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Review Article

Gene Mapping in Alzheimer's Disease: Unveiling Genetic Mechanisms and Therapeutic Insights

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Abstract

Neurodegenerative diseases are characterized by progressive neuronal loss and protein level changes in the brain, with gene defects playing a major role in their pathogenesis. Gene defects play a major role in the pathogenesis of degenerative disorders of the nervous system. In fact, it has been the very knowledge gained from genetic studies that has allowed the elucidation of the molecular mechanisms underlying the etiology and pathogenesis of many neurodegenerative disorders. To identify and rectify the deflects of neurodegenerative disease, advance technology such as gene mapping can be harnessed. Gene mapping is a method which is used to identify the locus of the gene and the distances between the genes. This technology serves as a map for researchers trying to discover the common genetic variation associated with complex disease as well as variations responsible for differences in drug and therapeutic response. With advancements in gene mapping techniques, researchers are gaining deeper insights into the genetic underpinnings of neurodegenerative diseases. In this review, we specifically focus on the status of genetic epidemiology in Alzheimer's disease, the most common form of neurodegeneration.

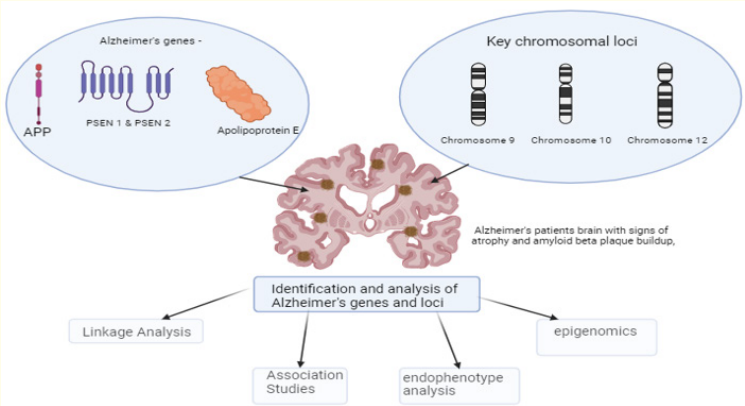

Figure 1: Genetic Epidemiology of Alzheimer's disease

Keywords: Alzheimer's Disease (AD); Gene Mapping; Neurodegenerative Disorders; Genetic Epidemiology; β-amyloid Precursor Protein (APP); Presenilin (PSEN); Genome-Wide Association Studies (GWAS); Next-generation Sequencing; Genetic Variation; Therapeutic Targets

Introduction

The familial clustering of neurodegenerative diseases has long been recognized, even before researchers had a grasp of the underlying genetic or biochemical mechanisms. This observation, often marked by the identification of specific disease-causing mutations in previously unknown genes, has been instrumental in highlighting the role of specific proteins and pathways in disease development. For example, mutations in the genes encoding β-amyloid precursor protein (APP) contribute to Alzheimer's disease (AD), α-synuclein mutations are implicated in Parkinson's disease (PD), and mutations in the microtubule-associated protein tau are linked to frontotemporal dementia (FTD) with parkinsonism [1]. It's becoming increasingly clear that age-related diseases like cancer and neurodegeneration are complex and influenced by numerous genetic and environmental factors acting throughout a person's life [2]. As research progresses, intriguing connections are emerging between these diseases, such as the shared roles of cell cycle proteins in both cancer and neurodegeneration [3] or the overlapping genetic influences of AD and cardiovascular disease on both normal aging and neurodegenerative processes [4].

A complete understanding of how genetic variability influences a specific phenotype or trait is very essential. Methods to accomplish this at a genomic level have become available over the last decade with the introduction of genome-wide genotyping and "next-generation" sequencing [5]. The widespread adoption and application of sequencing technologies allows two main types of studies: 1) sequencing of large cohorts of cases and controls to perform association studies with virtually complete genomic information; and 2) sequencing of individuals from families where a specific disease segregate. If the first application requires the analysis of as many individuals as possible, the second one requires instead a strict filtering of variants to allow for the identification of the causative one(s) [6].

Alzheimer's disease

Alzheimer's disease (AD), the most common form of dementia, is a progressive neurodegenerative disorder characterized by the loss of specific neurons and the accumulation of abnormal protein deposits in the brain. Understanding the genetic and environmental factors that influence neuronal fate during aging is crucial in the fight against AD. Initially, AD research focused on identifying genes responsible for rare, inherited forms of the disease. Subsequently, studies expanded to include hundreds of patients, families with affected individuals, and population-based approaches, sometimes involving isolated communities. This broader approach has led to the discovery of an increasing number of genes and mutations that can cause or increase susceptibility to AD [7].

Genes involved in familial AD aetiology.

APP (AD1)

Down syndrome (trisomy 21) is characterized by a triplication of chromosome 21, and individuals with Down syndrome exhibit a high prevalence of Alzheimer's disease (AD) at a younger age. This observation led researchers to hypothesize that a gene on chromosome 21 might contribute to AD pathogenesis. In 1987, linkage analysis in early-onset AD families identified a susceptibility locus (AD1) on chromosome 21q near the amyloid precursor protein (APP) gene [8].

The APP gene encodes a protein with various functions, including cell signaling, neurite growth, and possibly metal homeostasis within cells. However, the APP protein's most well-known function is its role in the production of β-amyloid peptides. These peptides are generated through the cleavage of APP by specific enzymes. While the exact physiological role of β-amyloid is not fully understood, its abnormal accumulation in the brain is a hallmark pathological feature of AD. Given its central role in β-amyloid production and its proximity to the AD1 locus, APP became a compelling candidate gene for AD. Subsequent studies in 1991 confirmed this hypothesis by identifying missense mutations in the APP gene that co-segregate with AD in families [7,8]. These findings established APP as the first genetically confirmed risk factor for AD (Table 1).

Normal processing of APP involves cleavage by α-, β- and γ-secretases. The cleavage by α-secretase occurs within the Aβ domain, preventing the formation of β-amyloid (Aβ), whereas β- and γ-secretases are involved in the cleavage and production of Aβ40 and Aβ42. Not surprisingly, all the identified pathogenic mutations (n=16) are located within exons 16 and 17 of the gene and are clustered around the β- and γ-secretase sites of the APP protein. Mutations such as Lys670Asn; Met671Leu, which is located upstream of the β-cleavage site, and Val717Ile and Val717Phe, which are situated close to the γ-site, result in an increase in the formation of Aβ40 and/or Aβ42 [9,10]. The identification of APP as the first gene shown to be involved in AD led to the generation of transgenic animal models over-expressing normal or mutated human AD

Alzheimer's disease locus	Chromosomal location	Genes and tested "candidates"	Mapping method	Molecular defects	References
AD1	21q21	APP	Linkage analysis (AD)	Single base substitutions (missense mutations, exon 16 and 17)	[27-29]
AD2	19cen-13.2	APOE	Linkage analysis (AD)	Susceptibility factor (APOE-Ɛ4)	[30]
AD3	14q24.3	PSEN1	Linkage analysis (AD)	Single base substitutions (missense, splicing) deletions, insertions	[31-33]
AD4	1q31-q42	PSEN2	Linkage analysis (AD)	Single base substitutions (missense mutations, exon 4, 5, 7 and 12)	34-36]
AD5	12p11.23-q13.12	Unknown, A2M, LRP1, LBP-1c/ CP2/LSF	Linkage analysis (parametric and nonparametric). FBATs	-	37-40]
AD6	10q24	Unknown, PLAU, IDE, CHAT, VACHT, TACR2, HK1, LIPA, NFKB2, VR22	Linkage analysis (parametric, nonparametric) and Association analysis	-	[41-44]
AD7	10p13	Unknown	Association and linkage disequilibrium	-	[45,46]
AD8	20p	Unknown	Covariate based linkage method	-	[47]

Table 1: Loci and genes related to Alzheimer's disease aetiology (AD autosomal dominant, AR autosomal recessive AAO age at onset, FBATs family-based association tests).

genes. As in human disease, Aβ over-expression and deposition greatly increases with age and occurs selectively in those brain regions most heavily affected in AD (hippocampus and cortex). Interestingly, most of the mouse models successfully mimic important features of the human disease, such as the presence of amyloid plaques, gliosis and neurodegeneration with age related cognitive impairment, but neurofibrillary tangles are absent [11,12].

PSEN1 (AD3)

Following the identification of APP as a risk factor for AD, researchers continued the search for additional genes involved in the disease. Earlier studies suggested a potential candidate gene, α1-antichymotrypsin (AACT), on chromosome 14 based on linkage analysis. However, the physical location of the AACT gene on chromosome 14q32.1 differed from the linked region and the presence of genetic recombinations excluded it as a strong candidate [13-15]. Interestingly, linkage analysis in families previously linked to the APP locus (chromosome 21) also revealed significant linkage to chromosome 14q. Notably, none of these families showed independent linkage to chromosome 21, and no APP mutations were identified. This suggested a distinct genetic contribution on chromosome 14 [16,17].

After excluding several candidate genes and refining the linked region on chromosome 14, researchers identified presenilin 1 (PSEN1) as the responsible gene within just three years of the initial linkage finding [16,17]. Mutations in the PSEN1 gene have been reported in approximately 268 families worldwide (AD mutation database, http://molgen-www.uia.ac.be/admutations/). While most of these families exhibit early-onset AD, some cases display atypical features like parkinsonism, frontotemporal dementia, epilepsy, myoclonus [18, 19], cerebral amyloid angiopathy, and spastic paraparesis [20-22].

PSEN2 (AD4)

In 1995, evidence for a locus on chromosome 1 (AD4 35) was reported in several kindreds known as the Volga-German families, a group of related kindreds of German-Russian origin with mul-

tiple cases of early-onset AD. Subsequently, the presenilin 2 gene (PSEN2) on chromosome 1 was quickly identified because of its high homology with PSEN1 and its localization within the genomic region previously identified on chromosome 1 by linkage analysis [23,24]. Unlike PSEN1 mutations that usually lead to an early disease onset, great disparity in AAO has been observed in carriers of PSEN2 mutations. Available neuropathological studies report moderate cortical atrophy and abundant neurofibrillary tangles with senile plaques throughout the cerebral cortex. During the last decade, an increasing number of mutations in APP, PSEN1 and PSEN2causing AD have been reported. Around 158 mutations have been identified in these three genes, most of them (n=133, 84.2%) in PSEN1, followed by the APP gene, which accounts for 10.1% of the mutations. Mutations in PSEN2 represent only a small percentage (5.7%) of all the mutations; a mere nine mutations in 15 families have been described (AD mutation database, http://molgen-www.uia.ac.be/admutations/ and http://www.alzforum.org/) [25-27].

In addition to pathological confirmation of the disease, the finding of pathogenic PSEN1, PSEN2 and APP mutations is used to confirm the diagnosis of AD. Although the factors involved in the cause and progression of AD are not yet well known, the discovery of PSEN1, PSEN2 and APP mutations involved in the monogenic forms of AD has made a huge contribution to the field of neuroscience. Presenilin activity is essential for the normal processing of APP [28,29] and is also required for the cleavage of Notch1 at the plasma membrane and the release of its intracellular domain. Transgenic mice overexpressing human wild-type or mutant PSEN1 have consistently shown elevated amounts of Aβ, especially Aβ42, disturbing the ratio Aβ40/Aβ42 and double mutants (APP/PSEN1) produce more Aβ than either transgene alone [30]. Moreover, the double transgenic mouse, PSEN2/APP, develops age related cognitive decline associated with severe amyloidosis and inflammation in discrete brain regions [29]. Mutations in the presenilins alter the γ-secretase cleavage of APP resulting in overproduction of the amyloidogenic Aβ42 peptides [31,32]. Indeed, it has been suggested that the presenilin1 protein could itself be a γ-secretase. Recent studies indicate that presenilin proteins interact with other proteins, such as niscatrin [33] (also implicated in Notch signalling), APH-1 and PEN-2 to form a complex responsible for γ-secretase activity [34-36]. Determination of the roles of each component of the complex may provide means of intercession to arrest or prevent the pathogenic processes leading to AD.

Loci implicated in the common form of AD APOE (AD2)

A major susceptibility factor for AD, the apolipoprotein gene (APOE), was initially discovered by linkage analysis. In 1991, evidence supporting linkage to this region on chromosome 19 (AD2) was found in a set of families with LOAD. Subsequent association studies have confirmed an increased risk in carriers of the ε4 isoform (APOE allele ε4) for late and early-onset forms of AD. Others have shown the protective effect of the ε 2 allele 92 and have estimated that the APOE genotype (ε 4/ε 4 and ε 2/ε 3) can make a difference of around 17 years in the AAO of AD [37]. The studies on transgenic animals have shown that APOE influences Aβ metabolism early in the amyloidogenic process and that APOE facilitates, in an isoform-dependent way, fibril and plaque formation [38,39]. Recently, APOE has been described to undergo proteolytic cleavage resulting in the accumulation of carboxyl terminal-truncated fragments of APOE, which are neurotoxic. Moreover, the cleavage of APOE-4 occurs in a more efficient way than that of APOE-3. APOE-4 C-terminal-truncated fragments are present in AD brains and are sufficient to provoke AD-like neurodegeneration and behavioural deficits in transgenic mice [40,41].

Chromosome 12 (AD5)

In 1997, a genome-wide association study (GWAS) employing various analytical methods identified a potential region on chromosome 12 (D12S373-D12S390) that might harbor a gene linked to AD [42]. This region was subsequently designated AD5. However, a follow-up study using a finer mapping approach within the same sample set failed to confirm the initial linkage. Interestingly, the follow-up study produced two distinct linkage peaks approximately 20 centimorgans (cM) apart, depending on how the data were analyzed. Factors such as the presence of the APOE-ε4 allele, Lewy body dementia diagnosis at autopsy, and family size all influenced the observed peaks. This highlights the importance of selecting appropriate analytical methods for genetic linkage studies, as the choice can significantly impact the results [42,43].

It is alarming to observe the amount of positive linkage reports obtained after multiple analyses of the genetic data without the appropriate correction or definition of stringent significance levels having been made. Although it is valid to perform exploratory analyses to assess the best genetic model or a better method of study, the results emerging from such analyses should not be interpreted as true linkage findings. In order to avoid some of these problems,

several groups have chosen the "candidate gene approach" as an alternative strategy to identify the AD5 gene(s). The alpha2macroglobulin (A2M), its receptor the low density lipoprotein receptor-related protein1 (LRP1) and the transcription factor LBP-1c/CP2/LSF genes have been intensively studied as candidates influencing the susceptibility to AD because of their chromosomal location within the critical regions and their role in βamyloid metabolism [41,43].

Chromosome 10 (AD6)

A two-staged genome screening was performed in ASP with LOAD from the National Institute of Mental Health (NIMH) AD Genetics Initiative; the sample was stratified on the basis of whether both or neither of the ASP members possessed at least one APOE-4 allele. The first stage involved genotyping 292 ASP by using a 20-cM marker interval [44,45]. During the second stage, 451 ASP were genotyped with an additional 91 markers, located within the 16 regions in which the multipoint LOD score was greater than 1 in stage I. Significance levels were estimated by simulation calculations. The best results in both stages corresponded to a region on chromosome 10q for which the initially obtained maxLOD score of 2.3 increased to 3.9 in stage II. The region on chromosome 10 was refined to approximately 44cM spanning from D10S1426 to D10S2327 [45]. Subsequently, Myers., *et al*. attempted to track the region by examining linkage disequilibrium in the area but they could not find a positive association when independent groups of discordant sib-pairs and a case-control sample were assessed. The same genomic region has been found by another group but, because of overlap in the sample set, these studies cannot be considered completely independent [46]. Evidence pointing to the same region on chromosome 10q was found in a sample of late-onset extended pedigrees that were selected based on probands with extremely high plasma values of Aβ42. The investigated region gave a maximum multipoint LOD score of 3.93 at 81cM, when high plasma values of Aβ42 were considered as a surrogate trait in a quantitative trait analysis. Abnormal levels of tau protein and Aβ42 in cerebrospinal fluid have been used as potential biological and diagnostic markers of AD, although other neurological disorders may also cause anomalous protein levels [47].

AD7

Following the identification of several AD risk genes on other chromosomes, researchers searched for additional loci using genome-wide association studies (GWAS). A study employing this approach identified a region on chromosome 10 (10p13) near the marker D10S1423 that showed allelic association with AD [48]. This means that specific variations (alleles) at certain genetic markers within this region were statistically associated with an increased risk of developing AD. Notably, six different markers within the region (D1S518, D1S547, D10S1423, D12S1045, D19S178, DX1047) exhibited this association.

The initial findings were further strengthened by independent replication studies. One study in Germany involving 80 AD patients and 300 controls confirmed the association. Another compelling piece of evidence came from a Finnish longitudinal study. This study followed 325 asymptomatic first-degree relatives of AD patients for 11.5 years. Researchers observed that individuals carrying both the 234-bp allele at D10S1423 and the APOE-ε4 allele had the highest age-specific risk of developing AD [49]. This suggests a potentially synergistic effect between these two genetic factors.

Interestingly, a separate GWAS study conducted in Finland using a linkage disequilibrium mapping approach also identified the same region (AD7, 10p13) approximately 5 centimorgans (cM) away from D10S1423. This study's strength lies in its focus on a population with a relatively homogenous genetic background, potentially reducing confounding factors [50].

In addition to the AD7 locus, this Finnish study identified six other chromosomal regions containing markers associated with AD: 1p36.12, 2p22.2, 3q28, 4p13, 18q12.1, and 19p13.3. These findings highlight the complex genetic architecture of AD, likely involving multiple genes located across different chromosomes.

AD8

In addition to the linkage signal repeatedly observed in the APP region (chromosome 21), a joint effect with chromosome 20p was reported in 272 ASP with AD by Olson., *et al*. 47. Using an interesting approach that incorporated covariates to the linkage analysis and that allowed for detection of genetic linkage in the presence of locus heterogeneity, this group was able to identify a region on chromosome 20p (AD8, 21 cM) when the current age of patients was taken into the analysis. The incorporation of the presence of the APOE-2 allele as a covariate yielded a higher LOD score (4.09). Moreover, a two loci model provided evidence of strong epistasis between chromosome 20p and the APP region on chromosome 21, especially in those patients who were of an older age and lacked

APOE-4. The development and/or rate of progression of AD in such families is influenced by the presence of high risk alleles at both loci, which probably interact biologically to increase disease risk [52].

A recent reanalysis of the genotypic data of 437 families from the NIMH Genetic Initiative, with a similar method that ordered subset of families by using covariates (in this case, AAO), detected regions on chromosome 2q34 (210 cM) in a subset of families with early-onset AD, 9p22 (42 cM) in families with LOAD and 15q22 (60–62 cM) in families with AD of very late onset (≥79 years) [53]. Despite the overlapping of the sample sets, only the 9p region has been reported before. On the other hand, a region 12 cM away from AD8 was also identified when the specific set of families were re-analyzed with the ordered subset method [53].

The chromosome 9 (32–45 cM) and chromosome 12 (~83 cM) regions were highly significant, whereas the chromosome 10 region (~105–115 cM) and the chromosome 2 region (~41 cM), which lies 6–10 cM away from a region previously detected by linkage-disequilibrium mapping in Finland [50], showed suggestive linkage [54]. Another recent genome scan carried out in the full NIMH Genetic Initiative sample (437 AD families, most of them with only one ARP) identified regions that overlapped with previous reports. For chromosome 1 (1q23 123, 148), a region close to the gene encoding niscatrin (NCSTN), which binds presenilin and is required for γ-secretase activity and Aβ generation was found 149. The 6p21 39, 123, 141, 148, 6q26 39, 145, 6q27 148 and 19q13 (close to APOE) 39, 123, 148 regions have been frequently reported. Patients sharing alleles at the 19q13 region had significantly more APOE-4 alleles than those who did not share alleles at the chromosome 19 marker, suggesting that the linkage signal on this region corresponds to the APOE gene 124 [55,56]. We believe that the presence of genetic heterogeneity, the lack of comprehension of the actual genetic model in complex disorders and methodological problems are influencing the successful mapping of susceptibly genes involved in AD etiology. Only our ability to overcome these difficulties will lead to the detection of predisposing genes that have modest effects and whose interaction ends in neurodegeneration and disease.

Most successful gene discovery studies to date have focused on syndromic phenotypes given the availability of large numbers of subjects who fit the clinical definitions of AD, ALS, MS, and PD that can be merged from multiple sources. Though this approach is convenient and reasonable, ignores that large fractions of the control populations used in these studies have subclinical features of the disease. This is particularly true for AD and PD and probably to a lesser extent for ALS. It includes the accumulation of neuritic amyloid plaques, neuronal loss in the substantia nigra and anterior horn, and other pathologies or symptoms, such as subtle cognitive impairment, bradykinesia, and muscle atrophy and weakness, that do not fulfill a syndromic definition [57]. These asymptomatic, affected subjects have most likely reduced the statistical power of studies of AD and perhaps PD; ALS and MS, because of their low incidence rate in the general population, have been less affected by this problem. Intermediate traits (also referred to as endophenotypes) that capture pertinent features of a neurodegenerative disease have been suggested to have greater statistical power for gene discovery efforts than syndromic phenotypes; for example, the known APOE AD-associated alleles have much larger effects on AD neuropathology and trajectories of cognitive decline than on a syndromic diagnosis of AD when investigated in the same set of deeply phenotyped subjects [57].

Endophenotype strategy

The endophenotype strategy has been widely used in Alzheimer's disease research, but its effectiveness hinges on the quality and statistical properties of the chosen trait. Studies focusing on pre-symptomatic features, also known as distal phenotypes, face specific challenges [58]. Firstly, researchers measure these intermediate traits inconsistently across studies, making it difficult to directly compare results [58]. Secondly, studies often rely on diverse subject groups, ranging from general population samples to specialized clinic patients or convenience samples. This heterogeneity can introduce confounding factors [58].

While estimating sample sizes for studies on cognitive decline, for example, may not be vastly different from studies on full-blown symptoms (syndromic traits), recent successful genome-wide association studies (GWAS) highlight the logistical hurdles. These GWAS, investigating hippocampal and intracranial volume, required large sample sizes (over 7,000 to 9,000 subjects) in some cases [59,60]. Combining data from studies using different measurement methods on diverse populations limits the power of combining results through meta-analysis [59,60].

Despite these challenges, investigating these clinical, imaging, and pathological endophenotypes, although more removed from the direct genetic cause of AD, has proven valuable. These studies have been instrumental in starting to understand the functional consequences of genetic variations associated with the disease [58].

APOEε4 with its very large effect size highlights this strategy well, [57,61] but the approach has already borne fruit with common variants such as the AD associated variants in CR1 and PICALM that have been implicated in the amyloid pathology that plays an important and early role in AD [62,63]. These and many other studies will gradually identify the pathophysiologic consequences of disease-associated variants and will help to assemble them into molecular pathways whose alterations lead to disease. Further, they will play an important role in the detailed dissection of associated loci, helping to (1) identify what may be the causal variant if there are several equivalent candidates at the end of the discovery genome-wide association study and/or (2) map the location of variants, within a susceptibility locus, with independent effects on the neurodegenerative process being studied [64].

Genetic link exploration with Biomarker data

In AD, treatment of symptomatic subjects has proven to be very challenging and new study designs are emerging to develop approaches to treating subjects with subclinical disease [65,66]. The use of key biomarker data such as radiolabeled positron emission tomography agents for amyloid imaging has opened the design of trials in this vein. Genetic data, when combined with pertinent biomarker data (some of which may be generated through genetic insights), may provide an efficient manner to stratify subpopulations of subjects in terms of their risk for a given disease. For example, APOE is sufficiently common and the associated risk sufficiently high that if knowledge of allele status was relevant to a clinical therapeutic decision, the field could consider recommending population screening. Genetic data will eventually emerge in clinical practice in some form. It is unlikely (aside from the highly penetrant mendelian variants) that genetic data will be enough, by itself, to be informative in a clinical setting. However, given the ease, precision, and cost of their measurement, genetic variants provide robust, if modest, information that can be integrated with other forms of information, such as cerebrospinal fluid biomarkers and imaging, for integrated risk assessments. Further, they are excellent candidates as a first line of diagnostic tools for paradigms that involve successive steps of profiling, in which only the higher-risk individuals from a given stratum are interrogated with the more costly or invasive profiling (lumbar puncture and imaging) of the later steps in the evaluation process.

Epigenomics-a genetic strategy

Epigenomics represents the natural progression of the study of the human genome; as we complete our catalog of genetic variation and the associated human traits, we must explore the 3-dimensional structure of chromosomes to understand whether the potential impact of an allele is realized in each cell. It is the local architecture of chromatin that dictates whether a segment of DNA is actively transcribed, repressed, or in another state, such as a "poised promoter" that has a certain probability of becoming transcribed given the correct stimulus. This architecture is determined in part by a range of epigenomic marks on the DNA strand itself and on the histones and other proteins on which the DNA is strand is bound.

Major challenges remain in the study of the epigenome: (1) Unlike DNA, chromatin is plastic, responding to its environment over the life course of an individual. (2) Unlike genomic DNA, which has 1 sequence per person, there are numerous chromatin marks across the DNA and attendant histones and other proteins, each of which requires unique profiling. (3) While there are shared patterns, each cell type (and possibly every cell) of an individual organism has a unique epigenome. (4) The technology to produce reliable results in large number of subject's epigenome-wide does not yet exist. Today, a first generation of disease-related epigenomic studies are being performed and beginning to be reported. They have focused on 2 approaches that are feasible today: (1) the generation of reference chromatin maps pertinent to the study of neurodegenerative diseases and (2) a first generation of epigenome-wide screens leveraging technologies that measure DNA methylation.

The great successes in gene discovery over the past 2 decades promise continued novel findings that relate to syndromic diagnoses in the short term, but these efforts are now mature and will run their course. Deploying these successful approaches in the realm of intermediate phenotypes and adapting them to the more complex task of exploring the epigenomic architecture of disease is where the larger insights will emerge in the coming decade. Leveraging the spirit and model of the consortia brought together for the study of syndromic phenotypes, collaborative groups that include the appropriate involvement of industry will generate the novel insights

that inform our study of neurodegenerative diseases. It will also inform the development of algorithms that are clinically meaningful and are used to safely inform patients as they make decisions on their management in the pre-symptomatic phase of disease with their physicians.

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