Defining the Genetic Architecture of Alzheimer’s Disease

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Alzheimer’s disease

- 35.6 million people worldwide living with dementia in 2010, increasing to 115.4 million by 2050

- 822,000 people in the UK with dementia
Cost

How the £23 billion cost of dementia is met

Long term institutional social care and informal care costs make up the majority of the £23 billion figure.

Most of the cost of dementia – £12.4 billion per year – is met by unpaid carers. Social care costs are £9 billion, health care £1.2 billion and productivity losses £29 million.
Alzheimer’s Disease

• Symptoms include:
  – memory loss
  – problems with recognition
  – difficulty with language and thought

• Caused by loss of nerve cells

• Regions which control memory and language are most affected

• Genes known to contribute to disease development (Heritability: 59-79%)
Finding Genes for Alzheimer’s Disease
Alzheimer’s Disease: Early Findings

DNA variants which contribute to rare forms of AD

Mutations/DNA errors:

- PSEN1: > 170
- PSEN2: < 20
- APP: < 32

- PSEN1
- APOE Risk variant
- APP

Heritability of AD 59 - 79%
Genome-wide Association

Millions of DNA variants can now be tested on each individual
Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer’s disease

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

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

Common variants at *MS4A4/MS4A6E, CD2AP, CD33* and *EPHA1* are associated with late-onset Alzheimer’s disease.
APOE

Genome-wide significance $P = 5 \times 10^{-8}$

CR1

$P = 1.3 \times 10^{-19}$

CLU

$P = 2.6 \times 10^{-22}$

MS42A locus

$P = 1.2 \times 10^{-16}$

PICALM

$P = 1.6 \times 10^{-19}$

CD2AP

$P = 8.6 \times 10^{-9}$

EPHA1

$P = 6.0 \times 10^{-10}$

BIN1

$P = 5.8 \times 10^{-15}$

CD33

$P = 1.6 \times 10^{-9}$

Genome-wide significance $P = 5 \times 10^{-8}$

Pericack-Vance, 2010

Seshadri, 2010

GierdraAs 2009; Kamboh, 2010; ADGC; 2010; Carrasquillo, 2010

APP, PSEN-1 & 2, MAPT

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Hollingworth et al, Nature Genetics 2011
Current Project
I-GAP: International Genomics Alzheimer’s Project

Collaboration between leading AD Genetics groups:

★ GERAD
★ European Alzheimer’s Disease Initiative
★ Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)
★ American Alzheimer’s disease Genetic Consortium
★ Over 150 scientists from Europe and USA

Purpose:
Increase power to identify common and rare variants contributing to disease development
1000G Imputation and Association analysis of Stage 1 Samples

Meta analysis of imputed datasets 18600 cases and 41370 controls

Selection of 15,000 SNPs for follow up genotyping in Stage 2

Stage 2: Genotyping 11386 cases & 14604 controls

Secondary analyses: APOE Gene-wide Pathway

Stage 3: Genotyping 8500 cases 8000 controls
Total Sample: 100,000+

GERAD+
EADI
CHARGE
ADGC
GERAD2+
Kungsholmen
Russian
Spanish
ADGC2

11 (13) new AD susceptibility genes
Susceptibility Genes for Alzheimer’s Disease

New genes shown in red

+2 novel genetic loci from gene-wide analyses
Endocytosis: bringing large molecules into cells

- PICALM recruits clathrin and AP2 to plasma membrane and recognises target proteins
- BIN1 recruits dynamin to plasma membrane

CD2AP- scaffold protein involved in the regulation of receptor mediated endocytosis

CD33- may act as endocytic receptor mediating endocytosis

http://seiri1.med.okayama-u.ac.jp/research_activities/research_contents/index003wuhtml.html
Ubiquitination: clearing rubbish from cells

- Endosome
- Ubiquitin
- Microtubule
- Cell membrane
Components of the complement system are involved in synaptic pruning during neurodevelopment.

Adapted from Barres and Smith (2001) Science, 294 (5545), 1296-1297.
Immunity

C1q, C1r, C1s complex

C3, C5

C3b

CR1, CR2

C9

CLU

CU5bC9

CD33-

Expresses cell-cell interaction, regulates innate & adaptive immune systems

EPHA1-

May have roles in apoptosis and immunity

MS4A-

May have immune function

TREM2

CR1 also expressed in neurons in APP animal models

ABCA7 - ++ expression in hippocampus and microglia. Modulates phagocytosis of apoptotic cells via C1q

C3b binds pathogen and to CR1 or CR2 receptors on B-lymphocytes.

Adaptive immune response

Innate immune response
Population Risk of Alzheimer’s Disease Development

Genetic and lifestyle factors
Conclusions

• Alzheimer’s disease is complex: 26 genes known to contribute more to find

• Cardiff has led research identifying 22 AD genes

• Better understanding of Alzheimer’s disease

• New targets for drug development
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Michael O’ Donovan
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Jade Chapman
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