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**Mental Capital and Wellbeing:
Making the most of ourselves in the 21st century**

**State-of-Science Review: SR-B12
Genetics of Ageing, Mental Ill-health and Dementia in the Elderly**

John Powell and Simon Lovestone
MRC Centre for Neurodegeneration Research
Institute of Psychiatry, King's College London

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Summary

In model organisms including mice, mutations in genes of the insulin signalling pathway increase longevity. In man, in contrast, while there is no evidence for simple gene mutations increasing longevity, rare genetic accelerated ageing disorders are found. Human longevity shows modest heritability with increasing importance beyond 60. Early cognitive ability is, to a large degree, heritable, affects longevity and healthy ageing, and influences late-life cognitive decline. Though dementia is thought to be primarily a disease of the elderly with onset after 65 years, patients with early-onset dementia are a significant group. Among these patients, a small proportion will have a familial dementia. Study of these patients has been remarkably productive in elucidating the molecular mechanisms of dementia, leading to re-categorisation of the dementias along genetic and pathological lines. Late-onset Alzheimer's disease (LOAD) is the commonest dementia of the elderly, with substantial evidence for a genetic contribution to the disorder; the $\epsilon 4$ allele of the APOE gene accounts for a large proportion of this genetic liability. In conclusion, genetic studies have shown promise in unravelling the molecular mechanism of ageing, mental ill-health and dementia.

1. Ageing, lifespan and non-human genes

Longevity, the property of having a long duration of life, has been extensively studied in a number of model organisms. However, ageing, the time-dependent loss of fitness, is much less amenable to study. Even so, we do know that mutations in single genes in simple organisms can extend life span by surprisingly large amounts.

For example, mutations in the *age-1* and *daf-2* genes of the nematode worm *C. elegans* can extend its normal three-week life span by one- to two-fold (Friedman and Johnson 1988; Kenyon et al., 1993). *Age-1* and *daf-2* code for components of an insulin/IGF-I signalling pathway, their activity depending on a forkhead/winged helix transcription factor DAF-16 (Ogg et al., 1997). In normal animals, insulin-like peptides activate DAF-2, an insulin/IGF-I receptor tyrosine kinase that acts through PI3/AKT/SGK kinase cascade to phosphorylate the DAF16/FOXO transcription factor (Paradis et al., 1999). Phosphorylated DAF16 is retained in the cytoplasm. However, in response to reduced insulin/IGF-I signalling, unphosphorylated DAF16 enters the nucleus and activates survival genes (Lee et al., 2003). These genes include those of oxidative stress, metabolism and heat shock pathways. The normal physiological role of this system is not to regulate life span but to regulate the response to limited food supplies in *C. elegans*. Mutations in this pathway may extend life span but do so at the expense of reproductive fitness.

Among other genes that promote survival in nematodes is SIR2 (Tissenbaum and Guarente, 2001). Sir2 (silencing information regulator 2) is a NAD-dependent histone deacetylase which regulates the mating type locus in yeast and over-expression of which extends yeast replicative life span (Kaeberlein et al., 1999). SIR2 is of interest because caloric restriction, a procedure that extends life span in many organisms, depends on an intact SIR2 (reviewed in Bordone and Guarente, 2005). The systems regulating longevity identified in the other well-studied model organism, the fruit fly *Drosophila melanogaster* are remarkably similar. Thus in *Drosophila*, life span is also regulated by an insulin/IGF signalling pathway. Loss of function mutations in the insulin receptor substrate (*chico*) extend life span, as do mutations in the insulin receptor (Clancy et al., 2001; Tatar et al., 2001).

Additionally, small molecule activators of sir2 extend life span in *Drosophila* (Wood et al., 2004). In mice also the same pathways affect life span. Those animals with defects in pituitary development such as the Ames and Snell dwarf mice live 40-70% longer than normal mice and show a reduced level of plasma IGF-I in response to growth hormone deficiency (Brown-Borg, Borg et al., 1996; Hsieh et al., 2002).

2. Human genes

The closest human homologue to yeast Sir2, SIRT1 represses the human homolog of DAF-16, FOXO3a (Motta et al., 2004). FOXO3a protects against oxidative stress by stimulating DNA repair and anti oxidant defence (Kops et al., 2002; Tran et al., 2002).

In humans, there is no evidence for single gene mutations having profound effects on longevity, but in contrast some very rare genetic disorders (for example Werner or Coackayne syndromes) that show features of accelerated ageing, are known. These are termed 'segmental progeroid syndromes' most of which are caused by mutations in a DNA repair or genome maintenance gene (reviewed in Navarro et al., 2006).

3. Family studies

Human family studies have consistently shown modest heritability of longevity, though genetic influences are increasingly important beyond the age of 60. For example, in a large study of Danish, Finnish and Swedish twins, mean life span for male identical twins increases by 0.39 years for every year his co-twin survives beyond 60. This value is significantly greater than that for non-identical twins (0.2) (vB Hjelmborg et al., 2006).

Similar evidence for the heritability of longevity is found in family studies, as relatives of centenarians have substantially increased lifespan compared to other members of the same birth cohort. In a study of the siblings of centenarians born in 1900, these had an average age of death of 76.7 and 70.4 for females and males, compared to 58.3 and 51.5 for females and males of the same birth cohort (Perls et al., 2002).

The identification of genes influencing life span in model organisms and the heritability of longevity in humans has led to studies seeking to identify human longevity genes. Such investigations have particular difficulties. Linkage studies, for example, are hampered by the lack of availability of multi-generational pedigrees of long-lived individuals. A particular difficulty with case-control studies is the lack of an appropriate control group, so here longitudinal studies may be more appropriate.

Despite these difficulties, a number of studies have attempted to identify loci and genes linked or associated with longevity and ageing (Lunetta et al., 2007). Results are consistent with the hypothesis that *no* major gene modulates life span in humans.

4. Genetics of cognition, behaviour and ageing

A considerable amount of evidence suggests that both cognitive abilities and some psychiatric disorders have a heritable component. General intellectual ability ('g') has a strong heritable component (reviewed in Greenwood and Parasuraman, 2003; Butcher et al., 2006; Plomin and Spinath, 2002; Deary et al., 2006), in addition to a substantial environmental component for performance and evidence for a gene x environment interaction effect (Harden et al., 2007). Large ongoing prospective studies (e.g. Oliver and Plomin, 2007) are seeking the genes responsible for the inherited component, but none has been reliably identified to date.

Childhood cognitive abilities have a substantial effect on ill-health and mortality in adulthood (Batty et al., 2006), and thence on overall longevity, probably because higher IQ is associated with reduced smoking, obesity and other factors associated with premature mortality (Batty et al., 2007). Pre-adult IQ may also have an effect on late-life cognitive performance through at least two independent mechanisms. First, it is possible that genetic factors associated with early cognitive development may also be associated with later-life cognitive decline. And secondly, high cognitive ability may offer some protection from dementia – the 'cognitive reserve' hypothesis (Richards and Deary, 2005).

It is clear, then, that early cognitive ability is, to a large degree, heritable, affects longevity and healthy ageing, and influences late-life cognitive decline. These associations could be a consequence of gene x environment effects (low childhood IQ x increased smoking in adulthood, for example). However, there may also be direct effects with the same sets of genetic variations being implicated in both neurodevelopmental and neurodegenerative processes (see De Ferrari and Moon, 2006 for hypotheses linking Wnt and Notch signalling to both development and degeneration, for example). Whether interactive, indirect or direct effects, the genetic variation underlying the early cognitive influences on late-life cognitive decline have not yet been reliably identified.

5. Mental ill-health

These data linking early- and late-life cognition through genetics are not mirrored in early and late-life psychiatric disorders. Late-life depression is common, affecting 12-15% of those over the age of 65 years but, although affective disorders have a heritable component in early- to mid-life (Levinson, 2006), there is little to suggest the same is true in older people. As for cognitive abilities, the genetic influence on mood disorders is most likely to be mediated through a gene x environment interaction effect, as illustrated by the finding that variation in the promoter region of the serotonin transporter gene influences risk of depression by moderating response to stressful life events (Caspi et al., 2003; Kendler et al., 2005; Uher and McGuffin, 2008).

Many other candidate gene studies have shown modest effects of multiple genes on a person's risk of mood disorder. Recent meta-analyses find evidence for association of unipolar depressive disorder with six genes (Lopez-Leon et al., 2007). Genome-wide studies are under way in both major depression and bipolar mood disorders, although for the most part these seem to have been underpowered (Elashoff et al., 2007). Even so, one very large case-control genome-wide study including bipolar depression has been reported (WTCC, 2007).

For the most part, late-life depression has not been subjected to the same intensive gene-based research as early-life affective disorder. There is little evidence one way or the other to suggest that late-life mood disorders have a heritable component, and no reliable evidence at all that we are aware of indicating what such an heritable component might be due to, if it exists.

The genetics of late-life psychotic disorders are, if anything, even less researched than late-life mood disorders. Late-onset psychosis, 'paraphrenia' in some terminologies, is a rather specific, albeit rare, condition. A search of the literature reveals only two genetic association studies with late-life psychosis in the absence of neurodegeneration. And neither finds a convincing association with variation APOE (Forsell et al., 1998; Howard et al., 1995).

6. Early-onset dementia

Though dementia is thought to be primarily a disease of the elderly with onset after 65 years, patients with early-onset dementia (<65 years) are a significant and under-recognised group (McMurtray et al., 2006). Among early-onset patients, a small proportion will have a familial dementia, typically Alzheimer's disease, Frontotemporal dementias or Creutzfeldt-Jacob disease. Study of these patients has been remarkably productive in elucidating the molecular mechanisms of dementia. Early-onset Alzheimer's disease is associated with mutations in three genes, the amyloid precursor protein, presenilin 1 and presenilin 2 (Hardy, 2006). Dominant, non-synonymous substitutions in the amyloid precursor protein (APP) identified in familial early-onset Alzheimer's disease cases cluster around the sites in APP that are proteolytically processed *in vivo* to generate the beta amyloid peptide (Goate et al., 1991).

Mutations in the presenilin 1 gene (PS1) are, however, the most common. This gene codes for a component of the γ -secretase – one of the enzymes responsible for the proteolytic cleavage of APP (Verdile et al., 2007). While patients with mutations in the PS1 gene typically present with early onset of a form of Alzheimer's disease indistinguishable from the much more common late-onset disease, a small proportion (Mendez and McMurtray, 2006) have features characteristic of a frontotemporal dementia (FTD). This is the most common non-Alzheimer's disease dementia. It is characterised by distinctive behavioural features that distinguish between three clinical syndromes: frontotemporal dementia, progressive nonfluent aphasia and semantic dementia (Neary et al 1998). Atrophy of the frontal and temporal lobes with intracellular deposition of abnormal proteins is FTD's distinguishing neuropathological feature. These intracellular deposits broadly divide patients into those with intracellular accumulations of abnormally phosphorylated tau protein which are not ubiquitinated, and those with ubiquitinated inclusions which do not contain tau. Recently, a hyperphosphorylated form of the TDP43 protein, a nuclear protein, has been found to be a constituent of ubiquitinated inclusions (Kwong et al., 2007). Mutations in the structural gene for microtubule associated protein tau (MAPT) are found in some patients with FTD and tau inclusions. These are characteristically associated with a form of FTD linked to chromosome 17 and show features of Parkinsonism (FTDP-17) (van Sweiten and Spillantini, 2007). These mutations are clustered chiefly in exons 9-13, either non-synonymous amino acid substitutions or mutations affecting alternate splicing of exon 10 (van Sweiten and Spillantini, 2007).

In a proportion of families linked to chromosome 17, null mutations in another gene progranulin – a growth factor – have been found (Baker et al., 2006). Recently, mutations in the charged multivesicular body protein 2B gene (CHMP2B) in another FTD syndrome showing features of amyotrophic lateral sclerosis have been identified (Skibinski et al., 2005). Finally, rare mutations at the PRNP gene that codes for the prion protein are associated (Mead, 2006) with inherited prion diseases clinically characterised as Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI).

7. Re-thinking the dementias

These findings have prompted a re-categorisation of the dementias along genetic and pathological lines (Blacker and Lovestone, 2006). For example, the tauopathies, characterised by pathological lesions in tau caused, in some cases, by mutations in MAPT, are contrasted to the synucleinopathies characterised by intracellular aggregations of synuclein in Lewy bodies and other lesions. These approaches to disease classification have proved productive in the research arena but do not replace clinical diagnoses based on symptom profile.

The insight provided by the findings of autosomal dominant genetic effects, however, has led to the development of a wide range of potential disease-modifying treatments, many of which are in late-stage clinical trials. The nosological revisions prompted by the autosomal dominant gene discoveries and accompanying neuropathological findings emphasise that clinically diverse disorders may have similar pathological processes and, hence, may share therapeutic targets. Thus, approaches to modify tau pathology may be as likely to be applicable to Alzheimer's disease, progressive supranuclear palsy and frontotemporal dementias, for example.

Autosomal dominant gene findings also raise the prospect of gene-testing for definitive differential diagnosis in life and predictive testing in unaffected family members (Williamson and LaRusse, 2004). Testing should be undertaken only in the context of familiarity with clinical genetics. Predictive testing in particular should be accompanied by extensive counselling, as is the case for Huntington's disease and other strongly familial disorders (Burgess, 1994; Karlinsky et al., 1994; Medical and Scientific Committee, Brodaty et al., 1996). These gene findings also raise difficult issues and concerns in relation to pre-natal testing and testing for non-health reasons such as insurance. This has been extensively discussed elsewhere.

8. Late-onset dementia

Late-onset Alzheimer's disease (LOAD) is the commonest dementia of the elderly, with substantial evidence for a genetic contribution to the disorder. The latest and largest twin study using the Swedish twin registry estimated heritability at 58%, with no difference between the sexes (Gatz et al., 2006). Family studies also lend support to this: relatives of LOAD patients show an increased risk of the disease compared to controls. In some studies, this reaches almost 50% compared to 10% in controls (reviewed in Shih et al., 2004).

Spurred by this apparent high genetic load, researchers have undertaken a number of studies. One early and consistently ill-health finding is the association of the $\epsilon 4$ allele of the APOE gene with LOAD. This finding is one of the most robust in complex disease genetics. The odds ratio for the $\epsilon 4/\epsilon 3$ genotype was 3.2 (95% confidence interval 2.8-3.8) and 14.9 for the $\epsilon 4/\epsilon 4$ homozygote in a meta-analysis of Caucasian samples (Farrer et al., 1997). The rarer $\epsilon 2$ allele shows evidence for a protective effect.

The $\epsilon 4$ allele of the APOE gene accounts for a large proportion of, but not all, the genetic liability for the disorder. The search for additional susceptibility genes has been the focus of much international endeavour. Several genome-wide linkage studies of affected sibling pairs have nominated susceptibility loci but, despite considerable effort, no well-replicated associations have been found. Nor have association studies of candidate genes. This research is efficiently catalogued in an online web site: (www.alzforum.org/res/com/gen/alzgene/default.asp). Meta-analysis of this data has revealed some evidence for loci of small effect acting in LOAD (Bertram et al., 2007).

The first whole genome association study of LOAD has recently been published. Its most striking finding is the absence of genes of effect size similar to APOE (Coon et al., 2007). Larger studies combined with meta-analytical techniques are needed to identify loci of moderate effect. Indeed, detailed analysis of the first data indicates that a locus acting with the APOE gene may be present (Reiman et al., 2007). Other types of variation, such as copy number variants or alleles of low frequency, would not be detected in this kind of study.

9. Behavioural and psychiatric symptoms in Alzheimer's disease

In addition to the characteristic dementia of Alzheimer's disease, sufferers also display non-cognitive symptoms. These Behavioural and Psychiatric Symptoms in Dementia (BPSD), as they are known, were recognised by Alzheimer himself. They include aggression, depression and psychosis and are present in 10-80% of patients. They are a major cause of carer stress, service costs and the most important determinant of entry into nursing homes. There is evidence that individual variation in BPSD expression may have a genetic component. In siblings with AD, depression and agitation are shared traits, while depression may be more frequent in first-degree relatives of probands with AD+depression (Strauss and Ogrocki, 1996). Psychotic symptoms also show significant familial aggregation. These are likely to be an increasingly important target for genetic research.

10. Other dementias

Other, non-AD late-onset dementias are common and constitute up to 40% or more of all dementia. Overlap conditions with an admixture of pathology are frequently found. Indeed, some evidence suggests that this may be the norm (MRC CFAS, 2001). A very large number of disorders may cause a dementia in late life, but vascular dementia in its various forms, dementia with Lewy bodies and frontotemporal variants are the most frequent non-AD disorders. There is no convincing evidence for a heritable component to any of these disorders, except for the rare familial forms.

11. Public anxieties

The frequent publicity attached to genetic findings in relation to AD, the robust association with APOE, and the very high prevalence of the disease in the population have all contributed to anxiety in relation to the use of genetic information in a clinical context. Currently, APOE testing is not recommended on the grounds that, although the association is robust, the risk is too modest to have any clinical value. However, this is a statement largely unsubstantiated by evidence. A trial is currently under way in the US designed to address the value to relatives of genetic information and the impact of APOE testing disclosure (Roberts et al., 2005).

12. Conclusions

- There are variable genetic influences on ageing, mental ill-health and dementia in the elderly, ranging from modest effects on ageing and mental ill-health in the elderly to substantial effects in rare familial dementias.
- Identification of the genetic basis of rare familial dementias has led to a greater understanding of these diseases and to dementia in general.
- The $\epsilon 4$ allele of the APOE gene remains the only well-replicated susceptibility locus for Alzheimer's disease but the search for other variants is the focus of much international effort and holds the promise of greater understanding of this disorder.

References

- Baker, M., Mackenzie, I.R., Pickering-Brown, S.M., Gass, J., Rademakers, R., Lindholm, C., Snowden, J., Adamson, J., Sadovnick, D.A., Rollinson, S., Cannon, A., Dwosh, E., Neary, D., Melquist, S., Richardson, A., Dickson, D., Berger, Z., Eriksen, J., Robinson, T., Zehr, C., Dickey, C.A., Crook, R., McGowan, E., Mann, D., Boeve, B., Feldman, H. and Hutton, M. 2006. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature*, 442:916-919.
- Batty, G.D., Der, G., Macintyre, S. and Deary, I.J. 2006. Does IQ explain socioeconomic inequalities in health? Evidence from a population based cohort study in the west of Scotland. *British Medical Journal*, 332:580-584.
- Batty, G.D., Deary I.J., Schoon, I. and Gale, C.R. 2007. Mental ability across childhood in relation to risk factors for premature mortality in adult life: the 1970 British Cohort Study. *Journal of Epidemiology and Community Health*, 61:997-1003.
- Bertram, L., McQueen, M.B., Mullin, K., Blacker, D. and Tanzi, R.E. 2007. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nature Genetics*, 39:17-23.
- Blacker, D. and Lovestone, S. 2006. Genetics and dementia nosology. *Journal of Geriatric Psychiatry and Neurology*, 19:186-191.
- Bordone, L. and Guarente, L. 2005. Calorie restriction, SIRT1 and metabolism: understanding longevity. *Nature Reviews Molecular Cell Biology*, 6:298-305.
- Brown-Borg, H.M., Borg, K.E, Meliska C.J. and Bartke, A. 1996. Dwarf mice and the ageing process. *Nature*, 384:33.

- Burgess, M.M. 1994. Ethical issues in genetic testing for Alzheimer's disease: lessons from Huntington's disease. *Alzheimer Disease Association Disorders*, 8:71-78.
- Butcher, L.M., Kennedy, J.K. and Plomin, R. 2006. Generalist genes and cognitive neuroscience. *Current Opinion on Neurobiology*, 16:145-151.
- Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A. and Poulton, R. 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*, 301:386-389.
- Clancy, D.J., Gems, D., Harshman, L.G., Oldham, S., Stocker, H., Hafen, E., Leivers, S.J. and Partridge, L. 2001. Extension of life-span by loss of CHICO, a *Drosophila* insulin receptor substrate protein. *Science*, 292:104-106.
- Coon, K.D., Myers, A.J., Craig, D.W., Webster, J.A., Pearson, J.V., Lince, D.H., Zismann V.L., Beach, T.G., Leung, D., Bryden, L., Halperin, R.F., Marlowe, L., Kaleem, M., Walker, D.G., Ravid, R., Heward, C.B., Rogers, J., Papassotiropoulos, A., Reiman, E.M., Hardy, J. and Stephan, D.A. 2007. A high-density whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset Alzheimer's disease. *Journal of Clinical Psychiatry*, 68:613-618.
- De Ferrari, G.V. and Moon, R.T. 2006. The ups and downs of Wnt signaling in prevalent neurological disorders. *Oncogene*, 25:7545-7553.
- Deary, I.J., Spinath, F.M. and Bates, T.C. 2006. Genetics of intelligence. *European Journal of Human Genetics*, 14:690-700.
- Elashoff, M., Higgs, B.W., Yolken, R.H., Knable, M.B., Weis, S., Webster, M.J., Barci, B.M., and Torrey, E.F. 2007. Meta-analysis of 12 genomic studies in bipolar disorder. *Journal of Molecular Neuroscience*, 31:221-243.
- Farrer, L.A., Cupples, L.A., Haines, J.L., Hyman, B., Kukull, W.A., Mayeux, R., Myers, R.H., Pericak-Vance, M.A., Risch, N. and Van Duijn, C.M. 1997. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *Journal of the American Medical Association*, 278:1349-1356.
- Forsell, Y., Basun, H., Corder, E.H., Lannfelt, L. and Winblad, B. 1998. Psychotic symptoms and apolipoprotein E genotypes in an elderly population. *Biology Psychiatry*, 44:139-140.
- Friedman, D.B. and Johnson, T.E. 1988. A mutation in the age-1 gene in *Caenorhabditis elegans* lengthens life and reduces hermaphrodite fertility. *Genetics*, 118:75-86.
- Gatz, M., Reynolds, C.A., Fratiglioni, L., Johansson, B., Mortimer, J.A., Berg, S., Fiske, A. and Pedersen, N.L. 2006. Role of genes and environments for explaining Alzheimer disease. *Archives of General Psychiatry*, 63:168-174.
- Goate, A., Chartier-Harlin, M.C., Mullan, M., Brown, J., Crawford, F., Fidani, L., Giuffra, L., Haynes, A., Irving, N., James, L., Mant, R., Newton, P., Rooke, K., Roques, P., Talbot, C., Pericak-Vance, M., Roses, A., Williamson, R., Rossor, M., Owen, M. and Hardy, J. 1991. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature*, 349:704-706.
- Greenwood, P.M. and Parasuraman, R. 2003. Normal genetic variation, cognition, and aging. *Behavioral and Cognitive Neuroscience Reviews*, 2:278-306.

- Harden, K.P., Turkheimer, E. and Loehlin, J.C. 2007. Genotype by environment interaction in adolescents' cognitive aptitude. *Behavior Genetics*, 37:273-283.
- Hardy, J. 2006. A hundred years of Alzheimer's disease research. *Neuron* 52:3-13.
- Howard, R., Denehey, J., Lovestone, S., Birkett, J., Powell, J.F., Castle, D., Murray, R. and Levy, R. 1995. Apolipoprotein e genotype and late paraphrenia. *International Journal of Geriatric Psychiatry*, 10:147-150.
- Hsieh, C.C., Deford, J.H., Flurkey, K., Harrison, D.E. and Papaconstantinou, J. 2002. Effects of the Pit1 mutation on the insulin signaling pathway: implications on the longevity of the long-lived Snell dwarf mouse. *Mechanics of Ageing and Development*, 123:1245-1255.
- Kaeberlein, M., McVey, M. and Guarente, L. 1999. The SIR2/3/4 complex and SIR2 alone promote longevity in *Saccharomyces cerevisiae* by two different mechanisms. *Genes and Development*, 13: 2570-2580.
- Karlinsky, H., Sadovnick, A.D., Burgess, M.M., Langlois, S., Hayden, M.R. and Berg, J.M. 1994. Issues in molecular genetic testing of individuals with suspected early-onset familial Alzheimer's disease. *Alzheimer Disease and Associated Disorders*, 8:116-125.
- Kendler, K.S., Kuhn, J.W., Vittum, J., Prescott, C.A. and Riley, B. 2005. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. *Archives of General Psychiatry*, 62: 529-535.
- Kenyon, C., Chang, J., Gensch, E., Rudner, A. and Tabtiang, R. 1993. A *C. elegans* mutant that lives twice as long as wild type. *Nature*, 366:461-464.
- Kops, G.J., Dansen, T.B., Polderman, P.E., Saarloos, I., Wirtz, K.W., Coffey, P.J., Huang, T.T., Bos, J.L., Medema, R.H., and Burgering, B.M.T. 2002. Forkhead transcription factor FOXO3a protects quiescent cells from oxidative stress. *Nature*, 419:316-321.
- Kwong, L.K., Neumann, M., Sampathu, D.M., Lee, V.M., Trojanowski, J.Q. 2007. TDP-43 proteinopathy: the neuropathology underlying major forms of sporadic and familial frontotemporal lobar degeneration and motor neuron disease. *Acta Neuropathologica*, 114: 63-70.
- Lee, S.S., Kennedy, S., Tolonen, A.C. and Ruvkun, G. 2003. DAF-16 target genes that control *C. elegans* lifespan and metabolism. *Science*, 300:644-647.
- Levinson, D.F. 2006. The genetics of depression: a review. *Biology Psychiatry*, 60: 84-92.
- Lopez-Leon, S., Janssens, A.C., Gonzalez-Zuloeta Ladd, A.M., Del-Favero, J., Claes, S.J., Oostra, B.A. and Van Duijn, C.M. 2008. Meta-analyses of genetic studies on major depressive disorder. *Molecular Psychiatry*. 13:772-85.
- Lunetta, K.L., D'Agostino, R.B., Karasik, D., Benjamin, E.J., Guo, C.Y., Govindaraju, R., Kiel, D.P., Kelly-Hayes, M., Massaro, J.M., Pencina, M.J., Seshadri, S. and Murabito, J.M. 2007. Genetic correlates of longevity and selected age-related phenotypes: a genome-wide association study in the Framingham Study. *BMC Medical Genetics*, 8:Supplement 1:S13.
- McMurtray, A., Clark, D.G., Christine, D. and Mendez, M.F. 2006. Early-onset dementia: frequency and causes compared to late-onset dementia. *Dementia and Geriatric Cognitive Disorders*, 21:59-64.

Mead, S. 2006. Prion disease genetics. *European Journal of Human Genetics*, 14:273-281.

Medical and Scientific Committee ADI, Brodaty, H., Conneally, M., Gauthier, S., Jennings, C., Lennox, A. and Lovestone, S. 1996. Consensus statement on predictive testing. *Alzheimer Disease and Associated Disorders*, 9:182-187.

Mendez, M.F. and McMurtray, A. 2006. Frontotemporal dementia-like phenotypes associated with presenilin-1 mutations. *American Journal of Alzheimer's Disease and Other Dementias*, 21:281-286.

Motta, M.C., Divecha, N., Lemieux, M., Kamel, C., Chen, D., Gu, W., Bultsma, Y., McBurney, M. and Guarente, L. 2004. Mammalian SIRT1 represses forkhead transcription factors. *Cell*, 116:551-563.

MRC CFAS. 2001. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Lancet*, 357:169-175.

Navarro, C.L., Cau, P. and Levy, N. 2006. Molecular bases of progeroid syndromes. *Human Molecular Genetics*, 15 Spec No 2:R151-R161.

Neary, D., Snowden, J.S., Gustafson, L., Passant, U., Stuss, D., Black, S., Freedman, M., Kertesz, A., Robert, P.D., Albert, M., Boone, K., Miller, B.L., Cummings, J. and Benson, D.F. 1998. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*, 51:1546-1554.

Ogg, S., Paradis, S., Gottlieb, S., Patterson, G.I., Lee, L., Tissenbaum, H.A. and Ruvkun, J. 1997. The Fork head transcription factor DAF-16 transduces insulin-like metabolic and longevity signals in *C. elegans*. *Nature*, 389:994-999.

Oliver, B.R. and Plomin, R. 2007. Twins' Early Development Study (TEDS): a multivariate, longitudinal genetic investigation of language, cognition and behavior problems from childhood through adolescence. *Twin Research and Human Genetics*, 10:96-105.

Paradis, S., Ailion, M., Toker, A., Thomas, J.H. and Ruvkun, G. 1999. A PDK1 homolog is necessary and sufficient to transduce AGE-1 PI3 kinase signals that regulate diapause in *Caenorhabditis elegans*. *Genes and Development*, 13:1438-1452.

Perls, T.T., Wilmoth, J., Levenson, R., Drinkwater, M., Cohen, M., Bogan, H., Joyce, E., Brewster, S., Kunkel, L. and Puca, A. 2002. Life-long sustained mortality advantage of siblings of centenarians. *Proceedings of the National Academy of Sciences USA*, 99:8442-8447.

Plomin, R. and Spinath, F.M. 2002. Genetics and general cognitive ability (g). *Trends in Cognitive Science*, 6:169-176.

Reiman, E.M., Webster, J.A., Myers, A.J., Hardy, J., Dunckley, T., Zismann, V.L., Joshipura, K.D., Pearson, J.V., Hu-Lince, D., Huentelman, M.J., Craig, D.W., Coon, K.D., Liang, W.S., Herbert, R.H., Beach, T., Rohrer, K.C., Zhao, A.S., Leung, D., Bryden, L., Marlowe, L., Kaleem, M., Mastroeni, D., Grover, A., Heward, C.B., Ravid, R., Rogers, J., Hutton, M.L., Melquist, S., Petersen, R.C., Alexander, G.E., Caselli, R.J., Kukull, W., Papassotiropoulos, A. and Stephan, D.A. 2007. GAB2 alleles modify Alzheimer's risk in APOE epsilon4 carriers. *Neuron*, 54:713-720.

Richards, M. and Deary I.J. 2005. A life course approach to cognitive reserve: a model for cognitive aging and development? *Annals of Neurology*, 58:617-622.

- Roberts, J.S., Cupples, L.A., Relkin, N.R., Whitehouse, P.J and Green, R.C. 2005. Genetic risk assessment for adult children of people with Alzheimer's disease: the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study. *Journal of Geriatric Psychiatry and Neurology*, 18:250-255.
- Shih, R.A., Belmonte, P.L. and Zandi, P.P. 2004. A review of the evidence from family, twin and adoption studies for a genetic contribution to adult psychiatric disorders. *International Review of Psychiatry*, 16:260-283.
- Skibinski, G., Parkinson, N.J., Brown, J.M., Chakrabarti, L., Lloyd, S.L., Hummerich, H., Nielsen, J.E., Hodges, J.R., Spillantini, M.G., Thusgaard, T., Brandner, S., Brun, A., Rossor, M.N., Gade, A., Johannsen, P., Sørensen, S.A., Gydesen, S., Fisher, E.M.C. and Collinge, J. 2005. Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. *National Genetics*, 37:806-808.
- Strauss, M.E and Ogrocki, P.K. 1996. Confirmation of an association between family history of affective disorder and the depressive syndrome in Alzheimer's disease. *American Journal of Psychiatry*, 153:1340-1342.
- Tatar, M., Kopelman, A., Epstein, D., Tu, M.P., Yin, C.M. and Garofalo, R.S. 2001. A mutant *Drosophila* insulin receptor homolog that extends life span and impairs neuroendocrine function. *Science*, 292:107-110.
- Tissenbaum, H.A. and Guarente, L. 2001. Increased dosage of a sir-2 gene extends lifespan in *Caenorhabditis elegans*. *Nature*, 410:227-230.
- Tran, H., Brunet, A., Grenier, J.M., Datta, S.R., Fornace, A.J., DiStefano, P.S., Chiang, L.W. and Greenberg, M.E. 2002. DNA repair pathway stimulated by the forkhead transcription factor FOXO3a through the Gadd45 protein. *Science*, 296:530-534.
- Uher, R. and McGuffin, P. 2008. The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: review and methodological analysis. *Molecular Psychiatry*, 13:131-46.
- Van Sweiten, J. and Spillantini, M.G. 2007. Hereditary frontotemporal dementia caused by Tau gene mutations. *Brain Pathology*, 17:63-73.
- vB Hjelmborg, J., Iachine, I., Skytthe, A., Vaupel, J.W., McGue, M., Koskenvuo, M., Kaprio, J., Pedersen, N.L. and Christensen, K. 2006. Genetic influence on human life span and longevity. *Human Genetics*, 119:312-321.
- Verdile, G., Gandy, S.E. and Martins, R.N. 2007. The role of presenilin and its interacting proteins in the biogenesis of Alzheimer's beta amyloid. *Neurochemical Research*, 32:609-623
- Williamson, J. and LaRusse, S. 2004. Genetics and genetic counseling: recommendations for Alzheimer's disease, frontotemporal dementia, and Creutzfeldt-Jakob disease. *Current Neurology and Neuroscience*, 4:351-357.
- Wood, J.G., Rogina, B., Lavu, S., Howitz, K., Helfand, S.L., Tatar, M. and Sinclair, D. 2004. Sirtuin activators mimic caloric restriction and delay ageing in metazoans. *Nature*, 430:686-689.
- WTCC. 2007. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*, 447:661-678.

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