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Brief communication

Polygenic score prediction captures nearly all common genetic risk for Alzheimer's disease

Valentina Escott-Price [a,*], Maryam Shoai [b], Richard Pither [c], Julie Williams [a], John Hardy [b,**]

[a] Institute of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics & Genomics, Cardiff University, Cardiff, UK
[b] Institute of Neurology, University College London, London, UK
[c] Cytox Ltd, UK, Oxford, UK

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ABSTRACT

We estimate the maximum prediction accuracy for the risk of Alzheimer's disease based on disease prevalence and heritability of liability. We demonstrate that the recently reported AUC values for predicting of Alzheimer's disease using polygenic scores reach about 90% of the estimated maximum accuracy that can be achieved by predictors of genetic risk based on genomic profiles.

1. Introduction

With increasing longevity due to better medical care, the prevalence of Alzheimer's disease (AD) is increasing. Hope for finding preventative and clinical therapies lies in the ability to gain a better understanding of the underlying biology of the disease, and genetics can provide a valuable starting point for advancement. Despite enormous efforts across the research community, and the successful identification of dozens of risk loci identified genes that associate with AD, the impact on therapies or prevention is negligible.

Rare monogenic forms of AD, the majority of which are attributable to mutations in 1 of 3 genes, *APP*, *PSEN1*, and *PSEN2*, exist, but common, late-onset AD is genetically complex. Along with the APOE polymorphism (Corder et al., 1993), 20 common susceptibility loci (*ABCA7*, *BIN1*, *CD33*, *CLU*, *CR1*, *CD2AP*, *EPHA1*, *MS4A4*, *PICALM*, *HLA-DRB5/DRB1*, *SORL1*, *PTK2B*, *SLC24A4/RIN3*, *ZCWPW1*, *SELF1*, *NME8*, *FERMT2*, *CASS4*, *INPP5D*, *MEF2C*, *CD33*) have been identified to be associated with AD (Harold et al., 2009; Hollingworth et al., 2011; Lambert et al., 2009, 2013; Naj et al., 2011; Seshadri et al., 2010). Two additional genes *TP53INP1* and *IGHV1-67* were reported as gene-based genome-wide significant, as well as *ZNF3* gene and a cluster of genes on chromosome 11 (*SPI1-MTCH2*), shown as gene-based genome-wide significant association with AD which are in proximity with those detected by genome-wide significant single nucleotide polymorphisms (SNPs; Escott-Price et al., 2014). Another moderately rare variant in *TREM2* has also shown evidence for association (Guerreiro et al., 2013). However, rare risk-increasing variants may not be tagged by single SNPs, as for example, the case for *CLU* in which significant enrichment of rare variants in cases was observed independent of the single locus genome-wide association signal (Bettens et al., 2012). Disease risk may reflect the coaction of several loci but the number of loci involved at the individual or the population levels are unknown, as is the spectrum of allele frequencies and effect sizes (Risch, 1990).

Recently, it has been reported that there is a large polygenic contribution to the overall heritable risk of AD (Escott-Price et al., 2015), implying that the genetic architecture of AD includes many common variants of small effect that is likely to reflect a large number of susceptibility genes and a complex set of biological pathways related to disease. The approach using the polygenic risk score (PRS), introduced by the International Schizophrenia Consortium (International Schizophrenia et al., 2009), has facilitated the creation of genomic profiles which combine the effects of many associated genetic variants to predict risk of disease.

* Corresponding author at: Institute of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics & Genomics, Cardiff University, Cardiff CF24 4HQ, UK. Tel.: +442920688429; fax: +442920687068.
** Corresponding author at: Institute of Neurology, University College London, UK. Tel.: +442034484722; fax: +442078331016.
E-mail addresses: EscottPriceV@cardiff.ac.uk (V. Escott-Price), j.hardy@ucl.ac.uk (J. Hardy).

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2. Material and methods

ROC curve analysis and area under the curve (AUC) provides the most widely accepted test of prediction accuracy in correctly classifying diseased and unaffected individuals. We were interested in investigating the maximal possible predictive power (AUC_{max}) of genomic profiles based on disease prevalence and heritability of AD. AUC_{max} is defined as the maximum AUC that could be achieved for a disease when the test classifier is a perfect predictor of genetic risk. To evaluate the maximal prediction accuracy of the genetic variability, we used the approach introduced by (Wray et al., 2010). This approach requires estimates of the heritability of liability (i.e., genetic variances on the liability scale) using genome-wide SNPs and disease prevalence. It has been reported that for AD the proportion of total variation tagged by all SNPs is 0.24 (SE 0.03; Lee et al., 2013). This variance was estimated using a restricted maximum likelihood (Yang et al., 2011) algorithm fitting all SNPs simultaneously in a data set of 3290 cases and 3849 controls (Genetic and Environmental Risk for Alzheimer's disease [GERAD1] consortium [Harold et al., 2009]), using a lifetime AD prevalence of 2% to transform the heritability on the observed scale to that on the liability scale (Brookmeyer et al., 1998).

The disease prevalence (K) is the other parameter, which has to be specified for the estimation of AUC_{max}. The prevalence of AD in the population depends very much on age. Recent estimates show a 3%, 17%, and 33% prevalence in the 65–74, 75–84, and 85+ age groups, respectively (Hebert et al., 2013). For the AUC_{max} calculations, we used the online calculator (Wray et al., 2010) and performed those for AD lifetime prevalence 2% and as well as prevalences for 3 age groups above.

Then we compared the theoretical AUC_{max} with the empirical AUC estimates provided in (Escott-Price et al., 2015). In that report, the empirical AUCs were calculated in a subsample of GERAD1 participants, for whom *APOE* genotype data were available (3049 cases and 1554 controls, mean age was 73 years [SD = 9.6]). Since the genetic architecture of AD may be different for early, medium, and late onset, therefore the heritability and, consequently, the prediction accuracy may also vary with age. Thus to make the comparison of theoretical and empirical estimates fair, we first matched the prevalence parameter used for heritability of liability estimation and AUC_{max}, and second, we compared the obtained maximum prediction accuracies with the empirical ones in the corresponding age groups. The heritability of liability h_l^2 for the disease prevalences (3%, 17%, and 33%) was re-calculated according to equation 23 in (Lee et al., 2011), $h_l^2 = h_O^2 \frac{K(1-K)}{z^2} \frac{K(1-K)}{P(1-P)}$, where P is the proportion of cases in the whole GERAD1 data set ($p = 30\%$), K is disease prevalence, h_l^2 is the estimate of heritability on the observed scale, and z^2 is the height of the standard normal probability density function at the truncation threshold K.

3. Results

The results are summarized in Table 1. Our analysis revealed that the maximum prediction accuracy is AUC_{max} = 82% (95% CI: 78%–85%) for a lifetime AD prevalence 2%. The best prediction accuracy of the PRS reported for that data set (Escott-Price et al., 2015) is AUC = 74.5% (95% CI = 0.73–0.76, see Fig. 1), calculated based on prediction results of logistic regression when *APOE* e4, e2, and PRS for SNPs with AD association p-values <0.5 were included in the model (SNPs with $r^2 > 0.2$ to the best associated SNP in the region of 1 MB were pruned out). Note that the PRS there included proxies to the 20 GWAS SNPs reported in (Lambert et al., 2013) and were based on the full IGAP data set, which includes the GERAD data set. To exclude the potential bias introduced by this fact, we recalculated the prediction accuracy based on SNPs selected only from the independent data set (IGAP-noGERAD), and the AUC was quite similar 73.7 (95% CI: 0.72–0.75). The 74% AUC accounts for about 90% (74% out of 82%) of the prediction accuracy, which can be reached using genetic data as a predictor.

In Table 1, we also present genetic variance estimates for *APOE* locus alone and for *APOE* and 20 genome-wide association study (GWAS) significant loci. Our estimates were similar to (Lee et al., 2013; Ridge et al., 2013), which were obtained using the same and an independent Alzheimer's Disease Genetics Consortium data sets, respectively. In addition, our results show the maximum AUC for *APOE* and *APOE* + GWAS loci, AUC_{max} = 65% (95% CI: 0.62–0.67) and 66% (95% CI: 0.64–0.67), respectively. A possible explanation is that in the (Escott-Price et al., 2015) article, the authors used directly genotyped e4 and e2 alleles, whereas the genetic variance estimates here were obtained with their proxies.

In the age group 65–74 (disease prevalence $K = 3\%$), the AUC_{max} came to 82% (see Table 1). This is very close to the actual AUC = 79.2% calculated in the younger group of subjects (Supplemental Table 5 in [Escott-Price et al., 2015]). Correcting for the bias in empirical AUC estimation due to not fully independent top significant SNPs, we get the AUC in this age group is 75% (95% CI: 73%–77%) which accounts for 91.5% of the AUC_{max} in this age group.

4. Conclusions

In summary, we have shown first that the pattern of the polygenic risk score prediction accuracy was similar to theoretical estimates of the accuracy based on heritability and AD prevalence. Second, the actual AUC values achieved for polygenic risk score when only ~87,600 SNPs (Escott-Price et al., 2015) were included are quite close to the upper limit (AUC_{max}) that could be achieved from that data set given the genetic epidemiology of the disease, namely disease prevalence and heritability. Thus, suggesting that while as yet unknown, the majority of the remaining common variant susceptibility loci are captured, either directly or indirectly within our polygenic risk score model for this data set.

A possible limitation of our study is that the predictive modeling (Escott-Price et al., 2015) and the estimates of the heritability of liability (Lee et al., 2013) were performed mostly on the same subjects (GERAD1 sample). However, we believe that this fact does not affect our results since the SNPs selection and the individual

Table 1
The maximum area under the ROC curve (AUC) possible, based upon the AD prevalence and heritability estimates (Lee et al., 2013)

	2% lifetime prevalence			3% prevalence (age 65–74)	17% prevalence (age 75–84)	33% prevalence (age 85+)
	All SNPs	APOE region[a]	APOE & GWAS loci[b]			
h_l^2	0.24 [0.18–0.30]	0.048 [0.032–0.063]	0.051 [0.039–0.063]	0.27 [0.20–0.33]	0.45 [0.34–0.57]	0.55 [0.41–0.68]
AUC_{max}	0.82 [0.78–0.85]	0.65 [0.62–0.67]	0.66 [0.64–0.67]	0.82 [0.78–0.86]	0.84 [0.80–0.88]	0.86 [0.81–0.90]

h_l^2 [95%CI], estimated genetic variance proportional to the total variance on the liability scale with 95% confidence intervals; AUC_{max} [95%CI], the maximum value of AUC based on the genomic profile on heritability and disease prevalence with 95% confidence intervals.
Key: AUC, area under the curve; SNPs, single nucleotide polymorphisms.
[a] The APOE region is defined between 44,400KB-46,500KB on chromosome 19 for the *APOE* locus.
[b] GWAS loci are defined as ± 500KB of both sides of the GWAS significant SNPs (Lambert et al., 2013). *APOE* region and GWAS loci were pruned with $r^2 = 0.2$.

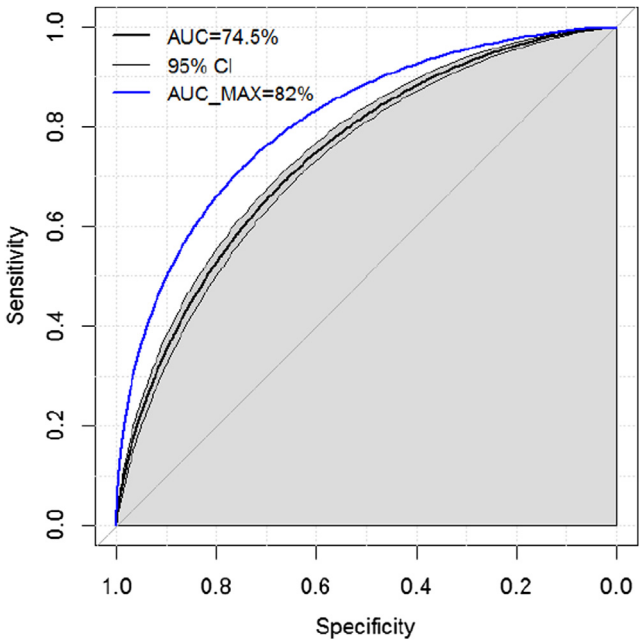

Fig. 1. Polygenic Risk score based estimation of AUC and AUC_{max} for 2% lifetime prevalence of AD. Abbreviations: AD, Alzheimer's disease; AUC, area under the curve.

SNP risk estimates for the PRS construction in the prediction modeling were based on an independent sample (IGAP without GERAD1 [Escott-Price et al., 2015]).

Considerable effort is being made through exome and genome sequencing to identify further risk loci and risk alleles for AD. Our analysis suggests that there likely to be additional genome-wide significant loci for the disease; however, identification of genome-wide significant loci, common or rare, will require substantial increase in sample sizes. This is consistent with the relatively low number of new findings achieved through the extensive AD sequencing efforts that have already been initiated (Fuchsberger et al., 2016). There will, almost certainly, be other allelic variants that influence disease risk identified at the known loci, however, since linkage disequilibrium between low frequency causal variants and commonly genotyped SNPs is low (Wray, 2005), it is likely that those variants will be rare. Our analysis also indicates that the contribution of any new findings, not already captured by polygenic risk score, to the overall prediction of AD risk is likely to be small and will be attributed to rare variants.

One can also further enhance the AUC by adding more environmental and/or clinical information. For example, the addition of age and gender to the prediction model increased the AUC value from 74.5% to 78.2% (95% CI: 77%–80%; Escott-Price et al., 2015). It is possible now to add to the genomic profile nonheritable genetic variants, such as de novo copy number variants or DNA methylation status. These variables do not contribute to heritability and therefore such genomic profiles could exceed the AUC_{max} presented here. The prediction accuracy could be hampered by the heterogeneity in AD definition. For example, (Corneveaux et al., 2010) have shown increased association effect sizes for neuropathologically confirmed AD cases and controls compared to international consortia which generally use clinically diagnosed samples. We advocate that more accurate classification of disease will further increase the risk prediction accuracy.

In conclusion, this analysis suggests that the polygenic risk profiling captures the SNP-heritability very well and is quite suitable for AD genetic risk prediction purpose. However, heritability estimates are very uncertain, especially in a late-onset disease. We would advocate, in view of our analysis, that the additional contribution of new AD loci or new pathways which are undiscovered (Jones et al., 2010), is not crucial for genetic prediction due to the small increase in AUC that this would achieve. The additional variability at the loci, which are at least partially captured by the polygenic risk SNPs, will account for small proportions of SNP-heritability (Steinberg et al., 2015). Further analysis will clarify the significance of loci that do not currently reach genome-wide significance in the biological pathways we have established as being important in disease. This will further inform the understanding of disease mechanisms and targets for future treatments.

Disclosure statement

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References

Bettens, K., Brouwers, N., Engelborghs, S., Lambert, J.C., Rogaeva, E., Vandenberghe, R., Le Bastard, N., Pasquier, F., Vermeulen, S., Van Dongen, J., Mattheijssens, M., Peeters, K., Mayeux, R., St George-Hyslop, P., Amouyel, P., De Deyn, P.P., Sleegers, K., Van Broeckhoven, C., 2012. Both common variations and rare non-synonymous substitutions and small insertion/deletions in CLU are associated with increased Alzheimer risk. Mol. Neurodegener. 7, 3.

Brookmeyer, R., Gray, S., Kawas, C., 1998. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am. J. Public Health 88, 1337–1342.

Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G.W., Roses, A.D., Haines, J.L., Pericak-Vance, M.A., 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261, 921–923.

Corneveaux, J.J., Myers, A.J., Allen, A.N., Pruzin, J.J., Ramirez, M., Engel, A., Nalls, M.A., Chen, K., Lee, W., Chewning, K., Villa, S.E., Meechoovet, H.B., Gerber, J.D., Frost, D., Benson, H.L., O'Reilly, S., Chibnik, L.B., Shulman, J.M., Singleton, A.B., Craig, D.W., Van Keuren-Jensen, K.R., Dunckley, T., Bennett, D.A., De Jager, P.L., Heward, C., Hardy, J., Reiman, E.M., Huentelman, M.J., 2010. Association of CR1, CLU and PICALM with Alzheimer's disease in a cohort of clinically characterized and neuropathologically verified individuals. Hum. Mol. Genet. 19, 3295–3301.

Escott-Price, V., Bellenguez, C., Wang, L.S., Choi, S.H., Harold, D., Jones, L., Holmans, P., Gerrish, A., Vedernikov, A., Richards, A., DeStefano, A.L., Lambert, J.C., Ibrahim-Verbaas, C.A., Naj, A.C., Sims, R., Jun, G., Bis, J.C., Beecham, G.W., Grenier-Boley, B., Russo, G., Thornton-Wells, T.A., Denning, N., Smith, A.V., Chouraki, V., Thomas, C., Ikram, M.A., Zelenika, D., Vardarajan, B.N., Kamatani, Y., Lin, C.F., Schmidt, H., Kunkle, B., Dunstan, M.L., Vronskaya, M., United Kingdom Brain Expression, C., Johnson, A.D., Ruiz, A., Bihoreau, M.T., Reitz, C., Pasquier, F., Hollingworth, P., Hanon, O., Fitzpatrick, A.L., Buxbaum, J.D., Campion, D., Crane, P.K., Baldwin, C., Becker, T., Gudnason, V., Cruchaga, C., Craig, D., Amin, N., Berr, C., Lopez, O.L., De Jager, P.L., Deramecourt, V., Johnston, J.A., Evans, D., Lovestone, S., Letenneur, L., Hernandez, I., Rubinsztein, D.C., Eiriksdottir, G., Sleegers, K., Goate, A.M., Fievet, N., Huentelman, M.J., Gill, M., Brown, K., Kamboh, M.I., Keller, L., Barberger-Gateau, P., McGuinness, B., Larson, E.B., Myers, A.J., Dufouil, C., Todd, S., Wallon, D., Love, S., Rogaeva, E., Gallacher, J., George-Hyslop, P.S., Clarimon, J., Lleo, A., Bayer, A., Tsuang, D.W., Yu, L., Tsolaki, M., Bossu, P., Spalletta, G., Proitsi, P., Collinge, J., Sorbi, S., Garcia, F.S., Fox, N.C., Hardy, J., Naranjo, M.C., Bosco, P., Clarke, R., Brayne, C., Galimberti, D., Scarpini, E., Bonuccelli, U., Mancuso, M., Siciliano, G., Moebus, S., Mecocci, P., Zompo, M.D., Maier, W., Hampel, H., Pilotto, A., Frank-Garcia, A., Panza, F., Solfrizzi, V., Caffarra, P., Nacmias, B., Perry, W., Mayhaus, M., Lannfelt, L., Hakonarson, H., Pichler, S., Carrasquillo, M.M., Ingelsson, M., Beekly, D., Alvarez, V., Zou, F., Valladares, O., Younkin, S.G., Coto, E., Hamilton-Nelson, K.L., Gu, W., Razquin, C., Pastor, P., Mateo, I., Owen, M.J., Faber, K.M., Jonsson, P.V., Combarros, O., O'Donovan, M.C., Cantwell, L.B., Soininen, H., Blacker, D., Mead, S., Mosley Jr., T.H., Bennett, D.A., Harris, T.B., Fratiglioni, L., Holmes, C., de Bruijn, R.F., Passmore, P., Montine, T.J., Bettens, K., Rotter, J.I., Brice, A., Morgan, K., Foroud, T.M., Kukull, W.A., Hannequin, D., Powell, J.F., Nalls, M.A., Ritchie, K., Lunetta, K.L., Kauwe, J.S., Boerwinkle, E., Riemenschneider, M., Boada, M., Hiltunen, M., Martin, E.R., Schmidt, R., Rujescu, D., Dartigues, J.F., Mayeux, R., Tzourio, C., Hofman, A., Nothen, M.M., Graff, C., Psaty, B.M., Haines, J.L., Lathrop, M.,

Pericak-Vance, M.A., Launer, L.J., Van Broeckhoven, C., Farrer, L.A., van Duijn, C.M., Ramirez, A., Seshadri, S., Schellenberg, G.D., Amouyel, P., Williams, J., Cardiovascular Health, S., 2014. Gene-wide analysis detects two new susceptibility genes for Alzheimer's disease. PLoS One 9, e94661.

Escott-Price, V., Sims, R., Bannister, C., Harold, D., Vronskaya, M., Majounie, E., Badarinarayan, N., Morgan, K., Passmore, P., Holmes, C., Powell, J., Brayne, C., Gill, M., Mead, S., Goate, A., Cruchaga, C., Lambert, J.C., van Duijn, C., Maier, W., Ramirez, A., Holmans, P., Jones, L., Hardy, J., Seshadri, S., Schellenberg, G.D., Amouyel, P., Williams, J., PERADES, G., Consortia, I., 2015. Common polygenic variation enhances risk prediction for Alzheimer's disease. Brain 138, 3673–3684.

Fuchsberger, C., Flannick, J., Teslovich, T.M., Mahajan, A., Agarwala, V., Gaulton, K.J., Ma, C., Fontanillas, P., Moutsianas, L., McCarthy, D.J., Rivas, M.A., Perry, J.R., Sim, X., Blackwell, T.W., Robertson, N.R., Rayner, N.W., Cingolani, P., Locke, A.E., Tajes, J.F., Highland, H.M., Dupuis, J., Chines, P.S., Lindgren, C.M., Hartl, C., Jackson, A.U., Chen, H., Huyghe, J.R., van de Bunt, M., Pearson, R.D., Kumar, A., Muller-Nurasyid, M., Grarup, N., Stringham, H.M., Gamazon, E.R., Lee, J., Chen, Y., Scott, R.A., Below, J.E., Chen, P., Huang, J., Go, M.J., Stitzel, M.L., Pasko, D., Parker, S.C., Varga, T.V., Green, T., Beer, N.L., Day-Williams, A.G., Ferreira, T., Fingerlin, T., Horikoshi, M., Hu, C., Huh, I., Ikram, M.K., Kim, B.J., Kim, Y., Kim, Y.J., Kwon, M.S., Lee, J., Lee, S., Lin, K.H., Maxwell, T.J., Nagai, Y., Wang, X., Welch, R.P., Yoon, J., Zhang, W., Barzilai, N., Voight, B.F., Han, B.G., Jenkinson, C.P., Kuulasmaa, T., Kuusisto, J., Manning, A., Ng, M.C., Palmer, N.D., Balkau, B., Stancakova, A., Abboud, H.E., Boeing, H., Giedraitis, V., Prabhakaran, D., Gottesman, O., Scott, J., Carey, J., Kwan, P., Grant, G., Smith, J.D., Neale, B.M., Purcell, S., Butterworth, A.S., Howson, J.M., Lee, H.M., Lu, Y., Kwak, S.H., Zhao, W., Danesh, J., Lam, V.K., Park, K.S., Saleheen, D., So, W.Y., Tam, C.H., Afzal, U., Aguilar, D., Arya, R., Aung, T., Chan, E., Navarro, C., Cheng, C.Y., Palli, D., Correa, A., Curran, J.E., Rybin, D., Farook, V.S., Fowler, S.P., Freedman, B.I., Griswold, M., Hale, D.E., Hicks, P.J., Khor, C.C., Kumar, S., Lehne, B., Thuillier, D., Lim, W.Y., Liu, J., van der Schouw, Y.T., Loh, M., Musani, S.K., Puppala, S., Scott, W.R., Yengo, L., Tan, S.T., Taylor Jr., H.A., Thameem, F., Wilson, G., Wong, T.Y., Njolstad, P.R., Levy, J.C., Mangino, M., Bonnycastle, L.L., Schwarzmayr, T., Fadista, J., Surdulescu, G.L., Herder, C., Groves, C.J., Wieland, T., Bork-Jensen, J., Brandslund, I., Christensen, C., Koistinen, H.A., Doney, A.S., Kinnunen, L., Esko, T., Farmer, A.J., Hakaste, L., Hodgkiss, D., Kravic, J., Lyssenko, V., Hollensted, M., Jorgensen, M.E., Jorgensen, T., Ladenvall, C., Justesen, J.M., Karajamaki, A., Kriebel, J., Rathmann, W., Lannfelt, L., Lauritzen, T., Narisu, N., Linneberg, A., Melander, O., Milani, L., Neville, M., Orho-Melander, M., Qi, L., Qi, Q., Roden, M., Rolandsson, O., Swift, A., Rosengren, A.H., Stirrups, K., Wood, A.R., Mihailov, E., Blancher, C., Carneiro, M.O., Maguire, J., Poplin, R., Shakir, K., Fennell, T., DePristo, M., Hrabe de Angelis, M., Deloukas, P., Gjesing, A.P., Jun, G., Nilsson, P., Murphy, J., Onofrio, R., Thorand, B., Hansen, T., Meisinger, C., Hu, F.B., Isomaa, B., Karpe, F., Liang, L., Peters, A., Huth, C., O'Rahilly, S.P., Palmer, C.N., Pedersen, O., Rauramaa, R., Tuomilehto, J., Salomaa, V., Watanabe, R.M., Syvanen, A.C., Bergman, R.N., Bharadwaj, D., Bottinger, E.P., Cho, Y.S., Chandak, G.R., Chan, J.C., Chia, K.S., Daly, M.J., Ebrahim, S.B., Langenberg, C., Elliott, P., Jablonski, K.A., Lehman, D.M., Jia, W., Ma, R.C., Pollin, T.I., Sandhu, M., Tandon, N., Froguel, P., Barroso, I., Teo, Y.Y., Zeggini, E., Loos, R.J., Small, K.S., Ried, J.S., DeFronzo, R.A., Grallert, H., Glaser, B., Metspalu, A., Wareham, N.J., Walker, M., Banks, E., Gieger, C., Ingelsson, E., Im, H.K., Illig, T., Franks, P.W., Buck, G., Trakalo, J., Buck, D., Prokopenko, I., Magi, R., Lind, L., Farjoun, Y., Owen, K.R., Gloyn, A.L., Strauch, K., Tuomi, T., Kooner, J.S., Lee, J.Y., Park, T., Donnelly, P., Morris, A.D., Hattersley, A.T., Bowden, D.W., Collins, F.S., Atzmon, G., Chambers, J.C., Spector, T.D., Laakso, M., Strom, T.M., Bell, G.I., Blangero, J., Duggirala, R., Tai, E.S., McVean, G., Hanis, C.L., Wilson, J.G., Seielstad, M., Frayling, T.M., Meigs, J.B., Cox, N.J., Sladek, R., Lander, E.S., Gabriel, S., Burtt, N.P., Mohlke, K.L., Meitinger, T., Groop, L., Abecasis, G., Florez, J.C., Scott, L.J., Morris, A.P., Kang, H.M., Boehnke, M., Altshuler, D., McCarthy, M.I, 2016. The genetic architecture of type 2 diabetes. Nature 536, 41–47.

Guerreiro, R., Wojtas, A., Bras, J., Carrasquillo, M., Rogaeva, E., Majounie, E., Cruchaga, C., Sassi, C., Kauwe, J.S., Younkin, S., Hazrati, L., Collinge, J., Pocock, J., Lashley, T., Williams, J., Lambert, J.C., Amouyel, P., Goate, A., Rademakers, R., Morgan, K., Powell, J., St George-Hyslop, P., Singleton, A., Hardy, J., 2013. TREM2 variants in Alzheimer's disease. N. Engl. J. Med. 368, 117–127.

Harold, D., Abraham, R., Hollingworth, P., Sims, R., Gerrish, A., Hamshere, M.L., Pahwa, J.S., Moskvina, V., Dowzell, K., Williams, A., Jones, N., Thomas, C., Stretton, A., Morgan, A.R., Lovestone, S., Powell, J., Proitsi, P., Lupton, M.K., Brayne, C., Rubinsztein, D.C., Gill, M., Lawlor, B., Lynch, A., Morgan, K., Brown, K.S., Passmore, P.A., Craig, D., McGuinness, B., Todd, S., Holmes, C., Mann, D., Smith, A.D., Love, S., Kehoe, P.G., Hardy, J., Mead, S., Fox, N., Rossor, M., Collinge, J., Maier, W., Jessen, F., Schurmann, B., van den Bussche, H., Heuser, I., Kornhuber, J., Wiltfang, J., Dichgans, M., Frolich, L., Hampel, H., Hull, M., Rujescu, D., Goate, A.M., Kauwe, J.S., Cruchaga, C., Nowotny, P., Morris, J.C., Mayo, K., Sleegers, K., Bettens, K., Engelborghs, S., De Deyn, P.P., Van Broeckhoven, C., Livingston, G., Bass, N.J., Gurling, H., McQuillin, A., Gwilliam, R., Deloukas, P., Al-Chalabi, A., Shaw, C.E., Tsolaki, M., Singleton, A.B., Guerreiro, R., Muhleisen, T.W., Nothen, M.M., Moebus, S., Jockel, K.H., Klopp, N., Wichmann, H.E., Carrasquillo, M.M., Pankratz, V.S., Younkin, S.G., Holmans, P.A., O'Donovan, M., Owen, M.J., Williams, J., 2009. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat. Genet. 41, 1088–1093.

Hebert, L.E., Weuve, J., Scherr, P.A., Evans, D.A., 2013. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology 80, 1778–1783.

Hollingworth, P., Harold, D., Sims, R., Gerrish, A., Lambert, J.C., Carrasquillo, M.M., Abraham, R., Hamshere, M.L., Pahwa, J.S., Moskvina, V., Dowzell, K., Jones, N., Stretton, A., Thomas, C., Richards, A., Ivanov, D., Widdowson, C., Chapman, J., Lovestone, S., Powell, J., Proitsi, P., Lupton, M.K., Brayne, C., Rubinsztein, D.C., Gill, M., Lawlor, B., Lynch, A., Brown, K.S., Passmore, P.A., Craig, D., McGuinness, B., Todd, S., Holmes, C., Mann, D., Smith, A.D., Beaumont, H., Warden, D., Wilcock, G., Love, S., Kehoe, P.G., Hooper, N.M., Vardy, E.R.L.C., Hardy, J., Mead, S., Fox, N.C., Rossor, M., Collinge, J., Maier, W., Jessen, F., Ruther, E., Schurmann, B., Heun, R., Kolsch, H., van den Bussche, H., Heuser, I., Kornhuber, J., Wiltfang, J., Dichgans, M., Frolich, L., Hampel, H., Gallacher, J., Hull, M., Rujescu, D., Giegling, I., Goate, A.M., Kauwe, J.S.K., Cruchaga, C., Nowotny, P., Morris, J.C., Mayo, K., Sleegers, K., Bettens, K., Engelborghs, S., De Deyn, P.P., Van Broeckhoven, C., Livingston, G., Bass, N.J., Gurling, H., McQuillin, A., Gwilliam, R., Deloukas, P., Al-Chalabi, A., Shaw, C.E., Tsolaki, M., Singleton, A.B., Guerreiro, R., Muhleisen, T.W., Nothen, M.M., Moebus, S., Jockel, K.H., Klopp, N., Wichmann, H.E., Carrasquillo, M.M., Pankratz, V.S., Sando, S.B., Aasly, J.O., Barcikowska, M., Wszolek, Z.K., Dickson, D.W., Graff-Radford, N.R., Petersen, R.C., van Duijn, C.M., Breteler, M.M.B., Ikram, M.A., DeStefano, A.L., Fitzpatrick, A.L., Lopez, O., Launer, L.J., Seshadri, S., Berr, C., Campion, D., Epelbaum, J., Dartigues, J.F., Tzourio, C., Alperovitch, A., Lathrop, M., Feulner, T.M., Friedrich, P., Riehle, C., Krawczak, M., Schreiber, S., Mayhaus, M., Nicolhaus, S., Wagenpfeil, S., Steinberg, S., Stefansson, H., Stefansson, K., Snaedal, J., Bjornsson, S., Jonsson, P.V., Chouraki, V., Genier-Boley, B., Hiltunen, M., Soininen, H., Combarros, O., Zelenika, D., Delepine, M., Bullido, M.J., Pasquier, F., Mateo, I., Frank-Garcia, A., Porcellini, E., Hanon, O., Coto, E., Alvarez, V., Bosco, P., Siciliano, G., Mancuso, M., Panza, F., Solfrizzi, V., Nacmias, B., Sorbi, S., Bossu, P., Piccardi, P., Arosio, B., Annoni, G., Seripa, D., Pilotto, A., Scarpini, E., Galimberti, D., Brice, A., Hannequin, D., Licastro, F., Jones, L., Holmans, P.A., Jonsson, T., Riemenschneider, M., Morgan, K., Younkin, S.G., Owen, M.J., O'Donovan, M., Amouyel, P., Williams, J., Neuroimaging, A.s.D., Consortium, C., Consortium, E., 2011. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. Nat. Genet. 43, 429–435.

International Schizophrenia, C., Wray, N.R., Stone, J.L., Visscher, P.M., O'Donovan, M.C., Sullivan, P.F., Sklar, P., 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460, 748–752.

Jones, L., Holmans, P.A., Hamshere, M.L., Harold, D., Moskvina, V., Ivanov, D., Pocklington, A., Abraham, R., Hollingworth, P., Sims, R., Gerrish, A., Pahwa, J.S., Jones, N., Stretton, A., Morgan, A.R., Lovestone, S., Powell, J., Proitsi, P., Lupton, M.K., Brayne, C., Rubinsztein, D.C., Gill, M., Lawlor, B., Lynch, A., Morgan, K., Brown, K.S., Passmore, P.A., Craig, D., McGuinness, B., Todd, S., Holmes, C., Mann, D., Smith, A.D., Love, S., Kehoe, P.G., Mead, S., Fox, N., Rossor, M., Collinge, J., Maier, W., Jessen, F., Schurmann, B., Heun, R., Kolsch, H., van den Bussche, H., Heuser, I., Peters, O., Kornhuber, J., Wiltfang, J., Dichgans, M., Frolich, L., Hampel, H., Hull, M., Rujescu, D., Goate, A.M., Kauwe, J.S., Cruchaga, C., Nowotny, P., Morris, J.C., Mayo, K., Livingston, G., Bass, N.J., Gurling, H., McQuillin, A., Gwilliam, R., Deloukas, P., Al-Chalabi, A., Shaw, C.E., Singleton, A.B., Guerreiro, R., Muhleisen, T.W., Nothen, M.M., Moebus, S., Jockel, K.H., Klopp, N., Wichmann, H.E., Ruther, E., Carrasquillo, M.M., Pankratz, V.S., Younkin, S.G., Hardy, J., O'Donovan, M.C., Owen, M.J., Williams, J., 2010. Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease. PLoS One 5, e13950.

Lambert, J.C., Heath, S., Even, G., Campion, D., Sleegers, K., Hiltunen, M., Combarros, O., Zelenika, D., Bullido, M.J., Tavernier, B., Letenneur, L., Bettens, K., Berr, C., Pasquier, F., Fievet, N., Barberger-Gateau, P., Engelborghs, S., De Deyn, P., Mateo, I., Franck, A., Helisalmi, S., Porcellini, E., Hanon, O., de Pancorbo, M.M., Lendon, C., Dufouil, C., Jaillard, C., Leveillard, T., Alvarez, V., Bosco, P., Mancuso, M., Panza, F., Nacmias, B., Bossu, P., Piccardi, P., Annoni, G., Seripa, D., Galimberti, D., Hannequin, D., Licastro, F., Soininen, H., Ritchie, K., Blanche, H., Dartigues, J.F., Tzourio, C., Gut, I., Van Broeckhoven, C., Alperovitch, A., Lathrop, M., Amouyel, P., 2009. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat. Genet. 41, 1094–1099.

Lambert, J.C., Ibrahim-Verbaas, C.A., Harold, D., Naj, A.C., Sims, R., Bellenguez, C., DeStafano, A.L., Bis, J.C., Beecham, G.W., Grenier-Boley, B., Russo, G., Thorton-Wells, T.A., Jones, N., Smith, A.V., Chouraki, V., Thomas, C., Ikram, M.A., Zelenika, D., Vardarajan, B.N., Kamatani, Y., Lin, C.F., Gerrish, A., Schmidt, H., Kunkle, B., Dunstan, M.L., Ruiz, A., Bihoreau, M.T., Choi, S.H., Reitz, C., Pasquier, F., Cruchaga, C., Craig, D., Amin, N., Berr, C., Lopez, O.L., De Jager, P.L., Deramecourt, V., Johnston, J.A., Evans, D., Lovestone, S., Letenneur, L., Moron, F.J., Rubinsztein, D.C., Eiriksdottir, G., Sleegers, K., Goate, A.M., Fievet, N., Huentelman, M.W., Gill, M., Brown, K., Kamboh, M.I., Keller, L., Barberger-Gateau, P., McGuiness, B., Larson, E.B., Green, R., Myers, A.J., Dufouil, C., Todd, S., Wallon, D., Love, S., Rogaeva, E., Gallacher, J., St George-Hyslop, P., Clarimon, J., Lleo, A., Bayer, A., Tsuang, D.W., Yu, L., Tsolaki, M., Bossu, P., Spalletta, G., Proitsi, P., Collinge, J., Sorbi, S., Sanchez-Garcia, F., Fox, N.C., Hardy, J., Deniz Naranjo, M.C., Bosco, P., Clarke, R., Brayne, C., Galimberti, D., Mancuso, M., Matthews, F., European Alzheimer's Disease, I., Genetic, Environmental Risk in Alzheimer's, D., Alzheimer's Disease Genetic, C., Cohorts for, H., Aging Research in Genomic, E., Moebus, S., Mecocci, P., Del Zompo, M., Maier, W., Hampel, H., Pilotto, A., Bullido, M., Panza, F., Caffarra, P., Nacmias, B., Gilbert, J.R., Mayhaus, M., Lannefelt, L., Hakonarson, H., Pichler, S., Carrasquillo, M.M., Ingelsson, M., Beekly, D., Alvarez, V., Zou, F., Valladares, O., Younkin, S.G.,

Coto, E., Hamilton-Nelson, K.L., Gu, W., Razquin, C., Pastor, P., Mateo, I., Owen, M.J., Faber, K.M., Jonsson, P.V., Combarros, O., O'Donovan, M.C., Cantwell, L.B., Soininen, H., Blacker, D., Mead, S., Mosley, T.H., Bennett Jr., D.A., Harris, T.B., Fratiglioni, L., Holmes, C., de Bruijn, R.F., Passmore, P., Montine, T.J., Bettens, K., Rotter, J.I., Brice, A., Morgan, K., Foroud, T.M., Kukull, W.A., Hannequin, D., Powell, J.F., Nalls, M.A., Ritchie, K., Lunetta, K.L., Kauwe, J.S., Boerwinkle, E., Riemenschneider, M., Boada, M., Hiltuenen, M., Martin, E.R., Schmidt, R., Rujescu, D., Wang, L.S., Dartigues, J.F., Mayeux, R., Tzourio, C., Hofman, A., Nothen, M.M., Graff, C., Psaty, B.M., Jones, L., Haines, J.L., Holmans, P.A., Lathrop, M., Pericak-Vance, M.A., Launer, L.J., Farrer, L.A., van Duijn, C.M., Van Broeckhoven, C., Moskvina, V., Seshadri, S., Williams, J., Schellenberg, G.D., Amouyel, P., 2013. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat. Genet. 45, 1452–1458.

Lee, S.H., Harold, D., Nyholt, D.R., Consortium, A.N., International Endogene, C., Genetic, Environmental Risk for Alzheimer's disease, C., Goddard, M.E., Zondervan, K.T., Williams, J., Montgomery, G.W., Wray, N.R., Visscher, P.M., 2013. Estimation and partitioning of polygenic variation captured by common SNPs for Alzheimer's disease, multiple sclerosis and endometriosis. Hum. Mol. Genet. 22, 832–841.

Lee, S.H., Wray, N.R., Goddard, M.E., Visscher, P.M., 2011. Estimating missing heritability for disease from genome-wide association studies. Am. J. Hum. Genet. 88, 294–305.

Naj, A.C., Jun, G., Beecham, G.W., Wang, L.S., Vardarajan, B.N., Buros, J., Gallins, P.J., Buxbaum, J.D., Jarvik, G.P., Crane, P.K., Larson, E.B., Bird, T.D., Boeve, B.F., Graff-Radford, N.R., De Jager, P.L., Evans, D., Schneider, J.A., Carrasquillo, M.M., Ertekin-Taner, N., Younkin, S.G., Cruchaga, C., Kauwe, J.S.K., Nowotny, P., Kramer, P., Hardy, J., Huentelman, M.J., Myers, A.J., Barmada, M.M., Demirci, F.Y., Baldwin, C.T., Green, R.C., Rogaeva, E., St George-Hyslop, P., Arnold, S.E., Barber, R., Beach, T., Bigio, E.H., Bowen, J.D., Boxer, A., Burke, J.R., Cairns, N.J., Carlson, C.S., Carney, R.M., Carroll, S.L., Chui, H.C., Clark, D.G., Corneveaux, J., Cotman, C.W., Cummings, J.L., DeCarli, C., DeKosky, S.T., Diaz-Arrastia, R., Dick, M., Dickson, D.W., Ellis, W.G., Faber, K.M., Fallon, K.B., Farlow, M.R., Ferris, S., Frosch, M.P., Galasko, D.R., Ganguli, M., Gearing, M., Geschwind, D.H., Ghetti, B., Gilbert, J.R., Gilman, S., Giordani, B., Glass, J.D., Growdon, J.H., Hamilton, R.L., Harrell, L.E., Head, E., Honig, L.S., Hulette, C.M., Hyman, B.T., Jicha, G.A., Jin, L.W., Johnson, N., Karlawish, J., Karydas, A., Kaye, J.A., Kim, R., Koo, E.H., Kowall, N.W., Lah, J.J., Levey, A.I., Lieberman, A.P., Lopez, O.L., Mack, W.J., Marson, D.C., Martiniuk, F., Mash, D.C., Masliah, E., McCormick, W.C., McCurry, S.M., McDavid, A.N., Mckee, A.C., Mesulam, M., Miller, B.L., Miller, C.A., Miller, J.W., Parisi, J.E., Perl, D.P., Peskind, E., Petersen, R.C., Poon, W.W., Quinn, J.F., Rajbhandary, R.A., Raskind, M., Reisberg, B., Ringman, J.M., Roberson, E.D., Rosenberg, R.N., Sano, M., Schneider, L.S., Seeley, W., Shelanski, M.L., Slifer, M.A., Smith, C.D., Sonnen, J.A., Spina, S., Stern, R.A., Tanzi, R.E., Trojanowski, J.Q., Troncoso, J.C., Van Deerlin, V.M., Vinters, H.V., Vonsattel, J.P., Weintraub, S., Welsh-Bohmer, K.A., Williamson, J., Woltjer, R.L., Cantwell, L.B., Dombroski, B.A., Beekly, D., Lunetta, K.L., Martin, E.R., Kamboh, M.I., Saykin, A.J., Reiman, E.M., Bennett, D.A., Morris, J.C., Montine, T.J., Goate, A.M., Blacker, D., Tsuang, D.W., Hakonarson, H., Kukull, W.A., Foroud, T.M., Haines, J.L., Mayeux, R., Pericak-Vance, M.A., Farrer, L.A., Schellenberg, G.D., 2011. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. Nat. Genet. 43, 436–441.

Ridge, P.G., Mukherjee, S., Crane, P.K., Kauwe, J.S., Alzheimer's Disease Genetics, C., 2013. Alzheimer's disease: analyzing the missing heritability. PLoS One 8, e79771.

Risch, N., 1990. Linkage strategies for genetically complex traits. I. Multilocus models. Am. J. Hum. Genet. 46, 222–228.

Seshadri, S., Fitzpatrick, A.L., Ikram, M.A., DeStefano, A.L., Gudnason, V., Boada, M., Bis, J.C., Smith, A.V., Carassquillo, M.M., Lambert, J.C., Harold, D., Schrijvers, E.M., Ramirez-Lorca, R., Debette, S., Longstreth, W.T., Janssens Jr., A.C., Pankratz, V.S., Dartigues, J.F., Hollingworth, P., Aspelund, T., Hernandez, I., Beiser, A., Kuller, L.H., Koudstaal, P.J., Dickson, D.W., Tzourio, C., Abraham, R., Antunez, C., Du, Y., Rotter, J.I., Aulchenko, Y.S., Harris, T.B., Petersen, R.C., Berr, C., Owen, M.J., Lopez-Arrieta, J., Varadarajan, B.N., Becker, J.T., Rivadeneira, F., Nalls, M.A., Graff-Radford, N.R., Campion, D., Auerbach, S., Rice, K., Hofman, A., Jonsson, P.V., Schmidt, H., Lathrop, M., Mosley, T.H., Au, R., Psaty, B.M., Uitterlinden, A.G., Farrer, L.A., Lumley, T., Ruiz, A., Williams, J., Amouyel, P., Younkin, S.G., Wolf, P.A., Launer, L.J., Lopez, O.L., van Duijn, C.M., Breteler, M.M., 2010. Genome-wide analysis of genetic loci associated with Alzheimer disease. JAMA 303, 1832–1840.

Steinberg, S., Stefansson, H., Jonsson, T., Johannsdottir, H., Ingason, A., Helgason, H., Sulem, P., Magnusson, O.T., Gudjonsson, S.A., Unnsteinsdottir, U., Kong, A., Helisalmi, S., Soininen, H., Lah, J.J., Aarsland, D., Fladby, T., Ulstein, I.D., Djurovic, S., Sando, S.B., White, L.R., Knudsen, G.P., Westlye, L.T., Selbaek, G., Giegling, I., Hampel, H., Hiltunen, M., Levey, A.I., Andreassen, O.A., Rujescu, D., Jonsson, P.V., Bjornsson, S., Snaedal, J., Stefansson, K., DemGene., 2015. Loss-of-function variants in ABCA7 confer risk of Alzheimer's disease. Nat. Genet. 47, 445–447.

Wray, N.R., 2005. Allele frequencies and the r2 measure of linkage disequilibrium: impact on design and interpretation of association studies. Twin Res. Hum. Genet. 8, 87–94.

Wray, N.R., Yang, J., Goddard, M.E., Visscher, P.M., 2010. The genetic interpretation of area under the ROC curve in genomic profiling. PLoS Genet. 6, e1000864.

Yang, J., Lee, S.H., Goddard, M.E., Visscher, P.M., 2011. GCTA: a tool for genome-wide complex trait analysis. Am. J. Hum. Genet. 88, 76–82.

Web Resources: http://gump.qimr.edu.au/genroc/genroc_calc_nrw.cgi