ASPIS

ONTOX

PRECISION TOX

RISK HUNT3R

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Open Symposium

2-3 July 2026

Maastricht
The Netherlands

Quantitative assessments of population-level susceptibility to toxicity: relevance to humans and wildlife

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Project: PrecisionTox

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Objectives of the Study

- To assess the impact of genetic variation on toxicity using a human genome diversity cell line panel
- To identify genetic variants (SNPs) and affected cellular mechanisms associated with toxic responses
- To compare the identified human mechanisms to mechanisms identified from Drosophila Melanogaster to enable human toxicity assessement in non-scentient species

Assay Set Up

Chemical selection screen; 91 chemicals, 20 LCL's

Select 13 with the highest variation; CADMIUM CHLORIDE, SODIUM (META) ARSENITE, ACRYLAMIDE, 4-METHYL IMIDAZOLE, GENISTEIN, DEXAMETHASONE, VALPROIC ACID, TAMOXIFEN, CYCLOSPORIN A, ROTENONE, DISULFIRAM, 5-FLUOROURACIL, (+DMSO)

Main screen; 13 chemicals, 261 Lymphoblastoid cell lines, 4 biological replicates, 2 viability endpoints, 8 concentrations

Anova, GWAS, Pathway analysis

The Human Lymphoblastoid Cell Line Panel

EUROPEAN
FIN – FINNISH
GBR – BRITISH
IBS – IBERIAN IN SPAIN

EAST ASIAN
CHS – HAN CHINESE SOUTH, CHINA
CDX – CHINESE DAI IN XISHUANGBANNA
KHV – KINH IN HO CHI MINH CITY, VIETNAM

SOUTH ASIAN
STU – SRI LANKAN TAMIL IN THE UK
PJL – PUNJABI IN LAHORE, PAKISTAN
BEB – BENGALI IN BANGLADESH

AMERICAN
PEL – PERUVIAN IN LIMA, PERU
MXL – MEXICAN ANCESTRY IN CALIFORNIA, USA
CLM – COLOMBIAN IN MEDELLIN
PUR – PUERTO RICAN IN PUERTO RICO

AFRICAN
ACB – AFRICAN CARIBBEAN IN BARBADOS
GWD – GAMBIAN IN WESTERN DIVISION - MANDINKA
YRI – YORUBA IN IBADAN, NIGERIA
ESN – ESAN IN NIGERIA

2 male + 2 female high variation cell lines from each population

99 lines from Yuruba
106 lines from Esan

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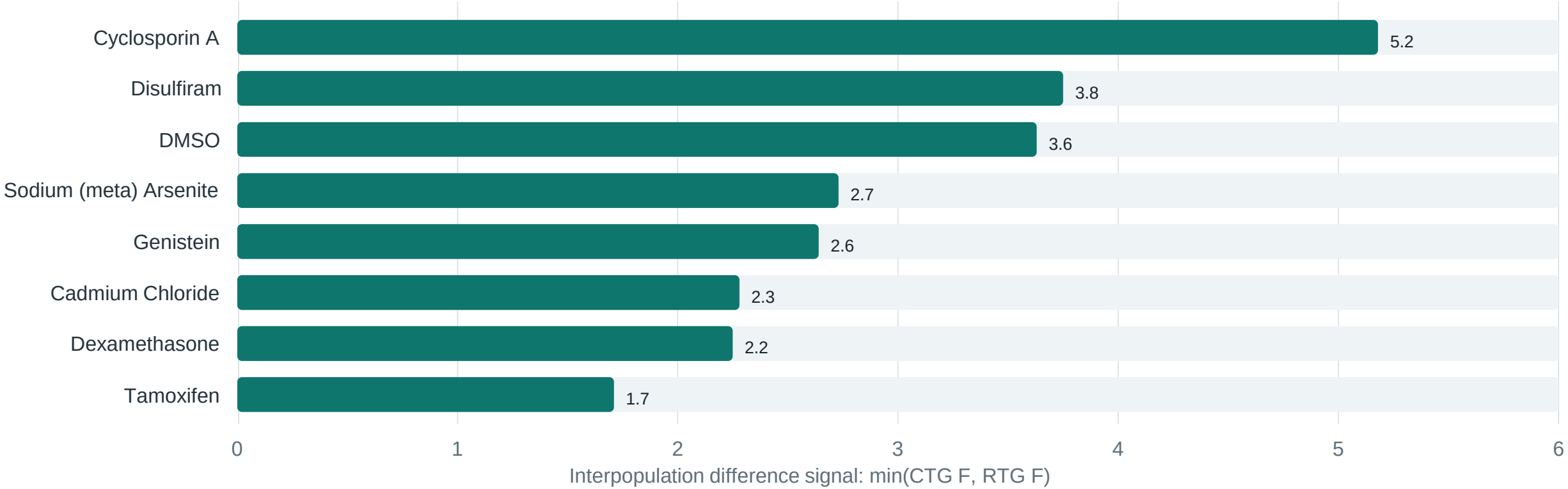
ANOVA Analysis: Interpopulation Variation

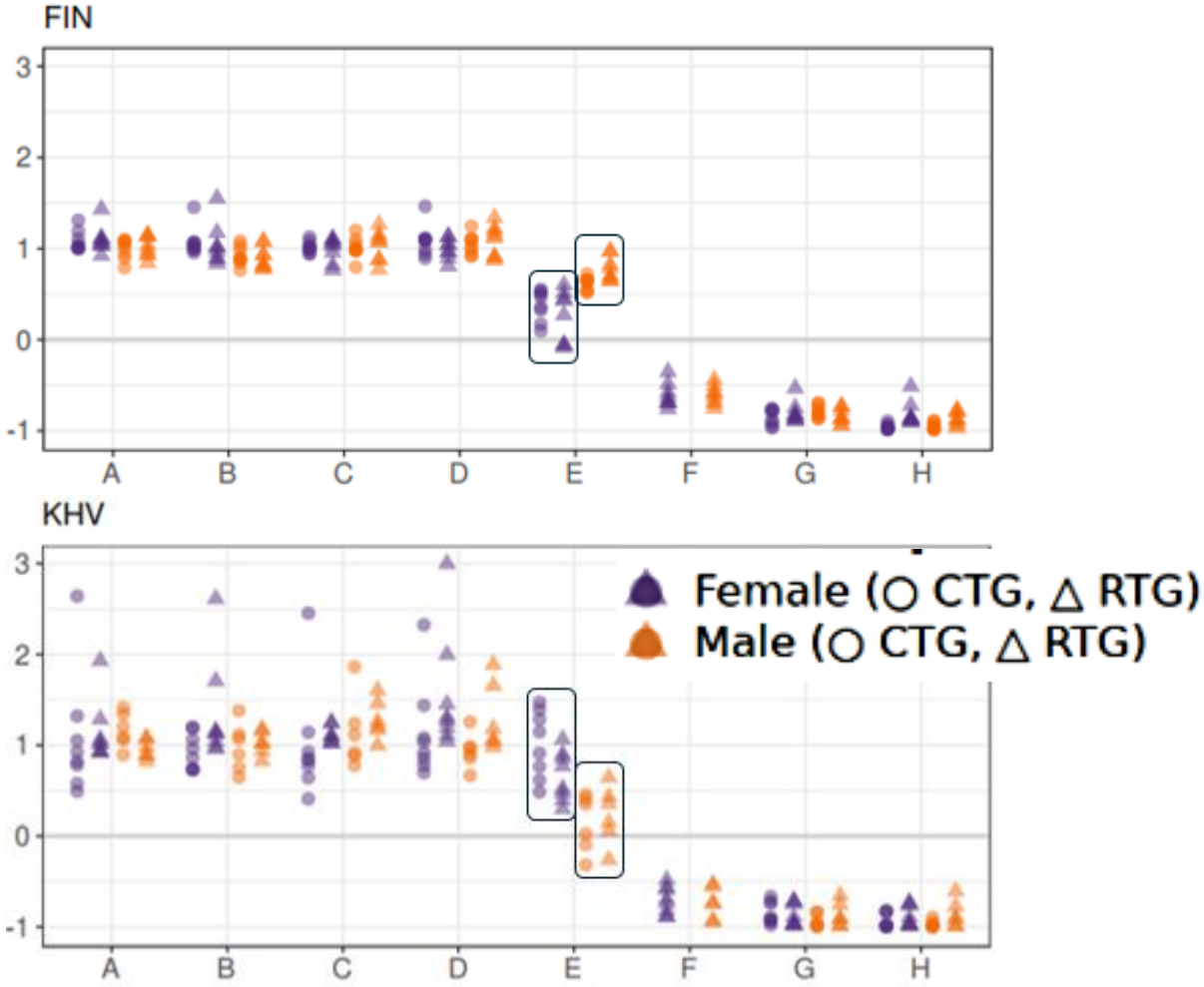


Chemicals with response differences between populations

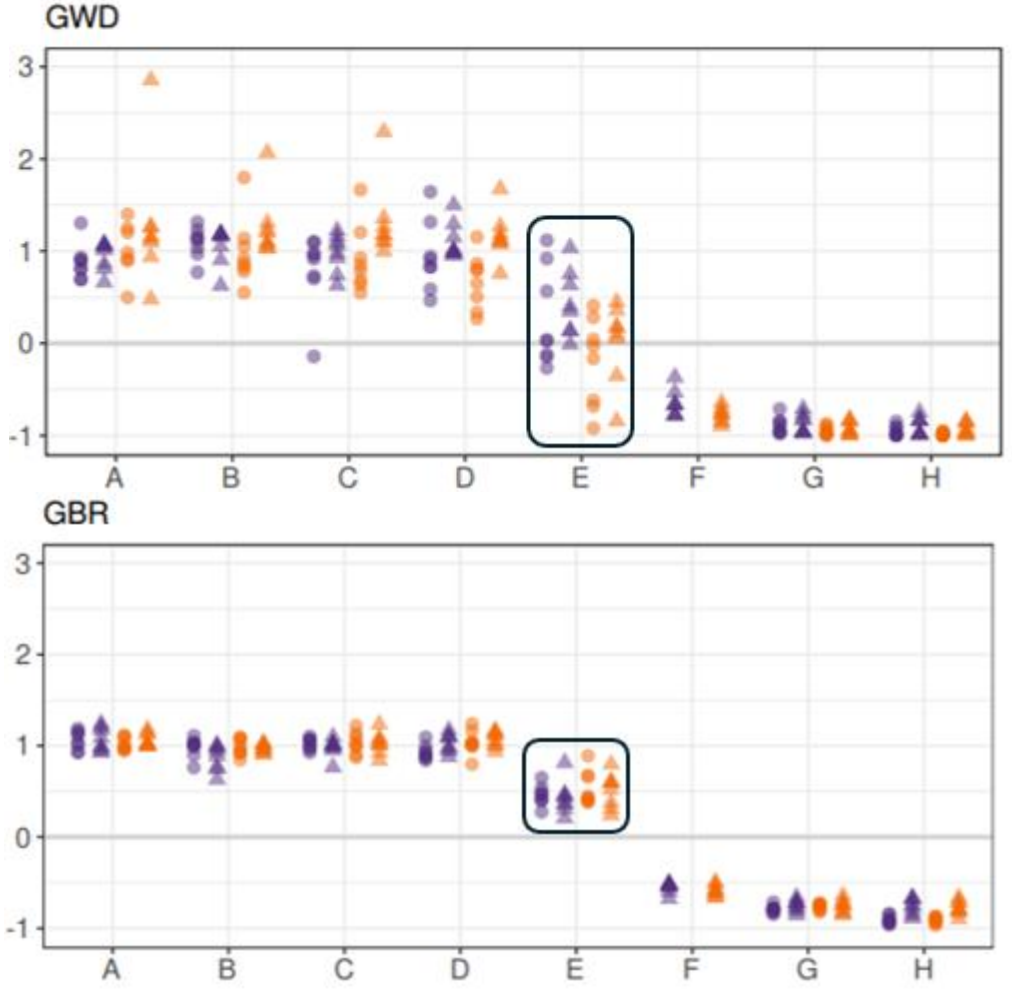
Bars are ranked by the smaller population F-statistic across both CTG and RTG assays. Longer bars indicate stronger interpopulation variability

Population-Specific Differences; Acrylamide

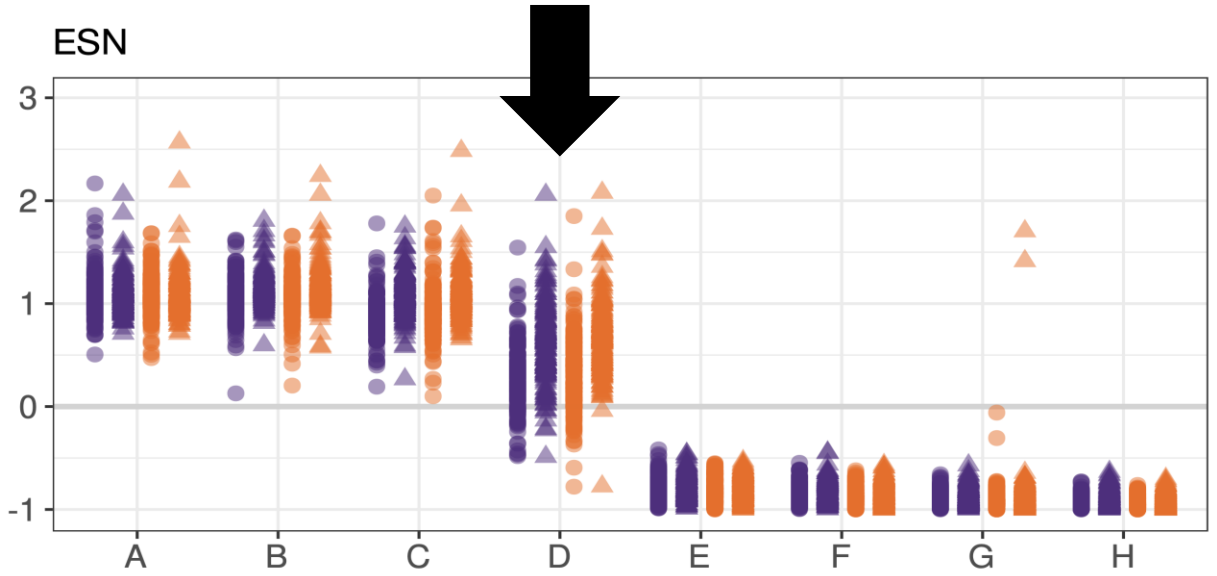
Sex differences; Finnish females are more sensitive than males. Opposite is true for Vietnamese.

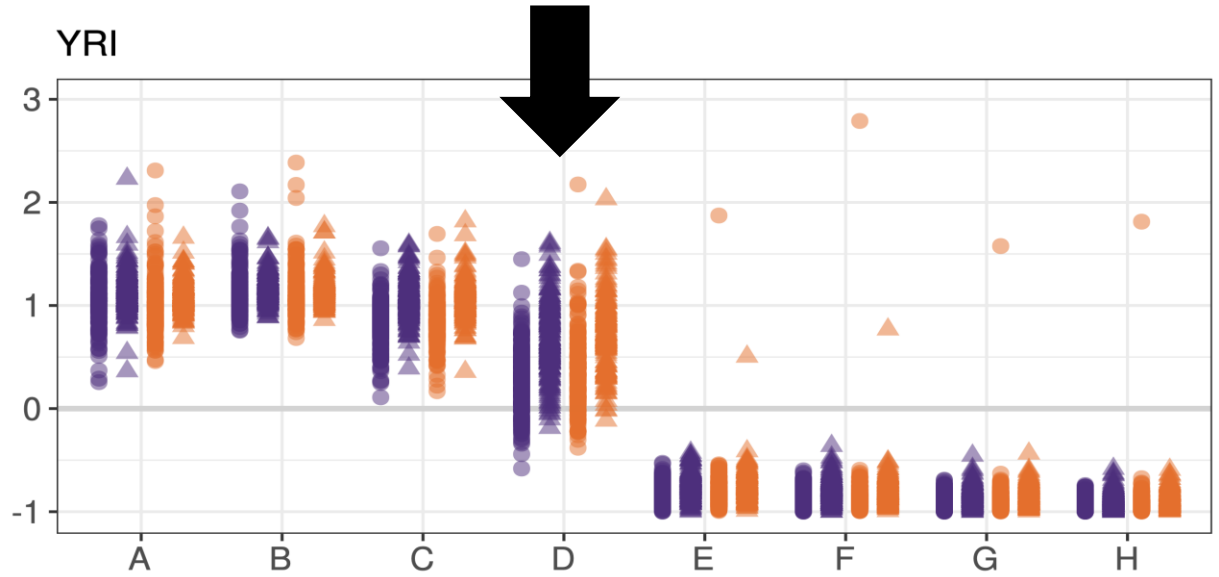


Population differences; Gambian are more sensitive than Brittish



GWA; Variation in Sensitivity to Cadmium Chloride Across Esan and Yoruba Populations





GWAS focused on the two Nigerian populations to gain adequate sample size and statistical power for further analyses.

ESN = Esan
YRI = Yoruba

Concentration (mM)
A: 3.494 e -4
B: 1.747 e -3
C: 8.734 e -3
D: 4.367 e -2
E: 2.184 e -1
F: 1.092 e 0
G: 5.459 e 0
H: 2.729 e 1

Sex x Endpoint
Female (○ CTG, △ RTG)
Male (○ CTG, △ RTG)

GWA Analyses for Two African Populations

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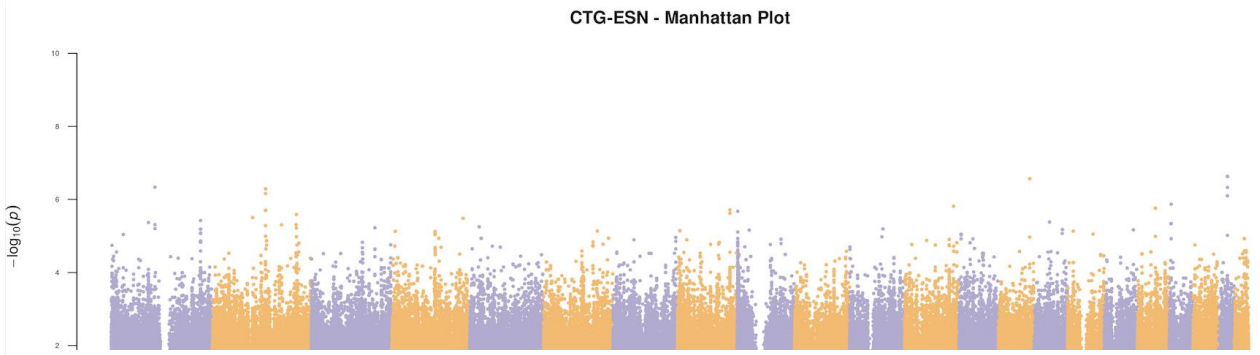
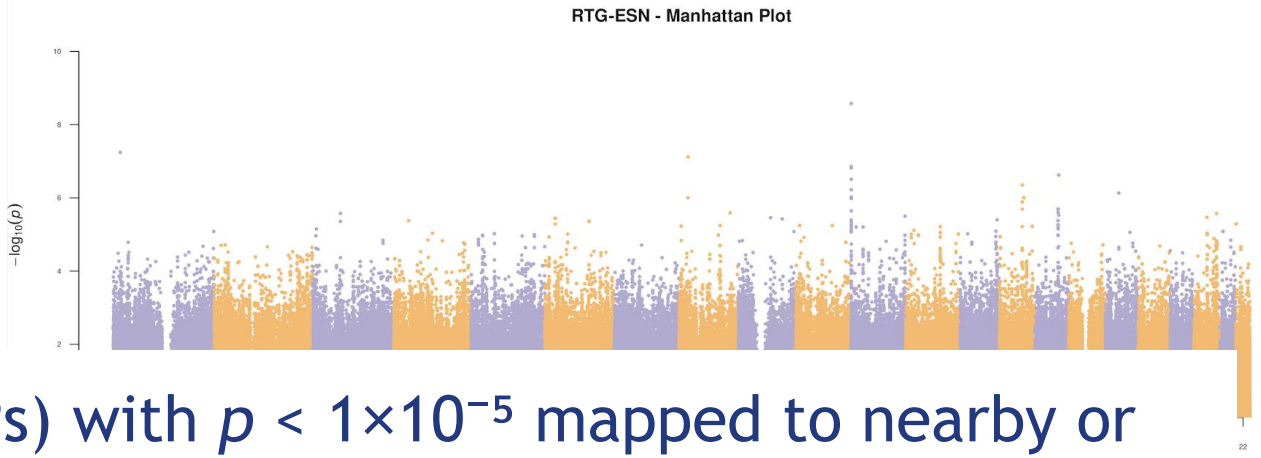
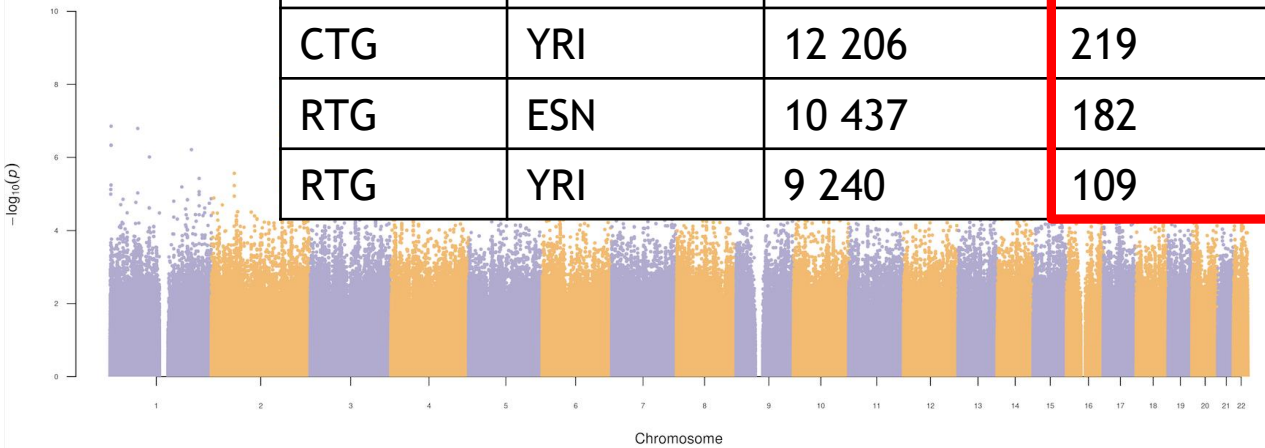
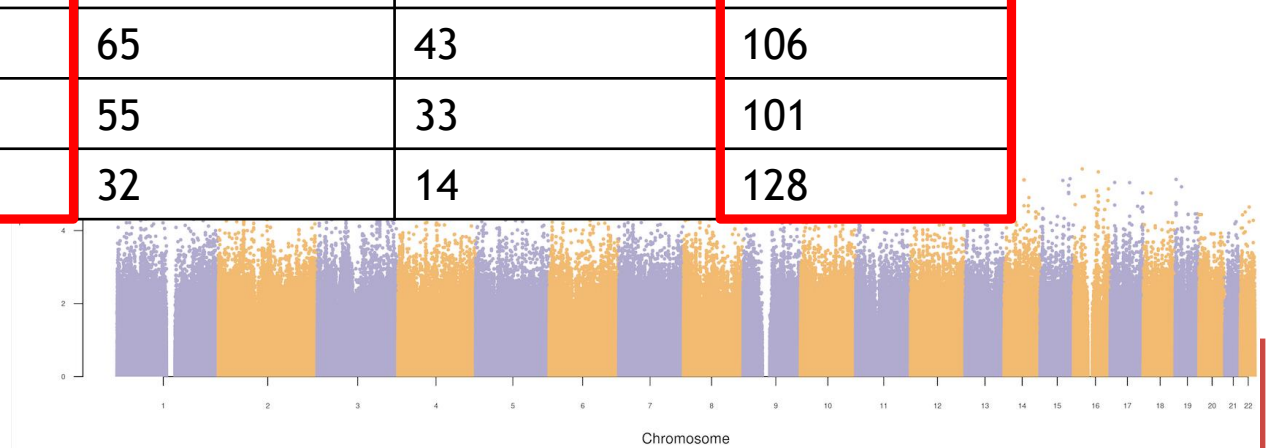




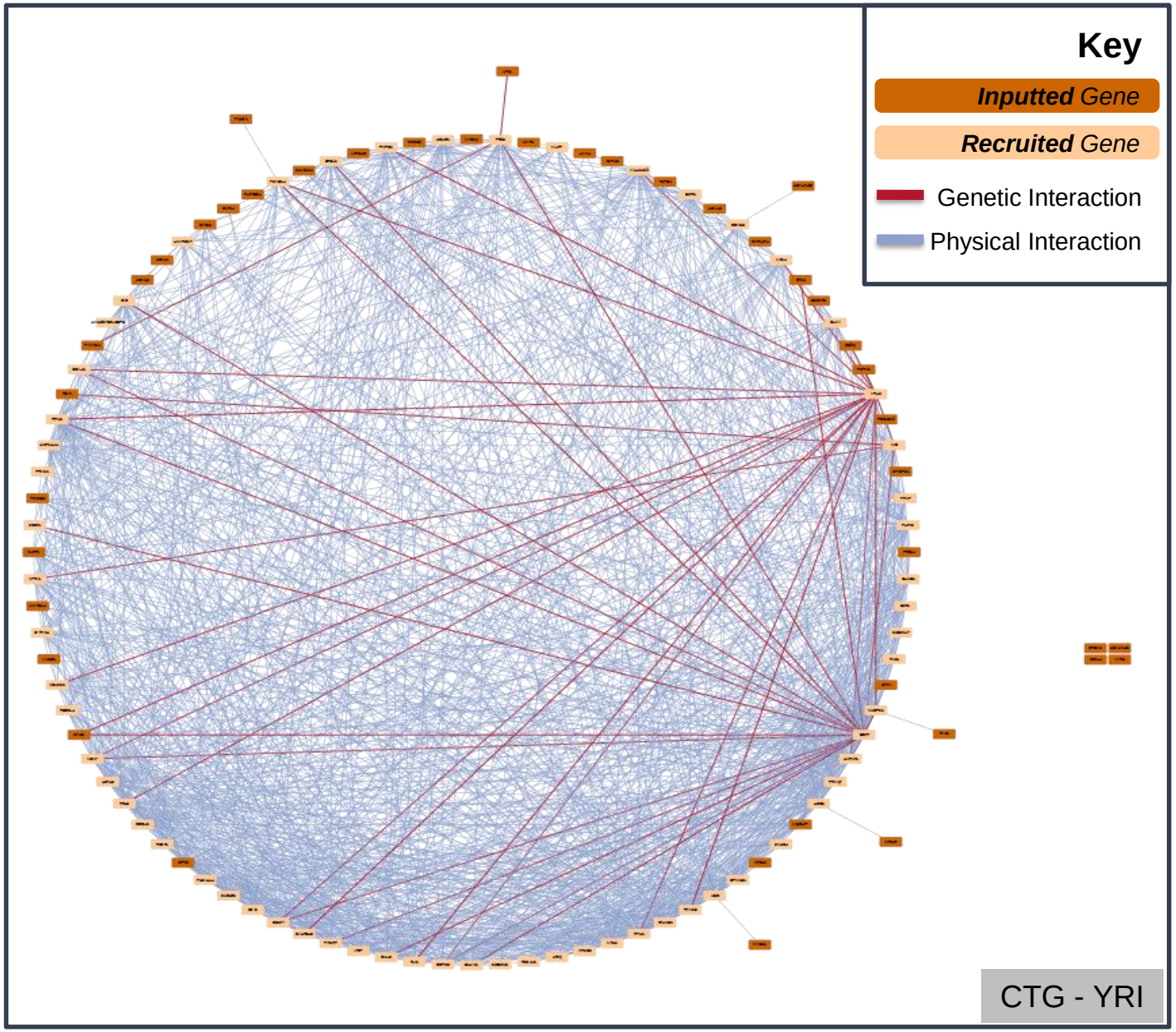
Single-nucleotide polymorphisms (SNPs) with $p < 1\times10^{-5}$ mapped to nearby or overlapping genes, enabling biological interpretation of association signals.

Endpoint	Population	Unique SNPs p < 0.001	Unique SNPs p < 0.00001	Unique Genes p < 0.00001	Unique Genes Network Input Set	Total Genes In Network
CTG	ESN	10 671	85	21	12	17
CTG	YRI	12 206	219	65	43	106
RTG	ESN	10 437	182	55	33	101
RTG	YRI	9 240	109	32	14	128





GWA; Interaction Network of Genes Associated with Exposure to Cadmium Chloride



- Significant SNPs were mapped to genes, which were then used to build **interaction networks.**

- **Recruited genes** are genes directly connected to at least three input genes.

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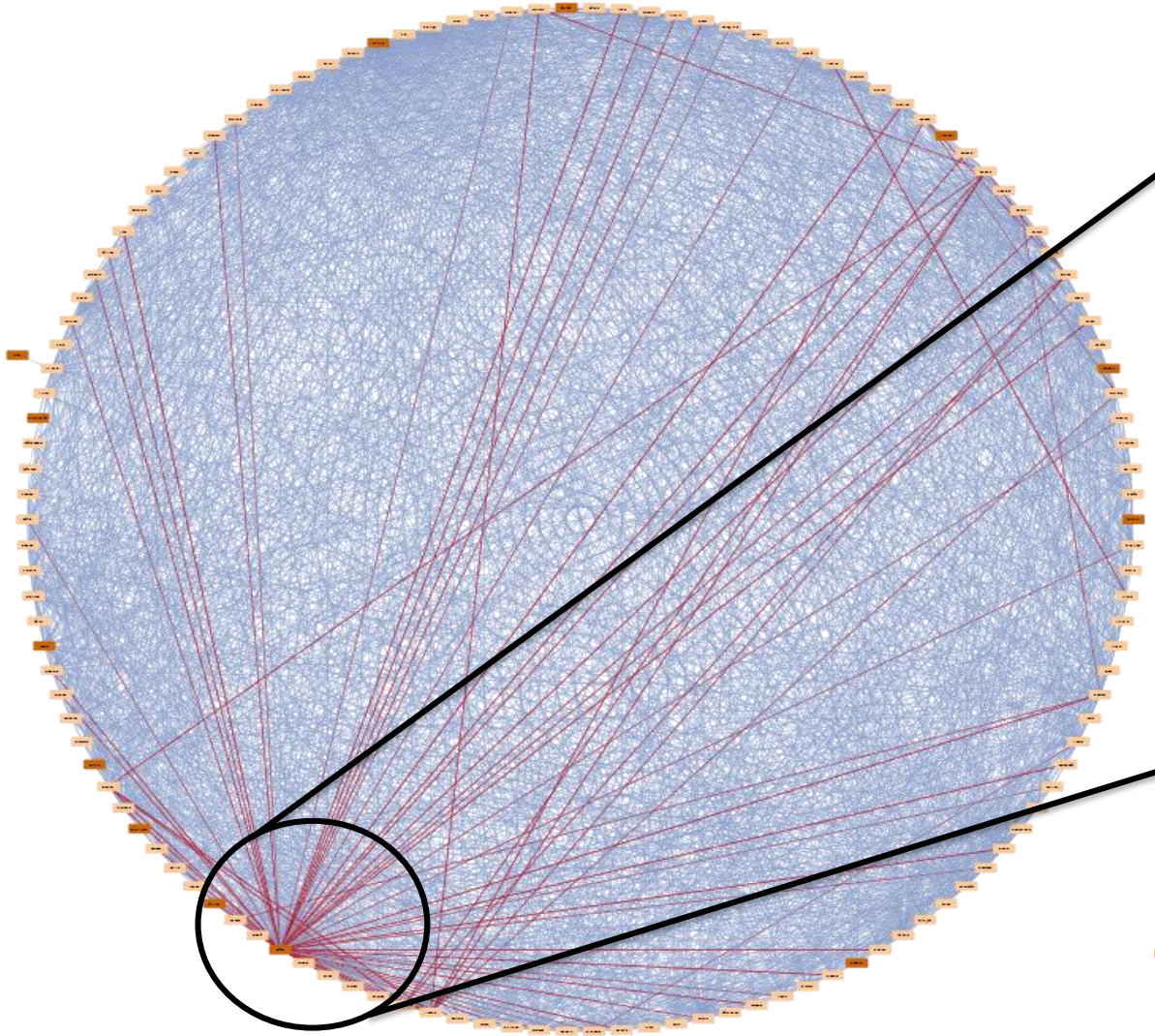
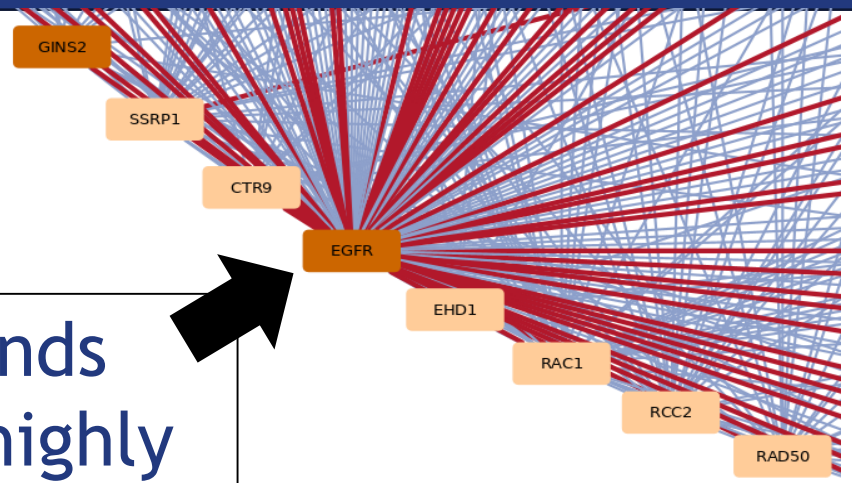
Interaction Network of Genes Associated With Exposure to Cadmium Chloride



RTG - YRI



EGFR stands out as a highly connected hub gene.

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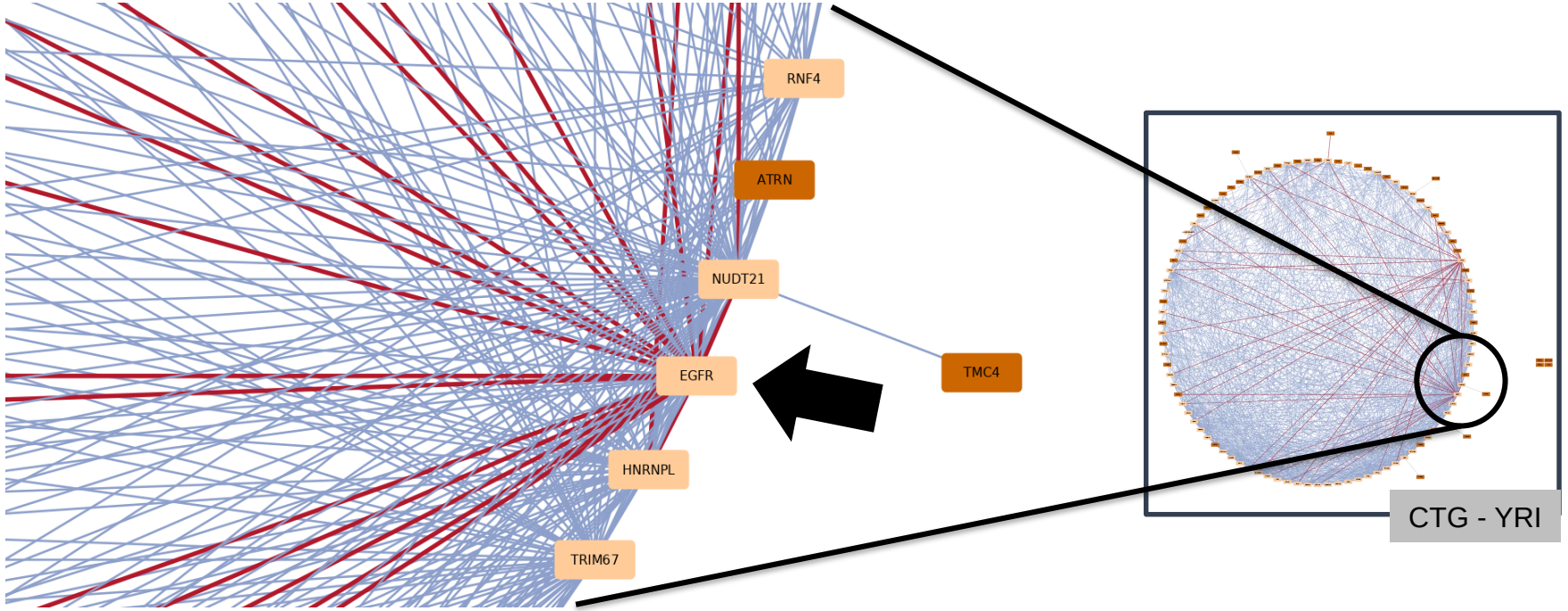
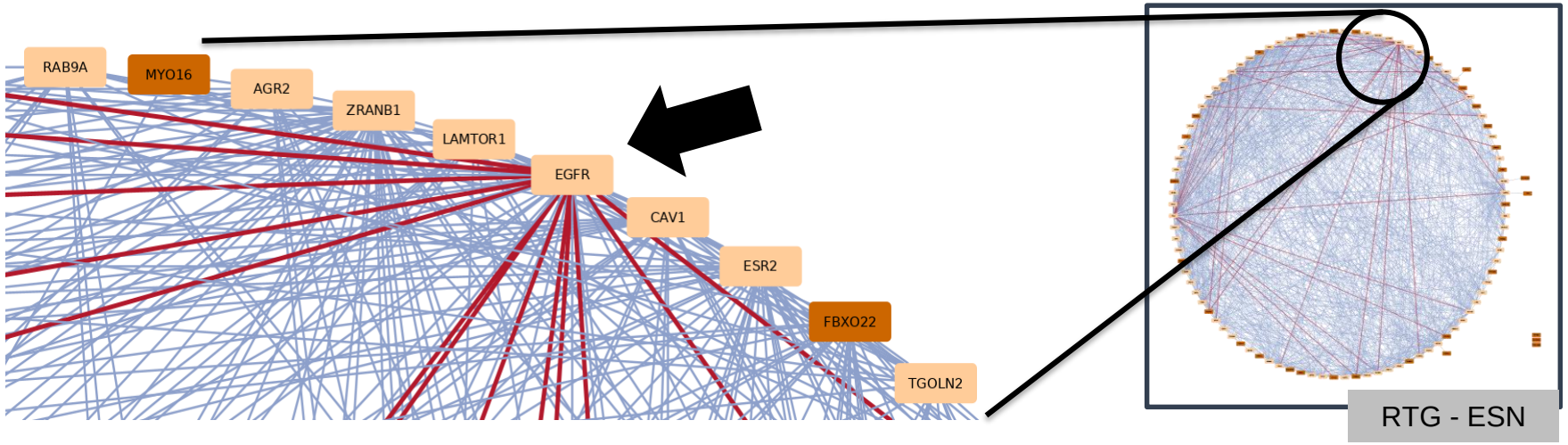
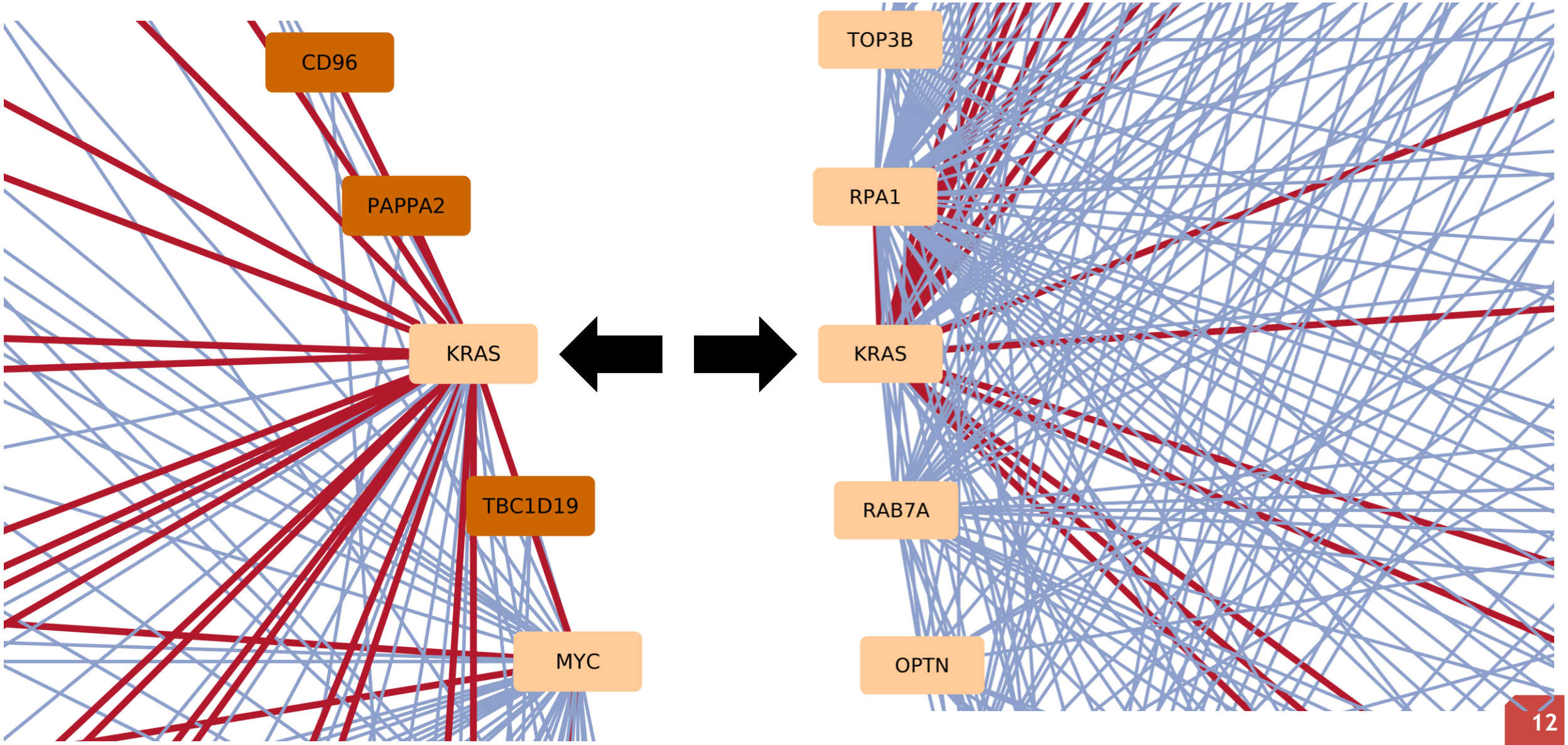
Recruitment of *EGFR* into Gene Interaction Networks from Additional Analyses





In addition to being a direct GWA - SNP hit, *EGFR* was independently recruited into two additional networks.

KRAS Identified as an Additional Highly Connected Hub Gene



Comparison to Drosophila Genome Diversity Line Panel GWA Analysis upon Cadmium Exposure

Drosophila melanogaster

Human lymphoblastoid cell lines

Cadmium GWA -> gene network

Egfr

Conserved gene of interest

EGFR

GWA / network recovery

Genes directly connected to fly Egfr

Genes directly connected to fly Egfr	Human ortholog	Recovered in
Fmr1	FXR2	1 GWA CTG-ESN
Shrm	SHROOM3	1 GWA RTG-ESN
Pp1-87B	PPP1CC	1 GWA CTG-YRI
Ras85D	KRAS	2 Networks CTG-YRI RTG-ESN

PrecisionTox Data Explorer Finds the EGFR Connection

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PTox/DEx | PrecisionTox Data Explorer

Data | Downloads

Transcriptomics | Metabolomics | Chemicals | Orthologs | Functions

Explore Data | Gene Centric View | Compare Data

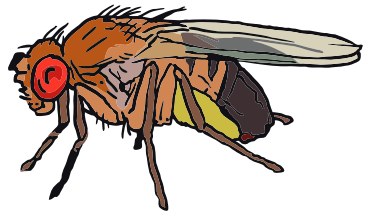
Choose an organism to search genes from:

Drosophila melanogaster

Search for a gene:

Egfr | Epidermal growth factor receptor (Egfr) (receptor) (Protein torpedo) | FBgn0003731

Submit



Exposure to Cadmium is the most significant inducer of fruit fly and zebrafish EGFR gene!

SORT

Expression tables

Show 50 entries | CSV | Excel | Print | Copy

Organism	Gene	Chemical	Dose	Timepoint (hrs)	log2FoldChange	log2FoldChange_SE	pvalue	padj
All	All	All	All	All	All	All	All	All
Danio rerio	LL0000009753	Cadmium chloride	BMD10	48	0.59	0.14	0	0
Drosophila melanogaster	Dmel_CG10079	Cadmium chloride	BMD10	24	0.43	0.1	0	0
Drosophila melanogaster	Dmel_CG10079	Cadmium chloride	BMD25	24	0.49	0.13	0	0
Drosophila melanogaster	Dmel_CG10079	DMSO	BMD25	4	-0.56	0.15	0	0
Drosophila melanogaster	Dmel_CG10079	DMSO	BMD25	6	-0.56	0.15	0	0
Homo sapiens	ERBB2	WY-14643 / Pirinixic acid	BMD10	48	-0.72	0.14	0	0
Homo sapiens	ERBB2	WY-14643 / Pirinixic acid	BMD25	24	-0.61	0.16	0	0
Homo sapiens	ERBB2	WY-14643 / Pirinixic acid	BMD25	24	-0.61	0.16	0	0
Homo sapiens	ERBB3	WY-14643 / Pirinixic acid	BMD25	48	0.78	0.13	0	0

AOP Analysis Using the PrecisionTox Data Explorer

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PTox/DEx | PrecisionTox Data Explorer

Transcriptomics | Metabolomics | Chemicals | Orthologs | Functions

Explore Data | Gene Centric View | Compare Data

Choose organisms to compare:

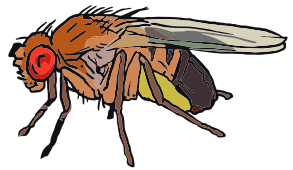
Danio rerio × Drosophila melanogaster × Homo sapiens ×

Choose chemical:

Cadmium chloride ×

Gene enrichment analysis identifies 5 AOPs common in humans vs flies vs fish in response to Cadmium

-> All AOPs linked to EGFR signalling!



Namespace: AOP

Path/Term	Name	Direction	Ratio	Fisher-pv	Fisher-C-pv	Genes
Event:1521	Decrease, Growth	ENRICHED	27.617	$4.6x10^{-10}$	$6.3x10^{-08}$	MT1A (1.00) MT1B (0.50) MT1E (1.00) MT1F (0.50) MT1G (1.00) MT1H (0.50) MT1X (0.50) MT2A (1.00)
Event:216	Decreased, PCK1 expression (control point for glycolysis/gluconeogenesis pathway)	ENRICHED	24.366	$6.4x10^{-09}$	$8.8x10^{-07}$	GCK (0.50) LDHA (1.00) LDHAL6A (0.50) LDHAL6B (1.00) LDHC (0.50) PCK1 (0.50) PGAM1 (1.00) PGAM4
Event:1512	Unfolded Protein Response	ENRICHED	7.446	$6.0x10^{-05}$	0.008	DNAJB1 (1.00) DNAJB4 (0.50) DNAJB5 (1.00) HSPA1B (1.00) HSPA1L (0.50) HSPA6 (1.00)
Event:1439	Systemic acute phase response	ENRICHED	8.668	$6.3x10^{-05}$	0.009	CCN1 (0.50) COMP (1.00) THBS1 (0.50) THBS2 (1.00) THBS3 (0.50) THBS4 (1.00)
Event:1605	Accumulation of misfolded proteins	ENRICHED	22.151	$1.5x10^{-04}$	0.021	HSPA1B (1.00) HSPA1L (0.50) HSPA6 (1.00)

Summary

- Significant response differences were observed between human populations and individual cell lines
- Minimal sex effects in cell lines
- GWAS for cadmium chloride identified gene networks linked to EFGR and KRAS signalling in humans
- Similar links to EFGR - KRAS signalling networks were discovered in fruit fly and in zebrafish
- Genetic variation in humans as well as in flies impacts toxic responses and should be considered in toxicity evaluations
- Next steps: Expression-QTL analysis will be carried out to further characterize SNP – gene interactions

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