Clinical Validity of Expanded Carrier Screening: Evaluating the Gene-Disease Relationship in more than 200 Conditions

Marie Balzotti
Clinical Genomics Scientist, Myriad Genetics

Presented at ACMG on March 18, 2020

ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

Financial Disclosure

All authors are current or former employees of Myriad Genetics or Baylor Genetics.

ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

Introduction

- The purpose of carrier screening is to determine whether couples are at high risk of having children affected with serious genetic conditions.
- Expanded carrier screening (ECS) is an acceptable testing strategy for pre-pregnancy and prenatal screening.
- Broader guideline support and payer adoption requires evidence of gene-disease association.

Objective

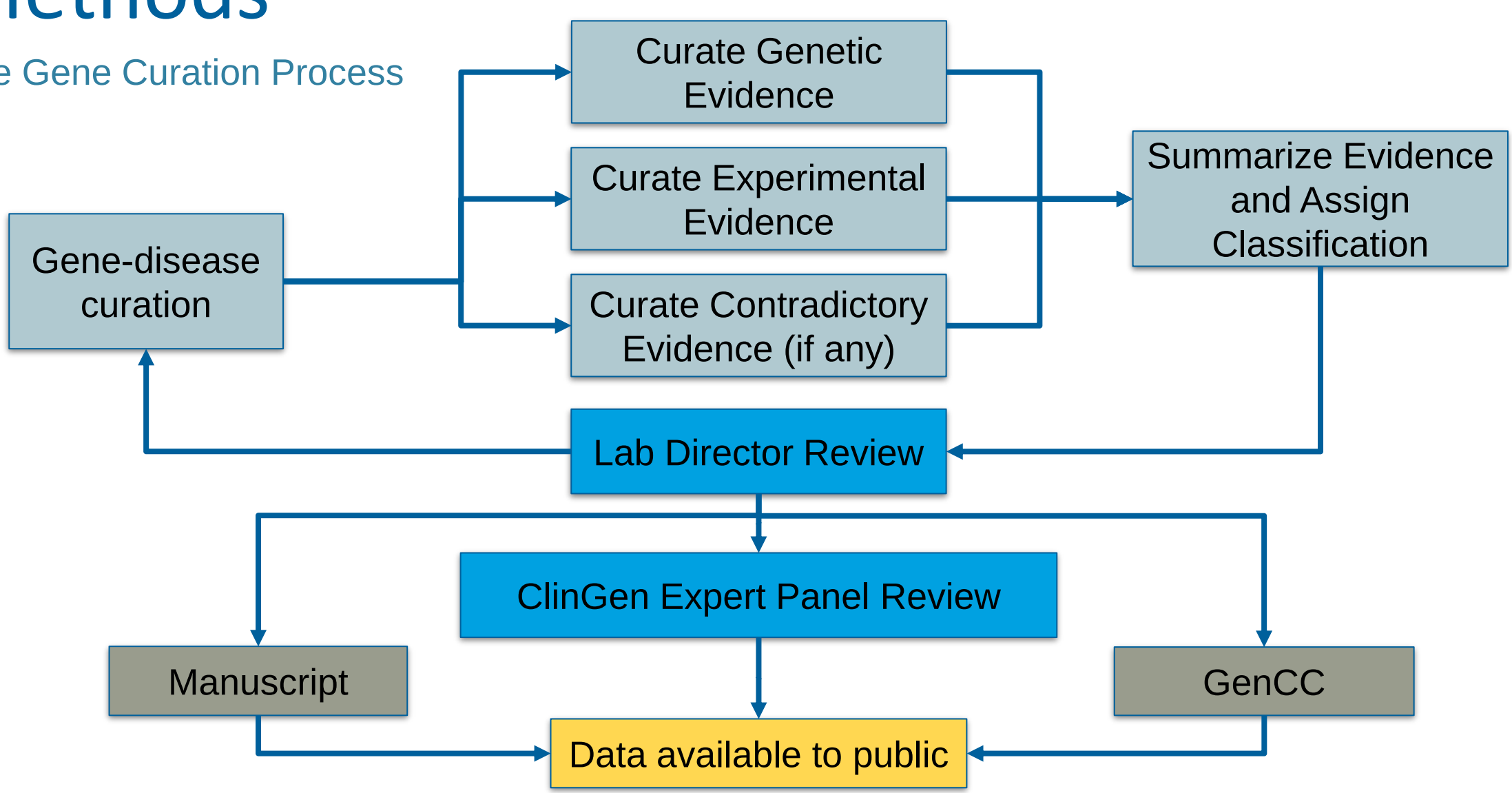
Apply a standardized framework for evaluation of gene-disease association to assess the clinical validity of conditions screened by ECS panels.

Methods

- The Clinical Genome Resource (ClinGen) gene curation framework was used to assess 208 genes and conditions:
  - Twenty-one conditions were previously classified by ClinGen
  - The remaining 187 were evaluated by curation teams at Myriad and Baylor.
- Concordance was evaluated on a subset of conditions.
- Myriad also evaluated nine rare recessive conditions not typically screened for ECS.

Methods

The Gene Curation Process



Methods

Evidence types

	Evidence Type		Case Information			Suggested Points/Case: Default	Suggested Points/Case: Range	Points Given	Max Score
Case-Level Data[A]	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
		Autosomal Recessive	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]			Suggested Points/Study		Points Given	Max Score
	Single Variant Analysis[Ha]		• Variant Detection Methodology[Ia] • Power[Ib]			0-6			12
	Aggregate Variant Analysis[Hb]		• Bias and Confounding Factors[Ic] • Statistical Significance[Id]			0-6			
TOTAL ALLOWABLE POINTS for Genetic Evidence									12

Evidence Category	Evidence Type	Suggested Points: Default	Suggested Points: Range	Points Given	Max Score
Function	Biochemical Function	0.5	0-2		2
	Protein Interaction		0-2		
	Expression		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 Allowable Points for Experimental Evidence					6

Strande et. al., AJHG 100(6), 895-906 (2017)

Methods

Evidence types

	Evidence Type		Case Information			Suggested Points/Case: Default	Suggested Points/Case: Range	Points Given	Max Score
Case-Level Data[A]	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
		Autosomal Recessive	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]			Suggested Points/Study		Points Given	Max Score
	Single Variant Analysis[Ha]		• Variant Detection Methodology[Ia] • Power[Ib]			0-6			12
	Aggregate Variant Analysis[Hb]		• Bias and Confounding Factors[Ic] • Statistical Significance[Id]			0-6			
TOTAL ALLOWABLE POINTS for Genetic Evidence									12

Evidence Category	Evidence Type	Suggested Points: Default	Suggested Points: Range	Points Given	Max Score
Function	Biochemical Function	0.5	0-2		2
	Protein Interaction		0-2		
	Expression		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 Allowable Points for Experimental Evidence					6

Strande et. al., AJHG 100(6), 895-906 (2017)

Methods

Evidence types

	Evidence Type		Case Information			Suggested Points/Case: Default	Suggested Points/Case: Range	Points Given	Max Score
Case-Level Data[A]	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
		Autosomal Recessive	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]			Suggested Points/Study		Points Given	Max Score
	Single Variant Analysis[Ha]		• Variant Detection Methodology[Ia] • Power[Ib]			0-6			12
	Aggregate Variant Analysis[Hb]		• Bias and Confounding Factors[Ic] • Statistical Significance[Id]			0-6			
TOTAL ALLOWABLE POINTS for Genetic Evidence									12

Evidence Category	Evidence Type	Suggested Points: Default	Suggested Points: Range	Points Given	Max Score
Function	Biochemical Function	0.5	0-2		2
	Protein Interaction		0-2		
	Expression		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 Allowable Points for Experimental Evidence					6

Strande et. al., AJHG 100(6), 895-906 (2017)

Methods

Evidence types

	Evidence Type		Case Information			Suggested Points/Case: Default	Suggested Points/Case: Range	Points Given	Max Score
Case-Level Data[A]	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
		Autosomal Recessive	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]			Suggested Points/Study		Points Given	Max Score
	Single Variant Analysis[Ha]		• Variant Detection Methodology[Ia] • Power[Ib] • Bias and Confounding Factors[Ic] • Statistical Significance[Id]			0-6			12
	Aggregate Variant Analysis[Hb]					0-6			
TOTAL ALLOWABLE POINTS for Genetic Evidence									12

Evidence Category	Evidence Type	Suggested Points: Default	Suggested Points: Range	Points Given	Max Score
Function	Biochemical Function	0.5	0-2		2
	Protein Interaction		0-2		
	Expression		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 Allowable Points for Experimental Evidence					6

Strande et. al., AJHG 100(6), 895-906 (2017)

Methods

Evidence types

	Evidence Type		Case Information			Suggested Points/Case: Default	Suggested Points/Case: Range	Points Given	Max Score
Case-Level Data[A]	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
		Autosomal Recessive	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]			Suggested Points/Study		Points Given	Max Score
	Single Variant Analysis[Ha]		• Variant Detection Methodology[Ia] • Power[Ib]			0-6			12
	Aggregate Variant Analysis[Hb]		• Bias and Confounding Factors[Ic] • Statistical Significance[Id]			0-6			
TOTAL ALLOWABLE POINTS for Genetic Evidence									12

Evidence Category	Evidence Type	Suggested Points: Default	Suggested Points: Range	Points Given	Max Score
Function	Biochemical Function	0.5	0-2		2
	Protein Interaction		0-2		
	Expression		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 Allowable Points for Experimental Evidence					6

Strande et. al., AJHG 100(6), 895-906 (2017)

Methods

Clinical Validity Classifications

- Definitive
- Strong
- Moderate
- Limited

Supportive evidence

- No reported evidence

- Disputed
- Refuted

Contradictory evidence

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 publications with convincing evidence over time (>3 yrs)
Assigned Points				
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 & Replicated Over Time	
Valid contradictory evidence (Y/N)*	List references and describe evidence:			
CURATOR CLASSIFICATION				
FINAL CLASSIFICATION				

Strande et. al., AJHG 100(6), 895-906 (2017)

Genetic Evidence Summary

	Evidence Type		Case Information			Suggested Default	Suggested Range	Points Given	Max Score	PMIDs/Notes
Case-Level Data	Variant Evidence	Autosomal dominant disease, OR X-linked disease, affected males	Variant is *de novo*			2	0-3	0	12	
			Proband with predicted or proven null variant			1.5	0-2	0	10	
			oband with other variant type with some evidence of gene impa			0.5	0-1.5	0	7	
		Autosomal recessive disease, OR X-linked disease, affected females	Two variants in *trans*, at least one is LOF or *de novo*			2	0-3	14.5	12	19232495, 25205138, 24725366, 21798101,
			Two non-LOF variants in *trans*			1	0-1.5	0		
	Segregation Evidence		Evidence of Segregation in one or more families		Sequencing Method			0	3	
				Total LOD Score	Candidate Gene Sequencing	Exome/Genome or all genes sequenced in linkage region				
				2-2.99	0.5	1				
				3-4.99	1	2				
				≥5	1.5	3				

	Case-Control Study Type	Case-Control Quality Criteria	Suggested points/study	Points Given	Max Score
Case-Control Data	Single Variant Analysis	Variant Detection Methodology	0-6	0	12
		Power			
	Aggregate Variant Analysis	Bias and Confounding Factors	0-6	0	
		Statistical Significance			
			Total Genetic Evidence Points (Maximum 12):	12	12

An Example:

NEB – Nemaline myopathy

Experimental Evidence Summary

Evidence Category	Evidence Type	Suggested Default	Suggested Range	Points Given	Max Score	
Function	Biochemical Function	0.5	0-2	0	2	
	Protein Interaction	0.5	0-2	0.5		25110572
	Expression	0.5	0-2	1		15266303, 22941678
Functional Alteration	Patient Cells	1	0-2	1	2	19944167
	Non-Patient Cells	0.5	0-1	0		
Models	Non-human model organism	2	0-4	5	4	22159874, 27215641, 16902413
	Cell culture model	1	0-2	0		
Rescue	Rescue in human	2	0-4	0		
	Rescue in non-human model organism	2	0-4	0		
	Rescue in cell culture model	1	0-2	0		
	Rescue in Patient Cells	1	0-2	0		
	Total Experimental Evidence Points (Maximum 6):			6	6	

Strande et. al., AJHG 100(6), 895-906 (2017)

Summary Matrix				
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 supports the gene-disease association	Sum of Genetic & Experimental Evidence	>2 publications with convincing evidence over time (>3 years)
Assigned Points	12	6	18	Y
Calculated Classification		Limited	1-6	
		Moderate	7-11	
		Strong	12-18	
		Definitive	12-18 AND replication over time	
Valid Contradictory Evidence (Y/N)	List PMIDs and describe evidence:			
Calculated Curator Classification:		Definitive	Date:	10/8/2018
Comments:				
LD Classification:		Definitive	Date:	11/15/18
Final Expert Classification:			Date:	

Strande et. al., AJHG 100(6), 895-906 (2017)

Summary Matrix				
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 supports the gene-disease association	Sum of Genetic & Experimental Evidence	>2 publications with convincing evidence over time (>3 years)
Assigned Points	12	6	18	Y
Calculated Classification		Limited	1-6	
		Moderate	7-11	
		Strong	12-18	
		Definitive	12-18 AND replication over time	
Valid Contradictory Evidence (Y/N)	List PMIDs and describe evidence:			
Calculated Curator Classification:		Definitive	Date:	10/8/2018
Comments:				
LD Classification:		Definitive	Date:	11/15/18
Final Expert Classification:			Date:	

Strande et. al., AJHG 100(6), 895-906 (2017)

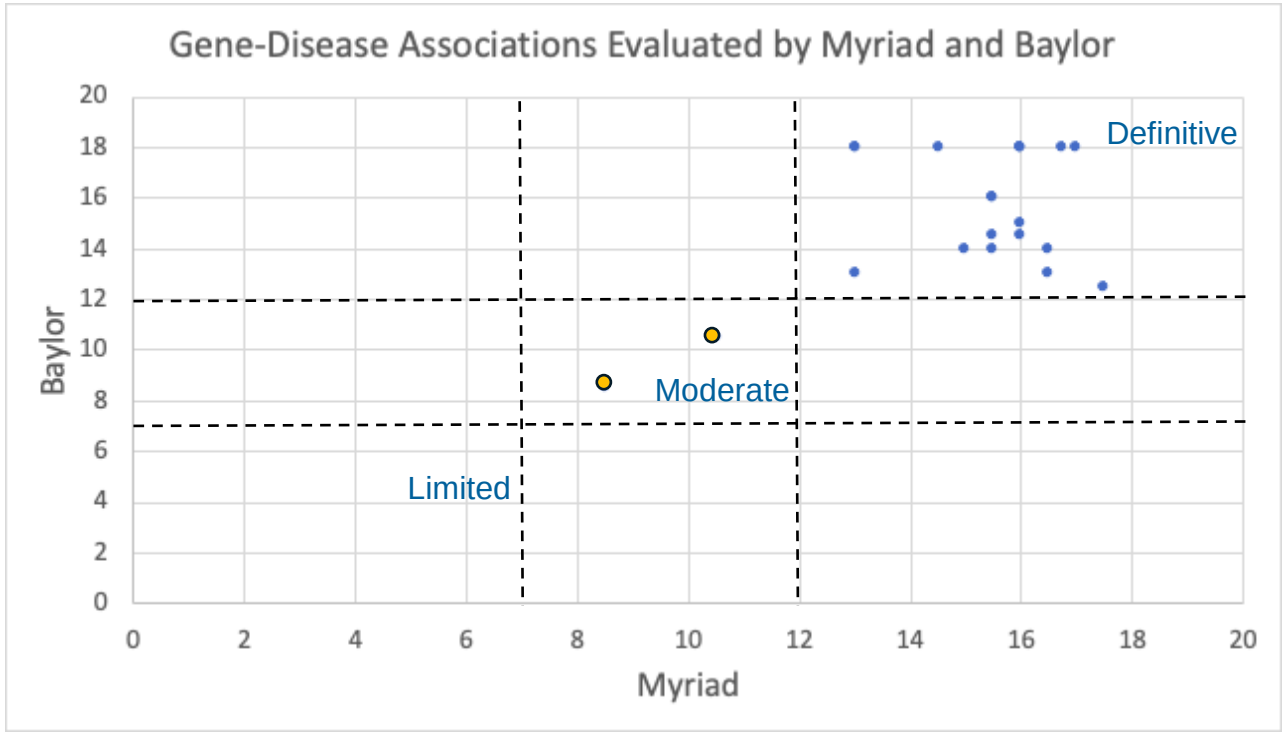
Results

- All 208 evaluated conditions met the evidence threshold for supporting a gene-disease association.
- 203 of 208 (98%) achieved the strongest ('Definitive') level of gene-disease association.
- Rare conditions predominantly showed 'Moderate' evidence.

	Definitive	Strong	Moderate	Limited	No Evidence	Disputed	Refuted	Total
ECS Panel	203	0	4	1	0	0	0	208
Rare Conditions	1	2	4	2	0	0	0	9

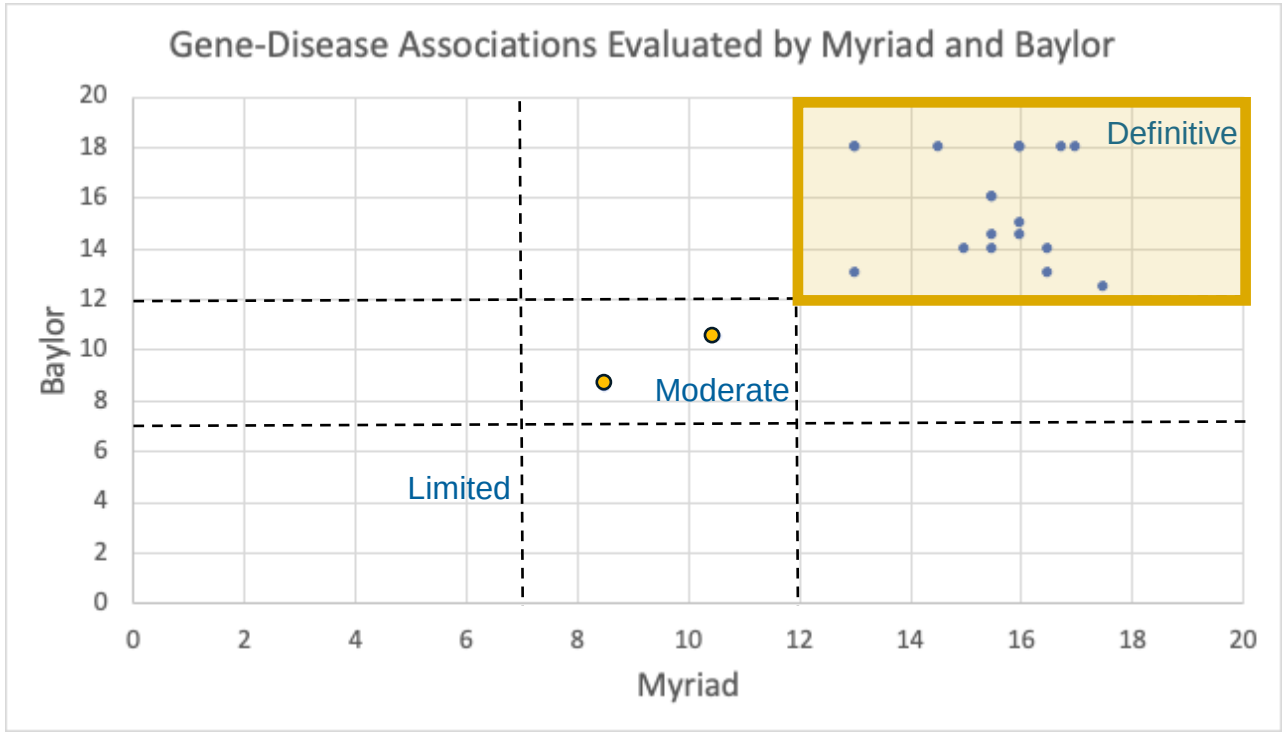
Results

- Conditions evaluated by both commercial laboratories were similarly classified.



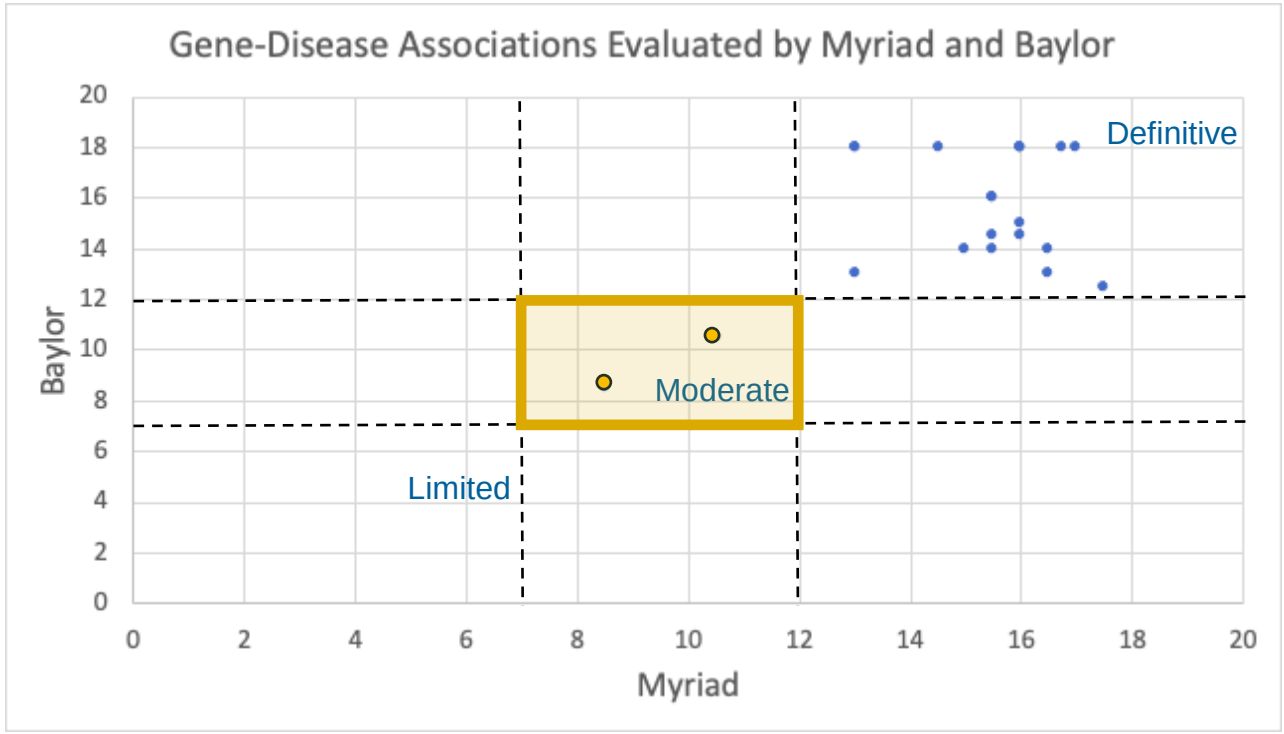
Results

- Conditions evaluated by both commercial laboratories were similarly classified.



Results

- Conditions evaluated by both commercial laboratories were similarly classified.



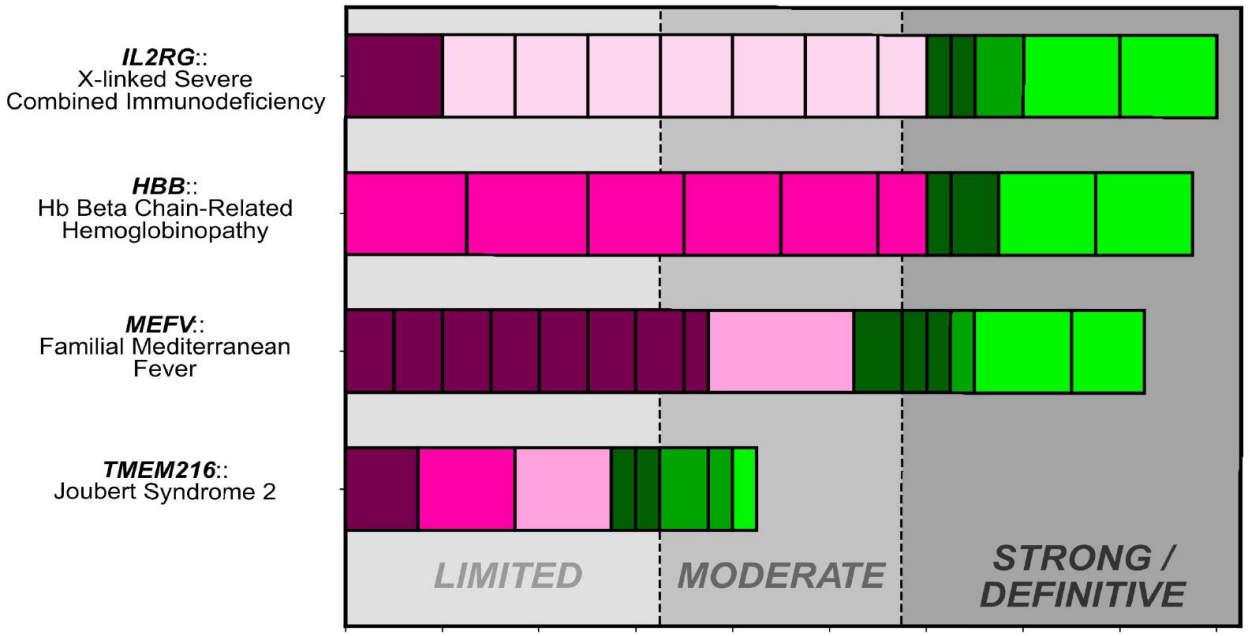
Results

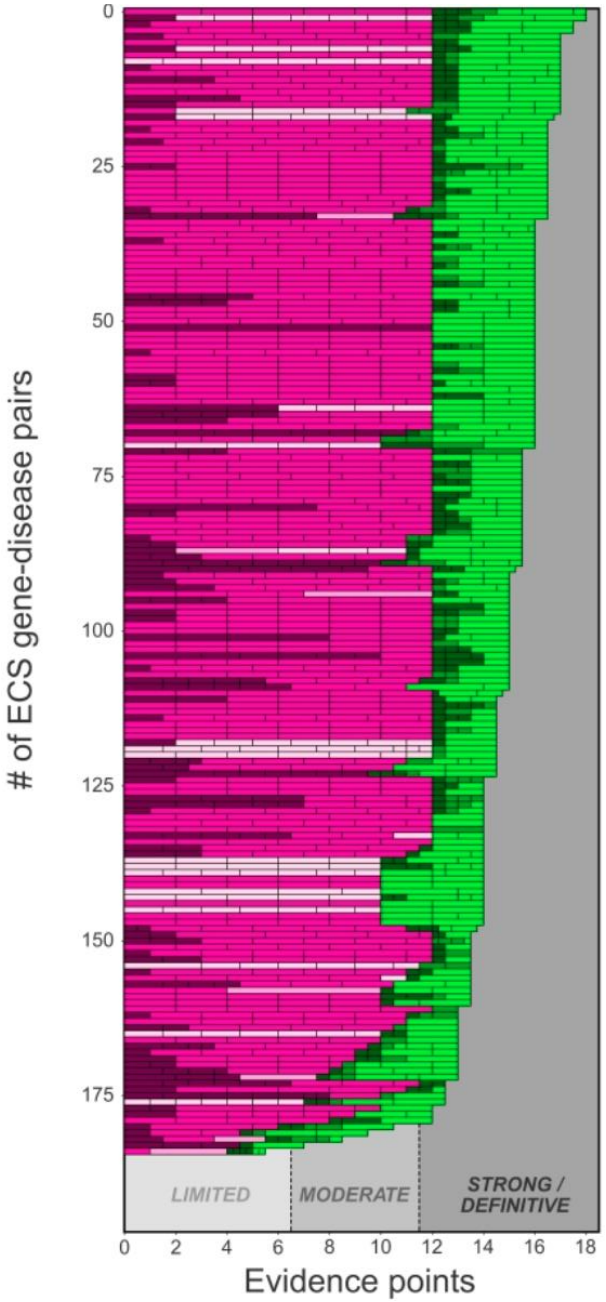
Genetic evidence

- 2 non-LOF variants in *trans* or de novo variant
- 2 variants in *trans*; ≥1 LOF or de novo
- case-control data
- proband w/ variant

Experimental evidence

- Functional data
- Functional alteration
- Models & Rescue



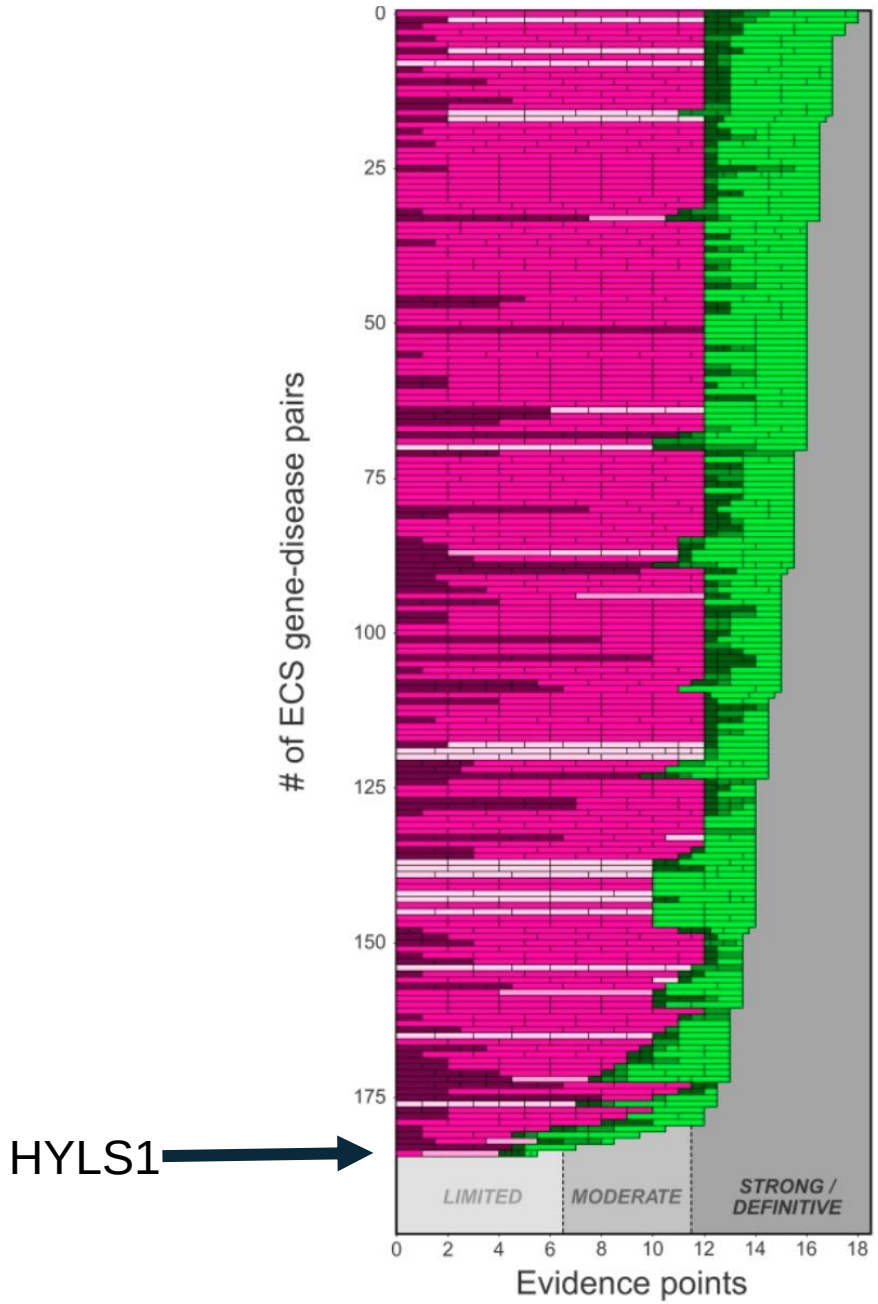


Results

‘Limited’ Gene-disease associations

HYLS1 – hydrolethalus syndrome (HLS)

- Borderline between 'Moderate' and 'Limited'
- Conservatively downgraded to 'Limited'



Conclusions

- Strong evidence shown for gene-disease association on two ECS panels.
- Established disease-level clinical validity of these panels.
- Clinical validity of gene-disease association is just one of many factors that influence the selection of conditions included on ECS panels.
- All classifications have been submitted to ClinGen for public availability.

Acknowledgements

- Krista Moyer
- Katie Johansen Taber
- Dale Muzzey
- Jenny Goldstein
- Becca Mar-Heyming
- Bethany Buckley
- Linyan Meng
- Jim Goldberg
- Anna Gardiner
- Myriad and Baylor Curation Teams

References

- Strande, N. T., Riggs, E. R., Buchanan, A. H., Ceyhan-Birsoy, O., DiStefano, M., Dwight, S. S., . . . Berg, J. S. (2017). Evaluating the Clinical Validity of Gene-Disease Associations: An Evidence-Based Framework Developed by the Clinical Genome Resource. Am J Hum Genet, 100(6), 895-906. doi:10.1016/j.ajhg.2017.04.015
- The Clinical Genome Resource Gene Curation Working Group. (2017). Gene Clinical Validity Curation Process Standard Operating Procedure, Version 5. Retrieved from https://www.clinicalgenome.org/site/assets/files/2169/gene_curation_sop_2016_version_5_11_6_17.pdf
- The Clinical Genome Resource. Gene Validity Curations. Retrieved from https://www.clinicalgenome.org/site/assets/files/2169/gene_curation_sop_2016_version_5_11_6_17.pdf
- Bean, L. J. H., Funke, B., Carlston, C. M., Gannon, J. L., Kantarci, S., Krock, B. L., … Bayrak-Toydemir, P. (n.d.). Diagnostic gene sequencing panels: from design to report - a technical standard of the American College of Medical Genetics and Genomics (ACMG). GENETICS in MEDICINE. https://doi.org/10.1038/s41436-019
- McGlaughon, J. L., Goldstein, J. L., Thaxton, C., Hemphill, S. E., & Berg, J. S. (2018). The progression of the ClinGen gene clinical validity classification over time. Hum Mutat, 39(11), 1494-1504. doi:10.1002/humu.23604