Published in final edited form as:
Curr Opin Genet Dev. 2011 June ; 21(3): 349–353. doi:10.1016/j.gde.2010.12.007.

Genetic Modifiers of Neurological Disease

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Abstract

Genetic modifiers make an important contribution to neurological disease phenotypes. Significant progress has been made by studying genetic modifiers in model organisms. The ability to study complex genetic interactions in model systems contributes to our understanding of the genetic factors that influence neurological disease. This will lead to the development of novel therapeutic strategies and personalized treatment based on genetic risk.

Introduction

Genetic modifiers play a significant role in influencing the clinical severity of neurological disease. Modifier loci that segregate independently from the primary mutation can influence penetrance, age of onset, progression or severity of disease. Identification of genetic modifiers is important for understanding the pathophysiology of inherited disease and may suggest genes and pathways that contribute to complex disease. Modifier loci have been mapped for several neurological diseases in human and mouse, including tremor, dystonia, epilepsy, motoneuron degeneration, and Huntington's disease [1–14]. Isolating modifier genes in humans is very challenging; however, genetic screens in model organisms can facilitate modifier identification and suggest candidate genes for follow-up study in human patients.

Mouse Models

Due to the availability of rich genomic resources and numerous inbred strains, mouse models are a tractable mammalian system for isolating genetic modifiers. Further, genetic engineering of mouse mutants enables the creation of sophisticated models that can recapitulate the human disease. A forward genetics approach can be used to identify genetic modifiers by systematically crossing a mutant onto different inbred strain backgrounds and comparing the phenotype. Modifiers can act to improve or exacerbate the mutant phenotype (Figure 1). The responsible genes can then be identified by conventional positional cloning or quantitative trait loci (QTL) mapping.

Scnm1

One of the first neurological modifier genes identified was *Scnm1* (sodium channel modifier 1), a single gene modifier of the mouse neurological mutant, med^J. The $Scn8a^{medJ}$ mutation

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is a deletion in a splice donor site that results in partial exon skipping [15]. On the C3H inbred strain background, med^J/med^J mice exhibit a progressive movement disorder with dystonia and ataxia, and live a normal lifespan. On the susceptible C57BL/6 strain background, med^J/med^J mice exhibit a severe phenotype, with progressive paralysis and lethality by one month of age [13;16]. The difference in phenotype severity correlates with the amount of correctly spliced transcript, with 10% correctly spliced in C3H and only 5% in B6. The dramatic effect on the $Scn8a^{medJ}$ phenotype was mapped to a single gene, *Scnm1*, by positional cloning in an F2 intercross [3;13]. Sequencing of *Scnm1* in the 2 strains revealed that the severely affected C57BL/6 strain has a mutation that results in a premature stop codon. *Scnm1* functions as an auxiliary spliceosomal protein and facilitates splicing of non-consensus splice sites [14;17;18]. The identification of *Scnm1* as a disease modifier highlighted splicing proteins as an important class of potential modifiers. Approximately 10% of human disease-causing mutations are predicted to affect pre-mRNA splicing; thus, variation in genes involved in splicing regulation may play a significant role in modifying disease [19;20].

Epilepsy

A similar approach has also been applied to study epilepsy. Although most epilepsy exhibits complex inheritance, modifiers of rare monogenic epilepsy are likely to contribute to susceptibility in disease with more complex inheritance. Mutations in the voltage-gated sodium channels *SCN1A* and *SCN2A* are the most frequent cause of monogenic epilepsy. Family members carrying the same mutation exhibit a high degree of variable expressivity and penetrance, suggesting a role for genetic modifiers. Similarly, in mouse epilepsy models with sodium channel mutations, phenotype severity varies depending on the inbred strain background. $Scn1a^{+/-}$ knock-out mice are a model for Dravet syndrome, a severe infant-onset epileptic encephalopathy. Heterozygous $Scn1a^{+/-}$ mice exhibit a dramatic difference in phenotype severity on different inbred strain backgrounds. On the 129 inbred strain background over 90% of mice survive to 3 months of age, while on the C57BL/6 strain background only 20% survive to 3 months [21]. The $Scn2a^{Q54}$ transgenic epilepsy model also shows strain-dependent differences in phenotype onset and severity. On the resistant C57BL/6 background fewer than 15% of mice exhibit spontaneous seizures during the first month of life, while on a (C57BL/6 × SJL)F1 background over 80% have seizure onset by one month of age. This dramatic difference in the age of onset is reflected in survival, with fewer than 25% of $Scn2a^{Q54}$ on the (C57BL/6 × SJL)F1 background surviving to 6 months of age, compared to over 75% on the C57BL/6 background [1].

We exploited the strain background difference to isolate genetic modifiers of epilepsy in the $Scn2a^{Q54}$ transgenic mouse model. QTL mapping identified two modifier loci that are responsible for the strain difference in $Scn2a^{Q54}$ mice: *Moe1* (modifier of epilepsy 1) on chromosome 11 and *Moe2* on chromosome 19. Standard QTL mapping does not have sufficient resolution for gene identification. Several different strategies can be used for fine mapping to higher resolution, including selective phenotyping, recombinant progeny testing, recombinant inbred segregation testing, haplotype analysis with *in silico* mapping, advance intercross lines, genetically heterogenous stocks and interval-specific congenic strains (reviewed in [22–25]). Generation of interval-specific congenic strains produces genetically identical individuals carrying a small chromosome interval from one strain (donor) at the modifier locus on the other strain background (recipient). The QTL interval can be dissected by generating several lines with varying donor-derived segments that are then used to determine which segment confers the modified phenotype (Figure 2). We used an interval-specific congenic approach to fine map the *Moe2* locus to a 5 Mb region on chromosome 19 and identified the voltage-gated potassium channel *Kcnv2* as a strong candidate modifier [2].

Huntington's Disease

Even in the highly penetrant, monogenic Huntington's disease (HD), modifier genes are believed to influence disease expression [26;27]. Although length of the CAG repeat accounts for approximately 70% of the variance in the age of onset, the remaining variance exhibits a high degree of heritability, suggesting a role for genetic modifiers [26;28;29]. Several modifier loci influencing age of onset have been mapped in human patients [5;8;26]. Further evidence for genetic modifiers influencing HD come from mouse models which exhibit phenotype variation depending on the inbred strain background [9;30]. The Hdh^{Q111} knock-in model shows variable phenotype severity on the C57BL/6, FVB and 129 inbred strain backgrounds by several measures, including intergenerational repeat instability, somatic repeat instability, nuclear accumulation of full-length mutant huntingtin and intranuclear N-terminal huntingtin inclusions [9]. Similarly, using the YAC128 transgenic model, variable phenotype severity was demonstrated on the C57BL/6, 129 and FVB strain backgrounds [30].

Strain background effects have also been reported in other mouse models of neurological disorders, including Parkinson's, Alzheimer's, amyotrophic lateral sclerosis (ALS), Charcot-Marie-Tooth, Rett Syndrome and spinocerebellar ataxia [31–37].

Lower-Model Organisms

Due to the late onset of age-related neurodegeneration, most studies have used lower model organisms to screen for potential genetic modifiers. Models with shorter generation times like yeast and *C.elegans* expedite screening of late-onset phenotypes like HD, Parkinson's, ALS and Alzheimer's. Transgenic models recapitulating a feature of the human disease process have been used for modifier screens. Protein misfolding models in *C.elegans* have been used for genome-wide screens to identify modifiers of α-synuclein inclusion formation, tau-induced pathology, polyglutamine aggregation, and mutant SOD1 aggregation [38–41]. Yeast models have been used to screen for modifiers of toxicity due to α-synuclein and huntingtin misfolding [42–45]. These studies have been reviewed in detail elsewhere [27;46]. *Drosophila* models have been used to screen for modifiers of presenilin function, polyglutamine disease and frontotemporal dementia (FTD) [47–49]. A recent screen for modifiers of non-coding polyglutamine repeat instability in *Drosophila* found novel modifiers that independently influence different aspects of repeat instability and identified a protein with homology to *CNOT2* as a modifier of germ-line repeat expansion [49]. Ahmad and colleagues developed a *Drosophila* model of FTD3 and identified serpin5 as a modifier in a genome-wide screen [47]. Genes identified in these lower-model organism screens suggest proteins and pathways that may influence the disease process, which can be subsequently tested in mammalian systems.

Candidate Gene Approach

Reverse genetic, hypothesis-driven approaches are another way to identify potential genetic modifiers. Hypotheses can be generated by screens in lower model organisms as discussed above or can be based on our current knowledge of disease mechanisms and pathways. The discovery of VEGF as a modifier of ALS came from such a reverse-genetics approach [50]. Hypotheses can be tested by crossing mouse mutants together. Between the wide selection of spontaneous and engineered mouse mutants already available (http://www.findmice.org) and the International Knock-out Mouse Consortium, which is working to generate null alleles of all protein coding genes in the mouse (http://www.knockoutmouse.org), this is possible in most cases. For example, based on the hypothesis that the potassium M-current may influence epilepsy susceptibility, we crossed our $Scn2a^{Q54}$ epilepsy model with a subclinical *Kcnq2* mutant allele. The $Scn2a^{Q54};Kcnq2^{V182M/+}$ double mutants exhibited a

dramatic exacerbation, changing the phenotype from a mild, late-onset syndrome to severe, juvenile-onset epilepsy with premature lethality [51]. Conversely, a genetic interaction may suppress the primary phenotype. Glasscock et al [52] hypothesized that absence epilepsy due to P/Q-type calcium-channel dysfunction in *tottering* mice could be improved by increasing excitability at axon terminals. To test this hypothesis, they crossed the *tottering* mutant with mice deficient in the voltage-gated potassium channel *Kcna1* (Kv1.1). The absence epilepsy phenotype was masked in the double mutant mice, supporting their hypothesis that some ion channel variants can interact to suppress hyperexcitability [52].

Sensitized Screens for Modifiers

Sensitized N-ethyl-N-nitrosourea (ENU) mutagenesis screens offer another unbiased, forward-genetic approach for identifying potential modifier genes. Sensitized screens have been widely applied in *Drosophila* and *C. elegans* to identify functional interaction between genes and elucidate physiologic pathways. This can also be applied in mice and provides a complementary approach to QTL analysis, which is based on existing inbred strain differences. Mutagenesis increases the pool of potential modifier genes by saturating the genome with ENU-induced point mutations. Sensitized ENU mutagenesis screens in mice have been used successfully to isolate modifiers of Waardenburg syndrome and thrombocytopenia [53;54]. We are currently using a sensitized ENU mutagenesis screen to identify suppressors of the severely affected $Scn2a^{Q54};Kcnq2^{V182M/+}$ double mutants described above [51].

FUTURE DIRECTIONS AND CONCLUSIONS

Studies of neurological disease in model organisms have demonstrated the significant influence of genetic modifiers on neurological phenotype expression. The ability to study more complex multigenetic interactions in model systems may increase our understanding of the balance of genetic interactions that contribute to complex neurological disease in humans. Identification of modifier genes and analysis of the underlying pathophysiology will help to elucidate the molecular pathways involved in neurological diseases and suggest novel targets for therapeutic intervention. This knowledge may also improve the utility of molecular diagnosis and enable personalized treatment based on genetic risk factors.

Acknowledgments

Thank you to Nicole Hawkins and Benjamin Jorge for critical reading of the manuscript. Related work in my lab is supported by NIH grant NS-053792.

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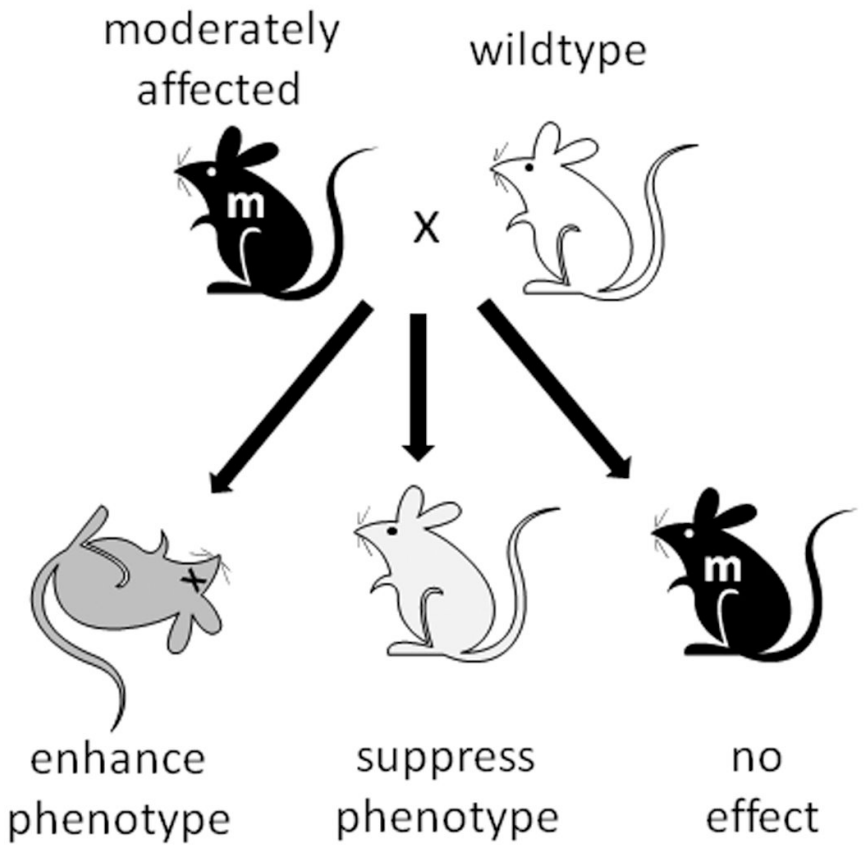

Figure 1.
Strain-dependent variation of phenotype in mouse models due to genetic modifiers. To search for modifier effects, a mouse mutant (m; black) can be crossed to a wildtype mouse from a different inbred strain background (white). Modifiers can act as enhancers that exacerbate the phenotype or suppressors that abrogate the phenotype. Alternatively, an inbred strain that does not carry modifier variants will have no effect on the phenotype.

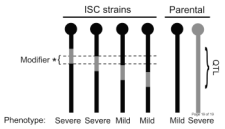

Figure 2.

Fine mapping of modifier QTL using interval-specific congenic strains. The QTL interval from the severely affected strain (donor; grey) is introgressed on the resistant strain background (recipient; black) by selective genotyping and breeding for multiple generations (≥5). Several lines are generated that carry varying donor-derived segments in the QTL interval. Each interval-specific congenic line is tested to determine the effect on the mutant phenotype. In this example, the modifier is localized to the region of overlap between the two lines that confer the modified phenotype.