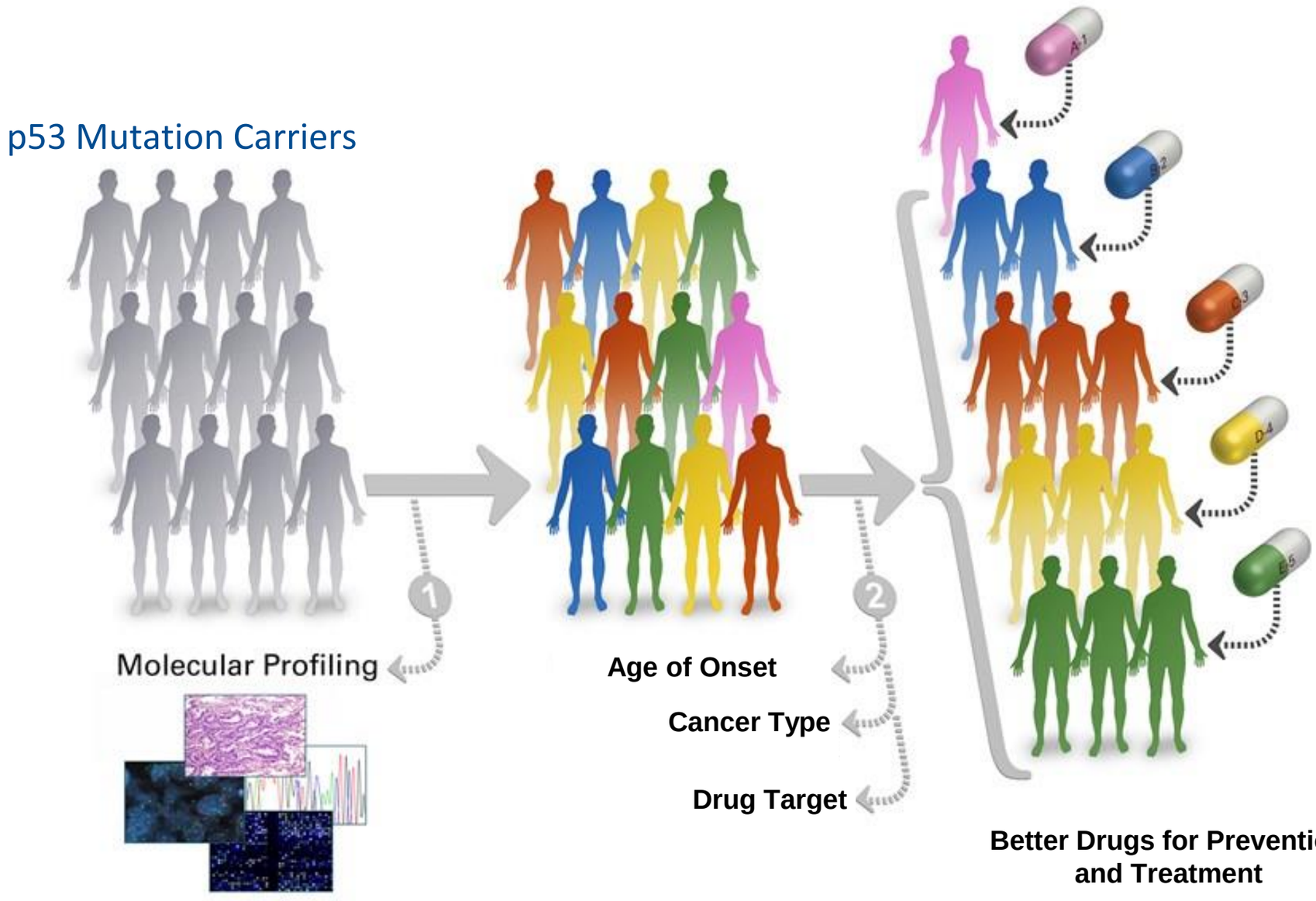
# Human Cancer Genetics Laboratory

est. February 2008

LUDWIG CANCER RESEARCH

# The Ambition



# SNPs

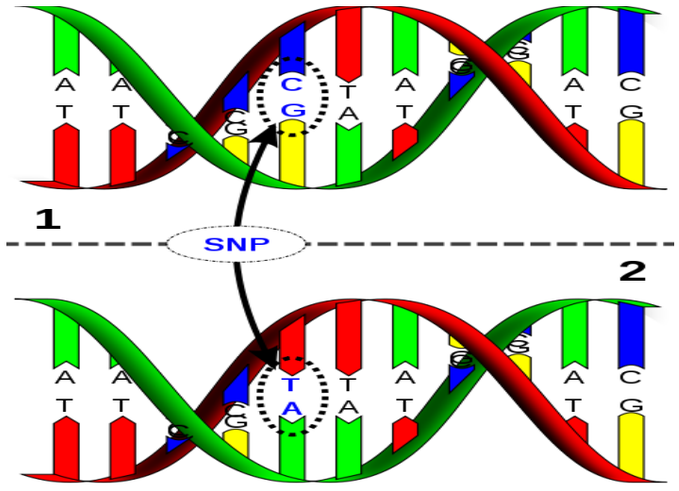
## Single Nucleotide Polymorphisms

Background

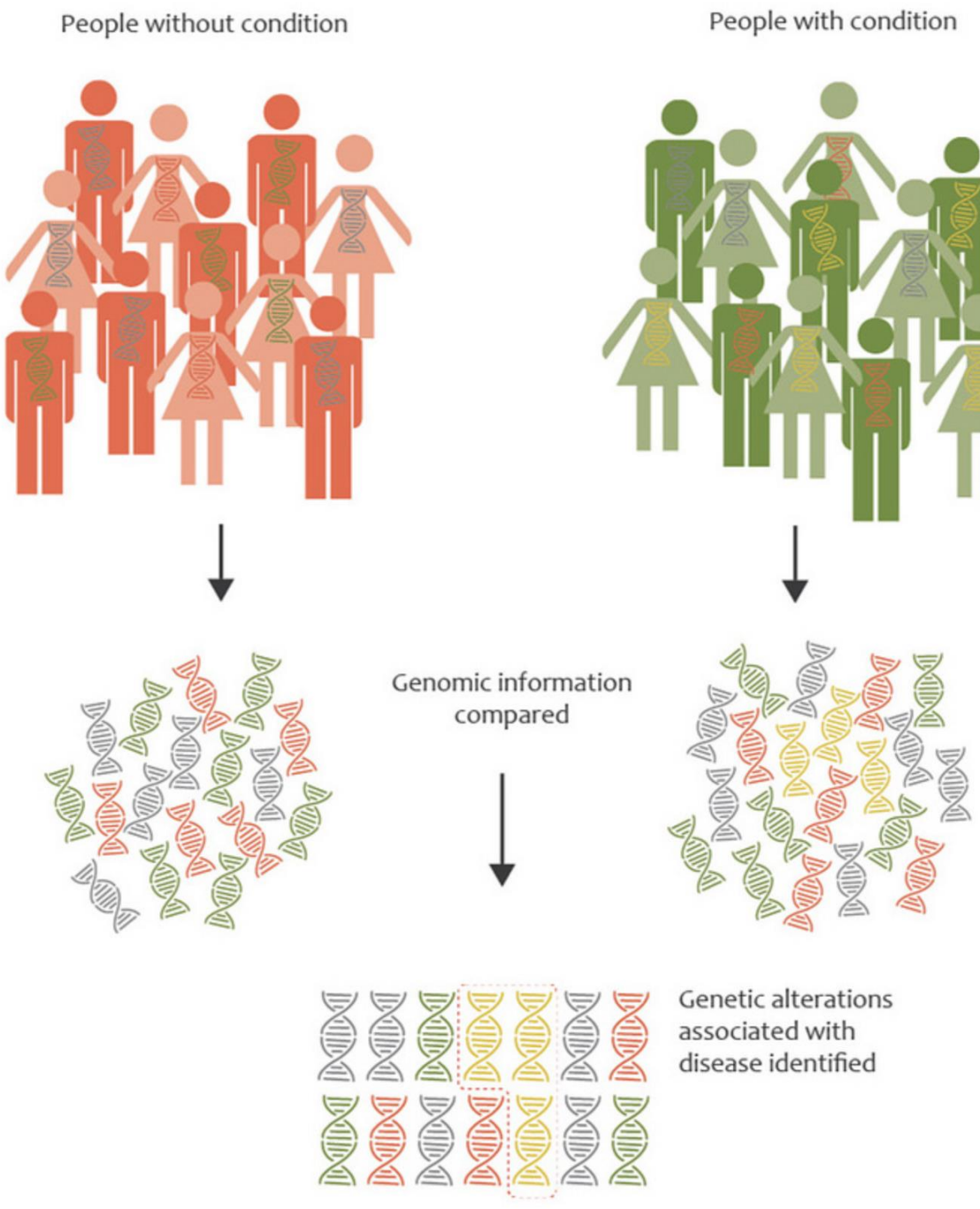
### Understanding genetic variation could be a key for Personalized Medicine

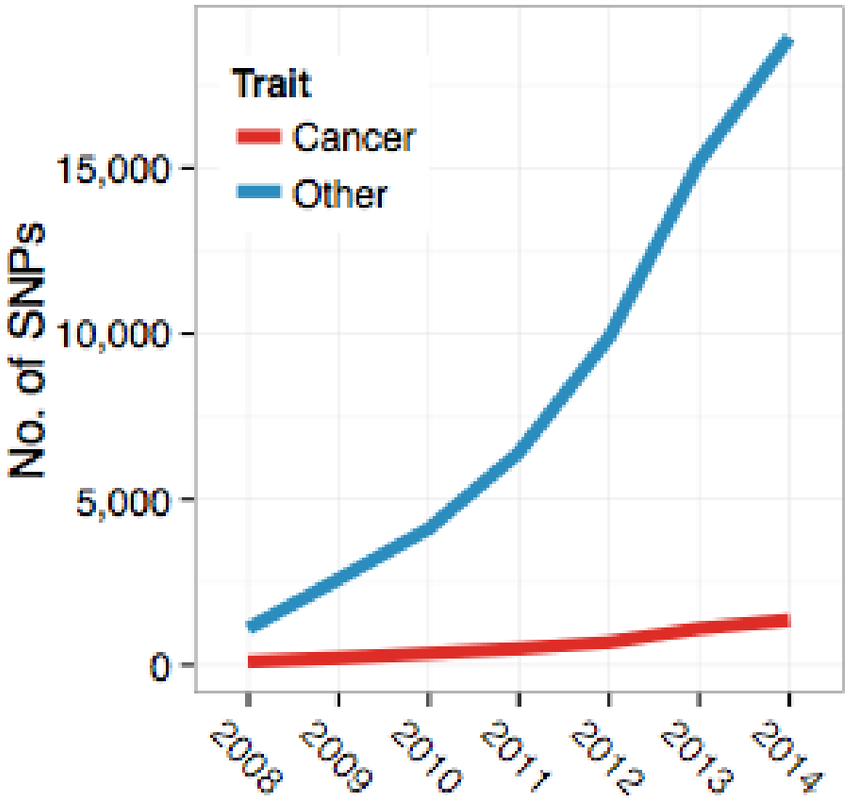
- Single Nucleotide Polymorphisms (SNPs) are one of the most common form of genetic variation (>13 M in dbSNP & 6.9 M validated by multiple investigators)

- SNPs occur when a single nucleotide (A, T, C or G) is replaced with another MAF >1%



# Genome Wide Association Studies (GWAS)



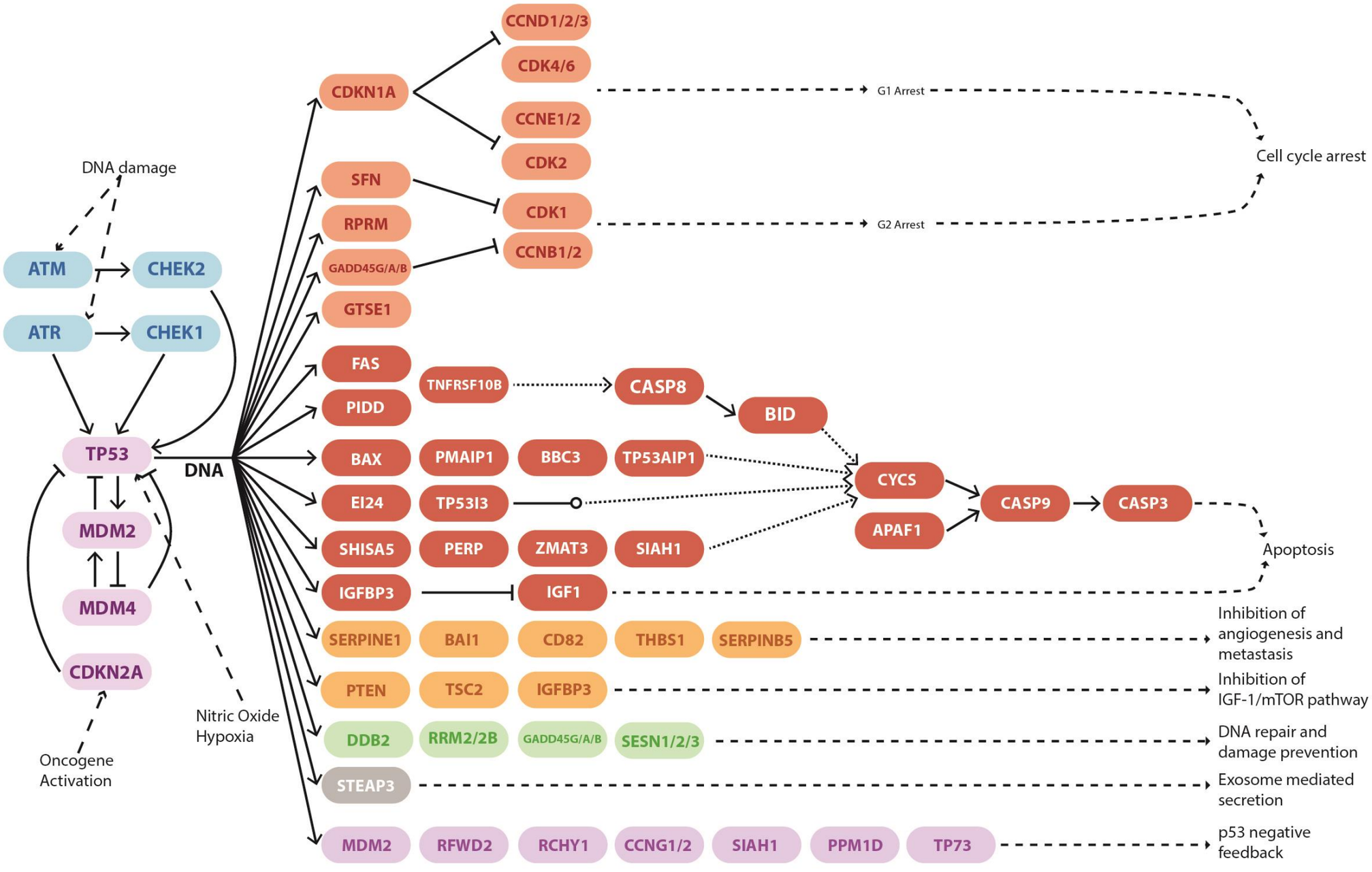




1,161 SNPs associated with app. 68 different cancers/cancer subtypes in 228 GWASs

- *median 1.2 OR*

# The p53 Network

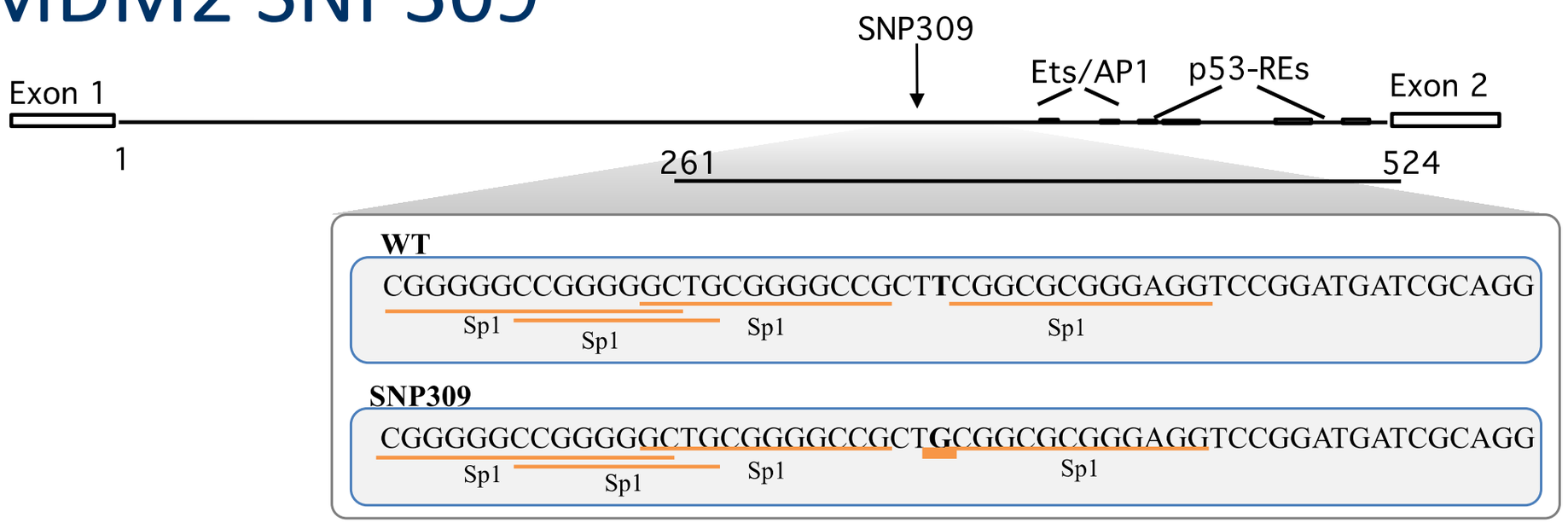
## p53 does not work in isolation

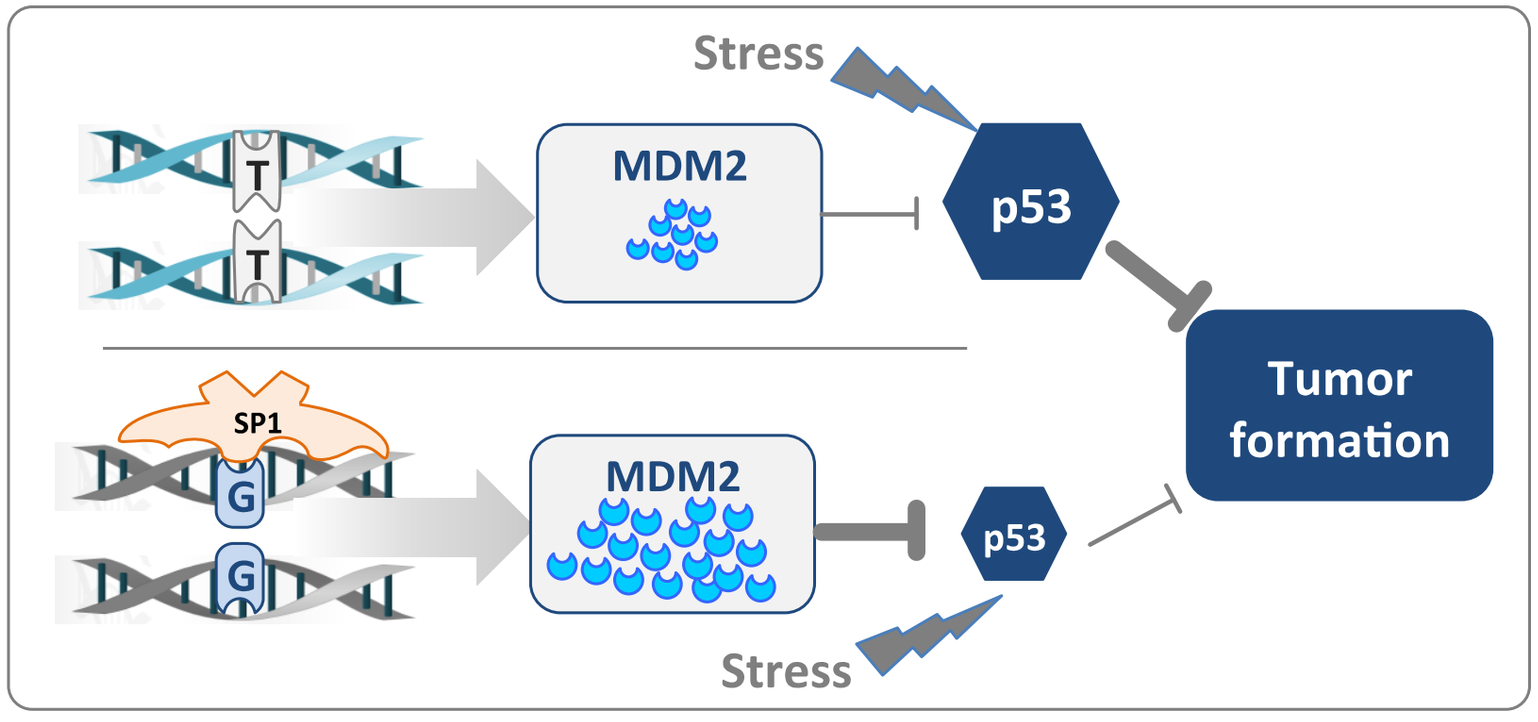


# A SNP in the p53 Network

## LFS

## MDM2 SNP309

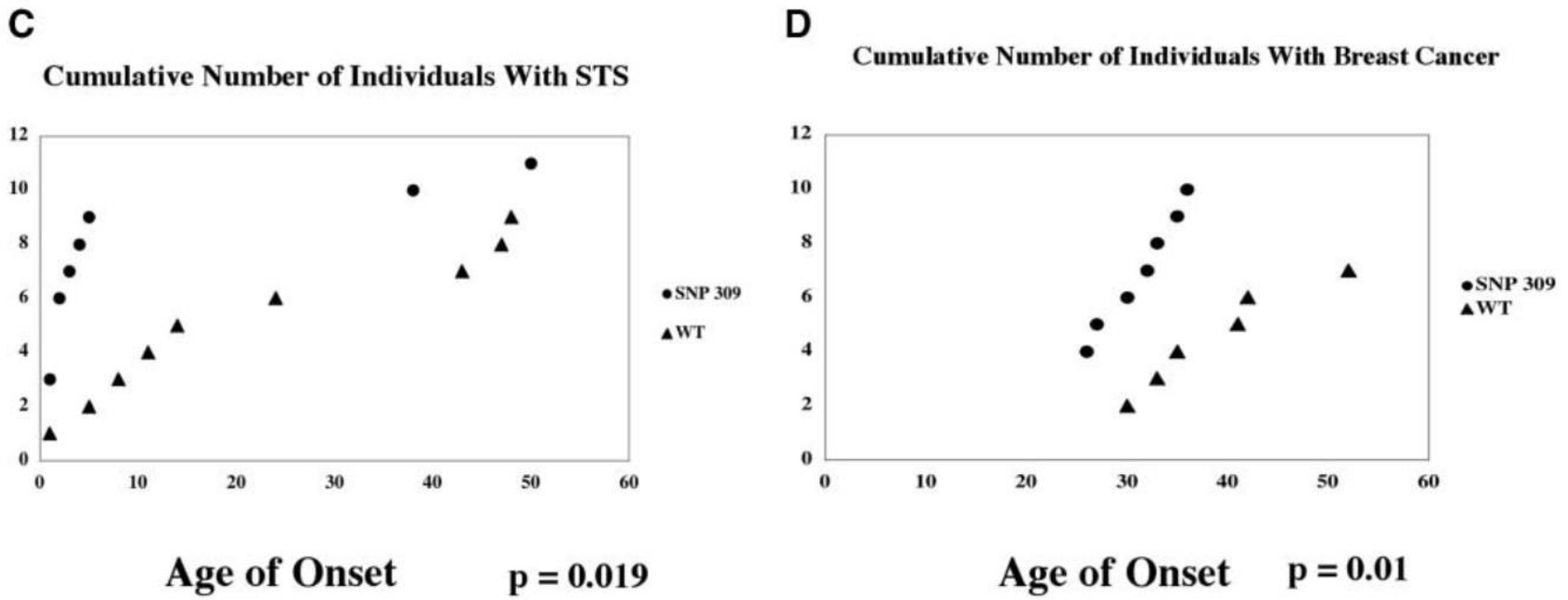



Bond, Wu *et al*., Cell, 2004

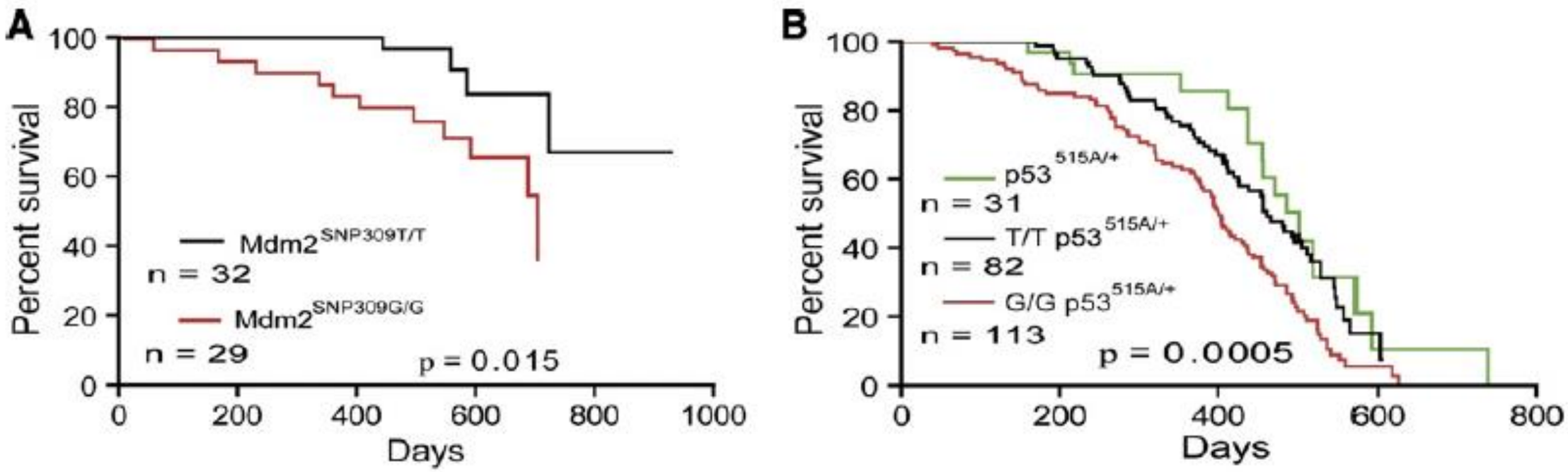
# MDM2 SNP309 in the p53 Network

LFS



# MDM2 SNP309 Survival

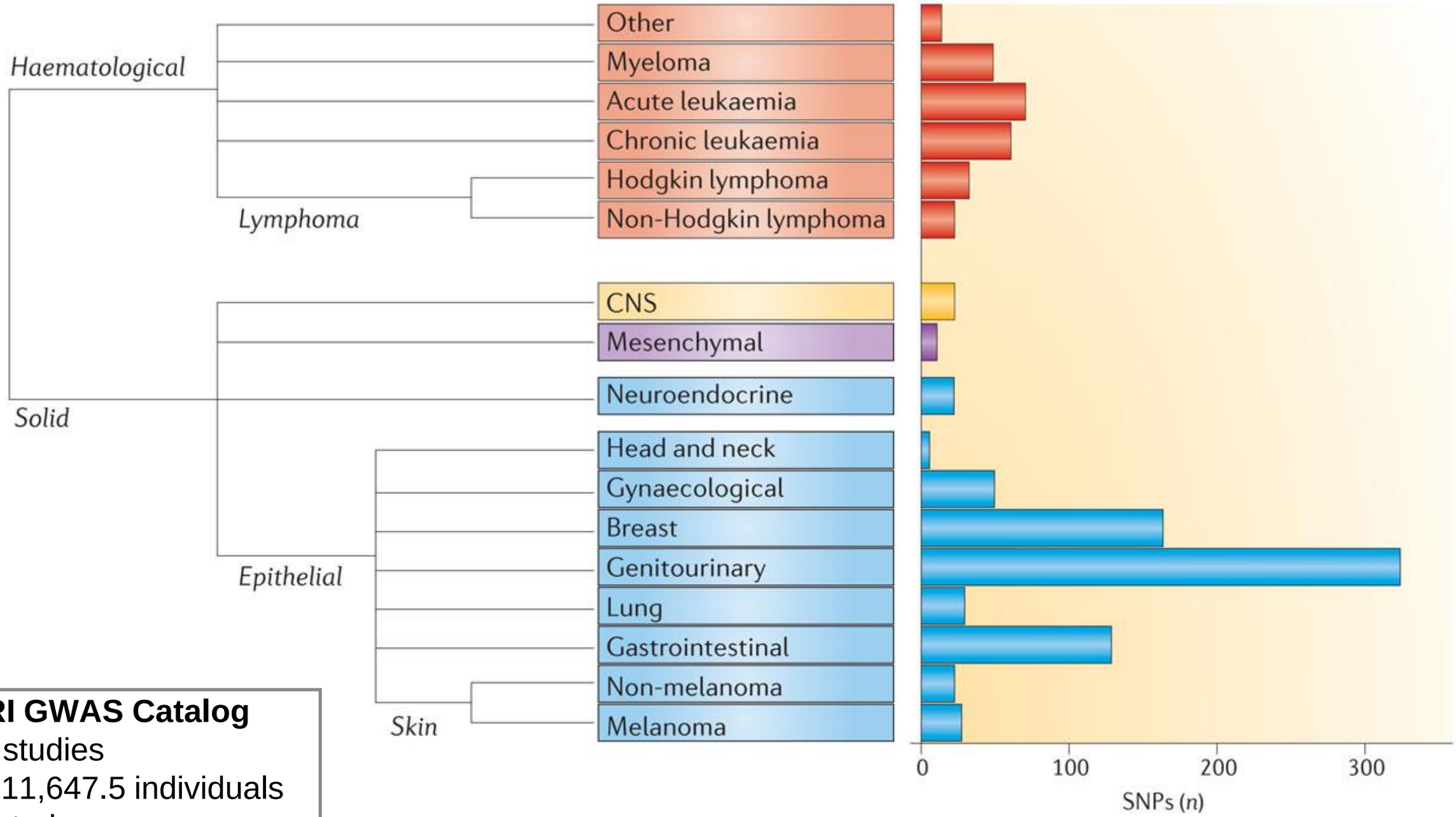
In Mice




Has GWAS identified more p53 network SNPs?

Post *et al*., Cancer Cell, 2010

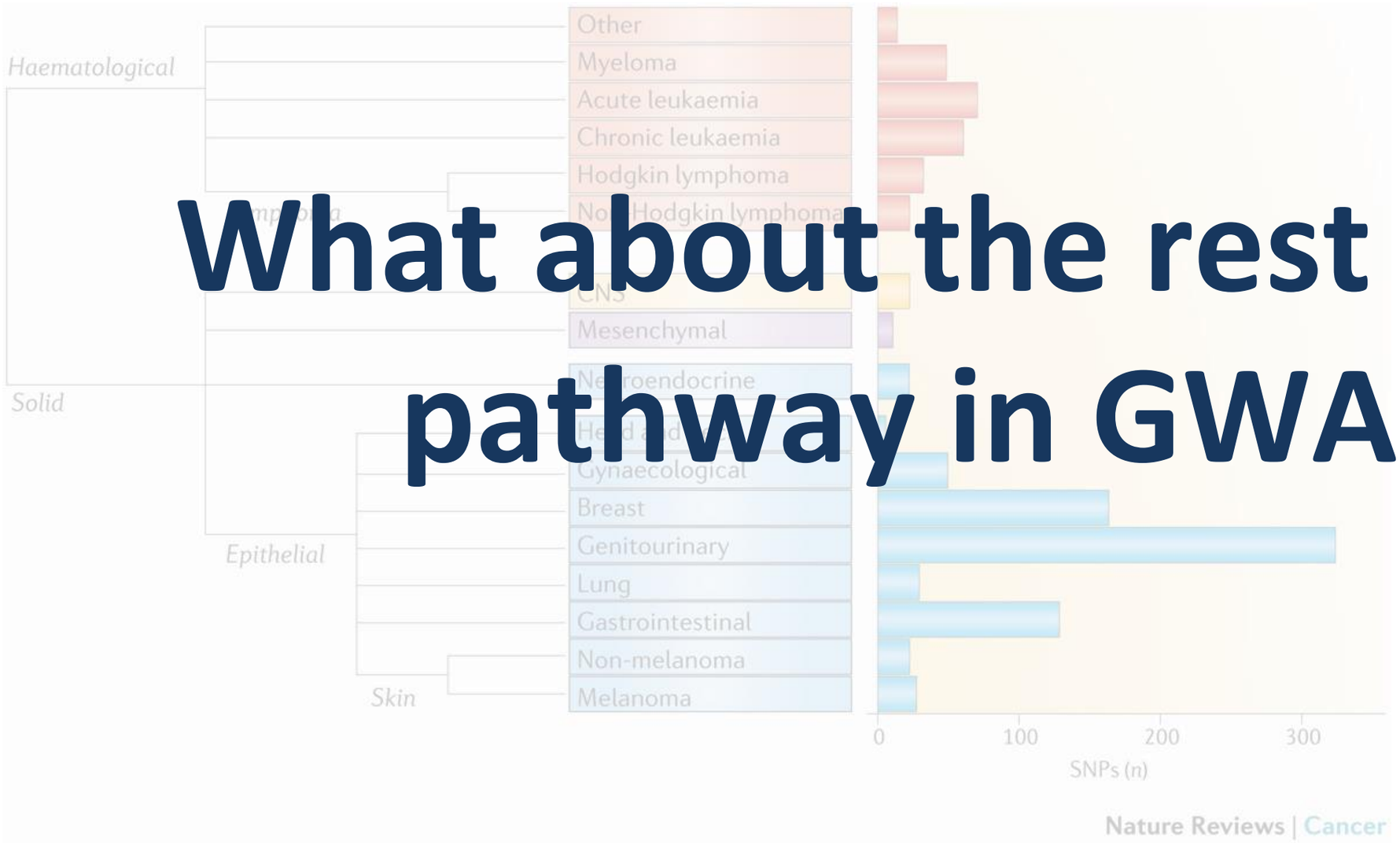
# Has cancer GWAS found more p53 pathway SNPs?




**NHGRI GWAS Catalog**

- 165 studies
- ave.11,647.5 individuals per study
- 750 unique SNPs
- 17 types of cancer

# Cancer GWAS SNPs in European Populations

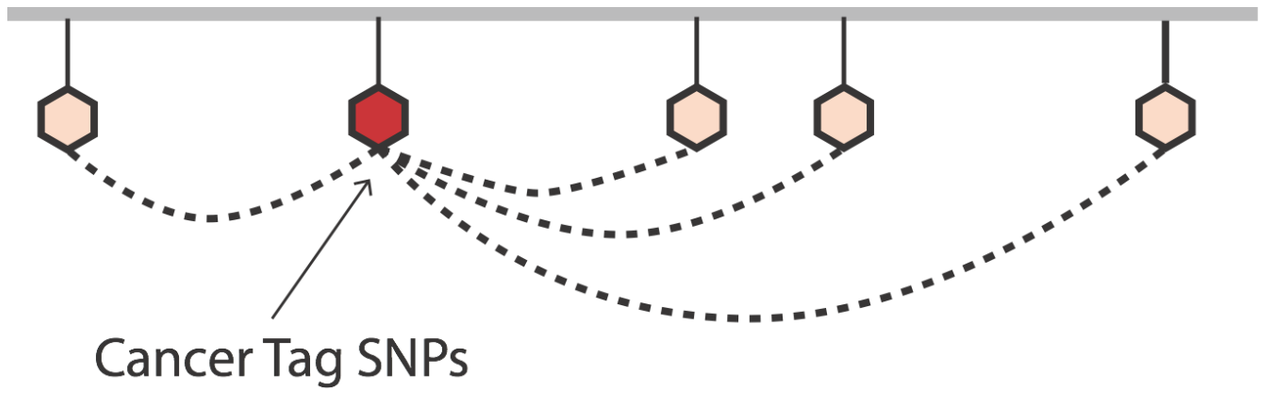



# What about the rest of the pathway in GWAS?

# From SNPs to genes

**Cancer SNPs (2,819 SNPs)**

- Tags + Linked SNPs
  - ✴ 1000 Genomes Phase 1
  - ✴ EUR populations
  - ✴ MAF ≥ 0.01
  - ✴ r2=1



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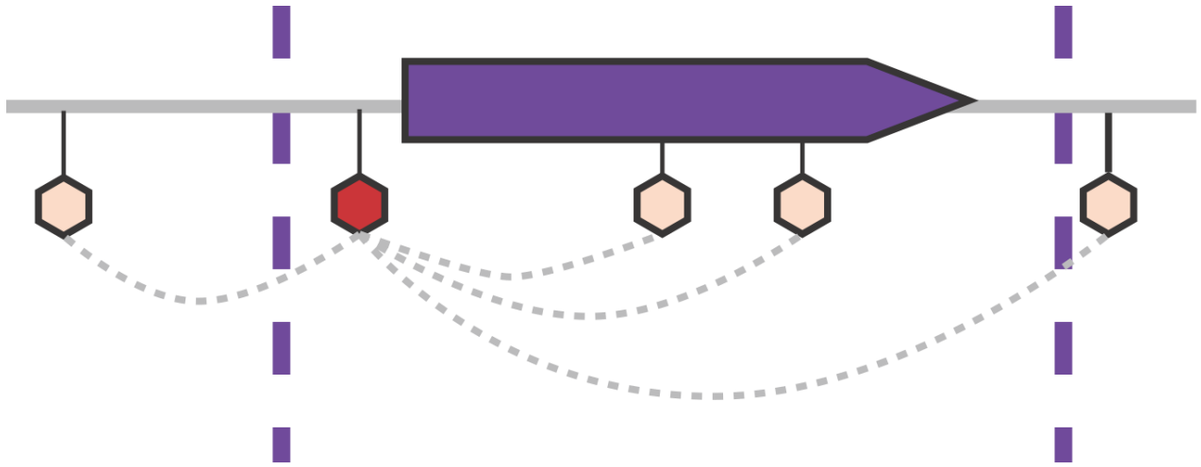
***Cancer Susceptibility Genes (CSGs)*** *are genes having ≥1 cancer SNP within ±10Kb from its boundaries.*

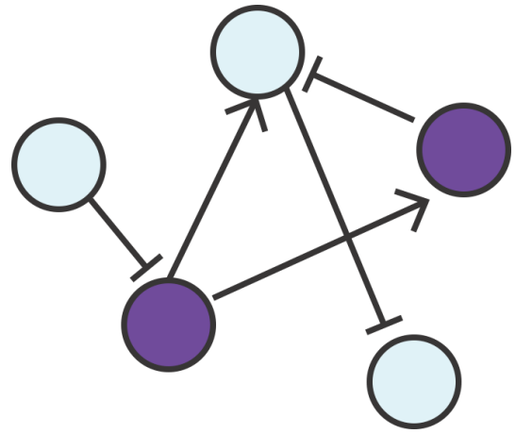
- **458** CSGs in the genome



# From genes to pathways

**Genes were assigned to pathways using the KEGG pathway annotation**

- 214 pathways
- 5 major categories*: Metabolism, Genetic Information Processing. Environmental Information Processing, Cellular Processes, Organismal Systems*



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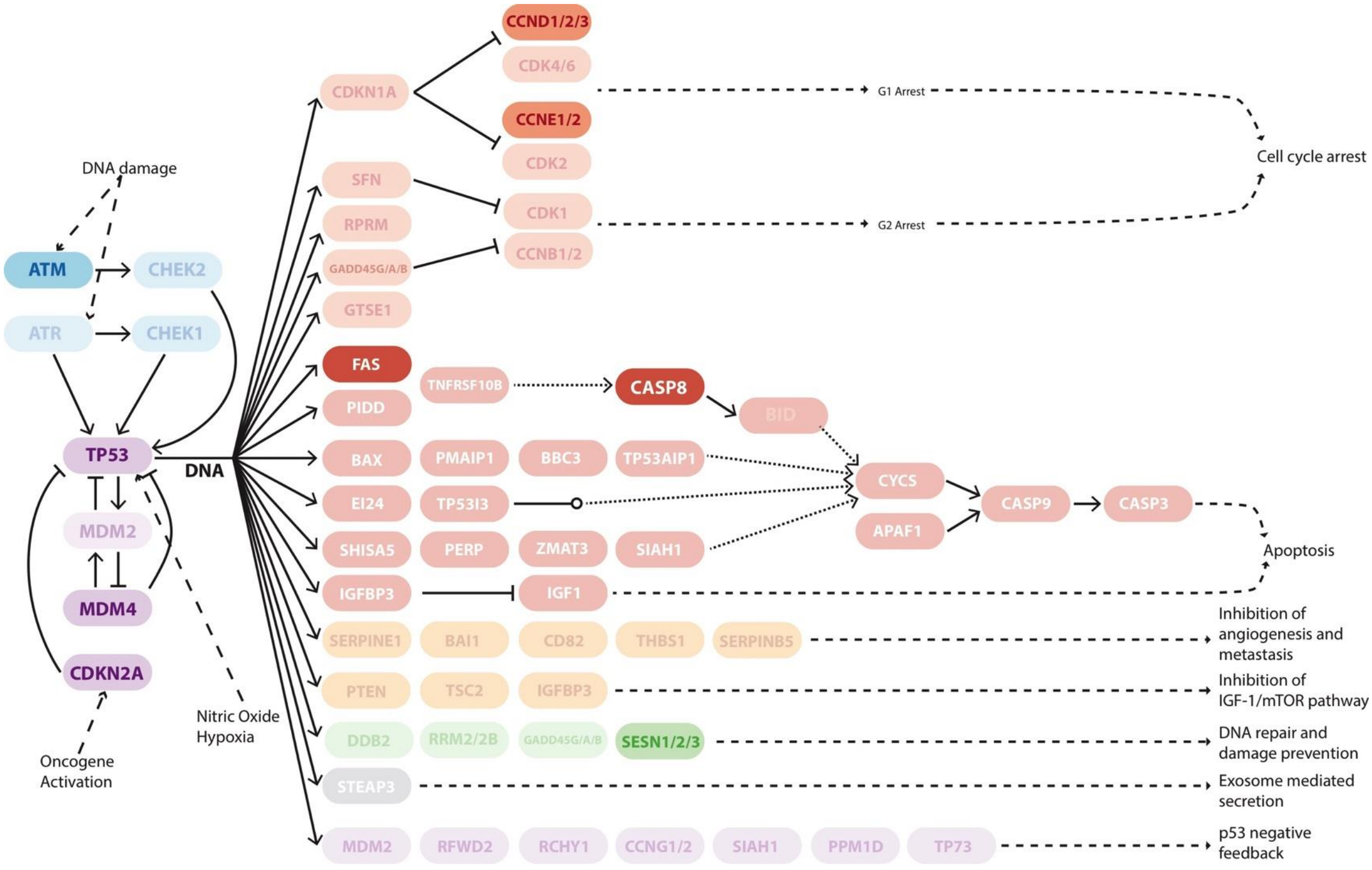
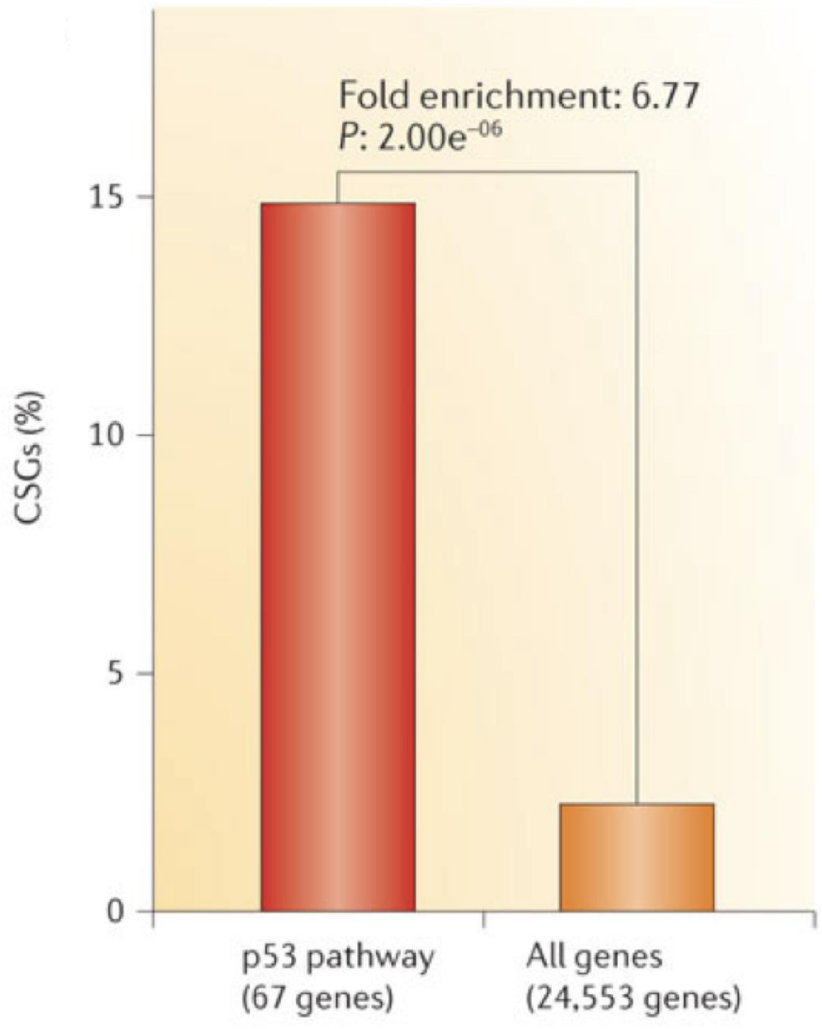
**Does the p53 pathway have more CSGs than expected by chance?**

- Hypergeometric enrichment test
- P-values adjusted for multiple hypothesis testing by permutations.

# 10 out of 67 p53 pathway genes are CSGs: is this a lot?



# CSGs are enriched in p53 pathway genes



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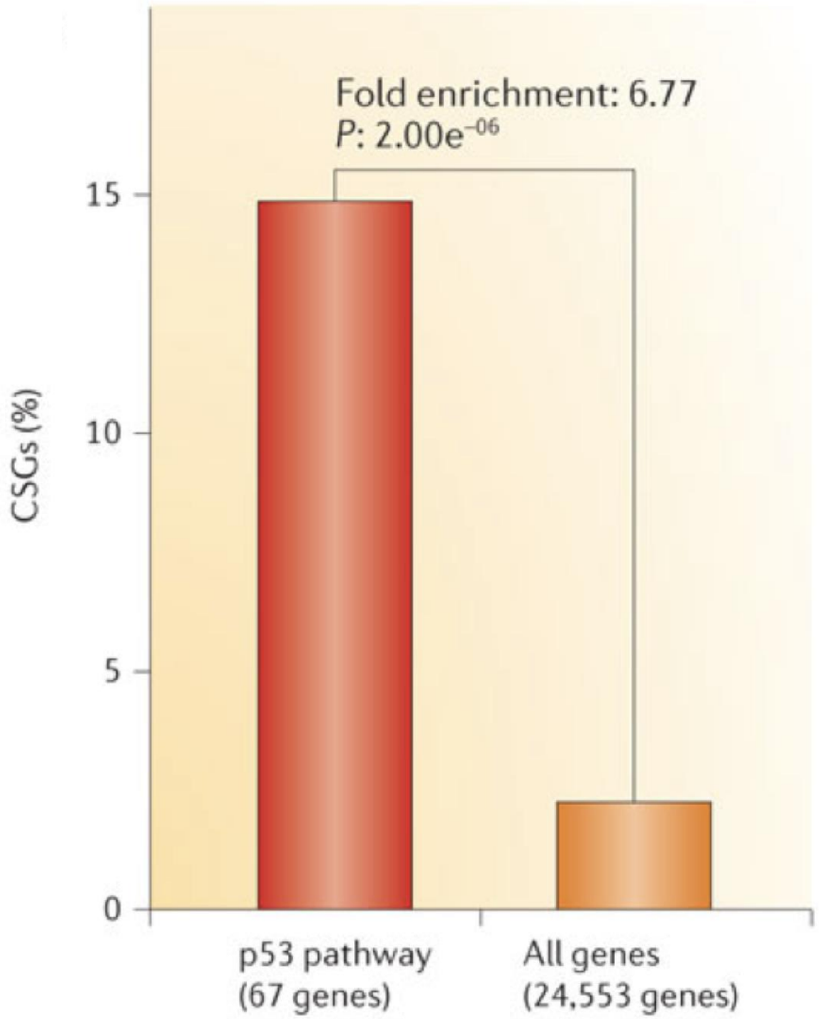
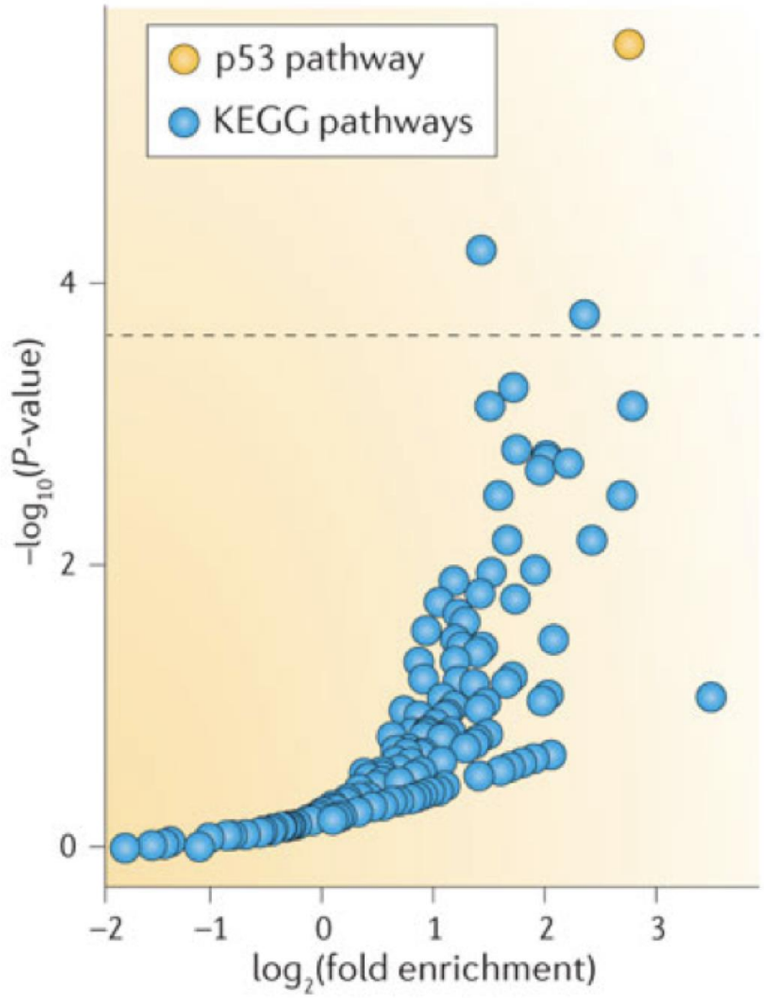
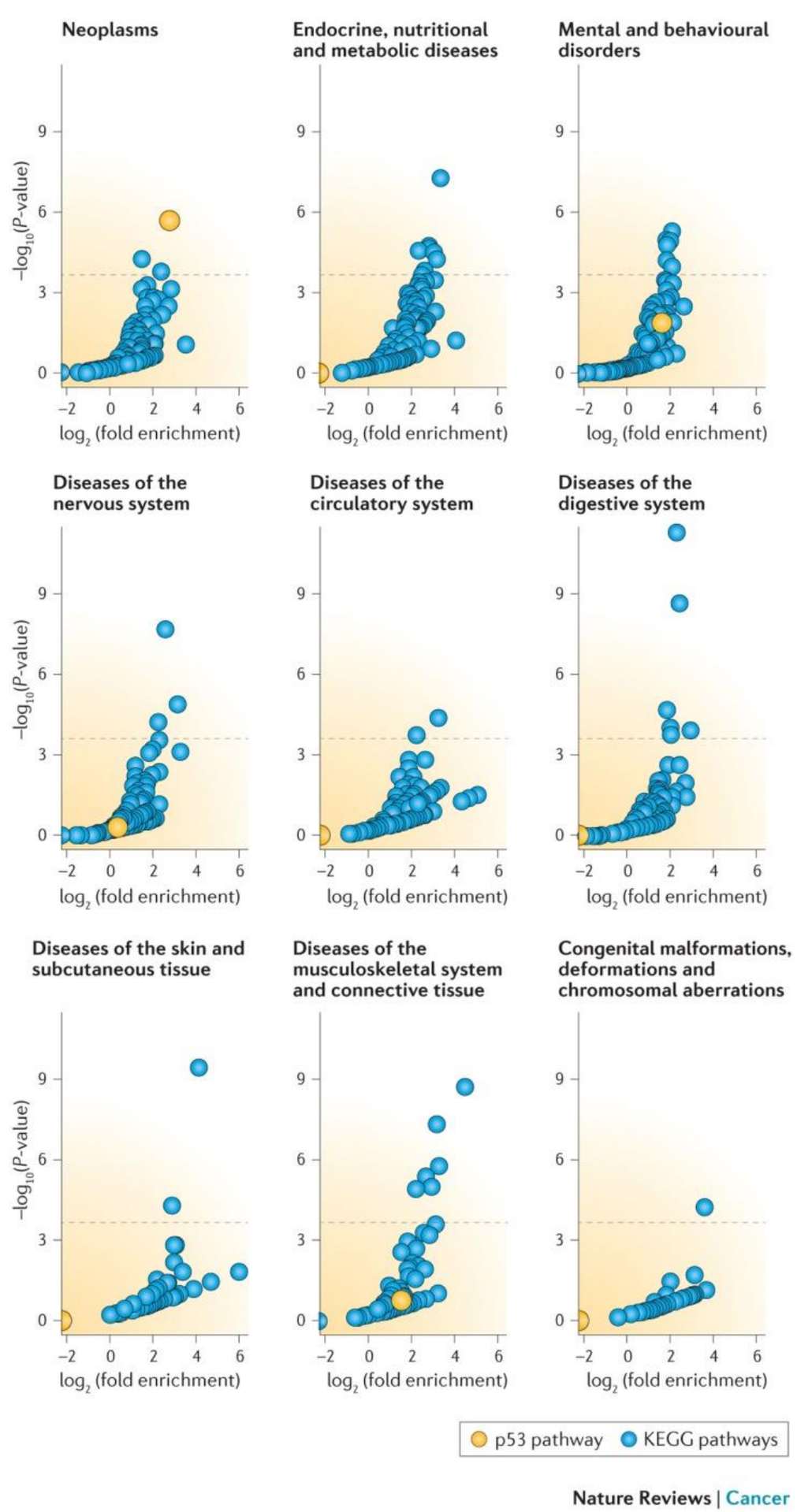


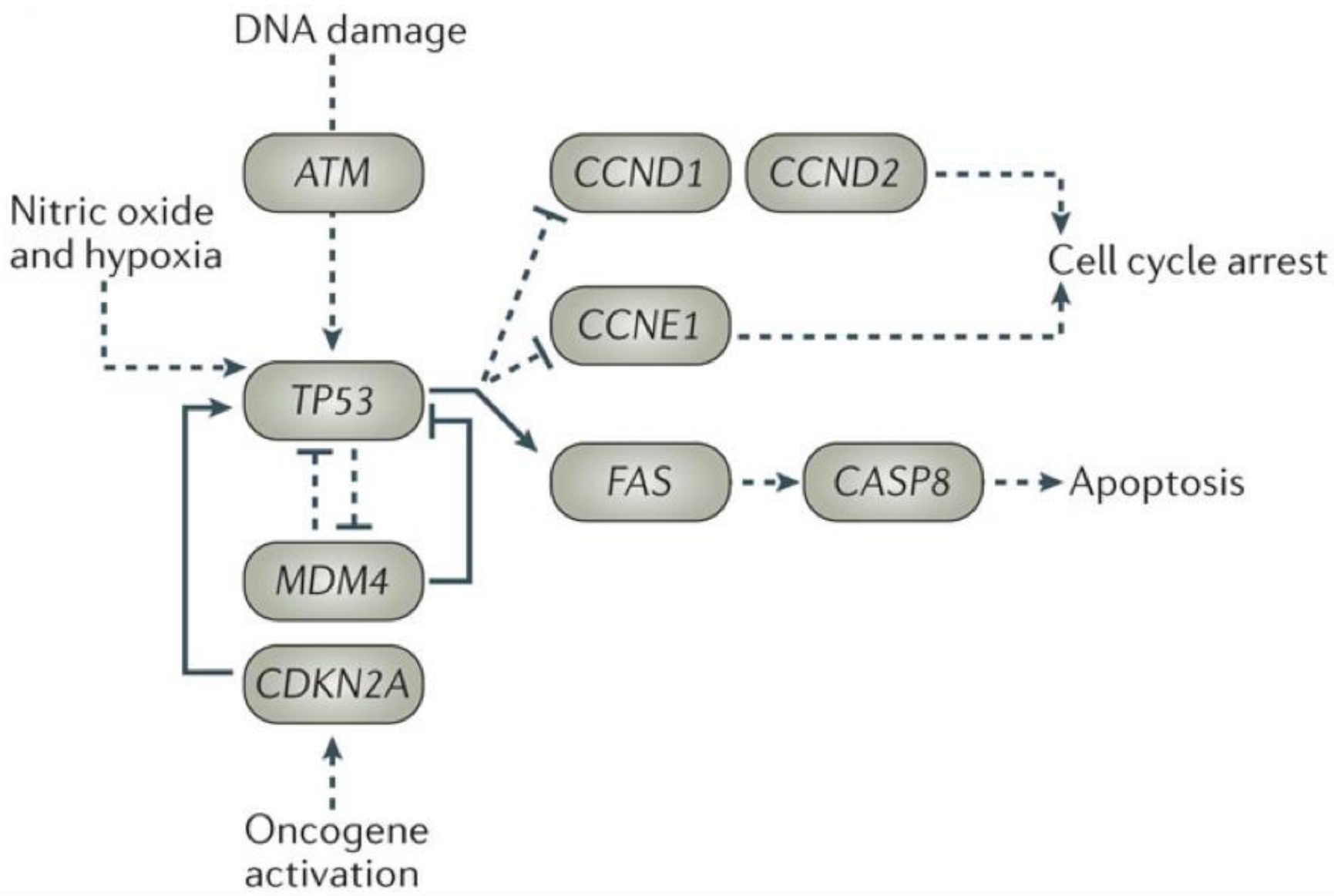




- **3/214 KEGG pathways show significant enrichment:**
  - ✴ p53
  - ✴ Adherens Junction
  - ✴ PI3K-AKT

# p53 Genes are not enriched in Susceptibility Loci for Other ICD10 Disease Groups



# p53 pathway CSGs are somatically mutated genes



# Potential Insights

- **p53 signaling pathway is highly sensitive to SNPs, and it can contribute to the observed heterogeneity of cancer risk in the broader population and in LFS.**
  - *Potential utility in risk assessment for a broad range of cancers to aid asymptomatic screening protocols.*
- **Many genes in the p53 pathway are highly sensitive to both heritable and somatic genetic variants, highlighting their central roles in regulating or affecting p53 signaling.**
  - *Targeting these genes could be an efficient method to modulate p53 signaling in the clinic.*
  - *We will need to incorporate somatic and inherited genetics of these genes and their interactors to maximize treatment efficacy.*
- **Genetic variants in the p53 pathway primarily affect susceptibility to cancer and not the other major disease groupings we tested.**
  - *As agents that modulate the levels of p53 signaling are entering the clinic, such information could be useful to predict and monitor potential side effects.*

# Brazilian Li-Fraumeni Syndrome

There are roughly 200-300,000 individuals that carry a lower penetrant p53 mutation in Southern Brazil

- 1 in 30 will develop adrenal corticoid carcinoma by the age of 15 years.

- There are seemingly low and high risk families (breast, brain, gastric and sarcomas).

- One third of the families have no cancer history.

- Recently 172,000 newborns were screened and clinical follow up was able to identify early stage tumors with good prognosis.

- Teaming up with Bonald Figueiredo to explore if p53 pathway SNPs could serve as modifiers of penetrance to better risk estimation.

Custodio et al., JCO 3013

# Acknowledgements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