Precision Medicine (aka Genetics) Drives Drug Discovery R&D

Dr.Tim Harris

Definition of Precision Medicine

PCAST

"Referring to the tailoring of medical treatment to the individual characteristics of each patient in order to classify individuals into subpopulations that differ in their susceptibility to disease or their response to a specific treatment. Preventative or therapeutic strategies can be focused on those patients who will benefit, sparing expense and avoiding potential side effects in those who will not benefit."

That is to say:

- Precision medicine aims to redefine the taxonomy of human disease
- Novel targets are identified based on causal mechanisms
- Proof of biology trials will be enhanced using patients with dysregulation of a known causal target pathway
- Patients are selected using genetic, biological and imaging biomarkers
- Associations between genotype and phenotype are used to define target patient populations

Major Drivers for Patient Stratification

- Financial
  - The payers will not pay for drugs which do not work in many patients treated
  - Cheap diagnostic tests can save large numbers of dollars of unnecessary treatment
  - Will the situation with European payers be replicated in the USA ? (IQWIG,NICE)
- Science & Technology
  - Increasing awareness that it is possible to segment patients into disease subsets using genetics and other biomarkers for both efficacy and side effects
- Regulatory
  - Increasing intolerance to side effects in drugs with marginal efficacy in most patients
- Patient advocacy and interest groups
  - Physician disintermediation
  - Patients are increasingly aware of the medicines that are available to treat them through social networking and other media

A Data Intensive Vision for Patient Care

- All patients will have their genomes sequenced
- All clinical data collected on patients from symptoms, MRI, clinical records, drug use and effect and outcome will be captured in integrated data bases
- All biomarker data from each patient from gene expression to serum analytes will be in the data base(s)
- The information will be in the “electronic patient record”
- The data and information will be collated, integrated and analysed to draw conclusions about what is the best medicine for each patient based on others like them
- The cost effectiveness of each medicine will be part of this assessment

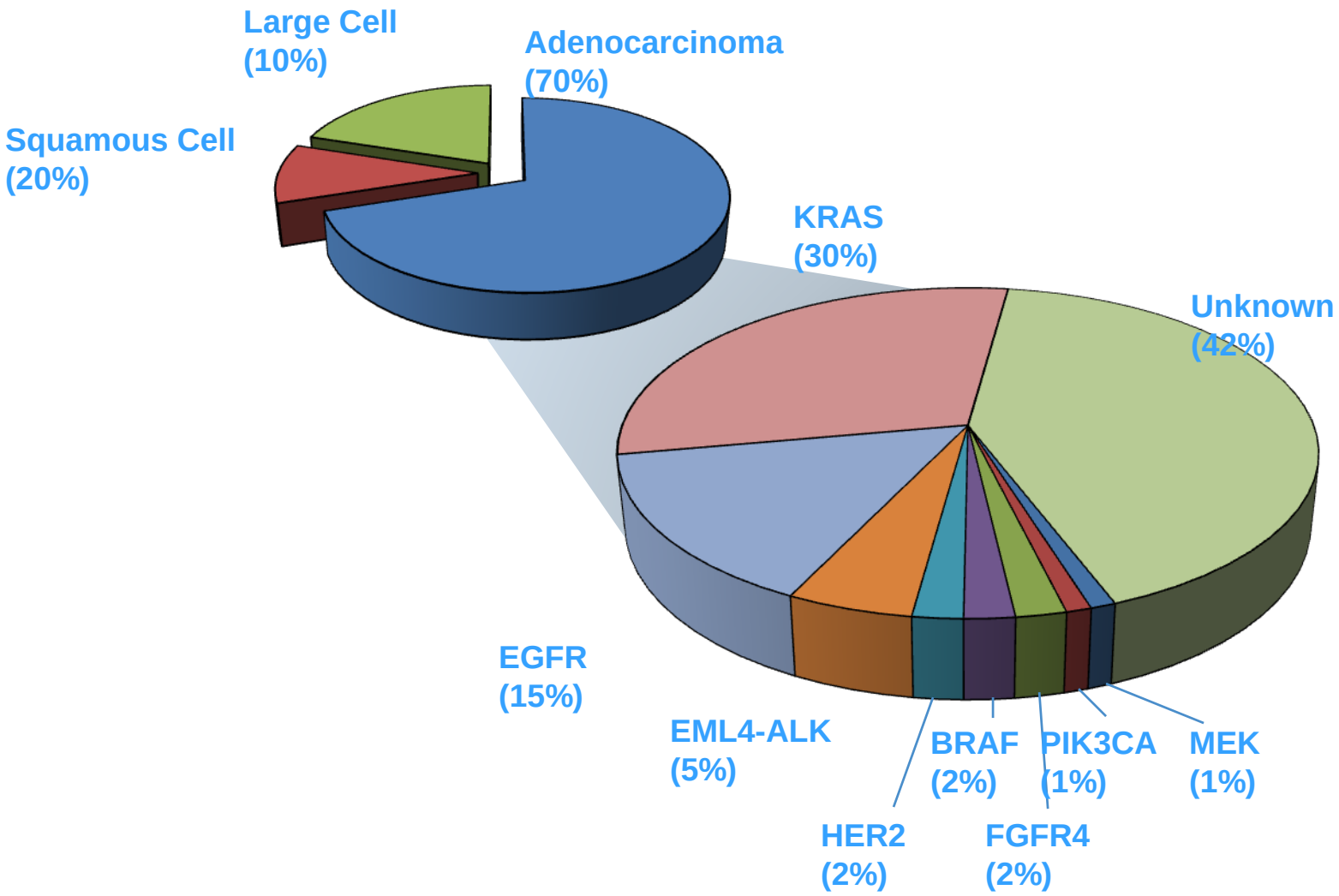
Disease Genetics

- Increasing interest in the Industry in genetically defined diseases
- Better understanding of the genes involved in causing or providing increased susceptibility to common diseases
- Whole genome and exome sequencing is helping to find both common and rare alleles of underlying disease genes
- Both germ line and somatic mutations (both new and old) are being discovered at a rapid rate
- The genetic cause of most diseases with Mendelian inheritance will be found within 3-5 years

Oncology is leading the Way

- Her2 and trastuzumab
- PDL1 immunohistochemistry: pembrolizumab (KEYTRUDA) and nivolumab (OPDIVO)
- Breast cancer management using gene expression analysis: Oncotype DX and Mammaprint, PAM 50
- EGFR mutations and EGFR kinase inhibitors
- KRAS mutations and use of anti-EGFR receptor antibodies
- Measuring mutations in multiple genes to determine best treatment in lung and other cancers
  - Bcr-Abl & Gleevec in CML
  - Eml4-Alk in NSCLC for crizotinib/ceretinib
  - BRCA1/PTEN (HR genes) and PARP inhibitors (olaparib)
  - BRAF V600E and vemurafinib
- Next step is to anticipate resistance and treat accordingly perhaps with drug combinations
- Analysis of both somatic cell and germ line mutations

Molecular Profiling in Lung Cancer



Personalised Drugs:Crizotinib & Vemurafinib

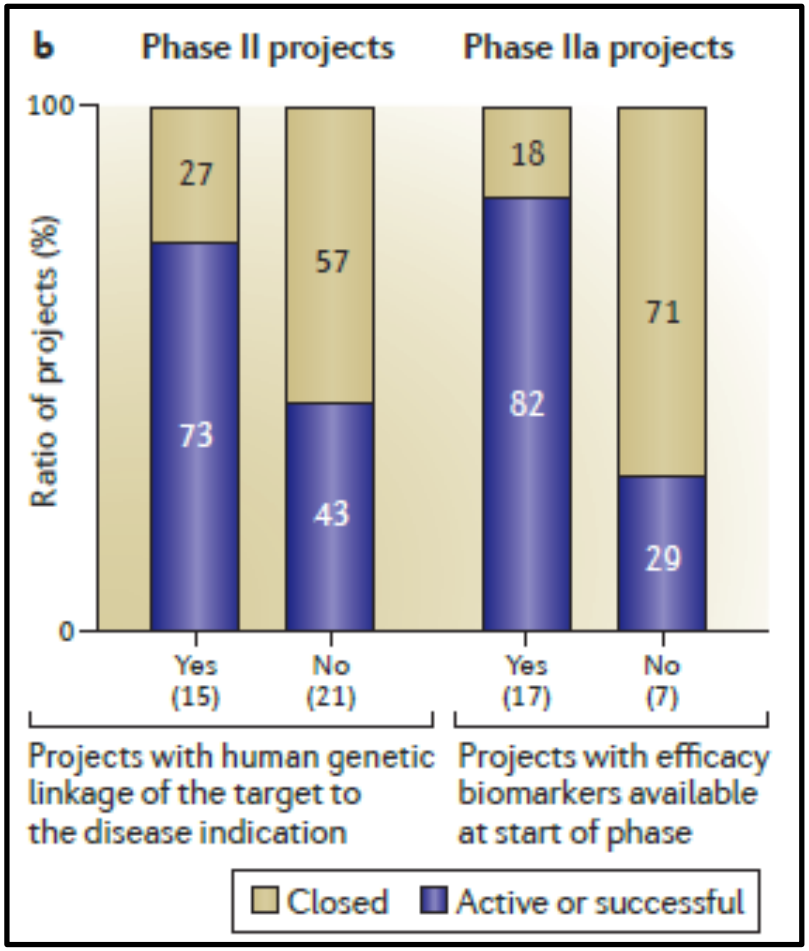
- FDA approved non-small cell lung cancer (NSCLC) drug Xalkori (crizotinib) and its companion anaplastic lymphoma kinase (ALK) FISH in October 2011
- Pfizer developed Xalkori, which was approved under the accelerated pathway for locally advanced or metastatic NSCLC in patients whose tumors are ALK-positive as determined by the FDA-approved test
- The drug is a dual inhibitor of c-Met receptor tyrosine kinase and ALK and their oncogenic variants
- The companion Vysis ALK Break Apart FISH Probe test from partner Abbott Labs uses fluorescence in situ hybridization technology (FISH) to detect translocations in genes encoding ALK
- The agency also approved the melanoma drug Zelboraf (vemurafenib) from Roche and its companion $BRAF^{V600E}$ mutation test
- This was the second time in nine days -- *and only the third time ever* -- that the FDA approved a drug simultaneously with a companion diagnostic

New Approaches to Single Gene Disorders

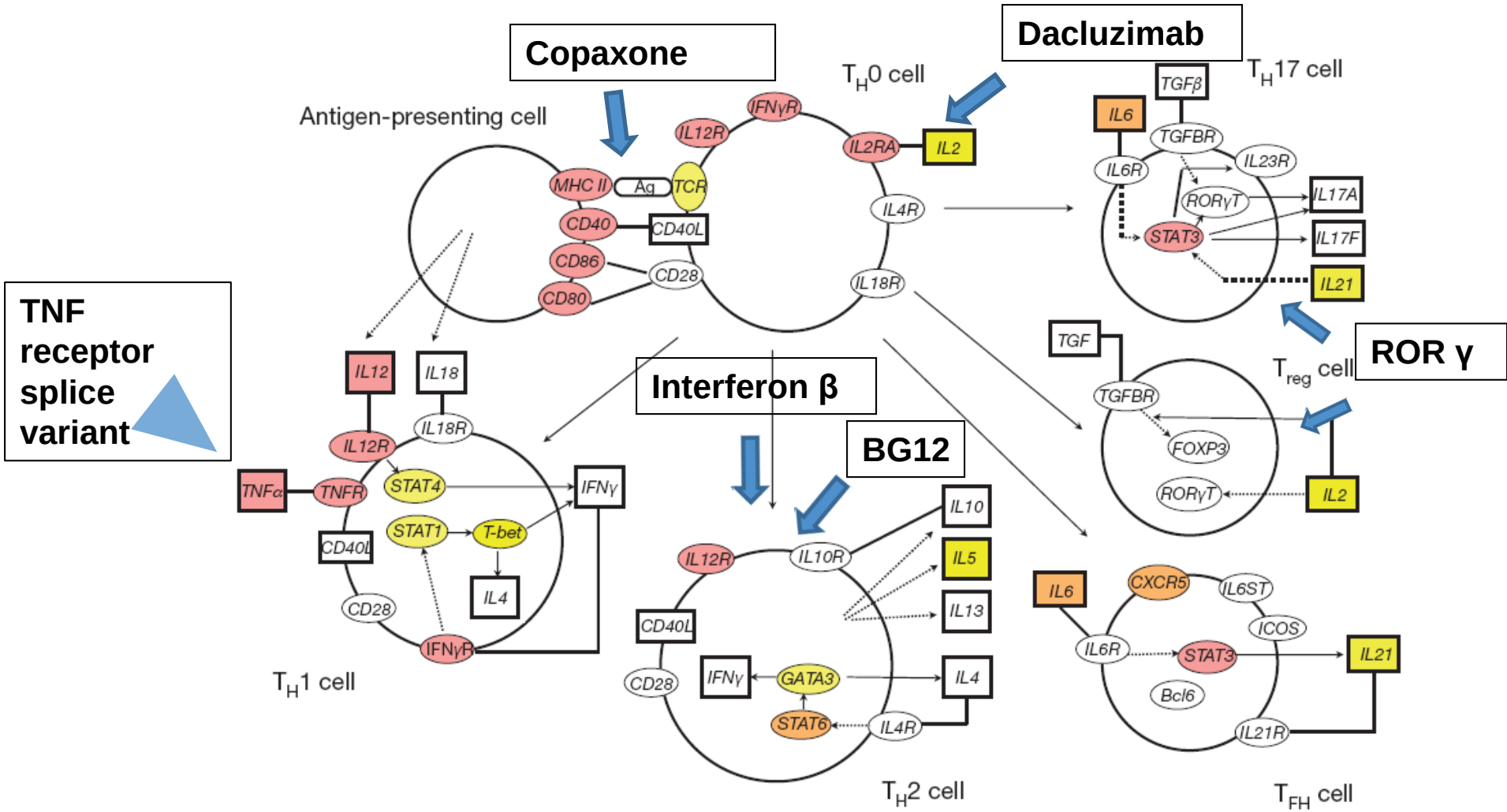
- CF caused by mutations in one gene : CFTR
  - Vertex compounds are directed to particular CFTR mutations (eg Kalydeco for G551D mutation and drug combinations for the Δ508 mutation
  - Ataluren for nonsense mutations in CFTR (PTC)
- Duchenne Muscular Dystrophy
  - Altering exon splicing by small molecules and ASOs (Prosensa, Sarepta etc)
- Haemophilia
  - Recessive X linked diseases
  - Biogen and others have developed long acting forms of Factor VIII and IX
  - Gene Therapy is coming
- Spinal muscular atrophy (Biogen/Ionis)
  - Exon splicing defect in SMN 2 gene targeted by splicing modifying ASO
- Myotonic Dystrophy (DM1) (Biogen/Ionis)
  - Autosomal dominant expanded repeat in DMPK1 gene
  - Target mRNA by ASO

Utility of Genetic Data in Drug Discovery

- Target ID and Validation: Genetic validation improves the likelihood of successful drug discovery at least 2 fold:
- Patient identification for Proof of Biology
- Stratification of patients into responders/non-responders
- Understanding and identifying rapidly progressing or relatively benign disease
- Pharmacogenomics/genetics and safety signals



GWAS for Common Alleles (MS)

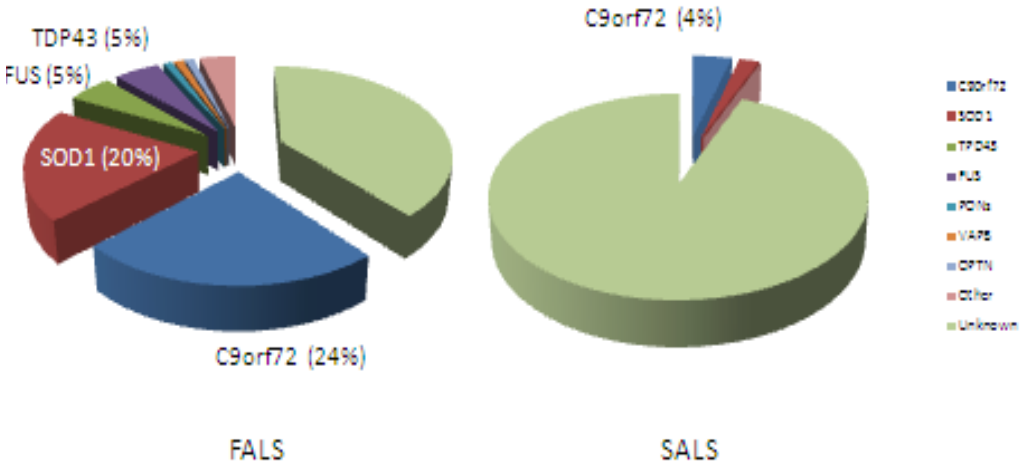


Graphic representation of theT-helper-cell differentiation pathway. Alphanumeric labels indicte the individual genes and gene complexes (nodes) included in the pathway. *Coloured nodes are those containing a gene implicated by proximity to an SNP showing evidence of association.*

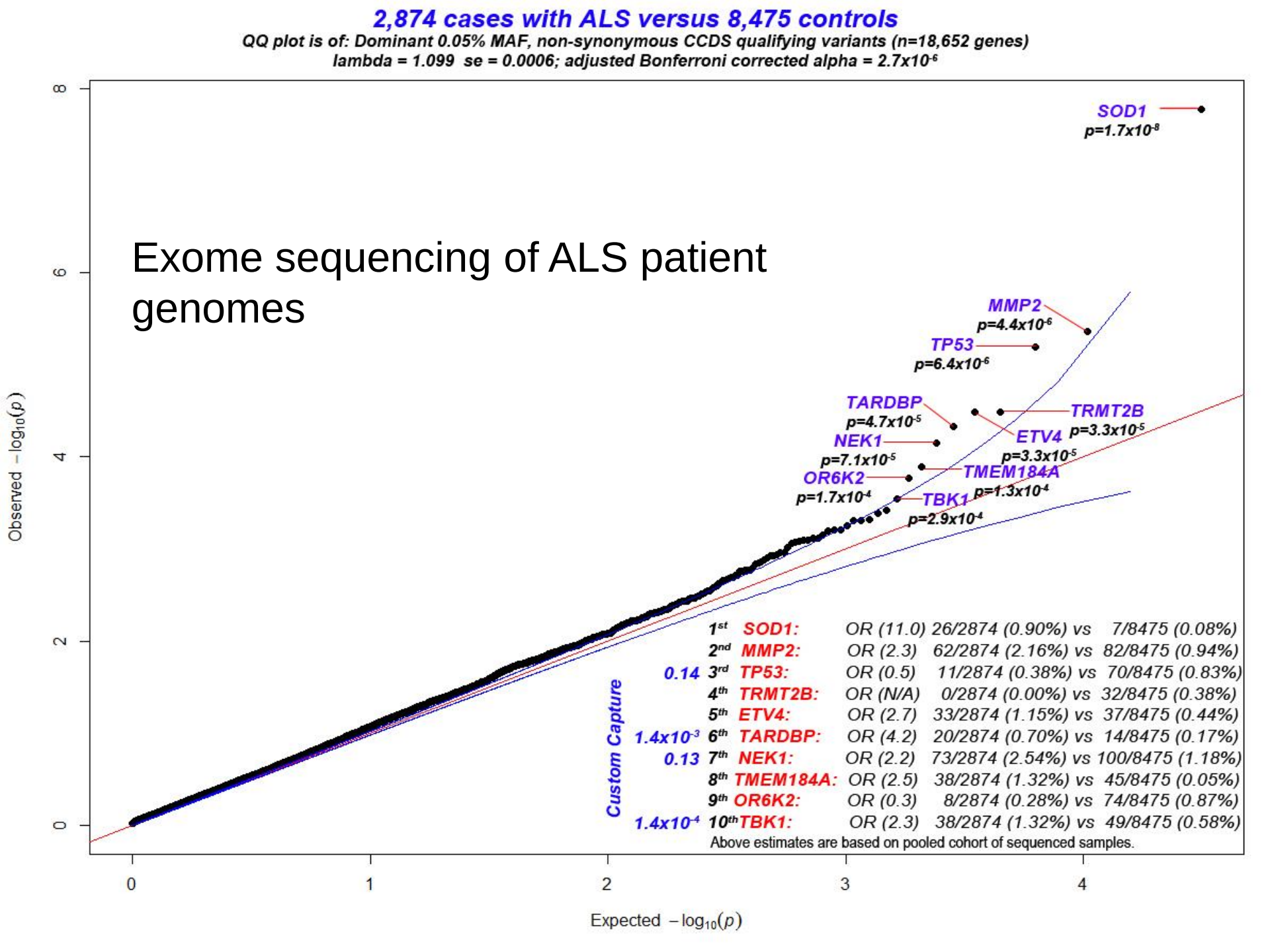
Rare alleles: ALS

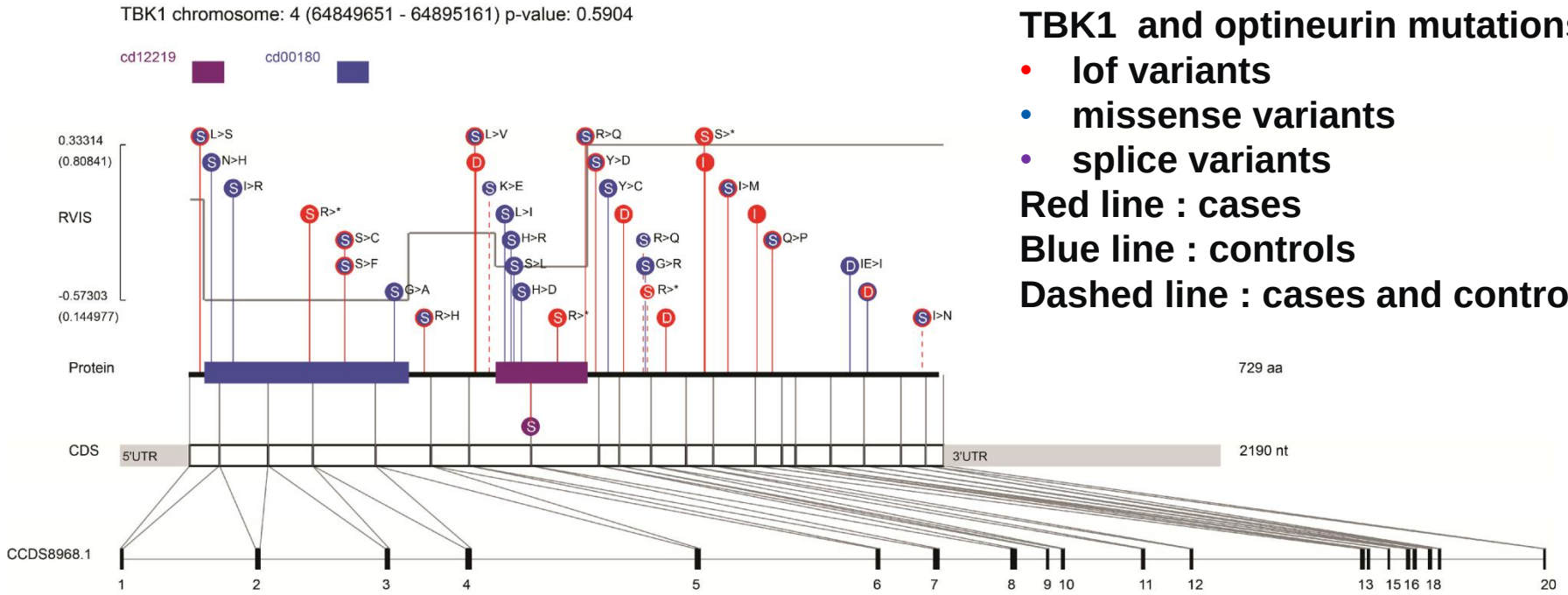
Amyotrophic Lateral Sclerosis				
23 genes (17 FALS, 6 SALS) 5 loci				
Familial (17)				*Sporadic (6)*
Genes				
ALS1	21q	SOD1		ANG
ALS2	2q	alsin		ELP3
ALS4	9q	senataxin		KIFAP3
ALS6	16q	FUS		CHGB
ALS8	20q	VAPB		UNC13A
ALS	10p	OPTN		Ataxin2
ALS	12q	d-amino oxidase		
ALS	19p	NTE		
ALS	1p	TDP-43		
ALS	2p	dynactin		
ALS	7q	PON1-3		
ALS	9q	VCP		
ALS	5q	SQSTM1p62		
ALS	X	ubiquilin 2		
ALS	9p	C9orf72		

The rate of gene discovery in ALS is increasing;
>50% of FALS is attributable to known variants.



More recent additions include mutations in profilin in a small number of FALS patients and CREST mutations in ALS trios


2,874 cases with ALS versus 8,475 controls
QQ plot is of: Dominant 0.05% MAF, non-synonymous CCDS qualifying variants (n=18,652 genes)
lambda = 1.099 se = 0.0006; adjusted Bonferroni corrected alpha = 2.7x10-6
Exome sequencing of ALS patient genomes
SOD1 p=1.7x10-8
MMP2 p=4.4x10-6
TP53 p=6.4x10-6
TARDBP p=4.7x10-5
TRMT2B p=3.3x10-5
NEK1 p=7.1x10-5
ETV4 p=3.3x10-5
OR6K2 p=1.7x10-4
TMEM184A p=1.3x10-4
TBK1 p=2.9x10-4
Custom Capture
0.14
1.4x10-3
0.13
1.4x10-4
1st SOD1: OR (11.0) 26/2874 (0.90%) vs 7/8475 (0.08%)
2nd MMP2: OR (2.3) 62/2874 (2.16%) vs 82/8475 (0.94%)
3rd TP53: OR (0.5) 11/2874 (0.38%) vs 70/8475 (0.83%)
4th TRMT2B: OR (N/A) 0/2874 (0.00%) vs 32/8475 (0.38%)
5th ETV4: OR (2.7) 33/2874 (1.15%) vs 37/8475 (0.44%)
6th TARDBP: OR (4.2) 20/2874 (0.70%) vs 14/8475 (0.17%)
7th NEK1: OR (2.2) 73/2874 (2.54%) vs 100/8475 (1.18%)
8th TMEM184A: OR (2.5) 38/2874 (1.32%) vs 45/8475 (0.05%)
9th OR6K2: OR (0.3) 8/2874 (0.28%) vs 74/8475 (0.87%)
10th TBK1: OR (2.3) 38/2874 (1.32%) vs 49/8475 (0.58%)
Above estimates are based on pooled cohort of sequenced samples.
Observed $-\log_{10}(p)$
Expected $-\log_{10}(p)$
0
1
2
3
4
0
2
4
6
8



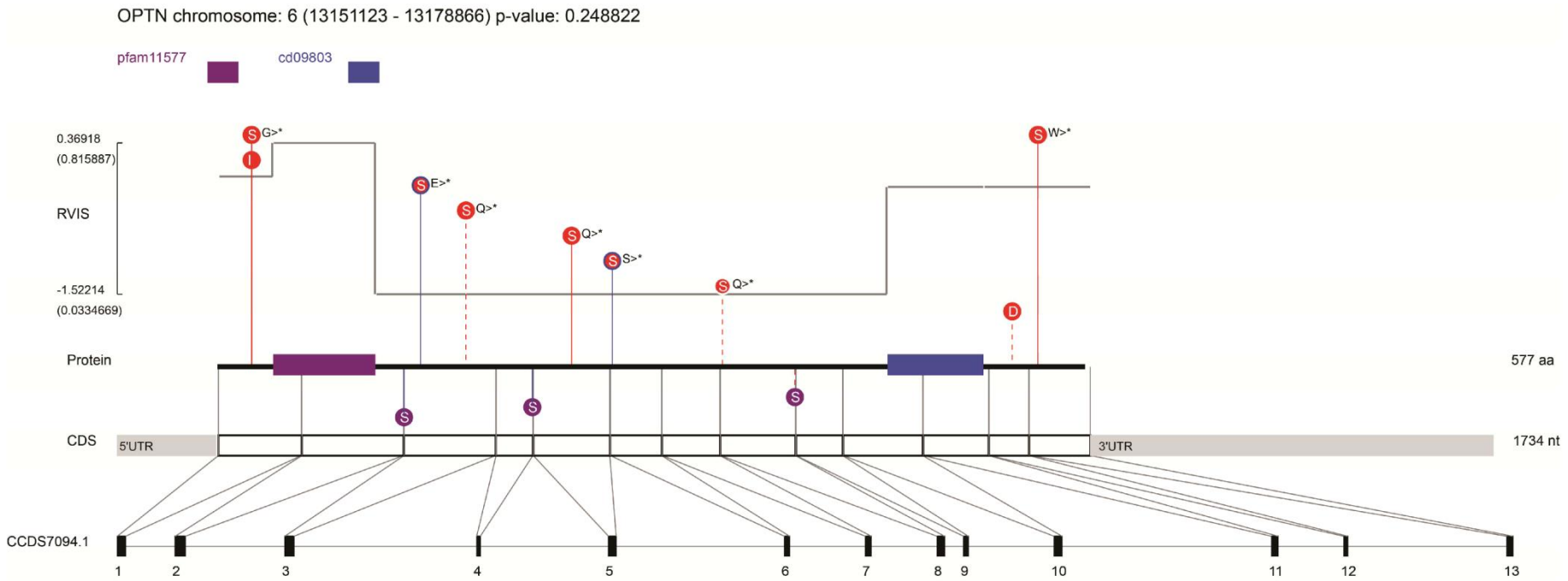
TBK1 and optineurin mutations

- lof variants
- missense variants
- splice variants

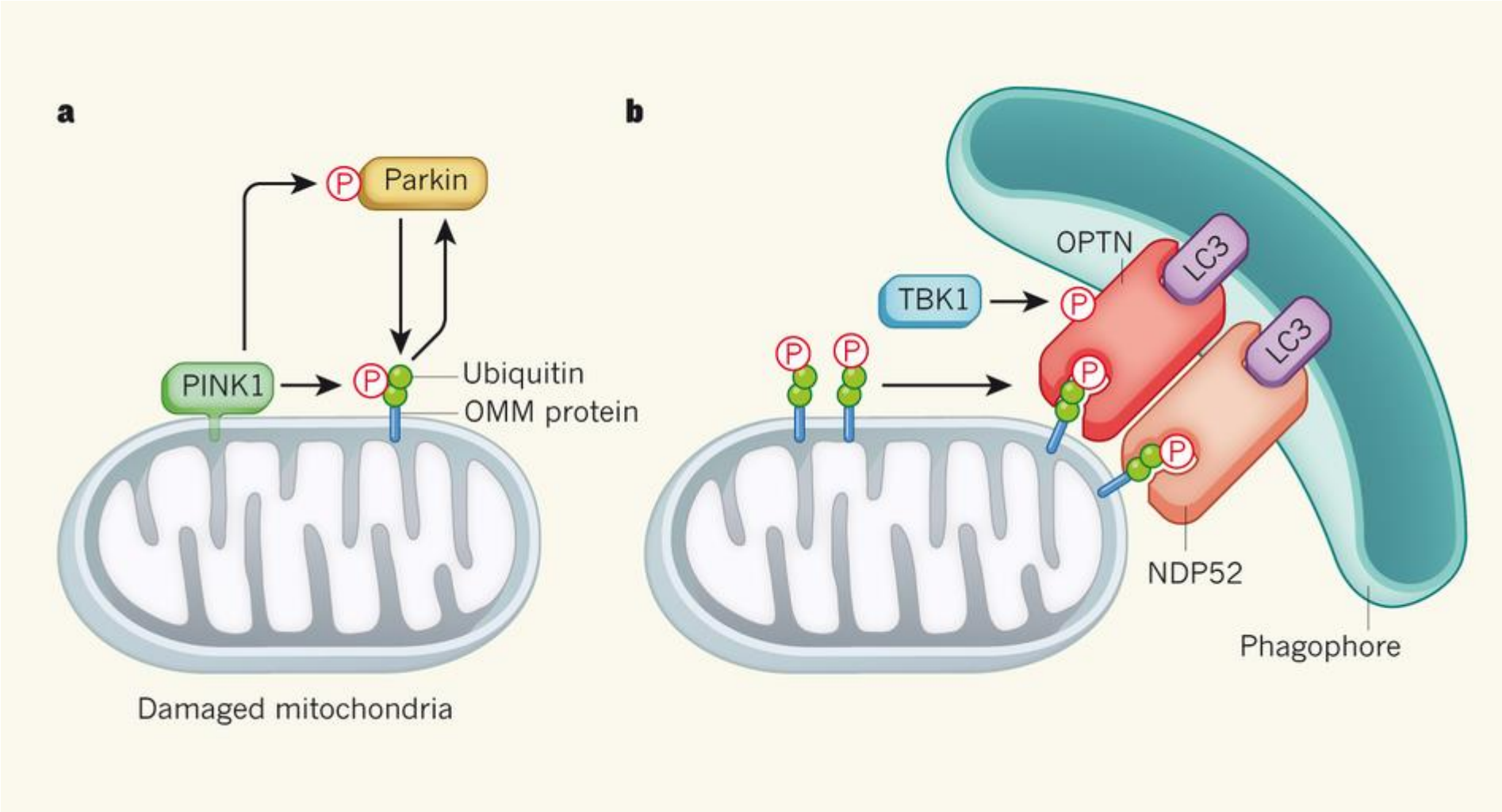
Red line : cases

Blue line : controls

Dashed line : cases and controls

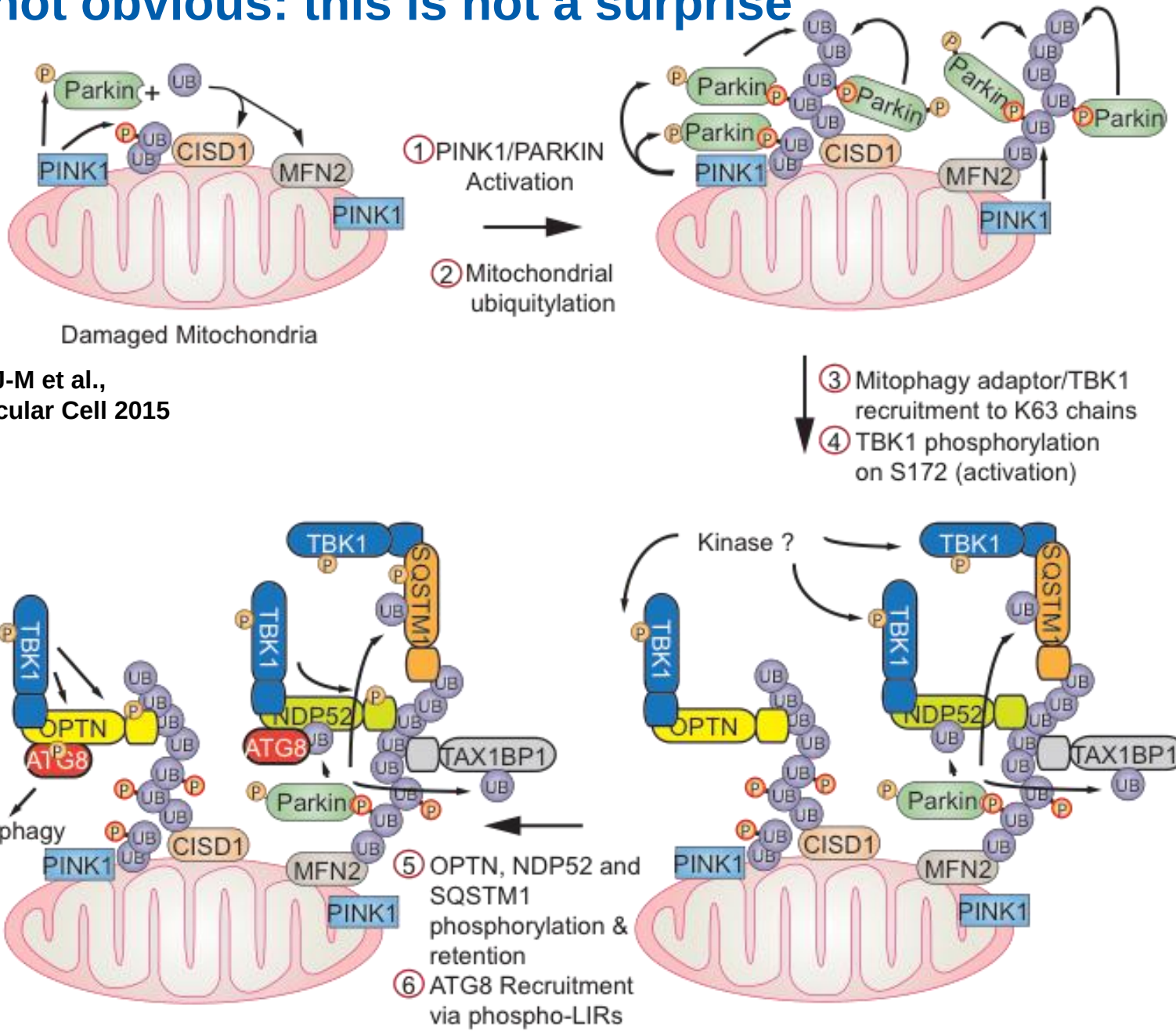


Simple Version of the Biology



PINK 1 and Parkin are genes known to be involved in Parkinson's disease

But it is more complicated and the drug discovery targets are not obvious: this is not a surprise



Heo,J-M et al.,
Molecular Cell 2015

Genetics of Parkinson's disease

- Like Alzheimer's Disease several genes are known to be involved in the familial forms of the disease
  - PARK;PINK;LRRK2, a-synuclein duplications and point mutations, GCase
- Understanding of the disease is coming from studying these mutations and the animal models derived from them
- Deriving iPS cells and reprogramming them to dopaminergic neurons is an important technology for translation
- Genetic methods could be used to select populations (eg GCase mutation carriers for agents targeted to α-syn)

Gaucher's Disease and PD

Gaucher's disease (GD) is an autosomal recessive disorder caused by mutations in the gene GBA-1 coding for the enzyme β glucocerebrosidase (GCase)

- Disease caused by loss of function mutations and treated by enzyme replacement therapy
- Type II and III GD have neurodegeneration

Analysis of GD carriers revealed a link between decreased GCase and increased risk of PD

- Loss of one GCase allele in Gaucher's disease carriers increases the risk of PD 5 fold
- Loss of GCase results in the accumulation of a-synuclein leading to aggregation and toxicity in dopaminergic neurons
- Observations confirmed in cellular and murine models of GD and PD

A Feedforward Loop Links Gaucher and Parkinson's Diseases?

Mark R. Cookson[1,*]
[1]Gene Expression Unit, Laboratory of Neurogenetics, National Institute on Aging, 35 Convent Drive, Bethesda, MD 20892-3707, USA
*Correspondence: cookson@mail.nih.gov
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Mutations in the *GBA* gene that encodes glucocerebrosidase cause the lysosomal storage disorder Gaucher disease but also increase the risk for Parkinson's disease. Mazzulli et al. (2011) uncover a possible mechanism to explain this connection: loss of glucocerebrosidase creates a positive feedback loop of reduced lysosomal function and α-synuclein accumulation, ultimately leading to neurodegeneration.

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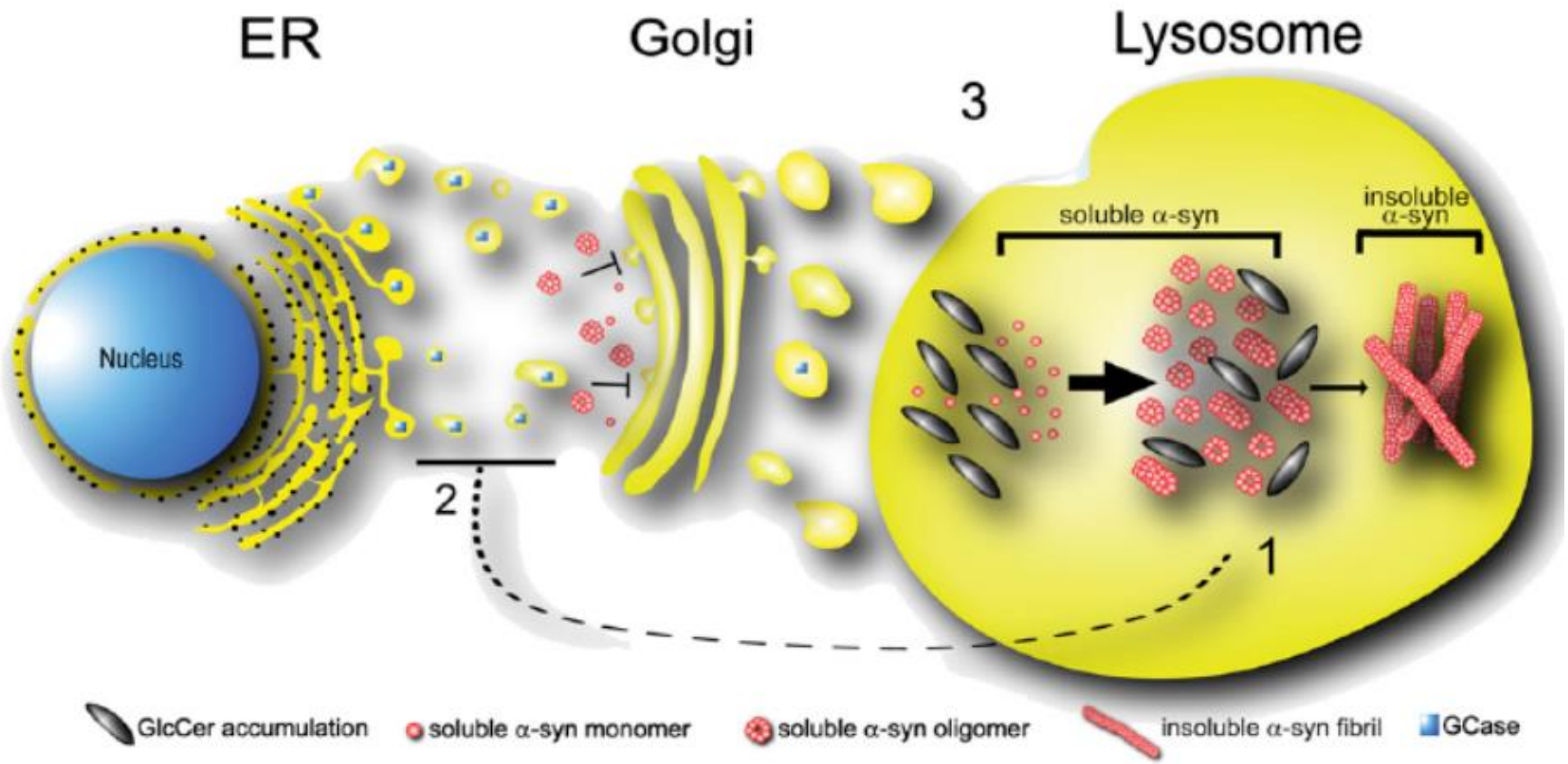
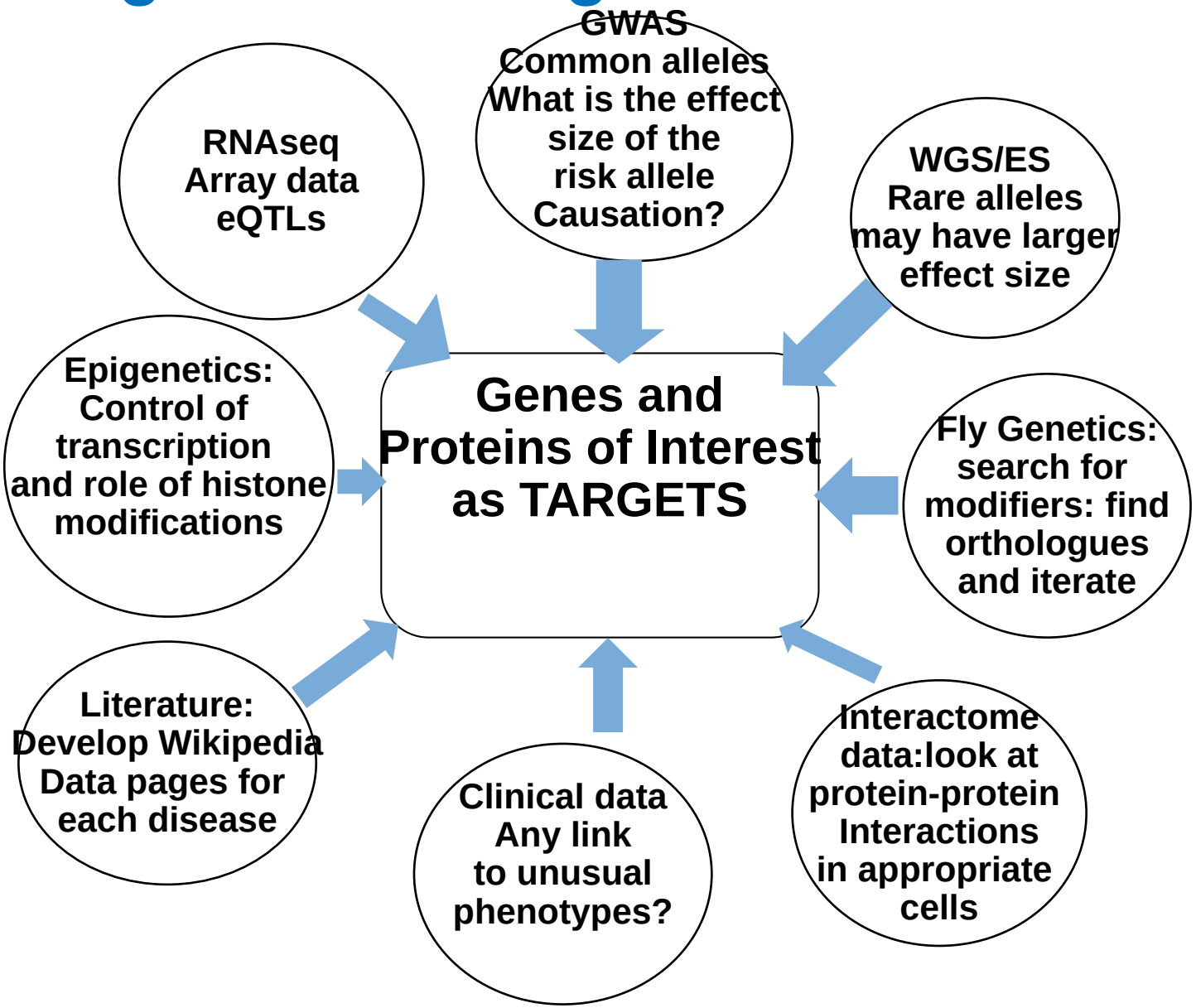


Disease genes are signposts to pathways affecting the molecular pathology of disease: sometimes they are targets in their own right

Integrate and triage the data



Find targets within pathways or consolidate targets into pathways

Conclusions

- Genetics and Genomics are driving drug discovery in 2016 and beyond
- Molecular pathology is being unraveled by using information derived from the genes known to be involved in the diseases
- Oncology leads the way but the same principles apply to neurological diseases such as ALS, PD, AD and MS
- Multiple drug modalities are needed to make the most of these discoveries:
  - Monoclonal antibodies
  - Small molecules
  - ASO’s
  - Gene Therapy