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The Correlation between Genotype and Phenotype of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most frequent cause of dementia, it manifests as a progressive decline in memory and other cognitive domains. The genetics of AD is complex and heterogeneous. Most cases are "sporadic late onset", however, a small percentage of cases have an early onset and usually aggregate within families. Early studies revealed that a number of genes, including both rare mutations and common polymorphisms, play an important role in the development of AD. More recently it has been proposed that genetic variation may also explain some of the other features of clinical phenotype, such as age at onset, disease duration, cognitive decline, behavioral and psychiatric symptoms and so on. In this review, we compared the clinical phenotypes of reported mutations within the three causative genes and some common polymorphisms, with an emphasis on their heterogeneity. Hopefully, the unique phenotypic features of individual mutation will enable us to study molecular mechanisms, potentially explaining phenotypic differences and providing useful knowledge for the development of new therapeutic agents.

Keywords: Alzheimer's disease; Genotype; Phenotype

Alzheimer's disease (AD; MIM# 104300) is a progressive neurodegenerative disorder and the most frequent cause of dementia. It afflicts 5.4 million individuals in the United States. Total direct and indirect cost is US$ 183 billion per year [1]. In a previous systemic review about the prevalence and incidence of dementia in China, it reported that the number of patients with AD was 5.69 million in 2010 and the incidence was 6.25 cases per 1000 person-years [2]. Besides, the prevalence of AD shows an age-dependent progression in the elderly. Thus, approximately 5% of all persons over age 70 have AD and this proportion rises to 25%-45% in the "oldest old" (>85 years) individuals [1]. It is characterized clinically by a progressive decline in memory and other cognitive domains. Behavioral and psychiatric symptoms such as agitation/aggression, mood disorders, and psychosis, may occur with disease progression [3]. Neuroimaging studies display atrophy in the cerebral cortex and the hippocampus of AD brain [4]. Pathologically, the disease is characterized by the formation of two distinct brain lesions: parenchymal amyloid plaques (senile plaques) consisting mainly of aggregated and deposited amyloid β (Aβ) peptides and intraneuronal neurofibrillary tangles composed of paired helical filaments of hyperphosphorylated microtubule-associated tau protein [5]. AD typically appears in older individuals, but may affect people as early as the second decade of life [6].

The genetics of AD is complex and heterogeneous. Most cases are "sporadic" with no apparent familial recurrence of the disease. However, a small percentage of AD cases (1-2% of all cases) have an early onset (early onset AD, EOAD), with symptoms appearing before 65 years of age. In these patients, the disease commonly aggregates within families and typically presents an autosomal dominant pattern of inheritance. Early studies revealed that a number of genes play an important role in the development of AD. Variation in these genes, including both rare mutations and common polymorphisms, appears to confer increased risk for the development of this disorder. However, the apparent increased risk may be largely explained by the effects that genetic variation has on the age at which the disease presents. More recently it has been proposed that genetic variation may also explain some of the other features of clinical phenotype, such as disease duration, cognitive decline, behavioral and psychiatric symptoms and so on. Here, we reviewed the clinical phenotypes of reported mutations within the three causative genes and some common polymorphisms, with an emphasis on their heterogeneity.

Causative Genes

The existence of families in whom the disease is transmitted in a clear autosomal dominant pattern indicates that genetics plays a very important role in the etiology of AD. Based on epidemiological data and the published mutation data, autosomal dominant familial AD (FAD) may account for 0.5% of all AD cases [7]. Study of one large pedigree revealed a single point mutation in the gene for amyloid precursor protein (APP), found on chromosome 21. Further studies led to the discovery of other mutations in the same gene and mutations in two others genes; encoding presenilin-1 (PSEN-1) and presentlin-2 (PSEN-2), found on chromosomes 14 and 1, respectively. To date, 51 AD-related pathogenic mutations have been discovered in the APP gene, 219 mutations in the PSEN-1 gene and 16 mutations in the PSEN-2 gene (AD&FTDMDB, http://www.molgen.vib-ua.be/ADMutations, accessed in August 2017).

APP

APP (OMIM 104, 760, chromosome 21q21) encodes an integral Type I membrane glycoprotein that exists as different alternatively spliced isoforms including APP751, APP770 and APP695 [8]. The proteolytic processing of APP results in the production of different peptides including Aβ. There are two mutually exclusive proteolytic pathways: the amyloidogenic pathway (successive cleavages by the

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β- and γ-secretase, fundamentally considered as the pathogenic pathway) and the non-amyloidogenic pathway (successive cleavages by the α- and γ-secretase). Mutations in the APP gene were the first to be identified to cause autosomal dominant EOAD [9]. To date, 51 different pathogenic mutations and 16 variants nonpathogenic or with unclear pathogenicity (AD&FTDMDB, http://www.molgen.vib-ua.be/ADMutations, accessed in August 2017) have been identified in APP. The mutation range encompasses mainly missense mutations as well as a few duplications. The missense mutations are located close to the major APP processing sites, either adjacent to the Aβ domain (the β and γ-secretase cleavage sites) or within the Aβ domain itself (the α-secretase cleavage site). The pathophysiologic mechanisms of these mutations vary. First of all, most of the mutations have been shown to functionally change the proteolytic processing of the APP protein. For example, the majority of the FAD-associated mutations in APP lie close to its γ-secretase site, such as the French (p.V715M) [10], German (p.V715A) [11], Florida(p.I716V) [12], London (p.V717I) [9] and Indiana (p.V717F) [13] mutations, which result in a relative increase in the production and deposition of the more fibrillogenic form of Aβ, Aβ42 [5]. Although the French (p.V715M) mutation results in a reduction of Aβ40 without affecting Aβ42 production, suggesting that it is the increase in the ratio of Aβ42 to Aβ40 that is important rather than the absolute amount of Aβ42. The only known mutation at the β secretase cleavage site is the Swedish (p.KM670/671NL) double mutation. This mutation results in increased total Aβ, by increasing both Aβ40 and Aβ42, although in brain parenchyma Aβ42 is predominantly deposited [14]. Mutations within the Aβ sequence, including the Flemish (p.A692G) [15], Dutch (p.E693Q) [16], Italian (p.E693K), Arctic (p.E693G) [17] and Iowa p.(D694N) [18] mutations, result in increased production of total Aβ [19] or enhanced propensity of Aβ to aggregate [20] and in increased resistance of Aβ to proteolytic degradation [21].

In addition to proteolysis, it was shown in different studies that gene dosage effects could also be causative. For instance, it has long been recognized that patients with Down syndrome lead to Aβ amyloid plaques and clinical and pathological AD from early adulthood, which is thought to be a gene dosage effect on the basis of the triplication of APP through the extra chromosome 21 [22]. More recently, five unrelated French families [23] with EOAD were first reported to harbor small chromosomal duplications including the APP locus, subsequent screens revealed additional APP duplications in nine French family [24-26], two Dutch families [27], one Finnish family [28], one Sweden family [29], five British families [30], and two Asian (Japanese) families [31,32], suggesting that increased expression of APP can lead to AD pathology in the absence of a full trisomy 21.

Mutations of the APP gene usually cause the disease of AD in an autosomal dominant pattern. However, two recessive mutations, A673V and E693Delta, causing disease in the homozygous state have also been reported [33,34]. Besides, the APP A713T mutation was identified to cause AD both in the homozygous and heterozygous state in one large pedigree [35]. In the affected persons, homozygosis for the APP A713T mutation does not aggravate the clinical phenotype of the disease, which is consistent with the classic definition of dominance.

Recently, a rare variant A673T was reported to play a protecting role against late-onset AD [36]. This variant was enriched in Icelandic elderly controls compared with AD cases from the same population. The frequency was 0.13% in AD cases and 0.45% to 0.79% in controls. However, Wang et al. [37] studied the frequency of this variant in AD cases and cognitively normal controls in the United States, and found the A673T variant was extremely rare in US cohorts (1 in 8943 AD cases and 2 in 10 480 controls) and might not play a substantial role in risk for AD in this population. Besides, the fact that this A673T allele was absent in a large Chinese sample (n=8721) suggests that this variant may be primarily restricted only in Scandinavian and Icelandic populations [38].

PSEN-1 and PSEN-2

PSEN-1 (OMIM 104,311, chromosome 14q24.3) and PSEN-2 (OMIM 600,759, chromosome 1q31-q42) genes have a very similar genetic structure and encode two proteins ubiquitously expressed in a multiplicity of tissues including the brain [39]. These are highly homologous, sharing an overall amino acid sequence identity of 67%. PSENs are integral membrane proteins that form the catalytic core of the γ-secretase complex [40]. The first disease causing mutations in PSEN-1 and PSEN-2 were identified in 1995 [39,41]. Today, 219 pathogenic mutations and 11 variants non-pathogenic or with unclear pathogenicity have been identified in PSEN-1. PSEN-2 harbors fewer mutations: 16 pathogenic mutations and 23 variants non-pathogenic or with unclear pathogenicity (AD&FTDMDB, http://www.molgen.ua.ac.be/ADMutations, accessed in August 2017).

PSEN-1 mutations are the most common identified genetic cause of AD. The PSEN-1 mutation range encompasses mainly missense mutations as well as some small deletions and insertions. The underlying pathogenic mechanism of most PSEN-1 mutations seems to be related to altered γ-secretase function. For instance, when stably transfected into cell lines, most PSEN-1 mutations cause increased production of Aβ42 which has a greater tendency to aggregate [42] and pathologic examination of brains with PSEN-1 mutations show increased Aβ42 deposition when compared to sporadic AD [43]. Deletions of PSEN-1 exon 9 (Δ9) may result either from mutations at a splice acceptor site (g.58304G>A/ g.58304G>T) [44] or from deletions of several kilobases of genomic DNA (g.56305_62162del/ g.56681_61235del) [6,44,45]. Biochemical studies suggest that it is the point mutation rather than the deletion itself that is critical for the pathological increase in Aβ42 production.

Mutations in PSEN-2 were first described in 1995 and only 16 pathogenic mutations have subsequently been reported, making this the least common genetic cause of AD. All the known PSEN-2 mutations are missense mutations. Moreover, most of the mutations were only found in a single family, with the exception of p.T122P (2 families) [46,47], p.N141I (10 families) [39,46,48], p.M174V (4 families) [49] and p.M239V (6 families) [25,50]. PSEN-2 is part of the γ-secretase complex and there is evidence that mutations in this protein decrease the production of Aβ40 relative to Aβ42 and result in a greater proportion of the more toxic Aβ42 [40].

Knowledge of the multiple causative mutations leading to familial EOAD is of great value for several reasons. In a clinical setting, knowledge of the pathological mutations and genotype-phenotype correlations might assist in making an accurate diagnostic decision prior to treatment. In a research setting, knowledge of the pathological mutations might reveal valuable indications towards the pathological mechanisms leading to this disease.

Genes as Risk Factors

APOE

The apolipoprotein E gene (APOE, OMIM 107,741, chromosome 19q13.2) encodes a glycoprotein that is highly expressed in the brain

and plays a major role in central nervous system cholesterol homeostasis during neuronal growth and in nerve regeneration [51]. There are three major APOE isoforms: ApoE2, ApoE3 and ApoE4. These isoforms differ from each other only by a Cys to Arg amino acid substitution at positions 112 or 158 (ε2: Cys112/Cys158; ε3: Cys112/Arg158; ε4 Arg112/Arg158) [52]. ApoE3 accounts for approximately 64% of alleles [53] and is considered the "neutral" ApoE genotype. In 1993, Saunders et al. [54] demonstrated an association between the ε4 allele and LOAD, which was well confirmed in most populations thereafter. This allele represents an increased risk of 3-fold for heterozygous carriers and up to 15-fold for ε4 homozygotes [55]. In contrast, ApoE2 is believed to be protective against LOAD [56]. The disparities associated with each genotype are due to the distinct binding properties of the different APOE isoforms to the Aβ peptide [57] and tau protein [58]. The ApoE4 isoform binds to the Aβ peptide more rapidly than the ApoE3 isoform to form novel monofibrillar structures [59]. The fact that ApoE4 does not bind to tau protein *in vitro* suggested that this interaction between ApoE3 and tau serves as a protection against tau phosphorylation and consequent neurofibrillary tangle formation [58]. In a recent meta-analysis, Ward et al. [60] studied the prevalence of ApoE4 genotype among patients with AD in different regions. The pooled estimates for APOE ε4 carrier prevalence is 48.7% and ε4/4 prevalence 9.6%. They also observed a variation from different geographic location, with the lowest regional estimates for the prevalence (41.9%) of ε4 carriers and the prevalence (7.7%) of ε4/4 in Asia or 40.5% and 4.6% in Southern Europe/Mediterranean. The highest were in Northern Europe, 61.3% of ε4 carriers and 14.1% of ε4/4.

Other risk variants

Besides the well-known APOE gene, large-scale genome-wide association studies (GWAS) of late-onset AD (LOAD) have identified and replicated at least ten loci that are associated with susceptibility of AD, including PICALM, CLU, CR1, BIN1, CD2AP, EPHA1, MS4A6A, MS4A4A, CD33 and ABCA7. The latest meta-analysis [61] to date further expands the list to some additional variants, including HLA-DRB5, PTK2B, SORL1, SLC24A4, DSG2, INPP5D, MEF2C, NME8, ZCWPW1, CELF1, FERMT2 and CASS4. In addition, a rare variant R47H in TREM2 was reported to be associated with AD [62,63]. However, these identified genetic loci have very modest effects in LOAD and in total can explain only about 33% of the heritability [64], which has been estimated to be 60% to 80% [65].

Genotype-phenotype correlations

Although many familial AD mutations have been reported during the past two decades, relatively few efforts were put on the detailed description of the corresponding clinical phenotypes, making genotype-phenotype correlations difficult. Generally the phenotype in familial AD is indistinguishable from that in sporadic AD. The age at onset (AAO) is usually earlier and the disease course shorter in familial AD. Moreover, some studies have also shown that patients with EOAD present more frequently with atypical clinical manifestations such as executive, behavioral, or language impairment compared with LOAD [66]. Although some early reports suggested that, apart from variation in AAO, there was little phenotypic heterogeneity in familial AD cases [67]. It has become increasingly apparent that there are differences in familial AD cases with different mutations at many aspects. More and more researches have noted intrafamilial homogeneity and interfamilial heterogeneity with respect to AAO, disease duration, and clinical and neuropathological features. The specific genotype-phenotype correlation in APP, PSEN-1 and PSEN-2 are summarized in (Supplemental Tables 1-3), respectively. The follows will highlight the correlations of these genotypes with different AD phenotypes including AAO, penetrance, disease duration and clinical manifestations.

AAO and penetrance

Variation in AAO is the most significant character of the clinical heterogeneity of AD, which was noted even before mutations were identified. Families carrying APP mutations have AAO largely within the range 40-65 years. However, the range can be very broad with the earliest AAO of 30 in a family with the p.T714I (Austrian APP) mutation [68,69]. The latest recorded AAO in APP were 82 years in a family with the p.A713T mutation [70,71]. Another two families with very late AAO of 75 years were families with the p.E682K (Leuven APP) mutation [72] and p.E693G (Arctic APP) mutation [17,73].

Families carrying PSEN-1 mutations have the earliest AAO, which fall largely within the range 35-55 years. The earliest reported AAO was 20 years in a family with p.P436Q mutation [6]. There are also some family members with the mutation p.P117A [74,75], p.P117L [76-78] and p.L173W [79] have recently been recorded with onset at 24 years. Very early onset of cognitive decline, before age 30 years, has been noted with the following PSEN-1 mutations: p.L85P [80], p.T116N [81-84], p.P117S [77], p.I143T [82,83,85-87], InsFI [82,88], p.L166H [89], p.S169L [90,91], p.S170F [92-94], p.G209V [95], p.M233V [96], p.M233I [97], p.L235Pr [98], p.Y256S [99], p.A260V [39,100], p.V272A [84,101], p.L381V [102], p.G384A [85], p.L424R [103], and p.A434C [82]. PSEN-1 mutations show almost complete penetrance by the age of 60 years. However, there are some recorded exceptions such as the p.A79V (78 years) [47,82,104,105], p.H163R (68 years) [101,106-108] and p.L271V mutations (68 years) [109]. The factors that contribute to reduced penetrance are not at present known.

Families carrying PSEN-2 mutations have the latest ages of onset, with a wide range 40-87 years and thus show some overlap with LOAD. The earliest reported AAO was 40 years in a family with the p.N141I mutation [39,46,48]. The latest reported AAO was 87 years in a family with p.A237V mutation [110]. Penetrance is high but may not be 100%. There are at least two reported cases of non-penetrance over the age of 80 years in the families with the p.N141I mutation [39,46,48] and p.Q228L mutation [111].

Generally speaking, apart from the variation of AAO between different gene mutations, the AAO of family members with the same mutation, especially the AAO of family members from one pedigree usually fall in a comparatively narrow range. However, this is not always the case. There are some reported pedigrees with range of AAO more than 30 years, for example, the p.A713T mutation within the APP gene (AAO range: 49-82) [70,71] and the p.N141I mutation within the PSEN-2 gene (AAO range: 40-82) [39,46,48]. The causes of this variability in AAO are not clear. There may be a long prodromal phase with subtle deficits of general intelligence and memory that may be easily neglected by the patient him/herself as well as the attending physicians. However, more and more studies indicated that potential genetic modifiers might delay or accelerate AAO of familial AD. For example, by using a subset of Caribbean Hispanic families that carry the PSEN1 p.G206A mutation, Lee et.al identified that SNX25, PDLIM3, and SORBS2 may serve as genetic modifiers of AAO in both EOAD and LOAD [112-115].

The familial influence on AAO in LOAD may be substantial. Corder et al. [116] found that the APOE ε4 allele shifted the disease onset to younger age following a dose effect pattern. In their study, the mean onset age was 84.3 years in subjects who did not have ε4,

75.5 years in subjects with one ε4, and 68.4 years in subjects with two ε4 alleles. In other word, in LOAD the onset age is approximately 20 years earlier in individuals who carry two copies of the APOE4 allele compared with non-carriers. This led to the hypothesis that the APOE4 allele is a risk factor for LOAD mainly because in old age AD and death are competing risks. Any factor leading to an earlier onset age of AD in the elderly will be associated with AD. Thus, it appears clear that the APOE4 allele has its predominant effect by determining when, but not if, an individual develops LOAD.

Disease duration

The mean duration of illness in families with PSEN-1 mutations is significantly shorter (range 5.8-6.8 years) than in families with both APP (range 9.0-16 years) and PSEN-2 (range 4.4-10.8 years) mutations, reflecting the severity of PSEN-1 associated AD. Studies of LOAD suggest that the duration of illness tends to be longer in people who have a positive family history or in carriers of the APOE4 allele. However, it has since been shown that this relationship no longer holds true once the confounding effects of AAO have been taken into account [117]. Thus, in LOAD, increased survival is more directly related to an earlier AAO, which is influenced by a number of factors that are not exclusively genetic.

Cognitive decline

To our knowledge, no study to date has looked at rates of decline in possession of APP, PSEN-1 and PSEN-2 mutations. And the majority of studies have also failed to show any relationships between carriers of the APOE4 allele and increase rates of decline [116]. This lack of association is interesting since it suggested that genetic factors might determine only when the disease starts, but not the rate of degeneration. However, a study by Craft et al. [118] found that there is an increased rate of cognitive decline in APOE4 carriers, which may be detectable by using a long follow up period. Clearly, caution is required when interpreting a negative finding. Associations will always be difficult to establish because there are many confounding factors that may influence cognitive deterioration as well as difficulties in calculating the rate of decline.

Myoclonus and seizures

Myoclonus is a common feature in sporadic AD. A cross-sectional study identified myoclonus in 5-10% of patients, particularly those with early onset and the prevalence increasing with time [119]. Although seizures are not very common in sporadic AD, they do occur more frequently than in the general population [120], particularly with increased duration of disease. Amatniek et al. [121] also found that seizure incidence is increased in patients starting with mild to moderate AD. In their study, they found that the cumulative incidence of unprovoked seizures at 7 years was nearly 8% and seizures in early onset familial AD occur several times more than in sporadic AD.

Patients carrying PSEN-1 mutations have the most frequency to develop these features. The reported families that developed myoclonus carrying the PSEN-1 mutations including p.L113Q, p.Y115H [46], p.P117R, p.H163R [101], p.S169P [122,123], p.S169L [90,91], p.S170F [94], p.L235P, p.R269H [98], p.L250V [124], and p.R269G [125]. The epilepsy/seizure-associated PSEN-1 mutations are spread throughout the PSEN-1. Larner [126] noted that epileptic seizures have been reported as part of the phenotype of 37 different PSEN-1 mutations. Myoclonus and seizures in patients with APP mutations are less common but not absent, for instance, the p.T714A (Iranian APP) mutation [68,127]. However, no patient with PSEN-2 mutations was reported to have such neurological features.

The pathological mechanism underlying this feature in patients with AD was unknown. However, there was some evidence indicating possible common neural mechanisms underlying these two conditions. For example, the first description of amyloid plaques in the human brain came from the neuropathologic examination of epilepsy patients in 1892, fifteen years before the first case report of AD in 1907 [128]. From then on, there were several studies that reported on the presence of senile plaques in patients with epilepsy [129]. Along with amyloid deposition, the other neuropathologic signature of dementia, tau, has also been reported in human epilepsy patients and in animal models of epilepsy [130]. Besides, atrophy of the mesial and lateral temporal regions on MRI and hypometabolism in the basal temporal region demonstrated by positron emission tomography studies were characteristic finding in both conditions [131,132].

Extrapyramidal sign and Parkinsonism

Extrapyramidal signs (EPS) such as bradykinesia and rigidity are very common in AD patients. In a community based study, Funkenstein et al. [133] discovered a strong association between EPS and AD. In some studies, AD patients with EPS showed accelerated cognitive decline and shorter survival time [134,135]. Many studies concur with this view. However, the reporting EPS frequency in AD varied from 6% to over 50% [119]. Clinicopathological correlation studies demonstrated that AD patients with concomitant Lewy bodies were more likely to manifest Parkinsonism than those without them [136].

EPS and Parkinsonism are also very common in familial EOAD. It was autopsy proved in patients with the dupAPP mutation [24], p.V272A mutation [84,101], ΔT440 mutation [137] in the PSEN-1 gene and p.A85V mutation [138] in the PSEN-2 gene.

Behavioral and psychiatric symptoms (BPS)

In the more advanced stages of AD, cognitive decline are usually accompanied by mood disorders, anxiety, apathy, dysphoria, psychotic symptoms (delusions, hallucinations), aggression or agitation. These symptoms, alongside other behavioral disturbances including wandering and inappropriate sexual behaviours, are often clustered together as behavioral and psychological symptoms (BPS). In the course of the illness BPS can be present in as many as 60-98% of demented individuals, with an average of around 80% in subjects with AD [139]. There have been some studies over the past several years looking at the genetic basis of psychosis in AD. Sweet et al. [140,141] found compelling evidence that BPS in AD is familial. Evidence of familial aggregation of psychosis in AD suggests that genetic play an important role in the development of this phenotype. However, despite the evidence of the heritability of psychosis in AD, the results of genetic studies to date were not definitive [142-145].

BPS sufficient to be reported as suggestive of the phenotype of frontotemporal dementia (FTD) has been noted in the patients carrying PSEN-1 mutations including p.L113P [146], p.M139V [111], p.L226F [101,147], p.M233L [148], p.V412I [71] and PSEN-2 mutations including p.T122R and p.Y231C [149]. In one case carrying p.G183V within PSEN-1, the neuropathological appearances were of Pick's disease without AD amyloid plaques [150]. In patients with p.M146L within PSEN-1, the neuropathology fulfilled the criteria of both the AD and Pick's disease.

Spastic paraparesis/variant AD

Spastic paraparesis, also called "variant AD", was first noted by Kwok et al. [45] in patients with the p.R278T and Δ9 splice acceptor site

mutations within PSEN-1. The clinical phenotype was characterized by memory impairment associated with spastic paraparesis. The pathological basis of this distinctive phenotype is Aβ positive "cotton wool" plaques without a congophilic core [151].

Although this phenotype can occur in mutations throughout the whole PSEN1 gene, the most common causes are the exon 9 genomic deletions. Most patients with the exon 9 genomic deletion (Δ9) in the PSEN-1 gene shared this phenotype, however, there is an exception, the Δ9 (g.58304G>T) mutation [6,44,45]. Other PSEN-1 mutations with dementia and spastic paraparesis have subsequently been described: ΔI83/M84 [6,152], p.L85P [80], p.N135S [46,153], p.Y154N [154], InsFI [82,88], p.Q223R [155], p.F237I [156], p.V261L [157], p.V261P [82], p.P264L [158], p.G266S [159], p.R278K [160], p.R278S [161], p.E280G [83], p.P284S [162], p.L381V [102], and p.P436Q [6]. No family with mutations in either the APP gene or PSEN-2 gene was reported to have spastic paraparesis.

Conclusion

It is well known by now that, in most cases, the clinical picture correlates with the underlying genotype changes. However, in a recent study, Balasa et al. [163] observed a frequent misdiagnose among patients with atypical presentations. As a result, the clinical and genetic heterogeneity of autosomal dominant inherited dementia must be taken into account in the genetic counselling and testing of families with autosomal dominantly inherited dementia. In the future, when there are more potent therapies for AD, it might be desirable to use AD biomarkers for the clinical diagnosis, such as cerebral spinal fluid biomarkers or *in vivo* amyloid neuroimaging techniques, in routine clinical practice. Moreover, many researches have noted intrafamilial homogeneity and interfamilial heterogeneity with respect to clinical phenotypes such as age at onset, disease duration, and clinical and neuropathological features. These findings of pedigrees but not mutation specificity argue strongly for the involvement of other genetic and/or epigenetic factors modulating the phenotype of AD. Hence, finding a causative/risk gene may be no more than a first step in understanding the phenotype of this disease. However, the unique phenotypic features of individual mutation still enable us to study molecular mechanisms, potentially explaining phenotypic differences and providing useful knowledge for the development of new therapeutic agents.

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