Pharmacogenomics: Science and Translation

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Pharmacogenomics

- Introduction
- Pharmacogenomic science
- Pharmacogenomic translation
- Conclusions

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Pharmacogenetics-Pharmacogenomics

The study of the role of inheritance in individual variation in drug response phenotypes.

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Pharmacogenetics-Pharmacogenomics

Clinical Goals

- Avoid adverse drug reactions
- Maximize drug efficacy
- Select responsive patients

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Pharmacogenetics-Pharmacogenomics

Scientific Goals

- Link variation in genotype to variation in phenotype
- Determine mechanisms responsible for that link
- Translate the link into enhanced understanding, treatment and prevention of disease

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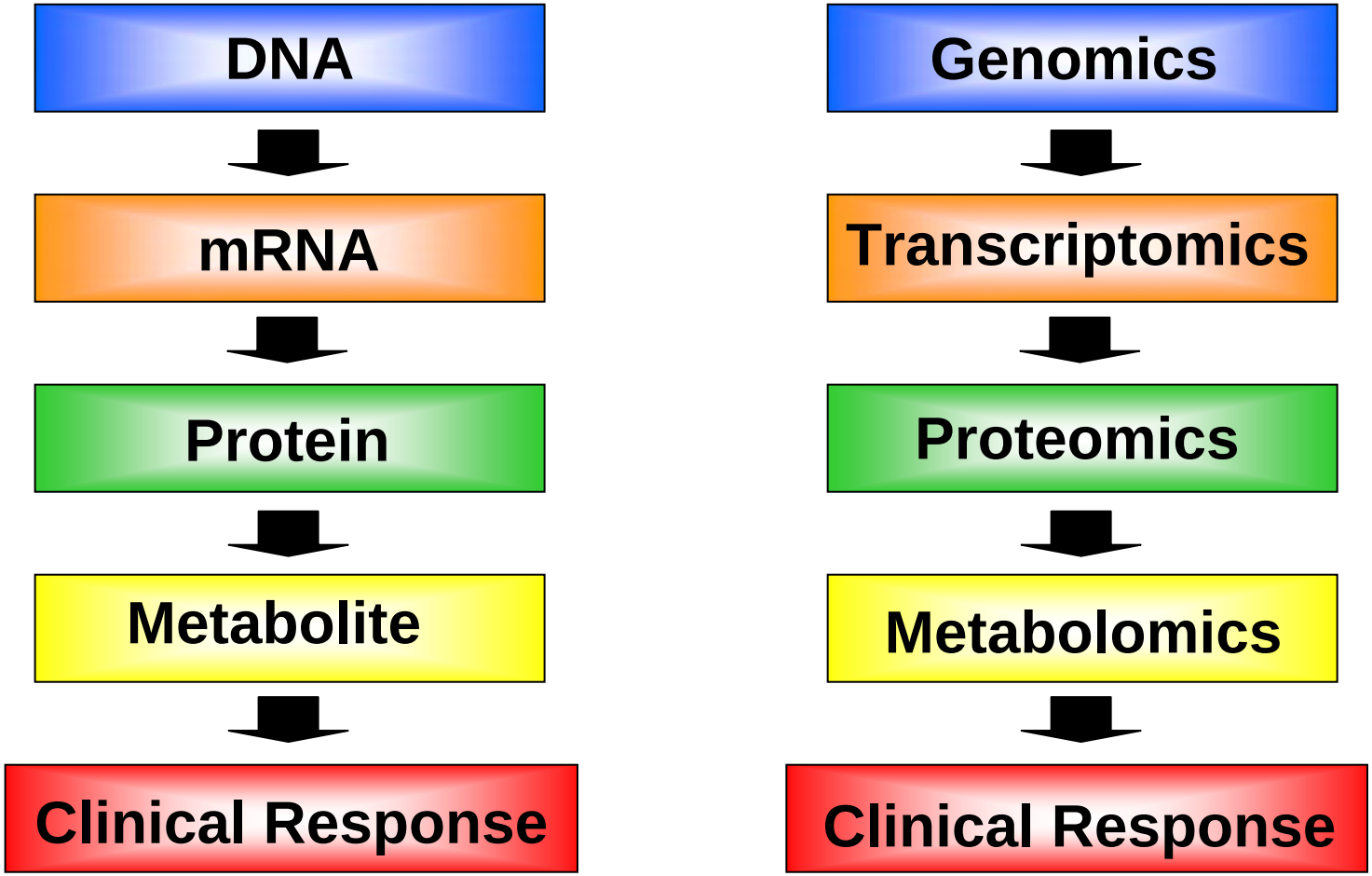
Pharmacogenetics-Pharmacogenomics

Drug Response Predictors



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Pharmacogenetics-Pharmacogenomics

Complementary Approaches

Basic	⇌	**Translational**
Phenotype	⇌	**Genotype**
Pharmacokinetic	⇌	**Pharmacodynamic**
Pathway-based	⇌	**Genome-wide**

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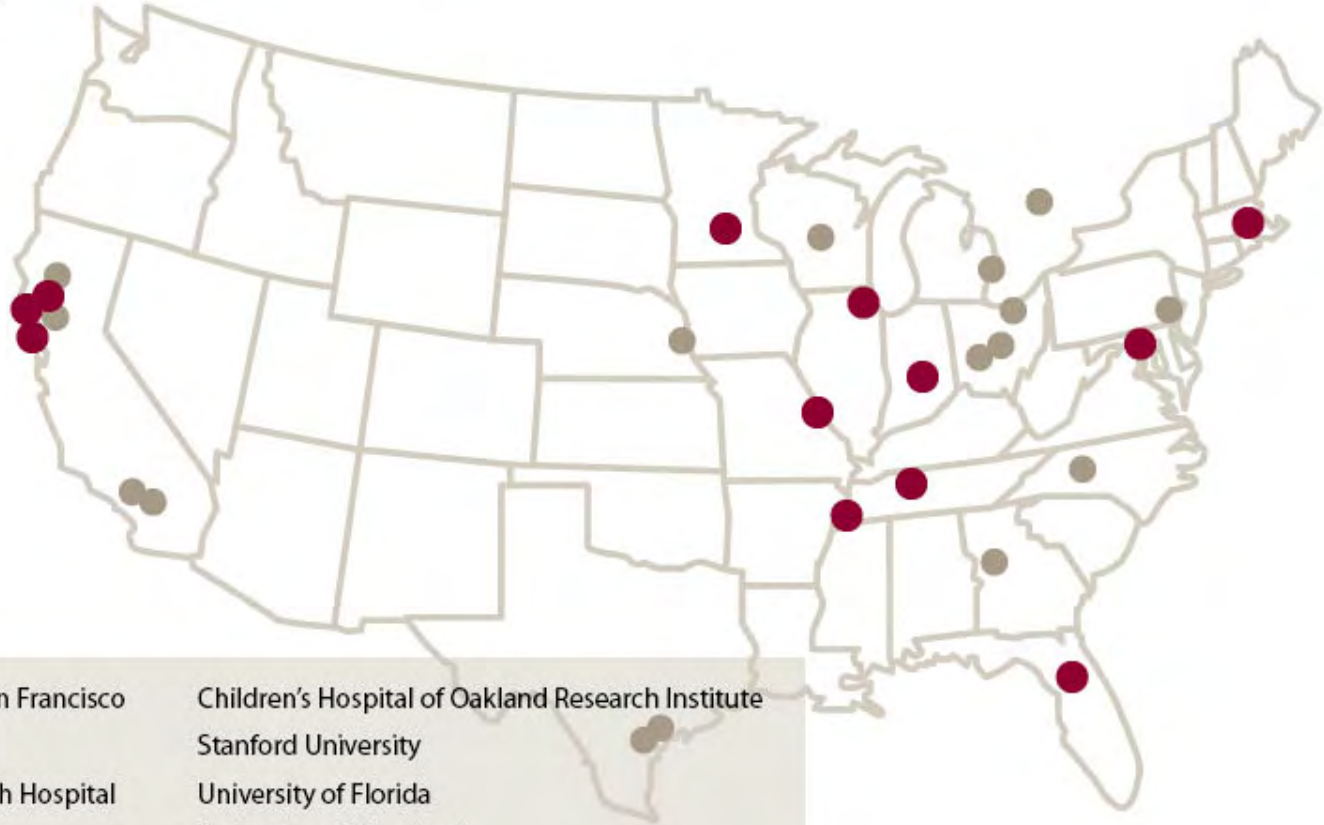
Pharmacogenetics Research Network

National Institutes of Health
U.S. Department of Health & Human Services

Research Sites

NIH Funding Institutes

NIGMS
NHLBI
NIDA
NCI
NIEHS
NIMH
NHGRI
NLM
ORWH



University of California, San Francisco	Children's Hospital of Oakland Research Institute
University of Chicago	Stanford University
St. Jude Children's Research Hospital	University of Florida
Mayo Clinic	University of Maryland
Vanderbilt University	Indiana University
Washington University	Brigham and Women's Hospital

● Primary Investigator Site
● Co-Investigator Site

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Pharmacogenetics-Pharmacogenomics

FDA Hearings
Pharmacogenetics and Drug Labeling

- Thiopurines – *TPMT*
- Irinotecan – *UGT1A1*
- Warfarin – *CYP2C9* and *VKORC1*
- Tamoxifen – *CYP2D6*

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2003 FDA "Draft Pharmacogenomic Guidance"

Valid Biomarkers

- Thiopurine S-methyltransferase (TPMT)
- Cytochrome P450 2D6 (CYP2D6)

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TPMT Pharmacogenomics

Basic Pharmacogenomics

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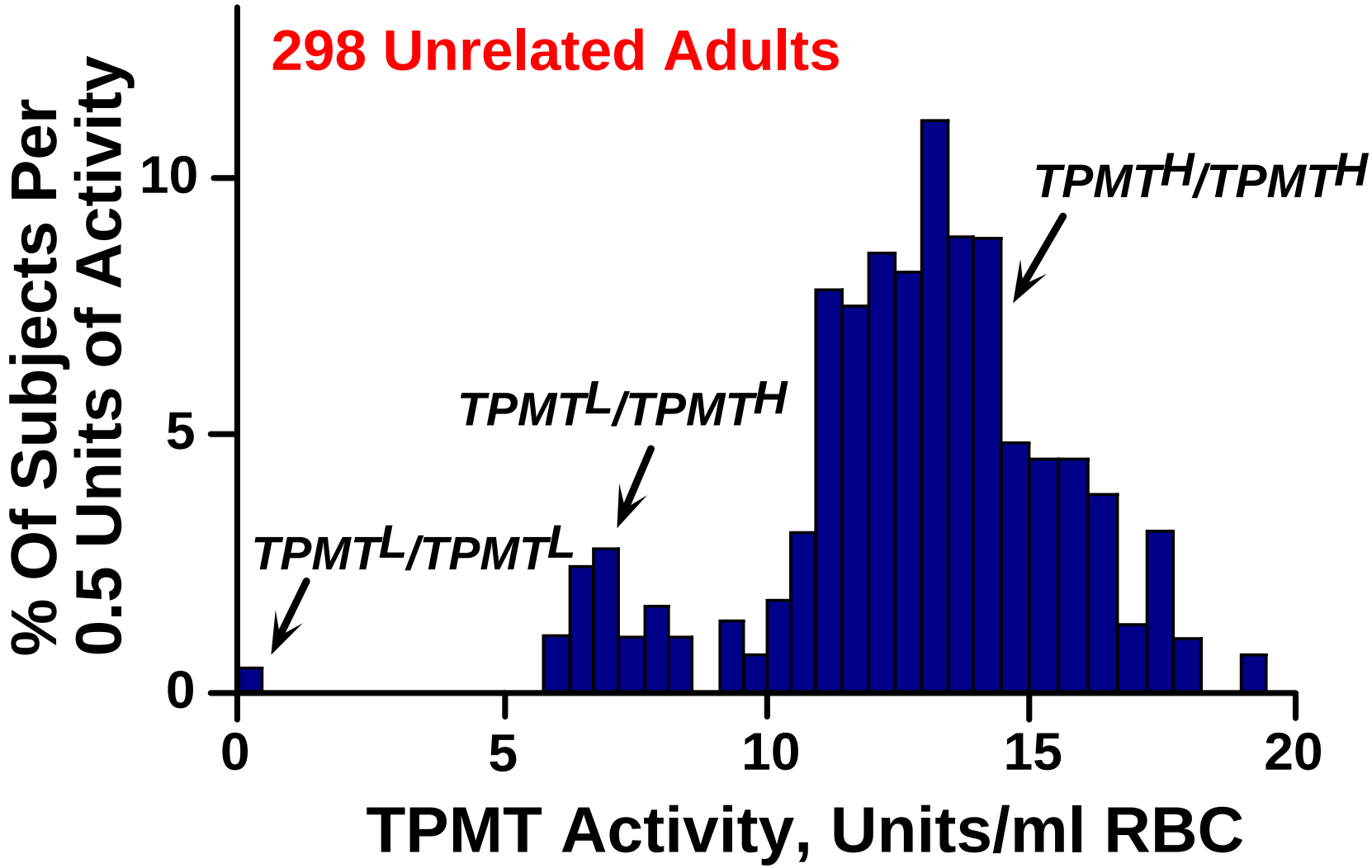
Human RBC TPMT



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TPMT
Genetic Polymorphism
Clinical Consequences

- **Low TPMT**
  - **Increased thiopurine toxicity**
  - **Increased risk for secondary neoplasm**
- **High TPMT**
  - **Decreased therapeutic effect**

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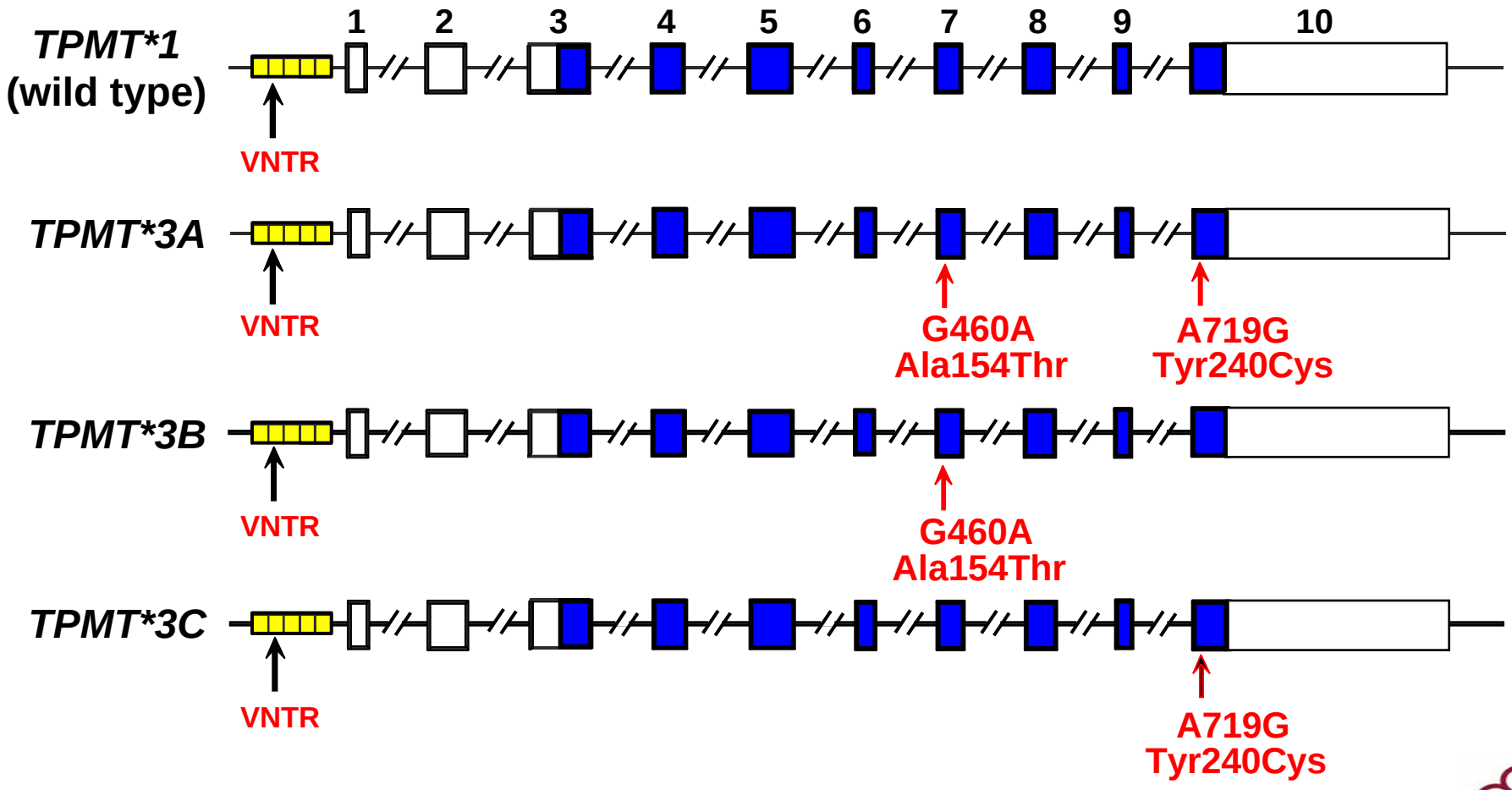
Selected Human TPMT Alleles



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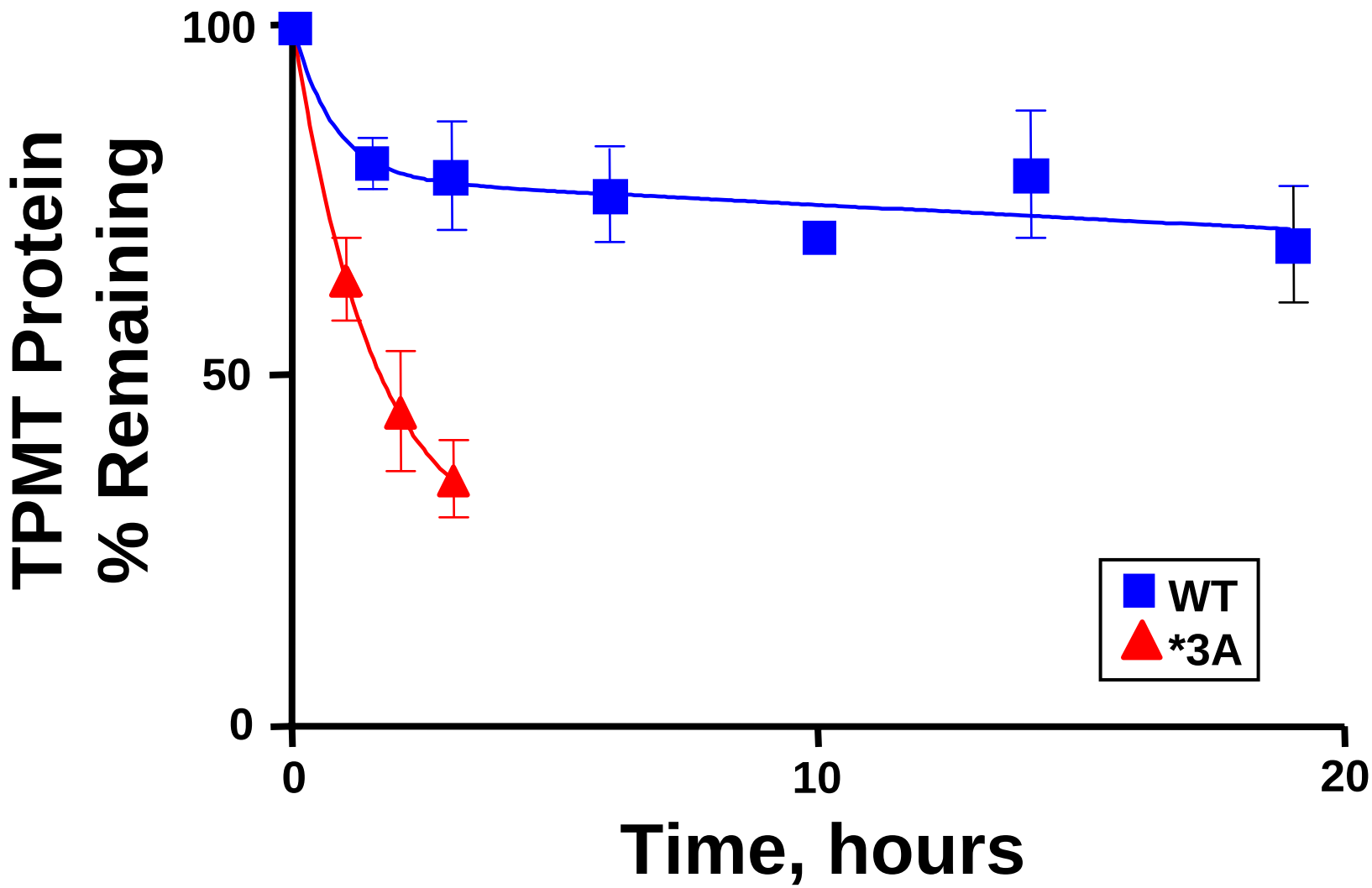
Human TPMT Protein RRL Degradation



Wang et al., Pharmacogenetics 13:555-64, 2003

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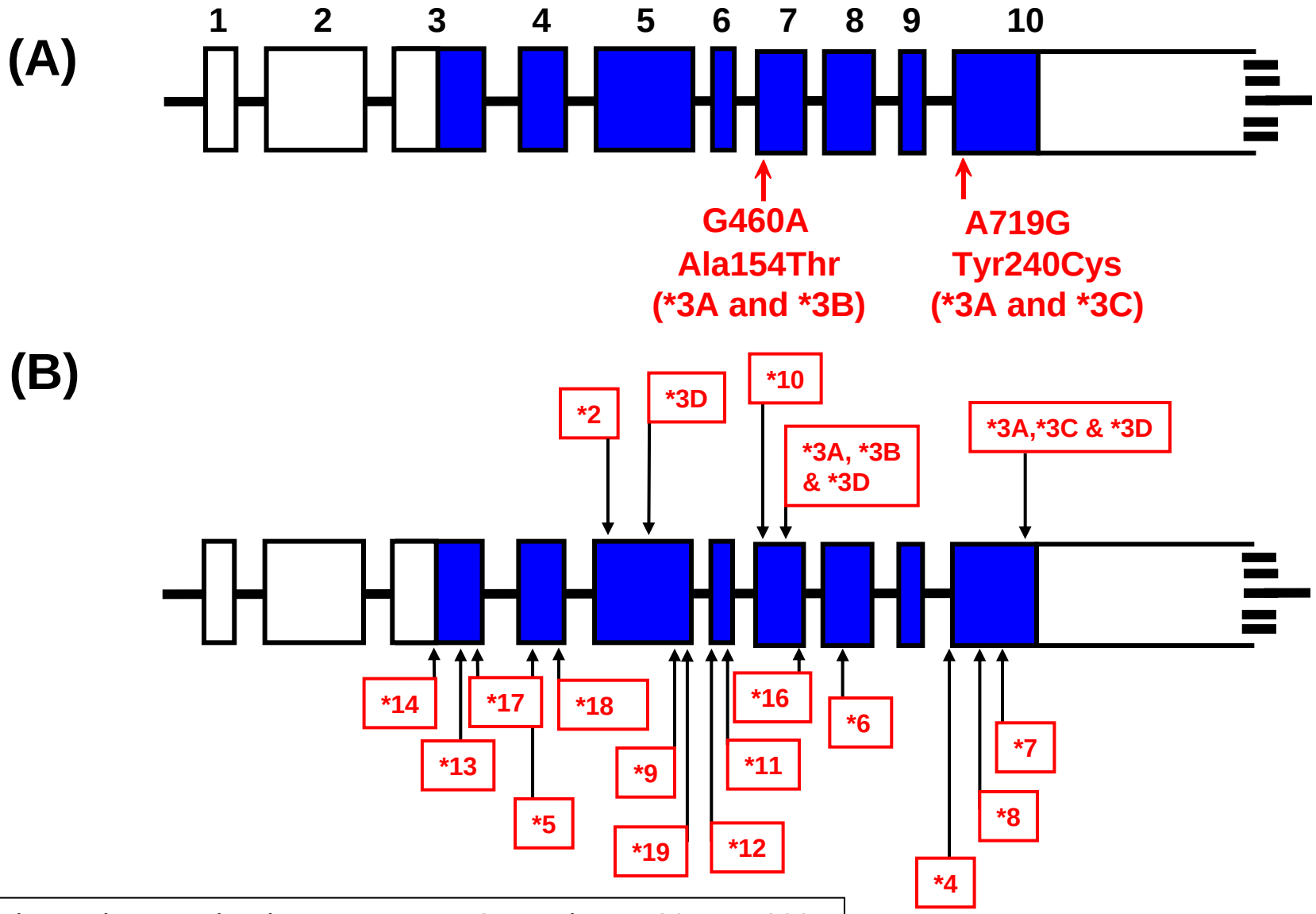
TPMT Gene Structure and Polymorphism/Mutation Locations



Salavaggione et al., Pharmacogenet. Genomics 15:801-15, 2005

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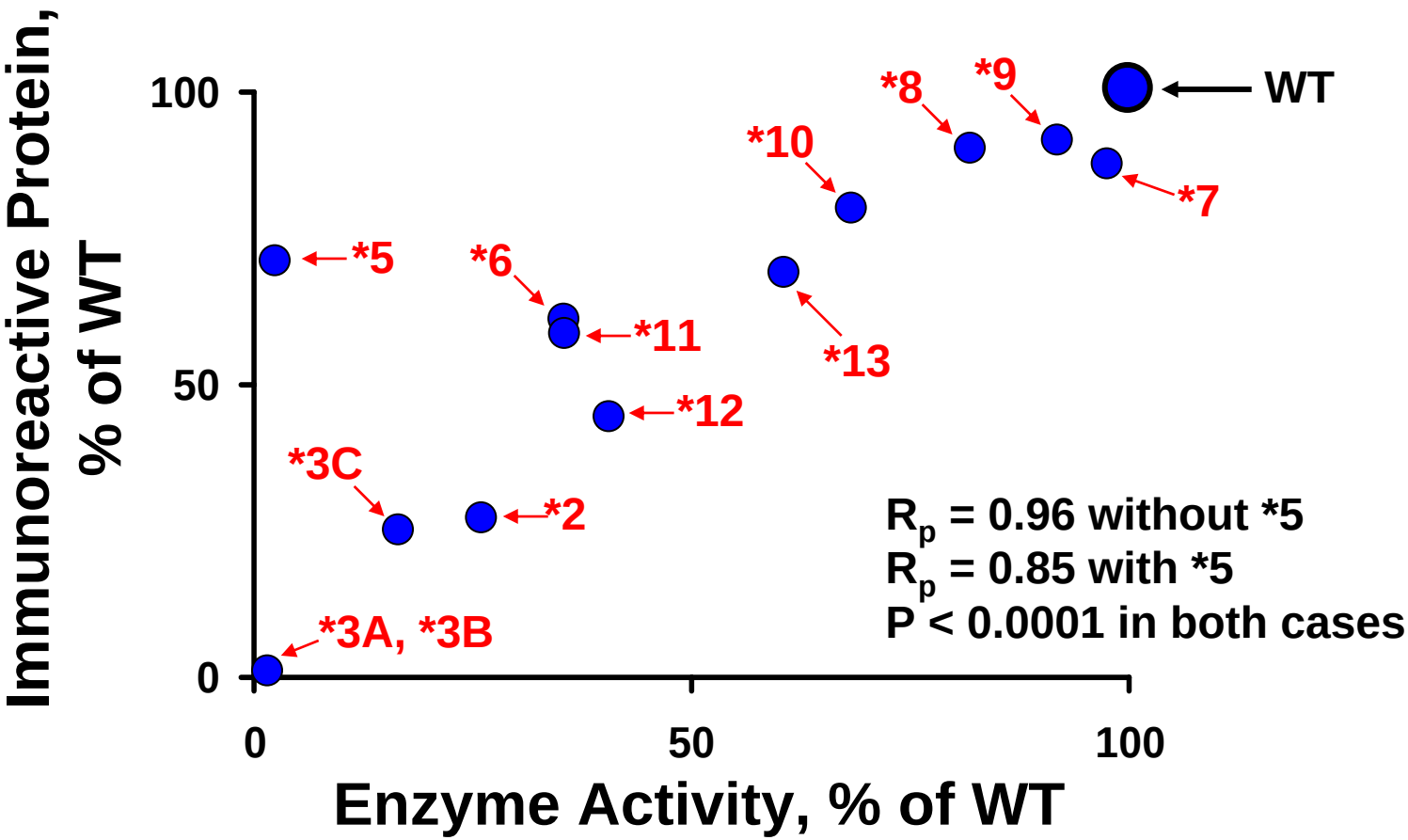
Recombinant Human TPMT Allozyme Activity and Protein Levels



Salavaggione et al., Pharmacogenet. Genomics 15:801-15, 2005

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Hypothesis

G460A (Ala154 Thr) and A719G (Tyr240Cys) might result in TPMT misfolding and aggregation

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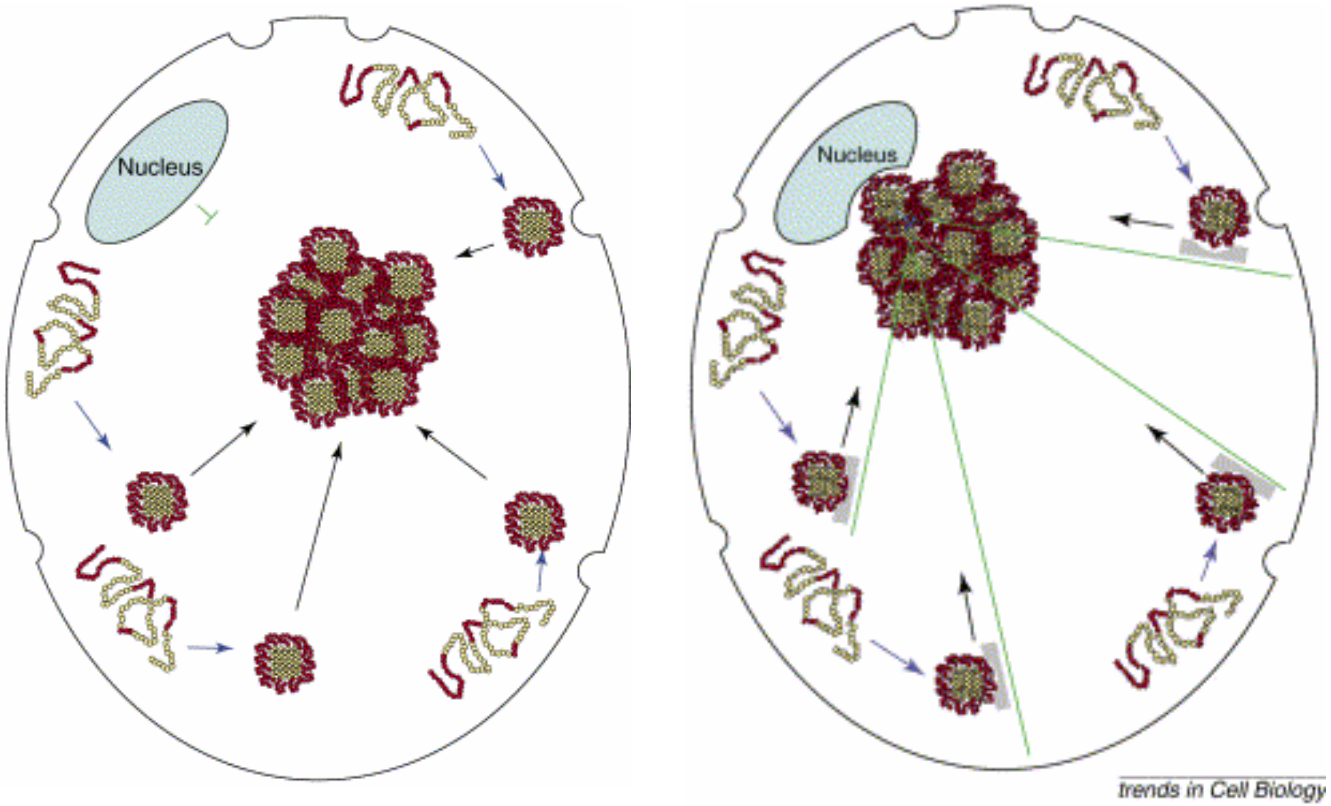
Aggresome Formation



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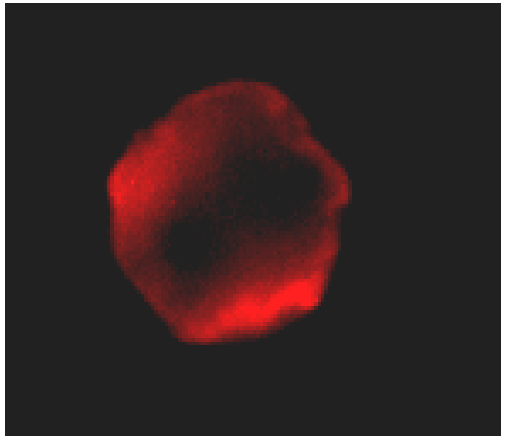
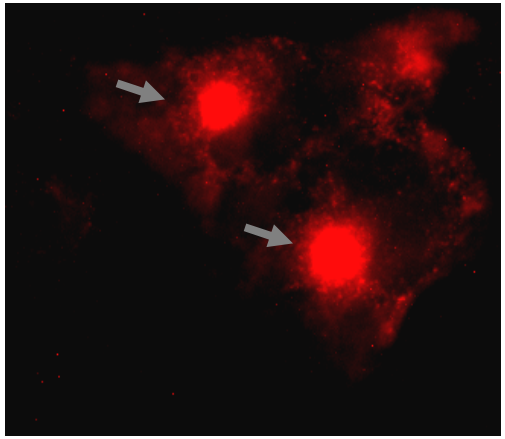
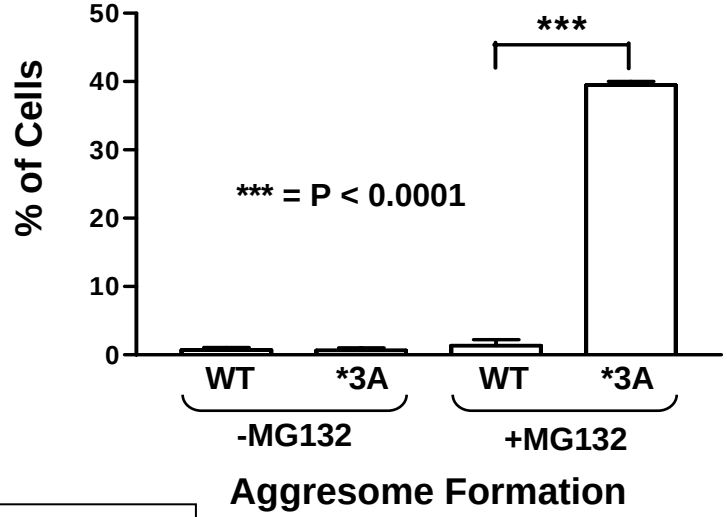
TPMT Aggresome Formation

WT ***3A**

TPMT
+MG132







Wang et al., PNAS 102:9394-99, 2005

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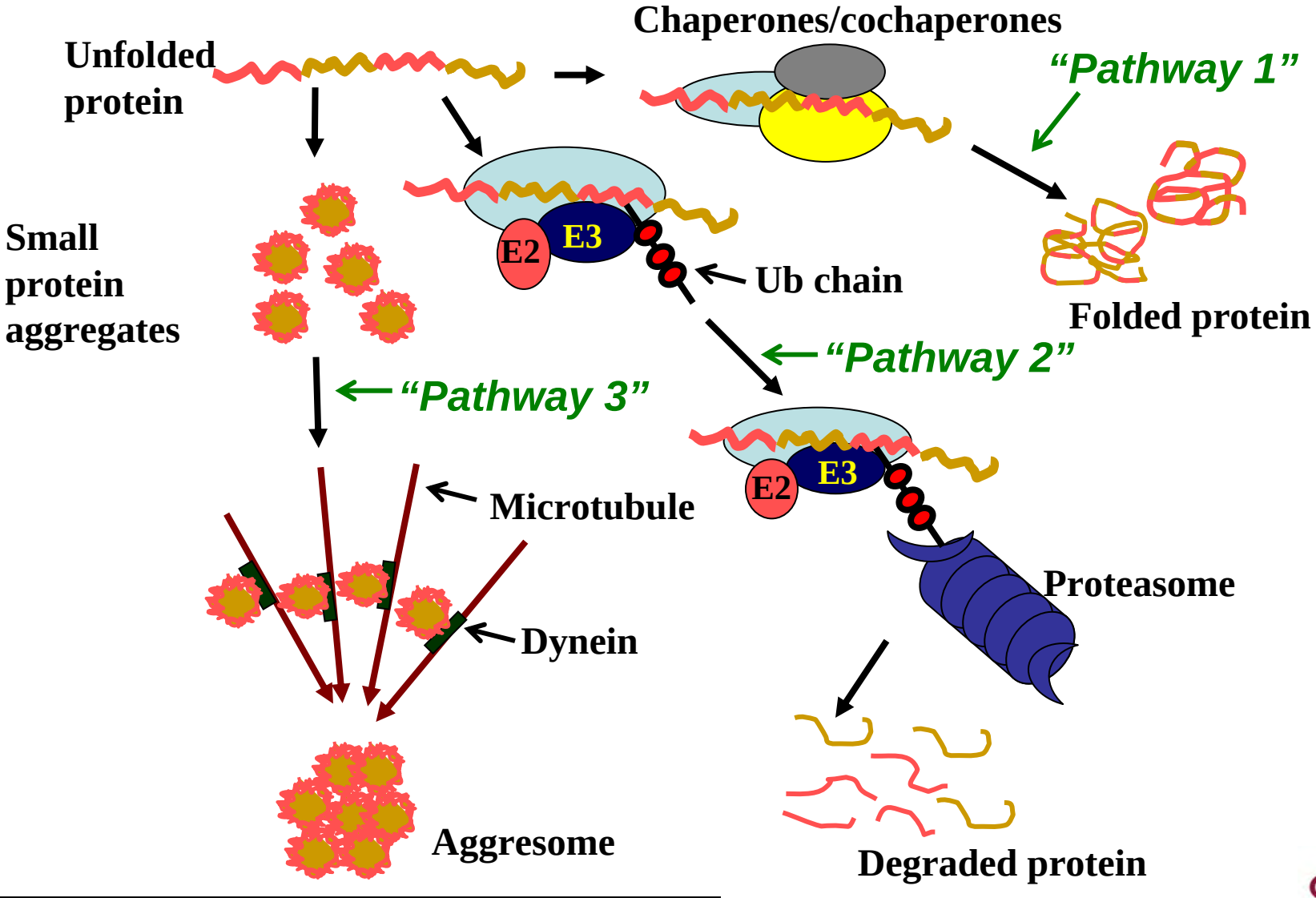
Protein Folding, Degradation and Aggregation



Wang and Weinshilboum, Oncogene 25:1629-38, 2006

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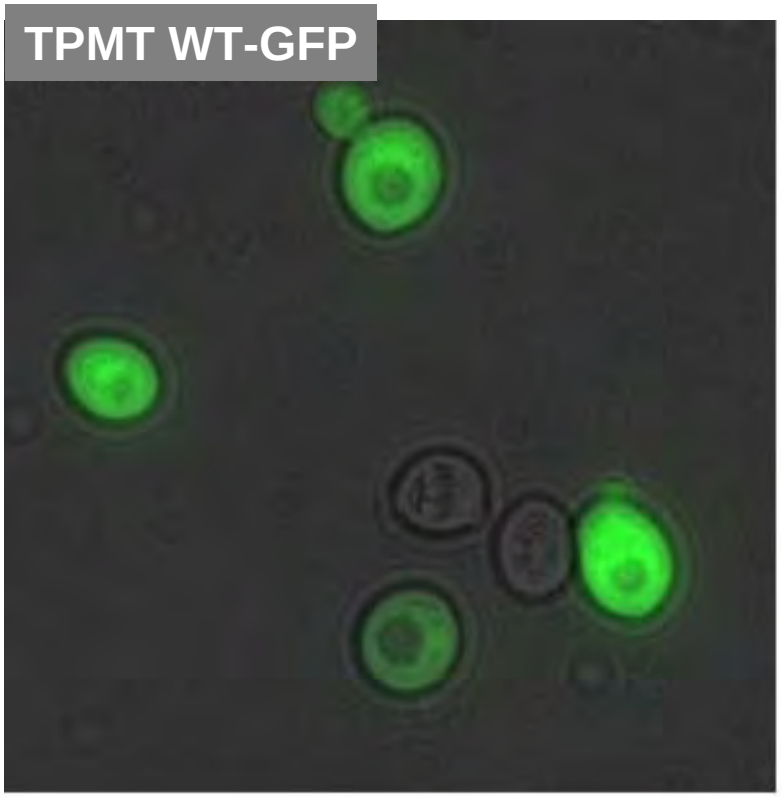
TPMT Allozymes in Yeast



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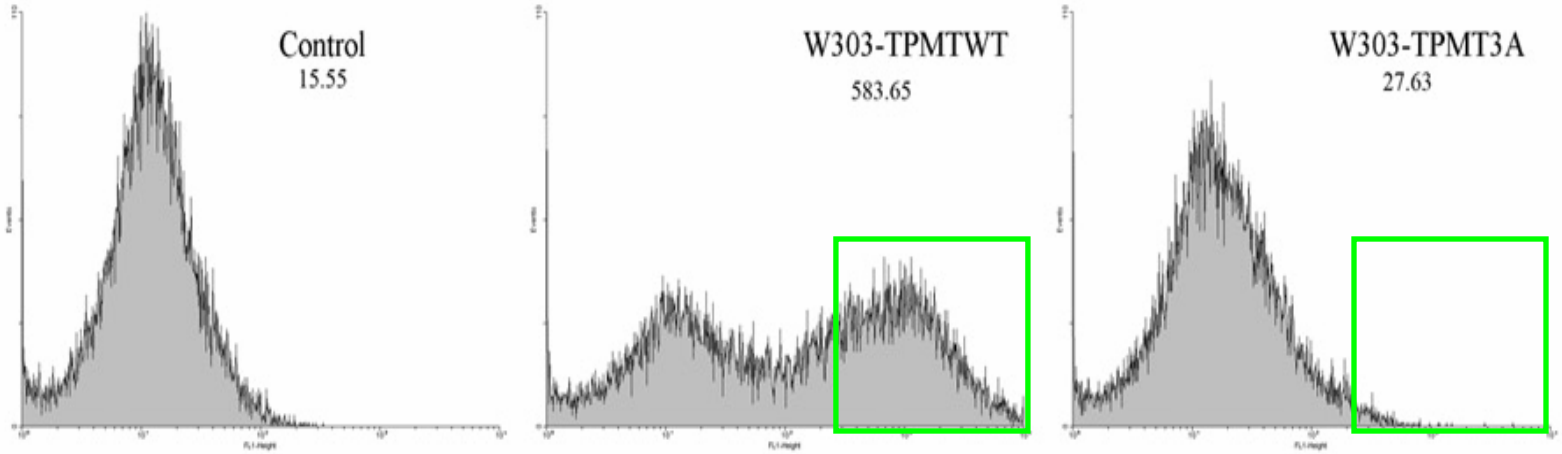
Yeast Flow Cytometry



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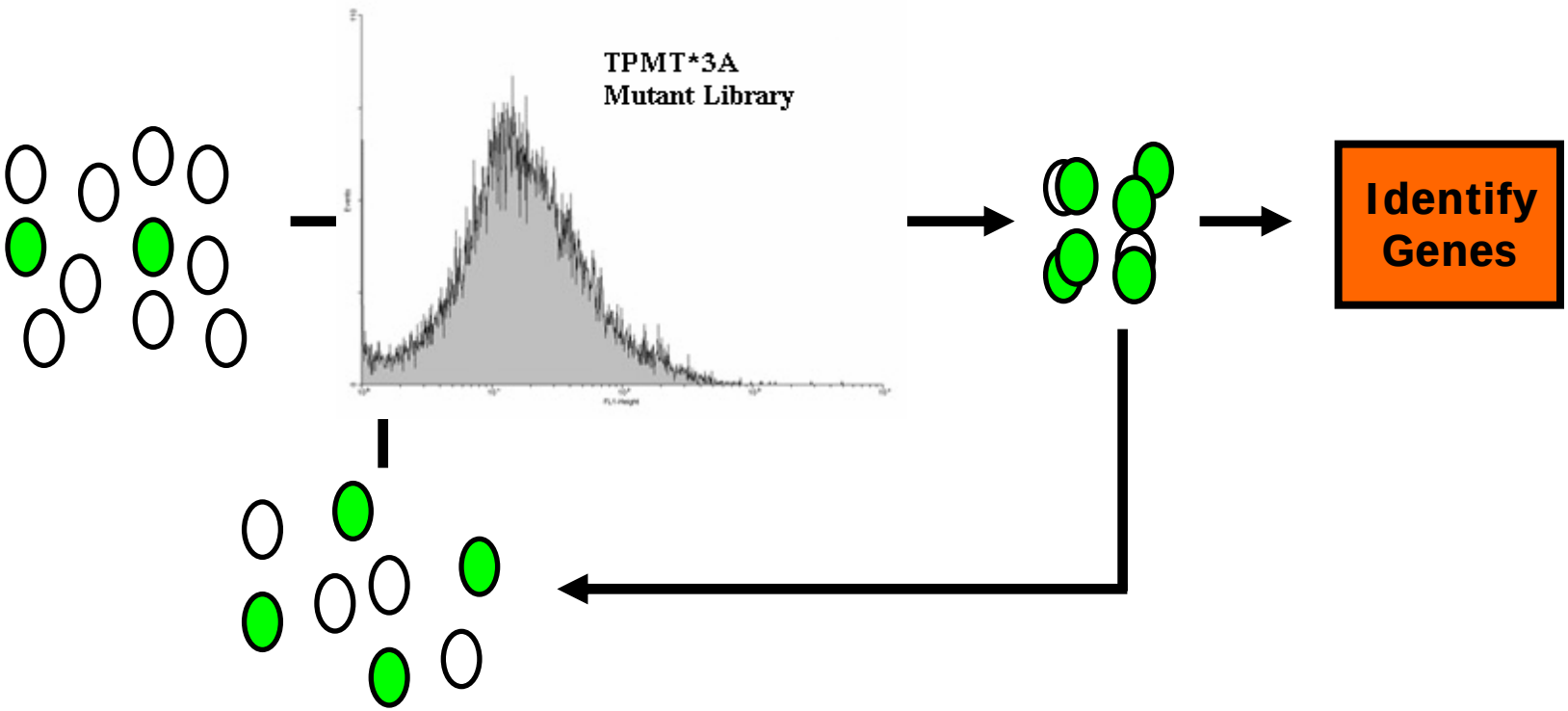
Yeast TPMT Cell Sorting



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Sorting Results

- Thirty-one genes identified
- Ubiquitin mediated degradation pathway (E2, E3, proteasome)
- Chaperones (Hsp70)
- Microtubules (tubulin, dynein regulation, spindle pole body)
- Vesicle processes (trafficking, autophagy)

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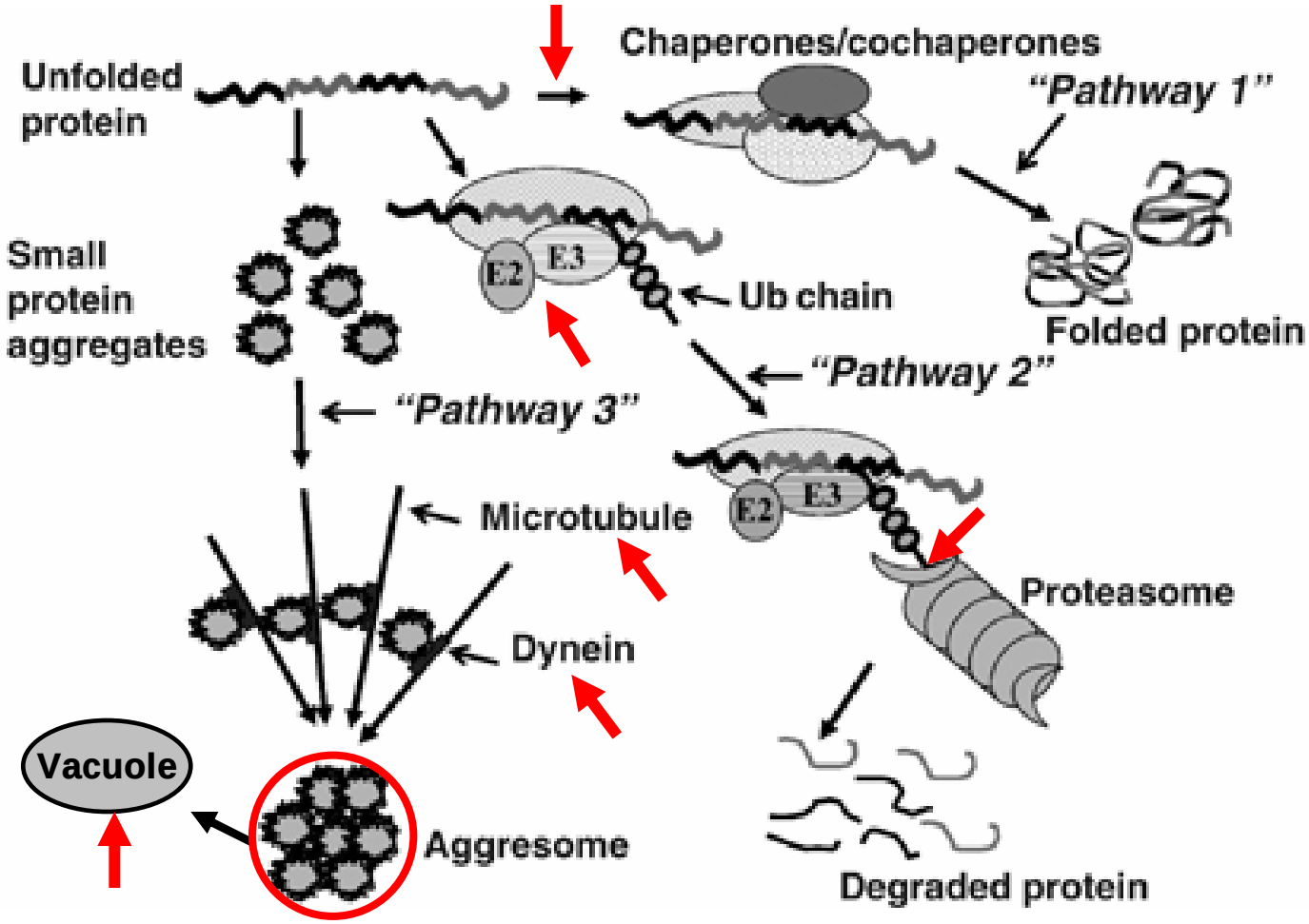
Protein Folding, Degradation and Aggregation



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Pharmacogenomics

Beyond Monogenic Pharmacogenomics

- Pathway-based
- Genome-wide association studies (GWA)
- Model systems – yeast, cell lines, etc.

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Pharmacogenomic Translational Studies

Evolution

- One gene, one or a few SNPs
- One gene, intragene haplotypes
- PK and PD pathways and haplotypes
- Genome-wide association studies

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- **Warfarin – *CYP2C9* and *VKORC1***
- **Tamoxifen – *CYP2D6***

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Tamoxifen Pharmacogenetics

Translational Pharmacogenomics

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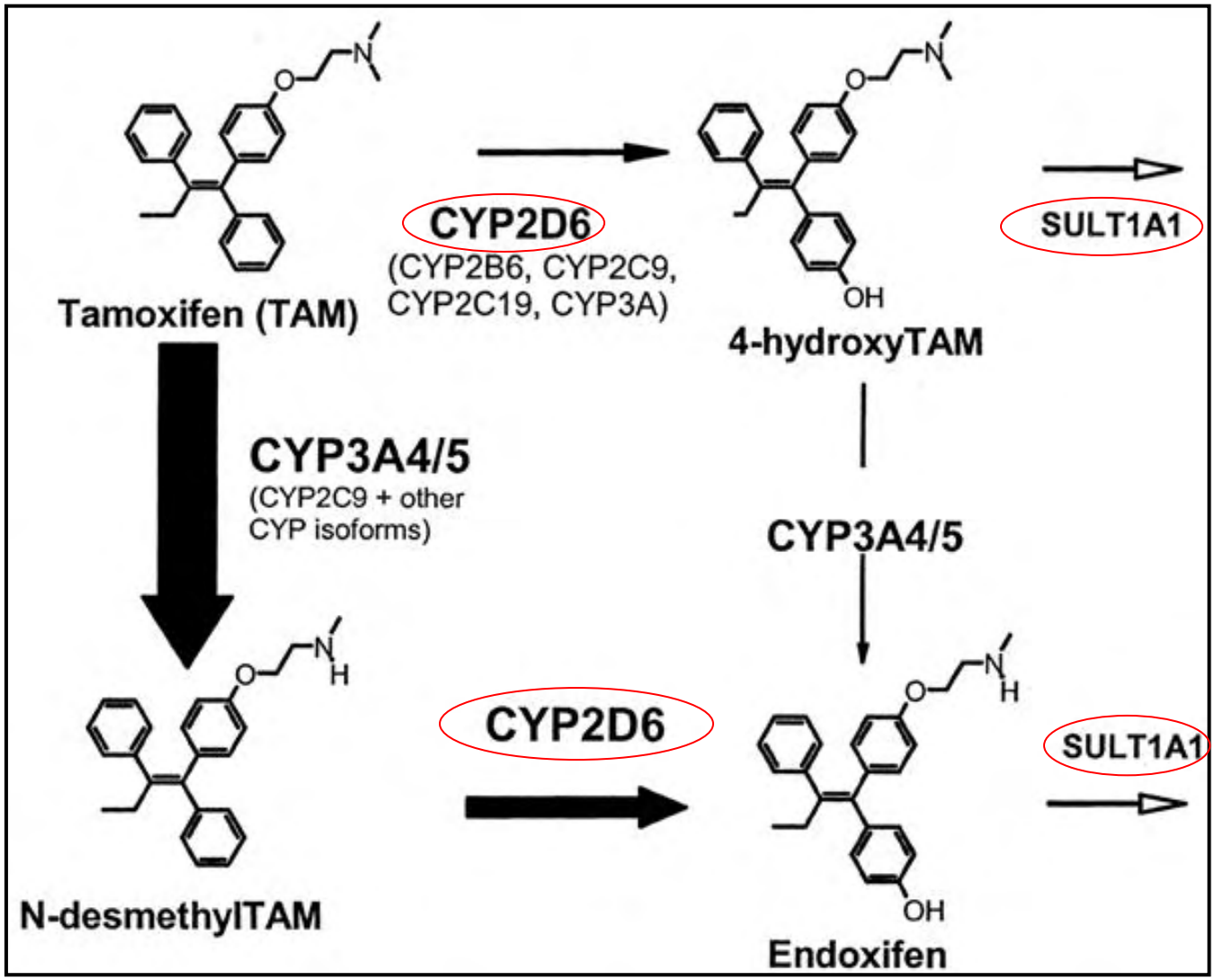
Tamoxifen Biotransformation



Jin et al., J. Natl. Cancer Inst. 97:20-39, 2005.

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Post-Menopausal Breast Cancer Prospective Tamoxifen Trial *CYP2D6* Genotype and Outcomes

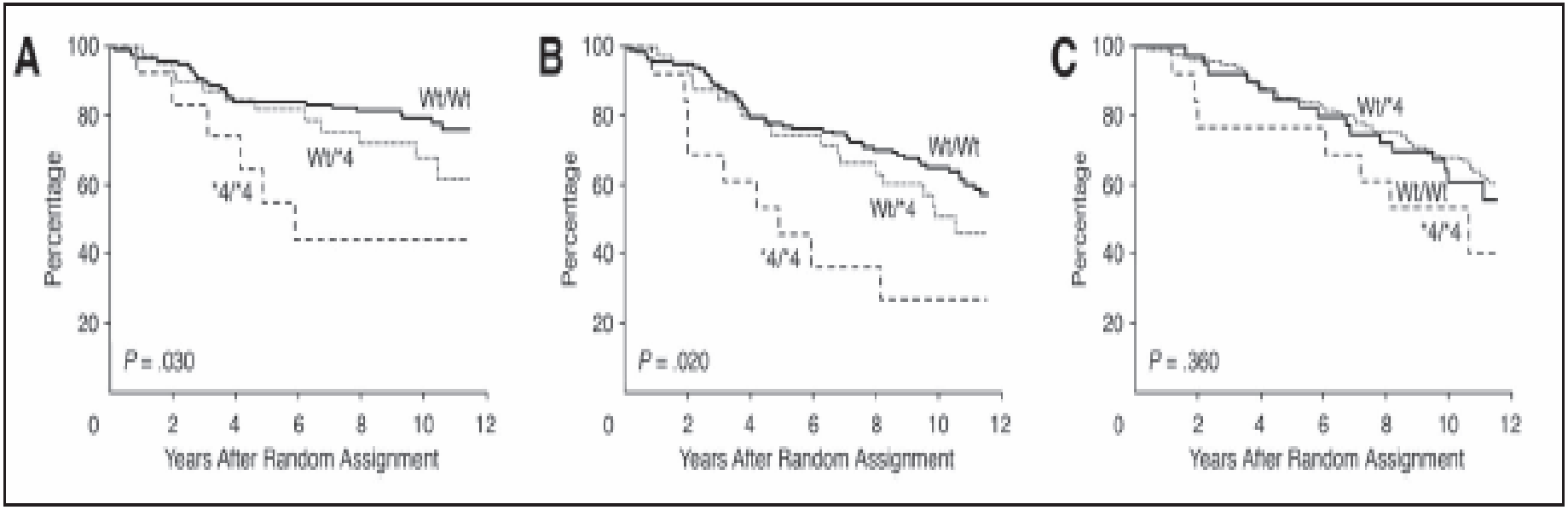

Fig 2. Kaplan-Meier estimates of (A) relapse-free time, (B) disease-free survival, and (C) overall survival for patients with the CYP2D6*4 genotype.

From Goetz M, Rae JM et al: *J Clin Oncol 23:9312-9318, 2005.*

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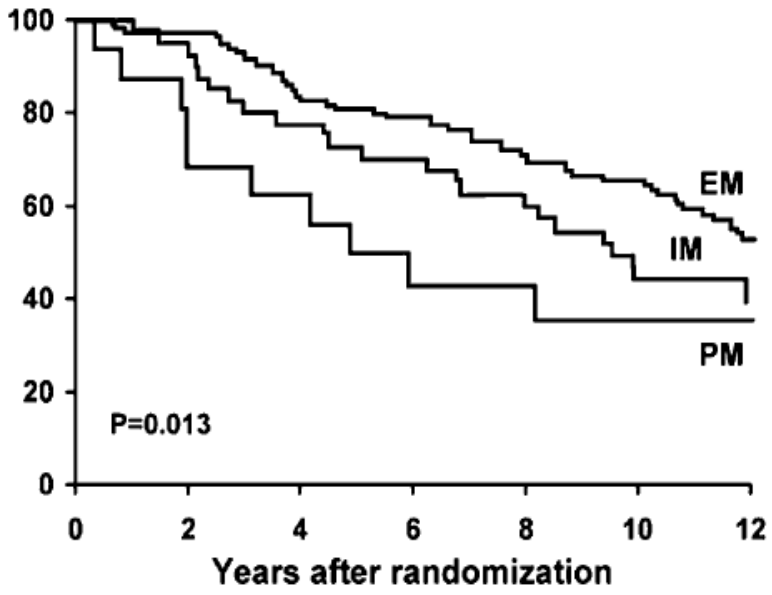
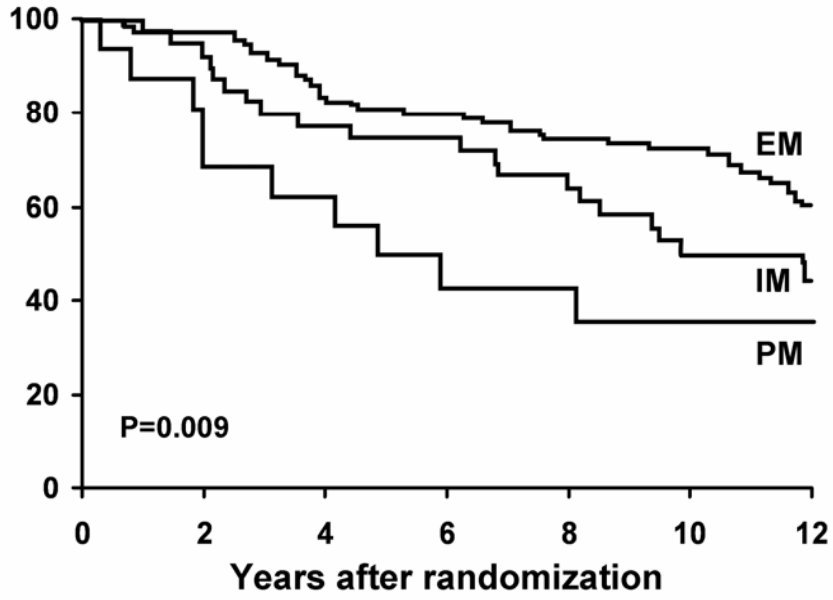
Tamoxifen Pharmacogenomics

Breast Cancer (190 Patients)

Relapse – Free Survival, %

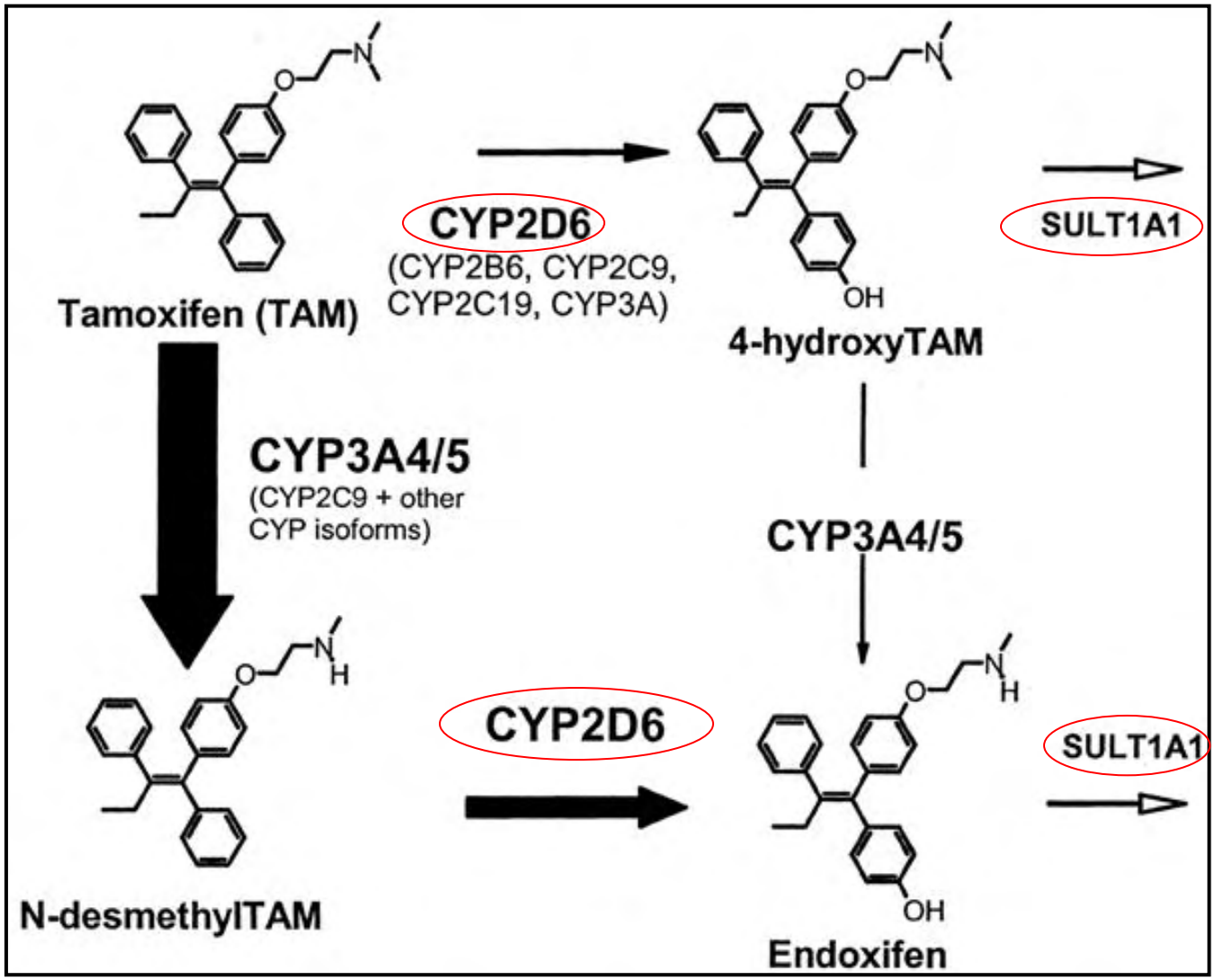


Disease – Free Survival



Goetz et al., Breast Cancer Res. Treat. 101:113-121, 2007.

Tamoxifen Biotransformation



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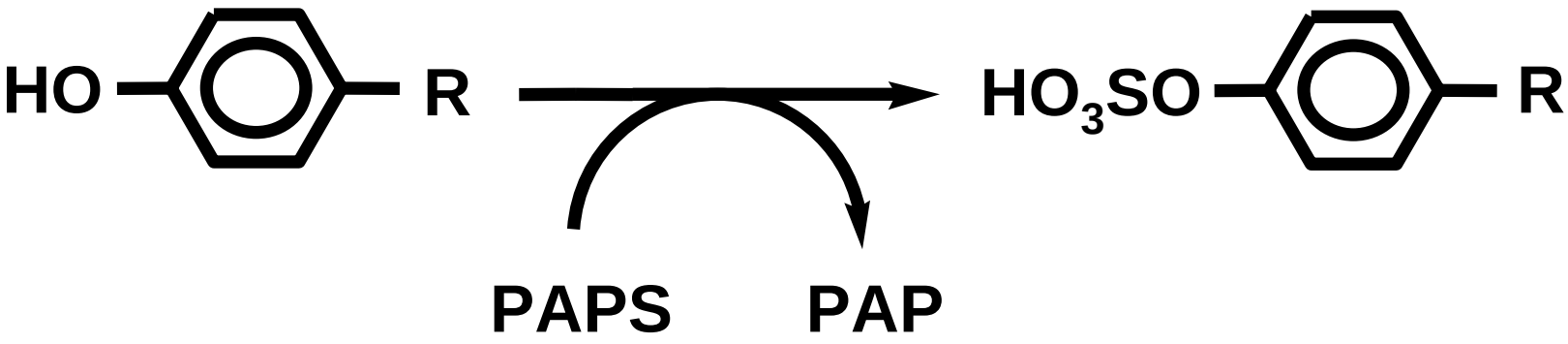
SULT Pharmacogenomics

Phenol Sulfation



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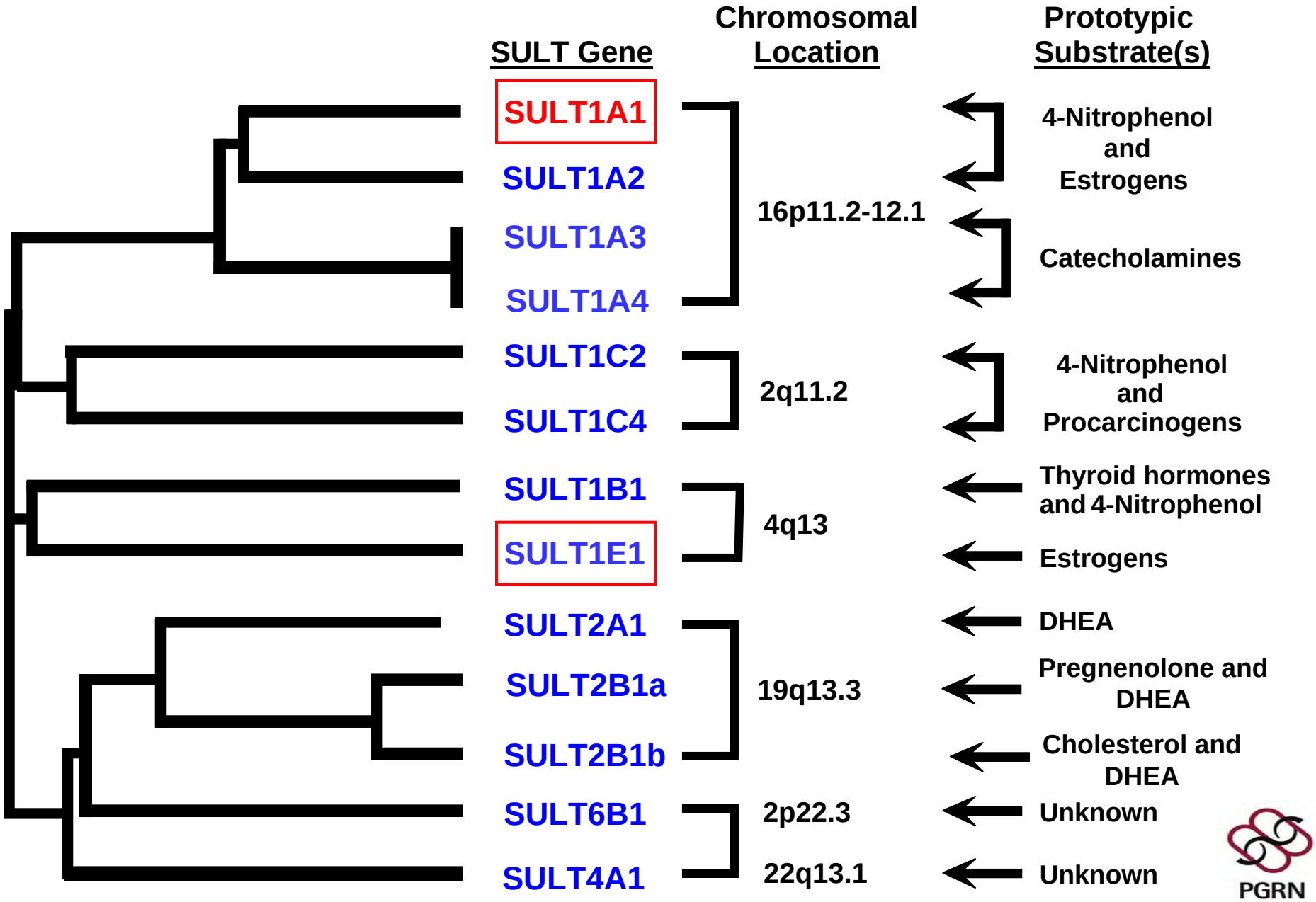
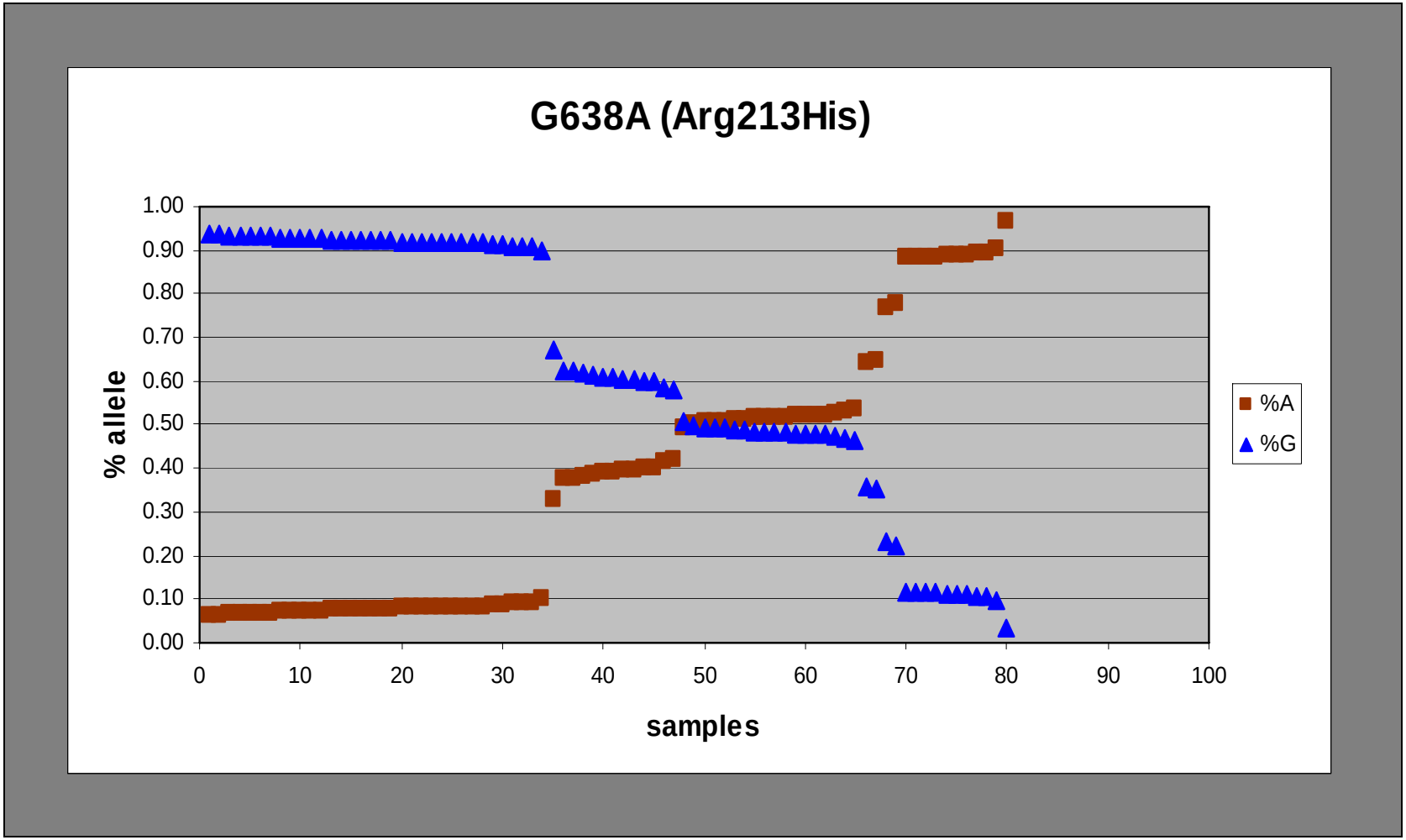
Human SULT Isoforms



SULT1A1 Pyrosequencing Results



Hebbring et al., Human Mol. Genet. 16:463-470, 2006.

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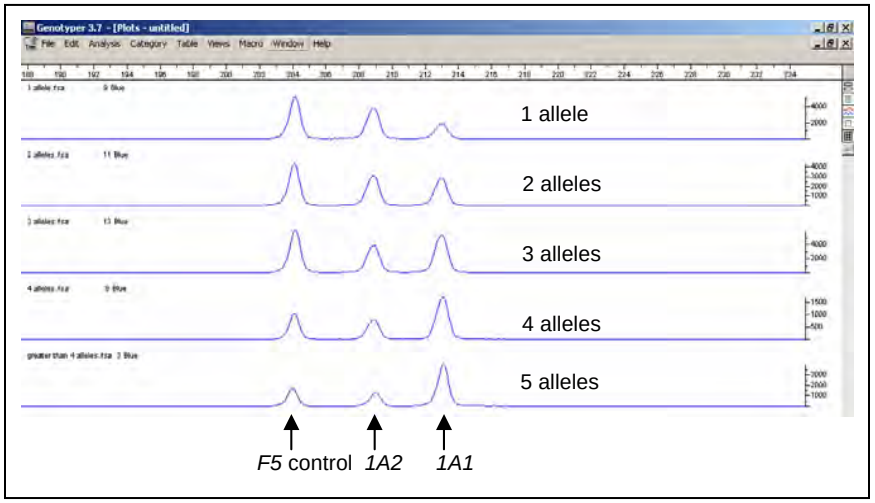
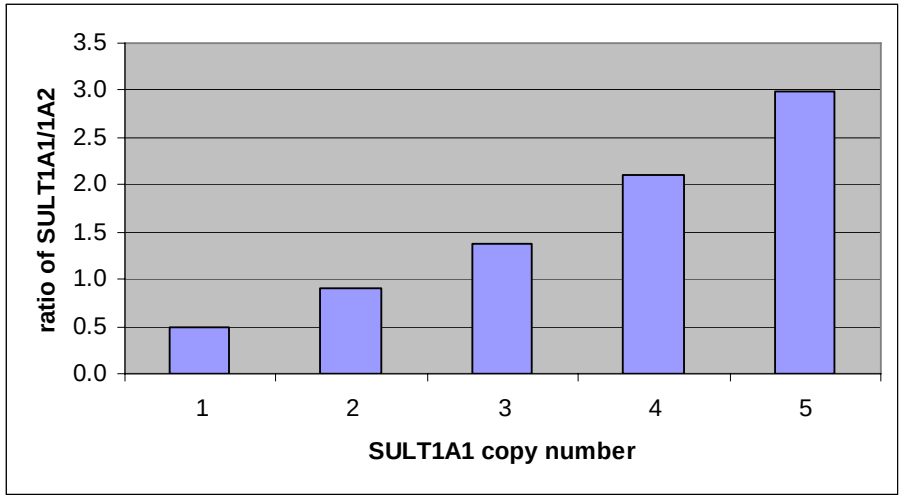
SULT1A1 Copy Number Assay





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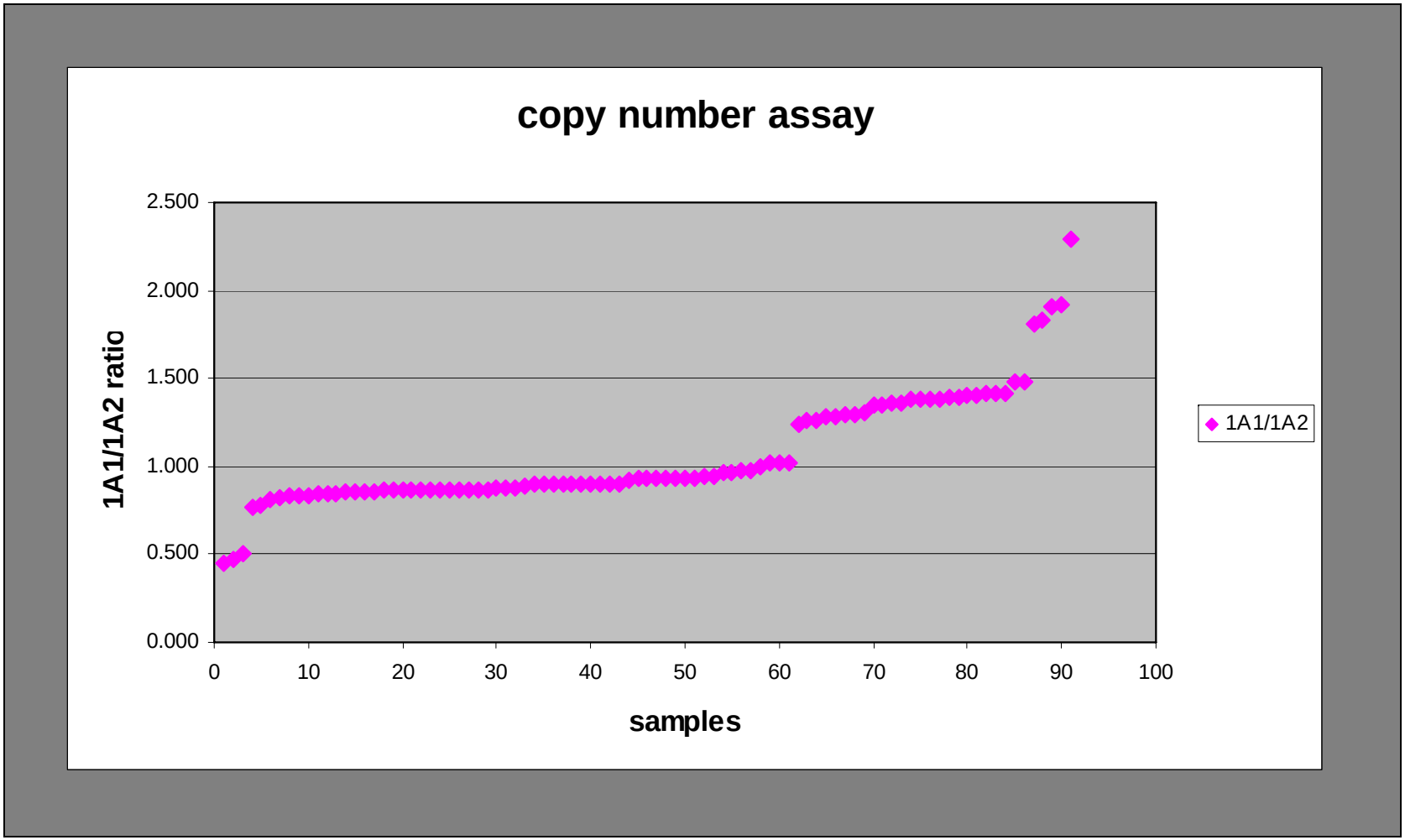

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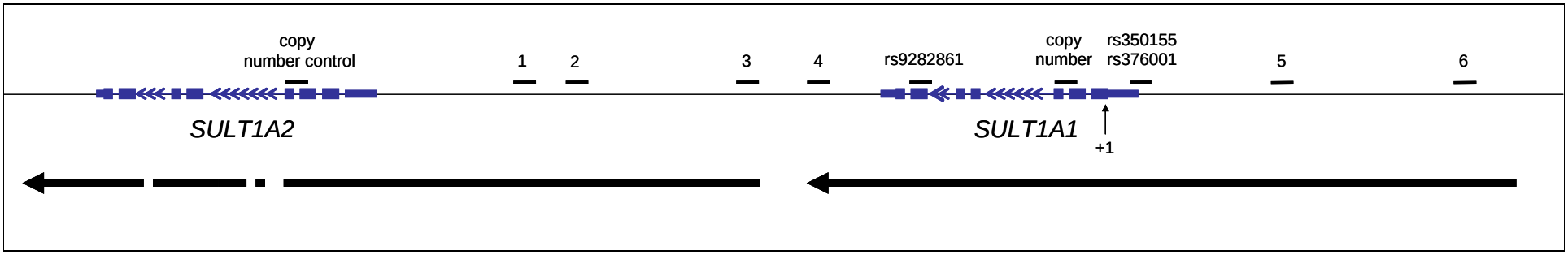
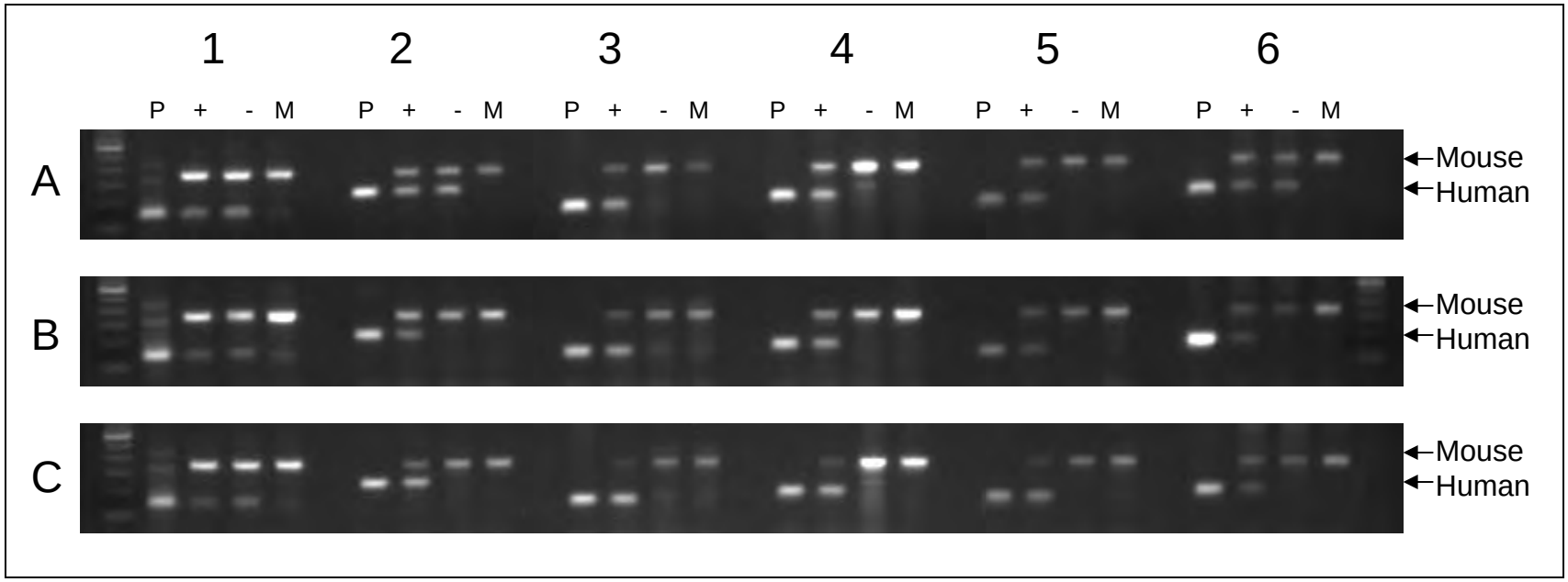
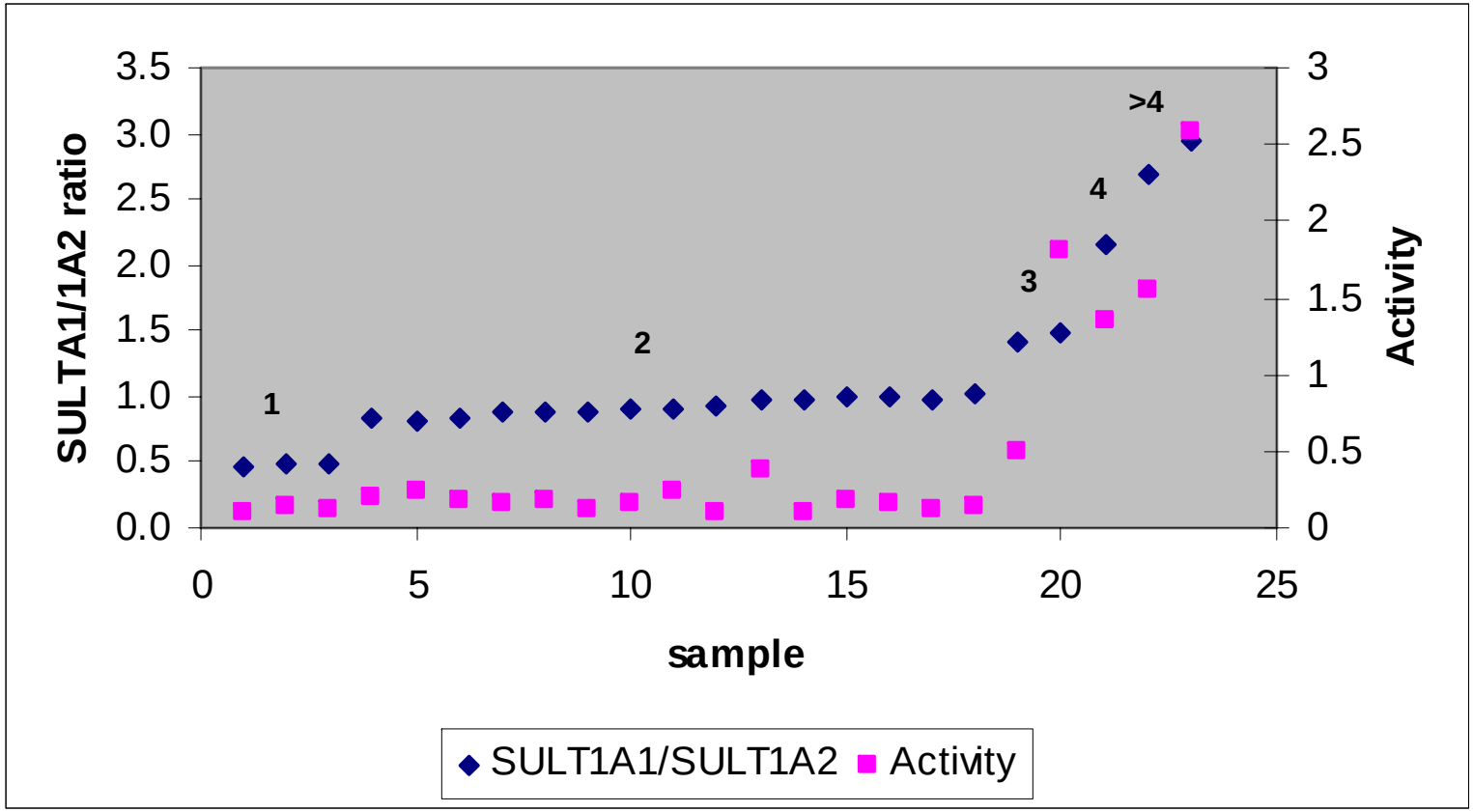
SULT1A1 Deletion Mapping





Hebbring et al., Human Mol. Genet. 16:463-470, 2006.

SULT1A1 Activity vs Copy Number Platelet Samples n=23



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Hebbring et al., Human Mol. Genet. 16:463-470, 2006.

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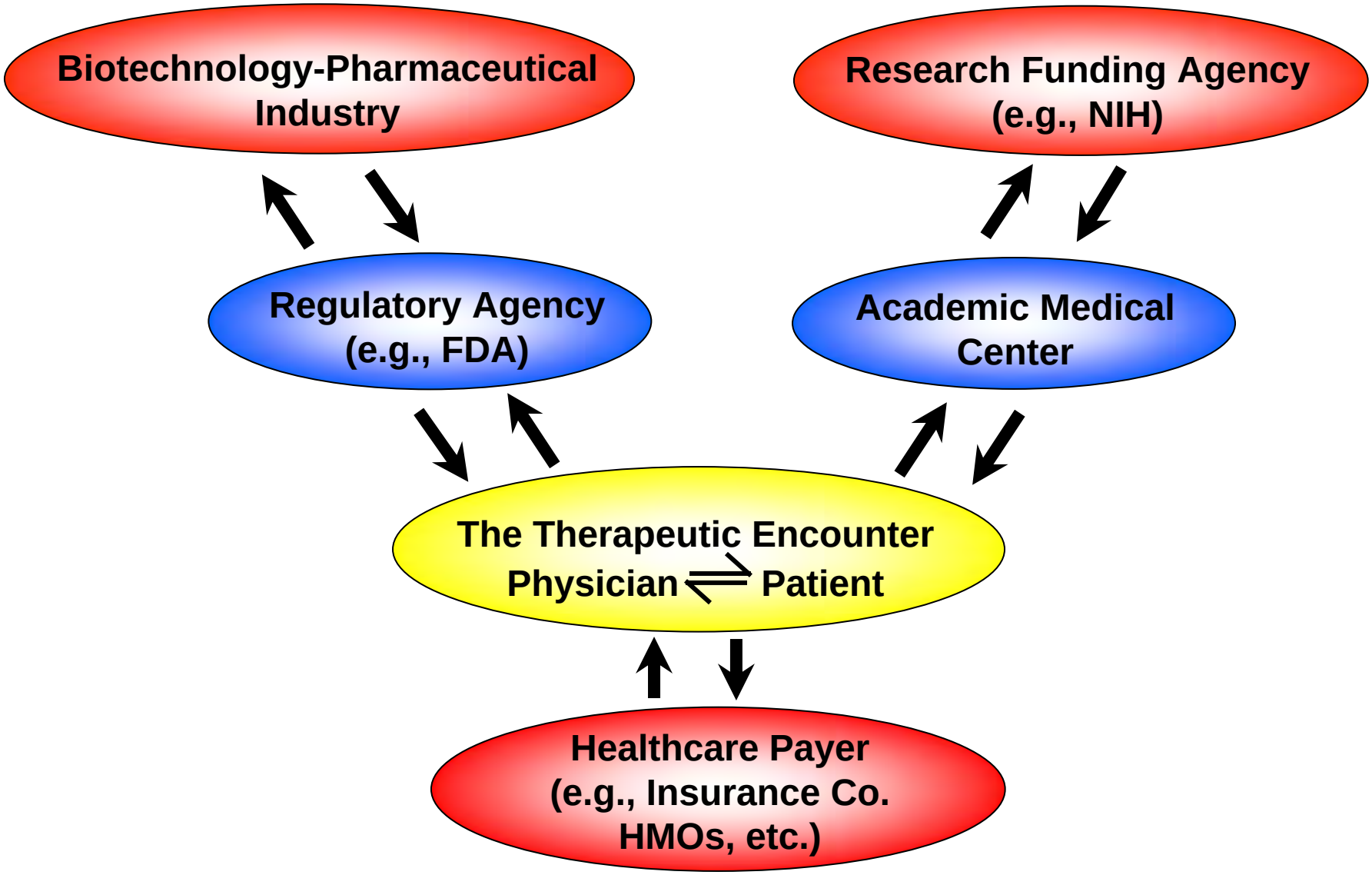
Pharmacogenomic Clinical Translation



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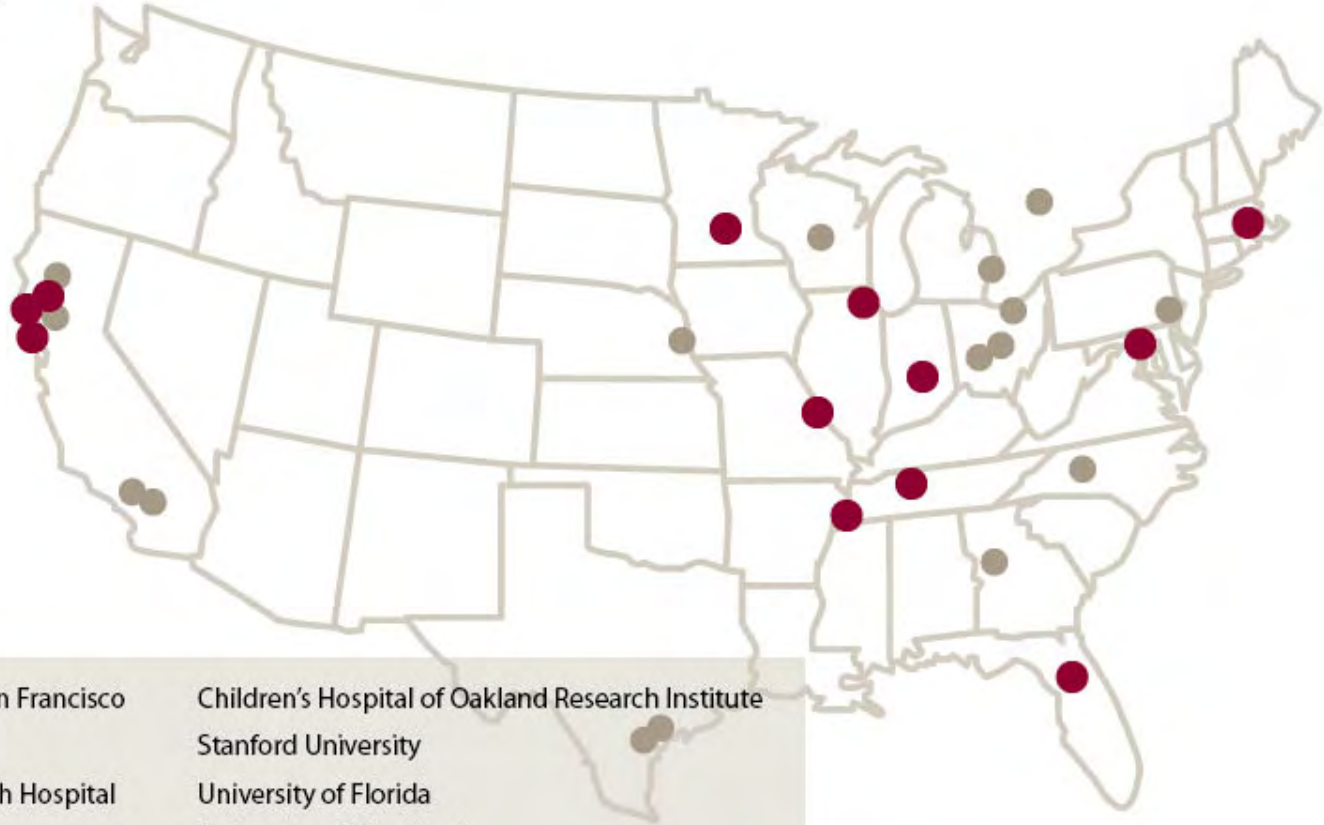

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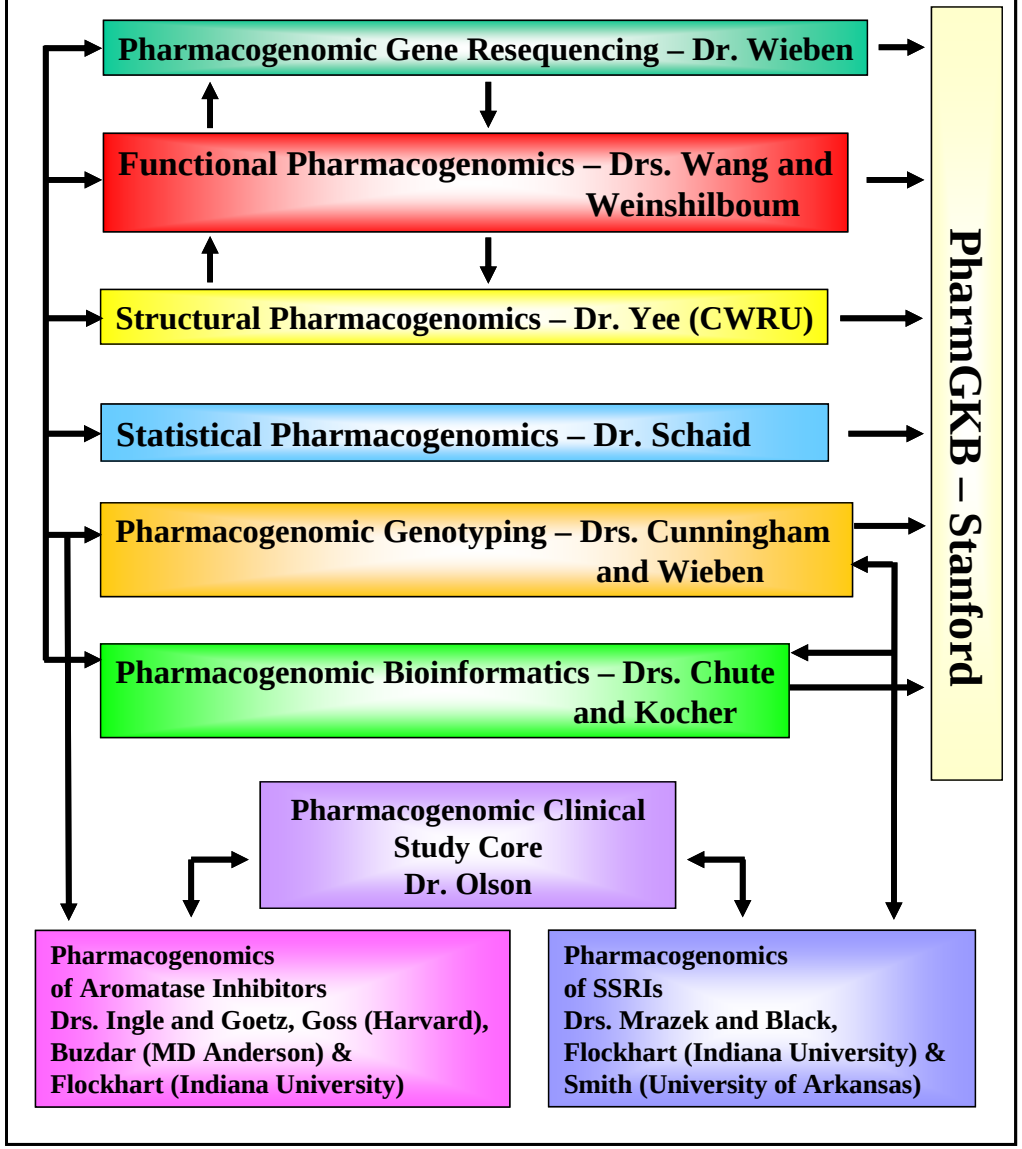
Washington University	Brigham and Women's Hospital

● Primary Investigator Site
● Co-Investigator Site

Mayo PGRN



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Pharmacogenetics-Pharmacogenomics

Discovery Science

and

Hypothesis-Based Science

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Pharmacogenetics Coworkers

Araba Adjei
Ibrahim Aksoy
Pinar Aksoy
Saime Aksoy
Robert J. Anderson
Janel Baer
Blanka Boudikova-Girard
Norman Campbell
Edward Carlini
Monika Deininger
Joel Dunnette
Qiping Feng
Robert Freimuth
Todd Glauser
Chengtao Her
Sergio Hernandez
Michelle Hildebrandt
Ronald Honchel
Geoffrey Johnson
Julie Johnson
Yuan Ji
Krishna Kalari
Richard Keith
Mani Keshtgarpour
Adrian Kerremans
Annette Klumpp
Daniel Lee
Fang Li
Liang Li
Bonnie Maidak
Yvette Martin
Timothy Maus
Irene Moon
Ann Moyer
Gabriel Mwaluko
Diane Otterness
Patricio Pazmino
Randall Pearson
Linda Pelleymounter
Charles Preuss
Rebecca Raftogianis Blanchard
Frederick Raymond
Christoph Reiter
Josephine Rini
Ezequiel Salavaggione
Alison Shield
Mary Scott
Susan Sladek
Rajah Sundarm
Carol Szumlanski
Bianca Thomae
Michael Thompson
Daniel Toft
Jon Van Loon
Randall Walker
Liewei Wang
Bill Watson
Thomas Wood
Lee Woodson
Luanne Wussow
Michael Xu
Lan Yan
Chen Yang
William Young Jr.
Jessica Zhang
Scott Hebbring

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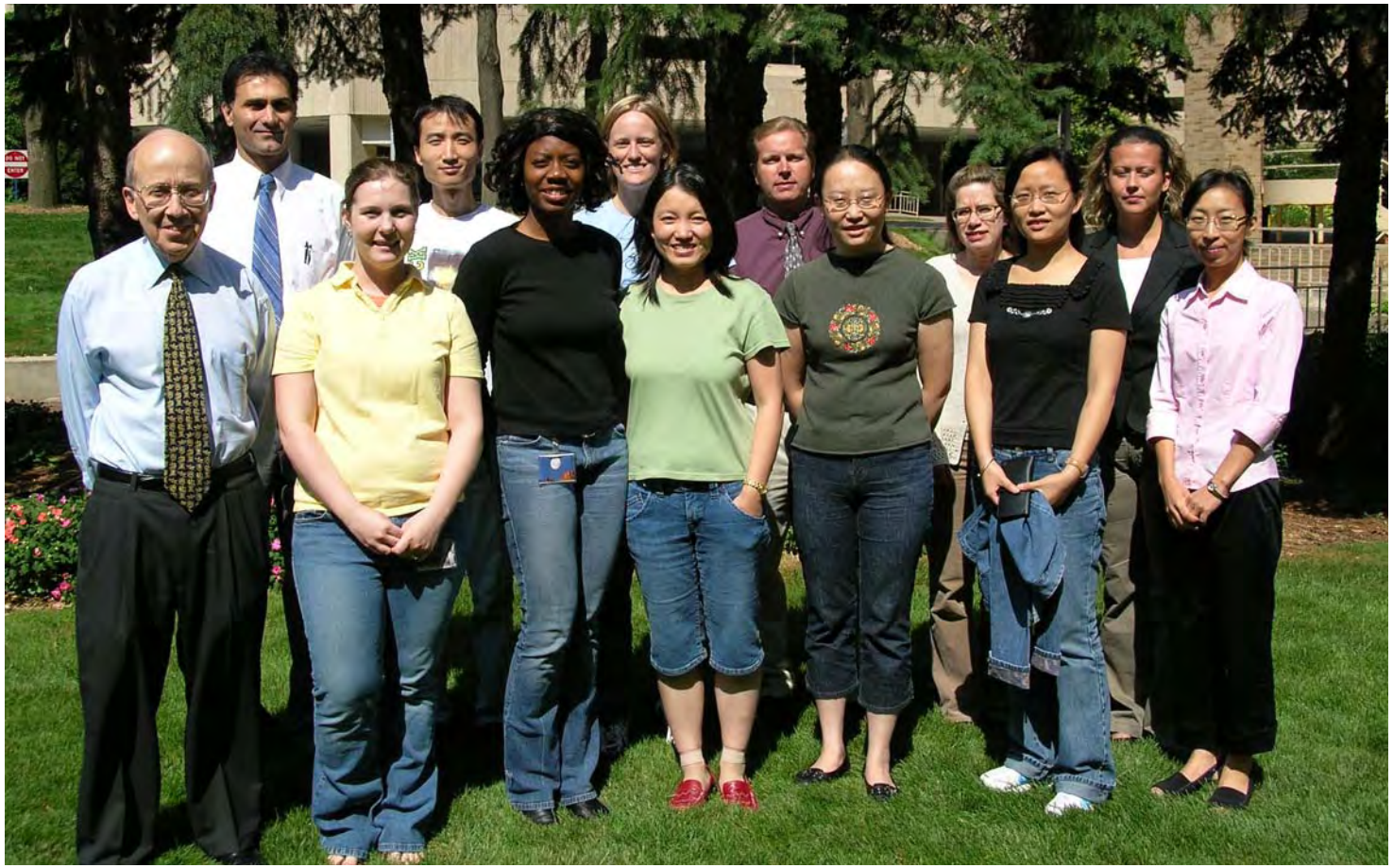
Mayo Pharmacogenomics Laboratory -- 2006



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