1. ABSTRACT

In recent years, genetic studies in humans have identified a handful of genes that are associated with common disorders, but our understanding of such diseases at the genetic level remains relatively rudimentary. The use of mice to dissect the complex genetic etiology of common disorders offers a viable alternative to human studies since experimental parameters, such as environmental influences, breeding scheme, and detailed phenotyping can be controlled. This review focuses on the utility of mouse genetics for identification of complex disease genes. Atherosclerosis is used as a representative example, followed by an overview for the prospects of successful gene discovery in the future.

2. GENETICS OF COMPLEX DISEASES

Genetic factors are an important component of common human diseases (1). Although there has been considerable success in identifying genes for rare, Mendelian disorders, our understanding of the genes involved in common diseases is still very incomplete. This can be attributed to a variety of factors, such as genetic heterogeneity, modest effects of the underlying genes as well as their interactions, population differences, and the influence of environmental factors. As a result, the genetic etiology of such diseases is complex and difficult to elucidate. While completion of the human genome project has been an extraordinary milestone in the quest to discover complex disease genes, genomic sequence is still only a
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tool that does not overcome the inherent difficulties of studying human populations.

In principle, there are two ways to identify genes that underlie diseases or physiological processes. The first, called “forward genetics”, utilizes naturally occurring (or induced) mutations that affect the process. The underlying gene is identified by first mapping the mutation using linkage analysis and then testing “positional candidates”. A related approach, termed the “candidate gene” approach, is based on following variations of a gene suspected of playing a role in a physiological process in cases versus controls. The second strategy, termed “reverse genetics”, involves mutating or otherwise perturbing a given gene and then examining its effect on the physiological process. Thus, by definition, such studies are not possible to perform in humans directly and require in vitro systems or animal models.

Both “forward” and “reverse” genetics strategies have been important for identifying genes that contribute to complex diseases. In terms of forward genetics, the most important advances have come from human geneticists studying rare Mendelian disorders. For example, nearly all of the known Mendelian diseases have either been mapped to chromosomal locations or the genes have already been identified (1). While this approach has also been applied to the dissection of complex genetic traits (2), progress in this field has been relatively slow, and most of the successes relevant to common diseases have been in cases where there was previous biochemical knowledge of the underlying gene’s effect (the “candidate gene” strategy).

Perhaps the most successful group thus far to identify genes for complex disorders using forward genetics is the private Icelandic firm, deCode Genetics (3). Their success can be primarily attributed to two main advantages. The first is the size of their study population, which essentially comprises the entire country of over 200,000 individuals, as well as detailed knowledge of each individual’s genealogy through historical records. The second is the Icelandic population’s relatively low genetic heterogeneity, which is a result of the genetic isolation of Iceland from other populations since it was first colonized about a thousand years ago. Taking advantage of these characteristics, deCode has used its genealogical database and centralized healthcare system to identify several genes for complex disorders, such as stroke, schizophrenia, and osteoarthritis (3-6). Importantly, some, but not all, of these genetic associations have been replicated in more outbred populations (7-10), suggesting that genes identified in genetic isolates can have effects in other populations as well. Similar studies using the Finnish genetic isolate also provide evidence for such a notion (11). The majority of gene discovery efforts therefore, have to rely on study populations that are for the most part outbred, and cannot carry out multiple studies on the same scale as deCode due to cost and man power constraints.

3. INBRED MOUSE STRAINS

Modern mouse genetics began in 1902 by William Castle and his student Clarence C. Little, with the help of Abbie Lathrop, a teacher and chicken farmer in Granby, Massachusetts (deleted; “and her farm”) who began breeding mice for mouse fanciers (Silver). Castle, a zoologist from Harvard, wanted to know whether the laws of Mendelian genetics, which were partially worked out on plants, also held true for complex mammalian species. It was Little who came up the concept of “inbred strains”, derived from continuous brother to sister matings over many generations, and the first inbred strain, DBA, was created in 1909. Little was also the founder of the Jackson Laboratories in Bar Harbor, Maine (www.jax.org), which today has over 2,500 genetically distinct strains, several hundred of which are inbred strains, and provides close to 2 million mice to researchers every year. In addition, there has been a strong effort by many scientists to collect wild mice and establish a variety of new wild-derived inbred strains. These have now provided additional polymorphisms and phenotypic variations, which are also extremely useful genetic studies.

With the availability of so many inbred mouse strains, one alternative approach to the difficulties encountered with human studies is to utilize naturally occurring variations in mice (or rats), which simplifies the analysis of complex traits. This is expected to provide information about a subset of the genetic variation that contributes to disease susceptibility in humans. As an example, Table 1 shows the wide array of disease-related traits that differ between two extensively studied inbred strains, C57BL/6 (B6) and DBA/2 (DBA). For instance, phenotyping of B6 mice has shown that they are prone to developing alcoholic behavior compared to DBA, whereas DBA is more susceptible to osteoporosis and autoimmune disorders. Such phenotypic variation is likely to be a result of genetic differences since B6 and DBA (and all other commonly used strains) are inbred and the impact of environmental effects can be minimized in the laboratory setting. As such, the underlying genes for these phenotypes can mapped using quantitative trait locus (QTL) analysis (described below). Indeed, numerous chromosomal regions have been identified for a variety of traits between B6 and DBA, (Table 1). In some cases, the regions identified in experiments with other strains overlap with those identified in the B6 and DBA cross, substantiating the importance of the underlying gene(s) in governing the phenotype. It is also important to note that, in any given cross, multiple loci are often identified for a trait (Table 1), demonstrating the genetic complexity that exists even in mice. Regardless, these studies illustrate the rich resource that inbred strains provide for carrying out studies to identify genes underlying a variety of disease-related phenotypes.

4. THE QUANTITATIVE TRAIT LOcus APPROACH

Like that of individual humans, the genomes of inbred strains of mice have sequence differences occurring every few thousand base pairs. Most of these are inconsequential, but those variants that influence gene expression or function give rise to the differences in disease susceptibility (or any other genetically based phenotype) among inbred strains. In humans also, it is this genetic variation that underlies the differential disease susceptibility that individuals exhibit.
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Table 1. Phenotypes that Differ Between Strains DBA/2 and C57BL/6 and Chromosomal Locations of Corresponding Quantitative Trait Loci

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>QTL Location (chromosome)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>2, 4, 7, 8, 9, 10, 11, 12, X</td>
<td>40-43</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>2, 4, 11, 13, 15, 18</td>
<td>44,45</td>
</tr>
<tr>
<td>Alcohol Preference</td>
<td>1, 2, 3, 4, 6, 9, 10, 11</td>
<td>46-48</td>
</tr>
<tr>
<td>Arthritis</td>
<td>6, 7, 8, 10</td>
<td>49</td>
</tr>
<tr>
<td>Atherosclerosis/ Vascular Calcification</td>
<td>7, 8, 10</td>
<td>50,51</td>
</tr>
<tr>
<td>Behavioral</td>
<td>1, 3, 4, 10, 12</td>
<td>52-54</td>
</tr>
<tr>
<td>Bone Density</td>
<td>1, 2, 3, 5, 6, 7, 8, 10, 13, 15, X</td>
<td>37,55</td>
</tr>
<tr>
<td>Brain/CNS Phenotypes</td>
<td>1, 2, 7, 8, 10, 11, 14, 17, 19</td>
<td>56-60</td>
</tr>
<tr>
<td>Cancer</td>
<td>4, 10</td>
<td>61-63</td>
</tr>
<tr>
<td>Cholesterol Absorption</td>
<td>--</td>
<td>64,65</td>
</tr>
<tr>
<td>Drug Response/ Substance Abuse</td>
<td>1, 2, 5, 9, 10, 11, 18</td>
<td>66-70</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>4, 6</td>
<td>71</td>
</tr>
<tr>
<td>Immune System</td>
<td>1, 2, 6, 11, 13, 15</td>
<td>72-75</td>
</tr>
<tr>
<td>Infectious Diseases</td>
<td>1, 3, 4, 6, 7, 17</td>
<td>76-80</td>
</tr>
<tr>
<td>Lipids</td>
<td>2, 3, 4, 5, 6, 7, 11, 17</td>
<td>37,51</td>
</tr>
<tr>
<td>Obesity/Diabetes</td>
<td>2, 4, 6, 13, 15, 19</td>
<td>34,37,81</td>
</tr>
<tr>
<td>Toxicity</td>
<td>1, 3, 4, 5, 6, 7, 9, 11, 12, 15, 18</td>
<td>82-86</td>
</tr>
</tbody>
</table>

Employing the QTL approach has allowed the mapping of those specific variations that are responsible for differences in disease susceptibility and other related traits. The overall strategy for this approach involves using either F2 or N2 mice generated from a cross (Figure 1), or employing recombinant inbred (RI) strains. RI strains are generated by an initial outcross of two parental inbred strains, followed by an F1 intercross and 20 generations of brother-sister mating. In the resultant set of inbred strains, the genomes of the progenitors are broken into homozygous intervals of different lengths. By comparing the distribution of a trait (e.g. atherosclerosis) in the strains from one RI set of animals with the distribution of the polymorphic genetic markers already typed for those strains, chromosomal loci that segregate with the trait of interest can be identified. RI strains were used for mapping loci underlying a variety of traits before the advent of the molecular and statistical tools required for analyzing a cross. In general, RI mapping has had low power and precision to detect QTLs, mainly due to the small number of available strains in each set. Recently, Williams et al. (12) have published a dense map for all RI sets that share B6 as a parental strain, which may provide a tool for RI mapping of some complex traits in the future.

Even though the QTL approach for dissecting complex traits is still a long and laborious undertaking, the development of large numbers of genetic markers in mice has allowed the identification of some important genes for common disorders such as atherosclerosis, hearing, and arthritis (13). QTL analysis basically analyzes whether the measured trait varies significantly across the population on the basis of the parental genotype at any given location in the genome, in the same manner as described for RI mapping. QTL studies begin with construction of a cross between two selected inbred mouse strains, typically differing in the expression of the primary trait of interest. The offspring of the initial mating (F1 generation) are either crossed back to one of the parental strains (backcross) or are crossed to one another (intercross) to create the F2 generation (Figure 1A). While the F1 mice are genetically identical, having one chromosome from each parent, the backcross or F2 mice are each genetically unique. This is due to independent segregation of chromosomes and crossovers occurring during the F1 intercross, which leads to unique combinations of genes from the original parental strains. Since these recombined regions are inherited as relatively large segments of chromosomes, the parental origins of each portion of the genome can be determined using polymorphic markers - selected to cover the entire genome at regular intervals - that can distinguish between the parental strains. Specific software is available for this analysis, and statistical standards have been established to determine the significance of the results. When positive, the data are frequently presented as a graph with a curve representing the statistical likelihood, represented by a LOD score, of a genotype giving rise to a phenotype across the length of a chromosome (Figure 1B). There will be a particular location along the chromosome where the likelihood of a genetic effect is greatest, referred to as the peak. For an F2 intercross, peak LOD scores above 2.8 and 4.3 are taken to represent suggestive and significant evidence for linkage, respectively, though empiric significance levels can be generated for each data set using permutation analysis. From the data, a region of the chromosome on either side of the peak can be defined within which there is a 95% or 99% statistical likelihood that the underlying gene will be present. In comparison with human studies, QTL mapping in mice provides at least an order of magnitude greater power to map genes for multigenic traits.

Typically, the regions identified by QTL mapping are relatively large and encompass several hundred genes across millions of base pairs. However, once the genes have been mapped to chromosomal regions, each of those particular genetic intervals can be isolated on a common genetic background as a “congenic strain”, which simplifies the genetics for further analysis (14). This is accomplished by repeated backcrossing of an F1 animal
Figure 1. The QTL approach: from mouse to man. QTL studies begin with a cross between two inbred strains (e.g. B6 and CAST) that differ in their susceptibility to the trait of interest (A). Statistical analysis of the correlation between the phenotypes of the F2 progeny and the genomic regions they inherited from the parental strains identifies the QTL, in this case coincident loci for aortic lesions and insulin levels on the middle of chromosome 6 (B). This is represented in graphical form by LOD scores, where the highest point of the curve is the most likely location of the underlying gene. The arrows along the X-axis depict the genetic markers used to genotype the F2 animals. A congenic strain is then constructed by repeated backcrossing of an F1 animal to one of the parental strains (i.e. B6), with selection of the chromosomal segment from the other parent (i.e. CAST) that encompasses the QTL (C). Phenotyping the congenic for the trait(s) originally identified in the linkage analysis confirms the locus (D). The underlying gene can be identified by testing positional candidate genes in the locus with either functional studies or transgenic models, in this example 5-LO knockout mice (E). The human ortholog of the gene (5-LO) can then be examined in human studies with family-based or case-control study designs (F).
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to one of the parental strains, selecting at each generation only those individual animals that carry the QTL region from the opposite parent for further study. After 10 or more backcross generations, a congenic strain is created in which the genome is comprised nearly entirely of the background strain with the exception of the introgressed region encompassing the QTL, which is derived from the donor strain (Figure 1C). By phenotyping these animals for the trait(s) that were initially identified in the QTL analysis, such congenic strains allow confirmation of the mapping studies (Figure 1D) and, in essence, “Mendelize” the complex trait, making fine mapping to ~1Mb feasible. Examining genes located in the finely mapped region, either with transgenic/knockout animals or through functional experiments, can then identify the underlying gene (Figure 1E). Ultimately, the human orthologs of such genes can be examined in populations comprised of either families or patient cases and matched controls (Figure 1F).

A key aspect of this approach is that it does not require any foreknowledge of the affected gene(s). QTL mapping therefore offers the possibility of identifying entirely novel genes that might otherwise not have been considered. Since a gene product is often part of a biological pathway, identifying one member may lead to elucidation of other, interacting genes as well.

5. FROM MOUSE TO THERAPY

Ultimately, the reason for identifying genes underlying disease-related traits in mice is to extrapolate those results to humans in order to develop novel diagnostic and therapeutic strategies. Studies of *Arteris*, an atherosclerosis susceptibility locus on mouse chromosome 6, are a successful example of this approach (Figure 1). Initially *Arteris* was identified in an F2 cross between the inbred strains B6 and CAST/Ei (CAST) with a highly significant LOD score of 6.7 (Figure 1B) (15). Interestingly, there was coincident linkage of insulin levels with this locus, raising the possibility that the underlying gene had pleiotropic effects on atherosclerosis and other related metabolic traits (Figure 1B). Subsequently, a congenic strain was developed to confirm the functional importance of the QTL and to identify the gene underlying resistance to lesion formation. Congenic animals carrying the middle region of chromosome 6 derived from CAST (Figure 1C) confirmed the phenotype of *Arteris* since these mice exhibited a dramatic resistance to aortic lesion formation and had lower insulin levels compared to control mice (Figure 1D). Among the candidate genes in the congenic interval was 5-lipoxygenase (5-LO), the rate-limiting enzyme in the production of leukotrienes, a class of inflammatory molecules derived from arachidonic acid. 5-LO is expressed primarily in leukocytes and has been studied mainly in the context of acute, not chronic, inflammation, particularly that associated with asthma. To evaluate 5-LO as a candidate gene, Mehrabian *et al.* (16) placed 5-LO knockout mice on a genetically hyperlipidemic background and fed them a high fat, high cholesterol diet. These mice exhibited a profound reduction in aortic lesion formation despite cholesterol levels in excess of 500 mg/dl (Figure 1E), suggesting the involvement of 5-LO in atherogenesis. Conservative amino acid substitutions at 3’ end of the protein were also identified between CAST and B6 but it was not known whether these variations influenced 5-LO function (16). By creating the same substitutions at the conserved positions in the human enzyme, Habenicht and colleagues demonstrated that the CAST form of 5-LO, which has the amino acid substitution, has a marked decrease in activity and expression levels (17). More recently, Funk and colleagues have observed decreased aeryurms in 5-LO deficient mice placed on a genetically hyperlipidemic apoE deficient background, whereas the effect of 5-LO deficiency on atherosclerosis was minimal in their study (18). Taken together, these studies provide strong evidence that 5-LO is the gene underlying *Arteris* and demonstrate the power of the QTL approach for identifying genes associated with complex traits.

The findings in the mouse have been extended to humans and preliminary findings suggest that genetic variation in the 5-LO gene also affects similar phenotypes in humans. For example, a promoter polymorphism consisting of a variable number of Sp1 transcription factor binding sites was associated with carotid intima-media thickness (IMT), an accepted surrogate marker that correlates positively with atherosclerosis. Specifically, IMT in those individuals homozygous for either the “3” or “4” allele (D alleles) of the polymorphism was increased by nearly 100µm compared to wildtype carriers, corresponding to an approximate 10-year progression in carotid wall thickness (19). Furthermore, the same individuals also exhibited significantly higher levels of C-reactive protein and interleukin-6, two markers of inflammation that have also been correlated with cardiovascular disease. Subsequent studies in Icelandic, British, Scottish, and American cohorts have further demonstrated the importance of other 5-LO pathway genes in atherosclerosis as well (6,9,20). Taken together, these results are consistent with the mouse studies and support the concept that the 5-LO pathway has pleiotropic effects on the development of atherosclerosis as well as known risk factors associated with it.

From a clinical standpoint, these findings have had a major impact on the development of potentially novel treatments for cardiovascular disease. For example, knowledge that 5-LO and leukotrienes are involved in asthma previously led to the development of drugs such as montelukast (Singular). This raises the exciting possibility of administering existing drugs, or newly developed ones, to target the 5-LO pathway for heart disease patients. Indeed, a recent report has demonstrated the efficacy of a 5-LO pathway inhibitor for reducing inflammatory biomarkers associated with atherosclerosis (21). Even though the therapeutic applications of the 5-LO studies can be considered somewhat serendipitous, this example elegantly illustrates how mouse genetic studies can ultimately lead to novel treatments for common diseases in humans.
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Table 2. Newly Developed Tools That Will Accelerate Gene Discovery

<table>
<thead>
<tr>
<th>Technology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome wide congenic panels</td>
<td>Over 150 congenic or chromosome substitution strains generated from either B6 X A/J, B6 x DBA, or B6 x CAST. Each panel spans the entire mouse genome in contiguous fashion.</td>
</tr>
<tr>
<td>Mouse genomic sequence, polymorphisms, and haplotypes</td>
<td>The sequence of five inbred strains has already been completed by the public effort and a private company. Researchers have also identified thousands of polymorphisms between several other strains in addition to those sequenced. Dense polymorphism mapping as also established genome wide haplotypes for many strains.</td>
</tr>
<tr>
<td>Expression arrays and eQTLs</td>
<td>Microarray technologies allow the expression of thousands of genes from different tissues to be measured simultaneously. These measured “quantitative traits” can also be analyzed to identify QTLs (eQTLs) for mRNA transcript abundance. Identification of eQTLs that are coincident with QTLs for clinical traits (e.g. aortic lesions) can provide additional information and significantly bolster positional cloning efforts.</td>
</tr>
<tr>
<td>Small interfering RNA strategies (siRNA)</td>
<td>Injection of siRNA into mice has recently been developed which may allow the rapid screening of positional candidate genes, provided that the phenotype and tissue specific expression of the gene being tested is suitable.</td>
</tr>
</tbody>
</table>

6. PROSPECTS FOR THE FUTURE

The ability to perform targeted manipulation of genes in mice via the construction of transgenic and knockout has been one of the most important contributions that this species has made to our understanding of common diseases. Studies of naturally occurring variations in the mouse, one the other hand, have also proved to be extremely useful for identifying new genes and pathways underlying disease. Thus far, many loci for disease-related traits have been mapped (Table 1), although few genes have been identified. Progress in the development of genomics and bioinformatics tools however, will undoubtedly accelerate this process (Table 2). It seems likely that, as we enter the post-genome era of elucidating gene function, combined genetic/genomic approaches will prove increasingly useful for the identification of novel pathways relevant to common diseases (22-27).

First and foremost, the currently available sequence of five mouse strains, including DBA, will allow rapid screening of candidate genes within QTLs and congenic regions. Once the QTL has been narrowed to several hundred kilobases, the entire sequence can be downloaded and examined to search for both known and unknown genes as candidates.

Recent studies have also identified numerous polymorphisms that differ between eight strains, adding further to the tools that geneticists have at their disposal for gene identification (28,29). If the fine mapping example described above were in a cross between B6 and DBA for example, the available genomics resources would allow all the nucleotide substitutions in that region as well as the entire sequence to be determined between these strains. By prioritizing those genetic variations that occur in or near genes, researchers will be able to focus their efforts on the most likely genetic causes first. More recently, investigators have established genome-wide haplotype blocks amongst the several inbred strains by high-density polymorphism genotyping. This will further help determine which regions of the genome are shared identical by state amongst the strains surveyed, particularly in QTL regions, and can help prioritize candidate genes as well.

Amongst the important new developments is the availability of genome wide congenic strains (30-32). As described above, once a QTL has been identified, congenics are created through repeated backcrossing, which can take 2-4 years, even with marker-assisted breeding. However, three panels of congenic strains that contiguously span the genome have already been constructed between B6 and A/J, B6 and CAST, and B6 and DBA. These resources will be of immense use for QTLs that have been identified between these strains since, rather than creating a congenic for each identified locus, the desired strain(s) can be obtained from the corresponding panel and one can directly proceed to confirming the QTL and fine mapping. For example, such resources would be perfectly suited for the loci identified between B6 and DBA that are shown in Table 1. In addition, a consortium of investigators interested in common diseases have begun large, long-term project called the Collaborative Cross to create a panel of 1000 RI strains derived from 8 founder strains (33). Although the ability to use these mice is still years away, their availability could also play a significant role in the search for disease genes using mice.

The feasibility of performing large-scale arrays for RNA expression in affected tissues is also highly complementary to QTL mapping. As demonstrated recently, traditional QTL analysis when combined with expression array experiments is an extremely powerful approach and yields tremendous insight into the genetic complexity underlying common diseases (34). In essence, measuring transcript abundances in specific tissues can be thought of as measuring any other quantitative trait (e.g., cholesterol) except that microarray technology allows the simultaneous quantitation of transcripts from thousands of genes (i.e., traits). Analogous to how QTLs for lipid levels or atherosclerosis have been identified in mouse crosses, QTLs have also now been identified for mRNA expression (eQTLs) (34,35). In the future, therefore, the criteria for prioritizing positional candidates will also include those genes that yield eQTLs over their own physical location, the linkage of which is coincident with the “clinical” QTL that was originally identified (36). On another level, performing concurrent measurement and analysis of multiple traits, gene-gene interactions can be identified, including a possible common genetic basis for apparently
diverse traits such as bone density and lipid metabolism (37). This can be performed with combinations of “clinical” traits and/or expression array traits, adding further to the wealth of knowledge that this approach is likely to provide. These approaches also demonstrate the utility of the mouse since it would be nearly impossible to carry out such studies in humans due to the inability of obtaining the appropriate tissues.

Recently, the in vivo use of small interfering RNA molecules (siRNA) to attenuate gene expression has come to the forefront and has the potential to allow rapid screening of positional candidate genes. This novel technique involves the injection of short, double stranded RNA oligonucleotides into mice via the tail vein under high hydrostatic pressure (38,39). The siRNA oligos, which are homologous to a target gene, are taken up by different tissues (the liver is a particularly good tissue) and cause the selective degradation of that gene’s mRNA. Compared to the time and expense it takes to create a transgenic or knockout mouse, siRNA strategies hold tremendous promise for functional testing of candidate genes. However, a major drawback is the short and transient inhibition of gene expression, on the order of 24-48h. Thus, for traits such as atherosclerosis or obesity, which can take months to develop, the use of siRNA may not be entirely feasible.

7. CONCLUSIONS

Common diseases have a very complex etiology, and because of this complexity, it has proven difficult to apply the mapping strategies that have revolutionized our understanding of Mendelian disorders. QTL approaches in mice offer a viable solution to the problem. The main difficulty encountered in this approach has been the challenge of fine mapping to reduce the number of positional candidate genes. Several new tools in mouse genetics promise to accelerate the identification of genes underlying QTLs. Ultimately, the identification of disease genes (in both mouse and human) will lead to a better understanding of the underlying patho-physiological perturbations and to the focused discovery of novel therapeutic agents and strategies.

8. ACKNOWLEDGMENTS

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Key Words: Genetics, Inbred Mice, Complex Diseases, Gene Mapping, Review

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