

Genomic Heterogeneity in Gastric Cancer : Therapeutic Implications and Challenges

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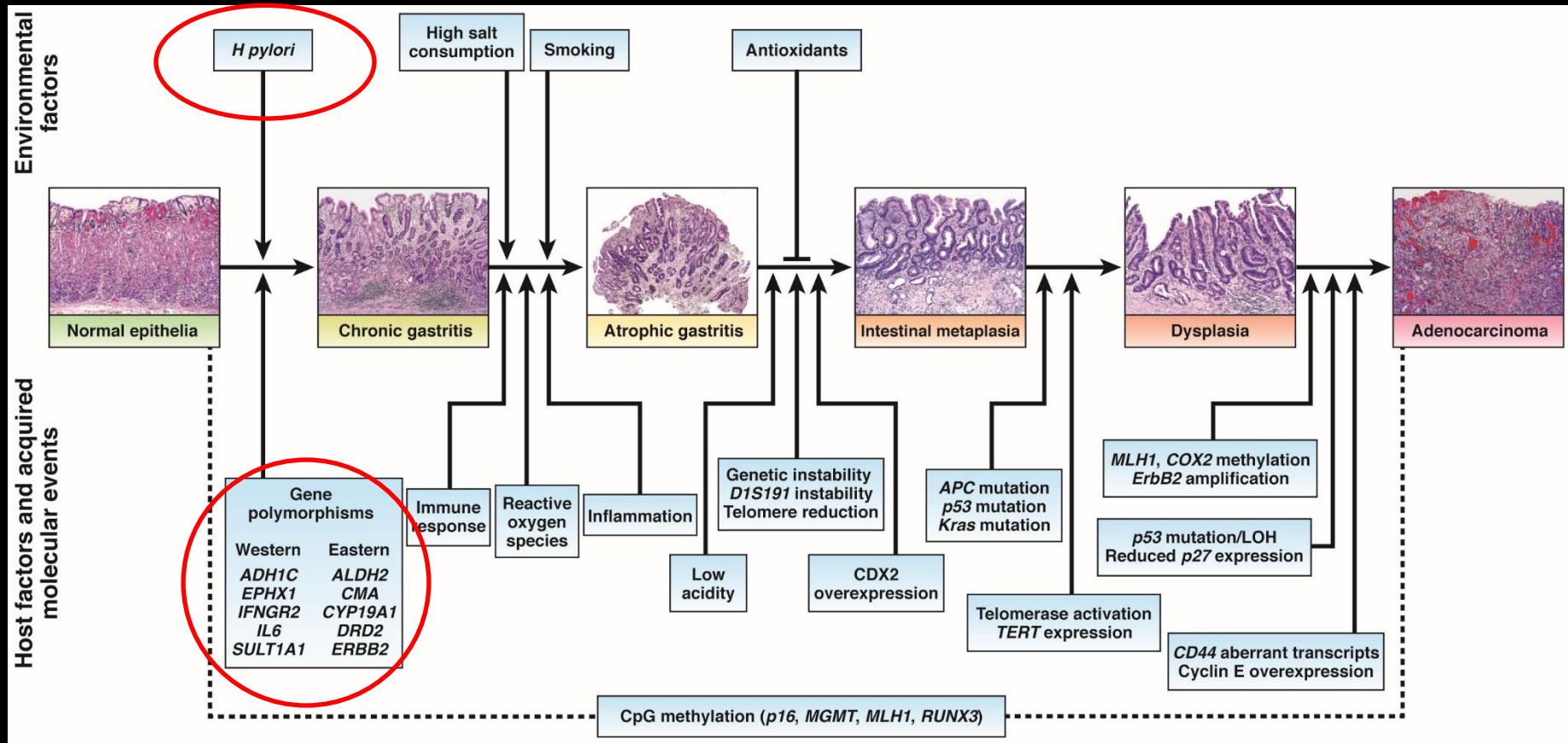
ESMO Asia Congress
Singapore, Dec 2015



Disclosure slide

- No disclosures

Gastric Cancer Pathogenesis : Interplay Between Environmental and Host Factors

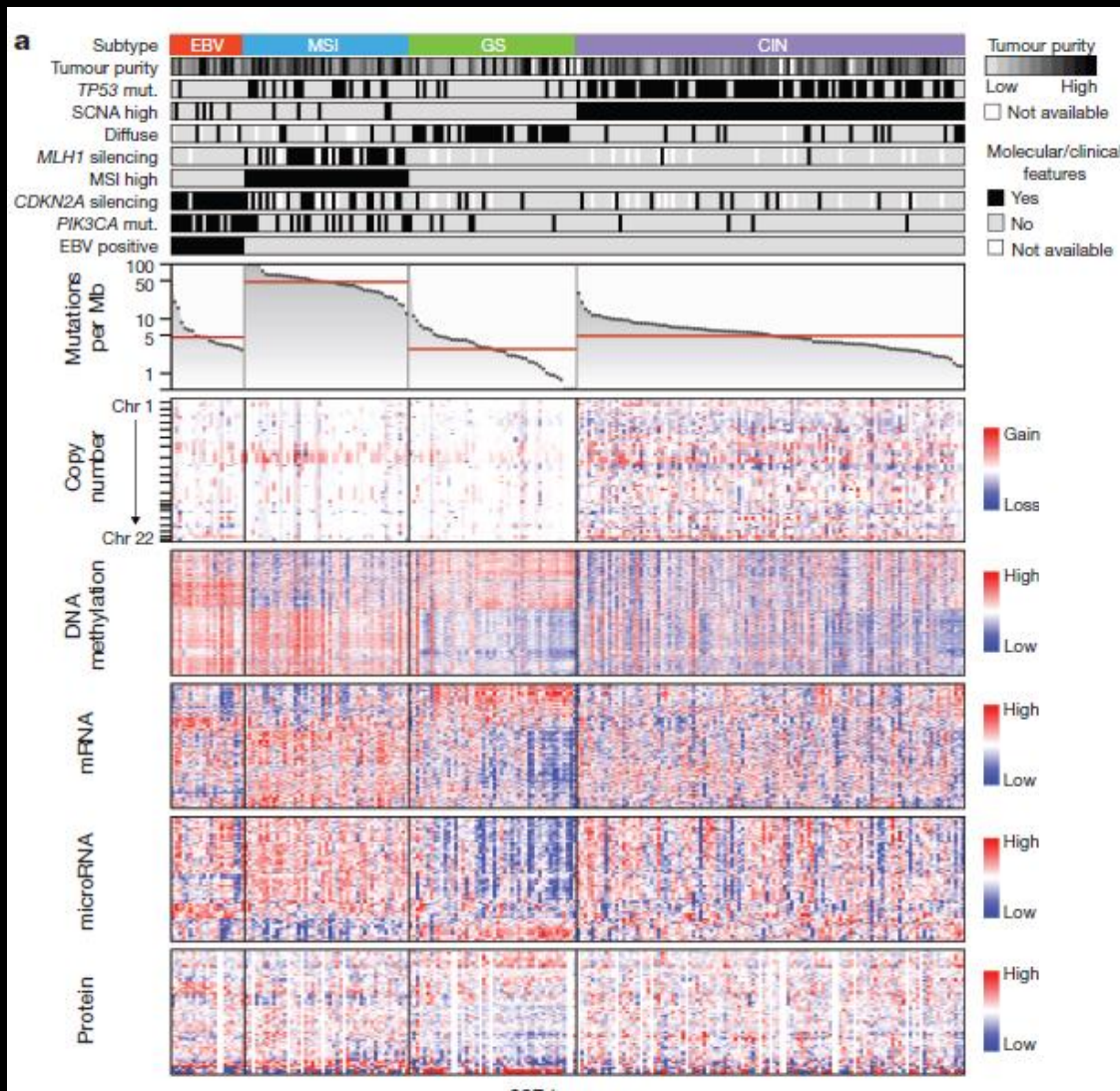


Yeoh and Tan (2015) *Gastroenterology*

Can Genomics Improve Gastric Cancer Patient Outcomes?

- 1) How many GC subtypes exist? What are their driver alterations and pathologic associations?
- 2) How can driver alterations reveals therapeutic opportunities and clinical responses?
- 3) How similar is GC across different countries?

There are ~3-4 Major GC Genomic Subtypes



A) Chromosomal Instability (CIN)

B) Microsatellite Instability (MSI)

C) Genome Stable (GS)

D) Epstein-Barr Virus (EBV)

GC Genomic Subtypes Show Distinct Molecular and Pathological Characteristics

Chromosomal Instability (CIN) (50%)

- Intestinal-type GCs
- *TP53* mutations
- Focal somatic gene amplifications in RTK/RAS genes

Microsatellite Instability (MSI) (20%)

- Intestinal-type GC ***ARID1A*, *CIMP***
- *TGFBR2*, *HLA-B* mutations

Genome Stable (GS) (20%)

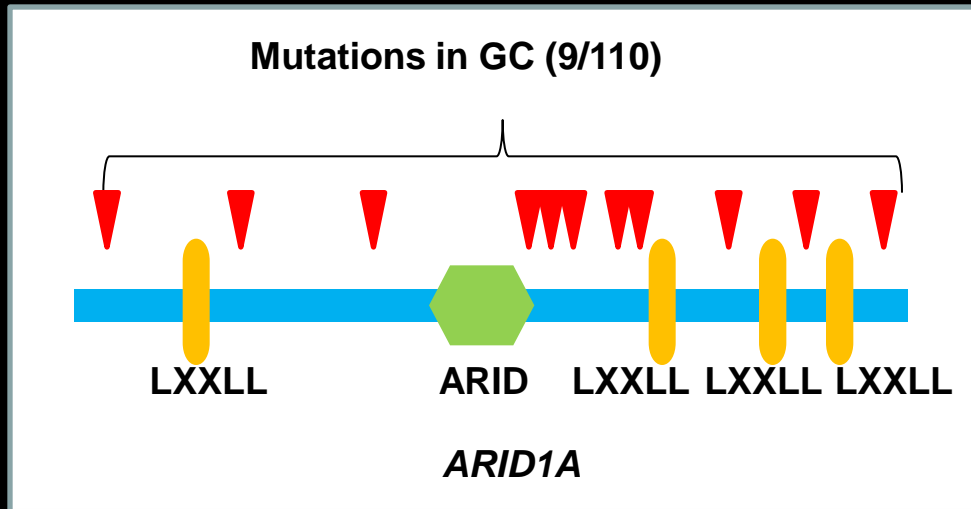
- Diffuse-type GC
- *CDH1*, *RHOA*** mutations

Epstein-Barr Virus (EBV) (10%)

- Global ***ARID1A*, *CIMP*** on
- *PDL-1/2* Gene Amplification**

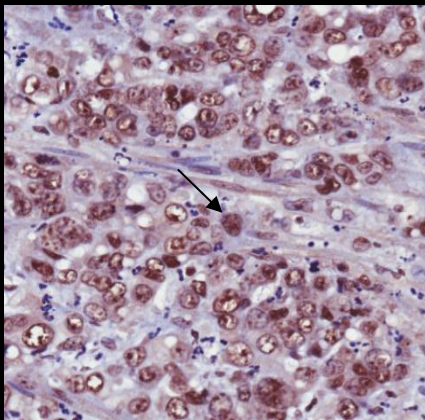
Matsusaka et al(2011) *Cancer Res*
Wang et al(2011) *Nat Genetics*
Zang et al (2012) *Nat Genetics*
Nagarajan et al (2012) *Gen Biol.*
Yoon et al (2013) *Genome Res*
Wang et al (2014) *Nat Genetics*
Kakiuchi et al (2014) *Nat Genetics*
USA TCGA (2014) *Nature*

GC Somatic Mutations in *ARID1A*, a SWI/SNF-related chromatin remodeling gene

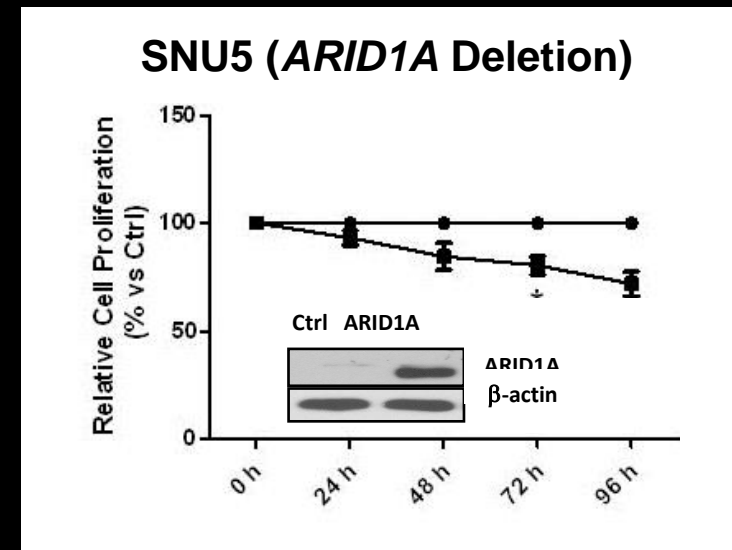
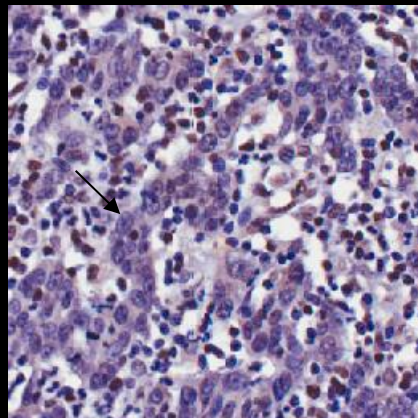


Associated with MSI
and EBV-positive GC

ARID1A (Wild-type)



ARID1A (Mutated)

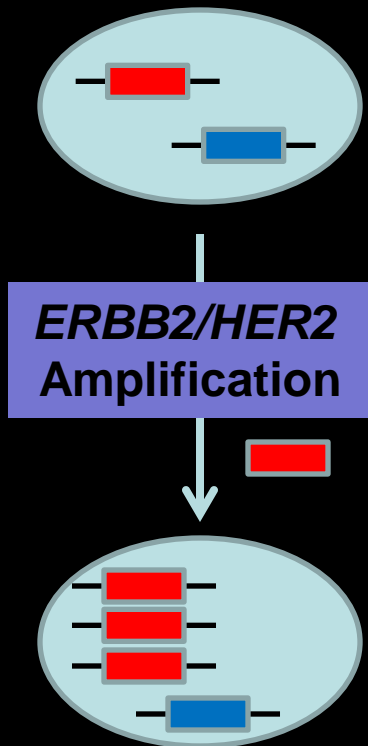


Wang et al., 2011 *Nature Genetics*
Zang et al., 2012 *Nature Genetics*

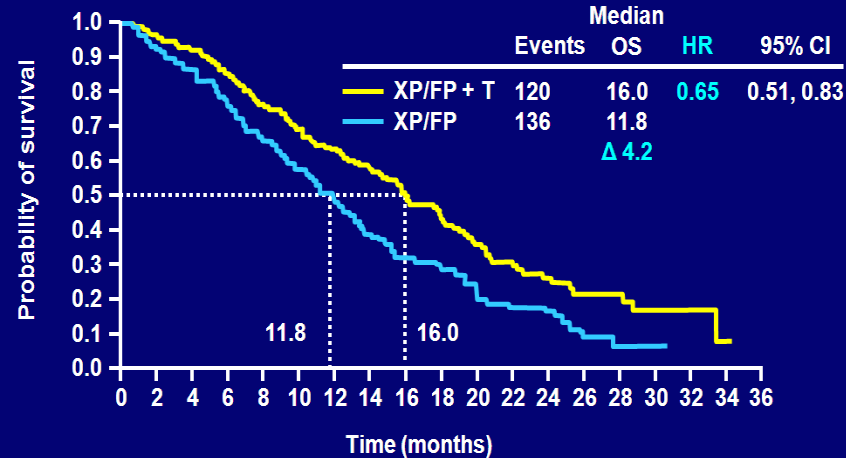
Can Genomics Improve Gastric Cancer Patient Outcomes?

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Targeted Therapies in Gastric Cancer

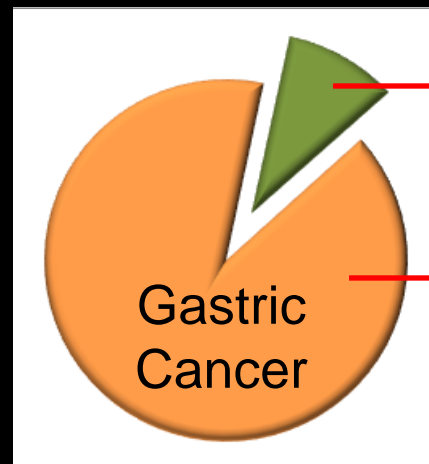


OS in IHC 2+ / FISH+ or IHC 3+
(exploratory analysis)



The TOGA Trial

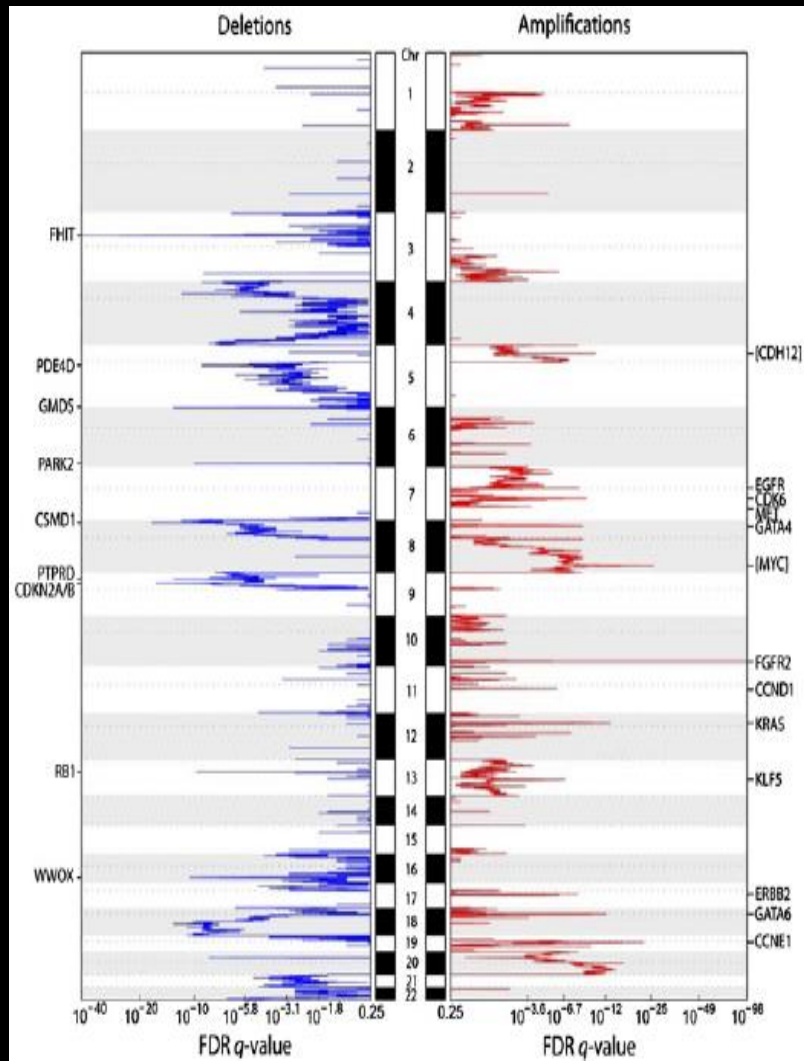
Bang et al (2011) *Lancet*



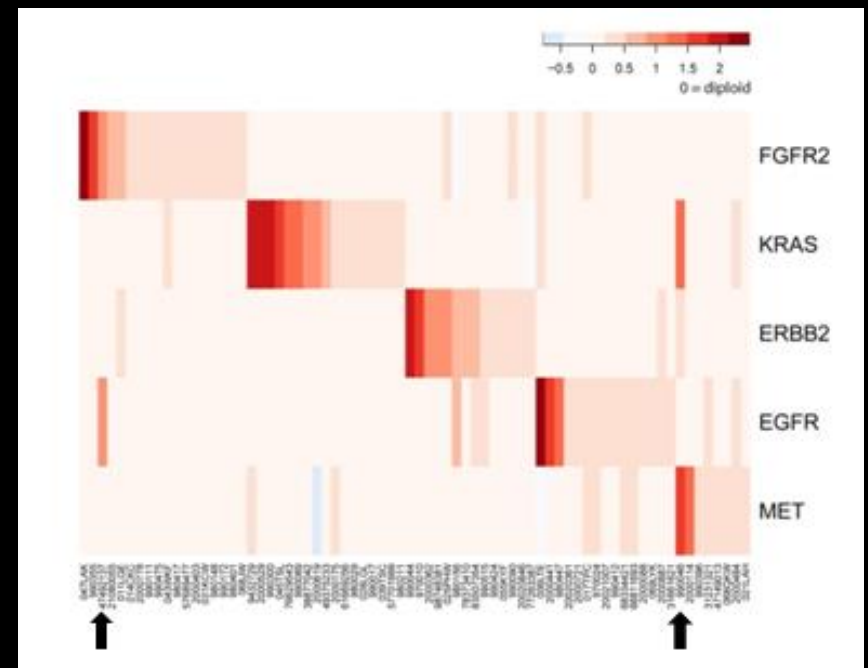
ERBB2 Positive
(8-10%)

?????

Focal Genomic Alterations Highlight Therapeutic Opportunities in GC

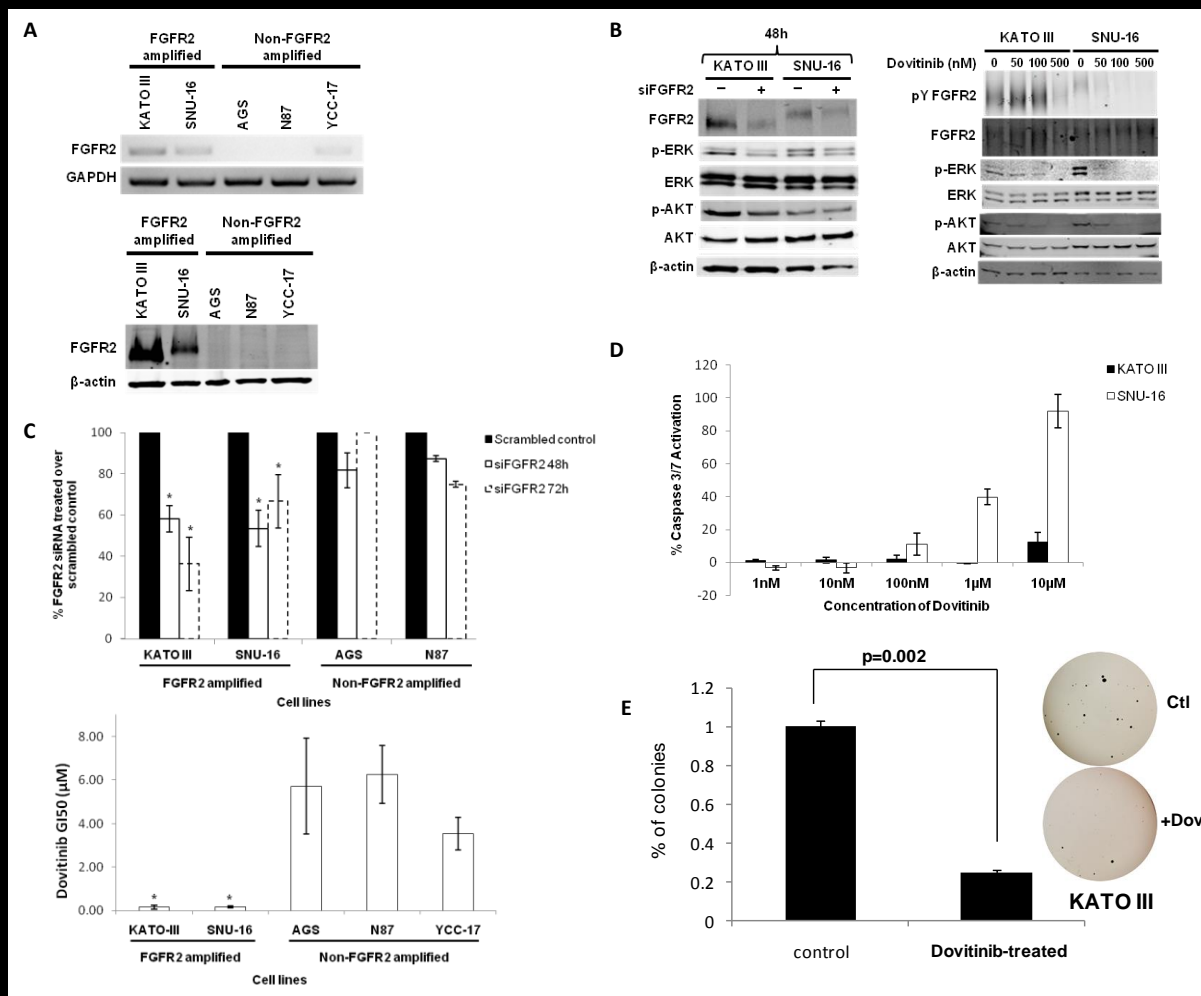


RTK/KRAS Amplifications

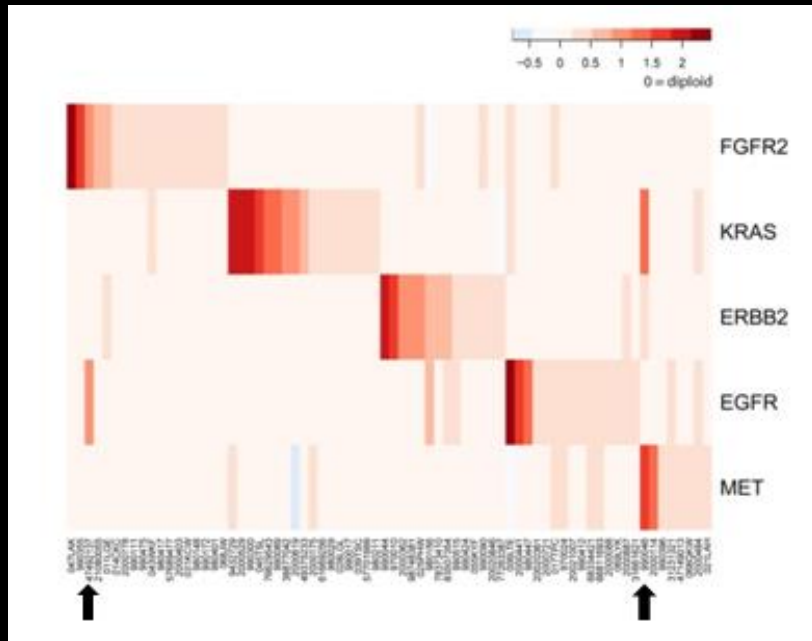


Deng et al., 2012 *Gut*

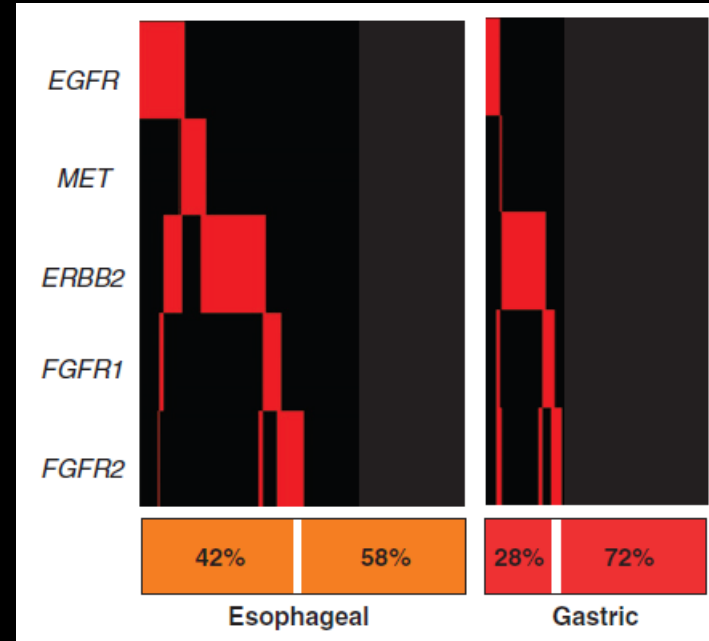
Dovitinib (TKI258) is a Subtype-Specific Therapy for FGFR2-Amplified GCs (Collaboration with Novartis)



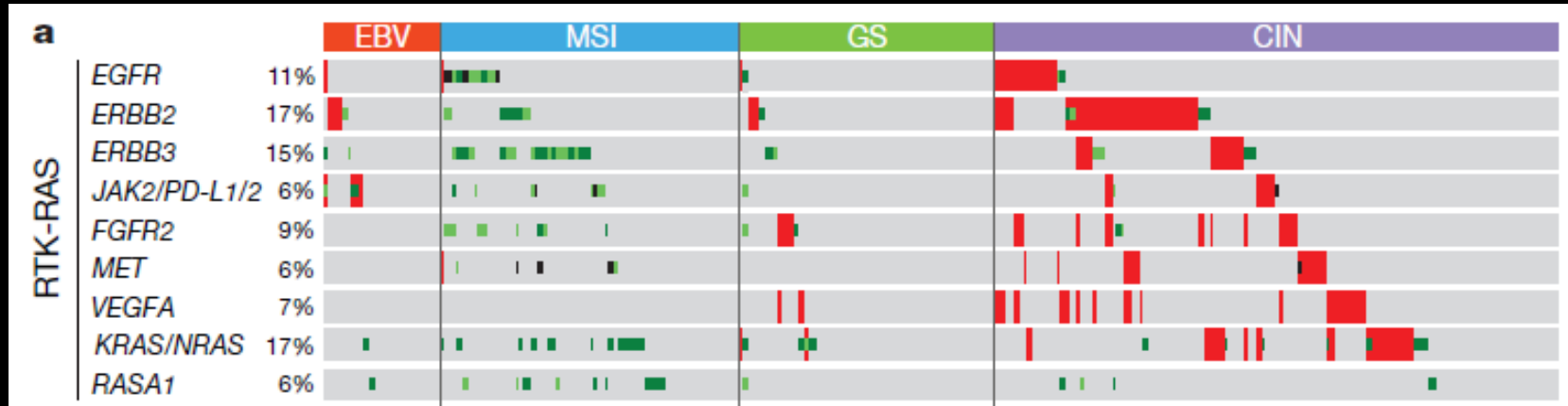
Relationships Between RTK Drivers?



Deng et al., 2012 *Gut*

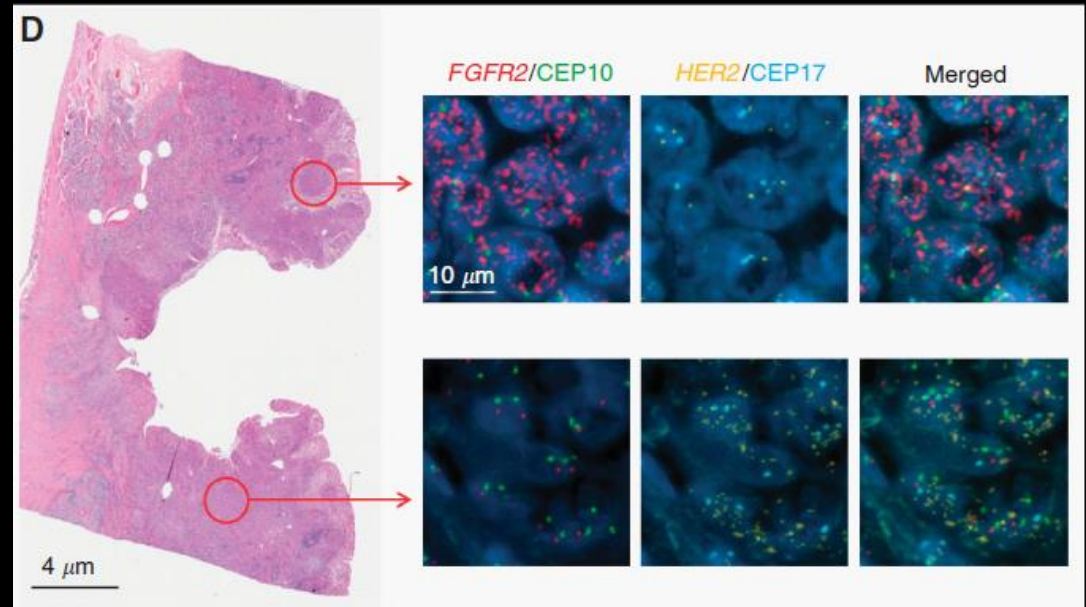
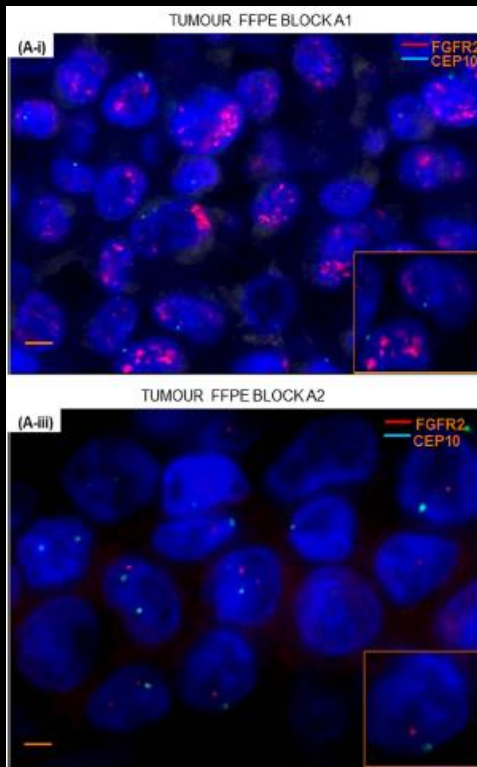


Dulak et al., 2012 *Cancer Research*



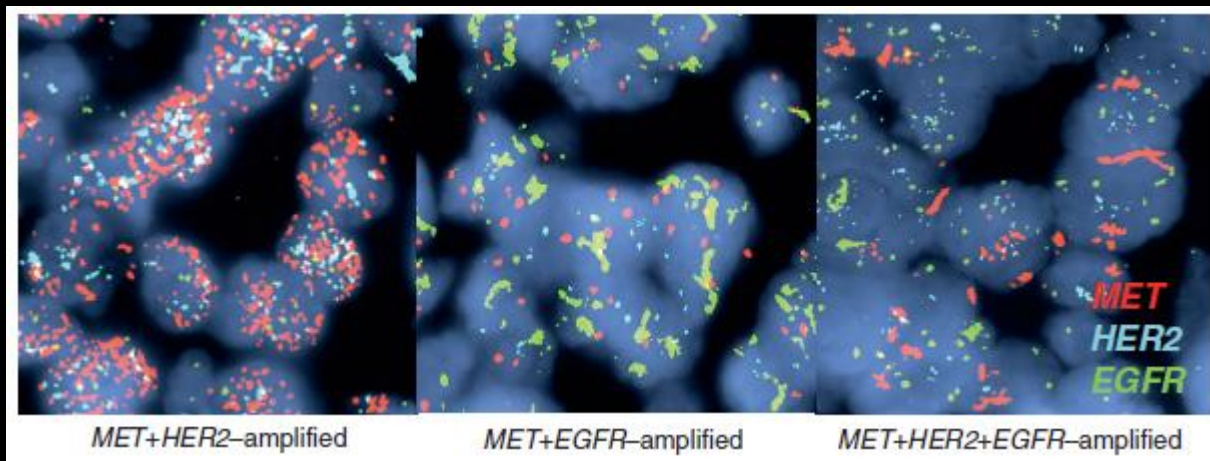
USA TCGA, 2014 *Nature*

Intra-Tumoral RTK Heterogeneity in GC



Kilgour et al., 2014 BJC

Das et al., 2015 Cancer Letters

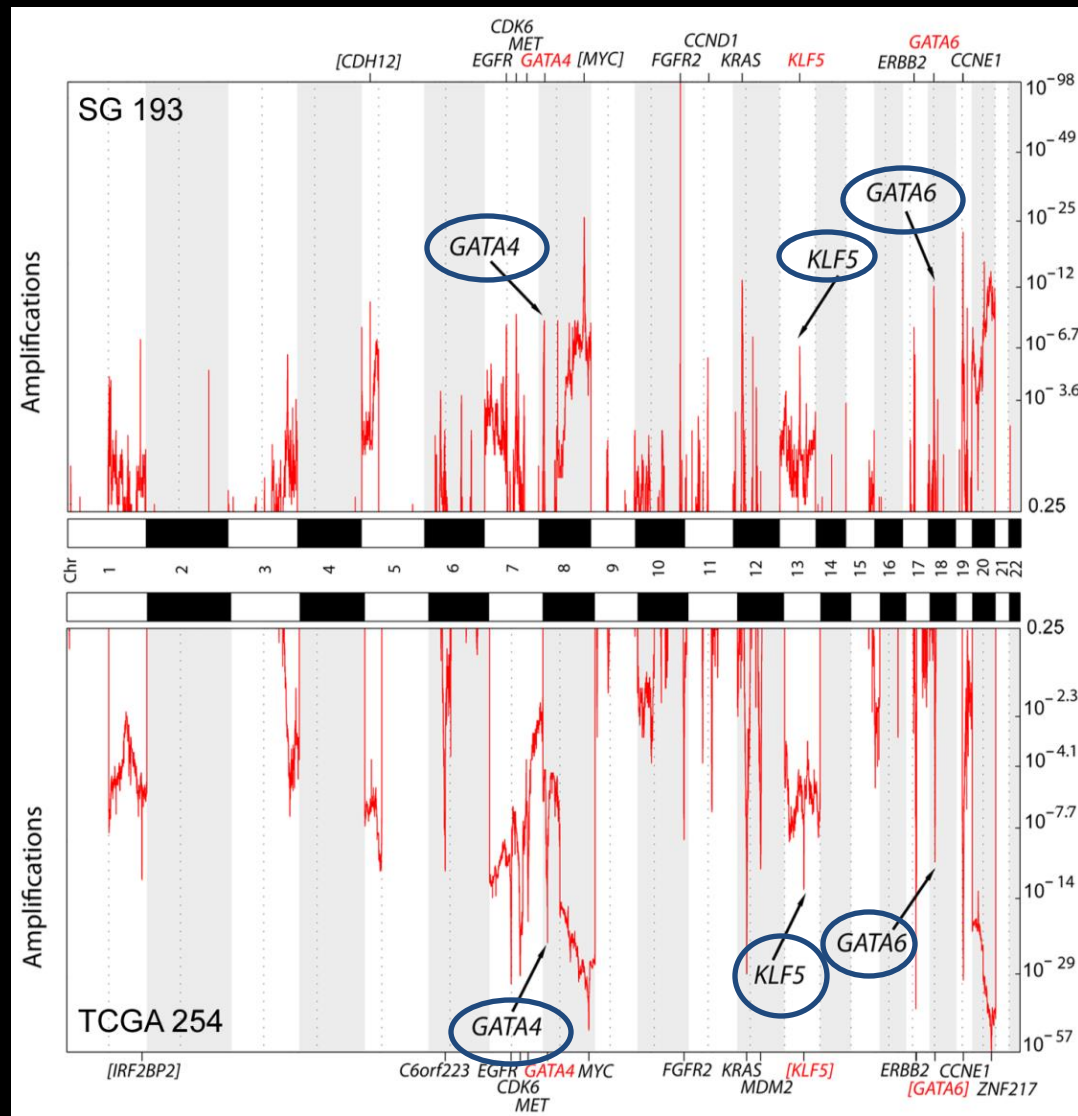


MET-therapy resistant
GC

Kwak et al., 2015
Cancer Discovery

Transcription factors **KLF5**, **GATA4** and **GATA6** are amplified in GC samples

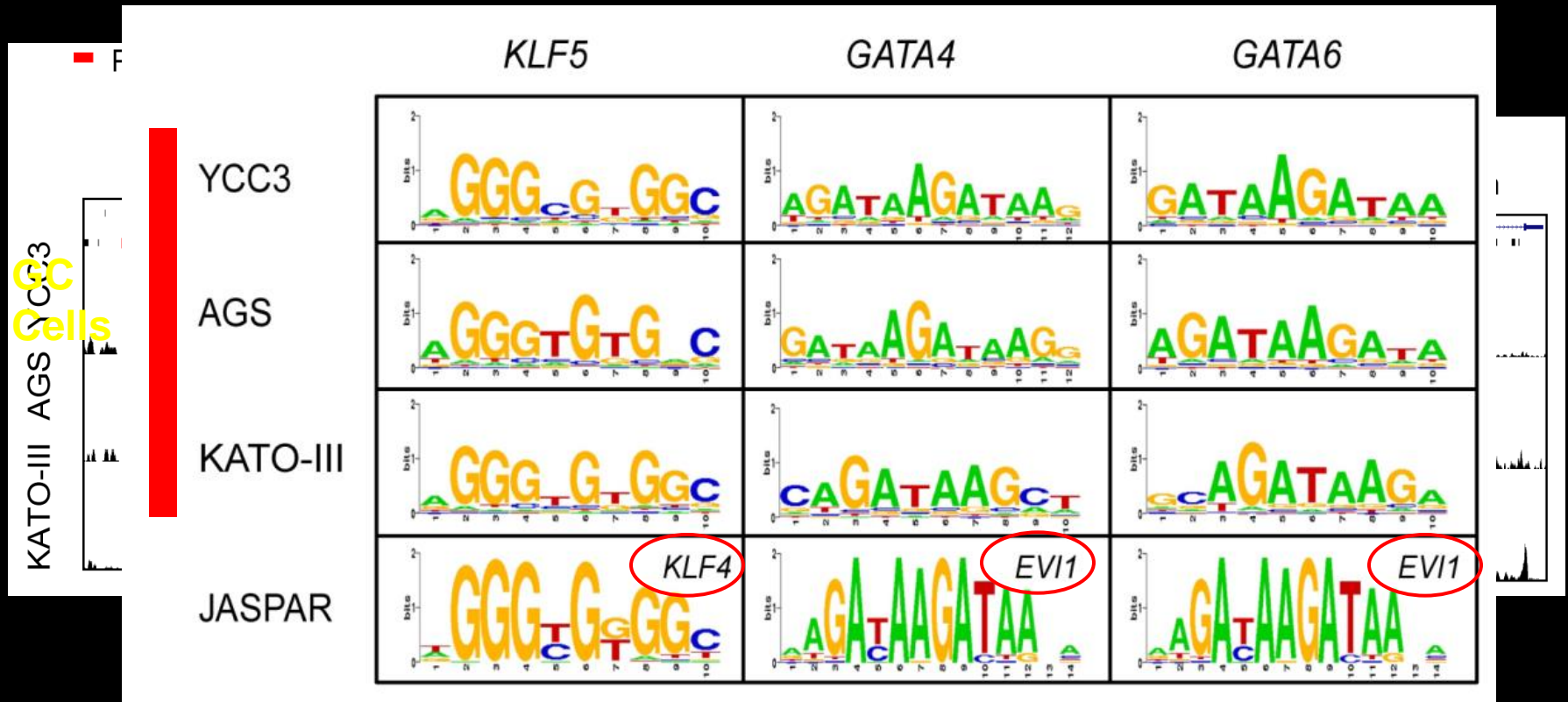
Singapore Cohort
(193 patients)



TCGA Cohort
(254 patients)

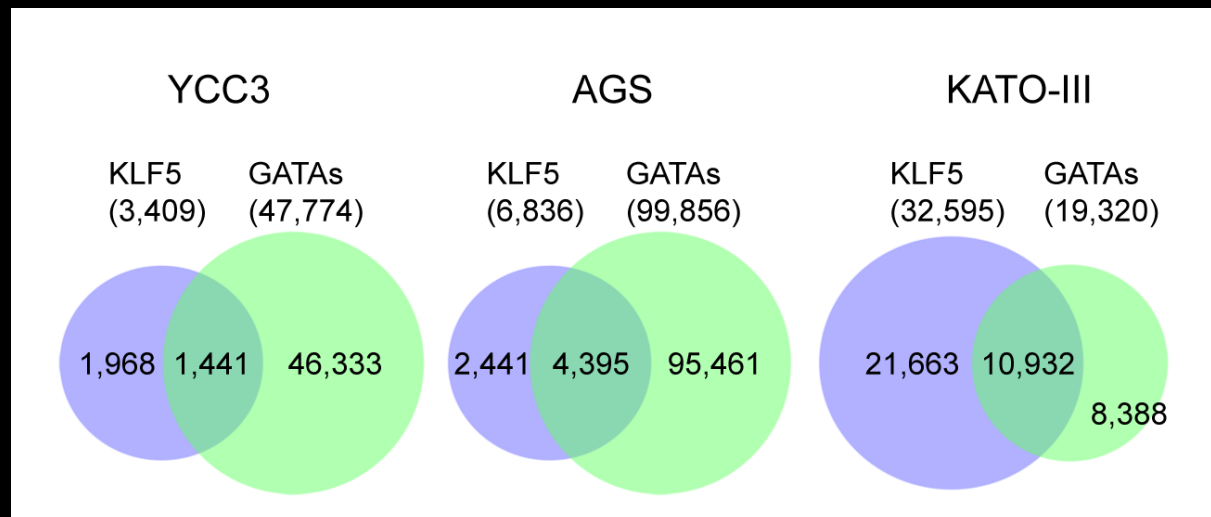
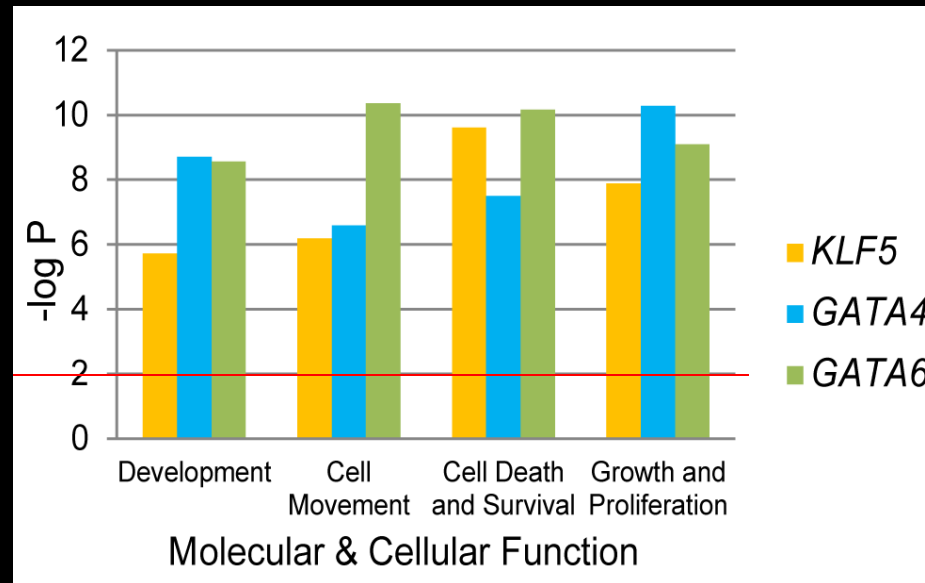
Genome-wide Binding Profiles of KLF5, GATA4 and GATA6 (ChIP-Sequencing)

Transcription Factors



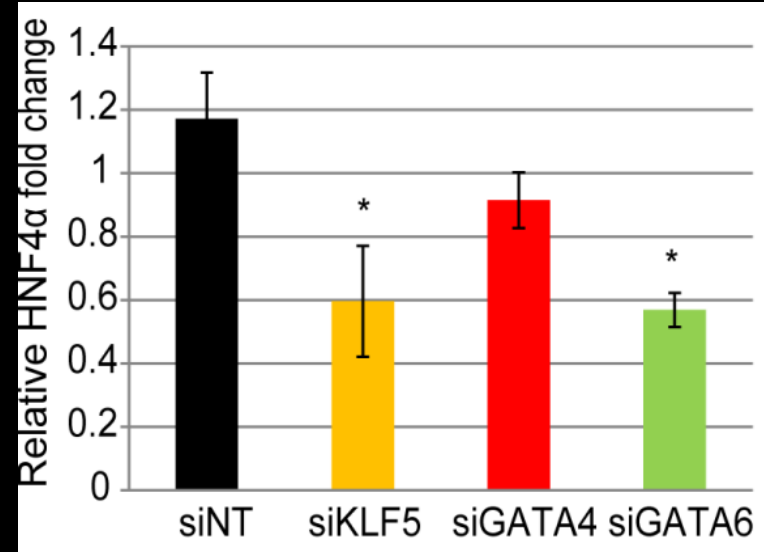
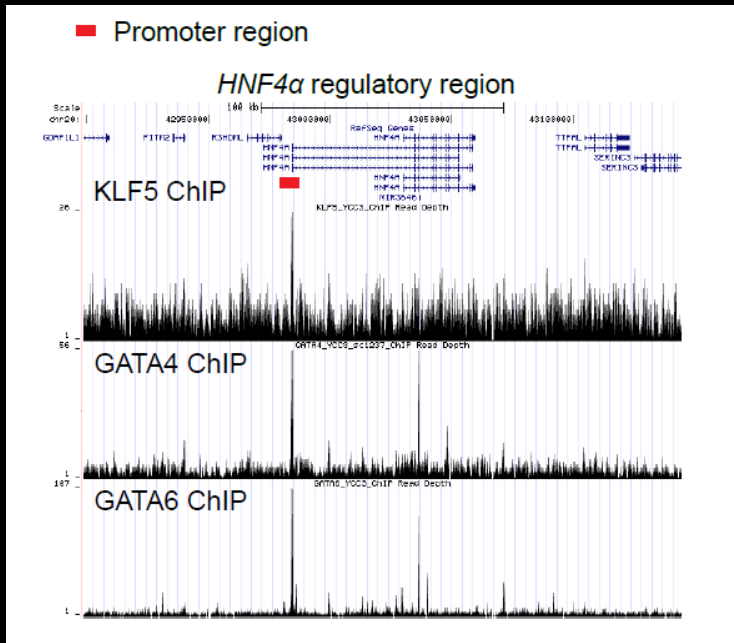
EVI1 = GATA-motif Binding Factor

KLF5, GATA4 and GATA6 target common downstream pathways and genes

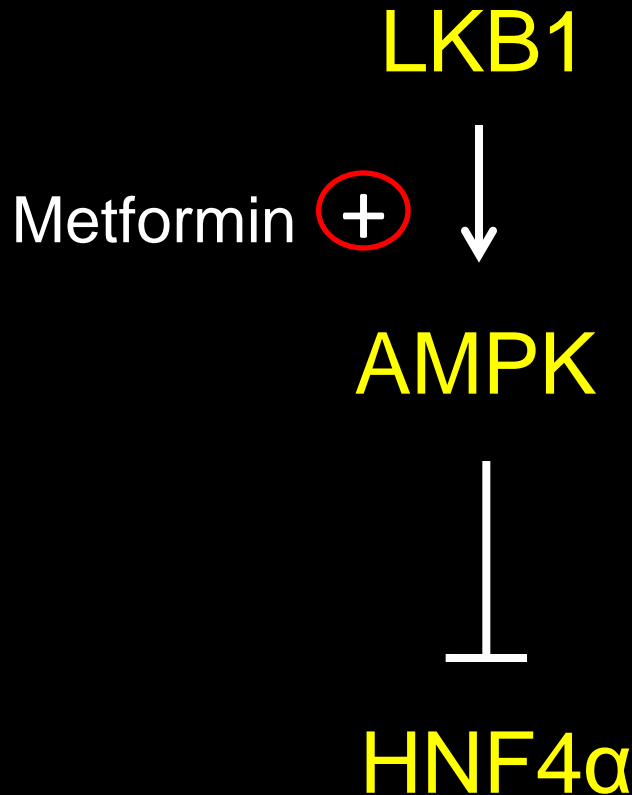


$P < 0.01$

***HNF4 α* is a Common Downstream Target of KLF5 and GATA Factors**

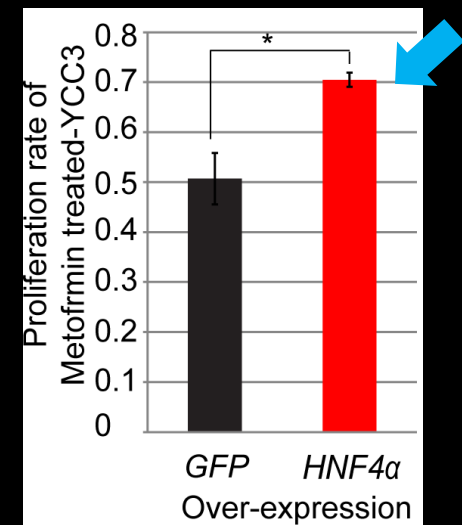
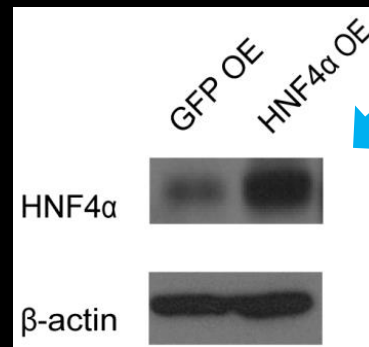
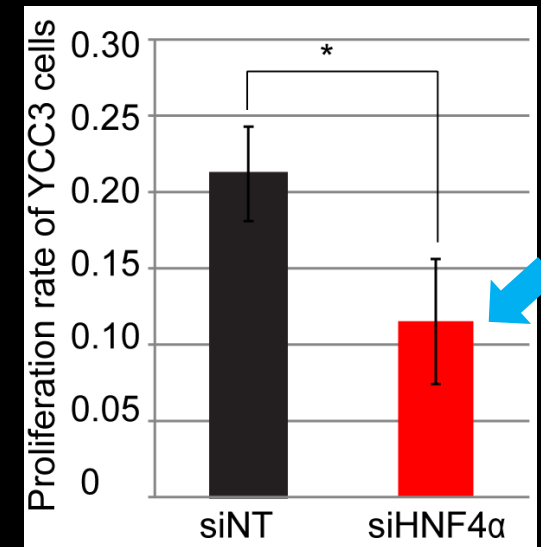
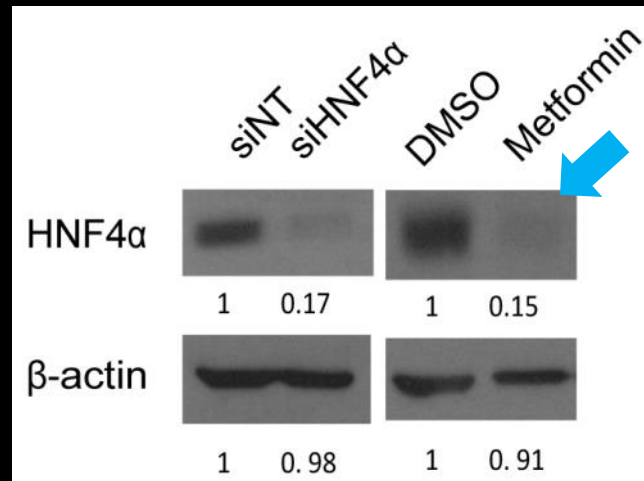
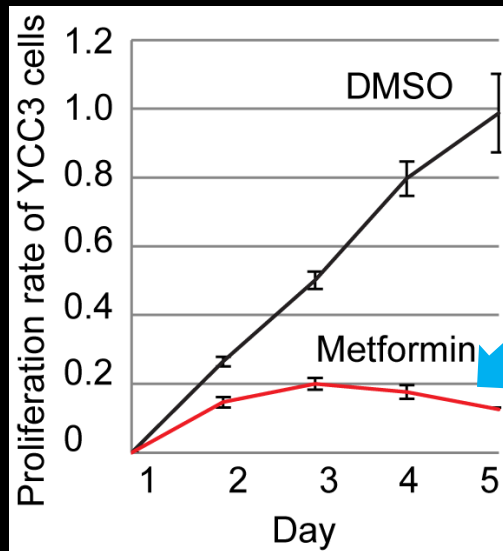


The Anti-diabetic Drug Metformin is a Potential HNF4 α Therapeutic



1. Treatment of type 2 diabetes
2. Poly Cystic Ovarian syndrome.

HNF4α is a potential predictor of Metformin response in GC



Summary

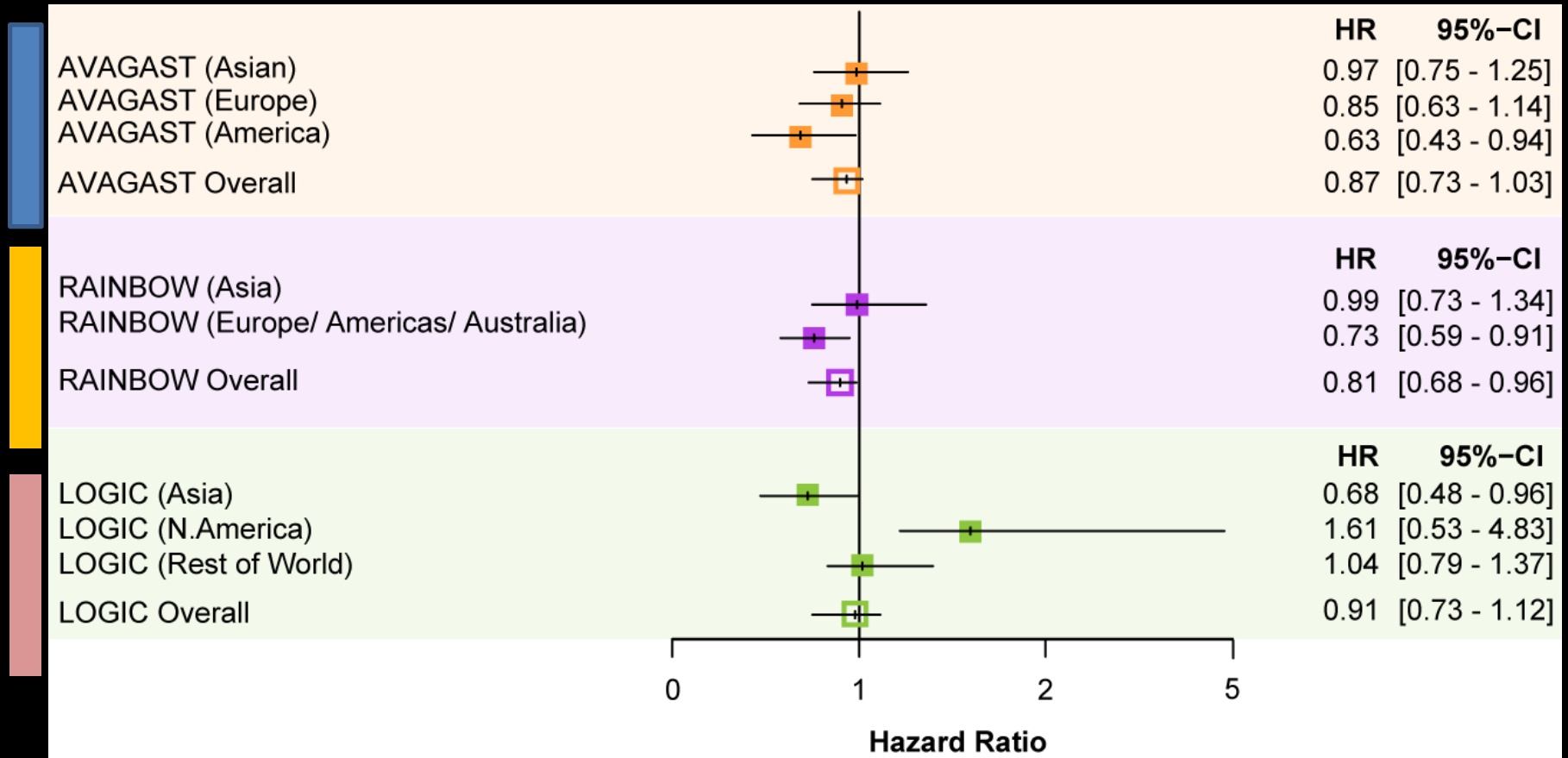
- *KLF5* and *GATA* Factors Exhibit Lineage-Specific Amplification in GI Tract Cancers
- *KLF5* and *GATA* Factors Interact and Collaborate to Regulate a Common Pro-oncogenic Expression Program
- *HNF4 α* is a common target of *KLF5* and *GATA* factors in GC
- *KLF5/GATA*-amplified tumors might be treated with Metformin, via *HNF4 α* downregulation

Chia et al., 2015 *Gut*

Can Genomics Improve Gastric Cancer Patient Outcomes?

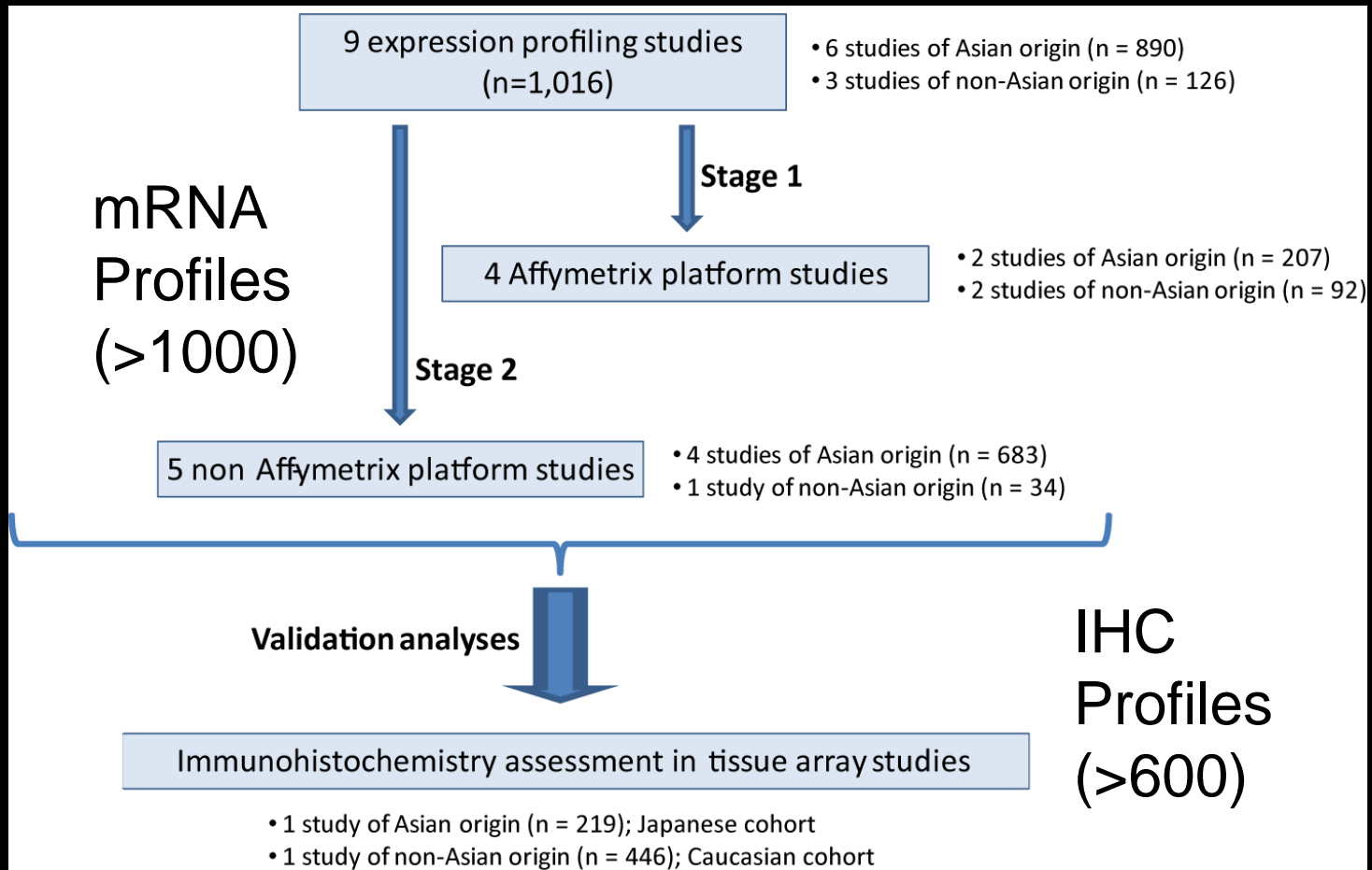
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Phase III GC Clinical Trials Reveal an Association between Geography and Clinical Outcome



Comparing Asian and Non-Asian GCs

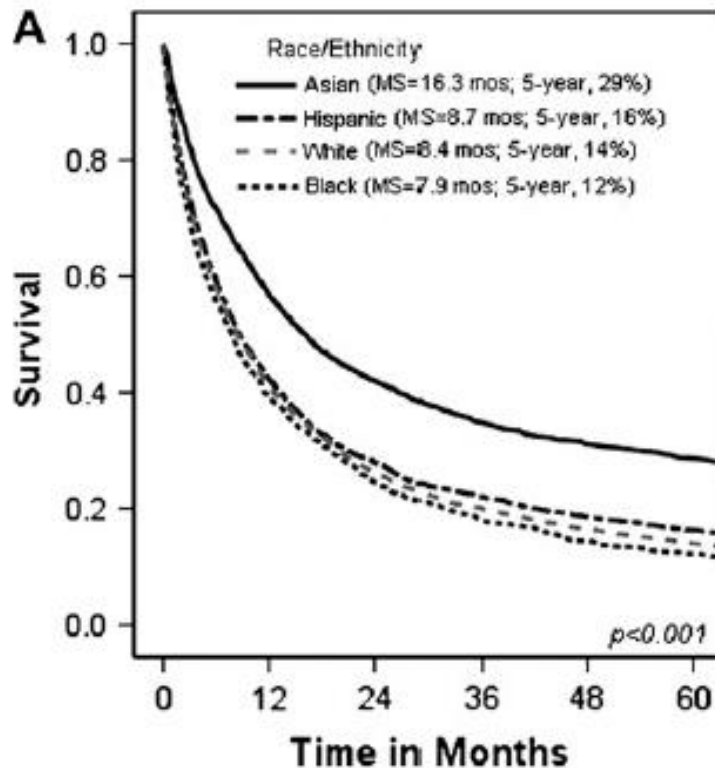
Analysis of 1,600 Gastric Tumors



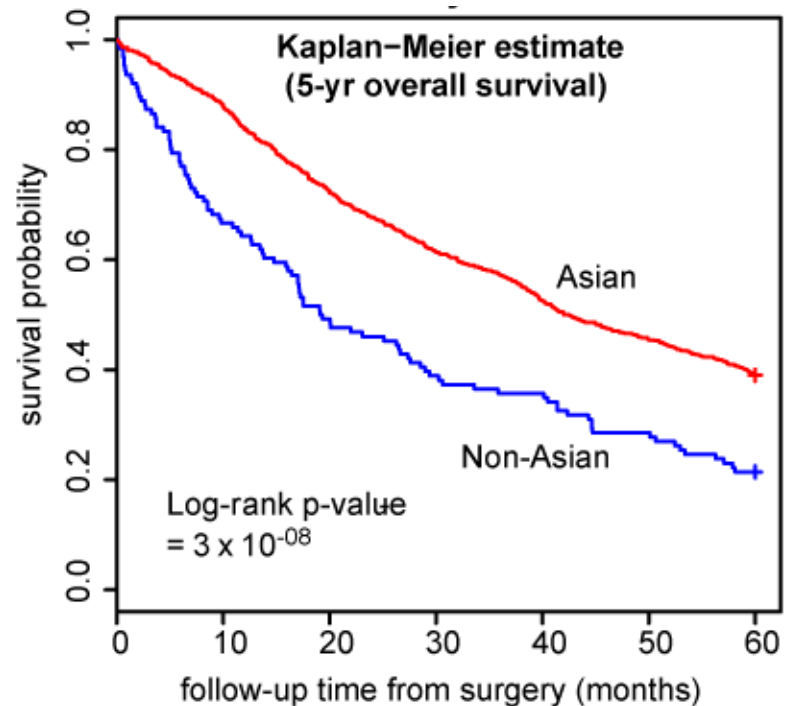
Collaboration : Johann A. Gagnon-Bartsch
Terry Speed, UC Berkeley
RUV algorithm : *Nature Biotechnology* (2014)



GC Expression Cohorts Recapitulate Well Known Geographic Differences in 5-yr Overall Survival

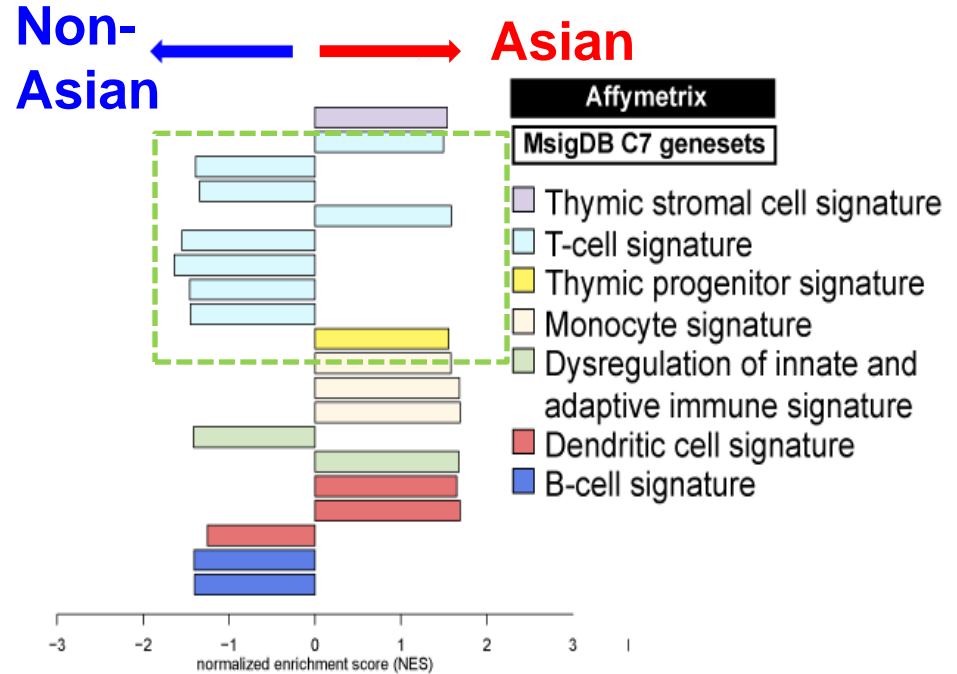
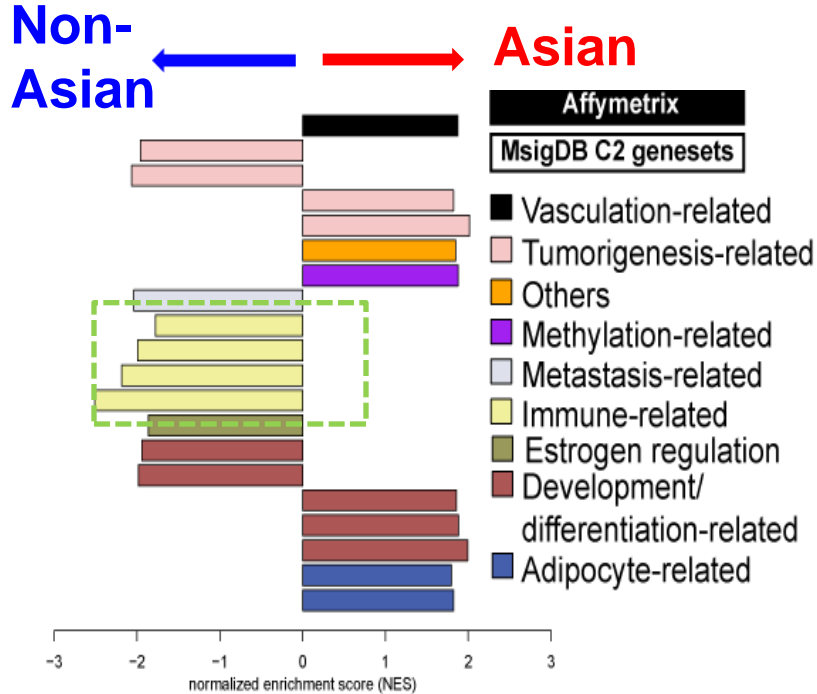


9 expression microarray cohorts

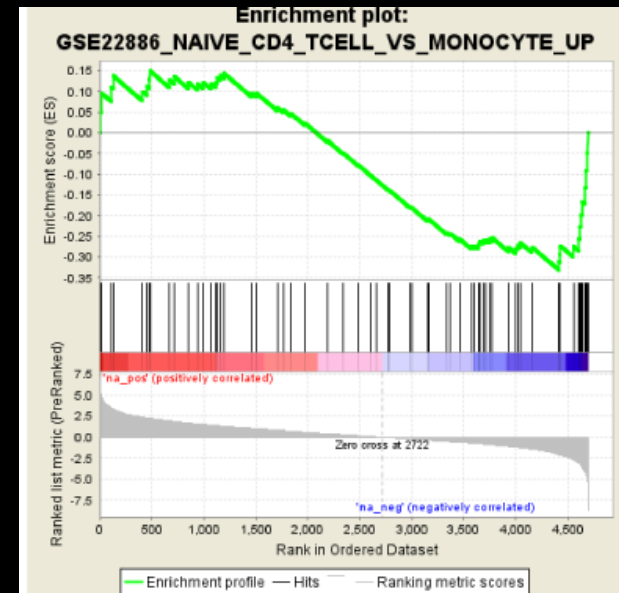
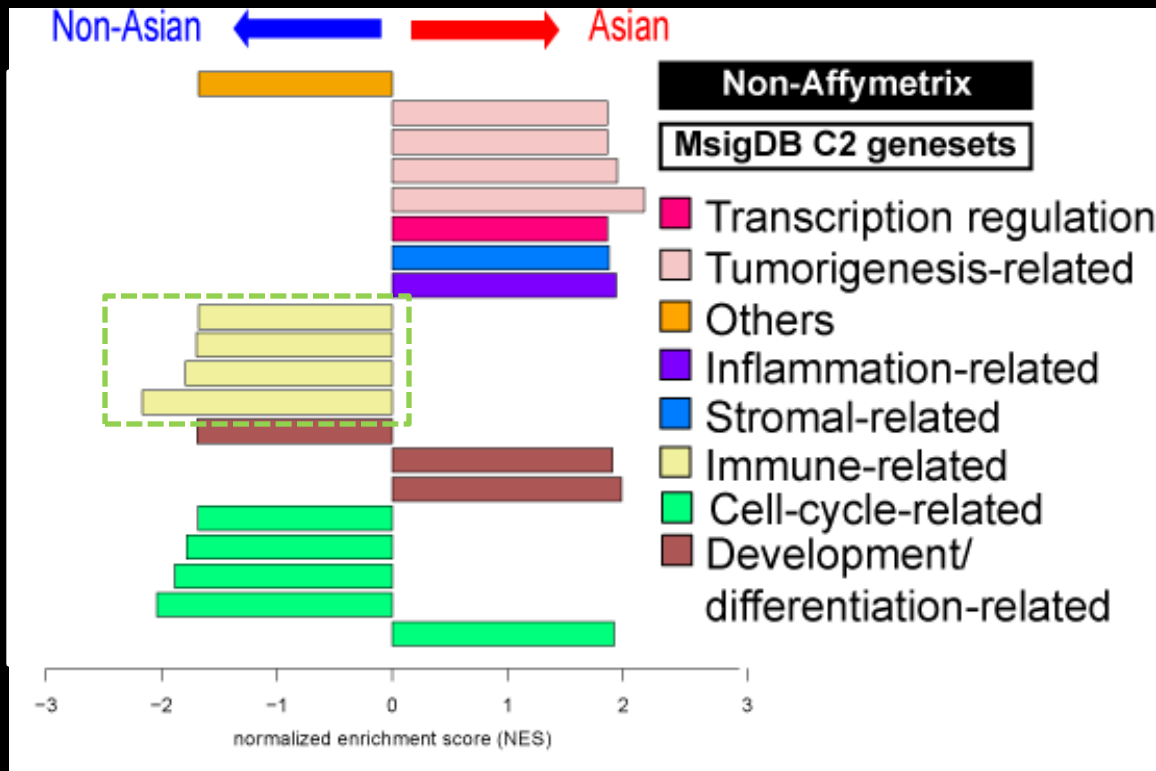


Kim et al (2010) *Annals of Oncology*

Stage I : Non-Asian GCs are Enriched in T-cell Gene Signatures Relative to Asian GCs



Stage 2 (Non-Affymetrix): Validation of T-cell Immune Signatures in non-Asian GCs



Normalized enrichment score = -1.46
FWER p-value < 0.05

GC Tissue Microarray Cohorts

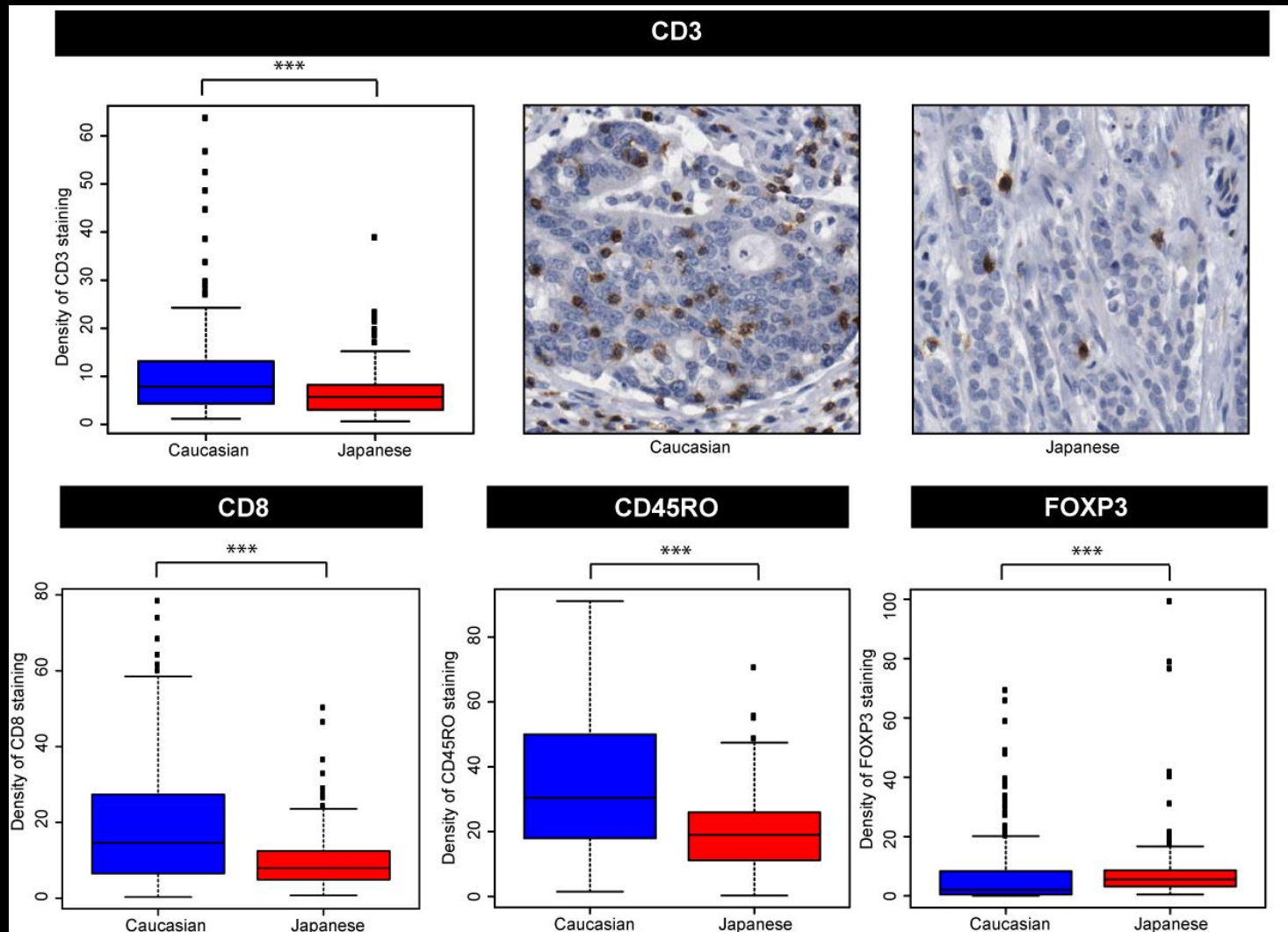
- **JUST cohort**

- Japanese high-volume cancer centre (Kanagawa Cancer Centre, Yokohama, Japan)
- Part of ACTS-GC and SAMIT Phase III trials
- 253 total cohort (110 5FU-related-chemotherapy)
- 219 total immunohistochemistry (IHC) cohort

- **Leeds cohort**

- St James's University Hospital, Leeds, United Kingdom
- 906 total cohort (62 5FU-related-chemotherapy)
- 446 total IHC cohort

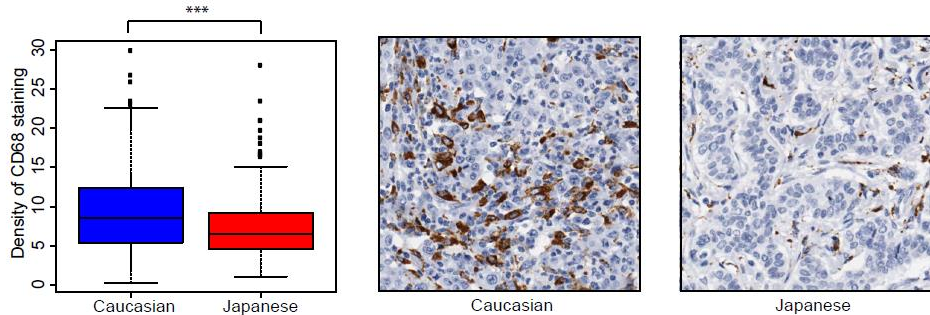
Immunohistochemistry Validation of T-cell Signatures in Non-Asian GCs



Asian and Non-Asian GCs

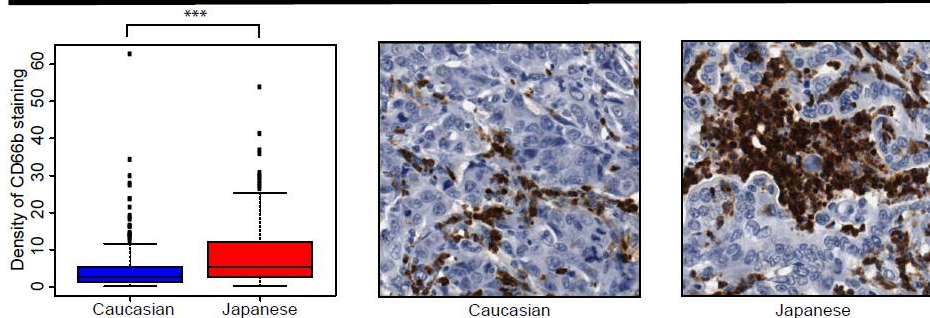
Differences in Other Immune Markers

CD68



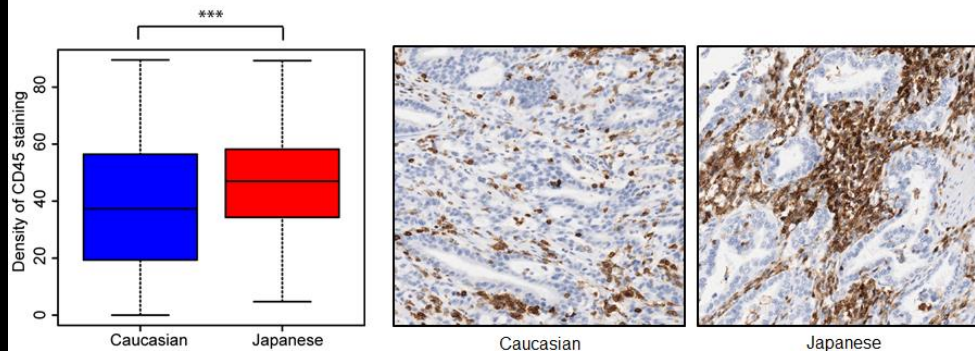
Macrophages
(> Caucasian)

CD66b



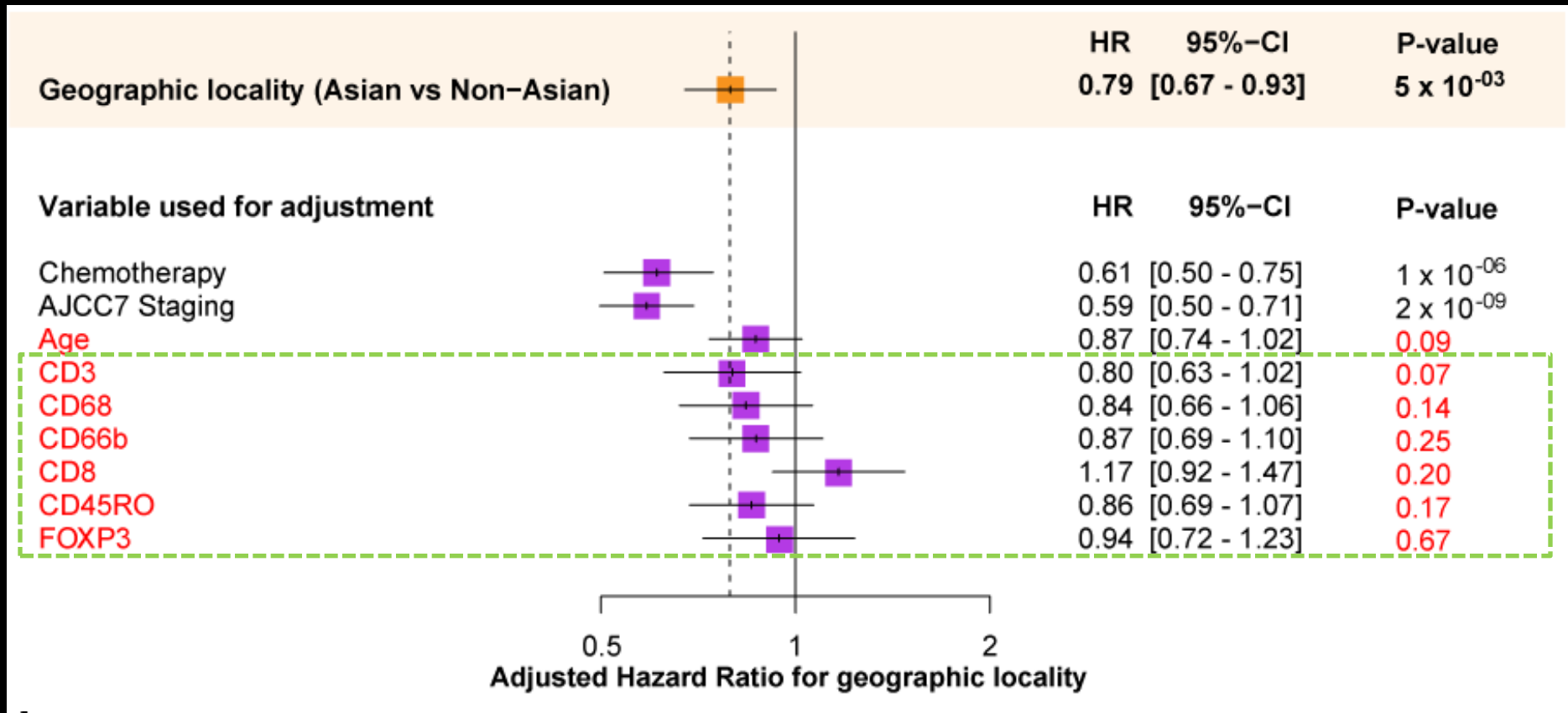
Neutrophils
(> Japanese)

CD45



Pan-Leucocyte
(> Japanese)

Adjusting for T-cell Signatures Impacts Geographic Differences in Overall Survival



East vs West GCs May Differ in Combined MSI/EBV Frequency

EBV (+)

12/216
(5.48%)

MSI (+)

21/216
(9.59%)



Chi-sq test of proportion
p-value = 2.8×10^{-07}

EBV (+)

15/437
(3.4%)

MSI (+)

13/175
(7.42%)



Conclusions and Discussion

- Large-scale expression analysis reveals differences in the immune microenvironment between Asian vs non-Asian GCs
- Non-Asian GCs appear enriched in T-cell pathways (eg CTLA-4) and other immune cells (eg macrophages)
- Tumor immunity differences may be due to differences in combined MSI/EBV frequency
- Adjusting for immune differences (esp CD68/CD3) impacts region-specific survival
- Tumor immunity differences may influence GC immunotherapy trials?

Lin et al 2015 *Gut*

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Sophie Earle

Louise Ruff

Katherine Pettinger

South Korea

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Won Ki Kang

Sung Kim

Jae Ho Cheong (Yonsei)

Sung Hoon Noh

Sun Young Rha

Hyun Cheol Chung

USA

Ju-Seog Lee

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Terry Speed

Johann Gagnon-Bartsch

