

The genetic basis of neurodegeneration

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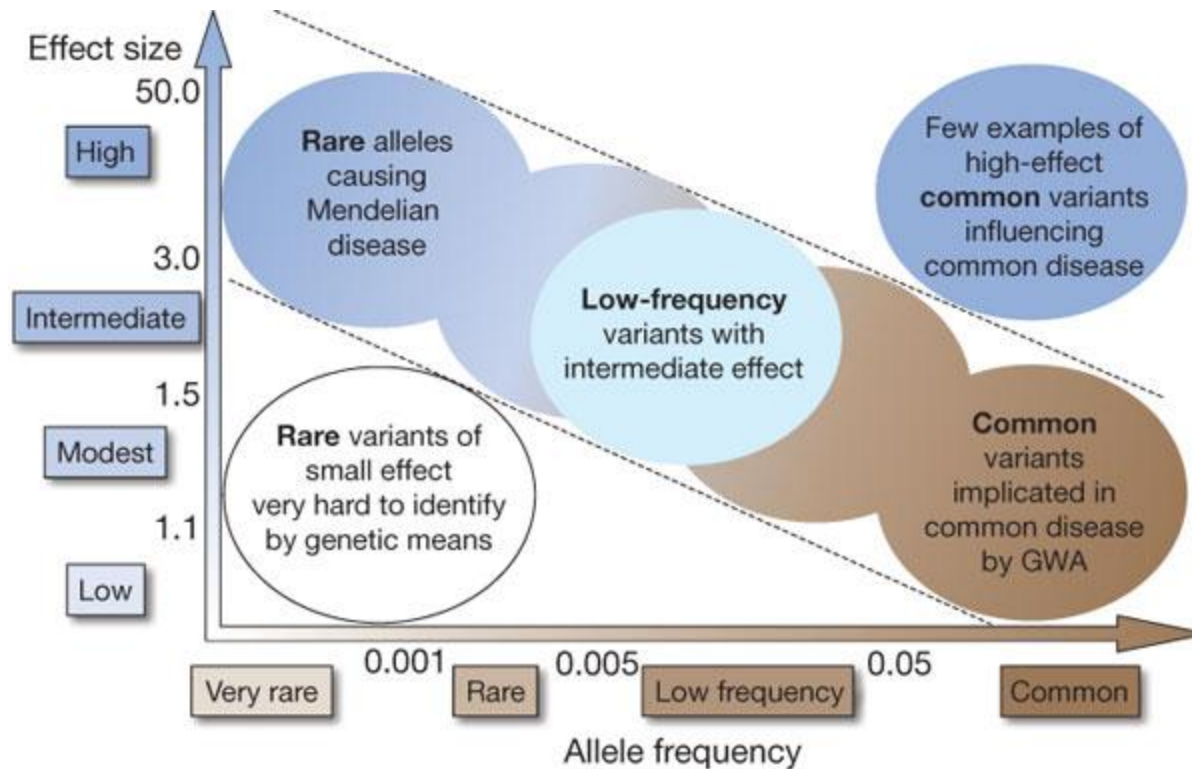


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Dissecting the genetic architecture of disease

- We have two aims:
 - 1) to develop statistical risk profiles for disease based on genetics
 - It is worth noting that, almost by definition, prediction can never be better than identical twins.
 - 2) to understand the pathways to pathogenesis
 - As we find risk genes, and map these to pathways, we will should be able to find other risk genes, out of those which do not quite achieve Bonnferroni significance

Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect (odds ratio).



TA Manolio *et al. Nature* **461**, 747-753 (2009) doi:10.1038/nature08494

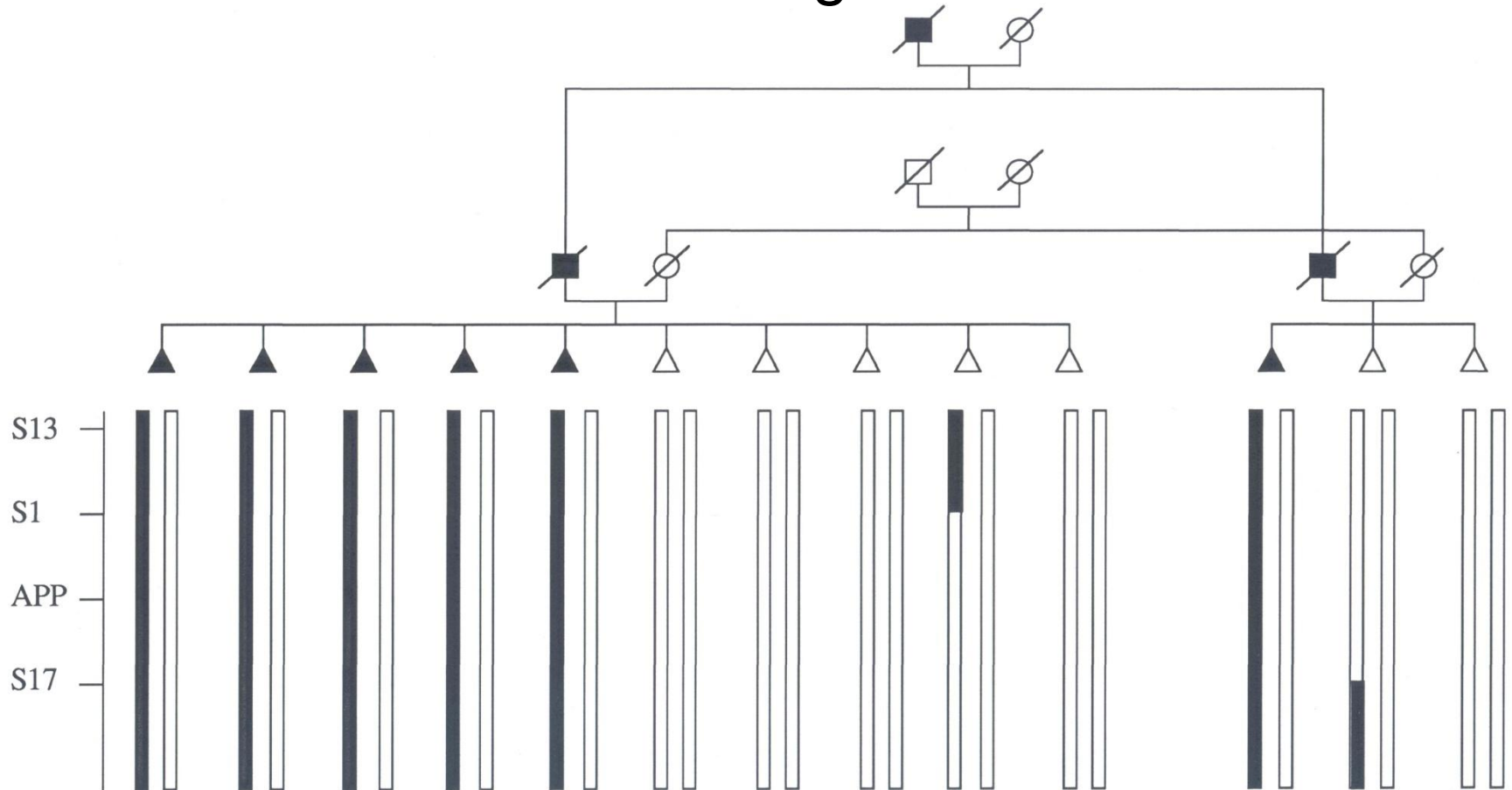
Processes

- Epilepsies
 - MS
 - CMT
 - Ataxia
 - MND
 - HSP
- Ionic balance
- Immune response
- Myelin integrity and axon interaction
- Ca homeostasis
- RNA processing
- Endosomal processing

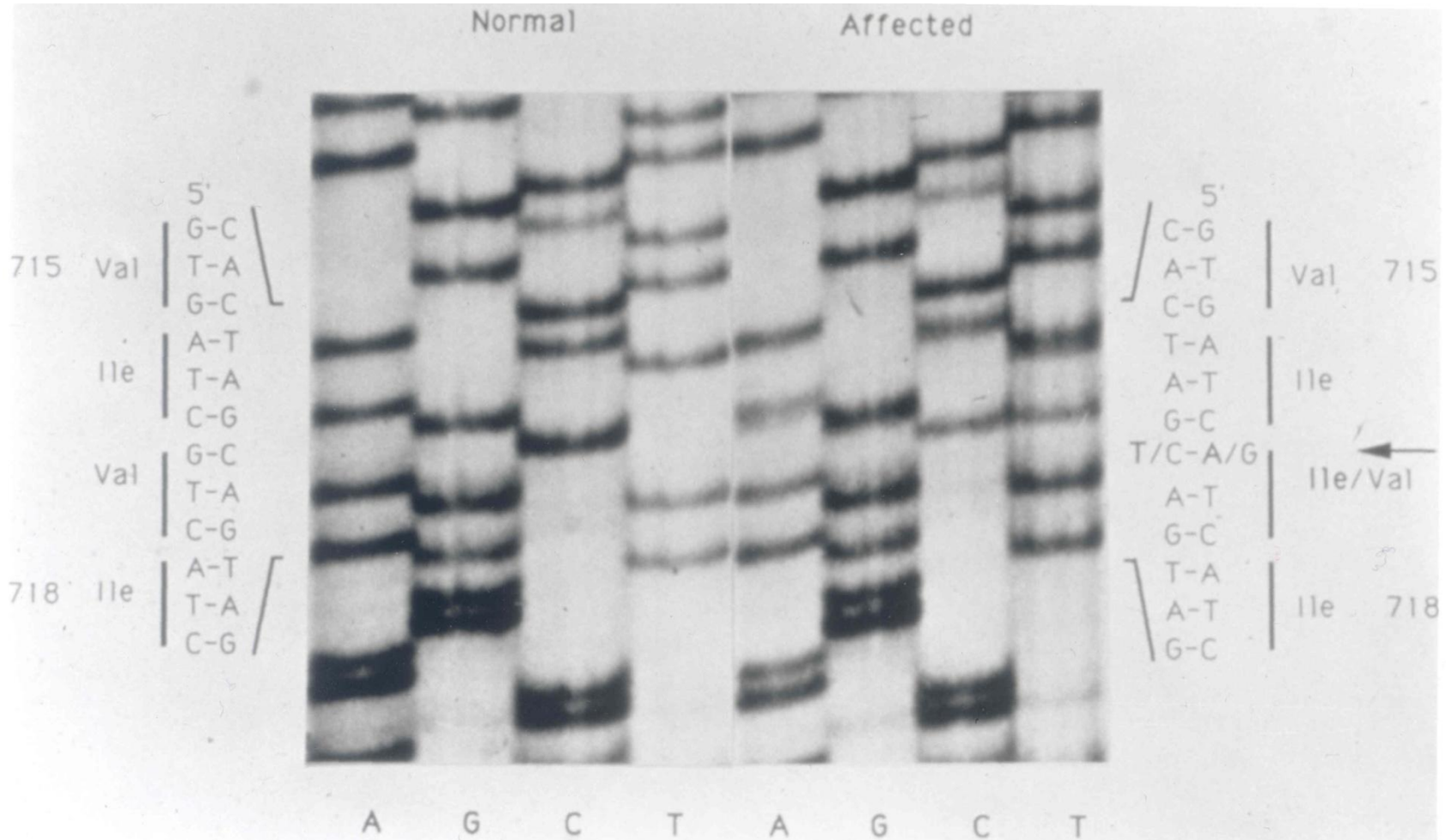
ALZHEIMER'S DISEASE

Mendelian Disease and GWAS (no exome data yet)

Recombination events in F23 localize the disease locus to a region between S1 and S17 that includes the APP gene



C/T mutation in exon 17 of APP in affected individual from F23 causes a Valine to Isoleucine substitution at codon 717



“It’s marvellous. In future it may be possible to prevent the disorder happening. While it will not help me. I hope it will help ...y children”
Carol Jennings, The Times, February 16th, 1991

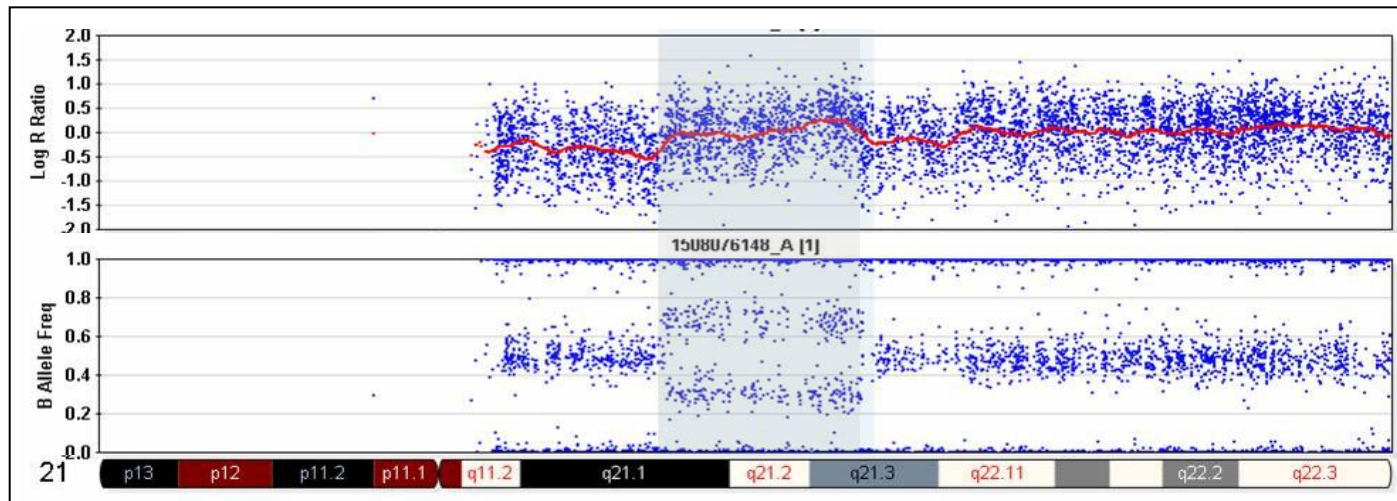
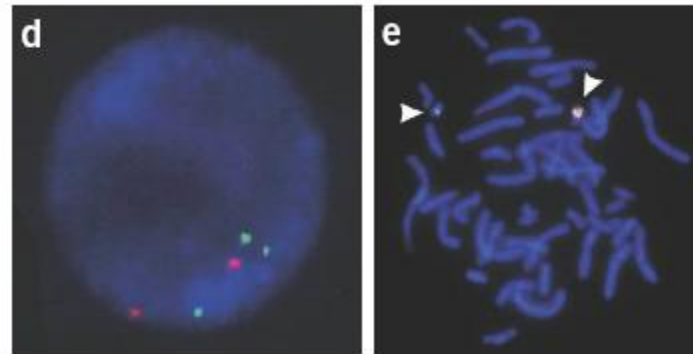


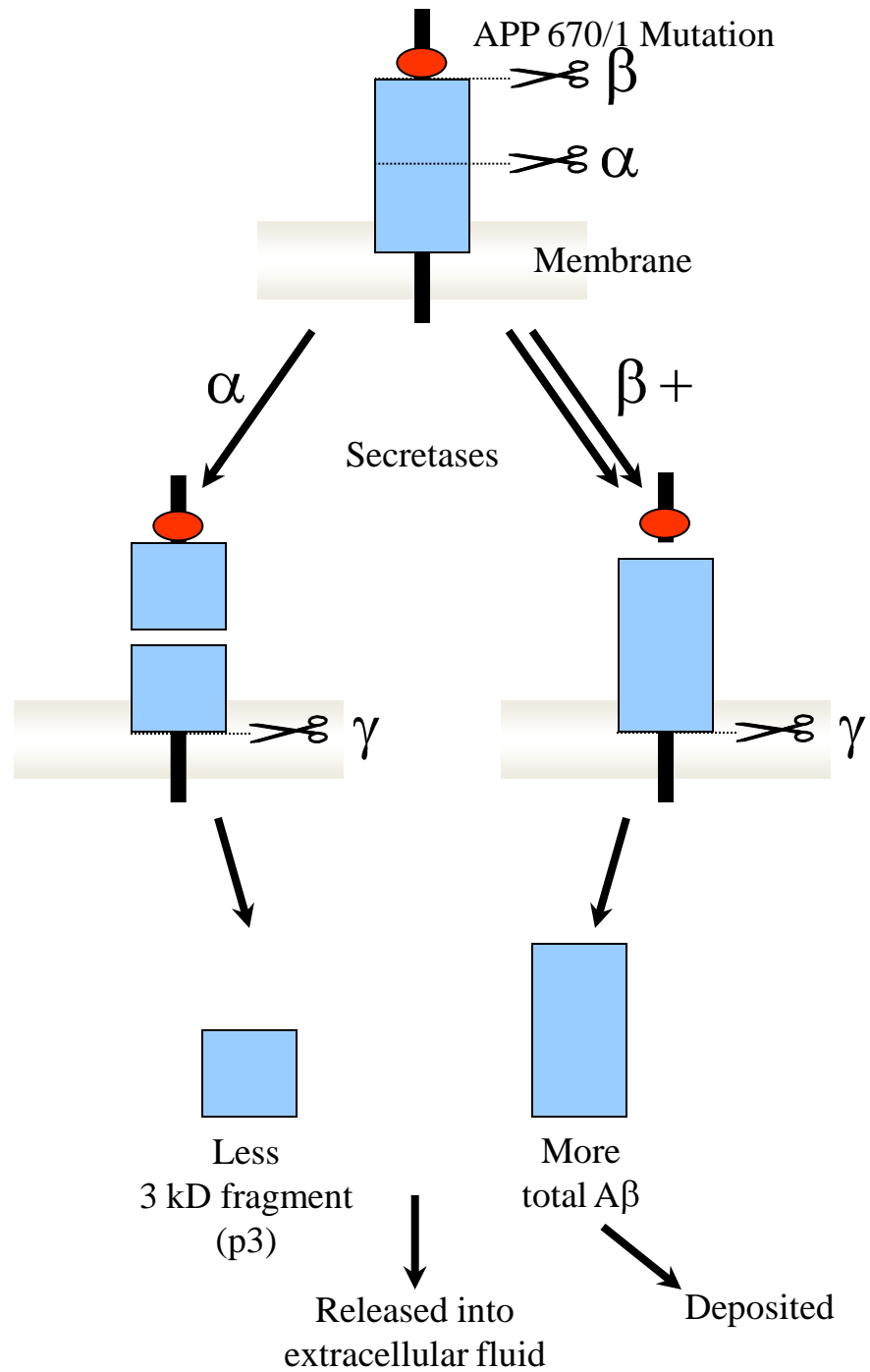
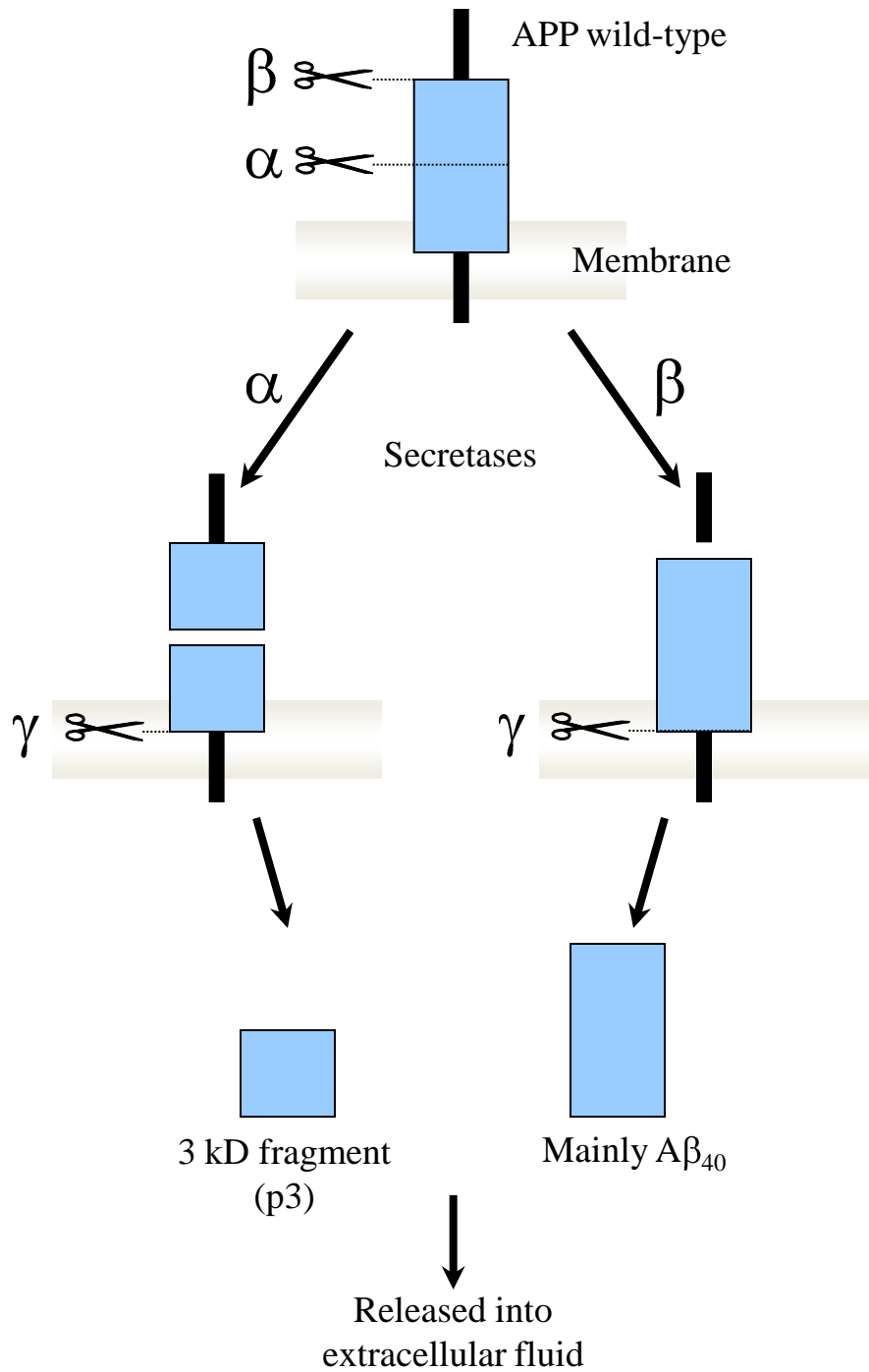
Carol Jennings and her children Emily and John who have been involved in research into Alzheimer's disease

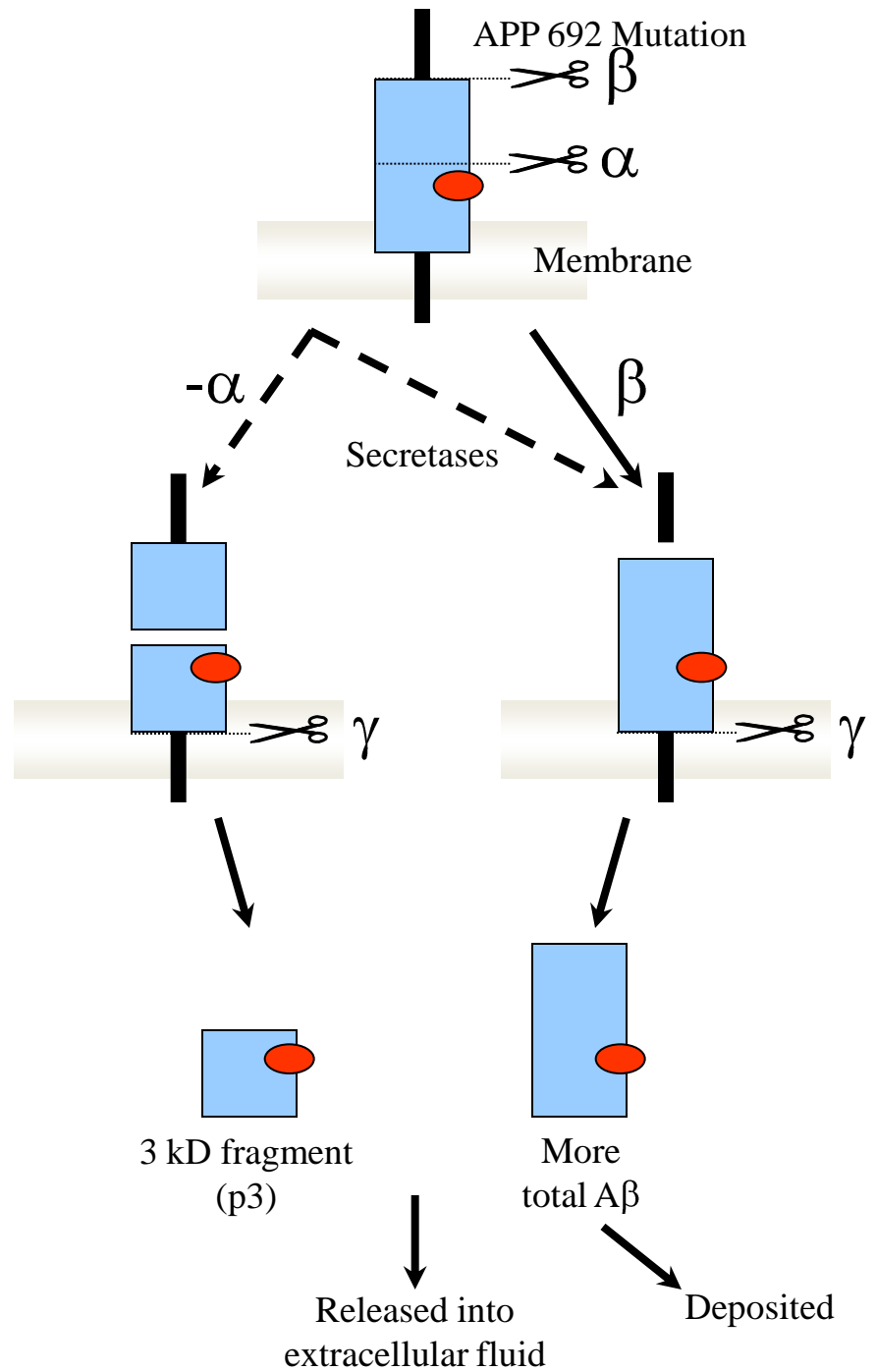
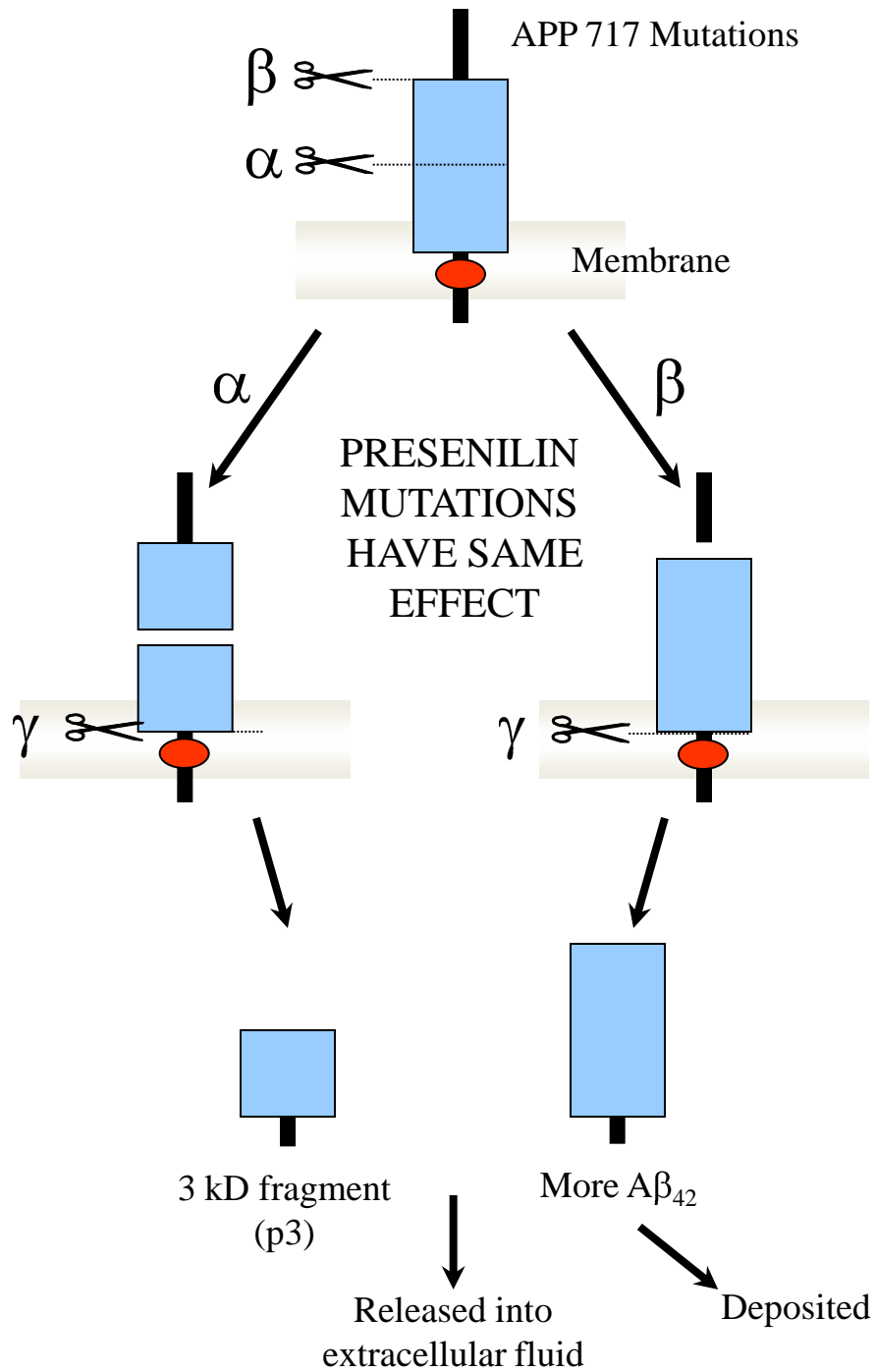
7Mb duplication of locus around APP

APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy

Anne Rovelet-Lecrux¹, Didier Hannequin^{1,2}, Gregory Raux¹, Nathalie Le Meur³, Annie Laquerrière⁴, Anne Vital⁵, Cécile Dumanchin¹, Sébastien Feuillette¹, Alexis Brice⁶, Martine Vercelletto⁷, Frédéric Dubas⁸, Thierry Frebourg¹ & Dominique Campion^{1,9}







Before Alzheimer GWAS

- Only APOE (identified as an A β binding protein by Strittmatter and Roses in 1994)
- Would other APP/A β metabolising proteins be found?

Alzheimer 2009-2011, 6000 cases

nature
genetics

nature
genetics

Genome-wide association study identifies variants at *CLU* and *PICALM* associated with Alzheimer's disease

Denise Harold^{1,4,5*}, Richard Abraham^{1,4,5}, Paul Hollingworth^{1,4,5}, Rebecca Sims¹, Amy Gerrish¹, Marian Hamshere¹, Jaspreet Singh Pahwa¹, Valentina Moskvina¹, Kimberley Dowzell¹, Amy Williams¹, Nicola Jones¹, Charlene Thomas¹, Alexandra Stretton¹, Angharad R Morgan¹, Simon Lovestone², John Powell³, Petroula Proitsi³, Michelle K Lupton³, Carol Brayne⁴, David C Rubinsztein⁵, Michael Gill⁶, Brian Lawlor⁶, Aoibhinn Lynch⁶, Kevin Morgan⁷, Kristelle S Brown⁷, Peter A Passmore⁸, David Craig⁸, Bernadette McGuinness⁸, Stephen Todd⁸, Clive Holmes⁹, David Mann¹⁰, A David Smith¹¹, Seth Love¹², Patrick G Kehoe¹², John Hardy¹³, Simon Mead¹⁴, Nick Fox¹⁵, Martin Rossor¹⁵, John Collinge¹⁴, Wolfgang Maier¹⁶, Frank Jessen¹⁶, Britta Schürmann¹⁶, Hendrik van den Bussche¹⁷, Isabella Heuser¹⁸, Johannes Kornhuber¹⁹, Jens Wiltfang²⁰, Martin Dichgans^{21,22}, Lutz Frölich²³, Harald Hampel^{24,25}, Michael Hüll²⁶, Dan Rujescu²⁵, Alison M Goate²⁷, John S K Kauwe²⁸, Carlos Cruchaga²⁷, Petra Nowotny²⁷, John C Morris²⁷, Kevin Mayo²⁷, Kristel Sleegers^{29,30}, Karolien Bettens^{29,30}, Sebastiaan Engelborghs^{30,31}, Peter De Deyn^{30,31}, Christine van Broeckhoven^{29,30}, Gill Livingston³², Nicholas J Bass³², Hugh Gurling³², Andrew McQuillin³², Rhian Gwilliam³³, Panagiotis Deloukas³³, Ammar Al-Chalabi³⁴, Christopher E Shaw³⁴, Magda Tsolaki³⁵, Andrew B Singleton³⁶, Rita Guerreiro³⁶, Thomas W Mühleisen^{37,38}, Markus M Nothen^{37,38}, Susanne Moebus³⁹, Karl-Heinz Jöckel³⁹, Norman Klopp⁴⁰, H-Erich Wichmann⁴⁰⁻⁴², Minerva M Carrasquillo⁴³, V Shane Pankratz⁴⁴, Steven G Younkin⁴³, Peter A Holmans¹, Michael O'Donovan¹, Michael J Owen¹ & Julie Williams¹

Genome-wide association study identifies variants at *CLU* and *CRI* associated with Alzheimer's disease

Jean-Charles Lambert¹⁻³, Simon Heath⁴, Gael Even^{1,2}, Dominique Campion⁵, Kristel Sleegers^{6,7}, Mikko Hiltunen⁸, Onofre Combarros⁹, Diana Zelenika⁴, Maria J Bullido¹⁰, Béatrice Tavernier¹¹, Luc Letenneur¹², Karolien Bettens^{6,7}, Claudine Berr¹³, Florence Pasquier^{3,14}, Nathalie Fiévet¹², Pascale Barberger-Gateau¹², Sebastiaan Engelborghs^{7,15}, Peter De Deyn^{7,15}, Ignacio Mateo⁹, Ana Franck¹⁶, Seppo Helisalmi⁸, Elisa Porcellini¹⁷, Olivier Hanon¹⁸, the European Alzheimer's Disease Initiative Investigators¹⁹, Marian M de Pancorbo²⁰, Corinne Lendon²¹, Carole Dufouil^{22,23}, Céline Jaillard²⁴, Thierry Leveillard²⁴, Victoria Alvarez²⁵, Paolo Bosco²⁶, Michelangelo Mancuso²⁷, Francesco Panza²⁸, Benedetta Nacmias²⁹, Paola Bossù³⁰, Paola Piccardi³¹, Giorgio Annoni³², Davide Seripa³³, Daniela Galimberti³⁴, Didier Hannequin⁵, Federico Licastro¹⁷, Hilka Soininen⁸, Karen Ritchie¹³, Hélène Blanché³⁵, Jean-François Dartigues¹², Christophe Tzourio^{22,23}, Ivo Gut⁴, Christine Van Broeckhoven^{6,7}, Annick Alperovitch^{22,23}, Mark Lathrop^{4,35} & Philippe Amouyel^{1-3,14}

LETTERS

nature
genetics

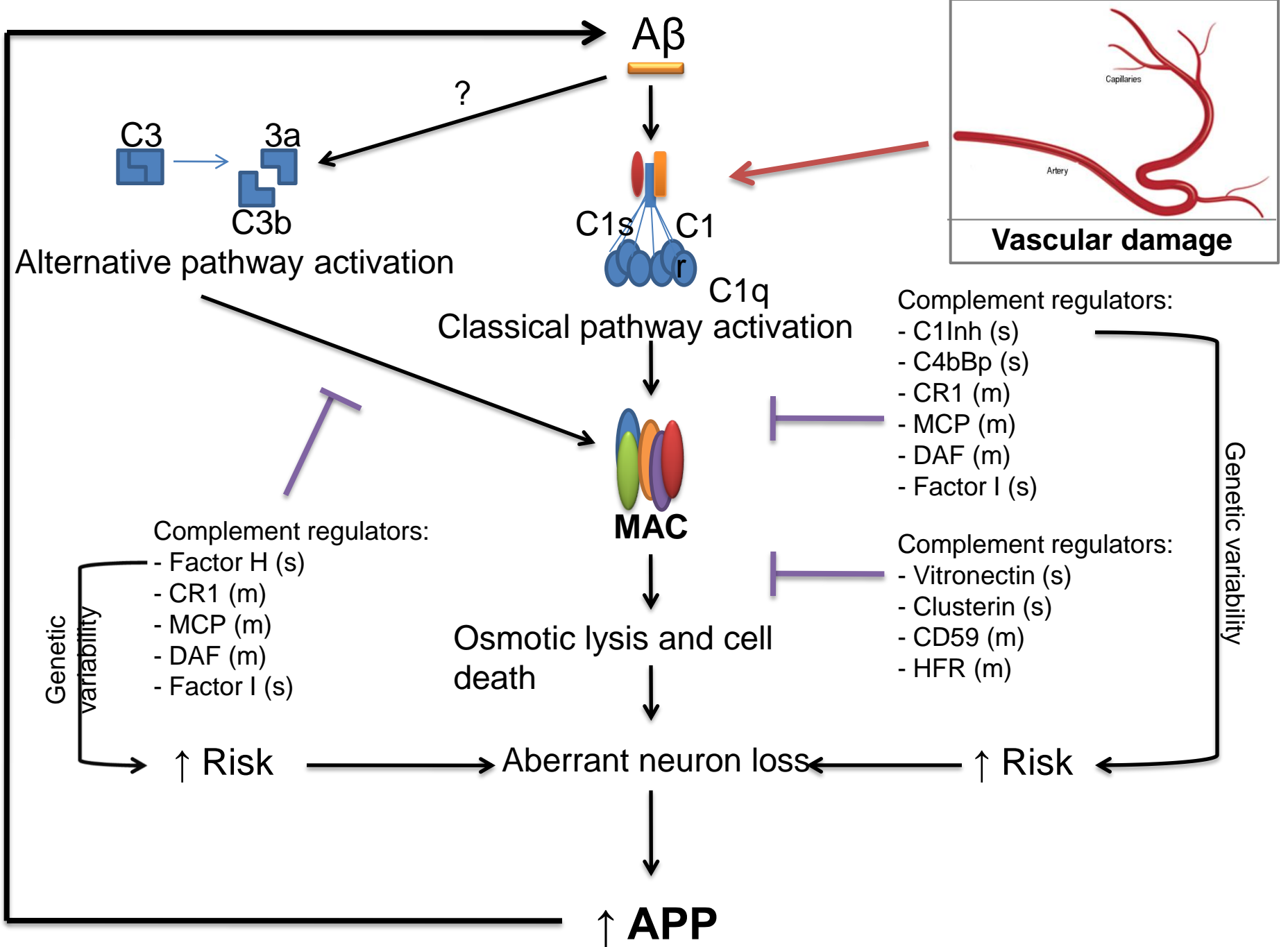
Common variants at *ABCA7*, *MS4A6A/MS4A4E*, *EPHA1*, *CD33* and *CD2AP* are associated with Alzheimer's disease

Risk Loci for Alzheimer's disease (~6,000 samples)

- Apolipoprotein E (~4) OR~4 cholesterol metabolism: coding and expression
- CLU (~1.2) OR~1.4 cholesterol metabolism: complement cascade: not coding, not simple expression
- PICALM (~1.1) (???) OR~1.4 endosomal vesicle recycling?: not coding
- ABCA7 (~1.1) OR~1.3 cholesterol metabolism: not known but Gly1527Ala is possible
- CR1 (~1.2) OR~1.4 complement cascade: very complicated: probably sequence and expression
- BIN1 (~1.1) OR~1.2 endosomal vesicle recycling?: not coding
- MS4A (~1.1) OR~1.2 (cell surface protein): not coding

Genetic Evidence Implicates the Immune System and Cholesterol Metabolism in the Aetiology of Alzheimer's Disease

Lesley Jones^{1,9}, Peter A. Holmans^{1,9}, Marian L. Hamshere¹, Denise Harold¹, Valentina Moskvina¹, Dobril Ivanov¹, Andrew Pocklington¹, Richard Abraham¹, Paul Hollingworth¹, Rebecca Sims¹, Amy Gerrish¹, Jaspreet Singh Pahwa¹, Nicola Jones¹, Alexandra Stretton¹, Angharad R. Morgan¹, Simon Lovestone², John Powell³, Petroula Proitsi³, Michelle K. Lupton³, Carol Brayne⁴, David C. Rubinsztein⁵, Michael Gill⁶, Brian Lawlor⁶, Aoibhinn Lynch⁶, Kevin Morgan⁷, Kristelle S. Brown⁷, Peter A Passmore⁸, David Craig⁸, Bernadette McGuinness⁸, Stephen Todd⁸, Clive Holmes⁹, David Mann¹⁰, A. David Smith¹¹, Seth Love¹², Patrick G. Kehoe¹², Simon Mead¹³, Nick Fox¹⁴, Martin Rossor¹⁴, John Collinge¹³, Wolfgang Maier¹⁵, Frank Jessen¹⁵, Britta Schürmann¹⁵, Hendrik van den Bussche¹⁶, Isabella Heuser¹⁶, Oliver Peters¹⁶, Johannes Kornhuber¹⁷, Jens Wiltfang¹⁸, Martin Dichgans^{19,20}, Lutz Frölich²¹, Harald Hampel^{22,23}, Michael Hüll²⁴, Dan Rujescu²³, Alison M Goate²⁵, John S. K. Kauwe²⁶, Carlos Cruchaga²⁵, Petra Nowotny²⁵, John C. Morris²⁵, Kevin Mayo²⁵, Gill Livingston²⁷, Nicholas J. Bass²⁷, Hugh Gurling²⁷, Andrew McQuillin²⁷, Rhian Gwilliam²⁸, Panos Deloukas²⁸, Ammar Al-Chalabi²⁹, Christopher E. Shaw²⁹, Andrew B. Singleton³⁰, Rita Guerreiro³⁰, Thomas W. Mühleisen^{31,32}, Markus M. Nöthen^{31,32}, Susanne Moebus³³, Karl-Heinz Jöckel³³, Norman Klopp³⁴, H.-Erich Wichmann³⁴⁻³⁶, Eckhard Rüther³⁷, Minerva M. Carrasquillo³⁸, V. Shane Pankratz³⁹, Steven G. Younkin³⁸, John Hardy⁴⁰, Michael C. O'Donovan¹, Michael J. Owen^{1*}, Julie Williams^{1*}



PARKINSON'S DISEASE

Mendelian Disease and GWAS (no exome data yet)

Glucocerebrosidase (GBA) as an example of a high risk rare variant

Mendelian Parkinson's Loci: one process or more?

LOCUS1	Inheritance	Onset	Protein	Path
PARK-1/4	AD	~45	SNCA	LB
PARK-2	AR	7-60	PKRN	None
PARK-6	AR	36-60	PINK-1	? one case with LB
PARK-7	AR	27-40	DJ-1	?
PARK-8	AD	45-57	LRRK2	Usually LB
PARK-9	AR	Teens	ATP13A2	?
PARK-14	AR	Teens	PLA2G6	LB
PARK-15	AR	Teens	FBXO7	?
PARK-17	AD	50-70	VPS35	?

All one pathway?

The Parkinson's disease protein DJ-1 is neuroprotective due to cysteine-sulfinic acid-driven mitochondrial localization

Rosa M. Canet-Avilés*, Mark A. Wilson†, David W. Miller*, Rili Ahmad*, Chris McLendon*, Sourav Bandyopadhyay*, Melisa J. Baptista*, Dagmar Ringe†, Gregory A. Petsko†, and Mark R. Cookson**

*Laboratory of Neurogenetics, National Institute on Aging, 9000 Rockville Pike, Bethesda, MD 20892-1589; and †Department of Biochemistry and Rosenstiel Basic Medical Sciences Research Center, Brandeis University, 415 South Street MS 029, Waltham, MA 02454-9110

Contributed by Gregory A. Petsko, April 27, 2004

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Drosophila pink1* is required for mitochondrial function and interacts genetically with *parkin

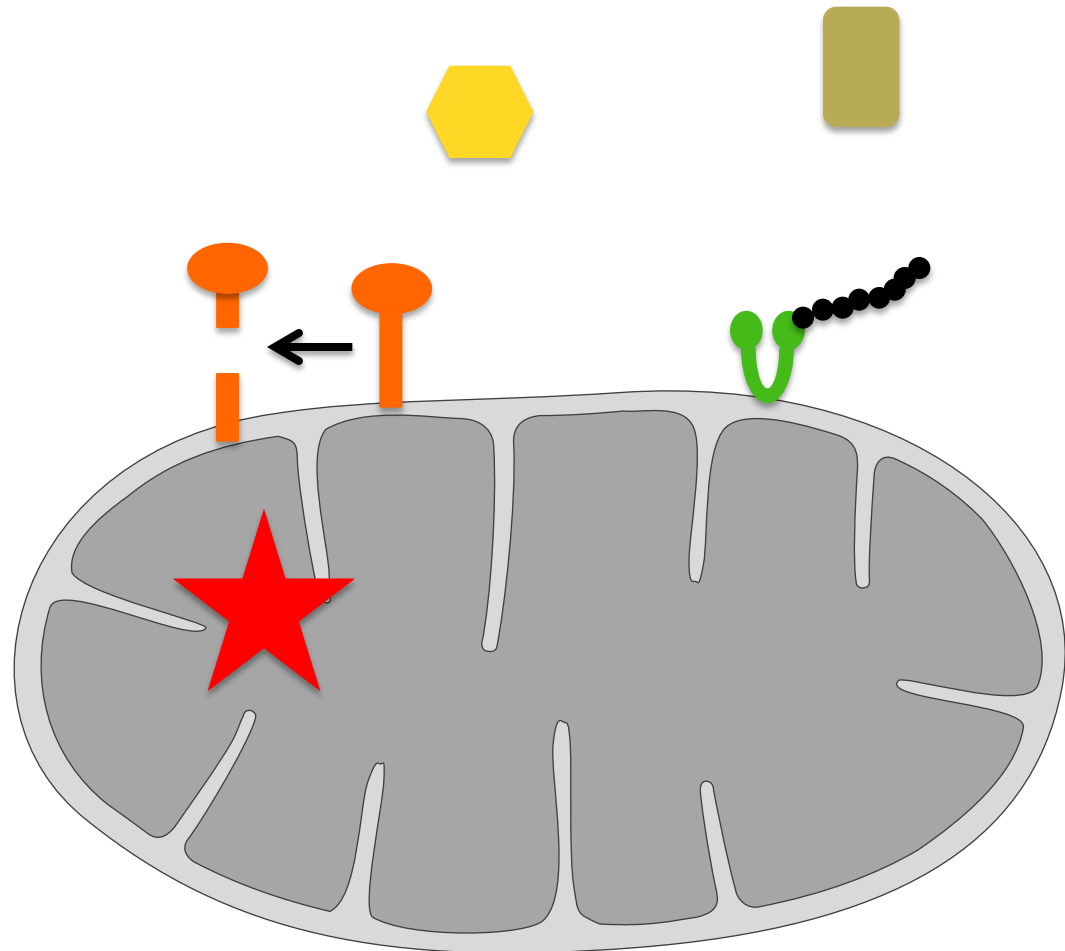
Ira E. Clark^{1*}, Mark W. Dodson^{1*}, Changan Jiang^{1*}, Joseph H. Cao¹, Jun R. Huh², Jae Hong Seol³, Soon Ji Yoo⁴, Bruce A. Hay² & Ming Guo¹

LETTERS

Mitochondrial dysfunction in *Drosophila PINK1* mutants is complemented by *parkin*

Jeehye Park^{1,2*}, Sung Bae Lee^{1,2*}, Sungkyu Lee^{1,2}, Yongsung Kim^{1,2}, Saera Song^{1,2}, Sunhong Kim^{1,2}, Eunkyung Bae³, Jaeseob Kim^{2,3}, Minho Shong⁴, Jin-Man Kim⁵ & Jongkyeong Chung^{1,2}

Fbxo7 and Parkin interact to mediate Parkin recruitment to mitochondria, Mfn ubiquitination and subsequent mitophagy

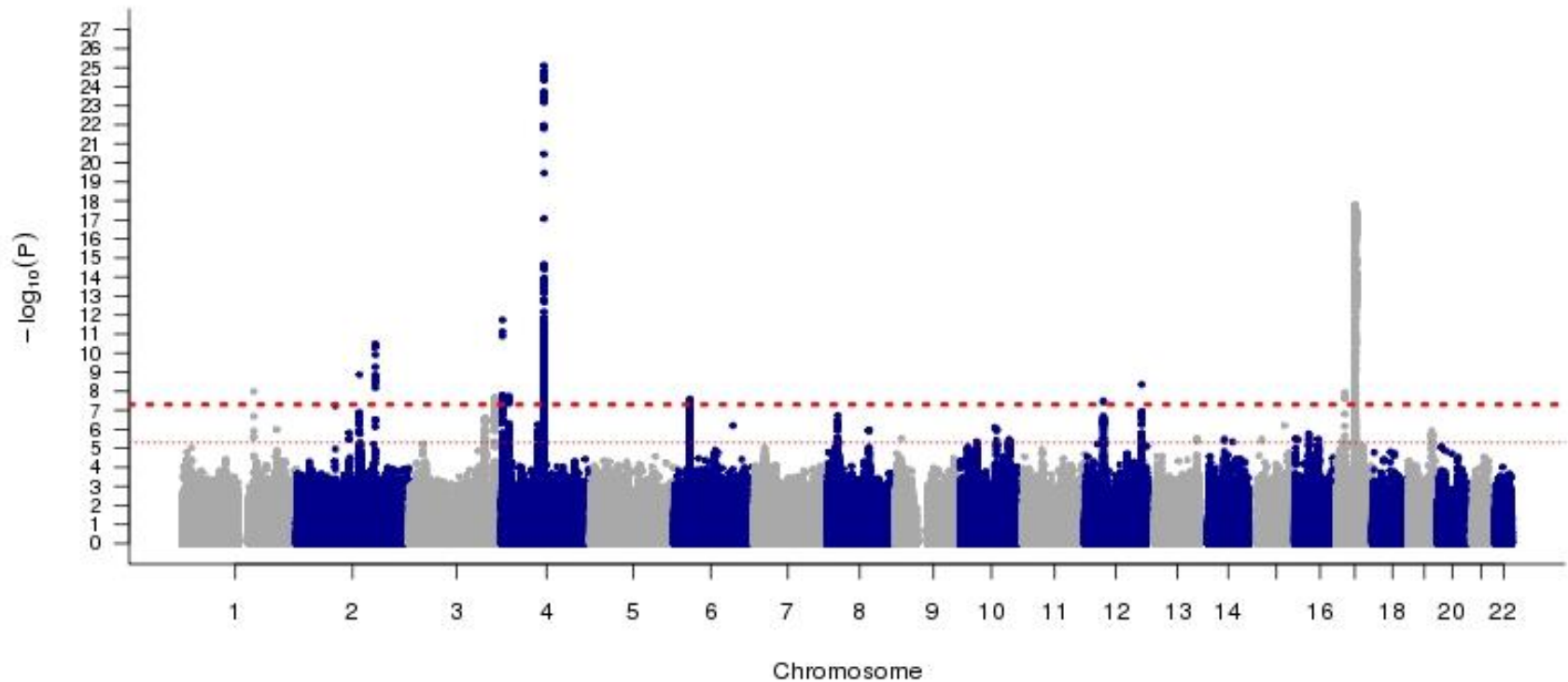


One pathway to parkinsonism

- Involves PINK1, PKRN, FBXO7 (DJ-1?)
- The mutations hamper the removal of damaged mitochondria
- In fly, muscle is susceptible, in humans, the nigra (perhaps DA metabolism is damaging?)
- Is this relevant to idiopathic PD?

Parkinson's Genome Wide Association Study

PD-code meta-analysis 01.13.2009, lambda = 1.035441



PD GWAs


D-10-08326R1

S0140-6736(10)62345-8

Funded by Wellcome Trust

Articles

LW

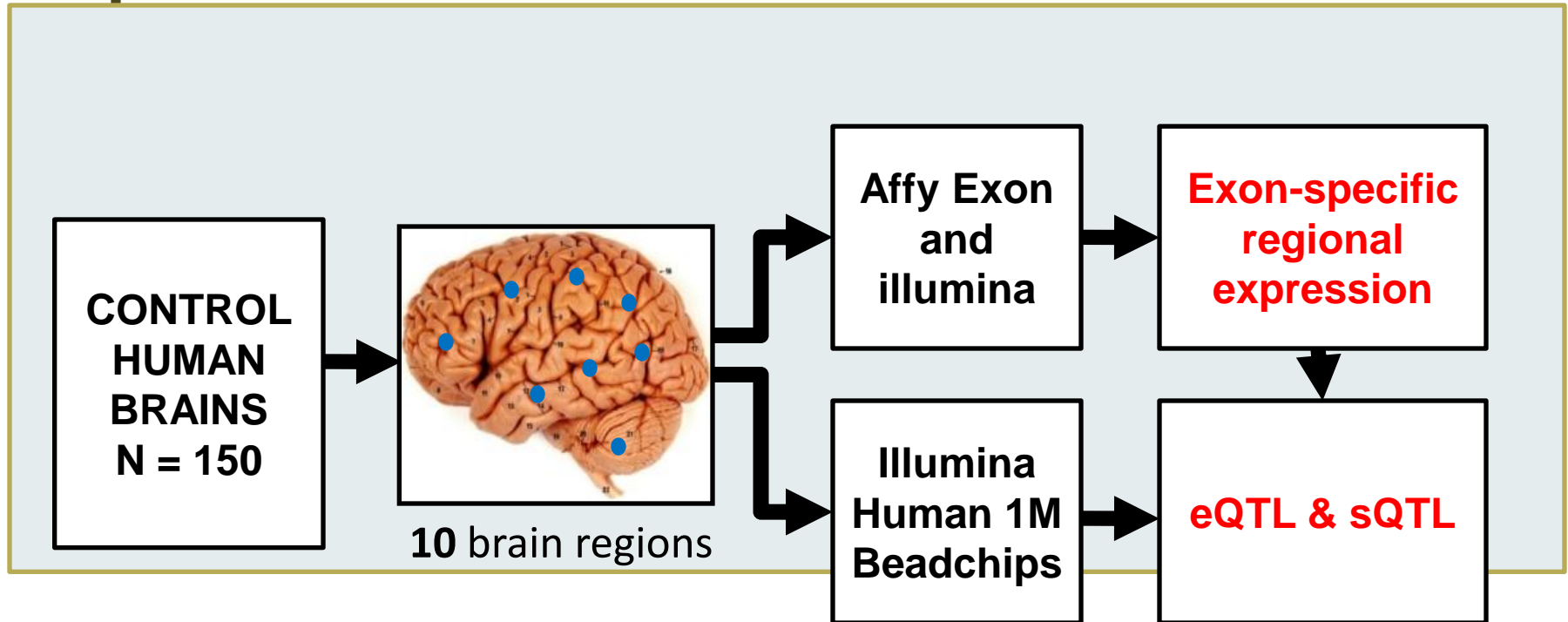
Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies 

*International Parkinson Disease Genomics Consortium**

Building a brain expression database

- UCL collection (Edinburgh and Sun Health) 140 brains X 10 brain regions
- NIH (Singleton/Cookson) collection (Maryland and other brain banks) 300 X 4 brain regions
- All genotyped on Illumina arrays. All have expression on Illumina arrays. UCL has expression on Affy exon arrays

Experimental Plan



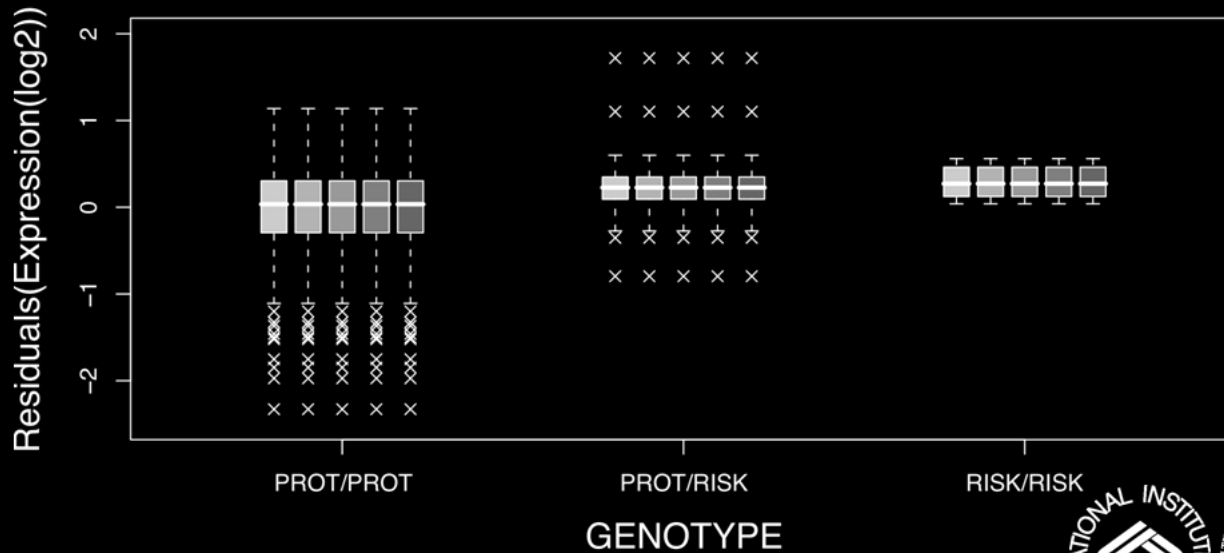
- Hypothalamus
- Occipital cortex (BA 17)
- Frontal cortex (BA 8 & 9)
- Hippocampus
- Medulla (inf. olivary nucleus)

- Top of spinal chord
- Cerebellar cortex
- Putamen
- Substantia nigra
- Intralobular white matter

SNCA



Cerebellum, SNCA112 eQTL



Laboratory of Neurogenetics, National Institute on Aging



Frequency

high



low



non-coding protective variants

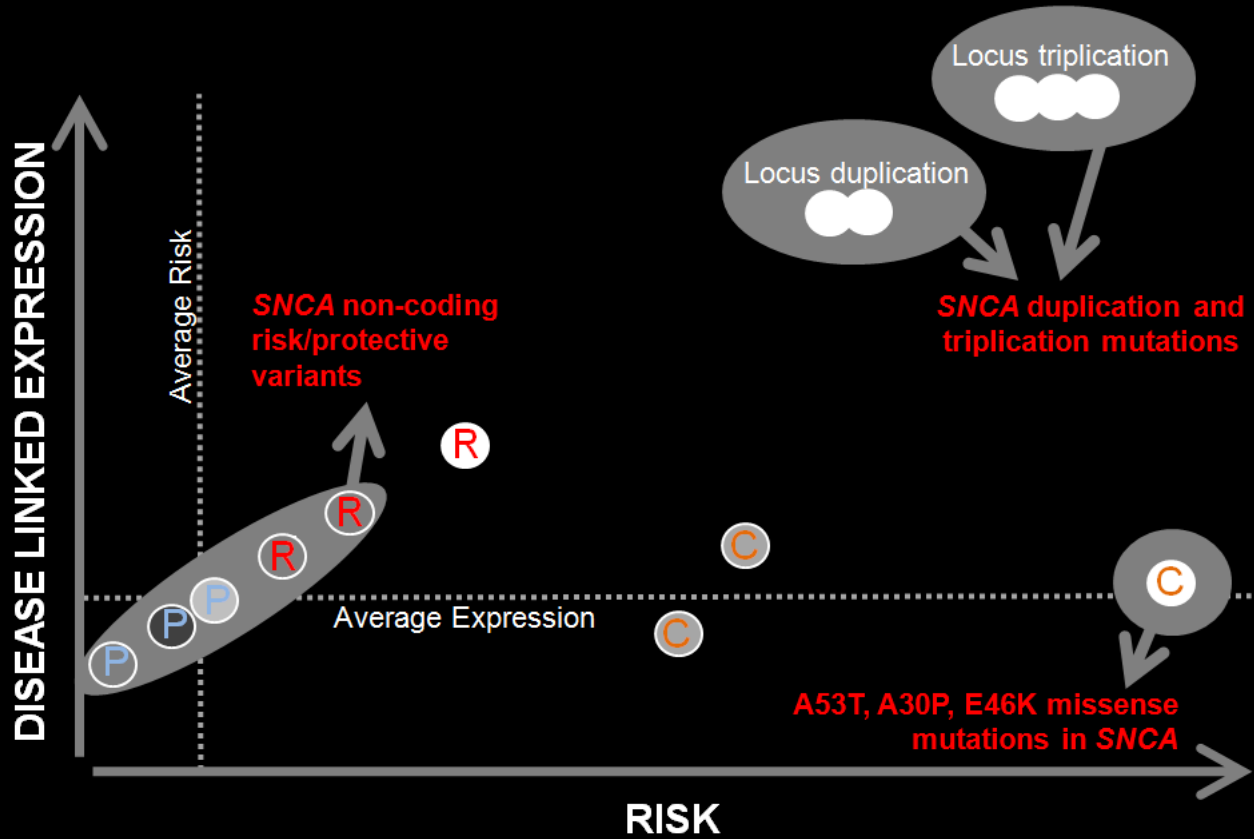


non-coding risk variants



Protein-coding variant

DISEASE LINKED EXPRESSION



Average Risk

**SNCA non-coding
risk/protective
variants**

Locus duplication

Locus triplication

**SNCA duplication and
triplication mutations**

Average Expression

**A53T, A30P, E46K missense
mutations in SNCA**

RISK

Dissecting the genetic architecture of disease

- We have two aims:
 - 1) to develop statistical risk profiles for disease based on genetics
 - It is worth noting that, almost by definition, prediction can never be better than identical twins.
 - 2) to understand the pathways to pathogenesis
 - As we find risk genes, and map these to pathways, we will should be able to find other risk genes, out of those which do not quite achieve Bonnferroni significance

Understanding the pathways to pathogenesis

- Much progress... many pathways identified
- No interventions to lay at the door of genetics
 - (pharmacogenetics)
- **MUCH WORK NEEDS TO BE DONE**

Developing statistical risk profiles for disease based on genetics

- For mendelian disease, clearly we have been successful
- Even for sporadic disease, we have come a long way... ~30%~40% of risk for PD and AD
- But
- We have not been as successful in making this clinically useful as we might... preimplantation diagnosis... early diagnosis and intervention.
- **COULD DO BETTER!**