Published in final edited form as:

Curr Genet Med Rep. 2018 March ; 6(1): 11–19. doi:10.1007/s40142-018-0133-1.

Genetic Modifiers in Neurodegeneration

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Abstract

PURPOSE OF REVIEW—To review the evidence for genetic modifier effects in the neurodegenerative diseases Huntington's Disease (HD), Frontotemporal Lobar Degeneration (FTLD), Alzheimer's Disease (AD), and Parkinson's Disease (PD).

RECENT FINDINGS—Increasingly, we understand human disease genetics less through the lens of single-locus/single-trait effects, and more through that of polygenic contributions to disease risk. In addition, specific examples of genetic modifier effects of the chromosome 7 gene *TMEM106B* on various target genes including those causal for Mendelian classes of FTLD – *GRN* and *c9orf72* – have emerged from both genetic cohort studies and mechanistic examinations of biological pathways.

SUMMARY—Here, we summarize the literature reporting genetic modifier effects in HD, FTLD, AD, and PD. We further contextualize reported genetic modifier effects in these diseases in terms of insight they may lend to the concept of a polygenic landscape for the major neurodegenerative diseases.

Keywords

Genetic modifier; neurodegeneration; FTLD; Alzheimer's Disease; Parkinson's Disease; *TMEM106B*; *APOE*

INTRODUCTION

Neurodegeneration – the progressive loss of neurons with ensuing effects on cognition, motor function, and other brain activities – affects millions worldwide, with numbers suffering from neurodegenerative diseases expected to increase at an alarming rate as the population ages [1,2]. Currently, there are no disease modifying therapies for the major neurodegenerative diseases: Huntington's disease (HD), Frontotemporal lobar degeneration (FTLD), Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic lateral

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Compliance with Ethics Guidelines

Conflict of Interest

Both authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

sclerosis (ALS). However, many genetic studies – ranging from traditional family linkage studies, to genomewide association studies (GWAS), to investigations of genetic effects on endophenotypes within each disease – have uncovered a wealth of loci, and in some cases, specific genetic variants, that confer varying levels of predisposition to specific diseases or specific manifestations of these diseases. Indeed, ~200 different loci have been linked to FTLD, AD, PD, ALS, and related neurodegenerative disorders by GWAS alone [3,4].

Concurrent with our discovery of ever-expanding numbers of genetic loci associated with the various neurodegenerative diseases is an evolving understanding of the landscape of human disease genetics. Specifically, the one gene-one trait model that dominated much of early human disease genetic investigations is giving way to a polygenic model, whereby multiple genes may interact to influence various traits in additive, synergistic, or even opposing ways [5,6]. Additionally, epistasis, the phenomenon whereby the interactions of genes are non-linear (*i.e.* not additive), has received considerable attention [7], although specific examples of epistatic effects are surprisingly rare in the human disease literature [8,9].

Thus, it is timely to consider the role of genetic modifiers in the neurodegenerative diseases. Genetic modifiers – defined as genes that alter the expression of other “target” genes – have traditionally been studied in the context of genetic modifier loci that affect the penetrance, severity, or other clinically-important features of diseases caused by rare mutations in target genes. These diseases are inherited in Mendelian fashion, and include examples such as cystic fibrosis [10]. We review here the evidence for traditional genetic modifiers in HD, a Mendelian neurodegenerative disease, as well as Mendelian subgroups of FTLD, ALS, PD, and AD. In broader terms, however, genetic modifiers serve as examples of the phenomenon of polygenic contributions to trait determination, be they by linear or epistatic effects. We thus also review the evidence for polygenic contributions to neurodegenerative disease phenomenology outside of the strictly Mendelian forms of disease. Finally, as our intent is to highlight the ways in which insight derived from genetic studies might inform therapeutic strategy, we focus particularly on areas where genetic modifier loci – both identified and to-be-identified – might be reasonable targets for therapeutic intervention.

HUNTINGTON’S DISEASE

HD is a rare, progressive neurodegenerative condition characterized by dementia and behavioral abnormalities [11]. Unlike the other diseases in this review, HD consists only of autosomal dominant cases defined by mutations in a single gene, *HTT*, encoding the protein huntingtin [12,13]. Specifically, HD is caused by a CAG repeat expansion in *HTT* exon 1, resulting in the translation of a polyglutamine tract of varying sizes, with age at disease onset inversely correlated with the length of the expansion [14,15].

Despite the evidence that the size of the CAG repeat expansion affects age at HD onset, considerable variability in presentation exists that is not explained by repeat size; for example, HD individuals carrying 44 CAG repeats may demonstrate disease onset ranging from 31 to 66 years of age [15]. To investigate the role of other genetic modifiers in HD, a recent GWAS was performed to identify loci associated with age at disease onset, finding

genetic variants at two loci – on chromosome 15 (chr15) and chromosome 8 (chr8), with what appear to be three independent effects – that associate with this endophenotype [16]. The genes associated with these loci that mediate these effects on age at onset are yet unknown, but likely candidates include nearby genes *MTMR10* and *FAN1* and pseudogene *HERC2P10* at the chr15 locus and the genes *RRM2B* and *UBR5* at the chr8 locus [16]. While results are promising, they await replication and further investigation into biological mechanism.

FRONTOTEMPORAL LOBAR DEGENERATION

FTLD is the second most common form of dementia in individuals under the age of 65. A progressive brain disorder with degeneration of the frontal and/or temporal lobes, FTLD affects a patient's behavior and language [17,18]. A subset of FTLD patients additionally experience motor neuron degeneration, with ensuing symptoms that resemble those of Amyotrophic Lateral Sclerosis (ALS) [17] – these patients are described as having FTLD-MND.

Autosomal dominant mutations in the genes encoding human progranulin (*GRN*) and the microtubule-associated protein tau (*MAPT*), as well as hexanucleotide expansions in *c9orf72*, have been shown to cause FTLD [19–23]. While *MAPT* mutations cause a form of FTLD characterized neuropathologically by inclusions containing the tau protein (FTLD-tau), *GRN* mutations and *c9orf72* expansions cause FTLD characterized neuropathologically by inclusions containing the HIV TAR DNA-binding Protein of 43 kD (TDP43), termed FTLD-TDP [24]. Additionally, while *MAPT* mutations are very rare, *GRN* mutations and *c9orf72* mutations are not, together affecting over half of all familial cases of FTLD [17,18,25–27]. Pathogenic mutations in *GRN*, *MAPT*, and *c9orf72* are all highly-penetrant causes of FTLD [28].

In contrast with these rare-variant/strong-effect FTLD genetic loci, all of which were found by family linkage studies, common variants in the gene encoding Transmembrane Protein 106B (*TMEM106B*) have been shown by GWAS to confer slightly increased risk of FTLD, with an odds ratio of ~1.6 for the risk-associated haplotype at the *TMEM106B* locus [29]. While the original GWAS focused on neuropathologically-confirmed cases of FTLD-TDP, and included a significant group of *GRN* mutation carriers in whom the *TMEM106B* locus risk association appeared to be particularly strong, subsequent studies have replicated the finding that common variants at this locus associate with risk for FTLD in additional clinical cohorts as well [30,31].

Additional rare genetic causes of FTLD have been reported, as reviewed previously [32]. However, here we focus on the more commonly-found genes associated with FTLD – namely, *GRN* and *c9orf72* – and the effects of common variation in *TMEM106B* on clinical presentation in FTLD individuals who harbor *GRN* mutations, *c9orf72* expansions, or no Mendelian mutations.

Modifier Effects in *GRN* Mutation-associated FTLD-TDP

Since mutations in *GRN* were first identified as a cause for FTLD [20,21,33], two major themes have emerged. First, all autosomal dominant FTLD-causing mutations in *GRN* appear to be haploinsufficiency mutations, suggesting that a scarcity of progranulin leads to neurodegeneration [33,34]. Second, among *GRN* mutation carriers, clinical presentation varies greatly, even within the same family [20,21,35], suggesting the presence of genetic or environmental modifiers of phenotype.

Progranulin is a secreted growth factor that may enhance neuronal survival [36]; both progranulin, and daughter granulin peptides derived from progranulin, have also been reported to function in wound healing and inflammation [37]. More recently, Sortilin-1, encoded by *SORT1*, has been reported as the neuronal receptor for progranulin, conferring on neurons the ability to internalize progranulin [38], although multiple groups have also described sortilin-independent effects of progranulin [39–41]. As progranulin and sortilin-1 may function as a ligand-receptor pair, there is strong scientific rationale for *SORT1* as a genetic modifier of progranulin-mediated effects. Indeed, the rs646776 SNP near *SORT1*, previously linked to *SORT1* expression levels as an expression quantitative trait locus (eQTL), has also been reported to associate with plasma progranulin levels [42].

Mechanistic data linking TMEM106B to progranulin exist as well. In particular, we and others have shown that manipulation of *TMEM106B* expression levels in cell culture results in changes in progranulin protein measures [43–46]. Moreover, *TMEM106B* deletion from *GRN* null animals ameliorates abnormal lysosomal phenotypes and rescues retinal degeneration seen in *GRN* null animals, possibly through a mechanism involving TMEM106B's interaction with components of the vacuolar ATPase complex (and particularly V-ATPase AP1) responsible for lysosomal acidification [47]. From a human genetics standpoint, *TMEM106B* common variants associated with risk for FTLD-TDP in the general population also associate with earlier age at FTLD onset for *GRN* mutation carriers [43].

Modifier Effects in *C9ORF72* Mutation-associated FTLD-TDP

TMEM106B has also been mechanistically linked to c9orf72. Specifically, we have shown that aberrant lysosomal phenotypes (vacuolar morphology, defect in acidification) induced by over-expression of *TMEM106B* are rescued with concomitant knockdown of *c9orf72* [48]. Moreover, genotypes at the sentinel single nucleotide polymorphism associated with FTLD-TDP by GWAS, rs1990622, associate significantly with age at onset and age at death for FTLD-TDP patients carrying expansions in *c9orf72* in our study of 89 neuropathologically-confirmed FTLD-TDP cases from 31 sites around the world [49].

Intriguingly, however, the direction of association differs for *TMEM106B* effects on *GRN* mutation carriers vs. *c9orf72* mutation carriers. That is, whereas the rs1990622 G allele associated with *decreased* risk of FTLD-TDP by GWAS is found in *GRN* mutation carriers with a *later* age at disease onset, this same rs1990622 G allele is found in *c9orf72* expansion carriers with an *earlier* age at disease onset and death. In theoretical genetic terms, this

constitutes an example of sign epistasis, a situation whereby the same genetic variation that is beneficial on one genetic background may be deleterious in another genetic background.

Further complication of the intriguing relationship between *TMEM106B* and *c9orf72* comes from the observation that, unlike *GRN* carriers, who manifest almost exclusively with FTLD-TDP, *c9orf72* expansion carriers may manifest with FTLD-TDP or with ALS/MND (or with a combination of the two) [34]. Indeed, in a study of 325 *c9orf72* expansion carriers, homozygous carriers of the *TMEM106B* rs1990622 G allele were significantly under-represented among FTLD patients, but not among MND patients. While the authors interpret this result to suggest that the rs1990622 GG genotype is highly protective, decreasing the penetrance of *c9orf72* expansions, reports that of >36,000 control samples screened for *c9orf72* expansions, only 40 (0.1%) asymptomatic individuals were found to harbor expansions suggest that there might be a more complicated interplay between *TMEM106B* genotype, *c9orf72* expansions, and ultimate clinical manifestation [50].

Additional genetic modifier effects for *TMEM106B*

TMEM106B may exert modifier effects in groups beyond individuals carrying *GRN* mutations or *c9orf72* expansions. Specifically, we first showed that *TMEM106B* genotypes correlate with cognitive phenotype in ALS, with carriers of the rs1990622 G allele more likely to show preserved cognition and lesser TDP-43 pathology in five brain regions [51]. Further support for a role for *TMEM106B* in modifying phenotypes beyond subsets of individuals with FTLD due to known Mendelian mutations comes from recent data demonstrating that the rs1990622 G allele (or proxy markers linked to this allele) may show a protective effect with respect to (1) hippocampal sclerosis of the aging [52], (2) general cognition among elderly individuals in the Religious Orders Study and Rush Memory and Aging Project [53], and (3) a frontal cortex brain expression profile representative of “aging” [54]. As the latter two results come from genomewide screens for modifiers of cognitive aging, support for a role for *TMEM106B* in these processes is substantial.

The evidence suggesting that *TMEM106B* genotypes may act as genetic modifiers of cognitive aging is furthermore supported by mechanistic work from multiple groups defining a role for TMEM106B in lysosomal function [44–46,48,55,56]. As genotypes at rs1990622 and linked SNPs act as *TMEM106B* eQTLs [3,29,57], likely through a mechanism involving differential recruitment of the chromatin organizing protein CTCF [3], the data, taken together, suggest that levels of TMEM106B expression impact lysosomal function, with ensuing effects on cellular health and brain aging.

ALZHEIMER’S DISEASE

AD is the most common form of dementia in the elderly, affecting ~50% of individuals 85 years or older [58]. AD is a progressive brain disorder associated with decline in memory and other cognitive domains [59–61]. Mutations in the genes encoding amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) have long been known to cause autosomal dominant, early-onset forms of AD [62–66]. However, unlike FTLD, familial forms of AD are rare, encompassing less than 5% of total cases [67,68].

In addition to rare, Mendelian causes of AD, common variation in the Apolipoprotein E gene (*APOE)* has been extensively studied as a genetic risk factor for development of AD [69]. Three major ApoE isoforms exist in the general population, termed the ApoE ε2, ε3, and ε4 isoforms, with corresponding ε2, ε3, and ε4 alleles [69]. The ε4 allele has been well established as a strong genetic risk factor for development of AD [70–72], with a reported odds ratio of 14.9 for a Caucasian population carrying the ε4/ε4 genotype [73]. As the ε4 allele is not uncommon (~14% frequency) [73], *APOE* is an important contributor to AD pathogenesis in terms of both effect size and numbers affected. In addition to contributing to risk for development of AD, the *APOE* ε4 allele associates with earlier age at onset for AD as a whole, as well as *PSEN1*-mutation and *PSEN2*-muation associated AD [73–77]. The ε2 allele has also been reported to exert effects on AD risk; specifically, ε2 allele carriers may be protected against late-onset AD [78]. Additionally a large-scale genome wide survival analysis reported that the rs1057233 G allele, within a previously reported *CELF1* AD risk locus, associates with a later age of disease onset for AD [79].

Apolipoprotein E is believed to function in the clearance of beta-amyloid (Aβ42), the major protein that accumulates in the senile plaques that, along with tau-filled neurofibrillary tangles, characterize AD neuropathologically [80]. As such, it is perhaps unsurprising that *APOE* genotypes have also been linked to other processes involving Aβ42. For example, the *APOE* ε4 allele has been associated with CSF levels of Aβ42 [81,82]. Moreover, in individuals who at baseline were without evidence of Aβ42 deposition by imaging, or dementia clinically, the *APOE* ε4 allele associated with subsequent brain accumulation of Aβ42 [83]. In addition, in PD, a distinct neurodegenerative disease in which Aβ42 deposition is also frequently observed [84–87], the ε4 allele of *APOE* has also been linked to cognitive decline and dementia [88–90].

PARKINSON'S DISEASE

PD is the second most common neurodegenerative disorder after AD, affecting 2–3% of the population older than 65 [91]. PD is characterized by neuronal loss in the substantia nigra, the development of inclusions including aggregates of alpha-synuclein (encoded by the gene *SNCA*), and development of many motor, as well as non-motor, symptoms [92–96]. The discovery of *SNCA* mutations, as well as *SNCA* duplications and triplications, as causes of familial PD, established alpha-synuclein as a central player in PD pathogenesis [92,97]. However, these mutations are rare, limited, in some cases, to a few families. In contrast, mutations in the leucine-rich repeat kinase 2 (*LRRK2*), also causal for PD, are more common, affecting approximately 5% of all PD [98,99], and higher proportions in PD patients from specific ancestral backgrounds, such as Ashkenazi Jews (~18% for *LRRK2*+ PD) [100], and North African Arabs (37–41% for *LRRK2*+ PD) [101,102]. Surpassing even *LRRK2* mutations in frequency are mutations in the gene encoding β-glucocerebrosidase (*GBA*), found in 7% of PD patients [103]. Long understood to be the autosomal recessive cause of the childhood-onset lysosomal storage disorder Gaucher's disease, *GBA* mutations were linked to increased risk for PD in 2009 [103]. Specifically, the presence of one *GBA* mutation is associated with an odds ratio of ~5 for development of PD [103]. Moreover, *GBA* mutations have been reported to modify the clinical presentation in PD, with carriers

of *GBA* mutations as well as the *GBA* E326K polymorphism at increased risk for GBA-related cognitive deficits [104,105].

Unlike the situation with *GRN* mutations or *c9orf72* expansions in FTLD, or *APP*, *PSEN1*, or *PSEN2* mutations in AD, all of which are highly penetrant, neither *LRRK2* nor *GBA* mutations are highly penetrant in PD. In the case of *LRRK2*, age-related penetrance for the most common LRRK2 Gly2019Ser mutation can range from ~30% to 70% [106]. In the case of *GBA*, age-related penetrance can range from ~7% to 30% [107].

Thus, given the high prevalence of *LRRK2* and *GBA* mutations, as well as their variable penetrance, the question of what additional genetic loci may modify the effects of *LRRK2* or *GBA* is an important one to answer in the field. No clear genetic modifier loci are known at this time. However, such genetic modifier loci, if they can be found, might be targets for manipulation to significantly delay PD onset (or avoid it entirely) in the sizeable number of individuals with *LRRK2* or *GBA* mutations.

CONCLUSION

We live in a data-rich age. Reflecting this, hundreds of genetic loci – be they in Mendelian "causal" genes, common risk variants, or loci representative of other types of effects – have been linked to the various adult-onset neurodegenerative diseases [3,4]. An understanding of their interplay and biological function is needed, however, to translate any of these discoveries into potential therapy for patients suffering from these diseases.

The insight that genetic loci may act together, in complex ways, has been valuable in the creation of models to derive meaning from the wealth of newly-available genetic/genomic data. Equally valuable, however, may be "sanity check" real-world examples derived from the preponderance of the evidence. For example, the recent advent of an "omnigenic" model [108] – in effect, the extreme example of a polygenic model – posits that complex traits may have a preponderance of heritability explained by effects of genes outside of core driver pathways because, essentially, most or all genes expressed in the relevant tissue types are connected to genes on driver pathways, leading to their "discovery" as risk factors for disease. If this is true of neurodegenerative disease genetics, implications for the common practice of finding genetic risk factors in order to identify targetable pathways are sobering.

Fortunately, the evidence as reviewed here suggests a less "omnigenic" landscape for at least FTLD and AD (the diseases in which we have the most data for genetic modifier effects) as we currently understand them (Figure 1). That is, genetic modifier loci, even the ones found by GWAS (*i.e. TMEM106B*), appear to interact with target genes in biologically specific pathways that are disease-relevant (*e.g.* lysosomal pathways for *TMEM106B/GRN/c9orf72*, receptor-ligand interactions for *SORT1/GRN*, APP processing for *APOE/PSEN1/PSEN2*). Thus, we continue to hope that an understanding of polygenic effects on human neurodegenerative diseases will lead to insight that can benefit the many millions worldwide suffering from these diseases.

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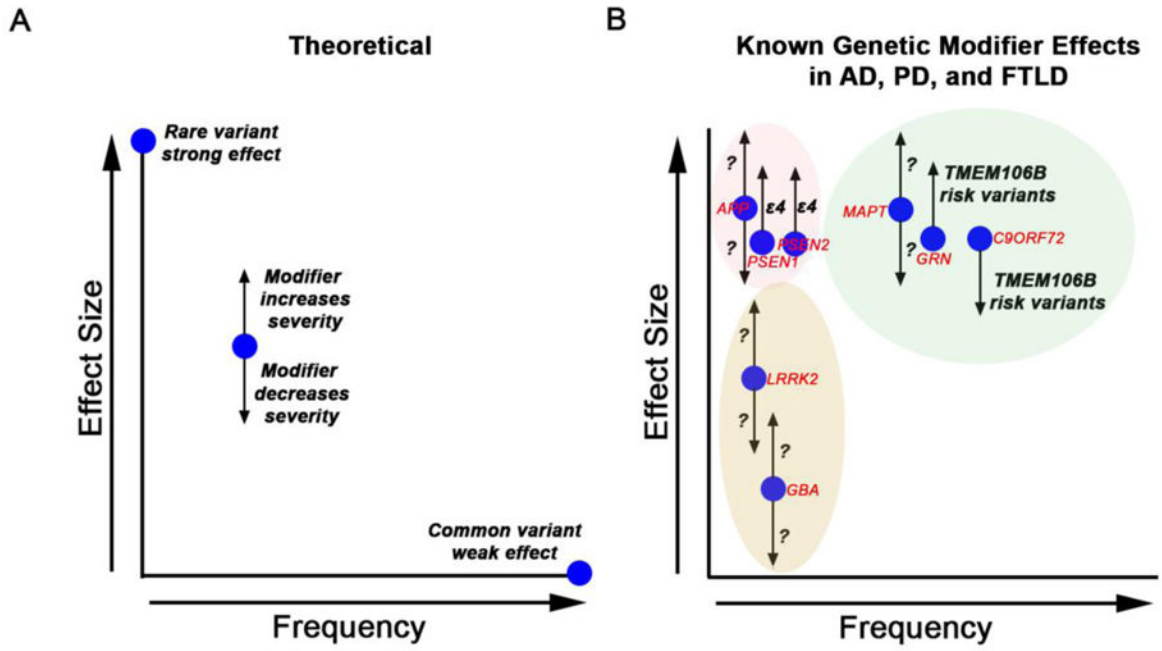

Figure 1.

A. Representation of types of genetic variants and effects on trait, with variant frequency on the X-axis and effect size on the Y-axis. Genetic modifier effects are represented by arrows emanating from target gene (blue dot) loci.

B. Known genetic modifier effects in AD, PD, and FTLD. Target gene names are shown in red, and modifier loci names are shown in black, with direction of effect indicated by arrow. AD loci are highlighted by the pink oval, FTLD loci by the green oval, and PD loci by the tan oval. Arrows are not drawn to scale, and some genetic modifier loci are unknown (question marks).

Table 1

Directional effect of modifier genes in Mendelian disease-causing mutations and all-comer populations

Target Gene	Modifier Gene	Directional Effect	References
Huntington's Disease			
HTT	loci on chromosome 8 and 15	chr8 locus associated with age at onset chr15 locus may harbor two loci with independent, opposing effects	Lee et al. 2015
Frontotemporal Lobar Degeneration			
GRN	*TMEM106B*	rs1990622 G allele associated with older age at onset	Cruchaga et al., 2011 Finch et al., 2011
	SORT1	rs646776 C allele associated with decreased GRN plasma expression	Carrasquillo et al., 2010 Hu et al., 2010
C9ORF72	*TMEM106B*	rs1990622 G allele associated with younger age at onset and death	Gallagher et al., 2014 Blitterswijk et al., 2014
MAPT	?	-	-
-	*TMEM106B*	rs1990622 G allele may show a protective effect on "cognitive aging"	Katsumata et al., 2017 White et al., 2017 Rhinn et al., 2017
Amyotrophic Lateral Sclerosis			
-	*TMEM106B*	rs1990622 G allele associated with less cognitive impairment	Vass et al., 2011
Alzheimer's Disease			
APP	*APOE*	-	-
PSEN1	*APOE*	ε4 allele associated with younger age at onset and death	Pastor et al., 2003
PSEN2	*APOE*	ε4 allele associated with younger age at onset and death	Wijsman et al., 2005
-	*APOE*	ε4 allele associated with younger age at onset and death	Corder et al., 1993 Rebeck et al., 1993 Farrer et al., 1997
-	*CELF1*	rs1057233 G allele associated with older age at onset	Huang et al., 2017
Parkinson's Disease			
LRRK2	?	-	-
GBA	?	-	-