Istituto di Tecnologie Biomediche
Consiglio Nazionale delle Ricerche

SINdem4juniors
6th winter seminar on dementia and neurodegenerative disorders

Exploring the genetic basis of the inverse relationship of occurrence between Alzheimer's Disease and Cancer

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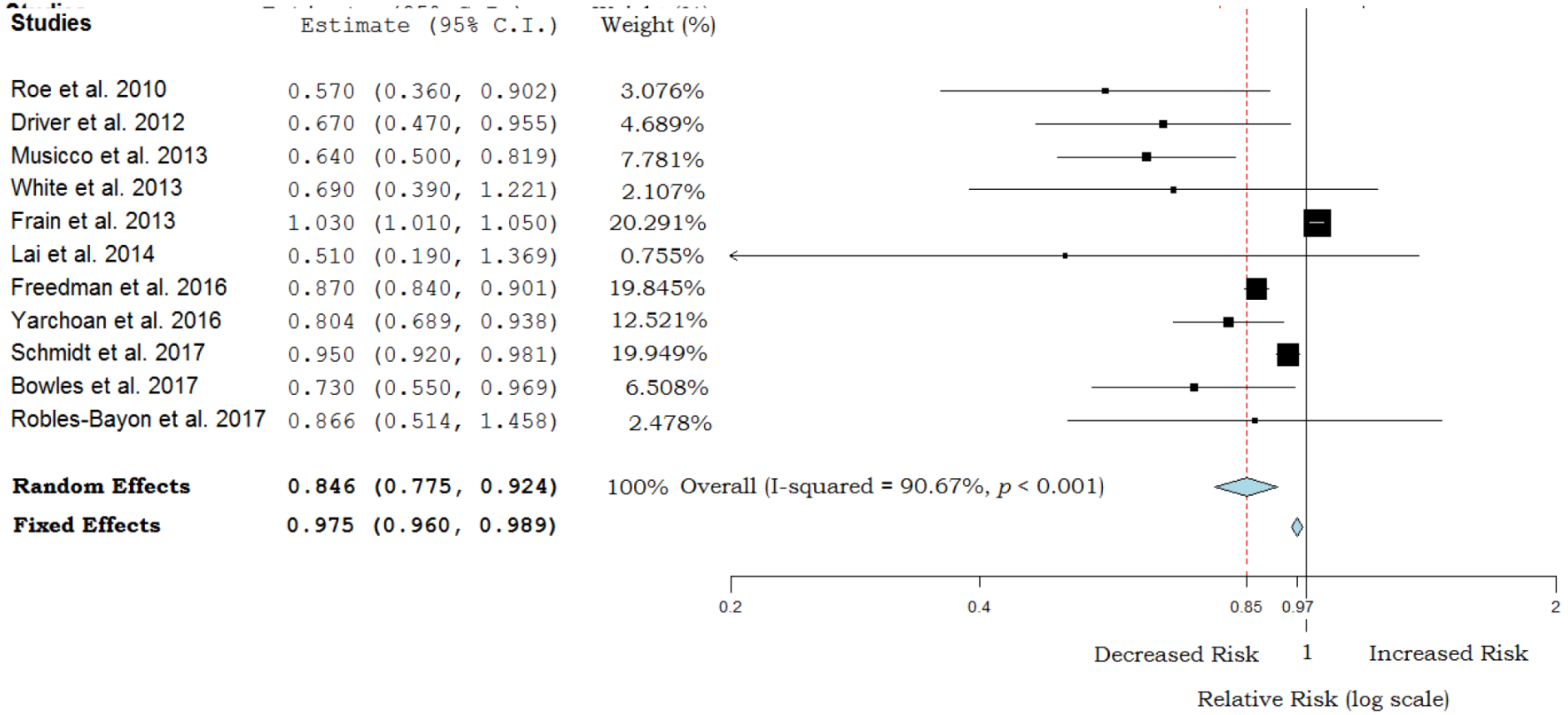
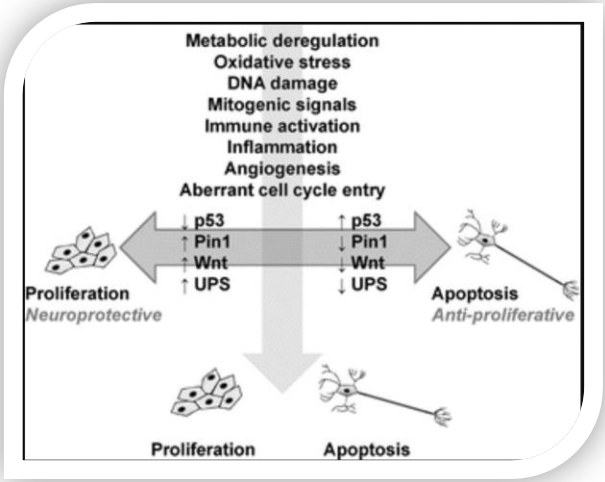
Background: risk of cancer among patients with Alzheimer's Disease



Hypothesis and aims

Hypothesis: the inverse comorbidity might be primarily driven by genetic pattern that individually predispose toward Alzheimer's Disease or Cancer phenotypes.



Driver, J.A, *Biogerontology* (2014), 15: 547

Aim of this study is to explore the underlying genetic link between the two diseases by applying an *a* posteriori approach.

Flow-diagram of Methods and Results

Methods

DATASET SEARCH STRATEGY: NCBI DbGap Genome Wide Association Studies (GWAS) repositories *Eligibility criteria*: age at study entry or onset of the disease ≥60 years old, Caucasian ethnicity, tissues, datatype, platform source.

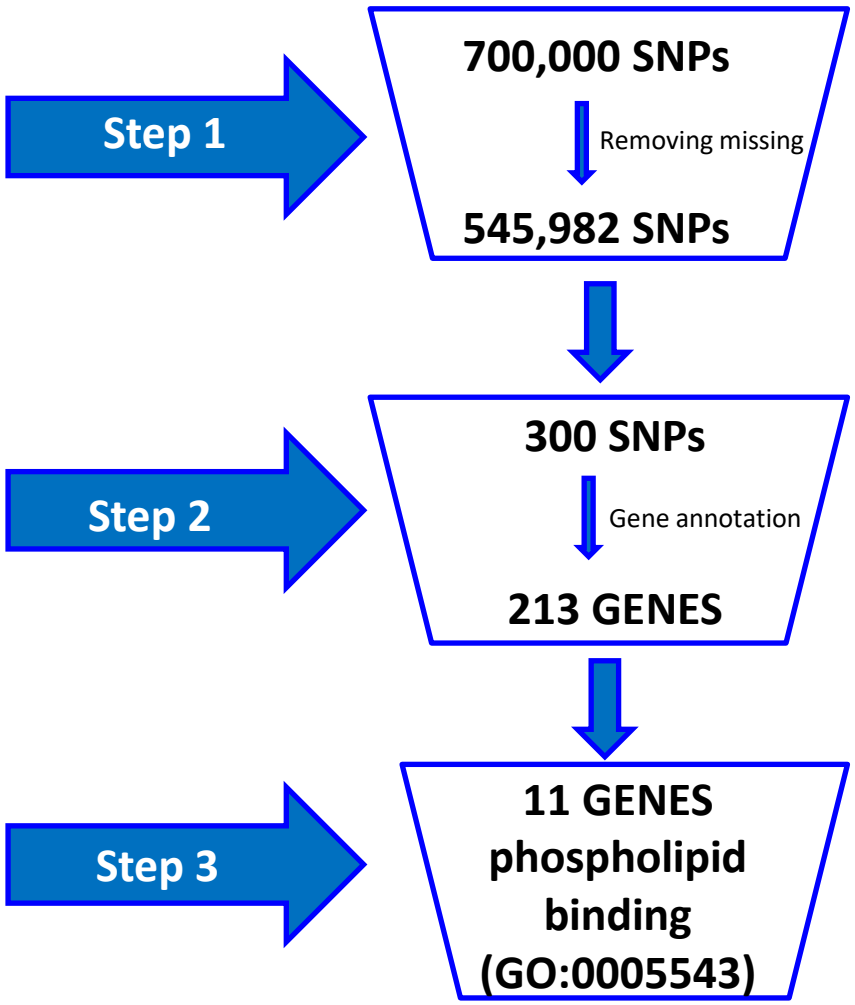
SELECTED DATASETS AND DATA CLEANING: Cancer i) pancreas, ii) renal, and iii) glioma (cancer cases N=4409, controls N=9927), and Alzheimer'Disease (AD cases N=1292, N=1278 controls)

GWAS AND GENE ANNOTATION:
Population stratification*: Principal Component Analysis (PCA) identified 20 PC.* The first two factors explained about 20% of the genotype variability of the total individuals.
Association analysis*: Logistic regression model analysis* of the pooled dataset was carried out adjusting for age, sex, the top five principal components and contrasting AD cases against cancer cases (OR, 95%CI), p-value < 10^{-5}).
Functional gene annotation*: map the phenotype-associated SNPs* to the human genome assembly hg19 (below the threshold p-level of 10^{-5}) via http://snp-nexus.org/ .

GENE ENRICHMENT ANALYSIS: functional annotation of the identified genes on the assembly hg19, explored the molecular processes significantly associated with the genes (p-value <10-5). https://toppgene.cchmc.org/

°https://www.ncbi.nlm.nih.gov/gap

Results

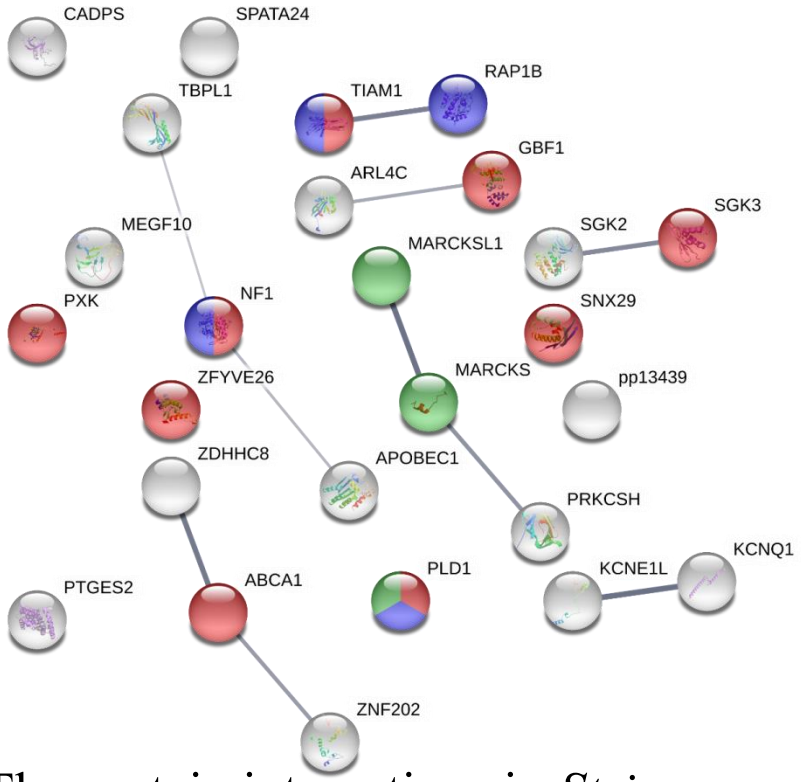


Results and Conclusion

- We identified 11 genes, associated with SNPs significantly different in the two diseases.
- The genes are involved in shared biological pathways, that, if deregulated, may explain the divergent trajectories of AD and cancer.
- A significant enrichment for phospholipid binding indicates a promising direction for future investigation.
- A preliminary investigation of protein –protein interaction in String databases has shown several significant enrichments, including pathways involved in carcinogenesis.
- Future investigation will also include a detailed analysis of interaction between the 11 identified genes and gene products as a potential target of an epidemiological, prognostic and diagnostic interest.

ID	Name	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input
GO: 0005543	**phospholipid binding**	**1.572E-5**	**9.620E-3**	**6.729E-2**	**9.620E-3**	**11**

Gene Name	Original Symbol
ABCA1	ATP binding cassette subfamily A member 1
GBF1	golgi brefeldin A resistant guanine nucleotide exchange factor 1
PXK	PX domain containing serine/threonine kinase like
NF1	neurofibromin 1
KCNQ1	potassium voltage-gated channel subfamily Q member 1
PLD1	phospholipase D1
SNX29	sorting nexin 29
TIAM1	T cell lymphoma invasion and metastasis 1
CADPS	calcium dependent secretion activator
ZFYVE26	zinc finger FYVE-type containing 26
MARCKS	myristoylated alanine rich protein kinase C substrate



The protein interactions in *String*
https://string-db.org/

number of nodes: 26
number of edges: 10
average node degree: 0.769
avg. local clustering coefficient: 0.538

expected number of edges: 1
PPI enrichment p-value: 1.54e-06
your network has significantly more interactions than expected (what does that mean?)

Molecular Function (GO)

pathway ID	*pathway description*	*count in gene set*	*false discovery rate*
GO:0005543	phospholipid binding	9	5.1e-07

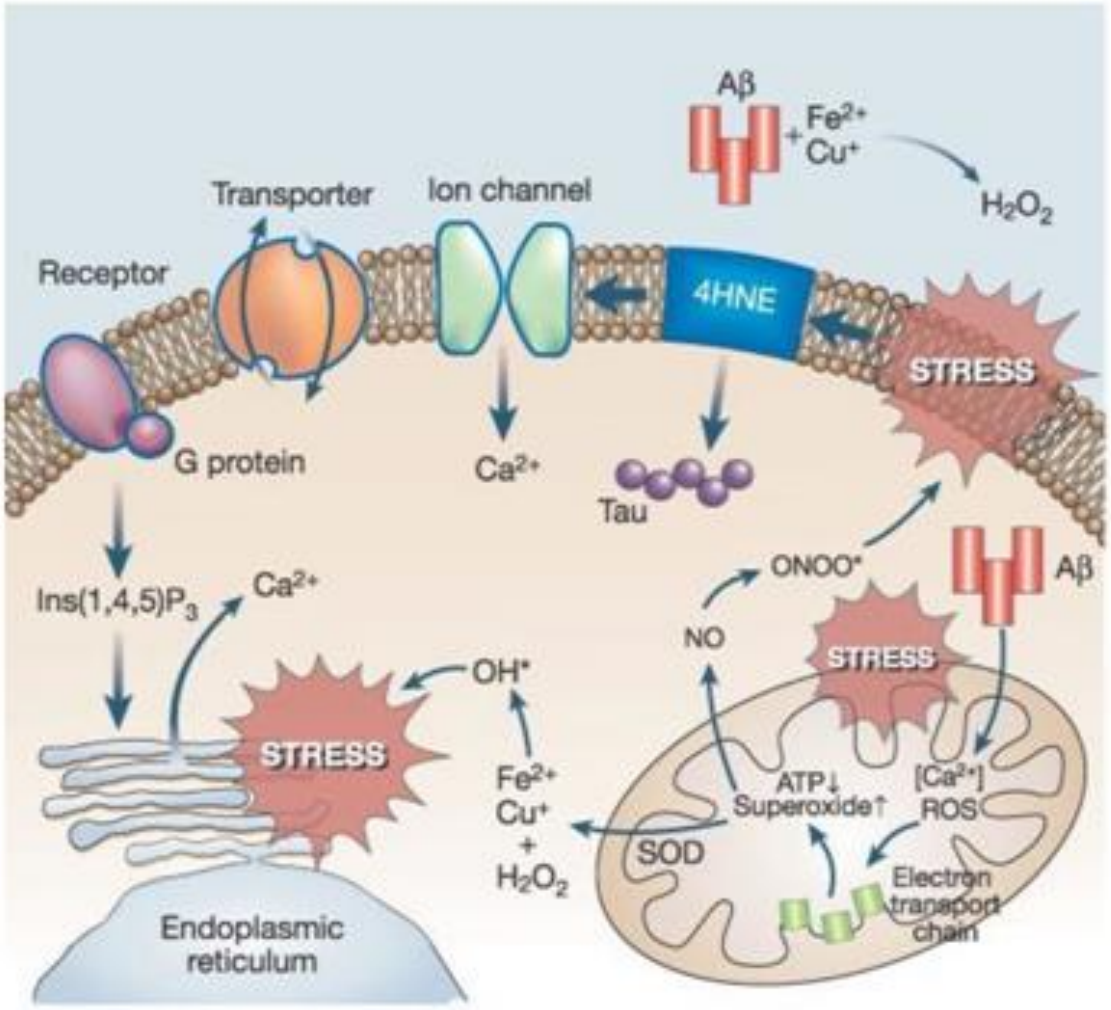
KEGG Pathways

pathway ID	*pathway description*	*count in gene set*	*false discovery rate*
04014	Ras signaling pathway	4	0.0258
04666	Fc gamma R-mediated phagocytosis	3	0.0258

Thank you !

- Technical
- Here is a brief technical summary:
- **p53** is upregulated in Alzheimer's disease and down-regulated in Cancer
- **Estrogen** is neuro-protective but increases the risk of cancers
- **Neurotrophins** and growth factors are neuroprotective but are also involved in tumor growth progression
- Age related decline in proliferation of new cells contribute to AD development while pathways and mechanisms that contribute to growth and proliferation delays AD
- **cAMP** provides survival signal for neurons and is also involved in tumor progression
- **EGFR** is overexpressed in cancer but EGFR is not found in Alzheimer's plaques
- **Bcl-2** downregulated in Alzheimer's disease but is overexpressed in cancer
- **Apoptosis** pathways are upregulated in Alzheimer's disease but downregulated in cancer
- **IGF-1** is decreased in Alzheimer's disease but increased in cancer, dysfunctional proliferation of neurons occurs in Alzheimer's but in cancer there is over-proliferation of cells
- **HSV** is oncolytic but contributes to Alzheimer's disease development
- **TDP-43** role in Alzheimer's disease and cancer and its relation to IGF signifies the inverse relationship between cancer and AD
- Alzheimer's risk decreases from **apoE4** to E3 to E2 but growth and survival improves respectively
- Pathophysiologic **notch** signals potentially contribute to cancer but presenilins are also involved in notch signaling and they mutate in familial early-onset AD
- **Neural cell adhesion molecules** decrease in AD but stain positive in neoplasia.
- **TNF-α** has anti-cancer properties and its overexpression causes neurotoxic environment but secondary signal is necessary for the induction of neuronal death
- **PI3K/AKT/MTOR** pathway is neuroprotective but in many cancers this pathway is overactive
- Telomerase in cancer cells prevents senescence related death and AD is associated with accelerated neuronal death
- **ROS** when excessive slows cancer proliferation and ROS are increased in Alzheimer's disease
- **ACE** levels are decreased in Cancer but are elevated in Alzheimer's disease

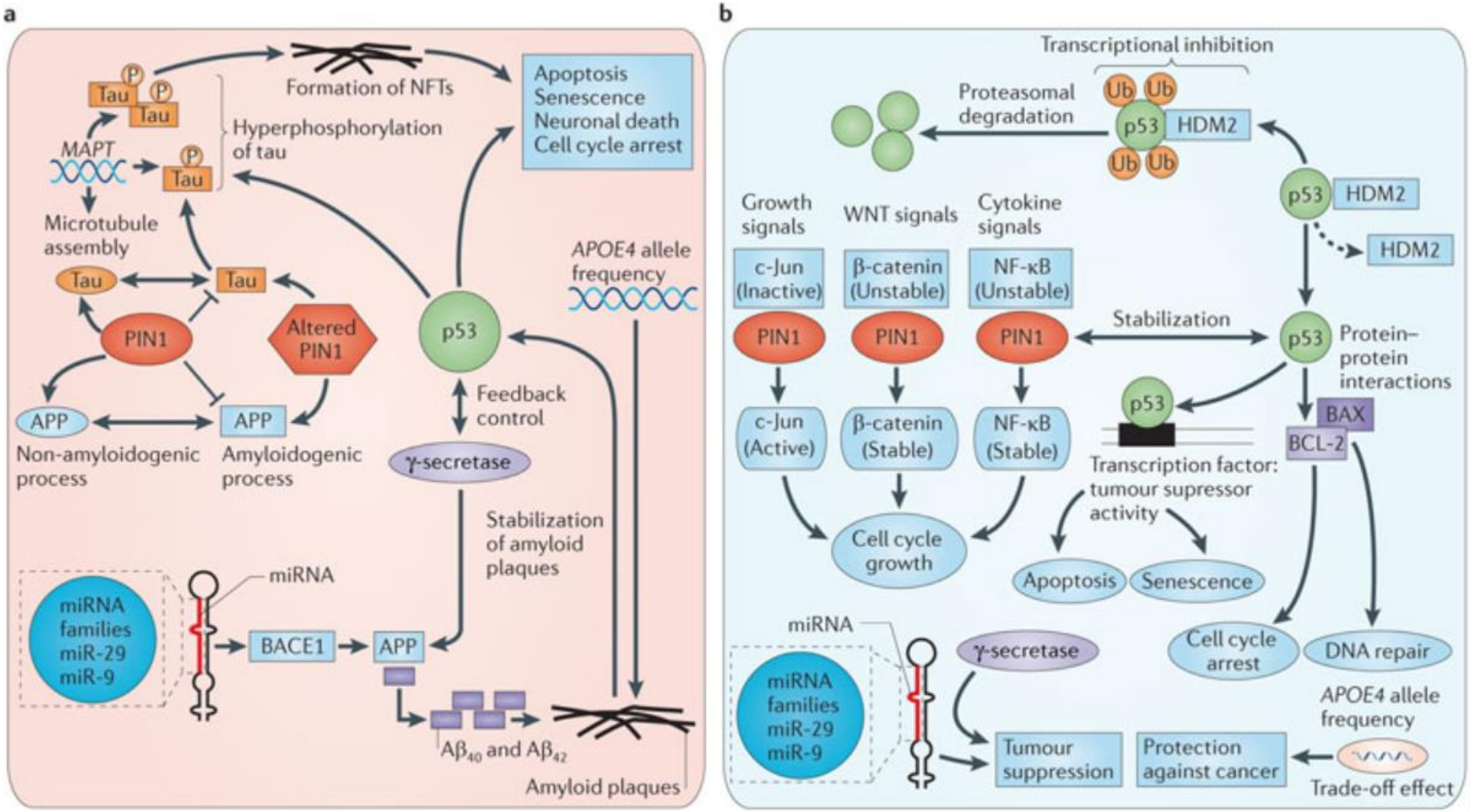
From: Pathways towards and away from Alzheimer's disease



Review

Pathways towards and away from Alzheimer's disease

Mark P. Mattson

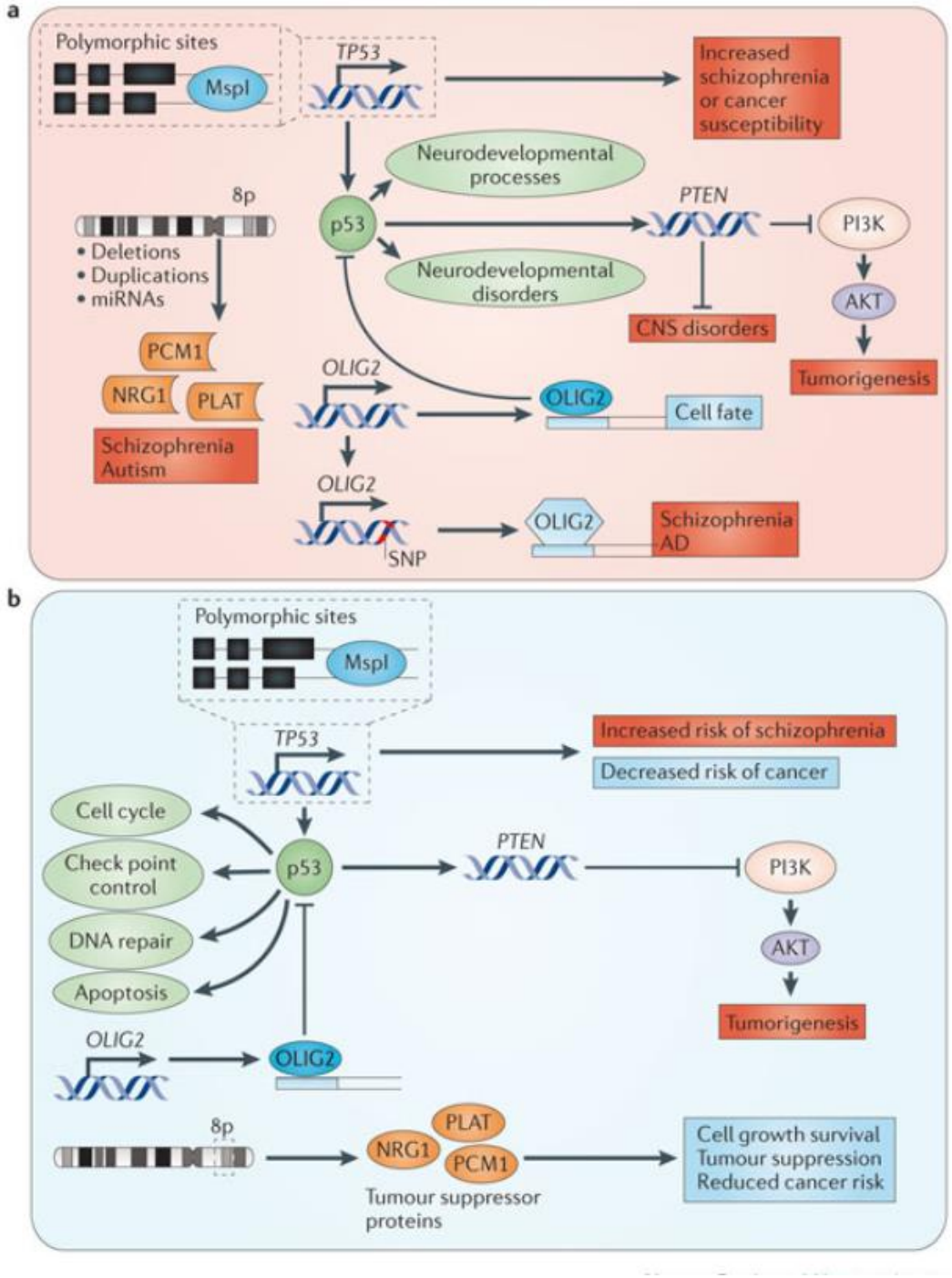


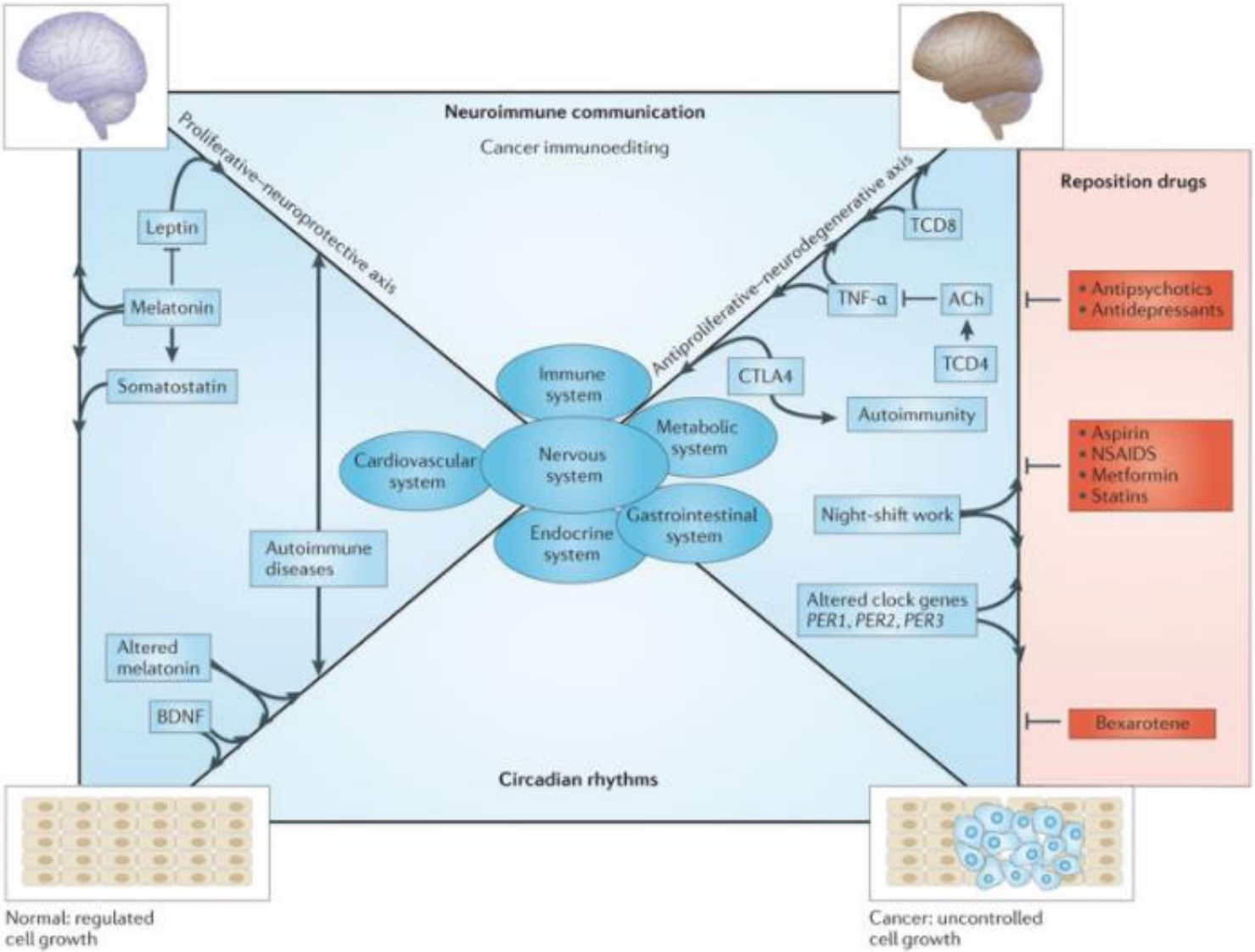
Inverse cancer comorbidity: A serendipitous opportunity to gain insight into CNS disorders

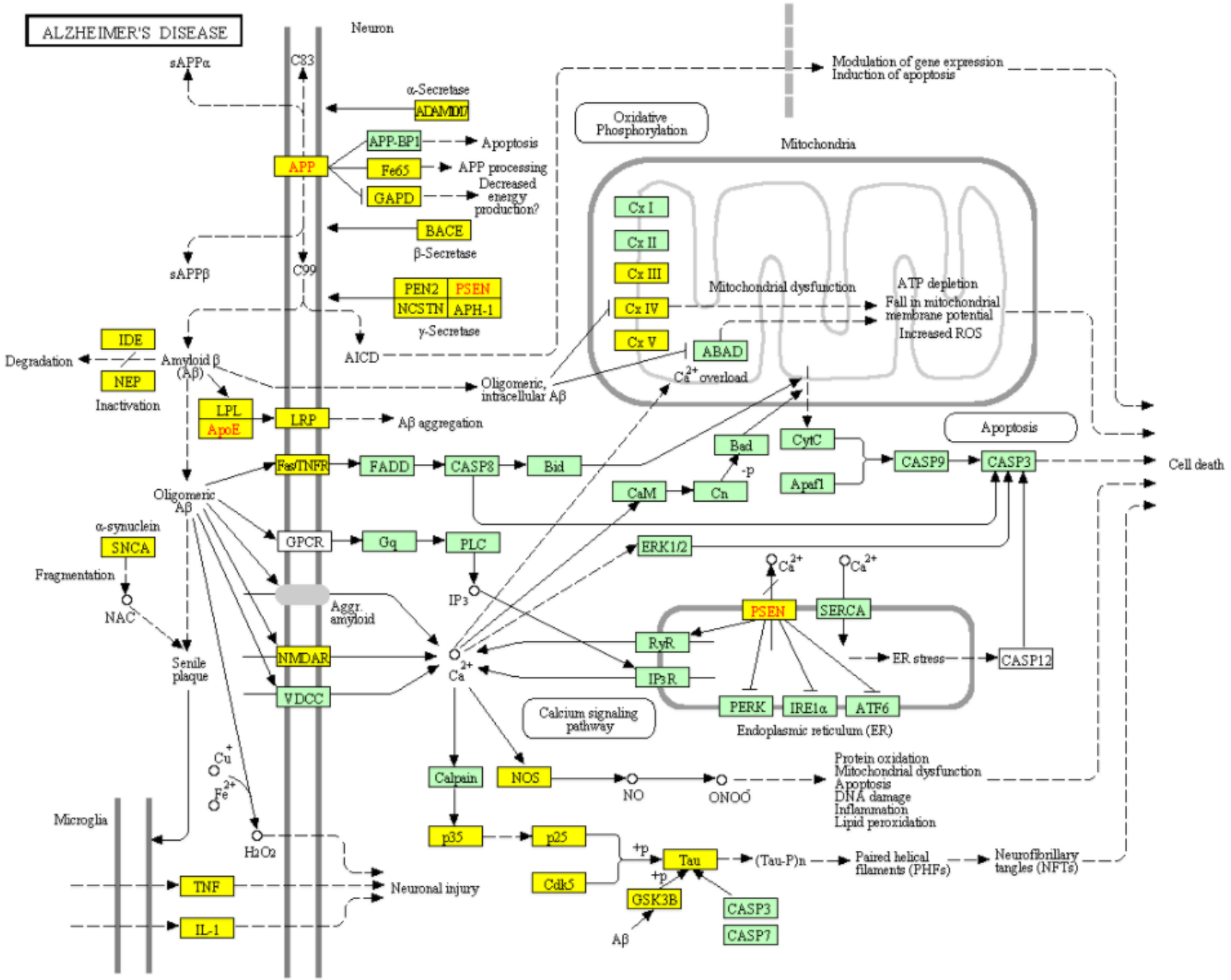
April 2013

Nature Reviews Neuroscience 14(4):293-304

DOI


a
Polymorphic sites
MspI
TP53
Increased schizophrenia or cancer susceptibility
Neurodevelopmental processes
8p
p53
PTEN
PI3K
• Deletions
• Duplications
• miRNAs
Neurodevelopmental disorders
AKT
CNS disorders
PCM1
NRG1
PLAT
Schizophrenia Autism
OLIG2
OLIG2
Cell fate
Tumorigenesis
OLIG2
OLIG2
Schizophrenia AD
SNP
b
Polymorphic sites
MspI
TP53
Increased risk of schizophrenia
Decreased risk of cancer
Cell cycle
Check point control
p53
PTEN
PI3K
DNA repair
AKT
Apoptosis
Tumorigenesis
OLIG2
OLIG2
8p
PLAT
NRG1
PCM1
Cell growth survival
Tumour suppression
Reduced cancer risk
Tumour suppressor proteins


Neuroimmune communication
Cancer immunoediting
Proliferative–neuroprotective axis
Antiproliferative–neurodegenerative axis
Leptin
Melatonin
Somatostatin
Autoimmune diseases
Altered melatonin
BDNF
TCD8
TNF-α
ACh
TCD4
CTLA4
Autoimmunity
Immune system
Metabolic system
Cardiovascular system
Nervous system
Gastrointestinal system
Endocrine system
Night-shift work
Altered clock genes PER1, PER2, PER3
Reposition drugs
• Antipsychotics
• Antidepressants
• Aspirin
• NSAIDS
• Metformin
• Statins
Bexarotene
Circadian rhythms
Normal: regulated cell growth
Cancer: uncontrolled cell growth



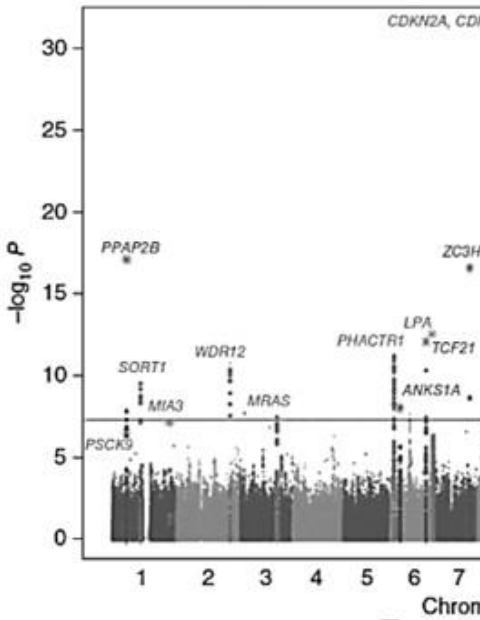
Meta-anaylsis and

Post-GWAS strategies

Fine-mapping
(use of 1000 Genomes
Project data,...)

Use of eQTL data
to interpret
GWAS findings

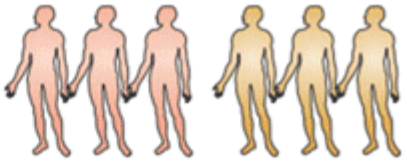
Next-generation
and whole-Exome
sequencing



In vitro
functional
experiments

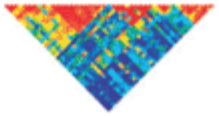
Identification of causative variants and elucidation of m
CAD/MI loci

Large cohort of cases and controls (n >1,000)
- Matched for confounding variables, such as race, ethnicity and sex
- Stratified in order to maximize signals

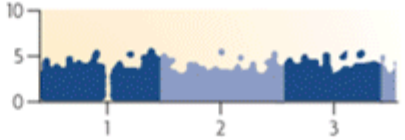


Microarray-based SNP genotyping
- ~1 million random marker SNPs or ~25,000 risk-enhancing SNPs (for example, nsSNPs)

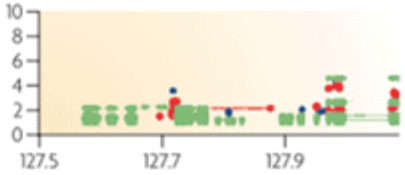
Derivation of haplotypes
- Predicated on International HapMap



Detection of association signals
- χ^2 or similar test
- Uncorrected P <10^{-7} or false discovery rate-like correction



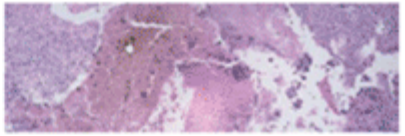
Fine mapping of association signal (see FIG. 2)
- Directed genotyping of additional SNPs in region
- Fine mapping of LD in region of association
- Empirical derivation of haplotypes
- Examination of effect of stratification, if available



Replication of association
- Large independent cohort of cases and controls (n >1,000)
- Genotyping of nominated candidate SNPs (<20)
- χ^2 or similar test; replication of initial signal

Genotypes	CC	AA	CA	Total
Cases observed	59	27	98	184
Controls observed	60	89	36	185
Total	119	116	134	369

Biological validation of association
- Identification of risk-enhancing variant
- Examination of functional consequence of variant
- Determination of mechanism of risk-enhancement



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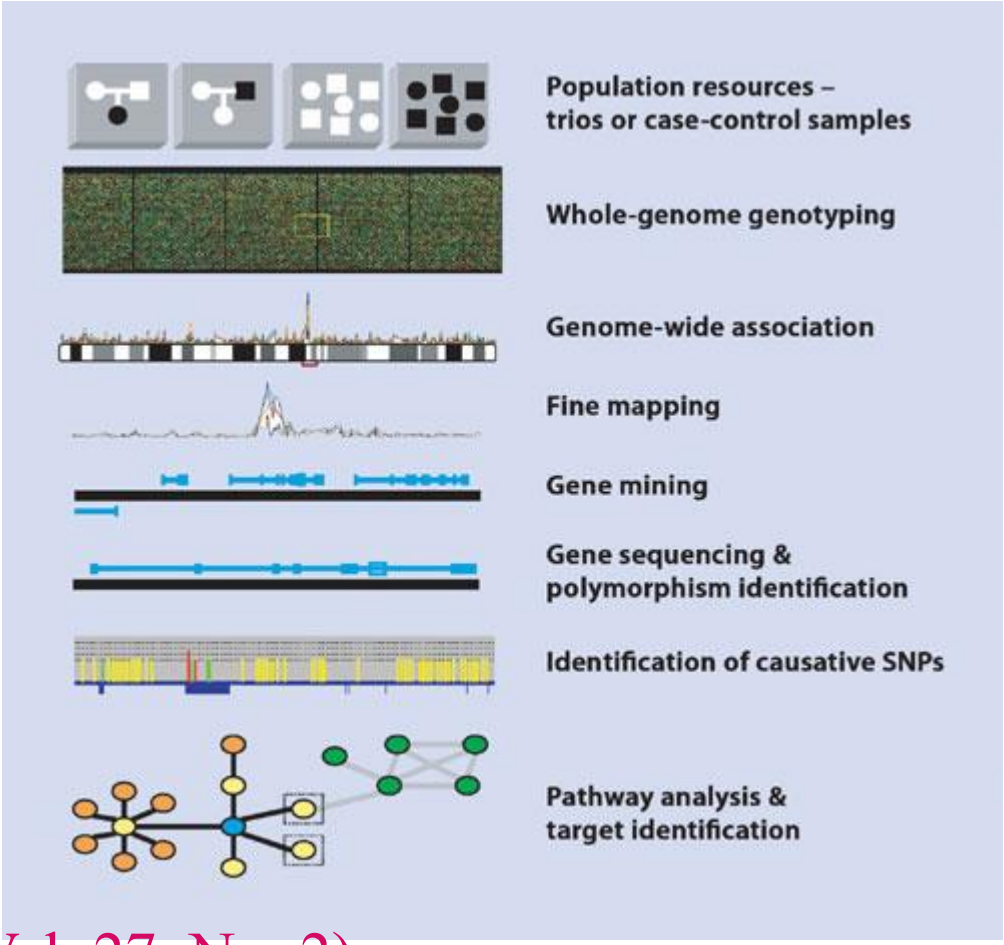
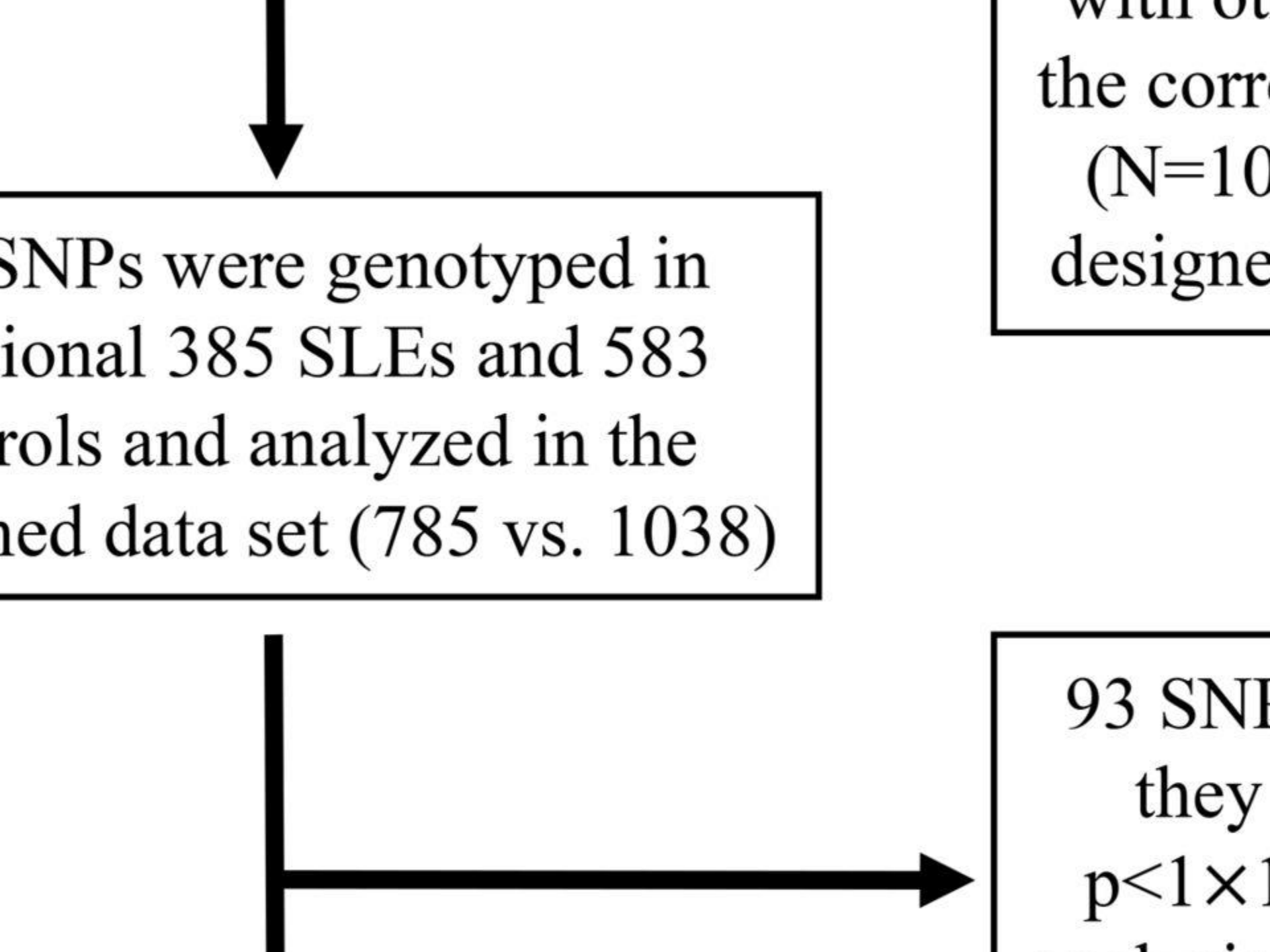


Tutorials

January 15, 2007 (Vol. 27, No. 2)

Human Genome-Wide Association Studies

Achieving Sufficient Power to Detect Disease Genes with the Quebec Founder Population


SNPs were genotyped in
ional 385 SLEs and 583
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(N=10
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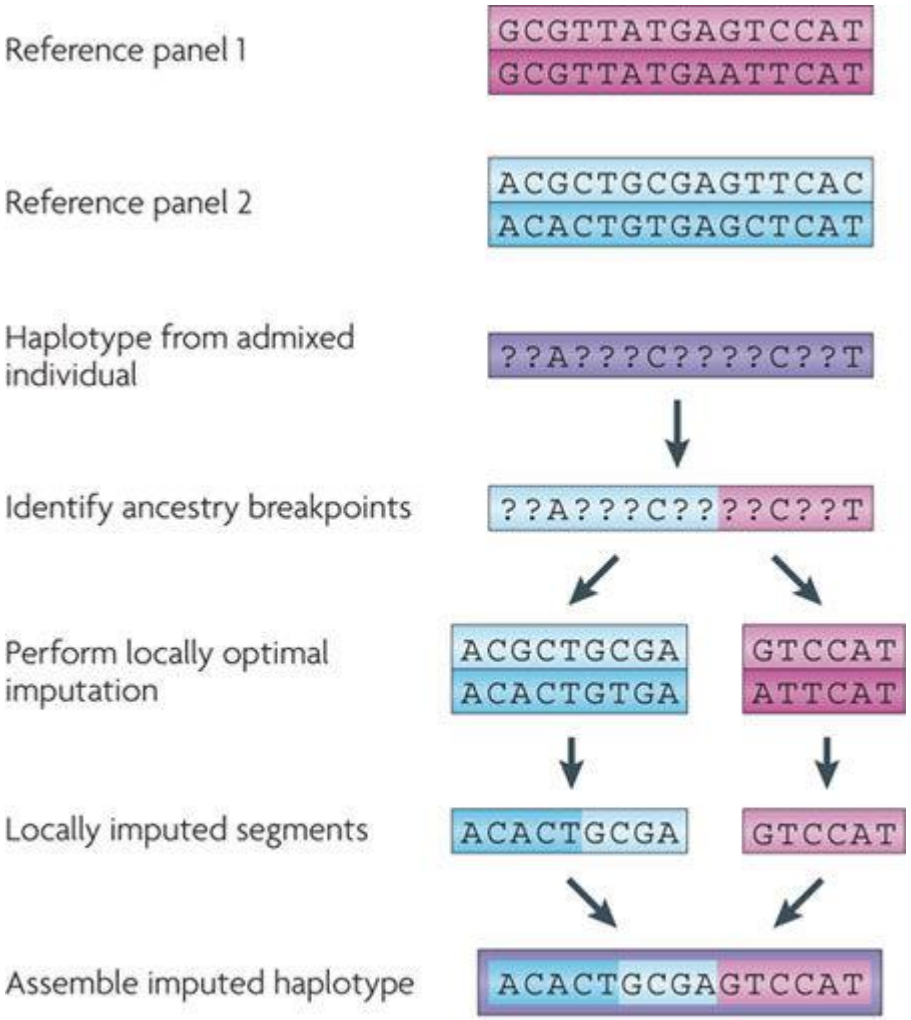
93 SNI
they
p<1×1



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