National Cancer Institute

Family Studies in Shanxi, China: Search for high-risk susceptibility genes

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NCI-IARC Tumor Workshop: ESCC

September 2016

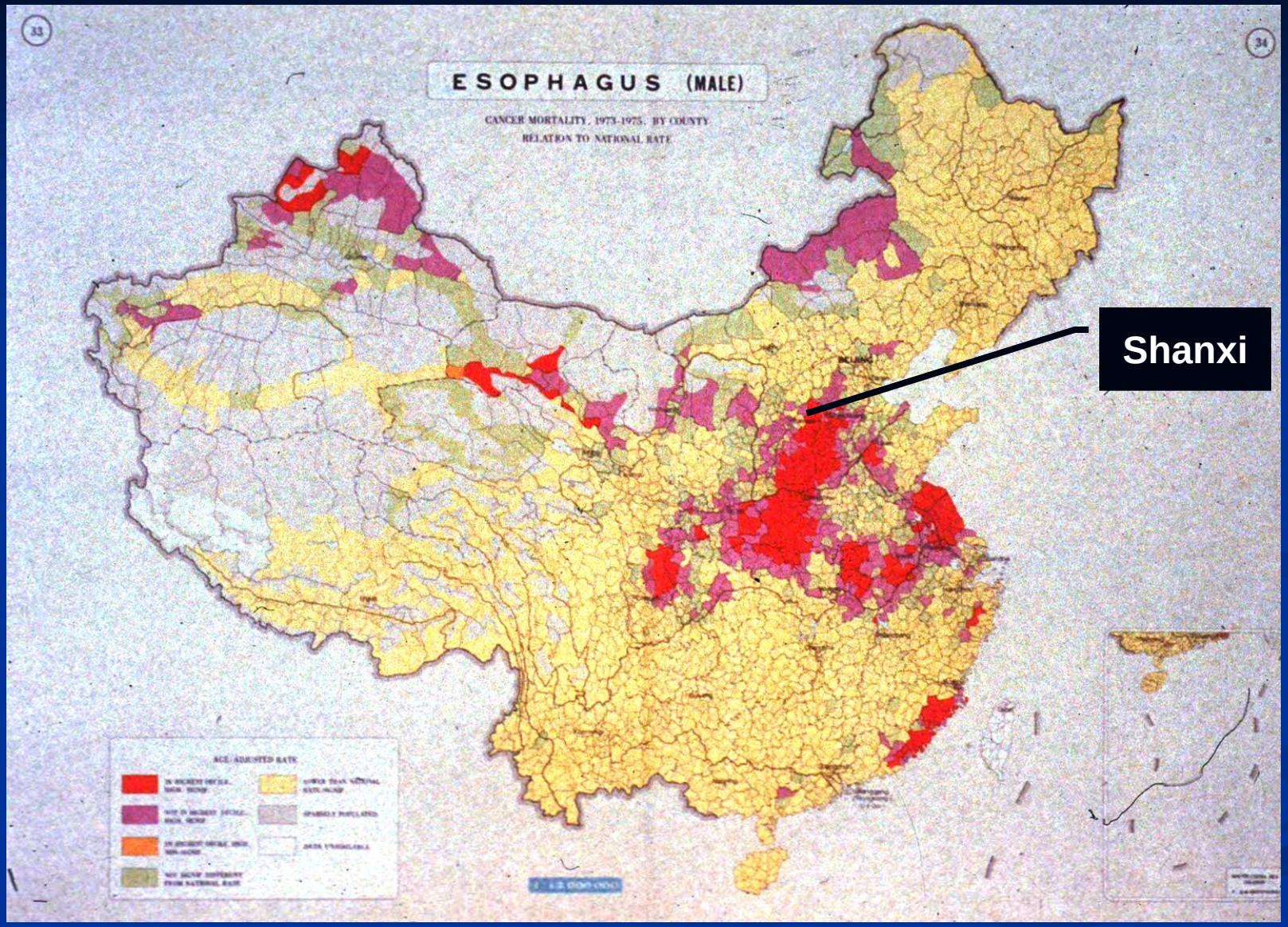
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Risk Variant Classification

Variant Type	Frequency	Penetrance Risk*
High-risk **Family Studies**	Very rare to Rare	Very High [5 - >20]
Moderate-risk **Family Studies/GWAS**	Rare [often <0.01]	Intermediate [1.5 - <5]
Low-risk **GWAS**	Common	Low [<1.5]

*Relative risk of carriers versus noncarriers



Areas in red are those with highest esophageal cancer rates from 1973-1975 national mortality survey.

Family History (FH) of ESCC in First-Degree Relatives (FDR) of 600 ESCC Cases/1514 Controls

[Gao et al, 2009 BMC Cancer]

Relatives	Ctrl/Case%	OR	95% CI
FH of ESCC (FDR)	6/16%	2.84	2.09-3.86
Father	3/7%	2.01	1.31-3.10
Mother	2/6%	3.27	1.96-5.47
Siblings	1/6%	4.66	2.67-8.13
1 relative with ESCC	6/14%	2.53	1.84-3.50
2+ relatives with ESCC	0.3/2%	10.0	3.24-31.2
Non-blood relatives	0.6/1%	1.86	0.68-5.10

Family History (FH) of Cancer in First-Degree Relatives of Cases/Controls*

[Gao et al, 2009 BMC Cancer]

FH of Cancer	ESCC OR (95% CI)	GCA OR (95% CI)	GNCA OR (95% CI)
Any UGI Cancer			
1 Affected	2.1 (1.6-2.7)	1.4 (1.1-1.9)	1.5 (1.1-2.2)
≥2 Affected	6.4 (2.8-15.6)	5.4 (2.3-12.7)	4.8 (1.7-13.6)
Any non-UGI Cancer	1.0 (0.7-1.3)	0.9 (0.7-1.3)	1.2 (0.8-1.8)

*600 ESCC ca, 598 GCA ca, 316 GNCA ca, 1514 controls

Shanxi Family Study

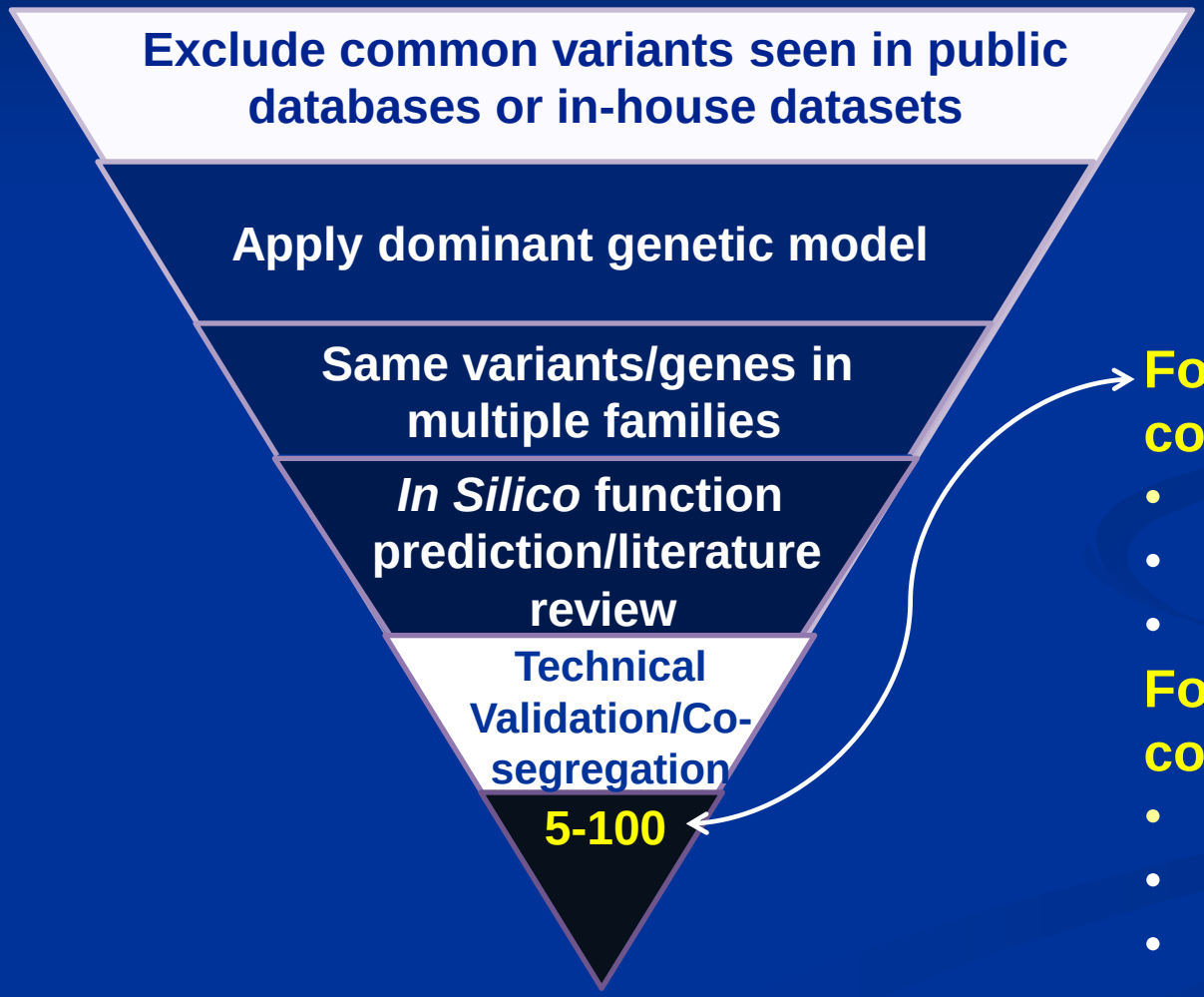
- Number of families: 148
  - Number of UGI cases/family: 2 - >8
    - Most families have 1-2 UGI cases with DNA
- 92 families with ≥3 UGI cases selected for whole exome sequencing (WES)
  - 24 families: ESCC only
  - 53 families: ESCC & Gastric cancer (GC)
    - 177 UGI cases/obligate carriers
      - 75% families ≤2 UGI cases with DNA

Genetic Syndromes of ESCC

- Tylosis with Esophageal Cancer
  - Genetic disorder characterized by thickening of the palms and soles (hyperkeratosis), white patches in the mouth (oral leukoplakia), and very high risk of ESCC
  - Disease gene: *RHBDF2* (17q25)
- Is tylosis seen in Shanxi? No
  - No disease-related mutations in *RHBDF2*

UGI WES Analysis Strategies

Although multiple candidate genes in 1-2 families, no frequent high-risk susceptibility genes identified



Follow-up in Shanxi case-control sample

- **Sequenced 21 genes**
- ~560 Cases
- ~590 Controls

Follow-up in Henan case-control sample

- **Genotyped ~50 variants**
- ~2600 ESCC cases
- ~2000 GC cases
- ~4500 Controls

Next Steps

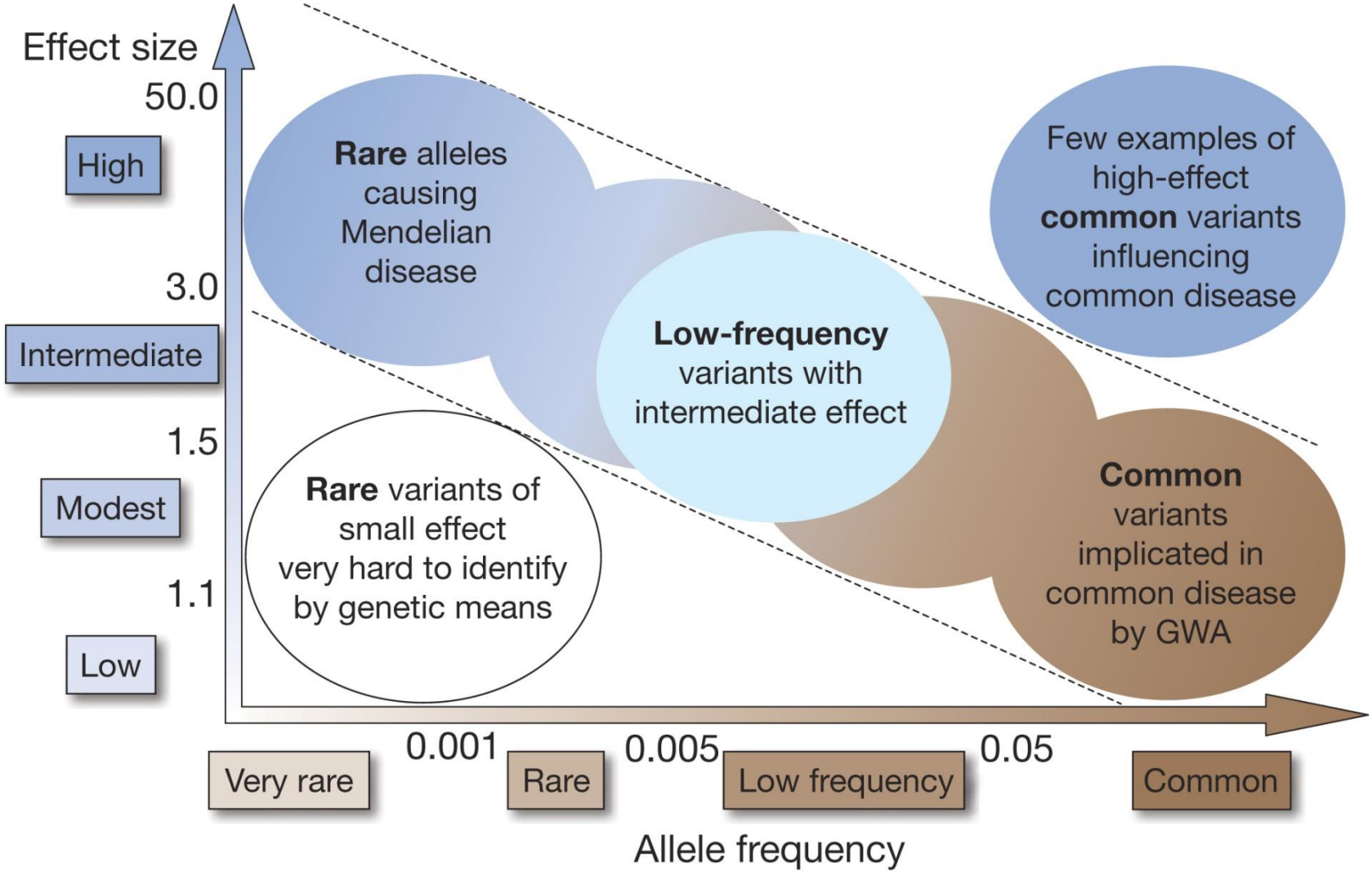
- Determination of top candidate genes/variants for further follow-up

- <u>Follow-up activities:</u>
- Functional studies of top genes/variants
  - In silico
  - Laboratory-based
- Genotyping/sequencing of more cases and/or controls
- Collaborations to share WES UGI data
  - Other populations with ESCC families?

High-Risk Gene Discovery Challenges

- Genetic heterogeneity – multiple genes responsible for disease susceptibility
- Lack of power/informativeness of sample
- Underlying complexity of disease cause(s)
  - Clinical/epidemiologic heterogeneity and/or misclassification
- Rarity of mutations
  - Proving causality for “private” mutations
  - Differentiating true positives from false positives
- No (or few) high-risk susceptibility genes

Genetic Risk Loci



Slide courtesy of Teri Manolio, NHGRI

Multiple low-risk variants in families?

- Recent evaluation in complex diseases suggested that multiple low-risk variants may explain disease risk in some families
  - Examine in exome families using OmniXpress
- Polygenic risk score (PRS) in ESCC
  - Low-risk ESCC loci identified from GWAS
  - Tested whether family history (FH) subgroups differed in extent of enrichment for polygenic effects
    - Shanxi ESCC FH+ vs FH- cases
      - Average PRS: 0.55 vs 0.49 (p=0.04)

Summary

- To search for high-risk genes in ESCC, we conducted a family study in Shanxi, China
- WES performed in 92 3+ UGI case families
  - Including 24 ESCC only and 53 ESCC + GC
- No frequent high-risk genes yet identified
  - Multiple candidate genes in 1-2 families each
    - Extensive follow-up including functional studies required to prove causation
- Examination of low-risk variants in WES families in process to determine whether risks in families result from multiple low-risk variants

Difficult Questions

- Although WES offers opportunities for identifying high-risk ESCC genes, studies are complex with many challenges
  - How to prove causality for “private” mutations?
- What are the best strategies for identifying high-risk ESCC genes?
- Do multiple low-risk variants explain disease risk in some families from high-risk regions?

- How do we reduce risk/prevent disease in ESCC families from high-risk regions?

Acknowledgements

- DCEG, NCI
  - Philip R. Taylor
  - Nan Hu
  - Wen-Qing Li
  - Hua Su
  - Lemin Wang
  - Chaoyu Wang
  - Melissa Rotunno
  - Jianxin Shi
  - Paula Hyland
  - Hyuna Sung
  - Margaret A. Tucker
  - Stephen J. Chanock
  - Geoffrey S. Tobias
- CCR, NCI
  - Maxwell Lee
- Shanxi, China
  - Ding Ti
  - He Li-Ji,
  - Han Xaio-Yu
- CGR, NCI
  - Cancer Genomics Research Laboratory, Leidos Biomedical Research, Inc.
- Henan, China
  - Li-Dong Wang
  - Xin Song
- IMS
  - Carol Giffen