

Evidence Level		Evidence Description
Supportive Evidence	DEFINITIVE	The role of this gene in this particular disease has been repeatedly demonstrated in both the research and clinical diagnostic settings, and has been upheld over time (in general, at least 3 years). No convincing evidence has emerged that contradicts the role of the gene in the specified disease.
	STRONG	<p>The role of this gene in disease has been independently demonstrated typically in at least two separate studies providing strong supporting evidence for this gene's role in disease, usually including both of the following types of evidence:</p> <ul style="list-style-type: none"> • Strong variant-level evidence demonstrating numerous unrelated probands with variants that provide convincing evidence for disease causality¹ as well as • Compelling gene-level evidence from different types of supporting experimental data². <p>In addition, no convincing evidence has emerged that contradicts the role of the gene in the noted disease.</p>
	MODERATE	<p>There is moderate evidence to support a causal role for this gene in this disease, typically including both of the following types of evidence:</p> <ul style="list-style-type: none"> • Several probands with variants that provide convincing evidence for disease causality¹ • Moderate experimental data² supporting the gene-disease association <p>The role of this gene in disease may not have been independently reported, but no convincing evidence has emerged that contradicts the role of the gene in the noted disease.</p>
	LIMITED	<p>There is limited evidence to support a causal role for this gene in this disease, such as:</p> <ul style="list-style-type: none"> • Fewer than three observations of variants that provide convincing evidence for disease causality¹ OR • Variants have been observed in probands, but none have sufficient evidence for disease causality. • Limited experimental data² supporting the gene-disease association <p>The role of this gene in disease may not have been independently reported, but no convincing evidence has emerged that contradicts the role of the gene in the noted disease.</p>
	NO REPORTED EVIDENCE	Evidence for a causal role in disease has not been reported. These genes might be "candidate" genes based on linkage intervals, animal models, implication in pathways known to be involved in human diseases, etc., but no reports have directly implicated the gene in human disease cases.
Contradictory Evidence	CONFLICTING EVIDENCE REPORTED	<p>Although there has been an assertion of a gene-disease association, conflicting evidence for the role of this gene in disease has arisen since the time of the initial report indicating a disease association. Depending on the quantity and quality of evidence disputing the association, the association may be further defined by the following two sub-categories:</p> <ol style="list-style-type: none"> 1. Disputed <ol style="list-style-type: none"> a. Convincing evidence <i>disputing</i> a role for this gene in this disease has arisen since the initial report identifying an association between the gene and disease. b. Refuting evidence need not outweigh existing evidence supporting the gene:disease association. 2. Refuted <ol style="list-style-type: none"> a. Evidence refuting the role of the gene in the specified disease has been reported and significantly outweighs any evidence supporting the role. b. This designation is to be applied at the discretion of clinical domain experts after thorough review of available evidence
NOTES		
<p>¹Variants that disrupt function and/or have other strong genetic and population data (e.g. <i>de novo</i> occurrence, absence in controls, strong linkage to a small genomic interval, etc.) are considered convincing of disease causality in this framework.</p> <p>²Examples of appropriate types of supporting experimental data based on those outlined in MacArthur et al. 2014.</p>		