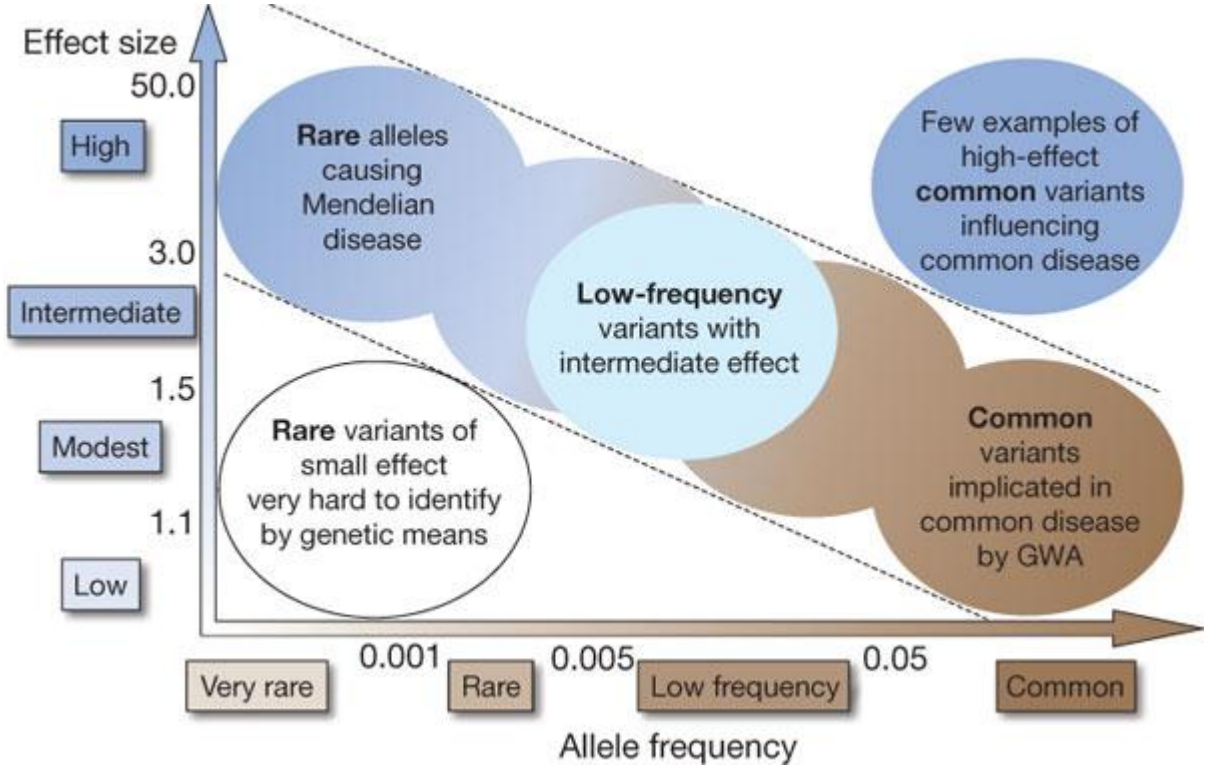
Neurogenetics: new technologies to understand genetic risk

John Hardy j.hardy@ucl.ac.uk

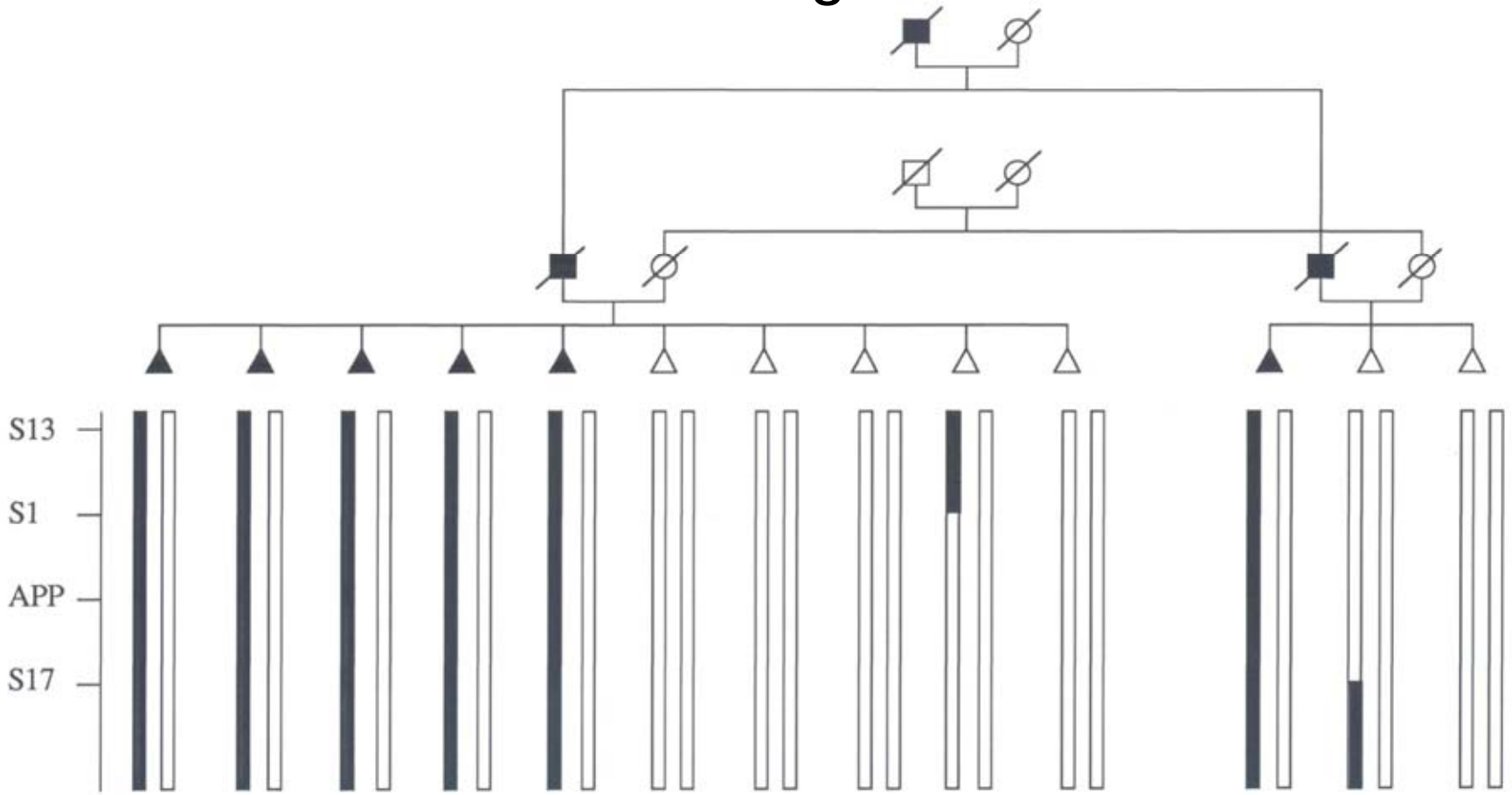
Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect (odds ratio).



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

nature

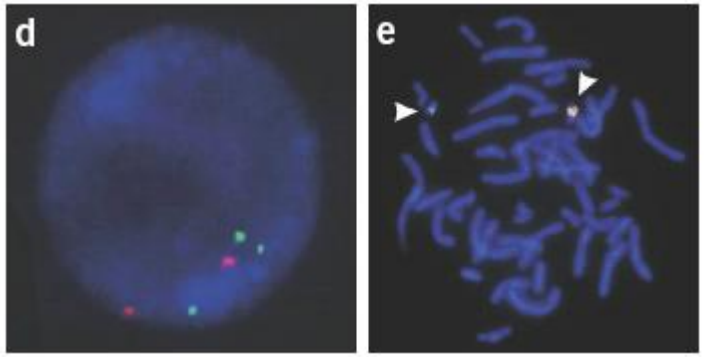
Recombination events in F23 localize the disease locus to a region between S1 and S17 that includes the APP gene

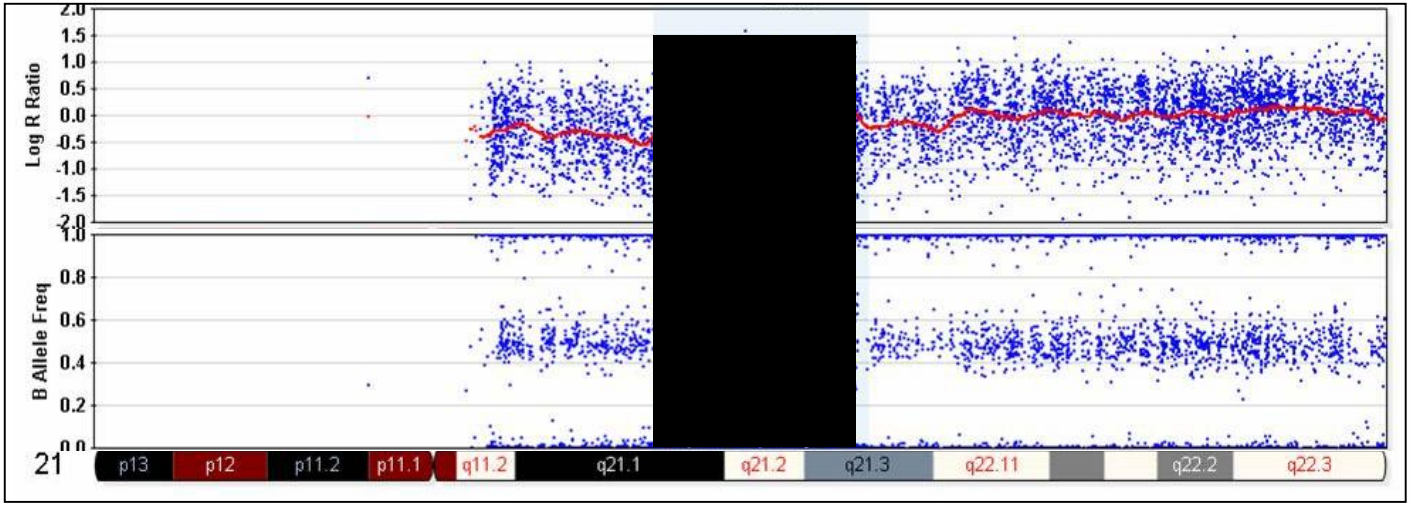


7Mb duplication of locus around APP

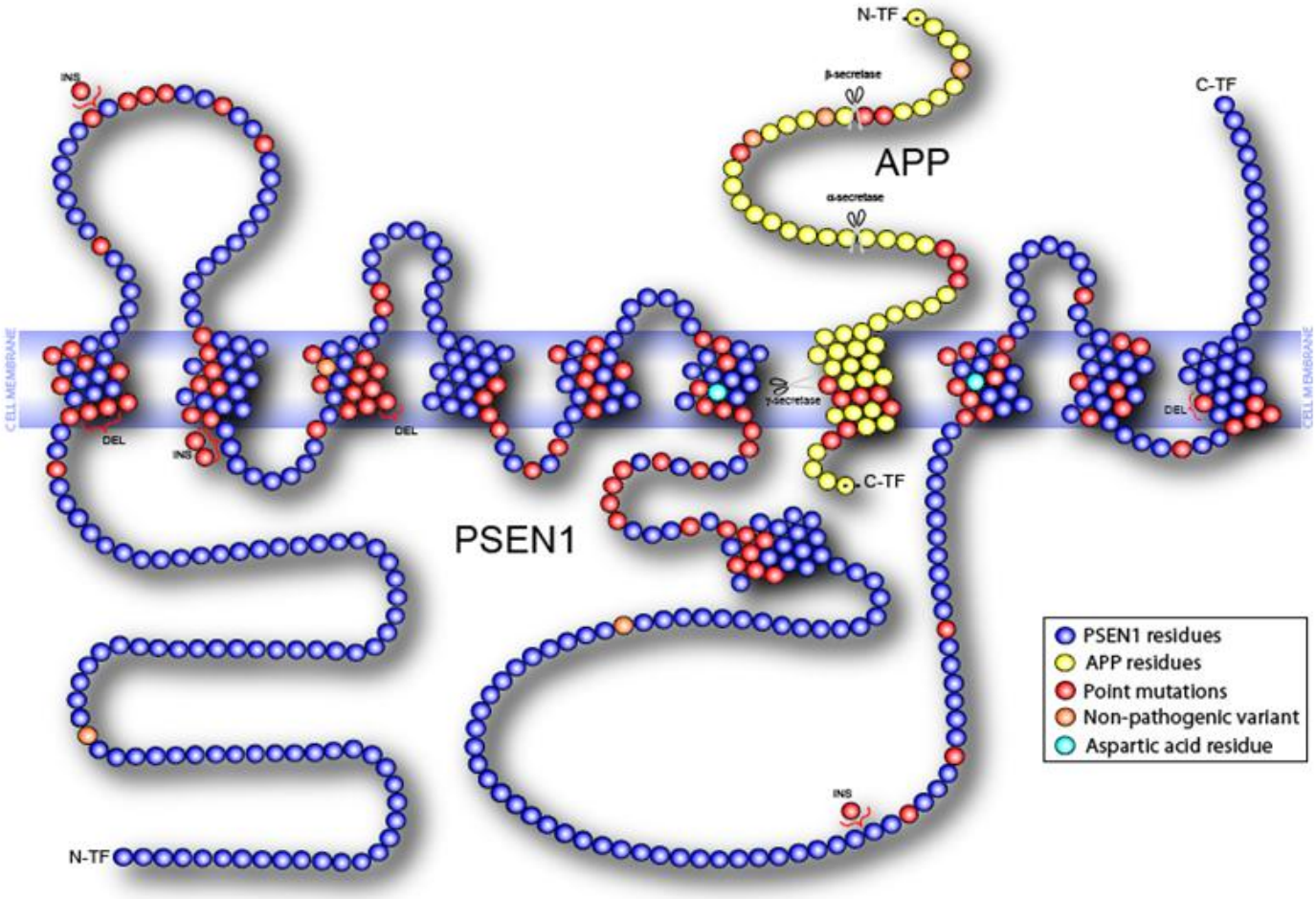
APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy

Anne Rovelet-Lecrux[1], Didier Hannequin[1,2], Gregory Raux[1], Nathalie Le Meur[3], Annie Laquerrière[4], Anne Vital[5], Cécile Dumanchin[1], Sébastien Feuillette[1], Alexis Brice[6], Martine Vercelletto[7], Frédéric Dubas[8], Thierry Frebourg[1] & Dominique Campion[1,9]

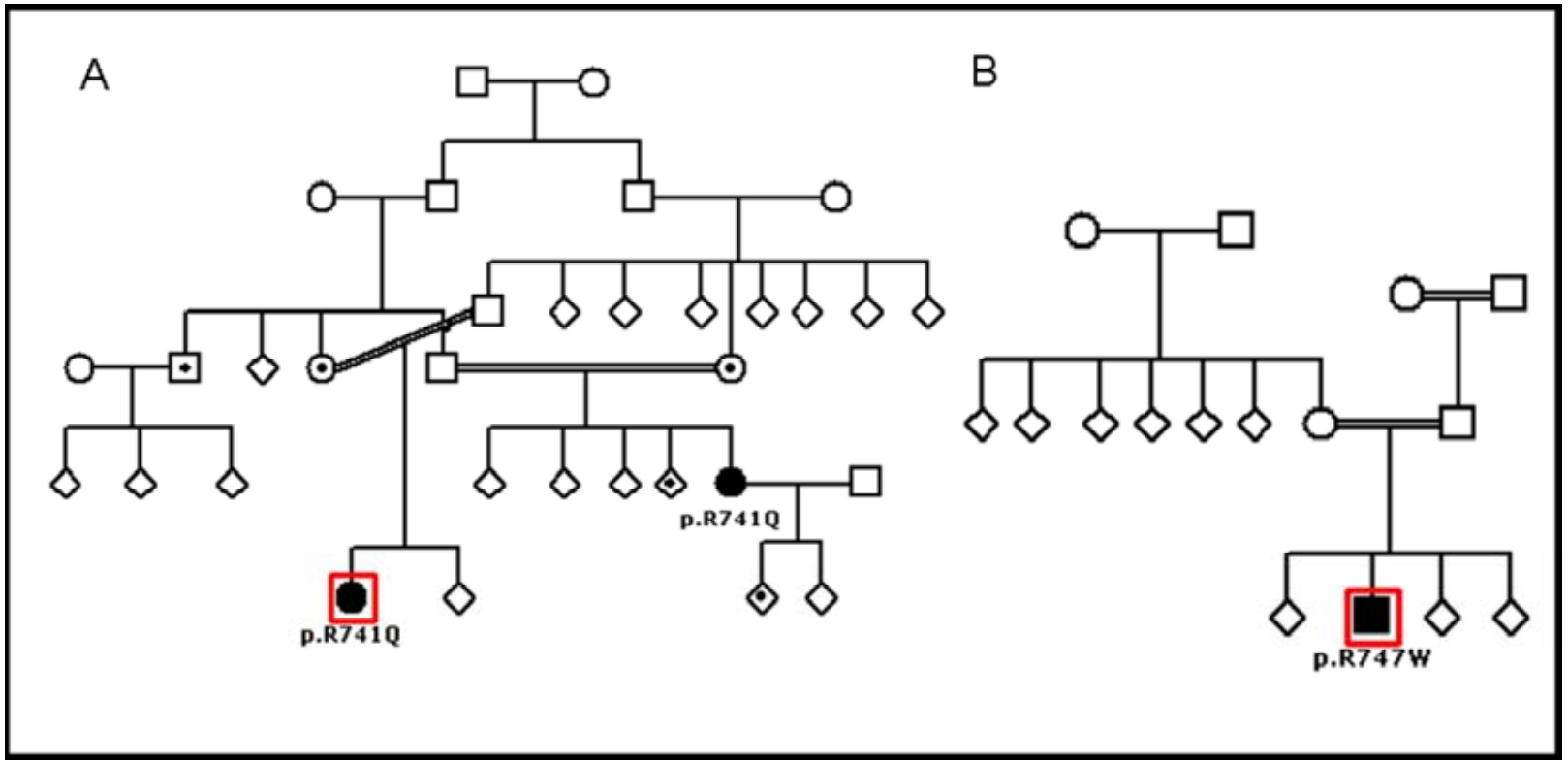




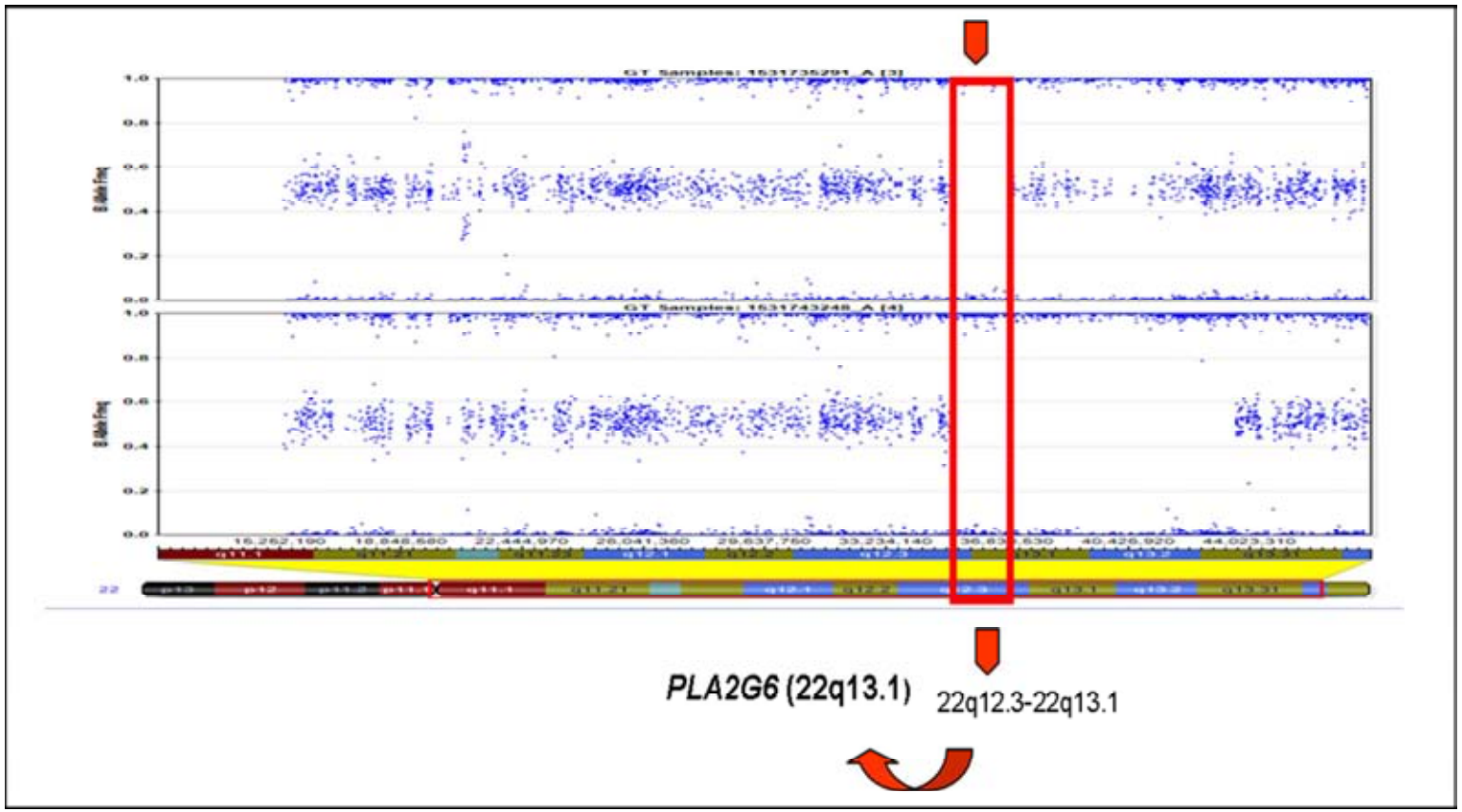
Presenilin with APP in the Active Site



Two consanguineous families with parkinsonism-dystonia



Identification of a locus for Parkinsonism-Dystonia



Characterization of PLA2G6 as a Locus for Dystonia-Parkinsonism

Coro Paisan-Ruiz,[1,2] Kailash P. Bhatia,[3] Abi Li,[2] Dena Hernandez,[1] Mary Davis,[2] Nick W. Wood,[2] John Hardy,[1,2] Henry Houlden,[2] Andrew Singleton,[1] and Susanne A. Schneider[3]

Background: Although many recessive loci causing parkinsonism dystonia have been identified, these do not explain all cases of the disorder.

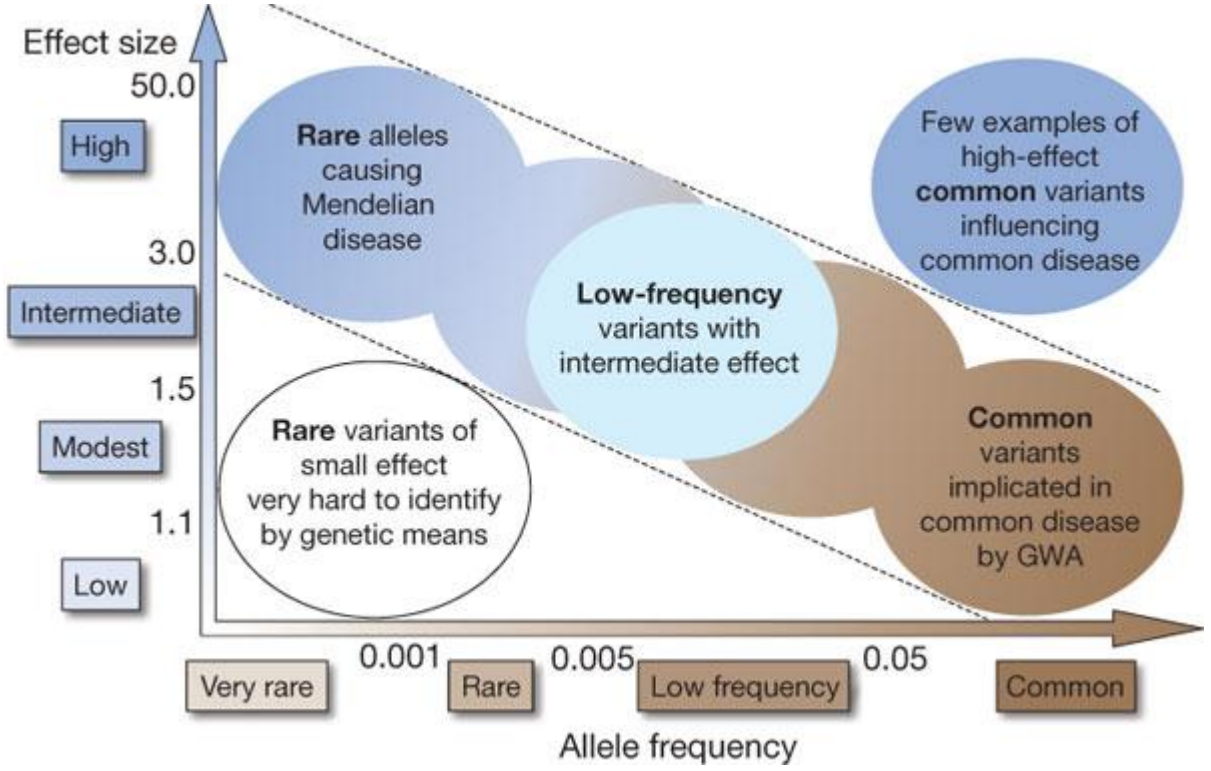
Methods: We used homozygosity mapping and mutational analysis in three individuals from two unrelated families who presented with adult-onset levodopa-responsive dystonia-parkinsonism, pyramidal signs and cognitive/psychiatric features, and cerebral and cerebellar atrophy on magnetic resonance imaging but absent iron in the basal ganglia.

Results: We identified areas of homozygosity on chromosome 22 and, subsequently, PLA2G6 mutations.

Interpretation: PLA2G6 mutations are associated with infantile neuroaxonal dystrophy and have been reported previously to have early cerebellar signs, and the syndrome was classified as neurodegeneration with brain iron accumulation (type 2). Our cases have neither of these previously pathognomic features. Thus, mutations in PLA2G6 should additionally be considered in patients with adult-onset dystonia-parkinsonism even with absent iron on brain imaging.

Ann Neurol 2008;63:000–000

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

nature

Recent whole genome studies identify innate immune system

nature genetics

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

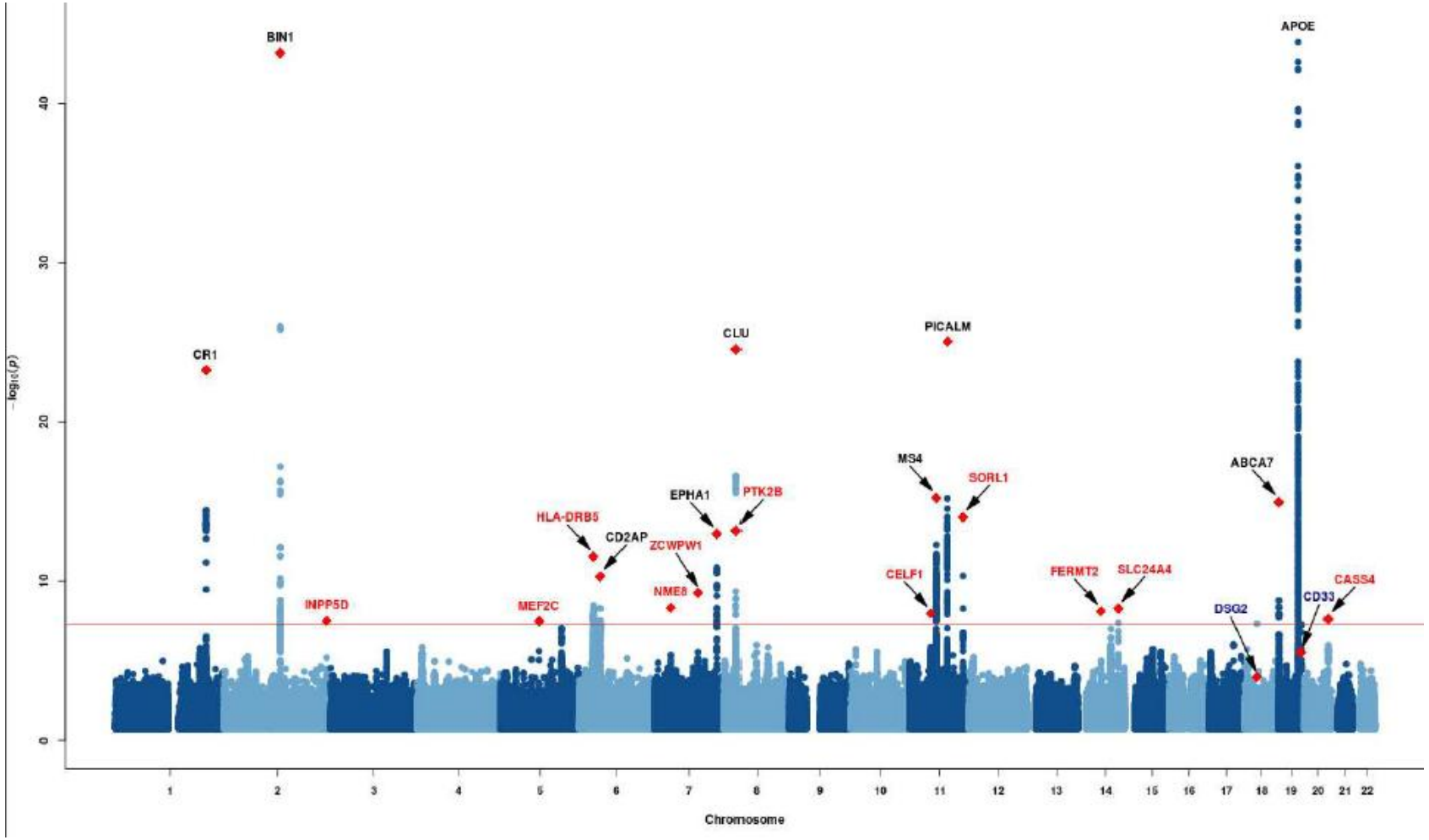
Denise Harold[1,45*], Richard Abraham[1,45], Paul Hollingworth[1,45], Rebecca Sims[1], Amy Gerrish[1], Marian Hamshere[1], Jaspreet Singh Pahwa[1], Valentina Moskvina[1], Kimberley Dowzell[1], Amy Williams[1], Nicola Jones[1], Charlene Thomas[1], Alexandra Stretton[1], Angharad R Morgan[1], Simon Lovestone[2], John Powell[3], Petroula Proitsi[3], Michelle K Lupton[3], Carol Brayne[4], David C Rubinsztein[5], Michael Gill[6], Brian Lawlor[6], Aoibhinn Lynch[6], Kevin Morgan[7], Kristelle S Brown[7], Peter A Passmore[8], David Craig[8], Bernadette McGuinness[8], Stephen Todd[8], Clive Holmes[9], David Mann[10], A David Smith[11], Seth Love[12], Patrick G Kehoe[12], John Hardy[13], Simon Mead[14], Nick Fox[15], Martin Rossor[15], John Collinge[14], Wolfgang Maier[16], Frank Jessen[16], Britta Schürmann[16], Hendrik van den Bussche[17], Isabella Heuser[18], Johannes Kornhuber[19], Jens Wiltfang[20], Martin Dichgans[21,22], Lutz Frölich[23], Harald Hampel[24,25], Michael Hüll[26], Dan Rujescu[25], Alison M Goate[27], John S K Kauwe[28], Carlos Cruchaga[27], Petra Nowotny[27], John C Morris[27], Kevin Mayo[27], Kristel Sleegers[29,30], Karolien Bettens[29,30], Sebastiaan Engelborghs[30,31], Peter De Deyn[30,31], Christine van Broeckhoven[29,30], Gill Livingston[32], Nicholas J Bass[32], Hugh Gurling[32], Andrew McQuillin[32], Rhian Gwilliam[33], Panagiotis Deloukas[33], Ammar Al-Chalabi[34], Christopher E Shaw[34], Magda Tsolaki[35], Andrew B Singleton[36], Rita Guerreiro[36], Thomas W Mühleisen[37,38], Markus M Nöthen[37,38], Susanne Moebus[39], Karl-Heinz Jöckel[39], Norman Klopp[40], H-Erich Wichmann[40–42], Minerva M Carrasquillo[43], V Shane Pankratz[44], Steven G Younkin[43], Peter A Holmans[1], Michael O'Donovan[1], Michael J Owen[1] & Julie Williams[1]

nature genetics

Genome-wide association study identifies variants at *CLU* and *CR1* associated with Alzheimer's disease

Jean-Charles Lambert[1–3], Simon Heath[4], Gael Even[1,2], Dominique Campion[5], Kristel Sleegers[6,7], Mikko Hiltunen[8], Onofre Combarros[9], Diana Zelenika[4], Maria J Bullido[10], Béatrice Tavernier[11], Luc Letenneur[12], Karolien Bettens[6,7], Claudine Berr[13], Florence Pasquier[3,14], Nathalie Fiévet[1,2], Pascale Barberger-Gateau[12], Sebastiaan Engelborghs[7,15], Peter De Deyn[7,15], Ignacio Mateo[9], Ana Franck[16], Seppo Helisalmi[8], Elisa Porcellini[17], Olivier Hanon[18], the European Alzheimer's Disease Initiative Investigators[19], Marian M de Pancorbo[20], Corinne Lendon[21], Carole Dufouil[22,23], Céline Jaillard[24], Thierry Leveillard[24], Victoria Alvarez[25], Paolo Bosco[26], Michelangelo Mancuso[27], Francesco Panza[28], Benedetta Nacmias[29], Paola Bossù[30], Paola Piccardi[31], Giorgio Annoni[32], Davide Seripa[33], Daniela Galimberti[34], Didier Hannequin[5], Federico Licastro[17], Hilkka Soininen[8], Karen Ritchie[35], Hélène Blanché[35], Jean-François Dartigues[12], Christophe Tzourio[22,23], Ivo Gut[4], Christine Van Broeckhoven[6,7], Annick Alpérovitch[22,23], Mark Lathrop[4,35] & Philippe Amouyel[1–3,14]

IGAP Alzheimer analysis (in press)
~30,000 cases and ~44,000 controls



Genome Wide Association Studies

IGAP study has 30,000 cases and 44,000 controls and has identified ~20 loci

What are the limitations of further increases?

1. Exhaustion: law of diminishing returns: OR of first hits were ~1.15… OR of last ~1.08
2. Populations stratification: as we move into more and more genetic variability between new populations becomes a risk
3. Contaminating diagnoses (vascular dementia, FTD)

OPEN ACCESS Freely available online

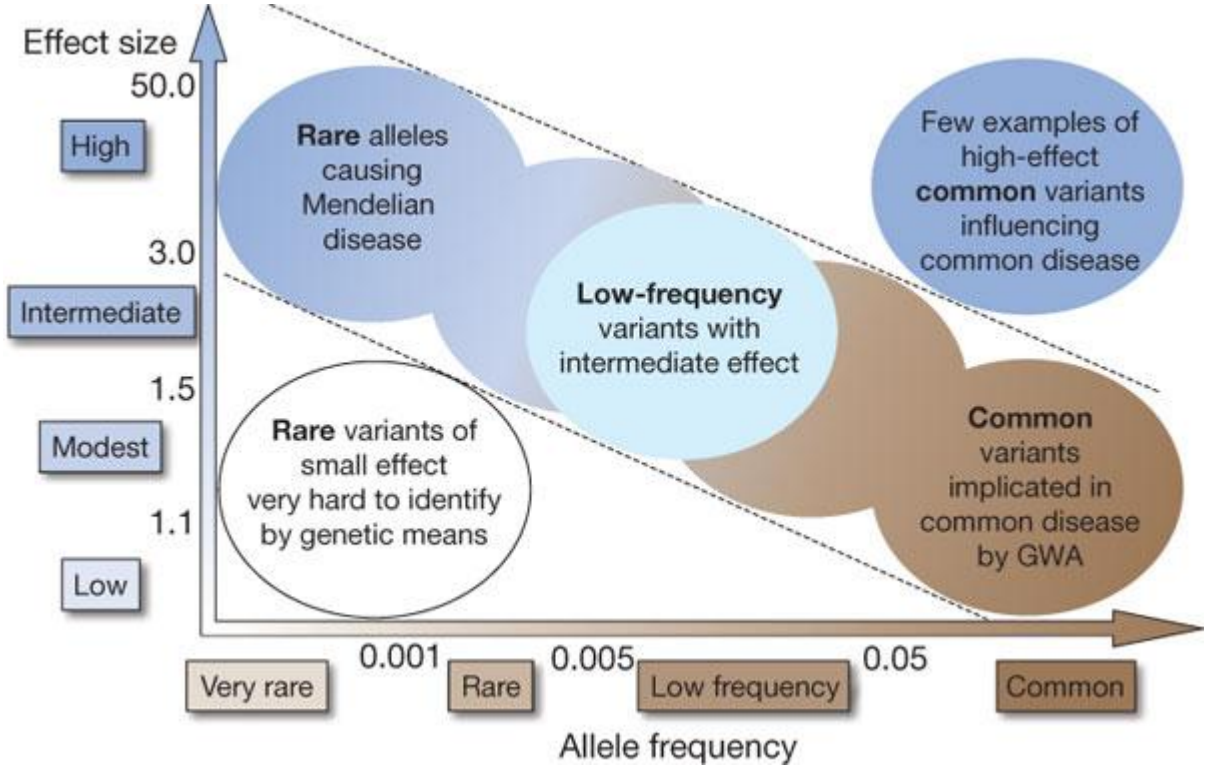
PLoS one

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

Lesley Jones[1☯], Peter A. Holmans[1☯], Marian L. Hamshere[1], Denise Harold[1], Valentina Moskvina[1], Dobril Ivanov[1], Andrew Pocklington[1], Richard Abraham[1], Paul Hollingworth[1], Rebecca Sims[1], Amy Gerrish[1], Jaspreet Singh Pahwa[1], Nicola Jones[1], Alexandra Stretton[1], Angharad R. Morgan[1], Simon Lovestone[2], John Powell[3], Petroula Proitsi[3], Michelle K. Lupton[3], Carol Brayne[4], David C. Rubinsztein[5], Michael Gill[6], Brian Lawlor[6], Aoibhinn Lynch[6], Kevin Morgan[7], Kristelle S. Brown[7], Peter A Passmore[8], David Craig[8], Bernadette McGuinness[8], Stephen Todd[8], Clive Holmes[9], David Mann[10], A. David Smith[11], Seth Love[12], Patrick G. Kehoe[12], Simon Mead[13], Nick Fox[14], Martin Rossor[14], John Collinge[13], Wolfgang Maier[15], Frank Jessen[15], Britta Schürmann[15], Hendrik van den Bussche[16], Isabella Heuser[16], Oliver Peters[16], Johannes Kornhuber[17], Jens Wiltfang[18], Martin Dichgans[19,20], Lutz Frölich[21], Harald Hampel[22,23], Michael Hüll[24], Dan Rujescu[23], Alison M Goate[25], John S. K. Kauwe[26], Carlos Cruchaga[25], Petra Nowotny[25], John C. Morris[25], Kevin Mayo[25], Gill Livingston[27], Nicholas J. Bass[27], Hugh Gurling[27], Andrew McQuillin[27], Rhian Gwilliam[28], Panos Deloukas[28], Ammar Al-Chalabi[29], Christopher E. Shaw[29], Andrew B. Singleton[30], Rita Guerreiro[30], Thomas W. Mühleisen[31,32], Markus M. Nöthen[31,32], Susanne Moebus[33], Karl-Heinz Jöckel[33], Norman Klopp[34], H.-Erich Wichmann[34–36], Eckhard Rüther[37], Minerva M. Carrasquillo[38], V. Shane Pankratz[39], Steven G. Younkin[38], John Hardy[40], Michael C. O'Donovan[1], Michael J. Owen[1]*, Julie Williams[1]*

In most recent analysis, protein degradation-ubiquitination also comes up

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

nature

Exome Sequencing of thousands of cases and thousands of controls

- Do burden analysis to find genes
- Do cases have significantly more mutations than controls?

Sequencing to find high risk rare variants

- More useful to cell biologists
- Rare…..so many will be need to be sequenced
- Many will be loss of function (TREM2/NasHak/AD, GBA/Gaucher/PD). Analysis by burden test.

- US Government sequencing 10,000 AD cases.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

TREM2 Variants in Alzheimer's Disease

Rita Guerreiro, Ph.D., Aleksandra Wojtas, M.S., Jose Bras, Ph.D., Minerva Carrasquillo, Ph.D., Ekaterina Rogaeva, Ph.D., Elisa Majounie, Ph.D., Carlos Cruchaga, Ph.D., Celeste Sassi, M.D., John S.K. Kauwe, Ph.D., Steven Younkin, M.D., Ph.D., Lilinaz Hazrati, M.D., Ph.D., John Collinge, M.D., Jennifer Pocock, Ph.D., Tammaryn Lashley, Ph.D., Julie Williams, Ph.D., Jean-Charles Lambert, Ph.D., Philippe Amouyel, M.D., Ph.D., Alison Goate, Ph.D., Rosa Rademakers, Ph.D., Kevin Morgan, Ph.D., John Powell, Ph.D., Peter St. George-Hyslop, M.D., Andrew Singleton, Ph.D., and John Hardy, Ph.D., for the Alzheimer Genetic Analysis Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Variant of *TREM2* Associated with the Risk of Alzheimer's Disease

Thorlakur Jonsson, Ph.D., Hreinn Stefansson, Ph.D., Stacy Steinberg Ph.D., Ingileif Jonsdottir, Ph.D., Palmi V. Jonsson, M.D., Jon Snaedal, M.D., Sigurbjorn Bjornsson, M.D., Johanna Huttenlocher, B.S., Allan I. Levey, M.D., Ph.D., James J. Lah, M.D., Ph.D., Dan Rujescu, M.D., Harald Hampel, M.D., Ina Giegling, Ph.D., Ole A. Andreassen, M.D., Ph.D., Knut Engedal, M.D., Ph.D., Ingun Ulstein, M.D., Ph.D., Srdjan Djurovic, Ph.D., Carla Ibrahim-Verbaas, M.D., Albert Hofman, M.D., Ph.D., M. Arfan Ikram, M.D., Ph.D., Cornelia M van Duijn, Ph.D., Unnur Thorsteinsdottir, Ph.D., Augustine Kong, Ph.D., and Kari Stefansson, M.D., Ph.D.

Article abstract—Progressive presenile dementia with lipomembranous polycystic osteodysplasia was first described by Jarvi and Hukola in an isolated region of Finland. We report the occurrence of this disorder in 4 of 10 siblings in an American family of Czechoslovakian ancestry. Characteristics of the disease include multiple bone cysts with pathologic fractures, progressive dementia with seizures and abnormal EEG, calcification of basal ganglia, and death in the fourth to sixth decades. Autosomal-recessive inheritance is likely. Electronmicroscopy of fat cells reveals peculiar membrane convolutions. Limited neuropathologic material has shown gliosis and demyelination of white matter, senile plaques, and neurofibrillary tangles. Leukemia and a disorder of intestinal motility may be associated findings. Prevalence of the disorder is unknown, partly because it may be confused with Alzheimer disease and fibrous dysplasia of bone. Radiographs of hands and feet should be part of the evaluation of patients with unexplained presenile dementia.

NEUROLOGY (NY) 1983;33:81-6

Lipomembranous polycystic osteodysplasia (brain, bone, and fat disease): A genetic cause of presenile dementia

Thomas D. Bird, M.D., Richard M. Koerker, M.D., Ph.D., Brenda J. Leaird, P.A., Brien W. Vlcek, M.D., and David R. Thorning, M.D.

….in general, loci which are mendelian hits are also GWAs hits and can also be sequencing hits

Human Molecular Genetics, 2011, Vol. 20, Review Issue 2 **R158–R162**
doi:10.1093/hmg/ddr358
Advance Access published on August 29, 2011

A generalizable hypothesis for the genetic architecture of disease: pleomorphic risk loci

Andrew Singleton[1] and John Hardy[2,*]

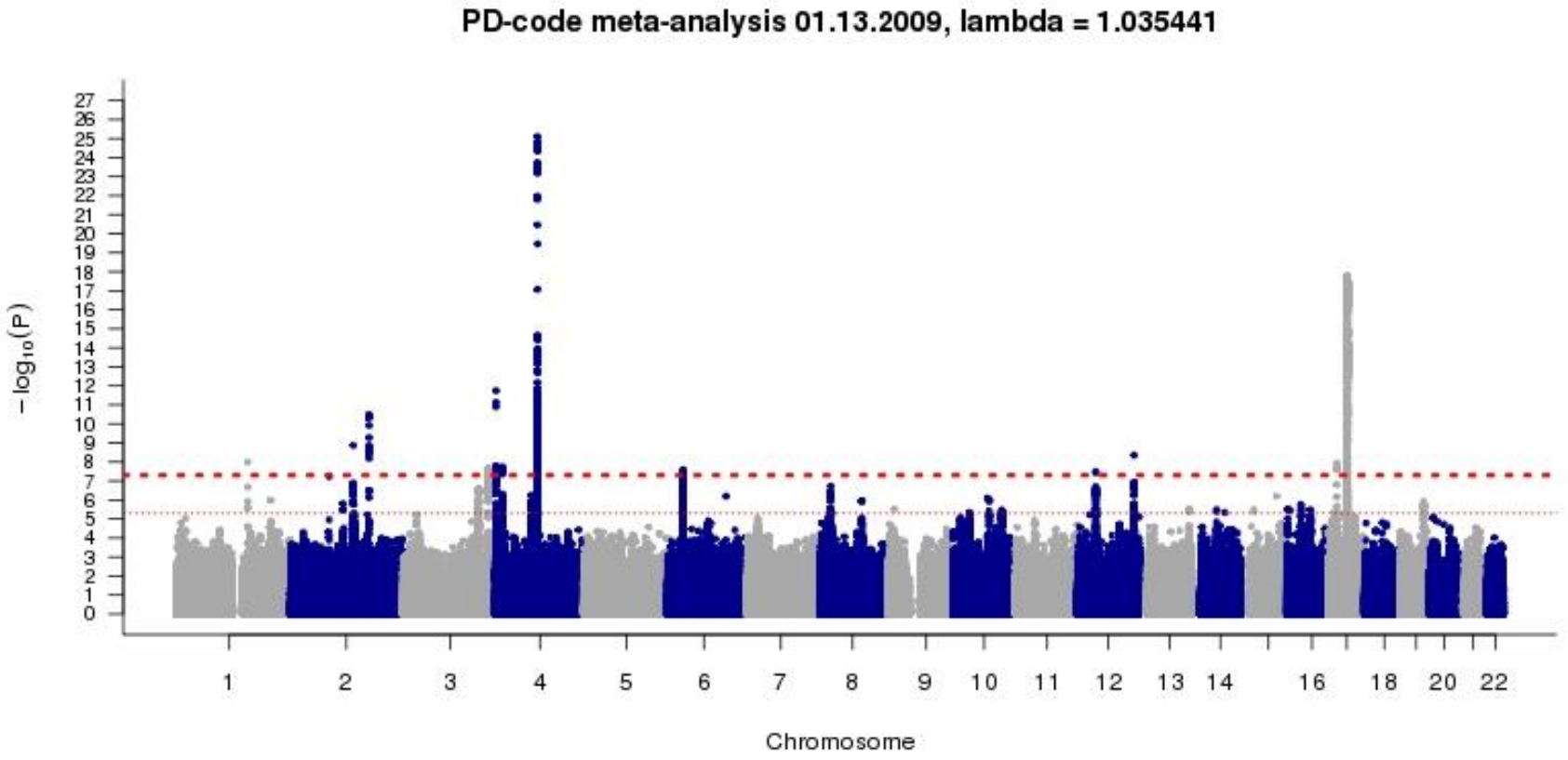
[1]Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA and [2]Department of Molecular Neuroscience and Reta Lilla Weston Laboratories, Institute of Neurology, London, UK

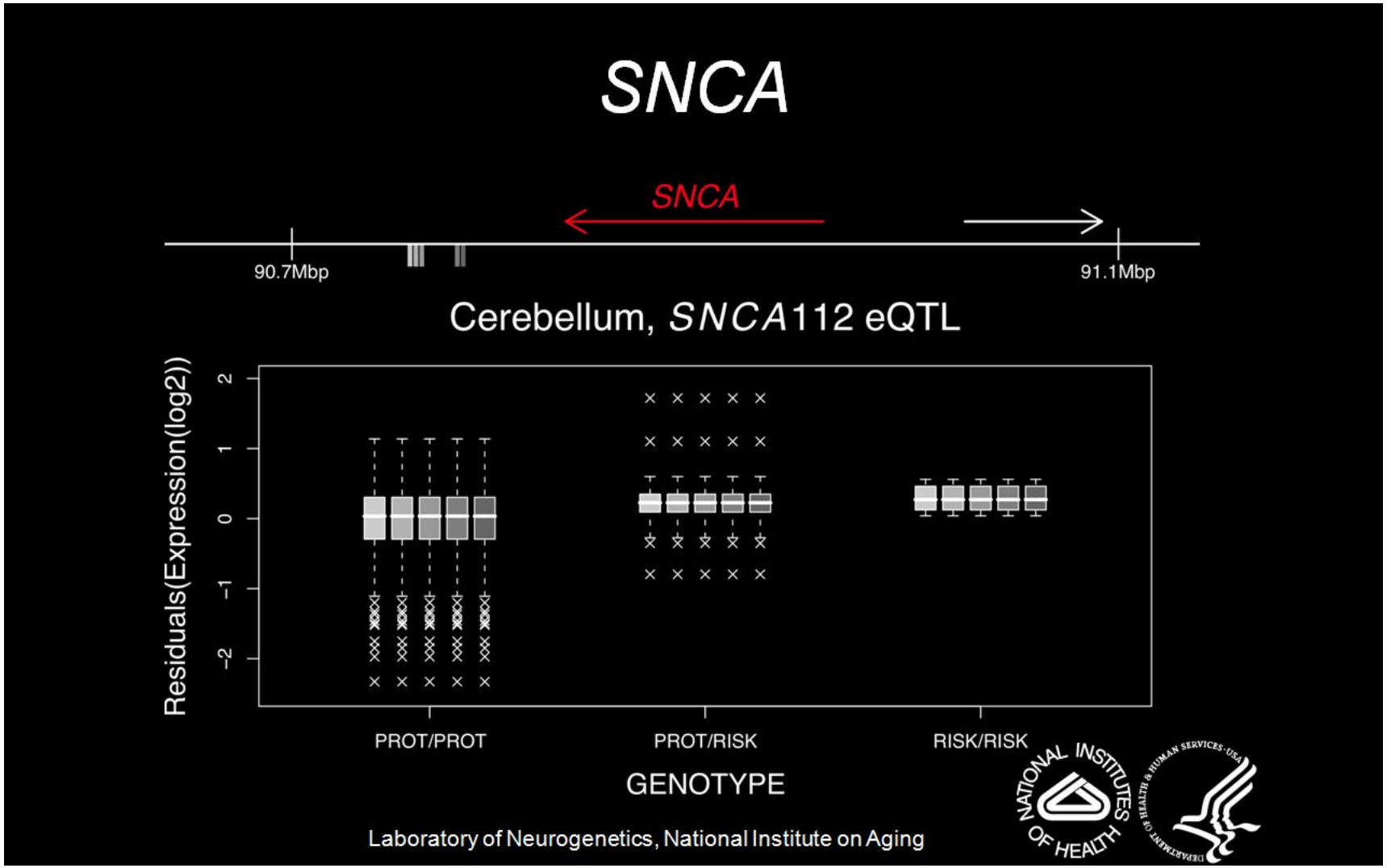
Received June 6, 2011; Revised and Accepted August 10, 2011

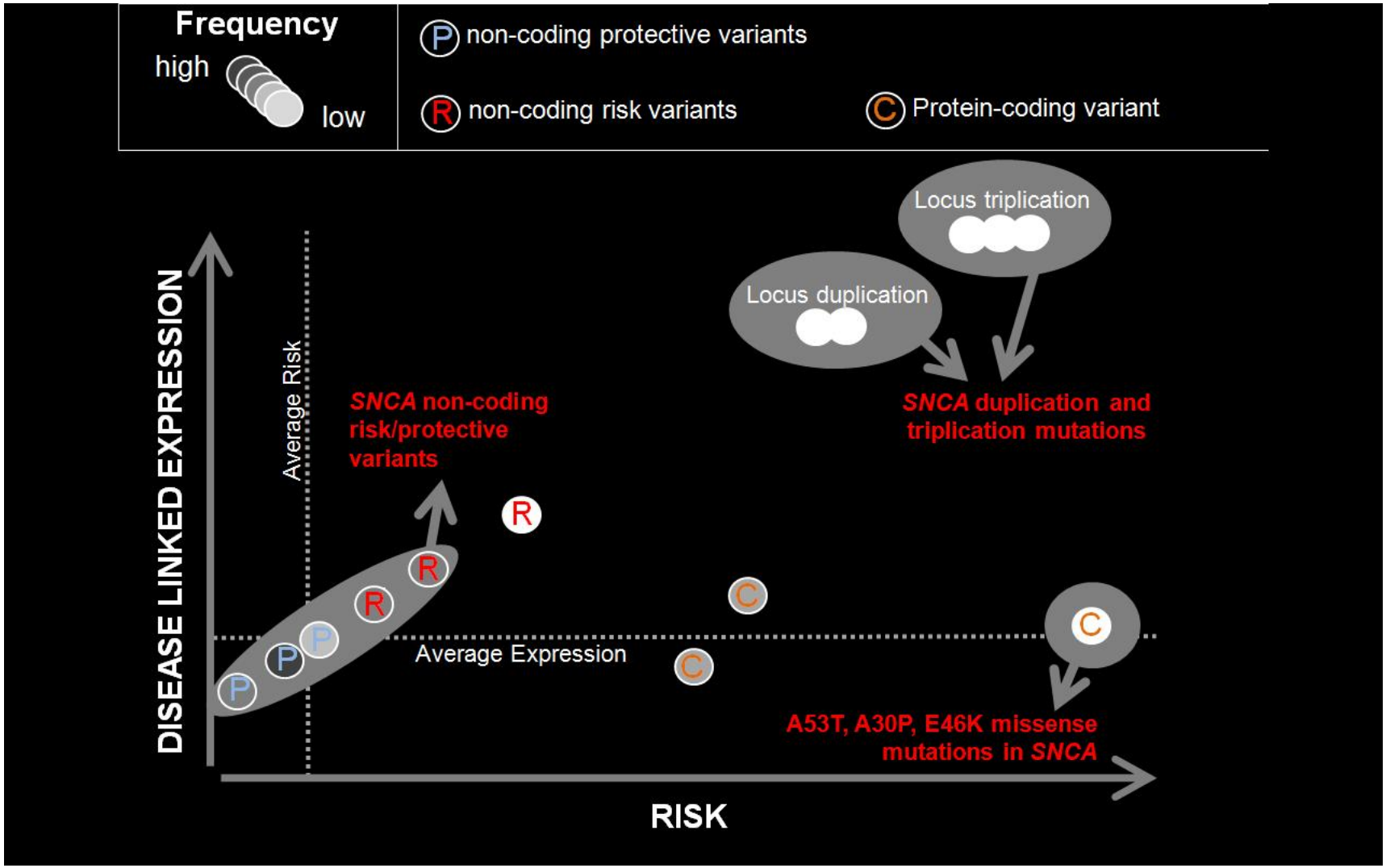
The dominant and sometimes competing theories for the aetiology of complex human disease have been the common disease, common variant (CDCV) hypothesis, and the multiple rare variant (MRV) hypothesis. With the advent of genome wide association studies and of second-generation sequencing, we are fortunate in being able to test these ideas. The results to date suggest that these hypotheses are not mutually exclusive. Further, initial evidence suggests that both MRV and CDCV can be true at the same loci, and that other disease-related genetic mechanisms also exist at some of these loci. We propose calling these, pleomorphic risk loci, and discuss here how such loci not only offer understanding of the genetic basis of disease, but also provide mechanistic biological insight into disease processes.

- Risk is predictable..
- Duplications lead to disease?: upregulation predisposes to disease.
- Deletion predisposes to disease?: downregulation weakly predisposes to disease.

Parkinson's Genome Wide Association Study




SNCA
SNCA
90.7Mbp
91.1Mbp
Cerebellum, SNCA112 eQTL
Residuals(Expression(log2))
2
1
0
−1
−2
PROT/PROT
PROT/RISK
RISK/RISK
GENOTYPE
Laboratory of Neurogenetics, National Institute on Aging
NATIONAL INSTITUTES OF HEALTH
DEPARTMENT OF HEALTH & HUMAN SERVICES-USA


Frequency
high
low
non-coding protective variants
non-coding risk variants
Protein-coding variant
Locus triplication
Locus duplication
SNCA duplication and triplication mutations
SNCA non-coding risk/protective variants
Average Risk
DISEASE LINKED EXPRESSION
Average Expression
A53T, A30P, E46K missense mutations in SNCA
RISK

So.. when will it be over?

- For diagnostic predictions, the incremental improvements are slight but may be interesting
- For pathways, the combination of sequencing, GWAs, network analyses and eQTL studies are going to delineate pathways at high resolution and (hopefully) guide cell biology increasingly over the next 5 years.

In summary…

- Find mendelian genes by positional cloning/sequencing
- Find high frequency low effect size hits by GWAS
- Find moderate frequency medium hits by exome sequencing
- Aid these processes by bioinformatic anaysis to dig into subsignificant hits (co-expression and GO analysis)
- Investigate whether rarer variants at GWAs hits have higher effects.

What will be left to do?

- Gene X gene interactions… needs colossal numbers unless it can de guided by biological insight
- Gene X environment interactions… very difficult….