Whole-exome sequencing analyses identify risk genomic loci for Nasopharyngeal Carcinomas

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Background and study design

Nasopharyngeal Carcinomas (NPC)

- High prevalence in southern China, southeast Asia and northern Africa[1]
- Knowledge on genetic etiology is confined to common variants (GWAS)[2]
- Narrow-sense heritability: 61.3%, of which only 16.9% from common SNPs[3]
- Epstein-Barr virus linked to NPC[4]

NPC Whole-Exome Sequencing Project

- Goal: identify germline rare mutations, genes and pathways for NPC.
- Samples collected from south China and Singapore
- Whole-exome sequencing from blood
- N_case=2,465,N_control=2,304
- Among cases:
  - Cases with family history: N=417

Material and Methods

Variants Calling and Quality Control

Whole blood DNA exome
- BWA alignment
- Variant Calling
  - GATK + Sentieon
- QC:
  - VQSR
  - SNV:
    - Read depth(DP)>=10;
    - 0.2<=Allelic Balance(AB)<=0.8;
    - Genotype quality(GQ) >=30

Dataset specific QC:
- Mutation rates per reads and strand bias

Post-QC SNVs: n=952,873

Statistical Test

Genetic contribution of Common VS Rare variation in exome:
- GREML-LDMS
  - 28 components:
  - 4 LD score groups
  - 7 MAF bins

Risk/Protective Gene and pathways for rare and common mutations in NPC:
- SNP-set (Sequence) Kernel Association Test (SKAT)
- Examined pathways:
  - Curated gene sets
  - GO ontology
  - Oncogenic gene sets

Result 1: Rare VS Common Variants

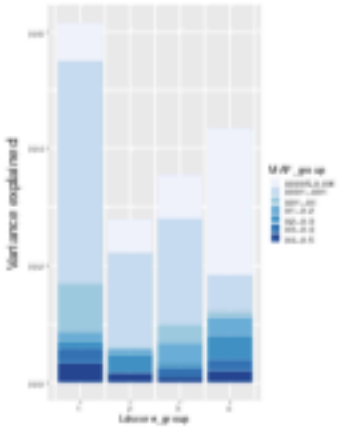

Figure 1. Phenotypic variance explained by each LDScore group and each minor allele frequency bin in NPC.

- Exome SNP heritability:
  - Overall: 16.8%(2.6%)
- Major contribution from rare variants
- Strong selection pushes causal SNV to low MAF.
- Contribution from extremely rare SNV hasn't been counted
- Contribution from MHC region hasn't been counted.

Result 2: Pathways and Genes

Set ID	P-value	N.Markers.All	N.Markers.Test	N. Marker. Conv	N.Marker.Comm on	FDR
GO_LEUKOCYTE_ADHESION_TO_VASCULAR_ENDOTHELIAL_CELL	1.22E-05	148	148	95	53	0.039
GO_CELLULAR_EXTRAVASATION	2.08E-05	301	301	200	101	0.039
GO_REGULATION_OF_LIPASE_ACTIVITY	2.53E-05	948	948	708	240	0.039
GO_RESPONSE_TO_INTERLEUKIN_1	3.32E-05	918	918	685	233	0.039
GO_COATED_PIT	3.80E-05	1162	1162	851	311	0.039
GO_REGULATION_OF_PHOSPHOLIPASE_ACTIVITY	6.06E-05	779	779	581	198	0.045
GO_ACTIVATION_OF_PHOSPHOLIPASE_C_ACTIVITY	6.15E-05	306	306	211	95	0.045
GO_POSITIVE_REGULATION_OF_PROTEIN_IMPORT	7.63E-05	1206	1206	915	291	0.049

Table 1. Significant pathways associated with NPC by SKAT analysis

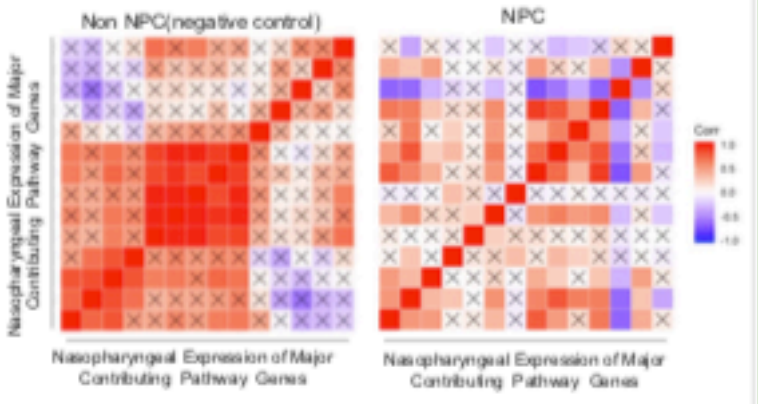

Figure 2. Nasopharyngeal Expression of Major contributing genes from NPC-associated pathways in NPC negative control samples VS NPC samples.

References

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