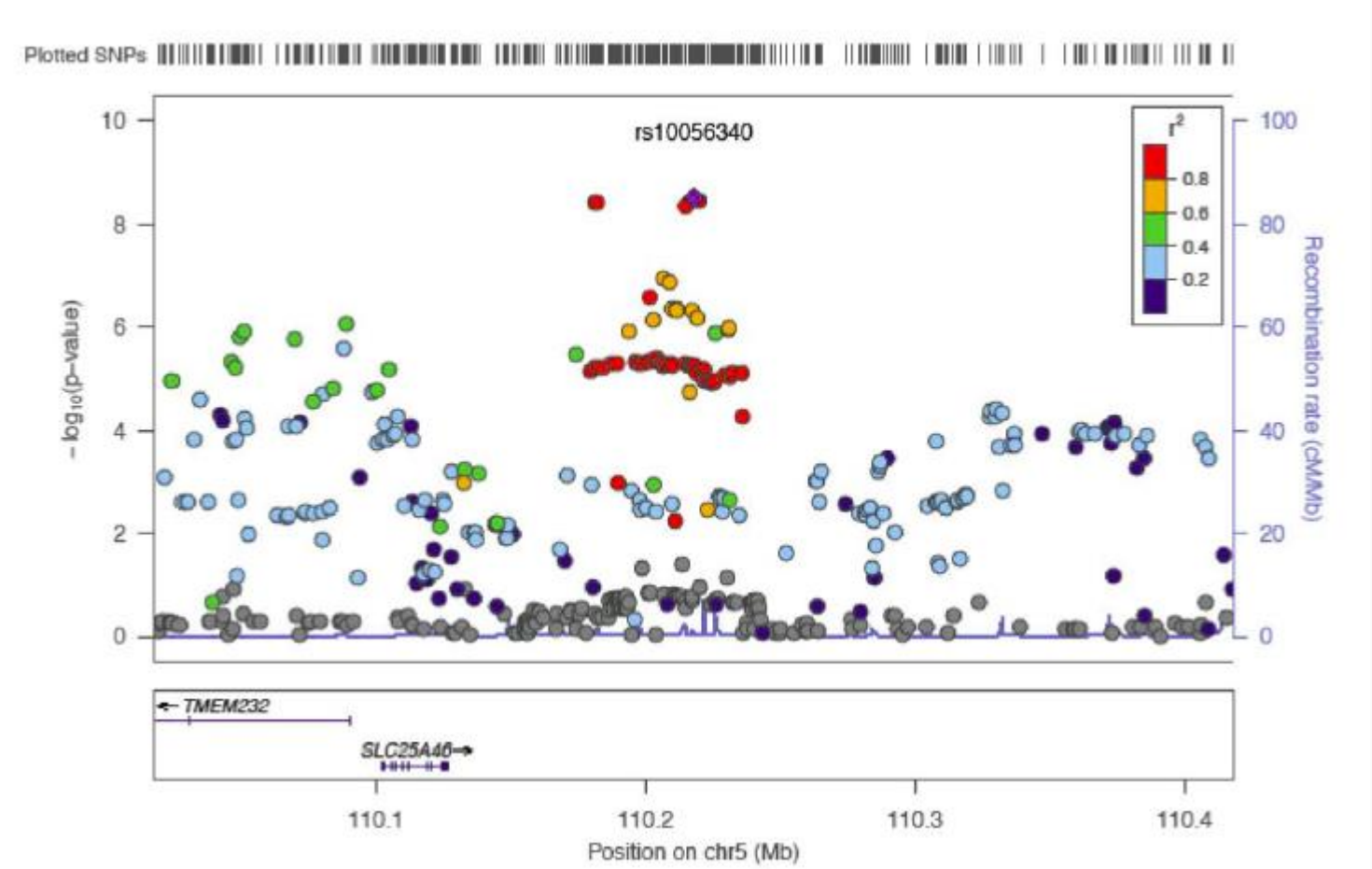
- 群体分层
  - PCA
  - MDS


b
Control
Case
eigenvector 2
0.010
0.005
0.000
-0.005
-0.010
0.005
0.010
0.015
0.020
0.025
eigenvector 1

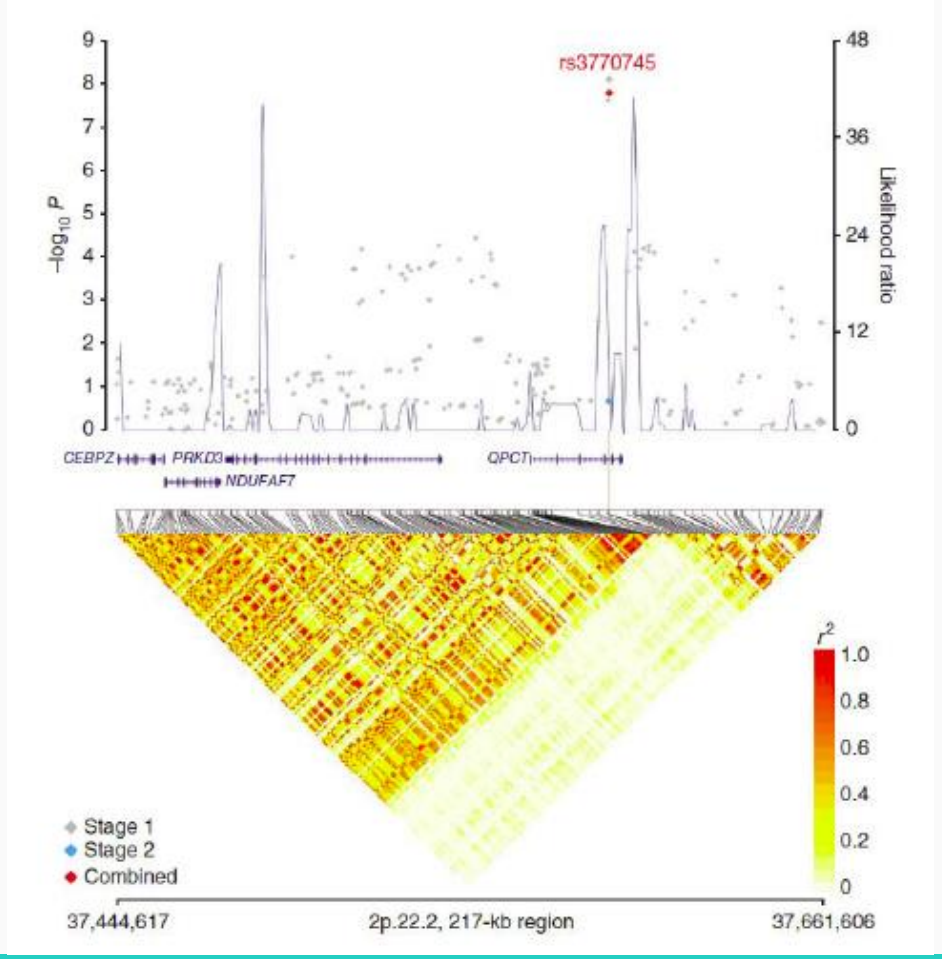
Manhattan plot



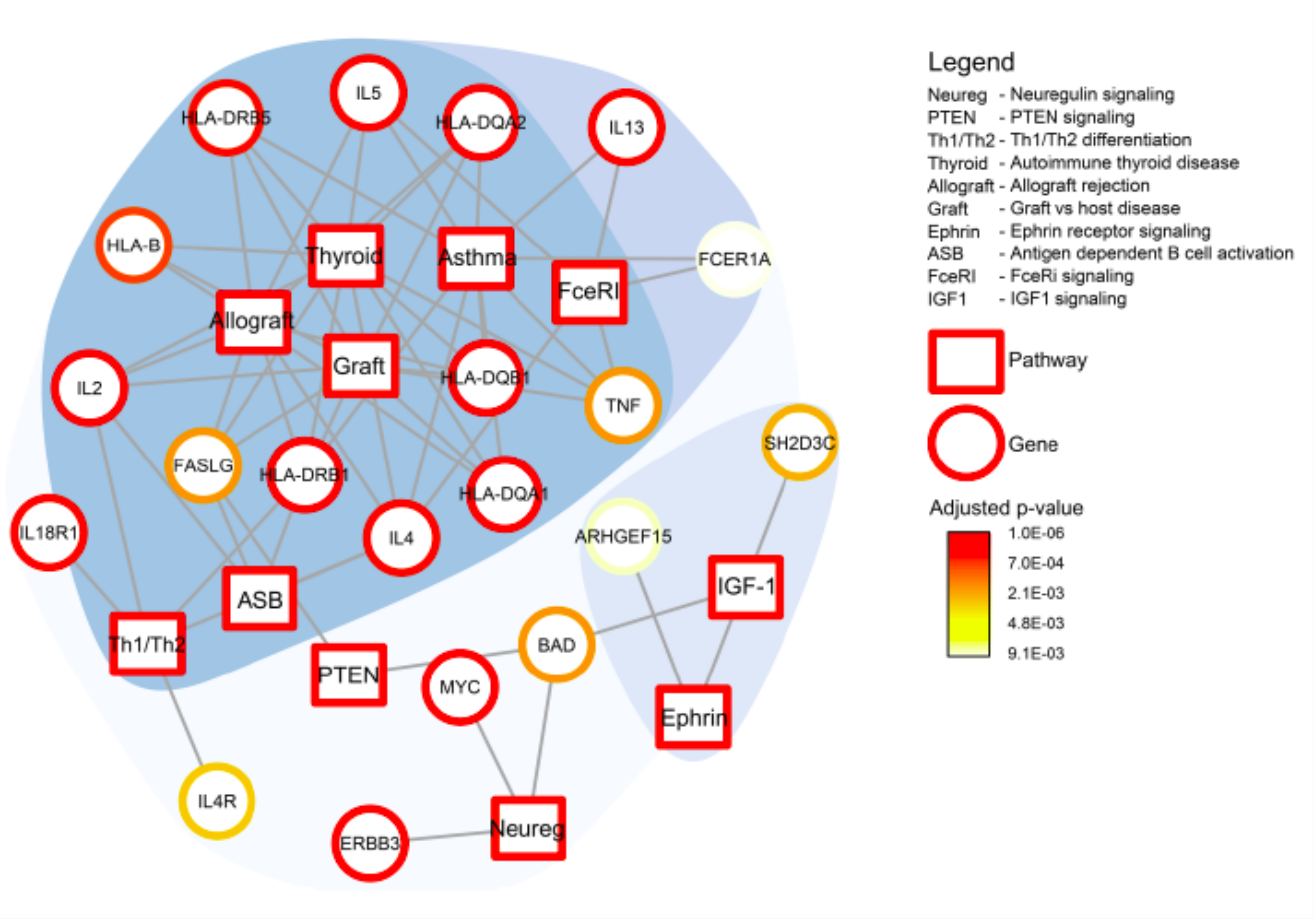
Regional association plot



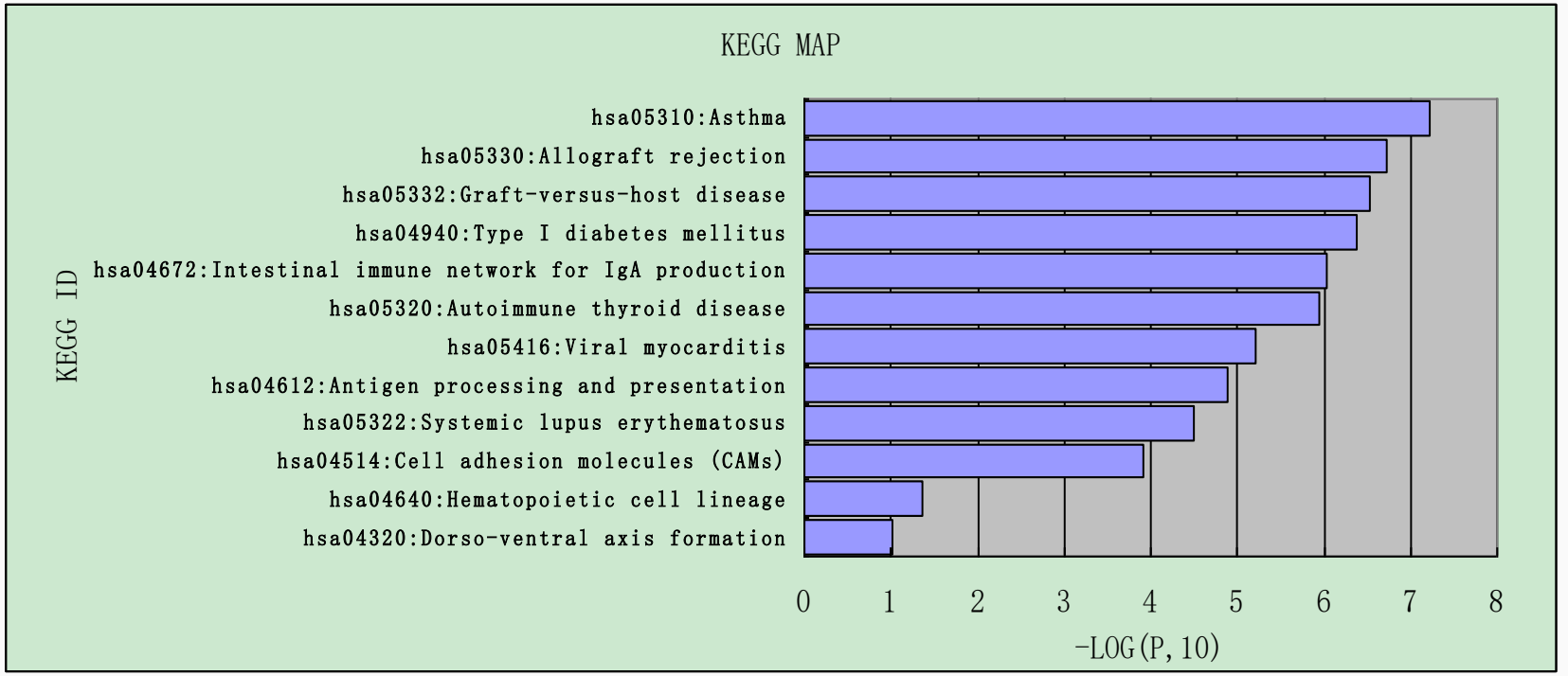
LD block


rs3770745
$-\log_{10} P$
Likelihood ratio
CEBPZ
PRKD3
NDUFAF7
QPCT
r^2
Stage 1
Stage 2
Combined
37,444,617
2p.22.2, 217-kb region
37,661,606

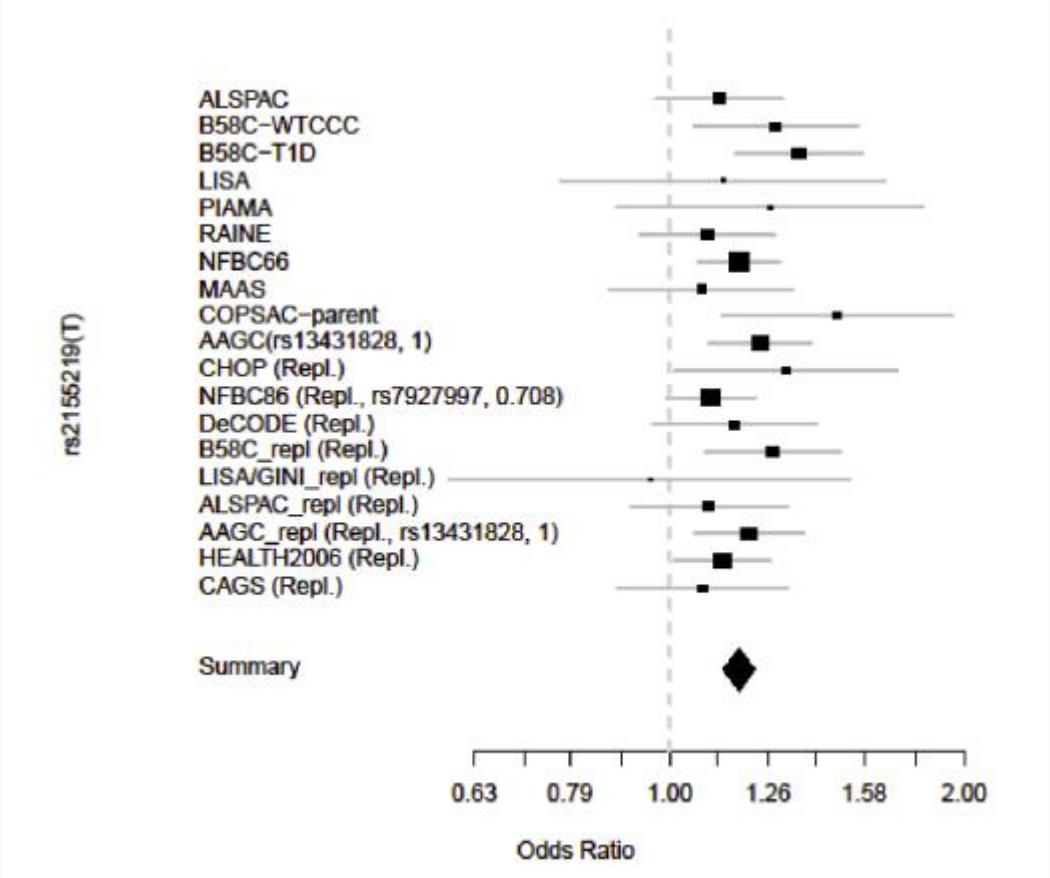
Bipartite network



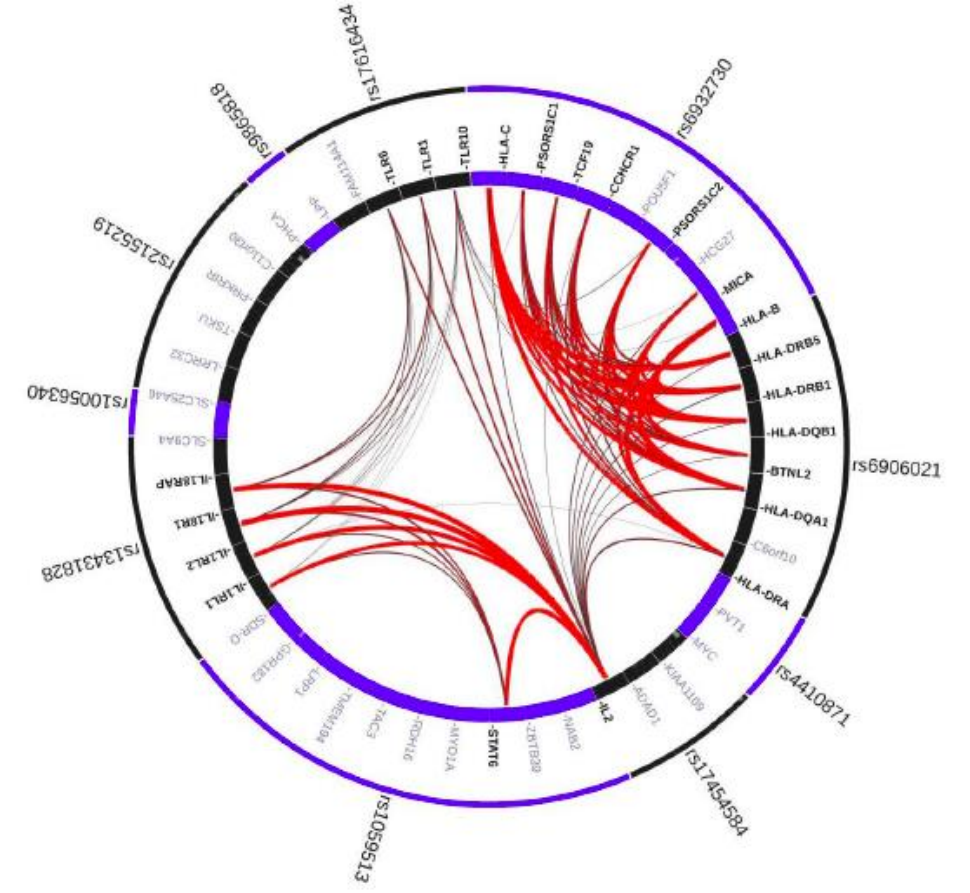
KEGG


KEGG MAP
KEGG ID
hsa05310:Asthma
hsa05330:Allograft rejection
hsa05332:Graft-versus-host disease
hsa04940:Type I diabetes mellitus
hsa04672:Intestinal immune network for IgA production
hsa05320:Autoimmune thyroid disease
hsa05416:Viral myocarditis
hsa04612:Antigen processing and presentation
hsa05322:Systemic lupus erythematosus
hsa04514:Cell adhesion molecules (CAMs)
hsa04640:Hematopoietic cell lineage
hsa04320:Dorso-ventral axis formation
0
1
2
3
4
5
6
7
8
-LOG(P,10)

Forest plot


rs2155219(T)
ALSPAC
B58C-WTCCC
B58C-T1D
LISA
PIAMA
RAINE
NFBC66
MAAS
COPSAC-parent
AAGC(rs13431828, 1)
CHOP (Repl.)
NFBC86 (Repl., rs7927997, 0.708)
DeCODE (Repl.)
B58C_repl (Repl.)
LISA/GINI_repl (Repl.)
ALSPAC_repl (Repl.)
AAGC_repl (Repl., rs13431828, 1)
HEALTH2006 (Repl.)
CAGS (Repl.)
Summary
0.63
0.79
1.00
1.26
1.58
2.00
Odds Ratio

GRAIL analysis



GWAS数据分析介绍

- 软件
  - Plink
  - GCTA
  - SNPstats
  - R package
  - SHEsis
  - ……

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