Published in final edited form as:
Eur J Epidemiol. 2012 November ; 27(11): 831–836. doi:10.1007/s10654-012-9742-2.

Next frontiers in the genetic epidemiology of Alzheimer's disease

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A recent report by Alzheimer Disease International showed that the number of persons suffering from Alzheimer's disease will quadruple by 2050 (http://www.alz.co.uk/research/world-report-2011). This increase is predicted to occur globally and will likely pose a great societal burden, both in terms of financial costs as well as suffering for patients and care-givers [1]. Thus, there is a strong incentive to develop effective preventive and therapeutic strategies. In order to develop such strategies, full knowledge of the pathophysiology of Alzheimer's disease is an essential first step. Similarly, identification of people at high risk of Alzheimer's disease is equally important. Fully understanding the disease pathology and early detection methods would facilitate implementation of targeted interventions in those people, who would benefit from it most.

Genetic research has been essential to the fundamental understanding of Alzheimer's disease. Family studies have repeatedly shown strong heritability of Alzheimer's disease, with heritability estimated to be between 60 and 80 % [2]. Against this background, linkage studies have long established *APP*, *PSEN1*, *PSEN2* as mendelian genes leading to familial Alzheimer's disease, which accounts for less than 5 % of all cases [3]. The discovery of *APOE* denoted the first gene to be involved in the more common non-mendelian form of Alzheimer's disease [4]. For almost two decades, *APOE* remained the only robustly replicated gene for sporadic Alzheimer's disease.

The recent advent of genome-wide association studies (GWAS) has revolutionized our understanding of genetic influence on various complex diseases, including Alzheimer's disease [3, 5, 6]. Whereas previously genetic research relied heavily on a priori knowledge to pre-select interesting genetic variants and genes for study, GWAS allow for immediate interrogation of the entire genome without relying on prior—often incomplete—biological knowledge [6]. Such increase in scale has been facilitated by both technologic advances in genotyping arrays, as well as advancing insights into human genetic obtained via the Human

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Genome Project and HapMap Project [7]. This enabled exact quantification of the correlation structure present across genomic variants (linkage disequilibrium), thereby allowing imputation of unknown genetic variants based on a set of genotyped variants. In turn, this facilitated meta-analysis across studies that had non-overlapping sets of genotyped variants, but similar imputed variants.

As early as 2007 the first GWAS studies on Alzheimer's disease emerged [8–10]. These studies were important primarily because they demonstrated the feasibility of the GWAS approach in Alzheimer's disease and secondly, because they further confirmed that *APOE* was by far the single most important genetic marker of Alzheimer's disease. These studies also highlighted various novel putative genes, many of which, unfortunately, have not been replicated in subsequent studies. The *GAB2*-gene was perhaps the only gene from these early GWAS that has subsequently been replicated in other studies [10, 11].

The first landmark discoveries in Alzheimer's disease using GWAS were done in 2009 when two concomitant papers revealed three novel genetic variants associated with Alzheimer's disease [12, 13]. Genes located in or close to these loci were *PICALM*, *CLU*, and *CR1*. Noteworthy was that the sample sizes used in these papers jumped from less than 1,500 in early reports to over 6,000 indicating the necessity of large numbers in genome-wide genetics to make robust discoveries.

The discovery of these genes was important as well as the demonstration that international consortia can have sufficient statistical power to bring forth new discovery.

Subsequently, in 2010 the *BIN1*-gene was additionally discovered and replicated by combining these two consortia with data from the CHARGE consortium [14, 15]. Following this approach of incrementally larger datasets, in 2011 another five loci were discovered by two large consortia, i.e. *ABCA7*, *MS4A6A/MS4A4E*, *EPHA1*, *CD33*, and *CD2AP* [16, 17]. Sample sizes for these more recent studies reached in excess of 20,000 participants.

When assessing the scientific value of these novel genes, their most important contribution has been in further elucidating previously known pathways and identifying novel disease pathways. For example, the discovery of *CLU* and *ABCA7* have expanded on the role of lipid-processing in Alzheimer's disease, whilst *PICALM*, *CD2AP*, *BIN1* involve cell-membrane trafficking and *CR1*, *CD33*, *EPHA1* affect the immune-system, both pathways not previously implicated in Alzheimer's disease pathology [18]. Importantly, identification of new biological systems associated with the Alzheimer's disease phenotype creates the opportunity to identify novel targets for future drug development. In contrast, the explained variance of these novel genes in the risk of Alzheimer's disease is still very much limited [19], signaling the fact that many more genetic variants are still to be discovered.

Noteworthy are several GWAS studies that have sought discovery or targeted replication of novel loci in non-Caucasian datasets, including Afro-American, Hispanics, Chinese, and Japanese [20–22]. Multi-ethnic approaches will greatly enhance genetic research, because significant findings across populations will likely identify common genetic influence possibly indicating biological processes fundamental to Alzheimer's disease, whereas findings detected only in one population, while important, might indicate a unique or less common risk. Also, multi-ethnic datasets will facilitate discovery of variants not detected in single homogeneous populations.

Given the co-occurrence and overlap in biology, interesting leads for Alzheimer's disease discovery can also be obtained by studying genetic associations with other neurologic endpoints. This is important because the brains of many Alzheimer's disease patients contain concurrent pathologies other than solely Alzheimer's disease at autopsy. In this

regard, GWAS studies on stroke, vascular dementia, and fronto-temporal dementia are important [23–27]. Generally, these GWAS have had less power than GWAS on Alzheimer's disease, mostly due to smaller sample sizes, and have not yet yielded overwhelmingly new data that can be readily applied to better understand Alzheimer's disease. Still, such an approach involving related but distinct diseases can be useful to elucidate Alzheimer's disease from a systems biology perspective, in which the affected organ system, i.e. central nervous system, as a whole is examined rather than only specific pathologies or anatomical tissues.

Whereas increasing sample sizes and diverse populations have shown to be an effective strategy in discovering novel genes, many potential genes underlying Alzheimer's disease still remain yet to be identified. An alternative approach is to further enrich the amount of genetic information that is being studied within the same number of samples. This can be achieved in two ways: (1) by increasing the number of SNPs being testing through more refined imputation or actual genotyping, i.e. sequencing, or (2) studying structural variations in DNA besides SNPS, such as copy number variations (CNV) including insertions/deletions.

Until 2010, GWAS studies had almost exclusively employed the HapMap dataset as the reference panel for imputation of their genetic data, which in initial releases was based on only 270 individuals [7]. From 2010 onwards, larger sequencing efforts in eventually 2,500 persons have created the 1,000 genome reference dataset [28]. This panel contains up to 11 million SNPs (compared to 2–3 million in HapMap), with many more rare variants included and also allows for improved imputation quality thereby increasing power to detect genetic influences due to less common variants. Most GWAS are currently using the 1000G reference datasets and results for Alzheimer's disease are anticipated to come out early 2013 [29].

Whereas conventional genotyping platforms used for GWAS genotyped SNPs dispersed throughout the genome, sequencing involves determining each consecutive base pair in the region under study. With the costs of genotyping decreasing dramatically as technologies evolve, sequencing is rapidly becoming a feasible option in large datasets. Currently, exome sequencing, in which only the exomic regions are sequenced, is the most practical solution in population-based study. Still, it is only a matter of time before whole genome sequencing will also be introduced in community samples. Although the analytical approach to sequencing data has not yet been fully established [30], the huge potential of genome sequencing in population-based samples is acknowledged [30], especially once conventional GWAS have reached their peak. Indeed, recently a protective mutation in *APP* was discovered using a sequencing approach [31] confirming its usefulness. Importantly, the advantage of detailed genomic sequencing is not limited to the discovery of novel associations, but can also be extended to fine-map previous loci identified by less sensitive methods such as GWAS, thereby pinpointing the putative causal variant(s). In fact, large-scale sequencing efforts for Alzheimer's disease are currently being established to directly address this important research question.

The vast majority of GWAS studies have investigated single nucleotide variation in DNA. However, structural variation in DNA also includes many other variations, the most promising of which are CNV. CNVs have shown to be important for various neurodevelopmental and psychiatric conditions, such as autism, bipolar disorder, and attention-deficit hyperactivity disorder [32]. Evidence implying CNVs in Alzheimer's disease is less abundant, though several studies are emerging with putative candidate CNVs [33, 34].

Apart from expanding datasets by increasing sample size or increasing genotype data, an important alternative is to develop newer analytical strategies that use existing datasets, but capture genetic variation beyond single genetic markers. The following techniques will be discussed: haplotype-based analysis, gene-based analysis, interaction-analysis, conditional analysis, and analysis of recessive effects.

Haplotype-based analysis relies on the fact that a combination of two or more SNPs can convey risk of disease not captured by solely testing a single SNP. Recently, a study by Lambert et al. [35] by testing haplotypes within sliding window identified a novel gene association with Alzheimer's disease. They showed that a haplotype in the *FRMD4A*-gene confers risk of Alzheimer's disease, possibly by modulating amyloid-metabolism. As proof of principle, they also showed that testing single SNPs at the locus would not have uncovered the association.

Gene-based analysis involves pre-selecting (a set of) genes, in which genetic variation will be tested. Basically, the hypothesis-free search of GWAS is restricted to the bounds of selected genes. Such genes are selected based on prior knowledge and therefore limit the hypothesis-free nature of this approach. The main advantage of a gene-based analysis over genome-wide analysis is that a more lenient statistical threshold can be used. Rather than the established $p = 5\ 9\ 10^{-8}$ a threshold is used which merely corrects for the number of SNPs tested within a certain gene—usually ranging from a few to a few hundred [36]. This can greatly enhance statistical power in light of limited sample sizes.

As previously stated, much of the heritability of Alzheimer's disease is still unexplained [19] and part of this is possibly due to effect modification between genes or between genes and environmental factors. Though gene by gene and gene by environment analyses are appealing conceptually, it has proven to be extremely difficult to obtain robust associations. The main limitation has been that for a sufficiently powered interaction analysis, the required numbers would far exceed even the largest GWAS dataset currently available for Alzheimer's disease genetic discovery. Recognizing this limitation, there are few studies that have explored interaction using a candidate gene approach based on GWAS, but those studies have yet to be replicated.

Another interesting concept is that a single locus might harbor more than one causal variant, possibly with opposing effects. Similar to haplotypes, a single marker association study will again fail to identify such multiple variants. Conditional analysis, in which the effect of a marker is investigated conditional on the effect of a second marker, can reveal multiple variants at the same locus [37]. Use of conditional analyses, however, has some limitation. Applying conditional analysis within a large multi-study consortium requires multiple analyses. For example, if the conditional effect of three variants is sequentially being investigated, each study will have to repeat the analysis three times followed by three meta-analyses. Recently, an alternative method for conditional analysis was reported, which does not require such an iterative approach [38]. Instead, only results from the overall meta-analysis along with linkage disequilibrium data that can be obtained from only one study is sufficient to perform conditional analysis. Results from application of such an approach to Alzheimer's disease genetic discovery have yet to be published.

Finally, in GWAS studies typically additive effects are studied, usually because modeling these effects yields maximum power when the underlying true effect is unknown. However, studies now also perform genomewide analyses investigating recessive or dominant models [39]. Such effects may also explain part of the missing heritability in Alzheimer's disease.

Statistical power is the main threat to genome-wide genetics, necessitating the formation of large international consortia that can provide sufficient number of cases and controls [40]. A

hallmark of complex disease is that very often a preclinical/subclinical stage exists, which can be quantified using various biomarkers [41]. Alzheimer's disease too is a multi-factorial disease involving different pathologies that steadily accumulate in the brain during life [41]. In fact, a recent model has been proposed that describes the sequence of events leading to clinical symptoms of Alzheimer's disease as well as describing the time course of different biological markers during the preclinical phase [41]. These preclinical biomarkers, i.e. endophenotypes include cerebral spinal fluid measures of beta amyloid 1–42, tau and phosphorylated tau. These biomarkers also include a variety of neuroimaging techniques from MRI to positron emission tomography (PET), including amyloid imaging. Increasing availability of these biological markers is now sufficient to perform large-scale genetic studies on such endophenotypes [41].

The use of endophenotypes in genetic discovery is aided by the fact that endophenotypes are usually more homogeneously distributed, are quantifiable continuous measures, suffer less from competing risks, and allow for investigation of the underlying pathologic process. The major limitation of endophenotypes is that they may not be specific to the disease outcome of interest [42]. For example, hippocampus and measures of white matter disease are clear endophenotypes of Alzheimer's disease, but have also been shown to signal other disease pathways, such as vascular pathology [43]. This limitation can be overcome by associating any novel genetic marker for the endophenotype with the specific disease outcome. An added advantage of this approach is that the second step (i.e. relating genetic marker to disease outcome) when done in an independent population, only require conventional statistical thresholds [44]. Also, by examining genetic influences on endophenotypes directly, researchers may identify more fundamental processes, that, while not directly related to the phenotype of interest, might lead to new insights regarding human biology. For example, the chromosome 17 inversion found for head size in adults was also shown to influence head circumference, as proxy for brain growth, in 18-month old infants [45, 46].

Use of endophenotypes has resulted in the identification of several novel genes. The strongest genetic marker associated with head size is an inversion on chromosome 17, which includes the *MAPT*-gene and *PGN*-gene [45, 46]. Loci associated with hippocampal volume include *MSRB3*-*WIF1*, *HRK*-*FBXW8*, *DPP4*, and *ASTN2*-genes [47, 48]. For white matter disease, a locus on chr17q25 was identified [49]. However, only a few of these genes have been associated with clinical Alzheimer's disease. To really establish these novel genes as Alzheimer's disease genes, it will be pivotal to establish their direct association with Alzheimer's disease. Of particular interest in this regard is a recent study that used brain expression levels as endophenotypes and identified SNPs associated with insulin degrading enzyme expression levels as well as with risk of Alzheimer's disease [50].

An important point to consider with MRI-based endophenotypes is that most of these markers can be analyzed in various ways. Typically, these are either aggregated over the whole brain or a specific region (volumes, means). Alternatively, these MRI-markers can be investigated on a voxelby-voxel level [51]. Basically, such voxel-based approach is a hypothesis-free search in the brain for regions that are associated with the clinical outcome. So far, GWAS studies on MRI-markers have mostly used aggregated markers. The potential yield of combining a hypothesis-free GWAS with a hypothesis-free voxel-based analysis has clearly been recognized. Several proof-of-concept studies have shown that this approach is computationally and mathematically feasible [52, 53]. In coming years, large-scale consortia will embark on performing these hypothesis-free genotype-phenotype association studies.

In addition, endophenotypes can be used to stratify genetics of complex disease such as Alzheimer's disease through refined selection of the Alzheimer's disease phenotype. For example, a relatively recent study by Cuenco et al. [54], evaluated genetic associations with

SORL1 using a sibling pair design. Using a dataset that did not show association with *SORL1* gene polymorphisms, the investigators repeated the analysis stratifying the group by extent of concurrent vascular disease seen on MRI. Results showed highly significant associations between SORL1 polymorphisms and dementia in those individuals with low vascular burden suggesting that the *SORL1* polymorphism marked a disorder more specific to Alzheimer's disease pathology. Use of endophenotypes, therefore, can enhance the power of GWAS studies by creating more homogeneous clinical groups than would otherwise be possible using the clinical phenotype.

In conclusion, genetic research has already proven important to our fundamental knowledge of the mechanisms of Alzheimer's disease. Recently, GWAS of Alzheimer's disease patients has identified a number of novel genes that contribute to the risk of Alzheimer's disease. Despite this success and possibly because Alzheimer's disease is a complex phenotype, new strategies are continuously being developed to identify multiple, more subtle genetic influences through GWAS studies of larger groups and the application of new techniques to better understand the interaction of multiple SNPs on the clinical phenotype with the goal of understanding the disease and developing a comprehensive test of genetic risk. In this regard, powerful new statistical methods of network analyses may provide insight into how subtle genetic influences in multiple nodes of a biological system may result in expression of clinical disease. Sequencing will refine these associations by removing uncertainties related to genotyping and imputation, but face numerous methodological challenges. Importantly, however, understanding of the human genome is only the first step to understanding the genetic influences on complex diseases such as Alzheimer's disease. Further work that examines regulation of genes (epigenetics) will likely add substantially to our understanding of this complex phenotype. Examining genetic influences on endophenotypes also is likely to improve our understanding of the biology of complex diseases such as Alzheimer's disease through improving subject selection for study as well as identifying novel associations with the endophenotype that might identify more fundamental biological processes beyond the disease of interest.

Many challenges still lie ahead…

Acknowledgments

This work was supported by the Netherlands Organization for Health Research and Development (ZonMW) Venigrant no. 916.13.054; CHARGE infrastructure grant no. HL105756; and NIH/NIA grant no. P30 AG10129.

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