Essential Genes and Human Genetic Disease

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Advanced article

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Essential genes are those genes required for an organism to complete development and survive to birth. There is debate as to whether essential genes play a role in human disease, because if they are critical for survival then mutations in these genes will cause lethality during development, removing individuals carrying these mutations from the population. Yet, essential genes can have diverse mutations that either limit or alter their function in a manner that allows individuals with these mutations to survive. These nonlethal, yet pathological, mutations in essential genes do contribute to human disease. Studies have demonstrated that essential disease genes are highly conserved, participate in many protein–protein interactions and may cause both Mendelian and complex disorders. These results confirm that essential genes are valid candidates as disease loci.

Introduction

There is much interest in understanding the genetic causes of human disease. Identifying the mutations that contribute to disease phenotypes is of great use to clinicians, and facilitates diagnosis, screening and therapeutic interventions. To aid in the dissemination of knowledge about the molecular basis of Mendelian genetic diseases, a database of gene descriptions and disease phenotypes, OMIM, has been generated (Online Mendelian Inheritance in Man, OMIM[®], 2013). As of May 2013, there are over 21 000 entries in OMIM. By far the largest component of the

database contains records summarising the description of genes with links to disease processes, comprising more than 14 000 entries (OMIM update 10 May 2013). The scale of the OMIM database highlights the significant burden that genetic mutations place on human health and emphasises the wide range of molecular functions and biological processes that can be altered to generate a disease state. It is therefore perhaps no surprise that much research effort has been dedicated to searching for links between specific genes and disease. See also: [Medical Genetics: History](#)

Disease Gene Characteristics

The expansive array of human disease phenotypes suggests that genes with diverse functions and tissue localisations can be perturbed to produce disease states. To find links between a specific gene and the diseases, the phenotype is evaluated to provide insights into the expression pattern or likely molecular function of candidate genes. Many diseases are specific to one particular tissue, and would therefore be expected to result from mutations in genes with a similarly restricted expression pattern. Likewise, a disease may affect a particular cell type, therefore suggesting that the proteins known to function in that cell type may be abnormal in individuals with the disease. Additionally, insights may be gained from studies of similar conditions. If a particular molecule has been identified that causes a disease-affecting muscle, then other muscle-related diseases may be caused by mutations in members of the same gene family as the known gene. A relatively recent advance that may aid in identifying disease genes is the study of protein–protein interaction (PPI) networks. It has been demonstrated that diseases affecting similar tissues are caused by mutations in genes whose protein products physically interact (Feldman *et al.*, 2008; Goh *et al.*, 2007). Therefore, constructing a PPI network from a known disease gene may identify other proteins likely to cause

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diseases affecting the same set of tissues or physiological functions. **See also:** [Genetic Disorders](#)

To accurately identify genes associated with human disease, the probability of different types of genes to cause disease must be evaluated. It has been assumed in many studies that genes that cause disease will normally perform important cellular or physiological functions. Therefore, disruptions to these functions result in a pathological state. However, a corollary to this argument exists, which is that if a gene performs a critical or essential function, then the loss of that gene will cause lethality. Thus, genes that have an absolute requirement in an organism would not be identified as disease genes, because individuals with mutations in those genes would fail to survive, and no longer be part of the population in which diseases are identified. Genes that are absolutely required for organismal survival are termed as 'essential genes', and many studies have investigated the significance of this group of genes in causing human disease.

Although it has been argued that essential genes are not a significant class of human disease genes due to their absolute requirement during development, this argument may be correct only for null alleles, which completely remove function from a gene and the protein product that it encodes. However, mutations can cause a variety of distinct alterations in gene function, as shown in **Figure 1**. Many genetic mutations cause a reduction, but not a total elimination of protein function, and are therefore considered hypomorphic mutations. If a hypomorphic mutation occurs in a gene that is essential for survival, an individual with this mutation may survive, albeit with an abnormal phenotype. Thus, hypomorphic mutations in essential genes do contribute to human disease (Dickerson *et al.*, 2011).

Classification of Disease Genes

One method to facilitate the large-scale identification of disease-associated genes is to impose a classification system for genes, based on their functions or expression patterns, and search for links between groups of genes and disease phenotypes. This classification system can

Figure 1 Different allele types generated by genetic mutations. The protein encoded by the wild type gene is shown on the left. The protein encoded following a null mutation is shown in the middle; note that there is no functional protein present. The protein encoded by a hypomorphic mutant allele is shown on the right. Protein activity is diminished but not completely eliminated.

then be applied to genes of interest to predict their likelihood of being associated with disease. This approach has enabled computational studies into the characteristics of disease genes, searching for patterns that distinguish genes likely to cause disease when mutated. In an initial study considering the sequence and evolutionary properties of 'morbid genes', which were defined as those genes known to cause human disease, it was determined that 34% of genes with unknown morbidity could be predicted by a computational algorithm to be associated with disease, whereas only 5% of disease genes were inaccurately classified as nonmorbid (Kondrashov *et al.*, 2004). Following the invention of high-throughput sequencing technologies, microarray and RNAseq protocols for expression analysis, and the generation of large-scale PPI datasets, additional computational studies have drawn on the vast amounts of information available in databases to interrogate sequence and expression information for large numbers of human genes and their orthologues in other species. Using a variety of parameters, researchers have considered the relationship of factors such as evolutionary conservation (Furney *et al.*, 2006; Kondrashov *et al.*, 2004; Park *et al.*, 2008; Thomas *et al.*, 2003; Tu *et al.*, 2006), expression pattern (Tu *et al.*, 2006) and PPI (Chavali *et al.*, 2010; Dickerson *et al.*, 2011; Feldman *et al.*, 2008; Goh *et al.*, 2007) with the probability of a gene-causing disease when mutated. These studies have defined several parameters associated with disease-causing genes, including an analysis of the role of essential genes in human disease.

Analysis of Essential Genes in Human Disease

One challenge in determining the role of essential genes in human disease is first identifying human essential genes. By definition essential genes are those required for embryonic survival. It is impossible to experimentally determine which genes are required for human survival postgestation. Therefore, many studies have relied on defining essential genes as the orthologues of genes found to be essential in model organisms, with most studies relying on the mouse knockout data as a proxy for human gene essentiality (Dickerson *et al.*, 2011; Feldman *et al.*, 2008; Georgi *et al.*, 2013; Goh *et al.*, 2007; Jin *et al.*, 2012; Park *et al.*, 2008). Other studies have relied on ubiquitous expression to define genes likely to be essential in humans (Tu *et al.*, 2006). Identifying those genes that cause human disease before the onset of puberty has allowed essential genes to be defined directly from an analysis of human gene function (Furney *et al.*, 2006), although this approach is likely to miss large numbers of essential genes because severe mutations result in lethality before birth.

Although a comprehensive list of human essential genes has not been verified, it is nonetheless possible to draw some conclusions about the significance of essential genes

in human disease from existing studies. A prerequisite for investigating disease genes as a group is that these genes have features that distinguish them from other genes. A study that assessed whether or not morbid genes, which are those known to cause human disease, differed (in a set of 18 parameters available from bioinformatic databases) from the remainder of all human genes provides evidence that disease genes are a distinct group (Kondrashov *et al.*, 2004). Notably, the authors found that morbid genes were evolutionarily more conserved than nonmorbid genes, encode longer proteins than nonmorbid genes and have higher and broader expression patterns than nonmorbid genes. All of these attributes may also be hallmarks of essential genes, leading to the proposal that gene essentiality and morbidity are tightly related, and that morbid genes responsible for Mendelian disease are essential (Kondrashov *et al.*, 2004). The authors identified 1273 genes as morbid, or disease-causing, in this study, and built their model for disease gene classification on this gene group (Kondrashov *et al.*, 2004). Given that currently more than 14 000 genes have OMIM entries, it is likely that the disease gene dataset used in this study is incomplete. Yet, even with a small gene set and potential confounding results from the existence of additional nonannotated morbid genes in the nonmorbid gene category, the authors were able to clearly distinguish morbid genes from other genes based on their attributes.

A later study to define properties of disease genes based on a larger dataset of 2789 disease genes separated these genes into categories based on the phenotype of mouse knockouts of their orthologues (Park *et al.*, 2008). The authors found that disease genes were more likely to have a mouse knockout with a discernable phenotype than no detected phenotype. Genes with embryonic lethal mouse knockouts, defined as essential genes, were less likely to cause disease than those genes with postnatal lethal or viable knockout phenotypes (Park *et al.*, 2008), suggesting that genes required early in development are not often mutated in manners that result in disease phenotypes. The early lethality displayed in mouse knockouts of the orthologues of these genes may be consistent with these genes causing severe birth defects or miscarriages when mutated to a null allele (Park *et al.*, 2008). However, hypomorphic alleles of essential genes may still play a role in human disease, and can be associated with adult-onset diseases (Dickerson *et al.*, 2011).

Evolutionary Properties of Essential Genes and Disease Genes

One hypothesis regarding essential genes is that they are evolutionarily well-conserved, due to their requirement for basal cellular functions in many species. Therefore, if there is overlap between the genes defined as essential and those defined as disease-causing, evolutionary conservation should be a hallmark of both gene sets. In a study on the

evolutionary pressures acting on oncogenes and tumour suppressor genes, significant overlap was discovered between human cancer-related genes and essential genes (Thomas *et al.*, 2003). The presence of essential genes within the cancer gene set may explain why cancer genes were found to be under stronger purifying selection than nondisease genes. The fact that many transcription factors are found in the cancer gene dataset (Thomas *et al.*, 2003), and that essential genes are also enriched for transcription factors (Chavali *et al.*, 2010; Dickerson *et al.*, 2011), suggests that transcription factor mutations may be a common mechanism leading to human disease attributed to essential genes.

Additionally, an evolutionary study of human disease genes segregated by the mode of inheritance of the disease revealed that disease genes with a dominant mode of inheritance are more conserved at the protein sequence level than those with a recessive mode of inheritance (Furney *et al.*, 2006). Evolutionary conservation of both dominant and recessive disease genes was highest in the group of genes that cause lethality before the onset of puberty (Furney *et al.*, 2006). This finding correlates with the high conservation levels observed in essential genes (Kondrashov *et al.*, 2004; Park *et al.*, 2008; Tu *et al.*, 2006), suggesting that diseases resulting in lethality early in life are caused by severe deleterious mutations in essential genes. From a population perspective, mutations resulting in lethality before reproductive capacity are removed from the gene pool and therefore further inheritance of these allelic variants is prevented.

Supporting the conclusion that mutations in essential genes contribute to early-life diseases that reduce the probability of the disease-causing mutation from persisting in the population, essential genes are considered a class of very severe disease genes (Tu *et al.*, 2006). To define these properties of these most severe disease genes, an analysis of their evolutionary history was performed (Tu *et al.*, 2006). Rather than relying on orthologues of mouse essential genes identified by experimental methods, Tu *et al.* (2006) directly evaluated human genes based on expression pattern as determined by microarray expression analysis on adult tissues. They termed ubiquitously expressed genes, otherwise considered as housekeeping genes, as essential human genes. Essential genes defined by the mouse knockout phenotype of their orthologues have been found to be enriched for ubiquitously expressed genes (Georgi *et al.*, 2013), supporting the definition of housekeeping genes as essential genes. Tu *et al.* (2006) identified human disease genes from the OMIM morbid map, and all remaining human genes were classified as 'other'. By analysing the evolutionary features and biochemical properties of these three gene groups, Tu *et al.* (2006) concluded that essential genes form a distinct class separate from disease genes and other genes. However, features of these groups overlap, suggesting that there is a continuous spectrum between essential genes and disease genes, such that essential genes can be considered disease genes in certain mutation contexts (Tu *et al.*, 2006).

Functional Properties of Essential Genes and Disease Genes

As several studies demonstrate that disease genes have properties that differ from other genes in the genome as a whole (Kondrashov *et al.*, 2004), and that there is overlap between the disease gene and essential gene sets (Thomas *et al.*, 2003; Tu *et al.*, 2006), further investigations to determine the role essential genes play in human disease have been undertaken. In considering the mechanisms by which mutations in essential genes may contribute to morbidity, the functions performed by the proteins encoded by essential genes have also been evaluated. Proteins have annotated domains associated with particular biochemical functions, subcellular localisations and interaction partners as defined by experimental studies. Therefore, these parameters can be determined for human proteins and their orthologues, and distinctions between essential genes and disease genes discovered. The profile of diseases associated with essential genes differs from the profile of diseases associated with nonessential genes, indicative of the differences in biochemical functions performed by these two groups (Dickerson *et al.*, 2011). As some biochemical functions are attributed to specific cellular locations (i.e. deoxyribonucleic acid (DNA) binding is a function performed mainly by proteins with a nuclear localisation), the subcellular localisation of disease-associated proteins may also be a discriminating feature. Indeed, proteins encoded by disease genes with essential mouse orthologues were found to be enriched for nuclear localisation, whereas the proteins encoded by nonessential genes were enriched for localisation to the plasma membrane and extracellular spaces (Dickerson *et al.*, 2011). These findings are supported by the biological function annotations for essential and nonessential disease genes, with essential disease genes enriched for transcription factors (Dickerson *et al.*, 2011).

Protein functions are largely mediated by the physical binding interactions these molecules undergo. Thus, a large-scale analysis of PPI networks also provides a mechanism for discriminating between essential and non-essential disease genes. Disease genes occupy highly connected 'hub' positions in PPI networks (Dickerson *et al.*, 2011; Feldman *et al.*, 2008; Goh *et al.*, 2007). When disease genes are segregated based on the essentiality of their mouse orthologues, excluding those human genes without mouse knockout data from the analysis, essential disease genes are more highly connected than nonessential disease genes (Dickerson *et al.*, 2011). Yet, genes with intermediate connectivity in PPI networks have the greatest likelihood of causing disease (Feldman *et al.*, 2008). Genes that are linked to more than one disease show a less-central position in PPI networks than essential genes (Chavali *et al.*, 2010), although the overlap between essential genes, disease genes and genes encoding proteins found at hubs has been interpreted differently in multiple studies (Dickerson *et al.*, 2011; Feldman *et al.*, 2008; Goh *et al.*, 2007). Additionally,

indicative of the shared physiological functions altered by pathological mutations, disease genes have a propensity to form PPIs with other genes-causing disease in the same tissues (Feldman *et al.*, 2008; Goh *et al.*, 2007). Therefore, disease genes encode proteins likely to perform functions mediated by interactions with many other binding partners, with the greatest degree of protein interactions performed by those disease genes with essential mouse orthologues. **See also:** [Protein Interaction and Genetic Disease](#)

Links between human disease genes and genes required for embryo development have also been explored through PPI networks. Because genes annotated as having a role in embryonic development will have a degree of overlap with essential genes, the results of this analysis are expected to concur with network analysis of essential genes. The authors found a significant association between embryonic development genes and genes associated with human disease (Gong *et al.*, 2011), similar to findings from studies exploring the relationship between essential genes and disease (Dickerson *et al.*, 2011). Both studies also found statistically significant links between genes causing cancer when mutated and essential or embryonic development genes (Dickerson *et al.*, 2011; Gong *et al.*, 2011). Thus, genes functioning in embryonic development have a similar network profile and disease association profile as essential genes.

The Role of Essential Genes in Different Types of Disease

It has been demonstrated that the human orthologues of mouse essential genes are associated with diverse diseases, and that the prevalence of disease types linked to essential disease genes varies from those linked to nonessential genes (Dickerson *et al.*, 2011). Additionally, genes that contribute to human disease can be causes of both Mendelian and complex disorders. In a study to identify attributes of genes that cause both Mendelian and complex disease, and separate them from genes causing only Mendelian, only complex disease or no disease, a comparison of genes in each of these categories with essential genes was performed (Jin *et al.*, 2012). In this work the authors defined essential genes based on the phenotype of the knockout of the mouse orthologue. However, only those genes annotated as not causing disease were then analysed for essentiality, so in this study essential genes found to be associated with disease were not separated out of the disease datasets. The authors conclude that genes causing both Mendelian and complex disease have more PPIs than those genes that cause only one form of disease, although the level of connectivity is lower than that of essential genes. Essential genes and those genes associated with Mendelian disease but not complex disease lacked evidence of recent selection, whereas the genes associated with complex disease were under stronger recent positive selection (Jin *et al.*, 2012).

This similarity may suggest that essential genes are likely to be associated with Mendelian disorders rather than complex disease. A further analysis of the Mendelian disease dataset used by the authors may reveal that essential genes are present in this category. **See also: Complex Multifactorial Genetic Diseases; Mendelian Genetic Disorders**

Support for the links between essential genes and Mendelian disease comes from a study of orphan diseases. Orphan diseases are rare, approximately affecting fewer than 6.5 individuals per 10 000 members of the population. Many of these diseases have severely debilitating pathologies, occurring early in life. The majority of orphan diseases are monogenic. Genes that cause orphan diseases when mutated are found at highly connected hub positions in PPI networks (Zhang *et al.*, 2011). Orphan disease-causing genes have also been found to have widespread expression (Zhang *et al.*, 2011). As essential genes also occupy highly-connected positions in PPIs (Feldman *et al.*, 2008; Goh *et al.*, 2007) and have been defined as those genes with ubiquitous expression (Tu *et al.*, 2006), it is tempting to speculate that orphan diseases are caused by mutations in essential genes. Indeed, a comparison of the mouse knockout phenotypes of orthologues of genes known to cause orphan diseases reveals an enrichment for essential genes (Zhang *et al.*, 2011).

In addition to their role in Mendelian disease, essential genes may also contribute to polygenic disease via the genetic interactions between their mutant alleles. Autism spectrum disorders, although still poorly understood, are associated with mutations in over 200 genes (Heil and Schaaf, 2013). Complex genetic interactions between mutant alleles are also thought to contribute to these disorders (Heil and Schaaf, 2013). Supporting a role for essential genes in polygenic disease, autism spectrum disorder associated genes were found to be enriched for essential genes (Georgi *et al.*, 2013). Individuals affected with autism spectrum disorders also displayed a higher rate of de novo mutations existing in a heterozygous state in essential genes than nonessential genes, a difference that was not detected in unaffected family members (Georgi *et al.*, 2013). Owing to the complex genetic interactions that may contribute to the development of autism spectrum disorders, it is likely that heterozygous mutations in multiple essential genes may cause disease.

Population Genetics of Essential Genes

In genetic mapping experiments of patients with Mendelian diseases, the phenomenon of linkage disequilibrium, where sequence variants surrounding a disease locus are not found in equilibrium with the expected population allele frequency, has been reported. However, a study of sequence variation in humans has demonstrated that genes listed in OMIM as disease-causing are significantly underrepresented in genes showing strong linkage

disequilibrium (Gibson *et al.*, 2013). Conversely, disease genes are overrepresented in the group of genes showing average levels of linkage disequilibrium, suggesting that they do not have a significantly different history of recombination or mutation to nondisease genes. The authors propose that disease-causing genes are not overrepresented in the set of genes with the strongest linkage disequilibrium because genes that perform essential cellular functions are likely to cause lethality when mutated, and thus individuals with deleterious variants of these genes are eliminated from the population (Gibson *et al.*, 2013). Therefore, essential genes would be unlikely to demonstrate the hallmark of strong linkage disequilibrium, because sequence variation introduced by mutation is not tolerated in this gene set. An analysis of the 1000 Genomes Phase 1 large-scale human genomic sequencing dataset (Abecasis *et al.*, 2010) supports this conclusion; essential genes contain more rare variants than known nonlethal genes (Georgi *et al.*, 2013). Conversely, genes with the weakest linkage disequilibrium are unlikely to be associated with disease because the definition of weak linkage disequilibrium is that these genes possess high-sequence variation in the population (Gibson *et al.*, 2013), and therefore this group of genes must be able to tolerate high levels of mutation to produce multiple-sequence variations that persist in the population.

Summary

A wealth of data demonstrates that disease genes have different properties from nondisease genes. Likewise, there is overlap between human disease genes and essential genes, demonstrating that essential genes form an important subcategory of disease genes. Although essential genes may be severely harmful to individual survival when mutated to a null allele, preventing the survival or reproduction of the affected individual, other mutations in essential genes can be associated with a variety of less severe diseases. Hypomorphic, gain-of-function, somatic and compound heterozygous mutations of essential genes are associated with a large number of diverse human diseases. Essential genes should therefore not be eliminated from consideration as candidate genes for a large spectrum of human genetic disorders.

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