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Supplemental Data

Evaluating the Clinical Validity of Gene-Disease Associations: An Evidence-Based Framework Developed by the Clinical Genome Resource

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A. Dominant/X-linked

$$Z = \log_{10}[1/(0.5)^n]$$

n = dominant segregations

n	LOD	Points
15	4.5	6.5
14	4.2	6.0
13	3.9	5.5
12	3.6	5.5
11	3.3	5.0
10	3.0	5.0
9	2.7	4.5
8	2.4	4.0
7	2.1	4.0
6	1.8	3.5
5	1.5	3.0
4	1.2	1.5

B. Recessive

$$Z = \log_{10}\{1/[(0.25)^{x-1}(0.75)^y]\}$$

x = affected individuals
y = unaffected individuals

x/*y*	LOD	Points
7 / 4	4.11	6.0
7 / 1	3.73	5.5
6 / 1	3.14	5.0
5 / 1	2.53	4.5
4 / 3	2.18	4.0
4 / 1	1.90	3.5
3 / 3	1.50	3.0
3 / 2	1.45	2.5
3 / 1	1.30	2.5
2 / 3	1.00	1.5
2 / 2	0.85	1.0
2 / 1	0.72	1.0

C. Proposed Matrix Scoring for LOD Ranges

LOD Range	Points (Max = 7)
≥ 5.00	7.0
4.50 – 4.99	6.5
4.00 – 4.49	6.0
3.50 - 3.99	5.5
3.00 – 3.49	5.0 (1000:1)
2.50 – 2.99	4.5
2.00 – 2.49	4.0 (100:1)
1.75 – 1.99	3.5
1.50 – 1.74	3.0
1.25 – 1.49	2.5 (10:1)
1.00 – 1.24	1.5
0.72 – 0.99	1.0

Figure S1: Guidelines for approximating LOD scores within the ClinGen clinical validity framework. (A, B) LOD score (Z) estimates are given for multiple segregation scenarios with a suggested number of points to be assigned in the genetic evidence category (Figure 3). **A.** LOD scores for disorders inherited in a dominant or X-linked manner should calculated using the same equation, where *n* equals the number of dominant segregations. **B.** For autosomal recessive disorders, both unaffected carriers (*y*) and affected genotype positive individuals (*x*) should be included in the calculation of the LOD score. In general, the number of affected individuals (*x*) - 1 is equal to the number of affected segregations and can be used interchangeably in this equation. **C.** A suggested number of points is provided for multiple ranges of LOD scores to facilitate consistent scoring in the summary matrix (Figure 4).

AGTR2 and X-linked intellectual disability											
Genetic Evidence	Case-Level Data[A]	Evidence Type		Case Information Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Variant Evidence	Autosomal Dominant or X- linked Disorder[B]	Variant is de novo[C]			2	0-3	12			
				Proband with predicted or proven null variant[D]			1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact[E]			0.5	0-1.5	7	0.5	0.5	Takeshita E et al. 2012 Oct (22269148)[1]
			Autosomal Recessive Disease	Two variants in trans and at least one de novo[C] or a predicted/proven null variant[D]			2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact[E] in trans			1	0-1.5				
		Segregation[F] Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7			
						2	4					
						1.5	3					
						1	1.5					
	Case-Control Data[G]	Case-Control Study Type[H]		Case-Control Quality Criteria[I]			Guidelines Points/Study		Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Single Variant Analysis[Ha]		1. Variant Detection Methodology[Ia] 2. Power[Ib] 3. Bias and confounding[Ic] 4. Statistical Significance[Id]			0-6		12			
		Aggregate Variant Analysis[Hb]					0-6		12			
		Total Genetic Evidence Points (Maximum 12)									0.5	
Experimental Evidence		Evidence Category		Evidence Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Function		Biochemical Function			0.5	0 - 2	2	0.5	0.5	Vervoort VS et al. 2002 Jun 28 (12089445)[2]
				Protein Interaction			0.5	0 - 2				
				Expression			0.5	0 - 2				
		Functional Alteration		Cells from affected individual			1	0 - 2	2	0.5	0.5	Pawlowski TL et al. 2009 Sep (19501643)[3]
				Engineered cells			0.5	0 - 1				
		Models & Rescue		Animal model			2	0 - 4	4	2.0	2	Maul B et al. 2008 May (18335189)[4]
				Cell culture model system			1	0 - 2				
				Rescue in animal model			2	0 - 4				
				Rescue in engineered equivalent			1	0 - 2				
		Total Experimental Evidence Points (Maximum 6)									3	

Figure S2: Summary of evidence for a relationship between *AGTR2* and X-linked intellectual disability.

Evidence for the examples presented in Table 1 and Figure 5 is summarized in Figures S2-S65. The number of points awarded for each type of evidence and their corresponding references are provided. Footnotes A-I are the guidelines used to assess genetic evidence within this framework and apply to all of the examples presented in the following figures.

A. Each case may be given points for A) variant evidence (in the context of the appropriate mode of inheritance) and B) segregation evidence, if applicable (see footnote F and Figure S1 for more details on segregation evidence).

B. In X-linked disorders, affected probands will often be hemizygous males and/or heterozygous females. Recognizing that there can be rare cases of females affected by X-linked recessive disorders (due to chromosomal aneuploidy, skewed X inactivation, or homozygosity for a sequence variant) evaluators must interpret individual cases and X-linked pedigrees with caution.

C. Points should be adjusted depending on statistical expectation of *de novo* variation in the gene in question for variants.

D. As described in the 2015 ACMG/AMP sequence variant interpretation guidelines[5], null variants (typically nonsense, frameshift, canonical +/−1 or 2 splice sites, initiation codon, single or multi-exon deletions) are considered "very strong evidence for pathogenicity" in genes for which loss of function is a known disease mechanism. Disease mechanism can be assumed loss of function (LOF) if the gene is LOF constrained. LOF constraint scores must be interpreted in the context of the disease in question – genes associated with severe, pediatric-onset disorders are more likely to show constraint than adult-onset conditions where overall fitness is not impacted.

E. For variants NOT considered to be "null" (typically missense), at least some impact to gene function must be demonstrated for the case to count. Impact based on predictions only would score less than the default 0.5 points and impact based on functional validation can score 0.5 or above (up to 1.5/case) depending on the validation quality and biological representativeness of the functional assay.

F. LOD scores reported by the authors of a peer-reviewed journal article may be used to assign segregation points as outlined in the scoring matrix above. If a LOD score is not provided by the authors, one may be estimated for informative families with rare, highly penetrant disorders in which phenocopies are expected to be rare or absent. Below are guidelines for calculating estimated LOD scores in the appropriate scenarios are included in the standard operating procedure available online.

G. Case-control studies should be independently assessed to evaluate the quality of the study design preferably in concert with an expert.

H. Case-control studies are classified based on how variation in cases and controls is evaluated: single variant analysis or aggregate variant analysis. Studies presenting both types of analyses may be counted in either category at the discretion of the curator/expert, but the same variants should not be counted in both categories.

   a. *Single variant analysis* studies are those in which individual variants are evaluated for statistical enrichment in cases compared to controls. More than one variant may be analyzed, but the variants should be independently assessed with appropriate statistical correction for multiple testing.

   b. *Aggregate variant analysis* studies are those in which the statistical enrichment of two or more variants as an aggregate is assessed in cases compared to controls. This comparison could be accomplished by genotyping specific variants or by sequencing the entire gene.

I. Points for case-control studies may be assigned at the discretion of expert opinion based on the overall quality of each study. The following should be considered when evaluating case-control study quality:

   a. *Variant Detection Methodology*: Cases and controls should ideally be analyzed using methods with equivalent analytical performance (e.g. equivalent genotype methods, sufficient and equivalent depth and quality of sequencing coverage, correction for batch effects).

   b. *Power*: The study should analyze a sufficient number of cases and controls given the prevalence of the disease, the allele frequency, and the expected effect size in question to provide appropriate statistical power to detect an association.

   c. *Bias and Confounding factors:* The manner in which cases and controls were selected for participation and the degree of case-control matching may impact the outcome of the study. The following are some factors that should be considered:

      i. Are there systematic differences between individuals selected for study and individuals not selected for study?

      ii. Are the cases and controls matched by demographic information (e.g., age, ethnicity, location of recruitment, etc.)?

      iii. Are the cases and controls matched for genetic ancestry, if not did investigators account for genetic ancestry in the analysis?

      iv. Have the cases and controls been equivalently evaluated for presence or absence of a phenotype, and/or family history of disease?

   d. *Statistical Significance* – The level of statistical significance should be weighed carefully. When an odds ratio is presented, its magnitude should be consistent with a monogenic disease etiology. When p-values or 95% confidence intervals (CI) are presented, the strength of the statistical association can be weighed in the final points assigned. Factors, such as multiple testing, that might impact that interpretation of uncorrected p-values and CIs should be considered when assigning points

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	**0.5**	**3**	**3.5**	**NO**
CALCULATED CLASSIFICATION		**LIMITED**	**1-6**	
		MODERATE	**7-11**	
		STRONG	**12-18**	
		DEFINITIVE	**12-18 AND replication over time**	
Valid contradictory evidence (Y/N)*	YES	Piton A et al. 2013 Aug 8 (23871722)[6]; (Piton et al. refutes the original gene-disease assertion and ExAC data demonstrates that almost all of the variants identified are common in the general population.)		
CALCULATED CLASSIFICATION (DATE)		**LIMITED**		
MODIFY CALCULATED CLASSIFICATION		**YES**		
CURATOR CLASSIFICATION (DATE)		**DISPUTED 10/10/2016**		
EXPERT CURATION (DATE)		**DISPUTED 11/16/16 "Disputed" based on Pitton et al. 2013[6] and ExAC[7] data.**		

Figure S3: Summary matrix and classification for *AGTR2* and X-linked intellectual disability.

AKAP9 and autosomal dominant long QT syndrome

						Guidelines			Scores		
		Evidence Type		Case Information Type		Default	Range	Max	Points	Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo		2	0-3	12			
				Proband with predicted or proven null variant		1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7	0.5	0.5	Chen L et al. 2007 Dec 26 (18093912)[8]
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples 3	5	0-7	7			
					2	4					
					1.5	3					
					1	1.5					
						Guidelines			Scores		
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria		Points/Study		Max	Points	Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance		0-6		12			
		Aggregate Variant Analysis				0-6		12			
		Total Genetic Evidence Points (Maximum 12)								0.5	

			Guidelines			Scores		
	Evidence Category	Evidence Type	Default	Range	Max	Points	Tally	PMIDs/Notes
Experimental Evidence	Function	Biochemical Function	0.5	0 - 2	2	0.5	0.5	Marx SO et al. 2002 Jan 18 (11799244)[9]
		Protein Interaction	0.5	0 - 2				
		Expression	0.5	0 - 2				
	Functional Alteration	Cells from affected individual	1	0 - 2	2	1.0	1	Chen L et al. 2007 Dec 26 (18093912)[8]
		Engineered cells	0.5	0 - 1				
	Models & Rescue	Animal model	2	0 - 4	4			
		Cell culture model system	1	0 - 2				
		Rescue in animal model	2	0 - 4				
		Rescue in engineered equivalent	1	0 - 2				
	Total Experimental Evidence Points (Maximum 6)						1.5	

Figure S4: Summary of evidence supporting a relationship between *AKAP9* and autosomal dominant long QT syndrome.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	0.5	1.5	2	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	LIMITED 04/05/16		
	EXPERT CURATION (DATE)	LIMITED 12/15/16		

Figure S5: Summary matrix and classification for *AKAP9* and autosomal dominant long QT syndrome.

ARSD and chondrodysplasia punctata

						Guidelines			Scores		
		Evidence Type		Case Information Type		Default	Range	Max	Points	Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo		2	0-3	12	0.0		
				Proband with predicted or proven null variant		1.5	0-2	10	0.0		
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7	0.0	0	
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2	0-3	12		0	
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1	0-1.5		0.0		
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples 3	5	0-7	7	0.0		
					2	4					
					1.5	3					
					1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria		Guidelines: Points/Study		Guidelines: Max	Scores: Points	Scores: Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance		0-6		12	0.0		
		Aggregate Variant Analysis				0-6		12	0.0		
		Total Genetic Evidence Points (Maximum 12)								0	No reports of variants in this gene associated with this condition.

	Evidence Category	Evidence Type	Guidelines: Default	Guidelines: Range	Guidelines: Max	Scores: Points	Scores: Tally	PMIDs/Notes
Experimental Evidence	Function	Biochemical Function	0.5	0 - 2	2			
		Protein Interaction	0.5	0 - 2				
		Expression	0.5	0 - 2				
	Functional Alteration	Cells from affected individual	1	0 - 2	2			
		Engineered cells	0.5	0 - 1				
	Models & Rescue	Animal model	2	0 - 4	4			
		Cell culture model system	1	0 - 2				
		Rescue in animal model	2	0 - 4				
		Rescue in engineered equivalent	1	0 - 2				
	Total Experimental Evidence Points (Maximum 6)						0	

Figure S6: Summary of evidence supporting a relationship between *ARSD* and chondrodysplasia punctata.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points		0	0	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
CALCULATED CLASSIFICATION (DATE)		NO REPORTED EVIDENCE 07/14/2016		
EXPERT CURATION (DATE)		NO REPORTED EVIDENCE 11/15/16		

Figure S7: Summary matrix and classification for *ARSD* and chondrodysplasia punctata.

ATF6 and autosomal recessive achromatopsia

		Evidence Type		Case Information Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo			2	0-3	12			
				Proband with predicted or proven null variant			1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact			0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant			2	0-3	12	9.0	12	Ansar M et al. 2015 Sep (26063662); Kohl S et al. 2015 Jul (26029869)[10; 11]
				Two variants (not predicted/proven null) with some evidence of gene impact in trans			1	0-1.5		3.5		
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7	7.0	7	Ansar M et al. 2015 Sep (26063662); Kohl S et al. 2015 Jul (26029869)[10; 11]
						2	4					
						1.5	3					
						1	1.5					

		Case-Control Study Type	Case-Control Quality Criteria	Guidelines Points/Study	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
Genetic Evidence	Case-Control Data	Single Variant Analysis	1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance	0-6	12			
		Aggregate Variant Analysis		0-6	12			
		Total Genetic Evidence Points (Maximum 12)					**14**	

	Evidence Category	Evidence Type	Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
Experimental Evidence	Function	Biochemical Function	0.5	0 - 2	2	0.5	0.5	Ansar M et al. 2015 Sep (26063662)[11]
		Protein Interaction	0.5	0 - 2				
		Expression	0.5	0 - 2				
	Functional Alteration	Cells from affected individual	1	0 - 2	2	0.5	0.5	Ansar M et al. 2015 Sep (26063662)[11]
		Engineered cells	0.5	0 - 1				
	Models & Rescue	Animal model	2	0 - 4	4	1.0	1	Kohl S et al. 2015 Jul (26029869)[10]
		Cell culture model system	1	0 - 2				
		Rescue in animal model	2	0 - 4				
		Rescue in engineered equivalent	1	0 - 2				
	Total Experimental Evidence Points (Maximum 6)						**2**	

Figure S8: Summary of evidence supporting a relationship between *ATF6* and autosomal recessive achromatopsia.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	12	2	14	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	STRONG 06/01/2016		
	EXPERT CURATION (DATE)	STRONG 11/16/2016		

Figure S9: Summary matrix and classification for *ATF6* and autosomal recessive achromatopsia.

BAG3 and autosomal dominant myofibrillar myopathy

Genetic Evidence	Case-Level Data	Evidence Type		Case Information Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo			2	0-3	12			
				Proband with predicted or proven null variant			1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact			0.5	0-1.5	7	7.0	7	Selcen D et al. 2009 Jan (19085932); Odgerel Z et al. 2010 Jul (20605452); Semmler AL et al. 2014 Aug 1 (25208129); Konersman CG et al. 2015 May (25728519); Kostera-Pruszczyk A et al. 2015 Dec (26545904); D et al. 2016 Jun (27443559); Jaffer F et al. 2012 Jun (22734908)[12-18]
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant			2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans			1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7			
						2	4					
						1.5	3					
						1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria			Guidelines Points/Study		Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance			0-6		12			
		Aggregate Variant Analysis					0-6		12			
		Total Genetic Evidence Points (Maximum 12)									7	
Experimental Evidence		Evidence Category		Evidence Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Function		Biochemical Function			0.5	0 - 2	2	1.0	1	Homma S et al. 2006 Sep (16936253); Selcen D et al. 2009 Jan (19085932)[12; 19]
				Protein Interaction			0.5	0 - 2				
				Expression			0.5	0 - 2				
		Functional Alteration		Cells from affected individual			1	0 - 2	2			
				Engineered cells			0.5	0 - 1				
		Models & Rescue		Animal model			2	0 - 4	4	6.0	4	Homma S et al. 2006 Sep (16936253); Hishiya A et al. 2010 Nov 12 (20884878)[19; 20]
				Cell culture model system			1	0 - 2				
				Rescue in animal model			2	0 - 4				
				Rescue in engineered equivalent			1	0 - 2				
		Total Experimental Evidence Points (Maximum 6)									5	

Figure S10: Summary of evidence supporting a relationship between *BAG3* and autosomal dominant myofibrillar myopathy.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	7	5	12	YES
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	DEFINITIVE		
	EXPERT CURATION (DATE)	DEFINITIVE 12/18/2016		

Figure S11: Summary matrix and classification for *BAG3* and autosomal dominant myofibrillar myopathy.

C1QB and autosomal recessive immunodeficiency due to an early component of complement deficiency

					Guidelines			Scores		
		Evidence Type		Case Information Type	Default	Range	Max	Points	Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo	2	0-3	12			
				Proband with predicted or proven null variant	1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3	12	8.0	10	Petry F et al. 1997 Dec (9476130); Marquart HV et al. 2007 Jul (17513176); McAdam RA et al. 1988 (2894352); Troedson C et al. 2013 May (23651859); Higuchi Y et al. 2013 Oct 28 (24160257); van Schaarenburg RA et al. 2015 Mar (25454803)[21-26]
				Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5		2.0		
		Segregation Evidence		Evidence of segregation in one or more families — LOD Score Examples: 3	5	0-7	7	3.5	3.5	Marquart HV et al. 2007 Jul (17513176); Higuchi Y et al. 2013 Oct 28 (24160257)[23; 25]
				2	4					
				1.5	3					
				1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria	Points/Study		Max	Points	Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance	0-6		12			
		Aggregate Variant Analysis			0-6		12			
		Total Genetic Evidence Points (Maximum 12)							12	

			Guidelines			Scores		
	Evidence Category	Evidence Type	Default	Range	Max	Points	Tally	PMIDs/Notes
Experimental Evidence	Function	Biochemical Function	0.5	0 - 2	2	1.0	1	van Schaarenburg RA et al. 2015 Mar (25454803); Higuchi Y et al. 2013 Oct 28 (24160257); McAdam RA et al. 1988 (2894352); Petry F et al. 1997 Dec (9476130); Marquart HV et al. 2007 Jul (17513176); van Schaarenburg RA et al. 2015 Mar (25454803))[21-24; 26]
		Protein Interaction	0.5	0 - 2				
		Expression	0.5	0 - 2				
	Functional Alteration	Cells from affected individual	1	0 - 2	2	2.0	2	McAdam RA et al. 1988 (2894352)[21]
		Engineered cells	0.5	0 - 1				
	Models & Rescue	Animal model	2	0 - 4	4	2.0	2	Miura-Shimura Y et al. 2002 Aug 1 (12133956)[27]
		Cell culture model system	1	0 - 2				
		Rescue in animal model	2	0 - 4				
		Rescue in engineered equivalent	1	0 - 2				
	Total Experimental Evidence Points (Maximum 6)						5	

Figure S12: Summary of evidence supporting a relationship between *C1QB* and autosomal recessive immunodeficiency due to an early component of complement deficiency.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	12	5	17	YES
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	DEFINITIVE 06/13/2016		
	EXPERT CURATION (DATE)	DEFINITIVE 01/09/2017		

Figure S13: Summary matrix and classification for *C1QB* and autosomal recessive immunodeficiency due to an early component of complement deficiency.

CD3E and autosomal recessive severe combined immunodeficiency

Genetic Evidence	Case-Level Data	Evidence Type		Case Information Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo			2	0-3	12			
				Proband with predicted or proven null variant			1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact			0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant			2	0-3	12	6.0	6	Soudais C et al. 1993 Jan (8490660); de Saint Basile G et al. 2004 Nov (15546002); Fuehrer M et al. 2014 May (24515816)[28-30]
				Two variants (not predicted/proven null) with some evidence of gene impact in trans			1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7	0.0	0	
						2	4					
						1.5	3					
						1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria			Guidelines Points/Study		Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance			0-6		12			
		Aggregate Variant Analysis					0-6		12			
		Total Genetic Evidence Points (Maximum 12)									6	
Experimental Evidence		Evidence Category		Evidence Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Function		Biochemical Function			0.5	0 - 2	2	1.5	1.5	Manolios N et al. 1991 Jul (1828760); Thoenes G et al. 1992 Jan 5 (1370449); Fuehrer M et al. 2014 May (24515816)[30-32]
				Protein Interaction			0.5	0 - 2				
				Expression			0.5	0 - 2				
		Functional Alteration		Cells from affected individual			1	0 - 2	2	2.0	2	de Saint Basile G et al. 2004 Nov (15546002)[29]
				Engineered cells			0.5	0 - 1				
		Models & Rescue		Animal model			2	0 - 4	4	2.0	2	Wang B et al. 1994 Sep 27 (7937778)[33]
				Cell culture model system			1	0 - 2				
				Rescue in animal model			2	0 - 4				
				Rescue in engineered equivalent			1	0 - 2				
		Total Experimental Evidence Points (Maximum 6)									5.5	

Figure S14: Summary of evidence supporting a relationship between *CD3E* and autosomal recessive severe combined immunodeficiency

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	6	5.5	11.5	YES
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
CALCULATED CLASSIFICATION (DATE)		DEFINITIVE 05/26/2016		
EXPERT CURATION (DATE)		**DEFINITIVE** 01/09/2017 Expert agrees with decision to round up to "Definitive," and is aware of additional unpublished genetic evidence to corroborate this claim.		

Figure S15: Summary matrix and classification for *CD3E* and autosomal recessive severe combined immunodeficiency.

CHD1L and autosomal dominant renal or urinary tract malformation (CAKUT)

Genetic Evidence	Case-Level Data	Evidence Type		Case Information Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo			2	0-3	12			
				Proband with predicted or proven null variant			1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact			0.5	0-1.5	7	2.5	2.5	Hwang DY et al. 2014 Jun (24429398)[34]
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant			2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans			1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7			
						2	4					
						1.5	3					
						1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria			Guidelines Points/Study		Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance			0-6		12			
		Aggregate Variant Analysis					0-6		12			
		Total Genetic Evidence Points (Maximum 12)									3.5	
Experimental Evidence		Evidence Category		Evidence Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Function		Biochemical Function			0.5	0 - 2	2	1.0	1	Brockschmidt A et al. 2012 Jun (22146311)[35]
				Protein Interaction			0.5	0 - 2				
				Expression			0.5	0 - 2				
		Functional Alteration		Cells from affected individual			1	0 - 2	2			
				Engineered cells			0.5	0 - 1				
		Models & Rescue		Animal model			2	0 - 4	4			
				Cell culture model system			1	0 - 2				
				Rescue in animal model			2	0 - 4				
				Rescue in engineered equivalent			1	0 - 2				
		Total Experimental Evidence Points (Maximum 6)									1	

Figure S16: Summary of evidence supporting a relationship between *CHD1L* and autosomal dominant renal or urinary tract malformation (CAKUT).

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	2.5	1	3.5	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	LIMITED 05/25/2016		
	EXPERT CURATION (DATE)	LIMITED 11/18/2016		

Figure S17: Summary matrix and classification for *CHD1L* and autosomal dominant renal or urinary tract malformation (CAKUT).

COL2A1 and autosomal dominant Spondyloepiphyseal dysplasia (Stanescu type)

Genetic Evidence	Case-Level Data	Evidence Type		Case Information Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo			2	0-3	12	2.0	2	Jurgens J et al. 2015 Oct (26183434)[36]
				Proband with predicted or proven null variant			1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact			0.5	0-1.5	7	1.0	1	Jurgens J et al. 2015 Oct (26183434); Hammarsjö A et al. 2016 Jan (26420734)[36; 37]
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant			2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans			1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7			
						2	4					
						1.5	3					
						1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria			Guidelines Points/Study		Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance			0-6		12			
		Aggregate Variant Analysis					0-6		12			
		Total Genetic Evidence Points (Maximum 12)									9	
Experimental Evidence		Evidence Category		Evidence Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Function		Biochemical Function			0.5	0 - 2	2			
				Protein Interaction			0.5	0 - 2				
				Expression			0.5	0 - 2				
		Functional Alteration		Cells from affected individual			1	0 - 2	2	2.0	2	Chan D et al. 1993 Jul 15 (8325895); Vandenberg P et al. 1991 Sep 1 (1881905); Garofalo S et al. 1991 Nov 1 (1946380)[38-40]
				Engineered cells			0.5	0 - 1				
		Models & Rescue		Animal model			2	0 - 4	4	4.0	4	Vandenberg P et al. 1991 Sep 1 (1881905); Garofalo S et al. 1991 Nov 1 (1946380)[39-40]
				Cell culture model system			1	0 - 2				
				Rescue in animal model			2	0 - 4				
				Rescue in engineered equivalent			1	0 - 2				
		Total Experimental Evidence Points (Maximum 6)									6	

Figure S18: Summary of evidence supporting a relationship between *COL2A1* and autosomal dominant Spondyloepiphyseal dysplasia (Stanescu type).

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	3	6	9	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	MODERATE 05/25/2016		
	EXPERT CURATION (DATE)	MODERATE 12/01/2016		

Figure S19: Summary matrix and classification for *COL2A1* and autosomal dominant Spondyloepiphyseal dysplasia (Stanescu type).

DICER1 and autosomal dominant pleuropulmonary blastoma

						Guidelines			Scores		
		Evidence Type		Case Information Type		Default	Range	Max	Points	Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo		2	0-3	12	12.0	12	Hill DA et al. 2009 Aug 21 (19556464); Doros L et al. 2012 Sep (22180160); Stewart DR et al. 2014 Nov (25118636)[41-43]
				Proband with predicted or proven null variant		1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7		
						2	4				
						1.5	3				
						1	1.5				
						Guidelines			Scores		
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria		Points/Study		Max	Points	Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance		0-6		12			
		Aggregate Variant Analysis				0-6		12			
									Total Genetic Evidence Points (Maximum 12)		12
						Guidelines			Scores		
Experimental Evidence		Evidence Category		Evidence Type		Default	Range	Max	Points	Tally	PMIDs/Notes
		Function		Biochemical Function		0.5	0 - 2	2	2.0	2	Hill DA et al. 2009 Aug 21 (19556464); Harris KS et al. 2006 Feb 14 (16452165)[41; 44]
				Protein Interaction		0.5	0 - 2				
				Expression		0.5	0 - 2				
		Functional Alteration		Cells from affected individual		1	0 - 2	2			
				Engineered cells		0.5	0 - 1				
		Models & Rescue		Animal model		2	0 - 4	4	2.0	2	Harris KS et al. 2006 Feb 14 (16452165)[44]
				Cell culture model system		1	0 - 2				
				Rescue in animal model		2	0 - 4				
				Rescue in engineered equivalent		1	0 - 2				
									Total Experimental Evidence Points (Maximum 6)		4

Figure S20: Summary of evidence supporting a relationship between *DICER1* and autosomal dominant pleuropulmonary blastoma.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	12	4	16	YES
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	DEFINITIVE 05/06/2016		
	EXPERT CURATION (DATE)	DEFINITIVE 01/08/2017		

Figure S21: Summary matrix and classification for *DICER1* and autosomal dominant pleuropulmonary blastoma.

FGFR3 and autosomal dominant achondroplasia

						Guidelines			Scores		
		Evidence Type		Case Information Type		Default	Range	Max	Points	Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo		2	0-3	12	10.0	10	Rousseau F et al. 1994 Sep 15 (8078586); Shiang R et al. 1994 Jul 29 (7913883)[45; 46] (Additional cases are available beyond those in these references.)
				Proband with predicted or proven null variant		1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7	1.0	1	Rousseau F et al. 1994 Sep 15 (8078586)[45] (Additional cases are available beyond those in this reference.)
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	7	2.0	2	Rousseau F et al. 1994 Sep 15 (8078586)[45]
						2	4				
						1.5	3				
						1	1.5				
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria		Guidelines			Scores		PMIDs/Notes
						Points/Study		Max	Points	Tally	
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance		0-6		12			
		Aggregate Variant Analysis				0-6		12			
		Total Genetic Evidence Points (Maximum 12)								12	Additional genetic evidence is available beyond this maximum score.
Experimental Evidence		Evidence Category		Evidence Type		Guidelines			Scores		PMIDs/Notes
						Default	Range	Max	Points	Tally	
		Function		Biochemical Function		0.5	0 - 2	2			
				Protein Interaction		0.5	0 - 2				
				Expression		0.5	0 - 2				
		Functional Alteration		Cells from affected individual		1	0 - 2	2	1.0	1	Naski MC et al. 1998 Dec (9811582); Cho JY et al. 2004 Jan 13 (14699054)[47; 48]
				Engineered cells		0.5	0 - 1				
		Models & Rescue		Animal model		2	0 - 4	4	2.0	2	Wang Y et al. 1999 Apr 13 (10200283)[49]
				Cell culture model system		1	0 - 2				
				Rescue in animal model		2	0 - 4				
				Rescue in engineered equivalent		1	0 - 2				
		Total Experimental Evidence Points (Maximum 6)								3	Additional experimental data may be available.

Figure S22: Summary of evidence supporting a relationship between *FGFR3* and autosomal dominant achondroplasia.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	12	3	15	YES
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	DEFINITIVE 04/05/2016		
	EXPERT CURATION (DATE)	DEFINITIVE 12/01/2016		

Figure S23: Summary matrix and classification for *FGFR3* and autosomal dominant achondroplasia.

HNRNPK and autosomal dominant Au-Kline syndrome

					Guidelines			Scores		
		Evidence Type		Case Information Type	Default	Range	Max	Points	Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo	2	0-3	12	6.0	6	Au PY et al. 2015 Oct (26173930); Lange L et al. 2016 Sep (26954065)[50; 51]
				Proband with predicted or proven null variant	1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families — LOD Score Examples: 3	5	0-7	7			
				2	4					
				1.5	3					
				1	1.5					
					Guidelines			Scores		
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria	Points/Study		Max	Points	Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance	0-6		12			
		Aggregate Variant Analysis			0-6		12			
								Total Genetic Evidence Points (Maximum 12)		6.5
					Guidelines			Scores		
Experimental Evidence		Evidence Category		Evidence Type	Default	Range	Max	Points	Tally	PMIDs/Notes
		Function		Biochemical Function	0.5	0 - 2	2	0.5	0.5	Fan X et al. 2015 Dec 7 (26638989)[52]
				Protein Interaction	0.5	0 - 2				
				Expression	0.5	0 - 2				
		Functional Alteration		Cells from affected individual	1	0 - 2	2			
				Engineered cells	0.5	0 - 1				
		Models & Rescue		Animal model	2	0 - 4	4			
				Cell culture model system	1	0 - 2				
				Rescue in animal model	2	0 - 4				
				Rescue in engineered equivalent	1	0 - 2				
								Total Experimental Evidence Points (Maximum 6)		0.5

Figure S24: Summary of evidence supporting a relationship between *HNRNPK* and autosomal dominant Au-Kline syndrome.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	6	0.5	6.5	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
CALCULATED CLASSIFICATION (DATE)		MODERATE		
EXPERT CURATION (DATE)		MODERATE 11/15/2016		

Figure S25: Summary matrix and classification for *HNRNPK* and autosomal dominant Au-Kline syndrome. Evidence is rapidly emerging supporting the association between *HNRNPK* and Au-Kline syndrome. Gallardo, et al. published a paper in 2015[53] describing an Hnrnpk +/- haploinsufficient mouse, which they developed to study its role in tumorigenesis. Personal communication with the senior author of that paper, Sean Post, in August 2016, revealed that the haploinsufficient mice appeared to have "significant reduction in overall size and had numerous structural/bone abnormalities," remniscient of the human phenotype, though he clarified that his group is not able to formally assess them for these types of phenotypes. Additionally, we are aware of at least one additional unpublished case - this evidence is not being formally considered, as it is not part of the public domain.

LAMB1 and autosomal recessive lissencephaly 5

Genetic Evidence	Case-Level Data	Evidence Type		Case Information Type		Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo		2	0-3	12			
				Proband with predicted or proven null variant		1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2	0-3	12	4.0	4	Radmanesh F et al. 2013 Mar 7 (23472759)[54]
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples: 3	5	0-7	7	4.0	4	Radmanesh F et al. 2013 Mar 7 (23472759)[54]
					2	4					
					1.5	3					
					1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria		Guidelines Points/Study		Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance		0-6		12			
		Aggregate Variant Analysis				0-6		12			
		Total Genetic Evidence Points (Maximum 12)								8	
Experimental Evidence		Evidence Category		Evidence Type		Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Function		Biochemical Function		0.5	0 - 2	2			
				Protein Interaction		0.5	0 - 2				
				Expression		0.5	0 - 2				
		Functional Alteration		Cells from affected individual		1	0 - 2	2			
				Engineered cells		0.5	0 - 1				
		Models & Rescue		Animal model		2	0 - 4	4	1.0	1	Lee J et al. 2007 Jun (17525174)[55]
				Cell culture model system		1	0 - 2				
				Rescue in animal model		2	0 - 4				
				Rescue in engineered equivalent		1	0 - 2				
		Total Experimental Evidence Points (Maximum 6)								1	

Figure S26: Summary of evidence supporting a relationship between *LAMB1* and autosomal recessive lissencephaly 5.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	8	1	9	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	MODERATE 11/03/2016		
	EXPERT CURATION (DATE)	MODERATE 11/15/2016		

Figure S27: Summary matrix and classification for *LAMB1* and autosomal recessive lissencephaly 5.

LBR and autosomal recessive anadysplasia-like, spontaneously remitting spondylometaphyseal dysplasia

		Evidence Type		Case Information Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo			2	0-3	12			
				Proband with predicted or proven null variant			1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact			0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant			2	0-3	12	4.0	4	Sobreira N et al. 2015 Jan (25348816); Borovik L et al. 2013 Aug (23824842)[56; 57]
				Two variants (not predicted/proven null) with some evidence of gene impact in trans			1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7			
						2	4					
						1.5	3					
						1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria			Guidelines Points/Study		Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance			0-6		12			
		Aggregate Variant Analysis					0-6		12			
		Total Genetic Evidence Points (Maximum 12)									4	

	Evidence Category	Evidence Type	Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
Experimental Evidence	Function	Biochemical Function	0.5	0 - 2	2	1.0	1	Olins AL et al. 2010 Jan-Feb (21327105)[58]
		Protein Interaction	0.5	0 - 2				
		Expression	0.5	0 - 2				
	Functional Alteration	Cells from affected individual	1	0 - 2	2	0.5	0.5	Zwerger M et al. 2010 Jan 15 (19940018)[59]
		Engineered cells	0.5	0 - 1				
	Models & Rescue	Animal model	2	0 - 4	4	1.0	1	Shultz LD et al. 2003 Jan 1 (12490533)[60]
		Cell culture model system	1	0 - 2				
		Rescue in animal model	2	0 - 4				
		Rescue in engineered equivalent	1	0 - 2				
	Total Experimental Evidence Points (Maximum 6)						2.5	

Figure S28: Summary of evidence supporting a relationship between *LBR* and autosomal recessive anadysplasia-like, spontaneously remitting spondylometaphyseal dysplasia.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	4	2.5	6.5	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
CALCULATED CLASSIFICATION (DATE)		MODERATE		
EXPERT CURATION (DATE)		MODERATE 12/01/2016		

Figure S27: Summary matrix and classification for *LBR* and autosomal recessive anadysplasia-like, spontaneously remitting spondylometaphyseal dysplasia.

MYO9A and autosomal recessive arthrogryposis

Genetic Evidence	Case-Level Data	Evidence Type		Case Information Type		Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo		2	0-3	12			
				Proband with predicted or proven null variant		1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2	0-3	12	2.0	2	Bayram Y et al. 2016 Feb (26752647)[61]
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples 3	5	0-7	7			
					2	4					
					1.5	3					
					1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria		Guidelines Points/Study		Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance		0-6		12			
		Aggregate Variant Analysis				0-6		12			
		Total Genetic Evidence Points (Maximum 12)								2	
Experimental Evidence		Evidence Category		Evidence Type		Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Function		Biochemical Function		0.5	0 - 2	2	1.0	1	Chieregatti E et al. 1998 Dec 18 (9819351); Gorman SW et al. 1999 Jul 15 (10409426)[62; 63]
				Protein Interaction		0.5	0 - 2				
				Expression		0.5	0 - 2				
		Functional Alteration		Cells from affected individual		1	0 - 2	2	0.5	0.5	Omelchenko T et al. 2012 Feb 21 (22305756)[64]
				Engineered cells		0.5	0 - 1				
		Models & Rescue		Animal model		2	0 - 4	4			
				Cell culture model system		1	0 - 2				
				Rescue in animal model		2	0 - 4				
				Rescue in engineered equivalent		1	0 - 2				
		Total Experimental Evidence Points (Maximum 6)								1.5	

Figure S30: Summary of evidence supporting a relationship between *MYO9A* and autosomal recessive arthrogryposis.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	2	1.5	3.5	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	LIMITED 09/08/2016		
	EXPERT CURATION (DATE)	LIMITED 11/24/2016 The expert scored this at 3 points, which corresponded to a solid Limited classification.		

Figure S31: Summary matrix and classification for *MYO9A* and autosomal recessive arthrogryposis.

NGLY1 and autosomal recessive congenital disorder of deglycosylation

						Guidelines			Scores		
		Evidence Type		Case Information Type		Default	Range	Max	Points	Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo		2	0-3	12			
				Proband with predicted or proven null variant		1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2	0-3	12	10.0	10	Need AC et al. 2012 Jun (22581936); Caglayan AO et al. 2015 Jan (25220016); Enns GM et al. 2014 Oct (24651605); Bosch DG et al. 2016 May (26350515); Heeley J et al. 2015 Apr (25707956)[65-69]
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples: 3	5	0-7	7			
					2	4					
					1.5	3					
					1	1.5					
						Guidelines			Scores		
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria		Points/Study		Max	Points	Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance		0-6		12			
		Aggregate Variant Analysis				0-6		12			
									Total Genetic Evidence Points (Maximum 12)		2

			Guidelines			Scores		
	Evidence Category	Evidence Type	Default	Range	Max	Points	Tally	PMIDs/Notes
Experimental Evidence	Function	Biochemical Function	0.5	0 - 2	2	1.0	1	Need AC et al. 2012 Jun (22581936); He P et al. 2015 Aug (25900930)[65; 70]
		Protein Interaction	0.5	0 - 2				
		Expression	0.5	0 - 2				
	Functional Alteration	Cells from affected individual	1	0 - 2	2	2.0	2	Need AC et al. 2012 Jun (22581936); Enns GM et al. 2014 Oct (24651605); Heeley J et al. 2015 Apr (25707956)[65; 67; 69]
		Engineered cells	0.5	0 - 1				
	Models & Rescue	Animal model	2	0 - 4	4	4.0	4	Huang C et al. 2015 Feb 3 (25605922)[71]
		Cell culture model system	1	0 - 2				
		Rescue in animal model	2	0 - 4				
		Rescue in engineered equivalent	1	0 - 2				
						Total Experimental Evidence Points (Maximum 6)		6

Figure S32: Summary of evidence supporting a relationship between *NGLY1* and autosomal recessive congenital disorder of deglycosylation.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	10	6	16	YES
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	DEFINITIVE 06/02/2016		
	EXPERT CURATION (DATE)	DEFINITIVE 12/01/2016		

Figure S33: Summary matrix and classification for *NGLY1* and autosomal recessive congenital disorder of deglycosylation.

NHP2 and autosomal recessive dyskeratosis congenital

Genetic Evidence	Case-Level Data	Evidence Type		Case Information Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo			2	0-3	12			
				Proband with predicted or proven null variant			1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact			0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant			2	0-3	12	1.0	2	Vulliamy T et al. 2008 Jun 10 (18523010)[72] (Variant points were downgraded because later papers suggest that the null variant may still result in functional protein product.)
				Two variants (not predicted/proven null) with some evidence of gene impact in trans			1	0-1.5		1.0		
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7			
						2	4					
						1.5	3					
						1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria			Guidelines Points/Study		Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance			0-6		12			
		Aggregate Variant Analysis					0-6		12			
		Total Genetic Evidence Points (Maximum 12)									2	
Experimental Evidence		Evidence Category		Evidence Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Function		Biochemical Function			0.5	0 - 2	2	1.5	1.5	Trahan C et al. 2010 Mar 1 (20008900); Freund A et al. 2014 Dec 4 (25467444)[73; 74]
				Protein Interaction			0.5	0 - 2				
				Expression			0.5	0 - 2				
		Functional Alteration		Cells from affected individual			1	0 - 2	2			
				Engineered cells			0.5	0 - 1				
		Models & Rescue		Animal model			2	0 - 4	4	2.5	2.5	Dez C et al. 2001 Feb 1 (11160879); Vulliamy T et al. 2008 Jun 10 (18523010); Vulliamy T et al. 2008 Jun 10 (18523010)[72; 75]
				Cell culture model system			1	0 - 2				
				Rescue in animal model			2	0 - 4				
				Rescue in engineered equivalent			1	0 - 2				
		Total Experimental Evidence Points (Maximum 6)									4	

Figure S34: Summary of evidence supporting a relationship between *NHP2* and autosomal recessive dyskeratosis congenital.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	2	4	6	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	LIMITED 08/04/2016		
	EXPERT CURATION (DATE)	LIMITED 01/25/2017 During expert review, the expert added more experimental evidence; however, the clinical validity classification remained limited.		

Figure S35: Summary matrix and classification for *NHP2* and autosomal recessive dyskeratosis congenital.

PALB2 and autosomal dominant hereditary breast cancer

Genetic Evidence	Case-Level Data	Evidence Type		Case Information Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo			2	0-3	12			
				Proband with predicted or proven null variant			1.5	0-2	10	7.5	7.4	Erkko H et al. 2007 Mar 15 (17287723); Heikkinen T et al. 2009 May 1 (19383810); Casadei S et al. 2011 Mar 15 (21285249); Hartley T et al. 2014 (25225577); Janatova M et al. 2013 Dec (24136930) [76-80]
				Proband with other variant type with some evidence of gene impact			0.5	0-1.5	7	0.0	0	
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant			2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans			1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7	3.0	3	Hartley T et al. 2014 (25225577); Janatova M et al. 2013 Dec (24136930) [79; 80]
						2	4					
						1.5	3					
						1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria			Guidelines Points/Study		Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance			0-6		12	5.0	5	Erkko H et al. 2007 Mar 15 (17287723); Heikkinen T et al. 2009 May 1 (19383810) [76; 77]
		Aggregate Variant Analysis					0-6		12	4.0	4	Cybulski C et al. 2015 Jun (25959805) [81]
		Total Genetic Evidence Points (Maximum 12)									17	

Experimental Evidence	Evidence Category	Evidence Type	Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
	Function	Biochemical Function	0.5	0 - 2	2	1.0	1	Xia B et al. 2006 Jun 23 (16793542) [82]
		Protein Interaction	0.5	0 - 2				
		Expression	0.5	0 - 2				
	Functional Alteration	Cells from affected individual	1	0 - 2	2	2.0	2	Erkko H et al. 2007 Mar 15 (17287723) [76]
		Engineered cells	0.5	0 - 1				
	Models & Rescue	Animal model	2	0 - 4	4	2.0	2	Bowman-Colin C et al. 2013 May 21 (23657012) [83]
		Cell culture model system	1	0 - 2				
		Rescue in animal model	2	0 - 4				
		Rescue in engineered equivalent	1	0 - 2				
	Total Experimental Evidence Points (Maximum 6)						5	

Figure S36: Summary of evidence supporting a relationship between *PALB2* and autosomal dominant hereditary breast cancer.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	12	5	17	YES
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	DEFINITIVE 06/02/2016		
	EXPERT CURATION (DATE)	DEFINITIVE 12/01/2016		

Figure S37: Summary matrix and classification for *PALB2* and autosomal dominant hereditary breast cancer.

PMS2 and pancreatic cancer

						Guidelines			Scores		
		Evidence Type		Case Information Type		Default	Range	Max	Points	Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo		2	0-3	12	0.0	0	
				Proband with predicted or proven null variant		1.5	0-2	10	0.0	0	
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7	0.0	0	
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2	0-3	12	0.0	0	
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1	0-1.5		0.0		
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples 3	5	0-7	7	0.0	0	
					2	4					
					1.5	3					
					1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria		Guidelines: Points/Study		Guidelines: Max	Scores: Points	Scores: Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance		0-6		12	0.0	0	
		Aggregate Variant Analysis				0-6		12	0.0	0	
		Total Genetic Evidence Points (Maximum 12)								0	No reports of variants in this gene associated with this condition.

			Guidelines			Scores		
	Evidence Category	Evidence Type	Default	Range	Max	Points	Tally	PMIDs/Notes
Experimental Evidence	Function	Biochemical Function	0.5	0 - 2	2	0.0	0	
		Protein Interaction	0.5	0 - 2				
		Expression	0.5	0 - 2				
	Functional Alteration	Cells from affected individual	1	0 - 2	2	0.0		
		Engineered cells	0.5	0 - 1				
	Models & Rescue	Animal model	2	0 - 4	4	0.0		
		Cell culture model system	1	0 - 2				
		Rescue in animal model	2	0 - 4				
		Rescue in engineered equivalent	1	0 - 2				
	Total Experimental Evidence Points (Maximum 6)						0	Experimental evidence not evaluated. Since no genetic evidence has been reported, the classification is automatically "No Evidence Reported."

Figure S38: Summary of evidence supporting a relationship between *PMS2* and pancreatic cancer.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points		0	0	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
CALCULATED CLASSIFICATION (DATE)		NO REPORTED EVIDENCE 07/18/2016		
EXPERT CURATION (DATE)		NO REPORTED EVIDENCE 12/01/2016		

Figure S39: Summary matrix and classification for *PMS2* and pancreatic cancer.

PSD3 and autosomal dominant antecubital pterygium syndrome

Genetic Evidence

Case-Level Data

Evidence Type		Case Information Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo			2	0-3	12			
		Proband with predicted or proven null variant			1.5	0-2	10			
		Proband with other variant type with some evidence of gene impact			0.5	0-1.5	7	0.5	0.5	Bayram Y et al. 2016 Feb (26752647)[61] (Only unrelated probands considered.)
	Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant			2	0-3	12			
		Two variants (not predicted/proven null) with some evidence of gene impact in trans			1	0-1.5				
Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7	4.0	4	Bayram Y et al. 2016 Feb (26752647)[61] (LOD score 1.8)
				2	4					
				1.5	3					
				1	1.5					

Case-Control Data

Case-Control Study Type	Case-Control Quality Criteria	Guidelines Points/Study	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
Single Variant Analysis	1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance	0-6	12			
Aggregate Variant Analysis		0-6	12			

Total Genetic Evidence Points (Maximum 12): 4.5

Experimental Evidence

Evidence Category	Evidence Type	Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
Function	Biochemical Function	0.5	0 - 2	2			
	Protein Interaction	0.5	0 - 2				
	Expression	0.5	0 - 2				
Functional Alteration	Cells from affected individual	1	0 - 2	2			
	Engineered cells	0.5	0 - 1				
Models & Rescue	Animal model	2	0 - 4	4			
	Cell culture model system	1	0 - 2				
	Rescue in animal model	2	0 - 4				
	Rescue in engineered equivalent	1	0 - 2				

Total Experimental Evidence Points (Maximum 6): 0

Figure S40: Summary of evidence supporting a relationship between *PSD3* and autosomal dominant antecubital pterygium syndrome.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	4.5	0	4.5	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	LIMITED 06/03/2016		
	EXPERT CURATION (DATE)	LIMITED 11/24/2016		

Figure S41: Summary matrix and classification for *PSD3* and autosomal dominant antecubital pterygium syndrome.

RAD51C and autosomal recessive Fanconi anemia

		Evidence Type		Case Information Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo			2	0-3	12			
				Proband with predicted or proven null variant			1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact			0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant			2	0-3	12		1	Vaz F et al. 2010 May (20400963)[84]
				Two variants (not predicted/proven null) with some evidence of gene impact in trans			1	0-1.5		1.0		
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7	1.0	1	Vaz F et al. 2010 May (20400963)[84]
						2	4					
						1.5	3					
						1	1.5					

		Case-Control Study Type	Case-Control Quality Criteria	Guidelines Points/Study	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
Genetic Evidence	Case-Control Data	Single Variant Analysis	1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance	0-6	12			
		Aggregate Variant Analysis		0-6	12			
		Total Genetic Evidence Points (Maximum 12)					**2**	

	Evidence Category	Evidence Type	Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
Experimental Evidence	Function	Biochemical Function	0.5	0 - 2	2	0.5	0.5	Somyajit K et al. 2012 Jan 27 (22167183)[85]
		Protein Interaction	0.5	0 - 2				
		Expression	0.5	0 - 2				
	Functional Alteration	Cells from affected individual	1	0 - 2	2	3.0	2	Vaz F et al. 2010 May (20400963); Somyajit K et al. 2012 Jan 27 (22167183) [84; 85]
		Engineered cells	0.5	0 - 1				
	Models & Rescue	Animal model	2	0 - 4	4	3.0	3	Vaz F et al. 2010 May (20400963)[84]
		Cell culture model system	1	0 - 2				
		Rescue in animal model	2	0 - 4				
		Rescue in engineered equivalent	1	0 - 2				
	Total Experimental Evidence Points (Maximum 6)						**5.5**	

Figure S42: Summary of evidence supporting a relationship between *RAD51C* and autosomal recessive Fanconi anemia.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	2	5.5	7.5	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	MODERATE 06/01/2016		
	EXPERT CURATION (DATE)	MODERATE 01/05/2017		

Figure S43: Summary matrix and classification for *RAD51C* and autosomal recessive Fanconi anemia.

RAD51D and autosomal dominant hereditary breast cancer

Genetic Evidence	Case-Level Data	Evidence Type		Case Information Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo			2	0-3	12			
				Proband with predicted or proven null variant			1.5	0-2	10	1.0	1	Baker JL et al. 2015 Feb (25445424); Loveday C et al. 2011 Aug 7 (21822267); Pelttari LM et al. 2012 Jul (22652533); Osher DJ et al. 2012 Apr 10 (22415235)[86-89] (Due to the common nature of the disease, opting to give 0.1 points per case.)
				Proband with other variant type with some evidence of gene impact			0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant			2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans			1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7			
						2	4					
						1.5	3					
						1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria			Guidelines Points/Study		Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance			0-6		12			
		Aggregate Variant Analysis					0-6		12			
		Total Genetic Evidence Points (Maximum 12)									4.5	
Experimental Evidence		Evidence Category		Evidence Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Function		Biochemical Function			0.5	0 - 2	2	1.5	1.5	Schild D et al. 2000 Jun 2 (10749867); Martin RW et al. 2007 Oct 15 (17942895)[90; 91]
				Protein Interaction			0.5	0 - 2				
				Expression			0.5	0 - 2				
		Functional Alteration		Cells from affected individual			1	0 - 2	2			
				Engineered cells			0.5	0 - 1				
		Models & Rescue		Animal model			2	0 - 4	4	2.0	2	Smiraldo PG et al. 2005 Mar 15 (15781618)[92]
				Cell culture model system			1	0 - 2				
				Rescue in animal model			2	0 - 4				
				Rescue in engineered equivalent			1	0 - 2				
		Total Experimental Evidence Points (Maximum 6)									3.5	

Figure S44: Summary of evidence for a relationship between *RAD51D* and autosomal dominant hereditary breast cancer.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	1	3.5	4.5	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	YES	Dowty JG et al. 2008 Nov (18058226); Jara L et al. 2010 Aug (20054644); Wickramanayake A et al. 2012 Dec (22986143); Gutiérrez-Enríquez S et al. 2014 May 1 (24130102)[93-96] (These studies have reported OR/HR that indicate no association between RAD51D and breast cancer, or found any truncating variants in breast cancer-only cases/families.)		
	CALCULATED CLASSIFICATION (DATE)	CONFLICTING EVIDENCE REPORTED		
EXPERT CURATION (DATE)		LIMITED 12/01/2016		

Figure S45: Summary matrix and classification for *RAD51D* and autosomal dominant hereditary breast cancer. The discrepancy between the experts and original biocurators is due to interpretation of the case-control studies. According to the experts consulted, current studies are not large enough to address the question of whether or not variants in *RAD51D* are relevant to breast cancer. Experimental evidence shows a link between *RAD51D* and homologous recombination, a function of other genes, such as *BRCA1* and *BRCA2*, known to be involved in hereditary breast cancer.

RPS10 and autosomal dominant Diamond-Blackfan anemia

Genetic Evidence	Case-Level Data	Evidence Type		Case Information Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo			2	0-3	12	4.0	4	Doherty L et al. 2010 Feb 12 (20116044); Smetanina NS et al. 2015 Sep (25946618)[97; 98]
				Proband with predicted or proven null variant			1.5	0-2	10	10.0	10	Doherty L et al. 2010 Feb 12 (20116044); Smetanina NS et al. 2015 Sep (25946618); Yazaki M et al. 2012 May (22510774)[97-99]
				Proband with other variant type with some evidence of gene impact			0.5	0-1.5	7	0.0	0	
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant			2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans			1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7			
						2	4					
						1.5	3					
						1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria			Guidelines Points/Study		Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance			0-6		12			
		Aggregate Variant Analysis					0-6		12			
		Total Genetic Evidence Points (Maximum 12)									12	
Experimental Evidence		Evidence Category		Evidence Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Function		Biochemical Function			0.5	0 - 2	2	1.5	1.5	Havugimana PC et al. 2012 Aug 31 (22939629); Kristensen AR et al. 2012 Sep (22863883); Doherty L et al. 2010 Feb 12 (20116044)[97; 100; 101]
				Protein Interaction			0.5	0 - 2				
				Expression			0.5	0 - 2				
		Functional Alteration		Cells from affected individual			1	0 - 2	2			
				Engineered cells			0.5	0 - 1				
		Models & Rescue		Animal model			2	0 - 4	4			
				Cell culture model system			1	0 - 2				
				Rescue in animal model			2	0 - 4				
				Rescue in engineered equivalent			1	0 - 2				
		Total Experimental Evidence Points (Maximum 6)									1.5	

Figure S46: Summary of evidence supporting a relationship between *RPS10* and autosomal dominant Diamond-Blackfan anemia.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	12	1.5	13.5	YES
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	DEFINITIVE 07/04/2016		
	EXPERT CURATION (DATE)	DEFINITIVE 01/19/2017		

Figure S47: Summary matrix and classification for *RPS10* and autosomal dominant Diamond-Blackfan anemia.

RPS24 and autosomal dominant Diamond-Blackfan anemia

						Guidelines			Scores		PMIDs/Notes
		Evidence Type		Case Information Type		Default	Range	Max	Points	Tally	
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo		2	0-3	12	6.0	6	Quarello P et al. 2010 Feb (19773262); Landowski M et al. 2013 Nov (23812780); Smetanina NS et al. 2015 Sep (25946618)[98; 102; 103]
				Proband with predicted or proven null variant		1.5	0-2	10	4.5	4.5	Gazda HT et al. 2006 Dec (17186470)[104]
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples 3	5	0-7	7			
					2	4					
					1.5	3					
					1	1.5					
						Guidelines			Scores		PMIDs/Notes
		Case-Control Study Type		Case-Control Quality Criteria		Points/Study		Max	Points	Tally	
	Case-Control Data	Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance		0-6		12			
		Aggregate Variant Analysis				0-6		12			
									Total Genetic Evidence Points (Maximum 12)	10.5	
		Evidence Category		Evidence Type		Guidelines			Scores		PMIDs/Notes
						Default	Range	Max	Points	Tally	
Experimental Evidence		Function		Biochemical Function		0.5	0 - 2	2	1.5	1.5	Choesmel V et al. 2008 May 1 (18230666); Havugimana PC et al. 2012 Aug 31 (22939629); Gazda HT et al. 2006 Dec (17186470)[100; 104; 105]
				Protein Interaction		0.5	0 - 2				
				Expression		0.5	0 - 2				
		Functional Alteration		Cells from affected individual		1	0 - 2	2	2.0	2	Choesmel V et al. 2008 May 1 (18230666)[105]
				Engineered cells		0.5	0 - 1				
		Models & Rescue		Animal model		2	0 - 4	4			
				Cell culture model system		1	0 - 2				
				Rescue in animal model		2	0 - 4				
				Rescue in engineered equivalent		1	0 - 2				
									Total Experimental Evidence Points (Maximum 6)	3.5	

Figure S48: Summary of evidence supporting a relationship between *RPS24* and autosomal dominant Diamond-Blackfan anemia.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	10.5	3.5	14	YES
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	DEFINITIVE 07/04/2016		
	EXPERT CURATION (DATE)	DEFINITIVE 01/17/2017		

Figure S49: Summary matrix and classification for *RPS24* and autosomal dominant Diamond-Blackfan anemia.

SCN4B and autosomal dominant Long QT Syndrome

						Guidelines			Scores		
		Evidence Type		Case Information Type		Default	Range	Max	Points	Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo		2	0-3	12			
				Proband with predicted or proven null variant		1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7	1.0	1	Medeiros-Domingo A et al. 2007 Jul 10 (17592081)[106] (Only unrelated probands considered.)
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples 3	5	0-7	7	1.0	1	Medeiros-Domingo A et al. 2007 Jul 10 (17592081)[106]
					2	4					
					1.5	3					
					1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria		Guidelines			Scores		PMIDs/Notes
						Points/Study		Max	Points	Tally	
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance		0-6		12			
		Aggregate Variant Analysis				0-6		12			
		Total Genetic Evidence Points (Maximum 12)								3	
Experimental Evidence		Evidence Category		Evidence Type		Guidelines			Scores		PMIDs/Notes
						Default	Range	Max	Points	Tally	
		Function		Biochemical Function		0.5	0 - 2	2	1.0	1	Medeiros-Domingo A et al. 2007 Jul 10 (17592081)[106] (8x increase in late sodium current by mutant form)
				Protein Interaction		0.5	0 - 2				
				Expression		0.5	0 - 2				
		Functional Alteration		Cells from affected individual		1	0 - 2	2			
				Engineered cells		0.5	0 - 1				
		Models & Rescue		Animal model		2	0 - 4	4			
				Cell culture model system		1	0 - 2				
				Rescue in animal model		2	0 - 4				
				Rescue in engineered equivalent		1	0 - 2				
		Total Experimental Evidence Points (Maximum 6)								1	

Figure S50: Summary of evidence supporting a relationship between *SCN4B* and autosomal dominant Long QT Syndrome.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	2	1	3	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
CALCULATED CLASSIFICATION (DATE)		LIMITED 06/14/2016		
EXPERT CURATION (DATE)		LIMITED 12/15/16		

Figure S51: Summary matrix and classification for *SCN4B* and autosomal dominant Long QT Syndrome.

SKI and autosomal dominant Shprintzen-Goldberg syndrome

Genetic Evidence	Case-Level Data	Evidence Type		Case Information Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo			2	0-3	12	12.0	12	Carmignac V et al. 2012 Nov 2 (23103230); Doyle AJ et al. 2012 Nov (23023332)[107; 108]
				Proband with predicted or proven null variant			1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact			0.5	0-1.5	7	5.0	5	Doyle AJ et al. 2012 Nov (23023332); Carmignac V et al. 2012 Nov 2 (23103230)[107; 108]
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant			2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans			1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7	2.0	2	Carmignac V et al. 2012 Nov 2 (23103230)[107]
						2	4					
						1.5	3					
						1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria			Guidelines Points/Study		Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance			0-6		12			
		Aggregate Variant Analysis					0-6		12			
		Total Genetic Evidence Points (Maximum 12)									16.5	Additional genetic evidence available beyond 12 point maximum score.
Experimental Evidence		Evidence Category		Evidence Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
		Function		Biochemical Function			0.5	0 - 2	2	1.5	1.5	Doyle AJ et al. 2012 Nov (23023332)[108]
				Protein Interaction			0.5	0 - 2				
				Expression			0.5	0 - 2				
		Functional Alteration		Cells from affected individual			1	0 - 2	2	1.0	1	Doyle AJ et al. 2012 Nov (23023332)[108]
				Engineered cells			0.5	0 - 1				
		Models & Rescue		Animal model			2	0 - 4	4	2.0	2	Doyle AJ et al. 2012 Nov (23023332)[108]
				Cell culture model system			1	0 - 2				
				Rescue in animal model			2	0 - 4				
				Rescue in engineered equivalent			1	0 - 2				
		Total Experimental Evidence Points (Maximum 6)									4.5	Additional experimental data may be available.

Figure S52: Summary of evidence supporting a relationship between *SKI* and autosomal dominant Shprintzen-Goldberg syndrome.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	12	4.5	16.5	YES
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	DEFINITIVE 06/02/2016		
	EXPERT CURATION (DATE)	DEFINITIVE 12/01/2016		

Figure S53: Summary matrix and classification for *SKI* and autosomal dominant Shprintzen-Goldberg syndrome.

SMAD3 and autosomal dominant aneurysm-osteoarthritis syndrome

Genetic Evidence

Case-Level Data

Evidence Type		Case Information Type			Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo			2	0-3	12			
		Proband with predicted or proven null variant			1.5	0-2	10	5.0	5	van de Laar IM et al. 2011 Feb (21217753); Regalado ES et al. 2011 Sep 2 (21778426); van de Laar IM et al. 2012 Jan (22167769)[109-111]
		Proband with other variant type with some evidence of gene impact			0.5	0-1.5	7	4.0	4	van de Laar IM et al. 2011 Feb (21217753); Regalado ES et al. 2011 Sep 2 (21778426); van de Laar IM et al. 2012 Jan (22167769)[109-111]
	Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant			2	0-3	12			
		Two variants (not predicted/proven null) with some evidence of gene impact in trans			1	0-1.5				
Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5	0-7	7	7.0	7	van de Laar IM et al. 2011 Feb (21217753); Regalado ES et al. 2011 Sep 2 (21778426)[109; 110]
				2	4					
				1.5	3					
				1	1.5					

Case-Control Data

Case-Control Study Type	Case-Control Quality Criteria	Guidelines Points/Study	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
Single Variant Analysis	1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance	0-6	12			
Aggregate Variant Analysis		0-6	12			

Total Genetic Evidence Points (Maximum 12)	17	Additional genetic evidence is available, but not curated due to achievement of maximum genetic evidence score.

Experimental Evidence

Evidence Category	Evidence Type	Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
Function	Biochemical Function	0.5	0 - 2	2	1.0	1	Verrecchia F et al. 2007 Jun 14 (17589920); van de Laar IM et al. 2011 Feb (21217753)[109; 112]
	Protein Interaction	0.5	0 - 2				
	Expression	0.5	0 - 2				
Functional Alteration	Cells from affected individual	1	0 - 2	2			
	Engineered cells	0.5	0 - 1				
Models & Rescue	Animal model	2	0 - 4	4	4.0	4	Yang X et al. 2001 Apr 2 (11285272); Tan CK et al. 2013 Jun 19 (23782924)[113; 114]
	Cell culture model system	1	0 - 2				
	Rescue in animal model	2	0 - 4				
	Rescue in engineered equivalent	1	0 - 2				

Total Experimental Evidence Points (Maximum 6)	5	

Figure S54: Summary of evidence supporting a relationship between *SMAD3* and autosomal dominant aneurysm-osteoarthritis syndrome.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	12	5	17	YES
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	DEFINITIVE 03/30/2016		
	EXPERT CURATION (DATE)	DEFINITIVE 12/01/2016		

Figure S55: Summary matrix and classification for *SMAD3* and autosomal dominant aneurysm-osteoarthritis syndrome.

SMARCA1 and autosomal dominant syndromic intellectual disability with Coffin-Syris-like features

						Guidelines			Scores		
		Evidence Type		Case Information Type		Default	Range	Max	Points	Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo		2	0-3	12			
				Proband with predicted or proven null variant		1.5	0-2	10	1.5	1.5	Karaca E et al. 2015 Nov 4 (26539891)[115]
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples 3	5	0-7	7			
					2	4					
					1.5	3					
					1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria		Guidelines			Scores		PMIDs/Notes
						Points/Study		Max	Points	Tally	
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance		0-6		12			
		Aggregate Variant Analysis				0-6		12			
		Total Genetic Evidence Points (Maximum 12)								1.5	
Experimental Evidence		Evidence Category		Evidence Type		Guidelines			Scores		PMIDs/Notes
						Default	Range	Max	Points	Tally	
		Function		Biochemical Function		0.5	0 - 2	2	1.0	1	Lopes F et al. 2016 Mar (26740508)[116]
				Protein Interaction		0.5	0 - 2				
				Expression		0.5	0 - 2				
		Functional Alteration		Cells from affected individual		1	0 - 2	2			
				Engineered cells		0.5	0 - 1				
		Models & Rescue		Animal model		2	0 - 4	4	2.0	2	Lopes F et al. 2016 Mar (26740508)[116]
				Cell culture model system		1	0 - 2				
				Rescue in animal model		2	0 - 4				
				Rescue in engineered equivalent		1	0 - 2				
		Total Experimental Evidence Points (Maximum 6)								3	

Figure S56: Summary of evidence supporting a relationship between *SMARCA1* and autosomal dominant syndromic intellectual disability with Coffin-Syris-like features.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	1.5	3	4.5	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	LIMITED 06/14/2016		
	EXPERT CURATION (DATE)	MODERATE 11/15/2016		

Figure S57: Summary matrix and classification for *SMARCA1* and autosomal dominant syndromic intellectual disability with Coffin-Syris-like features.

SOS2 and autosomal dominant Noonan syndrome

						Guidelines			Scores		
		Evidence Type		Case Information Type		Default	Range	Max	Points	Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo		2	0-3	12	4.0	4	Yamamoto GL et al. 2015 Jun (25795793); Cordeddu V et al. 2015 Nov (26173643)[117; 118]
				Proband with predicted or proven null variant		1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7	3.0	3	Yamamoto GL et al. 2015 Jun (25795793); Cordeddu V et al. 2015 Nov (26173643)[117; 118]
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples 3	5	0-7	7			
					2	4					
					1.5	3					
					1	1.5					
						Guidelines			Scores		
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria		Points/Study		Max	Points	Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance		0-6		12			
		Aggregate Variant Analysis				0-6		12			
									Total Genetic Evidence Points (Maximum 12)		7

			Guidelines			Scores		
	Evidence Category	Evidence Type	Default	Range	Max	Points	Tally	PMIDs/Notes
Experimental Evidence	Function	Biochemical Function	0.5	0 - 2	2	0.5	0.5	Cordeddu V et al. 2015 Nov (26173643)[118]
		Protein Interaction	0.5	0 - 2				
		Expression	0.5	0 - 2				
	Functional Alteration	Cells from affected individual	1	0 - 2	2	0.5	0.5	Cordeddu V et al. 2015 Nov (26173643)[118]
		Engineered cells	0.5	0 - 1				
	Models & Rescue	Animal model	2	0 - 4	4	0.0	0	Esteban LM et al. 2000 Sep (10938118)[119] (No points are given. A knock-out mouse described here and this disease mechanism is gain of function.)
		Cell culture model system	1	0 - 2				
		Rescue in animal model	2	0 - 4				
		Rescue in engineered equivalent	1	0 - 2				
						Total Experimental Evidence Points (Maximum 6)		1

Figure S58: Summary of evidence supporting a relationship between *SOS2* and autosomal dominant Noonan syndrome.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	7	1	8	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	MODERATE 05/26/2016		
	EXPERT CURATION (DATE)	MODERATE 12/05/16		

Figure S59: Summary matrix and classification for *SOS2* and autosomal dominant Noonan syndrome.

TMPO and autosomal dominant dilated cardiomyopathy

						Guidelines			Scores		
		Evidence Type		Case Information Type		Default	Range	Max	Points	Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo		2	0-3	12	0.0	0	Taylor MR et al. 2005 Dec (16247757)[120] (c.2068C>T is classified as Benign/Likely Benign by ClinVar submitters.)
				Proband with predicted or proven null variant		1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2	0-3	12			
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1	0-1.5				
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples 3	5	0-7	7			
					2	4					
					1.5	3					
					1	1.5					
						Guidelines			Scores		
		Case-Control Study Type		Case-Control Quality Criteria		Points/Study		Max	Points	Tally	PMIDs/Notes
	Case-Control Data	Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance		0-6		12			
		Aggregate Variant Analysis				0-6		12			
									Total Genetic Evidence Points (Maximum 12)		0
						Guidelines			Scores		
		Evidence Category		Evidence Type		Default	Range	Max	Points	Tally	PMIDs/Notes
Experimental Evidence		Function		Biochemical Function		0.5	0 - 2	2	0.5	0.5	Taylor MR et al. 2005 Dec (16247757) [120] (Interaction of mutated protein product with A-type Lamins)
				Protein Interaction		0.5	0 - 2				
				Expression		0.5	0 - 2				
		Functional Alteration		Cells from affected individual		1	0 - 2	2			
				Engineered cells		0.5	0 - 1				
		Models & Rescue		Animal model		2	0 - 4	4			
				Cell culture model system		1	0 - 2				
				Rescue in animal model		2	0 - 4				
				Rescue in engineered equivalent		1	0 - 2				
									Total Experimental Evidence Points (Maximum 6)		0.5

Figure S60: Summary of evidence for a relationship between *TMPO* and autosomal dominant dilated cardiomyopathy.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points		**0.5**	**0.5**	**NO**
CALCULATED CLASSIFICATION		**LIMITED**	**1-6**	
		MODERATE	**7-11**	
		STRONG	**12-18**	
		DEFINITIVE	**12-18 AND replication over time**	
Valid contradictory evidence (Y/N)*	YES	Taylor MR et al. 2005 Dec (16247757) [120] (The only variant that has been reported in association with human disease has been found at high publication frequency in ExAC.[7])		
CALCULATED CLASSIFICATION (DATE)		**CONFLICTING EVIDENCE REPORTED 10/07/16**		
EXPERT CURATION (DATE)		**REFUTED 11/30/2016**		

Figure S61: Summary matrix and classification for *TMPO* and autosomal dominant dilated cardiomyopathy.

VPS8 and autosomal recessive arthrogryposis

						Guidelines			Scores		
		Evidence Type		Case Information Type		Default	Range	Max	Points	Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo		2	0-3	12			
				Proband with predicted or proven null variant		1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2	0-3	12	0.0	0.5	Bayram Y et al. 2016 Feb (26752647)[61]
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1	0-1.5		0.5		
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples 3	5	0-7	7			
					2	4					
					1.5	3					
					1	1.5					
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria		Points/Study		Max	Points	Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance		0-6		12			
		Aggregate Variant Analysis				0-6		12			
		Total Genetic Evidence Points (Maximum 12)								0.5	
Experimental Evidence		Evidence Category		Evidence Type		Default	Range	Max	Points	Tally	PMIDs/Notes
		Function		Biochemical Function		0.5	0 - 2	2	1.5	1.5	Horazdovsky BF et al. 1996 Dec 27 (8969229); Epp N et al. 2013 (23840658)[121; 122]
				Protein Interaction		0.5	0 - 2				
				Expression		0.5	0 - 2				
		Functional Alteration		Cells from affected individual		1	0 - 2	2	0.0	0	
				Engineered cells		0.5	0 - 1				
		Models & Rescue		Animal model		2	0 - 4	4	0.0	0	
				Cell culture model system		1	0 - 2				
				Rescue in animal model		2	0 - 4				
				Rescue in engineered equivalent		1	0 - 2				
		Total Experimental Evidence Points (Maximum 6)								1.5	

Figure S62: Summary of evidence supporting a relationship between *VPS8* and autosomal recessive arthrogryposis.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	0.5	1.5	2	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
CALCULATED CLASSIFICATION (DATE)		LIMITED		
EXPERT CURATION (DATE)		LIMITED 11/24/2016		

Figure S63: Summary matrix and classification for *VPS8* and autosomal recessive arthrogryposis.

WRAP53 and autosomal recessive dyskeratosis congenital

						Guidelines			Scores		
		Evidence Type		Case Information Type		Default	Range	Max	Points	Tally	PMIDs/Notes
Genetic Evidence	Case-Level Data	Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo		2	0-3	12			
				Proband with predicted or proven null variant		1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7			
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2	0-3	12		3.5	Zhong F et al. 2011 Jan 1 (21205863)[123] (The expert chose to upgrade the variant points because of the specificity of the phenotype.)
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1	0-1.5		3.5		
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples 3	5	0-7	7			
					2	4					
					1.5	3					
					1	1.5					
						Guidelines			Scores		
	Case-Control Data	Case-Control Study Type		Case-Control Quality Criteria		Points/Study		Max	Points	Tally	PMIDs/Notes
		Single Variant Analysis		1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance		0-6		12			
		Aggregate Variant Analysis				0-6		12			
									Total Genetic Evidence Points (Maximum 12)		3.5

			Guidelines			Scores		
	Evidence Category	Evidence Type	Default	Range	Max	Points	Tally	PMIDs/Notes
Experimental Evidence	Function	Biochemical Function	0.5	0 - 2	2	2.5	2	Freund A et al. 2014 Dec 4 (25467444); Zhong F et al. 2011 Jan 1 (21205863); Mahmoudi S et al. 2010 Nov 2 (21072240)[74; 123; 124]
		Protein Interaction	0.5	0 - 2				
		Expression	0.5	0 - 2				
	Functional Alteration	Cells from affected individual	1	0 - 2	2	3.5	2	Zhong F et al. 2011 Jan 1 (21205863); Batista LF et al. 2011 May 22 (21602826)[123; 125]
		Engineered cells	0.5	0 - 1				
	Models & Rescue	Animal model	2	0 - 4	4	2.0	2	Zhong F et al. 2011 Jan 1 (21205863); Mahmoudi S et al. 2010 Nov 2 (21072240)[123; 125]
		Cell culture model system	1	0 - 2				
		Rescue in animal model	2	0 - 4				
		Rescue in engineered equivalent	1	0 - 2				
						Total Experimental Evidence Points (Maximum 6)		6

Figure S64: Summary of evidence supporting a relationship between *WRAP53* and autosomal recessive dyskeratosis congenital.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	3.5	6	9.5	NO
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
CALCULATED CLASSIFICATION (DATE)		MODERATE		
MODIFY CALCULATED CLASSIFICATION		YES		
CURATOR CLASSIFICATION (DATE)		LIMITED 08/04/2016		
EXPERT CURATION (DATE)		MODERATE 01/25/2017		

Figure S65: Summary matrix and classification for *WRAP53* and autosomal recessive dyskeratosis congenital. This gene/disease relationship was initially classified as limited by the curator. During expert review, the expert added more experimental evidence and it was increased to moderate.

Supplemental References

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