ESCC genetic susceptibility

NCI-IARC Tumor Workshop:
ESCC: Current insights & future priorities for a globally important cancer

Bethesda, MD, USA
Session 2: Genetics/Genomics

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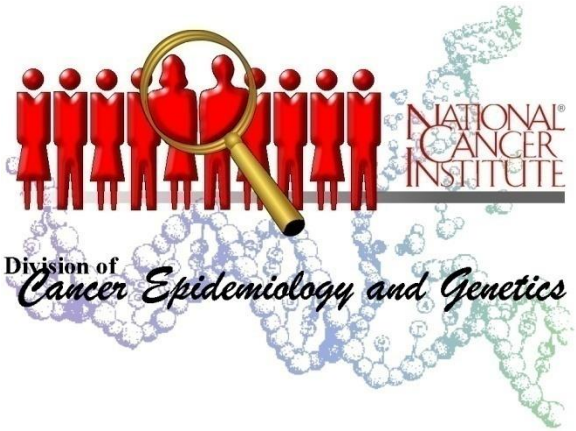


Lines of evidence for role of genetics in the etiology of ESCC

- Epidemiologic studies associate positive family history & ESCC
- ESCC shows evidence of familial aggregation
- Segregation analysis suggested a Mendelian pattern of inheritance for ESCC
- Cytogenetic studies showed greater chromosomal instability in healthy family members of ESCC cases than healthy persons from non-ESCC families

ESCC GWAS to date

Country	1st Author (year, journal)	Chip	#Cases scanned
Japan	Cui (2009, Gastro)	Illumina 550	188
	Tanaka (2010, Gut)	Affy 500K	226
China	Abnet (2010, NG)	Illumina 660W	2013
	Wang (2010, NG)	Illumina 660W	1375
	Lin (2011, NG)	Affy 6.0	1958
Europe	McKay (2011, PLoS Gen)	Illumina 300	314

LETTERS

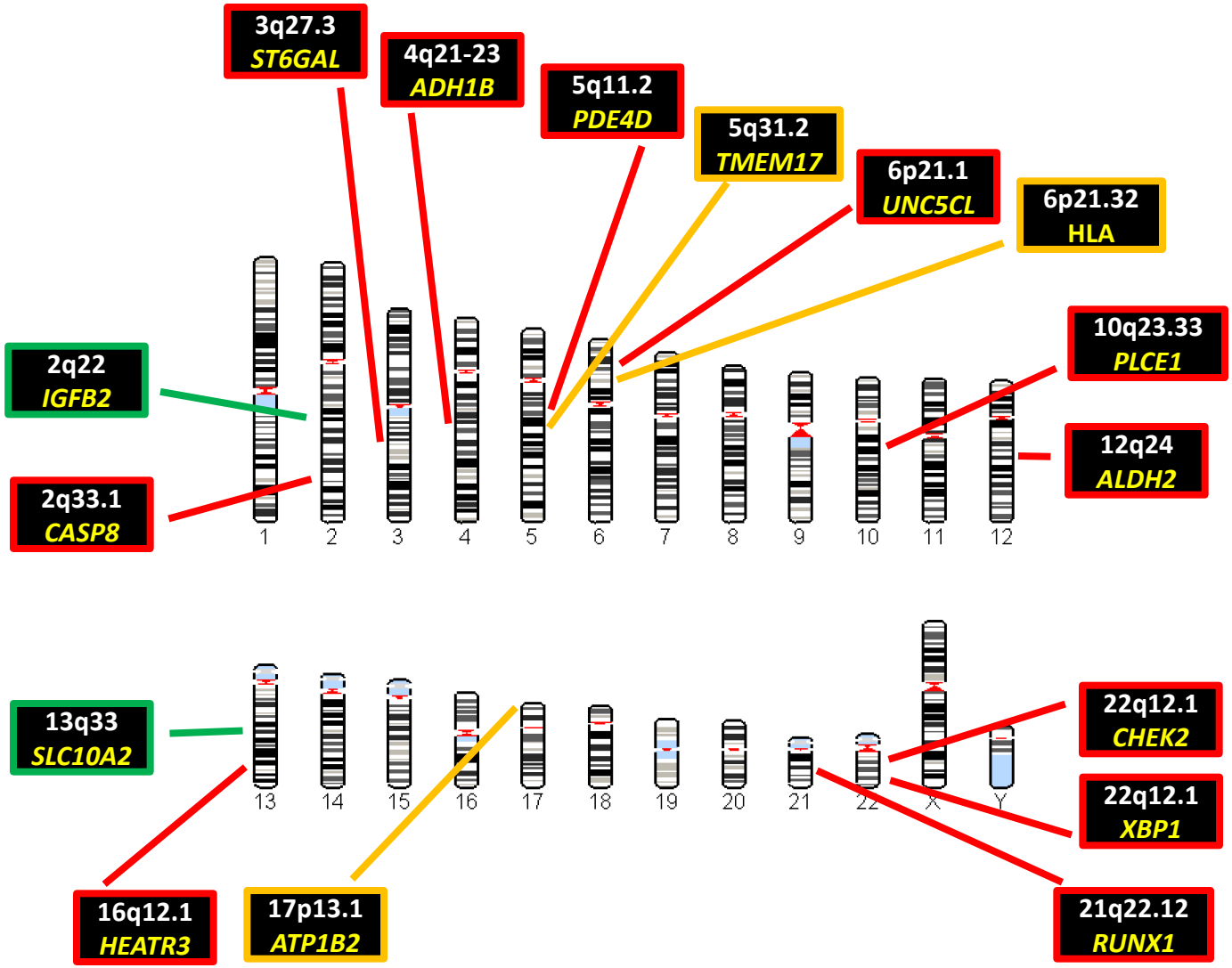
nature genetics

Joint analysis of three genome-wide association studies of esophageal squamous cell carcinoma in Chinese populations

- Joint analysis of 3 prior ESCC GWAS in Chinese
- Scanned: 5337 ESCCs, 5787 controls
- Replication: 9654 ESCCs, 10058 controls
- Results:
  - 2 new loci found (5q31.2/*TMEM173*, 17p13.1/*ATP1B*)
  - 3rd locus at 6p21.32 (HLA class II region)
  - 4 previously reported loci NOT confirmed

Wu C et al, Nat Genet 2014;46:1001

Summary of Asian ESCC GWAS loci after joint analysis (n=16,Feb2016)



Main effects

GxE only

New from joint analysis

Other GWAS analyses to discover & validate new ESCC risk loci

- Functional annotation
- PrediXcan, MetaXcan
- Pleiotropy
- Genes, pathways

GWAS estimates of cancer heritability:

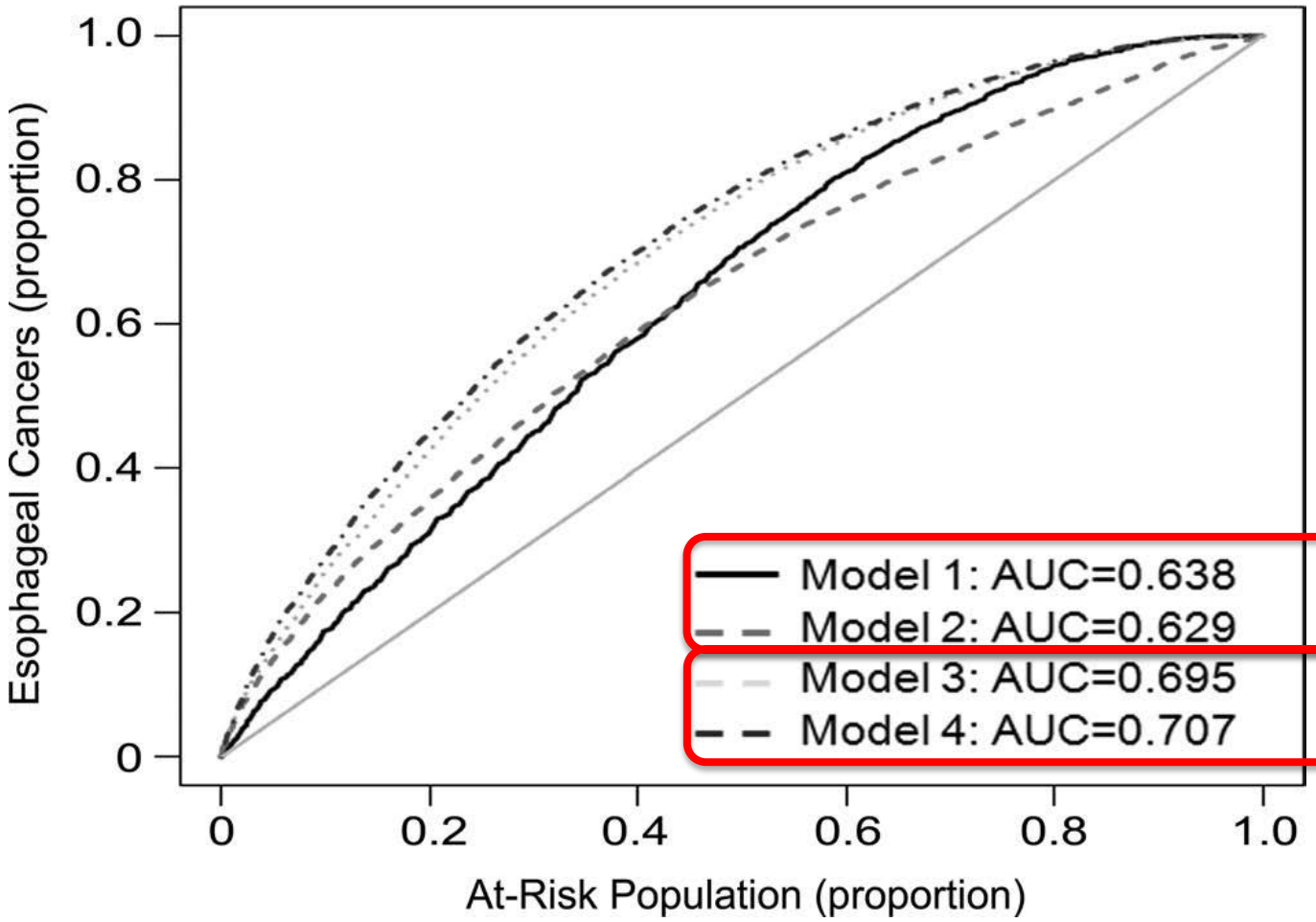
13 sites, 49492 cases, 34131 controls, liability scale

Cancer	h_l	Cancer	h_l
Bladder	0.123	Lymphoma (CLL)	0.220
Breast (ER-)	0.096	Lymphoma (DLBCL)	0.092
Endometrium	0.178	Osteosarcoma	0.159
Esophagus	0.381	Pancreas	0.098
Glioma	0.046	Prostate (overall)	0.378
Kidney	0.147	Prostate (nonadvanced)	0.351
Lung (Asian)	0.121	Prostate (advanced)	0.232
Lung (European)	0.206	Stomach (noncardia)	0.253
		Testes	0.299

Sampson J et al, JNCI 2015;107(12):djv279

ROC curves for 4 ESCC risk models:

Age, sex, Etoh & tobacco; 25 SNPs; 9805 cases & 10493 controls; China (Beijing, Jiangsu, Guangzhou, Henan, Hubei)



Chang J et al, Carcinogenesis 2013;34:1782

SNPs and ESCC in South Africans

① 12 SNPs from prior studies: *ADH1B, ALDH2, CASP8, ADH7*

- Blacks (358 Ca/477 Co); Mixed Ancestry (201 Ca/427 Co)
- Blacks: no assoc; Mixed Ancestry: *ADH1B, ALDH2, CASP8* associated

① 5 GWAS hits evaluated: *PLCE1, C20orf54, PDE4D, RUNX1, UNC5CL*

- Blacks (407 Ca/840 Co); Mixed Ancestry (257 Ca/860 Co)
- Blacks: no assoc; Mixed Ancestry: *RUNX1* associated
- *PLCE1* seq in Blacks ➔ rs17417407 associated

[1]Bye H et al, Carcinogenesis 2011;13:1855; [2]Bye H et al, Carcinogenesis 2012;33:2155

GWAS SNPs & ESCC in INHANCE

Upper Aero Digestive Tract Cancers (UADT)

- Discovery: 2091 UADT Ca/3513 Co; Replication: 6515 UADT Ca/7892 Co
- ≈314 ESCC in discovery, ≈123 in replication, ≈437 total
- Illumina 300K chip

Locus/Gene	SNP	Europeans	Chinese
4q21/*HEL308*	rs1494961	**1.24 (1.07-1.45)**	**1.07 (1.01-1.14)**
4q23/*ADH1B*	rs1229984	**0.38 (0.24-0.59)**	**1.07 (1.00-1.14)**
4q23/*ADH7*	rs1573496	**0.49 (0.36-0.66)**	---
4q23/*ADH1C*	rs698	**1.17 (1.00-1.37)**	1.08 (0.97-1.19)
12q24/*ALDH2*	rs4767364	**1.45 (1.24-1.69)**	0.99 (0.89-1.09)

McKay JD et al, PLoS Gen 2011;7:e1001333

Summary
ESCC genetic susceptibility

- GWAS data modest size for Chinese, but little else
- Strong evidence for heritability
- Risk prediction promising
- Population differences evident

Genetic susceptibility: difficult questions

1. What are the best strategies to maximize discovery & validation of susceptibility loci?
   a. More GWAS (new populations, larger numbers)?
   b. Better integration of GWAS with functional data?
   c. Better bioinformatic & data analytic methods?
   d. More creative GxE approaches?
   e. Better (cheaper, quicker, more accurate) ways to validate functionality of candidate loci?
2. How can we use susceptibility data to identify high-risk individuals to target for prevention?