



## The Genetics of Adult-Onset Neuropsychiatric Disease: Complexities and Conundra?

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## REVIEW

# The Genetics of Adult-Onset Neuropsychiatric Disease: Complexities and Conundra?

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Genetic factors play a major role in the etiology of adult-onset neurodegenerative and neuropsychiatric disorders. Several highly penetrant genes have been cloned for rare, autosomal-dominant, early-onset forms of neurodegenerative diseases. These genes have provided important insights into the mechanisms of these diseases (often altering neuronal protein processing). However, the genes associated with inherited susceptibility to late-onset neurodegenerative diseases, schizophrenia, and bipolar disorder appear to have smaller effects and are likely to interact with each other (and with nongenetic factors) to modulate susceptibility and/or disease phenotype. Several strategies have recently been applied to address this complexity, leading to the identification of a number of candidate susceptibility loci/genes.

Neurodegenerative diseases [e.g., Alzheimer's disease (AD), Parkinson's disease (PD), and fronto-temporal dementia (FTD)] and adult-onset neuropsychiatric disorders (e.g., schizophrenia and bipolar disorder) are highly prevalent but etiologically complex disorders of the adult brain that bring substantial emotional and economic burdens to patients, relatives, caregivers, and the state. Although both genetic and nongenetic factors contribute to susceptibility to these diseases, it is clear from a host of family, twin, and adoption studies that genetic factors play a major role in the etiology of these disorders (1–4). It has been

hoped that identification of these genetic factors might provide a means to learn more about the neural or biochemical mechanisms of these diseases and might provide a rational basis for the design of effective therapies.

This concept has been strongly endorsed by early genetic studies in AD and FTD. These studies used traditional genetic linkage methods, combined with informed guesses about candidate genes in the linked chromosomal intervals, to map and then clone several genes bearing causative mutations. These causative genes were found either to encode proteins that accumulate in

the brain in these diseases [amyloid precursor protein (APP) and tau] or to encode proteins that are involved in the posttranslational processing of these accumulating proteins (Fig. 1 and Table 1). Thus, in AD, mutations were found in APP (5), a neurotoxic proteolytic derivative of which, the A $\beta$ -peptide, is a principal component of amyloid or senile plaques (a pathological

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deposit in the brain of patients with AD). Mutations in the presenilin genes [(two homologous genes encoding polytopic transmembrane proteins (6, 7)] were found using the same “positional cloning” strategy. Subsequent functional studies revealed that the presenilins are components of novel enzyme complexes involved in the physiologic  $\gamma$ -secretase proteolytic cleavage of APP and that mutations cause this complex to produce an excess of a particularly neurotoxic isoform of  $A\beta$  ( $A\beta_{42}$ ) (8). A fourth AD gene, APOE, identified by the same positional mapping approach (9), seems to be involved in the clearance of  $A\beta$ . Similarly, linkage mapping and candidate gene analysis led to the discovery of mutations in the tau gene in cases of FTD (10), a disease characterized by intraneuronal deposits of the tau protein.

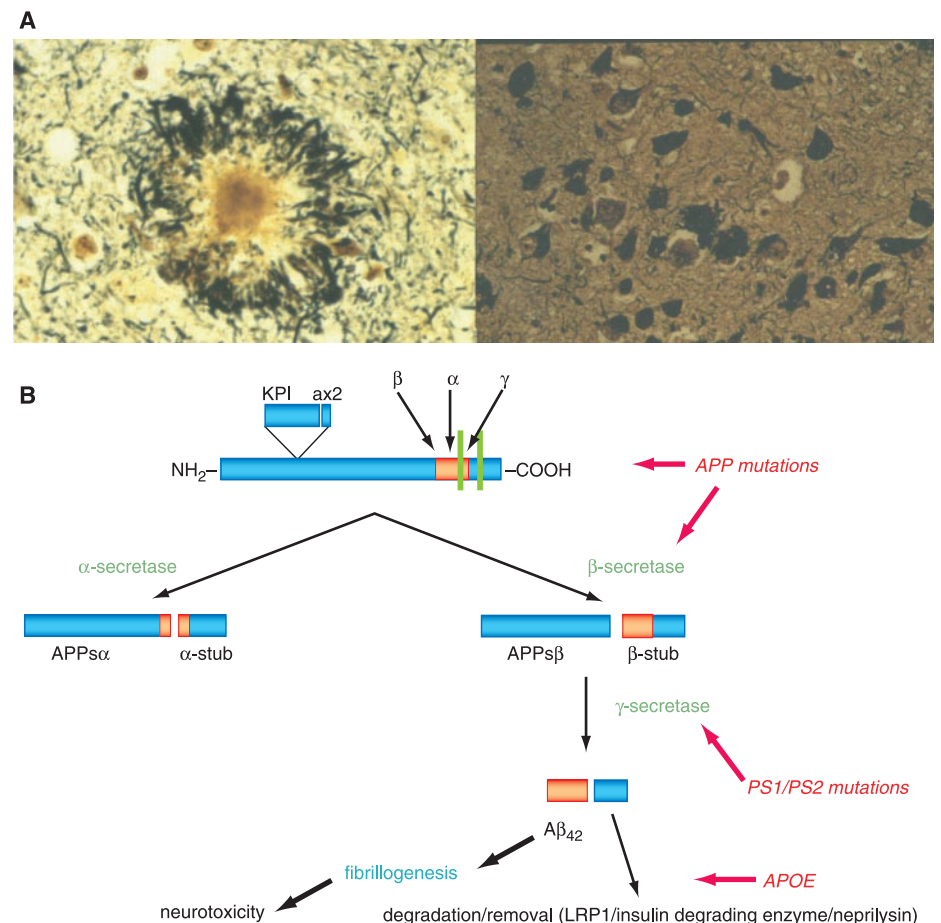
These early successes have been invaluable. They have proven that the discovery of genes causing adult-onset neuropsychiatric diseases is both possible and informative. Indeed, knowledge of these genes has led both to the creation of robust animal models and to the design of therapeutic strategies to block  $A\beta$  production, to inhibit its assembly into toxic aggregates, or to accelerate its removal (11). However, it has also become apparent that families segregating AD or FTD as simple autosomal-dominant traits are the exception rather than the rule. The majority of cases, especially those with onset after age 60, seem to have a more complex pattern of inheritance that does not fit the simple rules of classical Mendelian inheritance (one gene–one disorder that is transmitted as a dominant, codominant, or recessive trait). The same also seems to be true for schizophrenia and bipolar disease. Attempts to identify genes associated with susceptibility to these forms of adult-onset neuropsychiatric diseases have been less fruitful, although recent results provide some grounds for cautious optimism, especially for schizophrenia.

In both late-onset AD and schizophrenia, genome-wide linkage surveys (12–14) and genetic association methods [see (15) for details about these methods] have identified several rather broad chromosomal regions as the site of potential susceptibility genes. A proportion of these positive results have been replicated in independent data sets (although the replications have not been universal). When compared with the small mapping intervals, robust replications, and relatively straightforward identification of disease-causing mutations in other (primarily Mendelian) diseases, this apparent imprecision has led to concern that the methods (especially case-control association methods) may be unreliable and/or that the genetics of these diseases are intractably complex.

This pessimism, however, may not be entirely warranted. Rank-based genome scan meta-analysis on data from 20 genome-wide scans in schizophrenia, for example, reveals substantial evidence for linkage on 2q, with other positive results on chromosomes 1q, 3p, 5q, 6p, 8p, 10p, 11q, 13q, 14p, 20q, and 22q (12, 13). Indeed, meta-analyses of genetic association studies for other complex traits (e.g., diabetes and hypertension) reveal that there may be greater consistency among various studies than has been previously recognized (16). Furthermore, a small number of genes with plausible biological connections to the pathophysiology of schizophrenia are located within these linkage regions (Table 1) (17).

Neuregulin 1 maps in a well-replicated linkage peak on chromosome 8 and is a good candidate for schizophrenia, based on its effects on  $\gamma$ -aminobutyric acid

(GABA)–ergic and glutamatergic neurotransmission and in myelination (18) (for which there is relatively extensive support for a pathophysiologic role in schizophrenia). The same core risk haplotype of single nucleotide polymorphisms (SNPs) in the neuregulin 1 gene has been identified in Icelandic schizophrenics and in two separate U.K. samples (odds ratios across the three studies varying from 1.25 to 2.1) [reviewed in (17)]. Dysbindin, which is found in postsynaptic terminals (19), may play a role in receptor function and synaptic plasticity, and maps in a confirmed linkage peak on 6p. Three separate groups have reported considerable linkage between haplotypes of dysbindin and schizophrenia, although no single haplotype was common across all the samples (20). Chromosome 22q11 is of continuing interest for schizophrenia because small dele-



**Fig. 1. (A)** Photomicrographs of sections from the cerebral cortex of a patient with AD, showing neuropathological structures containing proteins that are causally related to neurodegenerative diseases. (Left) Extracellular amyloid plaques showing  $A\beta$  in the fibrillar core (orange) surrounded by halo of neuritic terminals (black); anti- $A\beta$  antibodies and Bielschowsky silver stain. (Right) Tau (black triangular intraneuronal inclusions) in neurofibrillary tangles; Bielschowsky silver stain. **(B)** The metabolic pathways for catabolism of APP; the  $\beta$ -/ $\gamma$ -secretase pathway leads to the production of neurotoxic  $A\beta$ . Several of the genes in the latter pathway are the sites of genetic variations that cause misprocessing of APP and/or of  $A\beta$  and the accumulation of  $A\beta$ . These genes segregate as simple Mendelian traits but show additive effects with each other (e.g., patients with APP717 + APOE4 have earlier onset than do relatives with APP717 only), indicating that they act in the same metabolic pathways (54, 55).

tions in this region lead to velo-cardio-facial syndrome (VCFS), and these patients have a greatly increased incidence of psychosis, in some cases indistinguishable from schizophrenia. In this region of 22q lies the gene for catechol-O-methyl transferase (COMT), which modulates catabolism of dopamine, a neurotransmitter that is functionally overactive in schizophrenia and that is blocked or down-regulated by antipsychotic medications. COMT is active in the frontal areas of the brain implicated in schizophrenia, but not in the striatum (21). Knockout of COMT improves memory function in mice (22).

Working memory deficits are well documented in schizophrenia, and schizophrenics who are Val/Val homozygous for the coding sequence polymorphism at codon 108 (158 in the membrane-bound version) perform worse on working memory tests than do heterozygote schizophrenics, who in turn do worse than Met/Met homozygous schizophrenics (working memory in normal subjects also displays a similar relationship with regard to the polymorphism) (23). Although several genome scans have pointed to the 22q region, the area of linkage is broad and often does not include the VCFS region containing

COMT. Neither of the COMT Val108Met alleles is consistently associated with schizophrenia, but haplotypes across the gene are showing more promise. A COMT haplotype implicated in Ashkenazi schizophrenia families has now been shown to have low COMT expression, and this is consistent with the classic frontal hyperdopaminergic theory of schizophrenia (24, 25). A replicated linkage peak on 13q contains a novel gene, G72, which is expressed in the brain and which has no known function or homology to other genes (26). G72 protein physically interacts with D-amino acid oxidase (DAAO), which catabolizes D-serine, an important modulator of *N*-methyl-D-aspartate (NMDA) receptor function. In two independent samples, G72 and DAAO appear to interact genetically to increase the risk for schizophrenia (26). The proof that these genes are indeed schizophrenia-susceptibility genes is less compelling than the proof produced to establish a role for genes like APOE in AD. It is also unclear how much of the attributable risk for schizophrenia is contributed by each of these genes. Nevertheless, they provide a series of plausible candidates and hypotheses available for further biological testing. As such, this represents an impor-

tant advance from the status of even a few years ago.

The search for genes causing late-onset AD and bipolar disease continues. In AD, genome-wide linkage and association studies have now impugned broad regions of chromosomes 9, 10q, and 12q (27–33). These intervals contain several attractive candidate genes. Chromosome 10 contains two enzymes putatively involved in degradation of neurotoxic A $\beta$  (insulin-degrading enzyme and urokinase-type plasminogen activator). The two linkage peaks on chromosome 12 contain two genes potentially interacting with APOE and A $\beta$  ( $\alpha$ 2-macroglobulin and low-density lipoprotein-related protein 1). Similarly, case-control studies in sporadic AD have also implicated a large number of individual genes on other chromosomes, whose function can also be tentatively linked to the known biochemistry of AD [reviewed in (34)]. However, the evidence that any of these candidate genes are truly the site of genetic variants that modulate risk for AD is controversial.

In bipolar disease, the rank-based genome scan meta-analysis of 18 scan data sets did not show any site that achieved genome-wide importance, and none of the suggestive linked regions (9p, 10q, 14q, 18p-q, and 8q) overlapped with schizophrenia (14). There has been debate as to whether or not a broader model of affected status should be used, including bipolar II and unipolar depression. Some argue that the former is a separate disorder and the latter is a very common condition that undoubtedly introduces phenocopies. Another problem is that parent-of-origin effects may be common in bipolar disorder, and analyses have not routinely accounted for these effects. Candidate genes showing replicated associations with bipolar disease include G72 (35) and the gene for brain-derived neurotrophic factor (BDNF). BDNF has a Val66Met polymorphism that alters intracellular transport of the preproteins. Individuals with the Val allele have better performance on episodic memory tests (36), and haplotypes containing the Val allele have been associated with bipolar disease in two large independent studies (37, 38).

#### What Are the Reasons for the Current Problems?

There are several reasons both for the initial success in mapping genes for some forms of AD and FTD and for the comparative difficulty of the hunt for genes causing late-onset AD and the psychoses. First, the forms of AD and FTD for which disease genes have already been cloned have been inherited as classical single-gene, highly penetrant, autosomal-dominant Mendelian traits. In contrast, the late-onset forms of

**Table 1.** Genes associated with neuropsychiatric diseases: some of the genes identified as contributing to common complex adult-onset neurodegenerative diseases and psychoses. This list does not include a larger number of genes (many identified through case-control studies) for which there is currently no widespread confirmation, nor does it include the rarer simple Mendelian traits such as Huntington's disease.

Disease	Gene	Mutational mechanism
Alzheimer's disease	Amyloid precursor protein (chr. 21q)	Accumulation of A $\beta$ . Missense mutations alter processing of precursor (APP) or solubility/folding of A $\beta$ product.
	Presenilin 1 (chr. 14q)	Accumulation of A $\beta$ . Missense or in-frame splicing mutations increase A $\beta$ 42 production. Presenilins are required for $\gamma$ -secretase.
	Presenilin 2 (chr. 1q)	Accumulation of A $\beta$ . Missense or in-frame splicing mutations increase A $\beta$ 42 production. Presenilins are required for $\gamma$ -secretase.
	Apolipoprotein E (chr. 19q)	Accumulation of A $\beta$ . Unknown. APOE4 coding sequence variant may modulate A $\beta$ handling.
Fronto-temporal dementia	Tau (chr. 17q)	Accumulation of Tau. Missense and in-frame splicing mutations increased free tau (nonmicrotubule bound), with its subsequent assembly into fibrils.
Schizophrenia	Neuregulin 1 (chr. 8p)	Plays a role in NMDA, GABA, and acetylcholine receptor regulation. Disease variant not yet identified.
	Dysbindin (chr. 6p)	May play a role in synaptic plasticity. Disease variant not yet identified.
	COMT (chr. 22q)	Mutations affect dopamine catabolism, leading to variations in functional dopamine activity, particularly in frontal cortex. Disease variant not yet identified.
	G72 (chr. 13q)	Unknown function. Interacts with DAAO, may modulate NMDA receptor function. Disease variant not yet identified.

AD and the psychoses appear to be complex genetic traits for which there may be multiple genes, each with alleles that are common in the general population, that have relatively weak effects on their own, that may produce more than one effect (pleiotropy), and that may interact with each other. Second, AD and FTD have relatively discrete, specific phenotypes with highly accurate diagnostic systems (90% autopsy confirmation). In contrast, the late-onset forms of AD and, especially, the psychoses have nonspecific pleomorphic phenotypes, making diagnosis and nosology difficult. Unmeasured environmental or social components also modulate the effects of weak genetic variants (39). These factors (e.g., diagnostic misclassification, inclusion of pedigrees with nonallelic forms of the disease, variable penetrance, and gene modifiers) all contribute confounders to the statistical linkage and association analyses. The power of these analyses to detect weak effects is then further diluted by statistical corrections required to address the fact that genome-wide screens are subjected to multiple tests (e.g., multiple genes and multiple SNPs). Finally, genetic research on the neurodegenerative diseases has benefited from the presence of biological markers (e.g., deposition of specific proteins in the brain), which provide valuable clues to candidate genes, and from biological tests for validation studies in *in vitro* or transgenic animal model systems.

### Future Directions

The solutions to these problems seem to lie in strategies to address phenotypic complexity and genetic heterogeneity and complexity, and perhaps in the development of new statistical methods to look simultaneously at gene-gene and gene-environment interactions.

The definition of phenotypes is a pressing problem that is currently being addressed in new ways. The psychoses and late-onset neurodegenerative disorders are almost exclusively diagnosed clinically using standardized criteria [e.g., the Diagnostic and Statistical Manual of Mental Disorders for the psychiatric diseases and the Alzheimer's Disease and Related Disorders Association—National Institute on Aging (ADDA-NIA) criteria for AD]. However, for genetic studies, the use of such simple binary diagnoses [affected versus unaffected (i.e., truly unaffected or asymptomatic but at-risk)] at best loses a lot of potential information and may confound matters by forcing the lumping of disease entities that, although similar, are not identical. The disease phenotype for these complex disorders likely reflects the aggregate of several subtraits, which in turn are likely to reflect the effects of multiple causative and modifier

factors. One potential, but as yet unproven, strategy is to search for more specific neurophysiologic, neuroimaging, neurocognitive, or neurochemical trait measures that might identify homogeneous groups of patients and/or that might be more closely linked to the underlying genetic mechanisms. Criteria for such "endophenotypes" are (i) the trait is associated with the disease in the population, (ii) it is heritable, (iii) it is not state-dependent (i.e., it is present even when the illness is not floridly symptomatic), (iv) it cosegregates with the illness within families, and (v) it is found in nonaffected family members at a higher rate than in the general population (40). This strategy has been most highly developed in genetic research on schizophrenia, where abnormalities in eye tracking, working memory, or measures of neurophysiological response such as prepulse inhibition are being used as endophenotypes. Serum A $\beta$  measurements (41) and memory function are potential endophenotypes for AD. The theoretical benefits of this strategy are that it reduces complexity by analyzing a single endophenotype at a time and that it may increase statistical power because these endophenotypes are present both in subjects with full-blown disease and in relatives with "subthreshold" forms of the disease. However, this strategy is not without its detractors, who point out that huge efforts will be needed to establish endophenotypes that fit the criteria and that endophenotypes such as defective eye-tracking may not be any less genetically complex and may not provide any greater insights into the disease process.

The issue of genetic heterogeneity is also a major problem that must be addressed. It is very likely that susceptibility to the majority of the neurodegenerative diseases and psychoses is imparted by several genes acting either individually (i.e., nonallelic genetic heterogeneity) or together (i.e., oligogenic or polygenic inheritance). It is also likely that these disease susceptibility genes will be modulated by gene-environment and/or gene-gene interactions. Theoretically, such genetic complexity can be reduced by studying endophenotypes and/or by studying population isolates in which there might be a limited number of disease-causing genes. Indeed, neuregulin was first identified as a candidate for schizophrenia in the Icelandic population isolate (42). However, studying population isolates runs the obvious risk of discovering genes that are unique to that population (as has been the case with rare recessive traits). Furthermore, if a disease phenotype requires the concurrence of susceptibility alleles at several different genes, this complexity will still be required even

in population isolates. Another proposed strategy has been to focus exclusively on families heavily affected by these diseases (ostensibly such families would segregate the same causative gene). Although this approach has worked for rare monogenic traits, it is to be avoided in the analysis of common complex traits for two reasons. First, such families are rare. Second, given the prevalence of these diseases, there is a considerable risk that the disease trait might also be introduced into the family from married-in members, which confounds the analysis.

Another strategy for the analysis of complex diseases arises from unsolved puzzles such as discordant monozygotic (MZ) twins and parental imprinting of disease genes. Discordance of MZ twins is 30 to 50% in diabetes, 50% in schizophrenia, and 80% in breast cancer [reviewed in (43, 44)]. This discordance is often ascribed to environmental factors. However, no such factors have been identified in schizophrenia, despite decades of research. A direct investigation of DNA methylation in the upstream region of the dopamine D2 receptor gene in MZ twins that were either concordant or discordant for schizophrenia revealed that the affected twin from the discordant pair was epigenetically more similar to the affected twins in the concordant pair than to his or her nonaffected twin partner (45). This result, along with the observation of replicating parent-of-origin effects in bipolar disorder (46–48), suggests that such mechanisms should be considered during the search for etiologic DNA sequence variants in the major psychoses. Finally, another related hypothesis is that the schizophrenia may arise from subtle alterations in the timing or level of expression of neurodevelopmental genes (49). If so, additional candidate genes might be mined by transcriptional and protein profiling in postmortem human brain tissue.

Perhaps the best way to address genetic complexity is to recognize it and to build it into the experimental design. This will require a major change in methodology. In particular, large-scale, prospective population-based studies will be needed for the specific purpose of collecting comprehensive phenotypic data. This is not the conventional descriptive phenotype (disease present or absent); rather, it is a systematic effort to quantify the manifestations that compose the overall phenotype. Such "phenomics" studies will collect data on genetic variation and on exposure to potential environmental agents, and will permit analysis of gene-environment interactions. Risk factor and biomarker data, which are critically important for proper assignment of many endophenotypes and for stratification

in linkage and association analyses, will have to be collected prospectively to avoid biases associated with amnesic information, use of proxy informants, and physiological changes that are a consequence of, rather than a cause of, the disease process. Family-based designs will be particularly attractive because they more effectively control for differences in the genetic background among affected and unaffected persons and for measured nongenetic risk factors (50, 51). Such an effort will require collaborations between clinicians, epidemiologists, and geneticists to develop and standardize the collection of phenotypes and to design new statistical approaches that can model complex multifactorial and polygenic causologies (52, 53). This will be useful not only for the adult-onset neuropsychiatric disorders discussed here but also for most other common, complex disorders.

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#### VIEWPOINT

## Postnatal Neurodevelopmental Disorders: Meeting at the Synapse?

Huda Y. Zoghbi

We often think of neurodevelopmental disorders as beginning before birth, and many certainly do. A handful, however, strike many months after birth, following a period of apparently normal growth and development. Autism and Rett syndrome are two such disorders, and here I consider some of their similarities at the phenotypic and pathogenic levels. I propose that both disorders result from disruption of postnatal or experience-dependent synaptic plasticity.

*Falling silent.* After a child is born, parents watch with anticipation the normal developmental program that ensues. The baby smiles and follows faces at 6 weeks, acquires sufficient motor control to sit and transfer toys by

6 months, and typically walks and says a couple of words by 12 to 15 months. Language and thought continue to develop as children begin to understand make-believe play, to use verbs to describe a mental state, and to imitate complex actions.

Ashley delighted her parents as she progressed through early developmental milestones. She learned to crawl, babble, walk, and sing nursery rhymes, all at the expected ages. At 18 months, however, her progress ceased.

No more songs or words, only a vacant stare. Ashley's ability—or inclination—to use her hands was overwhelmed by incessant hand-wringing; tremors, rocking, and loss of balance robbed her of normal motor control; apnea and hyperventilation indicated autonomic control was going haywire, too. Her head growth slowed, and her social interactions became almost nonexistent.

Alex, born to a different family at a different time, has a similar story. He was a healthy boy who smiled and followed faces by 6 weeks, made eye contact, and enjoyed interactive games. At 10 months of age he showed an unusually intense interest in wheels, but he continued to interact socially and was saying several words and walking by 13 months. Some time between 15 and 18 months, however, Alex, like Ashley, fell si-

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