CNV interpretation guidelines overview

EJ Cassidy

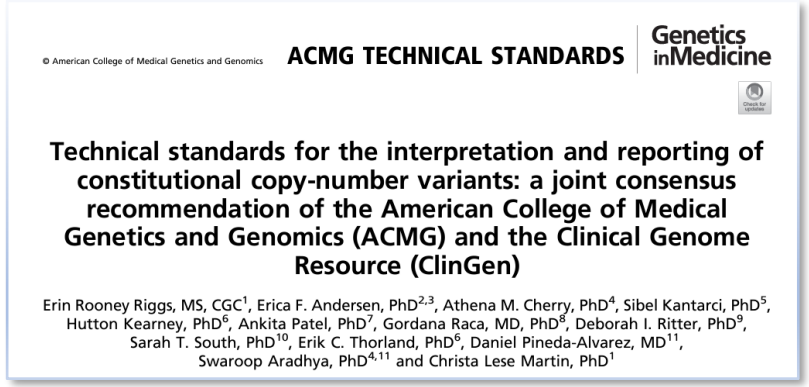
Wessex Regional Genetics Laboratory

emma-jane.cassidy@nhs.net

Best Practice Guidelines

ACMG/ClinGen CNV guidelines:

- Published update guidelines 2020 (previous guidelines 2011)
- Created a semi-quantitative evidence-based evaluation framework to help standardise classification of variants



ACGS variant interpretation guidelines:

- Will recommend the implementation of the scoring metrics

CN loss involving single gene: SNV or CNV guidelines?

Use CNV guidelines

- includes del/dup of exon/s

Semi-quantitative point-based scoring framework

Evidence categories most relevant to CNV classification were determined and put into 5 sections within a table:

Section 1:	Initial assessment of genomic content
Section 2:	Overlap with established/predicted haploinsufficiency (HI) or triplosensitive (TS) or established benign genes/genomic regions
Section 3:	Evaluation of gene number
Section 4:	Detailed evaluation of similar CNVs using cases from published literature, public databases, and/or internal lab data
Section 5:	Evaluation of inheritance pattern/family history and phenotype of your case

A relative weight was assigned to each piece of evidence in the sections in the form of suggested point values creating the semi-quantitative points-based scoring system.

Separate scoring metrics were developed for losses and gains

- **Table 1** for **CN loss**
- **Table 2** for **CN gain**

Semi-quantitative points-based scoring system

- A suggested number of points are added or subtracted per each piece of evidence
- Points values assigned based on evidence strength.
- The total number of points helps assign the classification

Suggested CNV Point Value (Pathogenic/Benign)	Comparable ACMG/AMP Evidence Strength
0.90/-0.90	Very Strong
0.45/-0.45	Strong
0.30/-0.30	Moderate
0.15/-0.15	Supporting

Combining rules are similar (e.g. 3 Moderate (0.30) = LP (0.90); 1 Very Strong (0.90) + ≥2 Moderate (0.30) = P (>0.99), etc.)

Classification	Total points score
Pathogenic	≥ 0.99
Likely Pathogenic	0.90 – 0.98
VUS	-0.89 – 0.89
Likely Benign	-0.90 – -0.98
Benign	≤ -0.99

CNV interpretation

- You select the appropriate table for your CNV type
  - Table 1 for CN loss
  - Table 2 for CN gain

- You work through the evidence sections and categories within them from top to bottom, assigning point values.
- If a section does not apply to your CNV, you move on to the next section.

- Add up the points (positive and negative) to determine the classification.

Table 1 CNV interpretation scoring metric: copy-number loss

Section 1: Initial assessment of genomic content			
Evidence type	**Evidence**	**Suggested points/case**	**Max score**
Copy-number loss content	**1A**. Contains protein-coding or other known functionally important elements.	0 (Continue evaluation)	0
	1B. Does NOT contain protein-coding or any known functionally important elements.	−0.60	−0.60
Section 2: Overlap with established/predicted haploinsufficiency (HI) or established benign genes/genomic regions *(Skip to section 3 if your copy-number loss DOES NOT overlap these types of genes/regions)*			
Overlap with ESTABLISHED HI genes or genomic regions and consideration of reason for referral	**2A**. Complete overlap of an established HI gene/genomic region.	1.00	1.00
	2B. Partial overlap of an established HI genomic region • The observed CNV does NOT contain the known causative gene or critical region for this established HI genomic region OR • Unclear if known causative gene or critical region is affected OR • No specific causative gene or critical region has been established for this HI genomic region	0 (Continue evaluation)	0
	2C. Partial overlap with the 5′ end of an established HI gene (3′ end of the gene not involved)…	See categories below	
	2C-1. …and coding sequence is involved	0.90 *(range: 0.45 to 1.00)*	1.00
	2C-2. …and only the 5′ UTR is involved	0 *(range: 0 to 0.45)*	0.45
	2D. Partial overlap with the 3′ end of an established HI gene (5′ end of the gene not involved)…	See categories below	
	2D-1. …and only the 3′ untranslated region is involved.	0 (Continue evaluation)	0
	2D-2. …and only the last exon is involved. Other established pathogenic variants have been reported in this exon.	0.90 *(range: 0.45 to 0.90)*	0.90
	2D-3. …and only the last exon is involved. No other established pathogenic variants have been reported in this exon.	0.30 *(range: 0 to 0.45)*	0.45
	2D-4. …and it includes other exons in addition to the last exon. Nonsense-mediated decay is expected to occur.	0.90 *(range: 0.45 to 1.00)*	1.00
	2E. Both breakpoints are within the same gene (intragenic CNV; gene-level sequence variant).	See ClinGen SVI working group PVS1 specifications • PVS1 = 0.90 *(Range: 0.45 to 0.90)* • PVS1_Strong = 0.45 *(Range: 0.30 to 0.90)* • PVS1_Moderate or PM4 (in-frame indels) = 0.30 *(Range: 0.15 to 0.45)* • PVS1_Supporting = 0.15 *(Range: 0 to 0.30)*	See categories at left

Table 1 continued

		• N/A = No points, but continue evaluation	
Overlap with ESTABLISHED benign genes or genomic regions	**2F**. Completely contained within an established benign CNV region.	−1	−1
	2G. Overlaps an established benign CNV, but includes additional genomic material.	0 (Continue evaluation)	0
Haploinsufficiency predictors	**2H**. Two or more HI predictors suggest that AT LEAST ONE gene in the interval is HI.	0.15	0.15
Section 3: Evaluation of gene number			
Number of protein-coding RefSeq genes wholly or partially included in the copy-number loss	**3A**. 0–24 genes	0	0
	3B. 25–34 genes	0.45	0.45
	3C. 35+ genes	0.90	0.90
Section 4: Detailed evaluation of genomic content using cases from published literature, public databases, and/or internal lab data ***(Skip to section 5 if either your CNV overlapped with an established HI gene/region in section 2, OR there have been no reports associating either the CNV or any genes within the CNV with human phenotypes caused by loss of function [LOF] or copy-number loss)***			
Individual case evidence—de novo occurrences	Reported proband (from literature, public databases, or internal lab data) has either: • A complete deletion of or a LOF variant within gene encompassed by the observed copy-number loss OR • An overlapping copy-number loss similar in genomic content to the observed copy-number loss AND…	See categories below	
	4A. …the reported phenotype is highly specific and relatively unique to the gene or genomic region,	Confirmed de novo: 0.45 points each Assumed de novo: 0.30 points each *(range: 0.15 to 0.45)*	0.90 (total)
	4B. …the reported phenotype is consistent with the gene/genomic region, is highly specific, but not necessarily unique to the gene/genomic region.	Confirmed de novo: 0.30 points each Assumed de novo: 0.15 point each *(range: 0 to 0.45)*	
	4C. …the reported phenotype is consistent with the gene/genomic region, but not highly specific and/or with high genetic heterogeneity.	Confirmed de novo: 0.15 point each Assumed de novo: 0.10 point each *(range: 0 to 0.30)*	
Individual case evidence—inconsistent phenotype	**4D**. …the reported phenotype is NOT consistent with what is expected for the gene/genomic region or not consistent in general.	0 points each *(range: 0 to −0.30)*	−0.30 (total)
Individual case evidence—unknown inheritance	**4E**. Reported proband has a highly specific phenotype consistent with the gene/genomic region, but the inheritance of the variant is unknown.	0.10 points each *(range: 0 to 0.15)*	0.30 (total)
Individual case evidence—segregation among similarly affected family members	**4F**. 3–4 observed segregations	0.15	0.45
	4G. 5–6 observed segregations	0.30	
	4H. 7 or more observed segregations	0.45	
Individual case evidence—nonsegregations	**4I**. Variant is NOT found in another individual in the proband's family AFFECTED with a consistent, specific, well-defined phenotype (no known phenocopies).	−0.45 points per family *(range: 0 to −0.45)*	−0.90 (total)
	4J. Variant IS found in another individual in the proband's family UNAFFECTED with the specific, well-defined phenotype observed in the proband.	−0.30 points per family *(range: 0 to −0.30)*	−0.90 (total)

Table 1 continued

	4K. Variant IS found in another individual in the proband's family UNAFFECTED with the nonspecific phenotype observed in the proband.	−0.15 points per family *(range: 0 to −0.15)*	−0.30 (total)
Case–control and population evidence	**4L**. Statistically significant increase amongst observations in cases (**with a consistent, specific, well-defined phenotype**) compared with controls.	0.45 per study *(range: 0 to 0.45 per study)*	0.45 (total)
	4M. Statistically significant increase amongst observations in cases (**without a consistent, nonspecific phenotype OR unknown phenotype**) compared with controls.	0.30 per study *(range: 0 to 0.30 per study)*	0.45 (total)
	4N. No statistically significant difference between observations in cases and controls.	−0.90 (per study) *(range: 0 to −0.90 per study)*	−0.90 (total)
	4O. Overlap with common population variation.	−1 *(range: 0 to −1)*	−1
Section 5: Evaluation of inheritance pattern/family history for patient being studied			
Observed copy-number loss is de novo	**5A**. *Use appropriate category from de novo scoring section in section 4.*	*Use de novo scoring categories from section 4 (4A–4D) to determine score*	0.45
Observed copy-number loss is inherited	**5B**. Patient with **specific, well-defined** phenotype and no family history. CNV is inherited from an apparently unaffected parent.	−0.30 *(range: 0 to −0.45)*	−0.45
	5C. Patient with **nonspecific** phenotype and no family history. CNV is inherited from an apparently unaffected parent.	−0.15 *(range: 0 to −0.30)*	−0.30
	5D. CNV segregates with a consistent phenotype observed in the patient's family.	*Use segregation scoring categories from section 4 (4F–4H) to determine score*	0.45
Observed copy-number loss—nonsegregations	**5E**. *Use appropriate category from nonsegregation section in section 4.*	*Use nonsegregation scoring categories from section 4 (4I–4K) to determine score*	−0.45
Other	**5F**. Inheritance information is unavailable or uninformative.	0	0
	5G. Inheritance information is unavailable or uninformative. The patient phenotype is nonspecific, but is consistent with what has been described in similar cases.	0.10 *(range: 0 to 0.15)*	0.15
	5H. Inheritance information is unavailable or uninformative. The patient phenotype is highly specific and consistent with what has been described in similar cases.	0.30 *(range: 0 to 0.30)*	0.30

Only those CNVs otherwise meeting the reporting thresholds determined by your laboratory should be evaluated using this metric. See Supplemental Material 1 for a detailed description of each evidence category. Scoring: *pathogenic* 0.99 or more points, *likely pathogenic* 0.90 to 0.98 points, *variant of uncertain significance* 0.89 to −0.89 points, *likely benign* −0.90 to −0.98 points, *benign* −0.99 or fewer points.
CNV copy-number variant, *SVI* sequence variant interpretation, *UTR* untranslated region.

Table 2 CNV interpretation scoring metric: copy-number gain

Evidence type	Evidence	Suggested points/case	Max score
Section 1: Initial assessment of genomic content			
Copy-number gain content	**1A**. Contains protein-coding or other known functionally important elements.	0 (Continue evaluation)	0
	1B. Does NOT contain protein-coding or any known functionally important elements.	−0.60	−0.60
Section 2: Overlap with established triplosensitive (TS), haploinsufficient (HI), or benign genes or genomic regions *(Skip to section 3 if the copy-number gain DOES NOT overlap these types of genes/regions)*			
Overlap with ESTABLISHED TS genes or genomic regions	**2A**. Complete overlap; the TS gene or minimal critical region is fully contained within the observed copy-number gain.	1	1
	2B. Partial overlap of an established TS region • The observed CNV does NOT contain the known causative gene or critical region for this established TS genomic region OR • Unclear if the known causative gene or critical region is affected OR • No specific causative gene or critical region has been established for this TS genomic region.	0 (Continue evaluation)	0
Overlap with ESTABLISHED benign copy-number gain genes or genomic regions	**2C**. Identical in gene content to the established benign copy-number gain.	−1	−1
	2D. Smaller than established benign copy-number gain, breakpoint(s) does not interrupt protein-coding genes.	−1	−1
	2E. Smaller than established benign copy-number gain, breakpoint(s) potentially interrupts protein-coding gene.	0 (Continue evaluation)	0
	2F. Larger than known benign copy-number gain, does not include additional protein-coding genes.	−1 *(range: 0 to −1.00)*	−1
	2G. Overlaps a benign copy-number gain but includes additional genomic material.	0 (Continue evaluation)	0
Overlap with ESTABLISHED HI gene(s)	**2H**. HI gene fully contained within observed copy-number gain.	0 (Continue evaluation)	0
Breakpoint(s) within ESTABLISHED HI genes	**2I**. Both breakpoints are within the same gene (gene-level sequence variant, possibly resulting in loss of function [LOF]).	See ClinGen SVI working group PVS1 specifications • PVS1 = 0.90 *(Range: 0.45 to 0.90)* • PVS1_Strong = 0.45 *(Range: 0.30 to 0.90)* • N/A = 0 (Continue evaluation)	
	2J. One breakpoint is within an established HI gene, patient's phenotype is either inconsistent with what is expected for LOF of that gene OR unknown.	0 (Continue evaluation)	0
	2K. One breakpoint is within an established HI gene, patient's phenotype is highly specific and consistent with what is expected for LOF of that gene.	0.45	0.45
Breakpoints within other gene(s)	**2L**. One or both breakpoints are within gene(s) of no established clinical significance.	0 (Continue evaluation)	0
Section 3: Evaluation of gene number			
Number of protein-coding RefSeq genes wholly or partially included in the copy-number gain	**3A**. 0–34 genes	0	0
	3B. 35–49 genes	0.45	0.45
	3C. 50 or more genes	0.90	0.90
Section 4: Detailed evaluation of genomic content using cases from published literature, public databases, and/or internal lab data *(Note: If there have been no reports associating either the copy-number gain or any of the genes therein with human phenotypes caused by triplosensitivity, skip to section 5)*			
Individual case evidence—de novo occurrences	Reported proband (from literature, public databases, or internal lab data) has either: • complete duplication of one or more genes within the observed copy-number gain OR • an overlapping copy-number gain similar in genomic content to the observed copy-number gain AND…	See categories below	
	4A. …the reported phenotype is highly specific and relatively unique to the gene or genomic region.	Confirmed de novo: 0.45 points each Assumed de novo: 0.30 points each *(range: 0.15 to 0.45)*	0.90 (total)
	4B. …the reported phenotype is consistent with the gene/genomic region, is highly specific, but is not necessarily unique to the gene/genomic region.	Confirmed de novo: 0.30 points each Assumed de novo: 0.15 point each *(range: 0 to 0.45)*	
	4C. …the reported phenotype is consistent with the gene/genomic region, but not highly specific and/or with high genetic heterogeneity.	Confirmed de novo: 0.15 point each Assumed de novo: 0.10 point each *(range: 0 to 0.30)*	
Individual case evidence—inconsistent phenotype	**4D**. …the reported phenotype is NOT consistent with the gene/genomic region or not consistent in general.	0 points each *(range: 0 to −0.30)*	−0.30 (total)
Individual case evidence—unknown inheritance	**4E**. Reported proband has a highly specific phenotype consistent with the gene/genomic region, but the inheritance of the variant is unknown.	0.10 points each *(range: 0 to 0.15)*	0.30 (total)

Table 2 continued

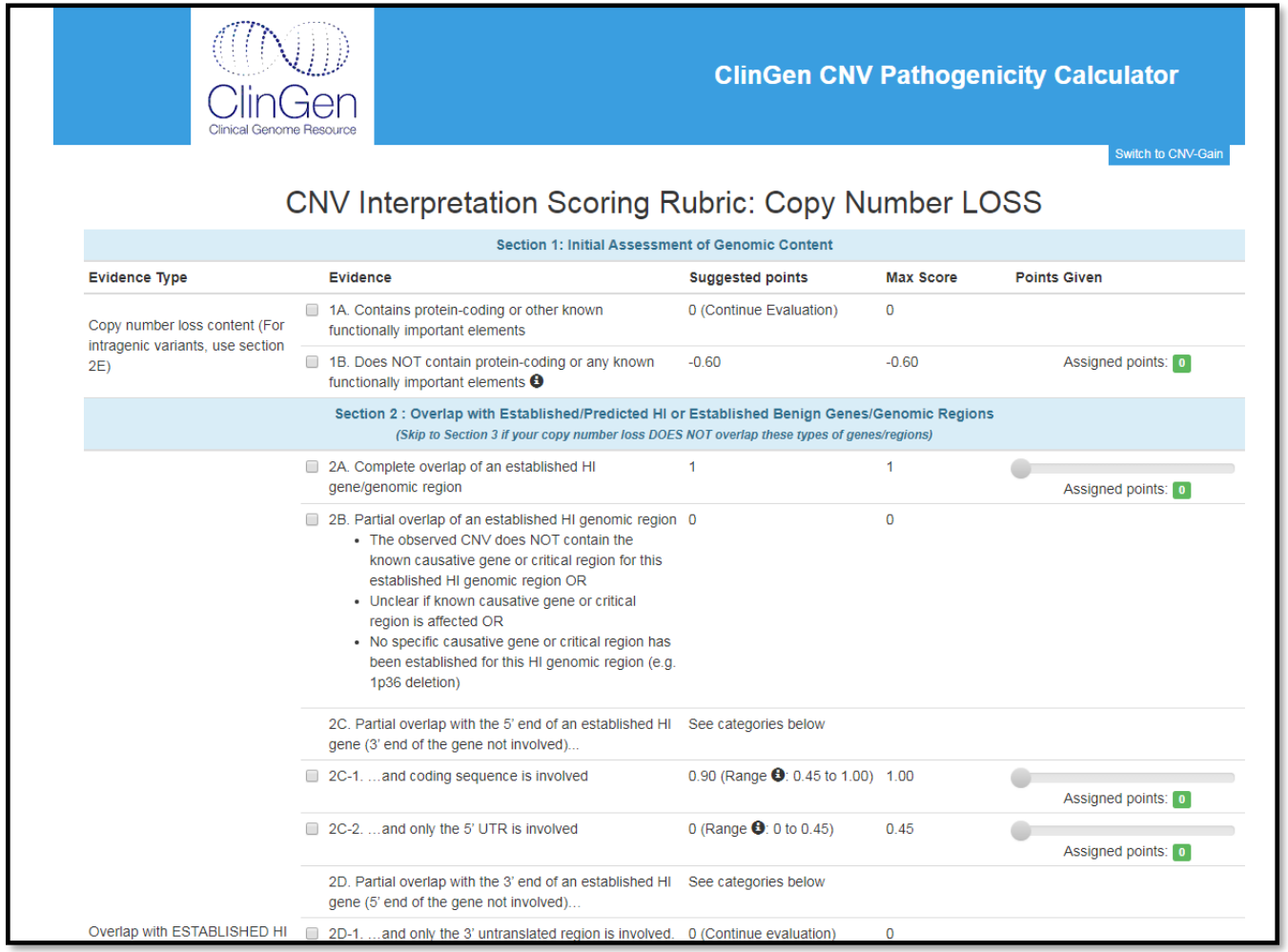
Individual case evidence—segregation among similarly affected family members	**4F**. 3–4 observed segregations	0.15	0.45
	4G. 5–6 observed segregations	0.30	
	4H. 7 or more observed segregations	0.45	
Individual case evidence—nonsegregations	**4I**. Variant is NOT found in another individual in the proband's family AFFECTED with a consistent, specific, well-defined phenotype (no known phenocopies).	−0.45 points per family *(range: 0 to −0.45)*	−0.90 (total)
	4J. Variant IS found in another individual in the proband's family UNAFFECTED with the specific, well-defined phenotype observed in the proband.	−0.30 points per family *(range: 0 to −0.30)*	−0.90 (total)
	4K. Variant IS found in another individual in the proband's family UNAFFECTED with the nonspecific phenotype observed in the proband.	−0.15 points per family *(range: 0 to −0.15)*	−0.30 (total)
Case–control and population evidence	**4L**. Statistically significant increase among observations in cases (with a consistent, **specific, well-defined phenotype**) compared with controls.	0.45 per study *(range: 0 to 0.45 per study)*	0.45 (total)
	4M. Statistically significant increase among observations in cases (with a consistent, **nonspecific phenotype or unknown phenotype**) compared with controls.	0.30 per study *(range: 0 to 0.30 per study)*	0.45 (total)
	4N. No statistically significant difference between observations in cases and controls.	−0.90 per study *(range: 0 to −0.90 per study)*	−0.90 (total)
	4O. Overlap with common population variation.	−1 *(range: 0 to −1)*	−1
Section 5: Evaluation of inheritance patterns/family history for patient being studied			
Observed copy-number gain is de novo	**5A**. *Use appropriate category from de novo scoring section in section 4.*	*Use de novo scoring categories from section 4 (4A–4D) to determine score*	0.45
Observed copy-number gain is inherited	**5B**. Patient with a **specific, well-defined phenotype** and no family history. Copy-number gain is inherited from an apparently unaffected parent.	−0.30 *(range: 0 to −0.45)*	−0.45
	5C. Patient with **nonspecific phenotype** and no family history. Copy-number gain is inherited from an apparently unaffected parent.	−0.15 *(range: 0 to −0.30)*	−0.30
	5D. CNV segregates with consistent phenotype observed in the patient's family.	*Use segregation scoring categories from in section 4 (4F–4H) to determine score*	0.45
Observed copy-number gain—nonsegregations	**5E**. *Use appropriate category from nonsegregation section in section 4.*	*Use nonsegregation scoring categories from section 4 (4I–4K) to determine score*	−0.45
	5F. Inheritance information is unavailable or uninformative.	0	0
	5G. Inheritance information is unavailable or uninformative. The patient phenotype is nonspecific, but is consistent with what has been described in similar cases.	0.10 *(range: 0 to 0.15)*	0.15
	5H. Inheritance information is unavailable or uninformative. The patient phenotype is highly specific and consistent with what has been described in similar cases.	0.15 *(range: 0 to 0.30)*	0.30

Only those CNVs otherwise meeting the reporting thresholds determined by your laboratory should be evaluated using this metric. See Supplemental Material 1 for full description of each evidence category. Scoring: *pathogenic* 0.99 or more points, *likely pathogenic* 0.90 to 0.98 points, *variant of uncertain significance* 0.89 to −0.89 points, *likely benign* −0.90 to −0.98 points, *benign* −0.99 or fewer points.
CNV copy-number variant, *SVI* sequence variant interpretation.

Table 1 CNV interpretation scoring metric: copy-number loss

Evidence type	Evidence	Suggested points/case	Max score
Section 1: Initial assessment of genomic content			
Copy-number loss content	**1A**. Contains protein-coding or other known functionally important elements.	0 (Continue evaluation)	0
	1B. Does NOT contain protein-coding or any known functionally important elements.	−0.60	−0.60
Section 2: Overlap with established/predicted haploinsufficiency (HI) or established benign genes/genomic regions *(Skip to section 3 if your copy-number loss DOES NOT overlap these types of genes/regions)*			
Overlap with ESTABLISHED HI genes or genomic regions and consideration of reason for referral	**2A**. Complete overlap of an established HI gene/genomic region.	1.00	1.00
	2B. Partial overlap of an established HI genomic region • The observed CNV does NOT contain the known causative gene or critical region for this established HI genomic region OR • Unclear if known causative gene or critical region is affected OR • No specific causative gene or critical region has been established for this HI genomic region	0 (Continue evaluation)	0
	2C. Partial overlap with the 5′ end of an established HI gene (3′ end of the gene not involved)…	See categories below	
	2C-1. …and coding sequence is involved	0.90 *(range: 0.45 to 1.00)*	1.00
	2C-2. …and only the 5′ UTR is involved	0 *(range: 0 to 0.45)*	0.45
	2D. Partial overlap with the 3′ end of an established HI gene (5′ end of the gene not involved)…	See categories below	
	2D-1. …and only the 3′ untranslated region is involved.	0 (Continue evaluation)	0
	2D-2. …and only the last exon is involved. Other established pathogenic variants have been reported in this exon.	0.90 *(range: 0.45 to 0.90)*	0.90
	2D-3. …and only the last exon is involved. No other established pathogenic variants have been reported in this exon.	0.30 *(range: 0 to 0.45)*	0.45
	2D-4. …and it includes other exons in addition to the last exon. Nonsense-mediated decay is expected to occur.	0.90 *(range: 0.45 to 1.00)*	1.00
	2E. Both breakpoints are within the same gene (intragenic CNV; gene-level sequence variant).	See ClinGen SVI working group PVS1 specifications • PVS1 = 0.90 *(Range: 0.45 to 0.90)* • PVS1_Strong = 0.45 *(Range: 0.30 to 0.90)* • PVS1_Moderate or PM4 (in-frame indels) = 0.30 *(Range: 0.15 to 0.45)* • PVS1_Supporting = 0.15 *(Range: 0 to 0.30)*	See categories at left

CNV interpretation calculator https://cnvcalc.clinicalgenome.org/cnvcalc/



ClinGen Clinical Genome Resource

ClinGen CNV Pathogenicity Calculator

Switch to CNV-Gain

CNV Interpretation Scoring Rubric: Copy Number LOSS

Section 1: Initial Assessment of Genomic Content

Evidence Type	Evidence	Suggested points	Max Score	Points Given
Copy number loss content (For intragenic variants, use section 2E)	☐ 1A. Contains protein-coding or other known functionally important elements	0 (Continue Evaluation)	0	
	☐ 1B. Does NOT contain protein-coding or any known functionally important elements	-0.60	-0.60	Assigned points: 0

Section 2 : Overlap with Established/Predicted HI or Established Benign Genes/Genomic Regions

(Skip to Section 3 if your copy number loss DOES NOT overlap these types of genes/regions)

	☐ 2A. Complete overlap of an established HI gene/genomic region	1	1	Assigned points: 0
	☐ 2B. Partial overlap of an established HI genomic region • The observed CNV does NOT contain the known causative gene or critical region for this established HI genomic region OR • Unclear if known causative gene or critical region is affected OR • No specific causative gene or critical region has been established for this HI genomic region (e.g. 1p36 deletion)	0	0	
	2C. Partial overlap with the 5' end of an established HI gene (3' end of the gene not involved)...	See categories below		
	☐ 2C-1. ...and coding sequence is involved	0.90 (Range: 0.45 to 1.00)	1.00	Assigned points: 0
	☐ 2C-2. ...and only the 5' UTR is involved	0 (Range: 0 to 0.45)	0.45	Assigned points: 0
	2D. Partial overlap with the 3' end of an established HI gene (5' end of the gene not involved)...	See categories below		
Overlap with ESTABLISHED HI	☐ 2D-1. ...and only the 3' untranslated region is involved.	0 (Continue evaluation)	0	

Range of points for evidence: effects standardisation?

The standard should be that the default recommended points is applied for each piece of evidence.

CNV Interpretation Calculator scale is in integers of 0.05 points:

If a decision is made to upgrade or downgrade the points it is recommended the choice of points you can allocate is static:

(+/-) 0.15 (supporting), 0.30 (moderate), 0.45 (strong), 0.90/1.00 (very strong)

For example:

If the default recommended points is 0.30 and the range is (0 to 0.45)

- to downgrade apply 0.15
- to upgrade apply 0.45

Otherwise labs could assign any of the following options: 0.05, 0.10, 0.15, 0.20, 0.25, 0.35, 0.40, 0.45

Table sections

Section 1:	Initial assessment of genomic content
Section 2:	Overlap with established/predicted haploinsufficiency (HI) or triplosensitive (TS) or established benign genes/genomic regions
Section 3:	Evaluation of gene number
Section 4:	Detailed evaluation of genomic content using cases from published literature, public databases, and/or internal lab data
Section 5:	Evaluation of inheritance pattern/family history and phenotype of patient being studied

Section 1: Initial assessment of genomic content

Section 1: Initial assessment of genomic content			
Evidence type	**Evidence**	**Suggested points/case**	**Max score**
Copy-number loss content	**1A**. Contains protein-coding or other known functionally important elements.	0 (Continue evaluation)	0
	1B. Does NOT contain protein-coding or any known functionally important elements.	−0.60	−0.60

Section 2: Overlap with established/predicted HI genes/genomic regions

Section 2: Overlap with established/predicted haploinsufficiency (HI) or established benign genes/genomic regions ***(Skip to section 3 if your copy-number loss DOES NOT overlap these types of genes/regions)***

ACGM/ClinGen guidelines:
must be an *"established haploinsufficient (HI)" gene*

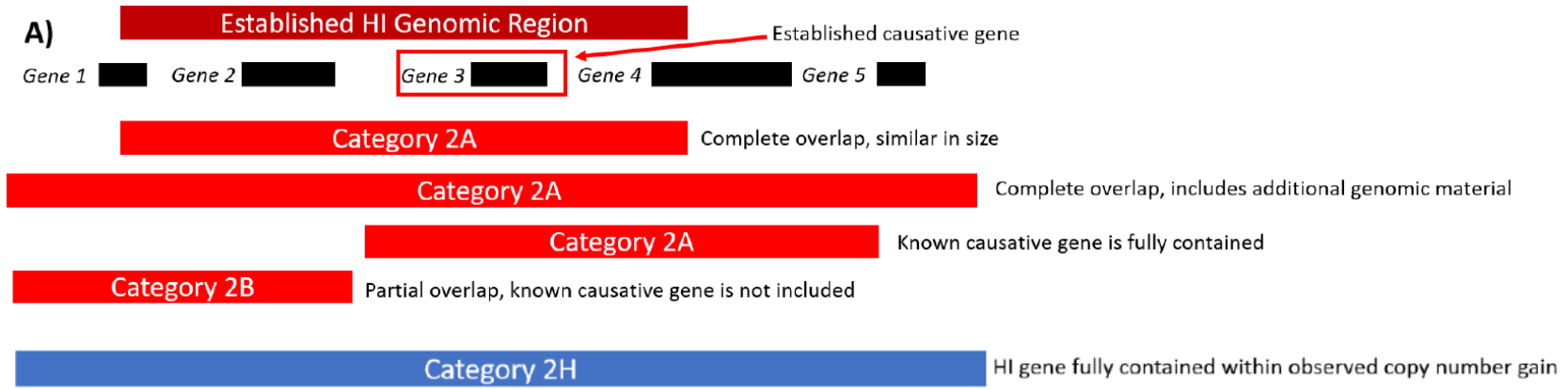
ACGS guidelines:
recommends the wording *"established loss-of-function mechanism"*

"Established"

- Genes with a ClinGen Dosage haploinsufficiency score of 3
- Monoallelic Gene2Phenotype (G2P) genes with a *"definitive"* status and *"absent gene product"* as the consequence
- Biallelic G2P genes with a *"definitive"* status and *"absent gene product"* as the consequence
- Gene-Disease Validity (ClinGen) with *"definitive"* status and evidence of predicted or proven null variants (either AD or AR genes)

Section 2: Overlap with established/predicted HI genes/genomic regions

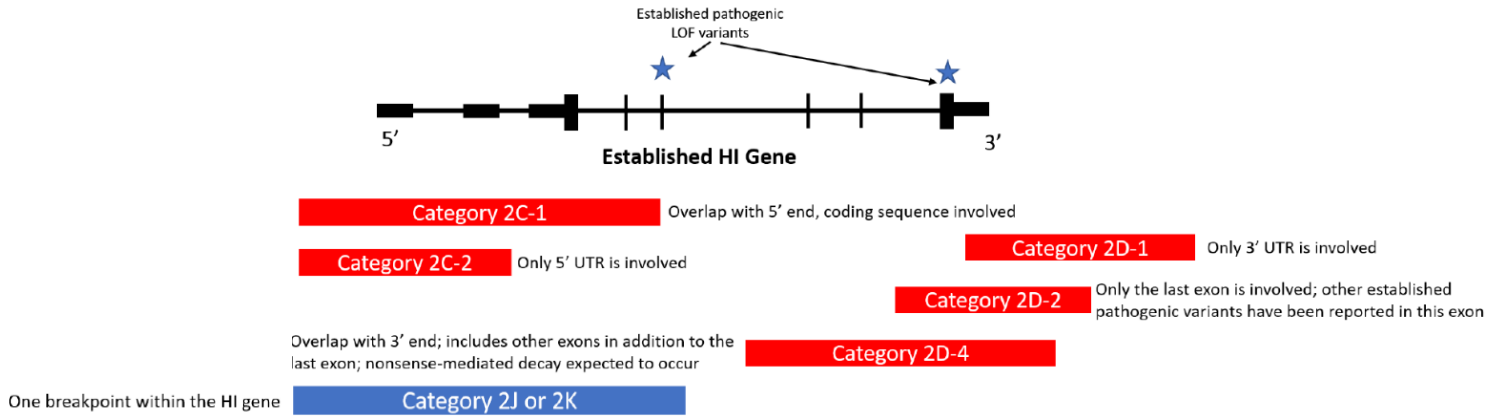
Section 2: Overlap with established/predicted haploinsufficiency (HI) or established benign genes/genomic regions *(Skip to section 3 if your copy-number loss DOES NOT overlap these types of genes/regions)*			
Overlap with ESTABLISHED HI genes or genomic regions and consideration of reason for referral	**2A**. Complete overlap of an established HI gene/genomic region.	1.00	1.00
	2B. Partial overlap of an established HI genomic region • The observed CNV does NOT contain the known causative gene or critical region for this established HI genomic region OR • Unclear if known causative gene or critical region is affected OR • No specific causative gene or critical region has been established for this HI genomic region	0 (Continue evaluation)	0
	2H. HI gene fully contained within observed copy-number gain.	0 (Continue evaluation)	



Section 2: Overlap with established/predicted HI genes/genomic regions

2C. Partial overlap with the 5′ end of an established HI gene (3′ end of the gene not involved)…	See categories below	
2C-1. …and coding sequence is involved	0.90 *(range: 0.45 to 1.00)*	1.00
2C-2. …and only the 5′ UTR is involved	0 *(range: 0 to 0.45)*	0.45
2D. Partial overlap with the 3′ end of an established HI gene (5′ end of the gene not involved)…	See categories below	
2D-1. …and only the 3′ untranslated region is involved.	0 (Continue evaluation)	0
2D-2. …and only the last exon is involved. Other established pathogenic variants have been reported in this exon.	0.90 *(range: 0.45 to 0.90)*	0.90
2D-3. …and only the last exon is involved. No other established pathogenic variants have been reported in this exon.	0.30 *(range: 0 to 0.45)*	0.45
2D-4. …and it includes other exons in addition to the last exon. Nonsense-mediated decay is expected to occur.	0.90 *(range: 0.45 to 1.00)*	1.00

2J. One breakpoint is within an established HI gene, patient's phenotype is either inconsistent with what is expected for LOF of that gene OR unknown.	0 (Continue evaluation)
2K. One breakpoint is within an established HI gene, patient's phenotype is highly specific and	0.45



Section 2: Overlap with established/predicted HI genes/genomic regions

2E. Both breakpoints are within the same gene (intragenic CNV; gene-level sequence variant).	See ClinGen SVI working group PVS1 specifications • PVS1 = 0.90 ~~*(Range: 0.45 to 0.90)*~~ • PVS1_Strong = 0.45 ~~*(Range: 0.30 to 0.90)*~~ • PVS1_Moderate *or* PM4 (in-frame indels) = 0.30 ~~*(Range: 0.15 to 0.45)*~~ • PVS1_Supporting = 0.15 ~~*(Range: 0 to 0.30)*~~	See categories at left
2I. Both breakpoints are within the same gene (gene-level sequence variant, possibly resulting in loss of function [LOF]).	See ClinGen SVI working group PVS1 specifications • PVS1 = 0.90 ~~*(Range: 0.45 to 0.90)*~~ • PVS1_Strong = 0.45 ~~*(Range: 0.30 to 0.90)*~~	

To align with the sequence variant guidelines & strength of evidence applied to PVS1 specifications static points should be applied to CNVs:

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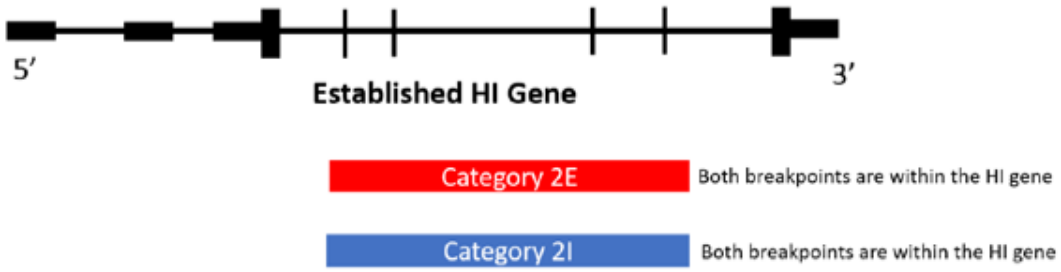
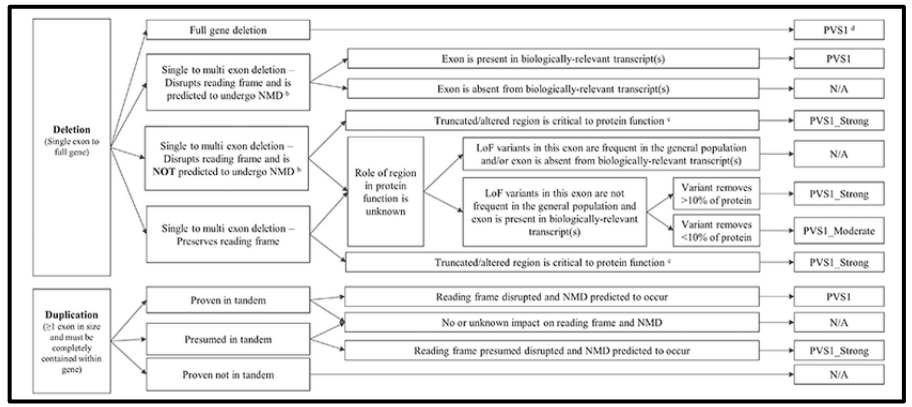
PVS1 = 0.90
PVS1_strong = 0.45
PVS1_moderate = 0.30
PVS1_supporting = 0.15





Difference between guidelines

- Common combination of criteria using SNV guidelines:

  PVS1 + PM2 = Pathogenic

  PVS1_strong + PM2 = Likely Pathogenic

- No PM2 (*absent from controls*) equivalent in the CNV guidelines

  Due to under representation of the mapping of structural variants in population datasets

- Classification using CNV guidelines
  - PVS1 = 0.90 = Likely Pathogenic (out of frame + disrupts protein function)

  - In-frame CNVs
    - PVS1_strong = 0.45
    - PVS1_moderate = 0.30

    } VUS

Section 4: Case Control and Population Evidence

Case–control and population evidence	**4L**. Statistically significant increase among observations in cases (with a consistent, **specific, well-defined phenotype**) compared with controls.	0.45
	4M. Statistically significant increase among observations in cases (with a consistent, **nonspecific phenotype or unknown phenotype**) compared with controls.	0.30

- If the CNV has been studied as part of a well-powered case-control study, points may be added based on enrichment in the clinical population
  - 4L = 0.45 points
  - 4M = 0.30 points

- But case-control study data is rarely available for rare diseases
  - Can apply 4L at 0.15 points

If the variant has been previously identified in multiple (two or more) unrelated affected individuals (with a *rare* well-defined phenotype) and has not been reported in gnomAD-SV

Out of frame CNVs

PVS1 = 0.90

In-frame CNVs

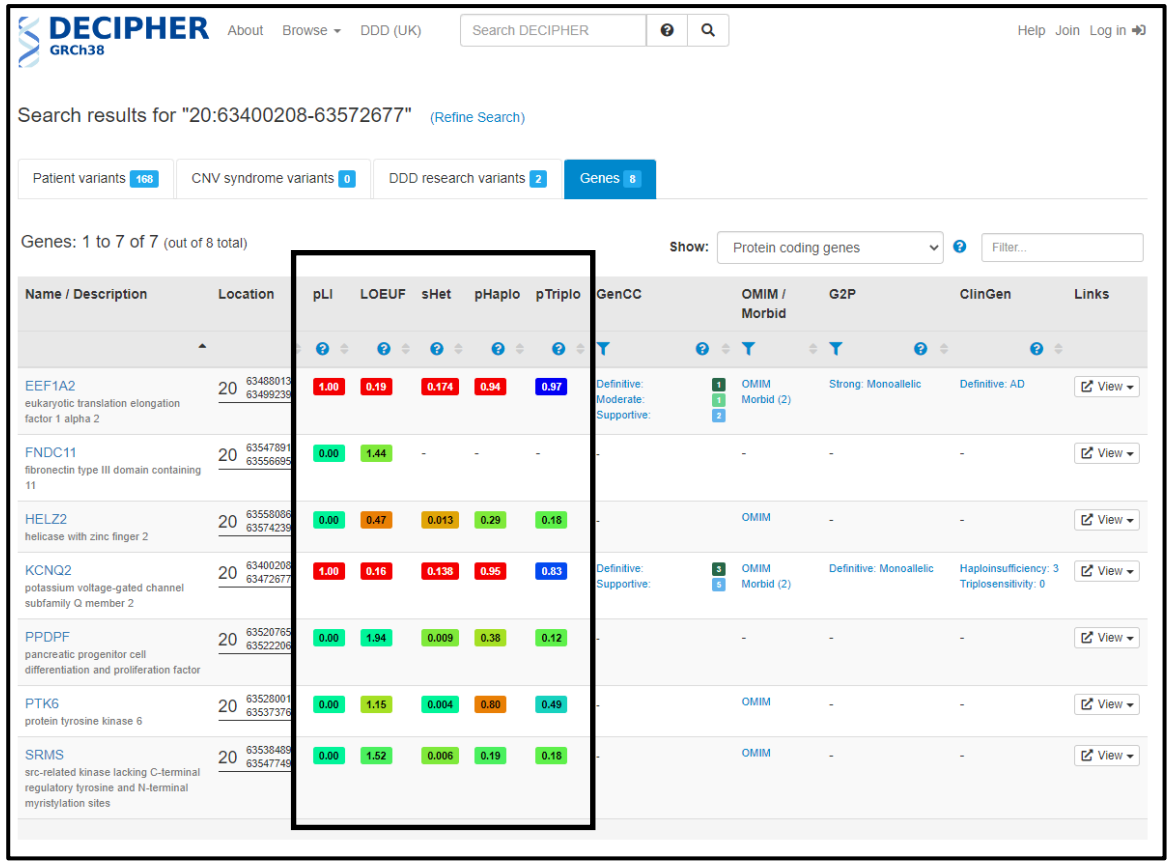
PVS1_strong = 0.45

PVS1_moderate = 0.30

Classification	Total points score
Pathogenic	≥ 0.99
Likely Pathogenic	0.90 – 0.98
VUS	-0.89 – 0.89

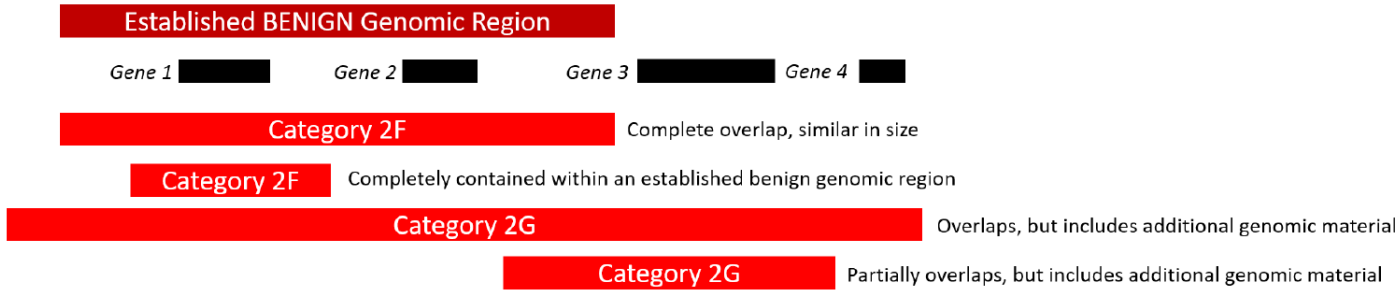
Section 2: Overlap with established/predicted HI genes/genomic regions

Haploinsufficiency predictors	**2H**. Two or more HI predictors suggest that AT LEAST ONE gene in the interval is HI.	0.15



Section 2: Overlap with established benign genes/genomic regions

Overlap with ESTABLISHED benign genes or genomic regions	**2F**. Completely contained within an established benign CNV region.	−1
	2G. Overlaps an established benign CNV, but includes additional genomic material.	0 (Continue evaluation)



"Established"

- ClinGen Dosage sensitivity score of "dosage sensitivity unlikely"
- Commonly seen CNV within cohort that has a platform frequency of >1%
- A frequency >1% on the DGV Gold Standard dataset, gnomAD-SV or DECIPHER CNV consensus datasets

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Section 4: Case Control and Population Evidence

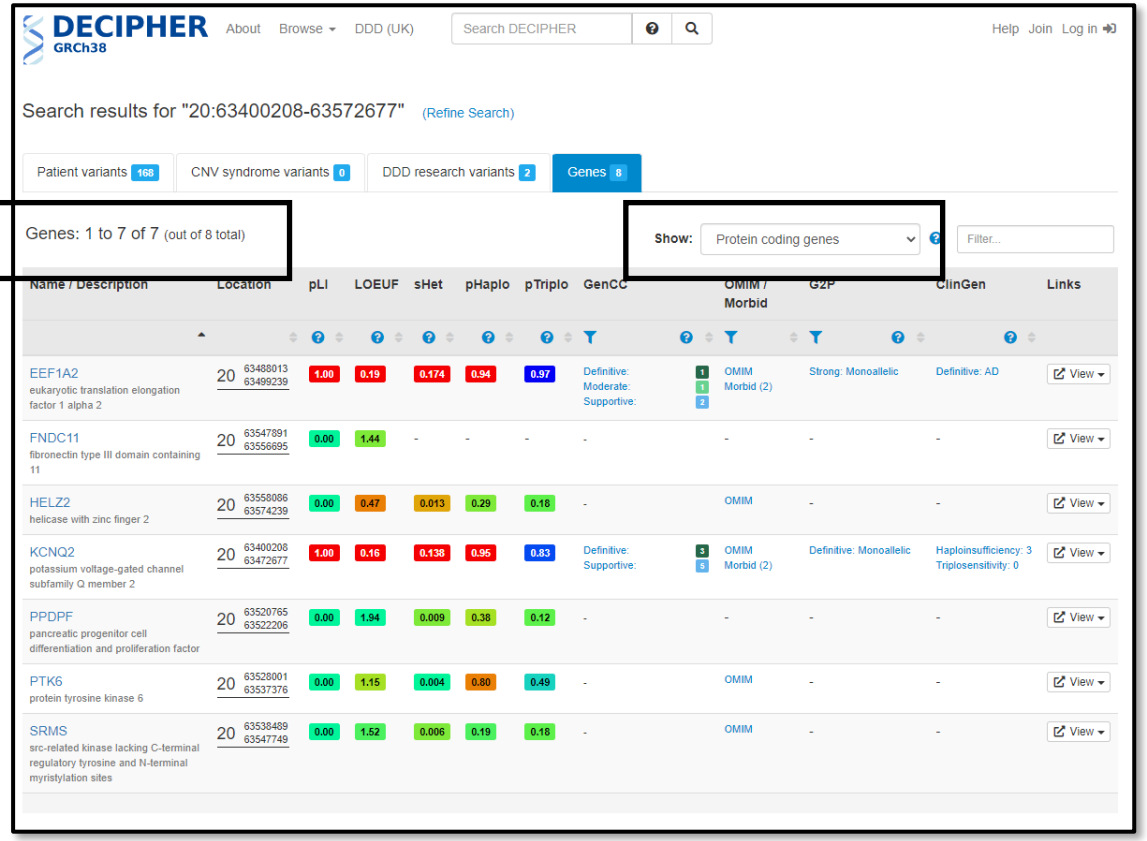
Case–control and population evidence	**4L**. Statistically significant increase among observations in cases (with a consistent, **specific, well-defined phenotype**) compared with controls.	0.45 per study *(range: 0 to 0.45 per study)*
	4M. Statistically significant increase among observations in cases (with a consistent, **nonspecific phenotype or unknown phenotype**) compared with controls.	0.30 per study *(range: 0 to 0.30 per study)*
	4N. No statistically significant difference between observations in cases and controls.	−0.90 per study *(range: 0 to −0.90 per study)*
	4O. Overlap with common population variation.	−1 *(range: 0 to −1)*

4O: This category covers CNVs that involve regions seen in population databases

- used for variants that are present at a frequency < 1%

Section 3: Evaluation of gene number

Section 3: Evaluation of gene number			
Number of protein-coding RefSeq genes wholly or partially included in the copy-number loss	**3A**. 0–24 genes	**0-34 genes**	0
	3B. 25–34 genes	**35-49 genes**	0.45
	3C. 35+ genes	**50+ genes**	0.90



Section 4: Detail evaluation of genomic content using literature and databases

Section 4: Detailed evaluation of genomic content using cases from published literature, public databases, and/or internal lab data *(Skip to section 5 if either your CNV overlapped with an established HI gene/region in section 2, OR there have been no reports associating either the CNV or any genes within the CNV with human phenotypes caused by loss of function [LOF] or copy-number loss)*			
Individual case evidence—de novo occurrences	Reported proband (from literature, public databases, or internal lab data) has either: • A complete deletion of or a LOF variant within gene encompassed by the observed copy-number loss OR • An overlapping copy-number loss similar in genomic content to the observed copy-number loss AND…	See categories below	
	4A. …the reported phenotype is highly specific and relatively unique to the gene or genomic region,	Confirmed de novo: 0.45 points each Assumed de novo: 0.30 points each *(range: 0.15 to 0.45)*	0.90 (total)
	4B. …the reported phenotype is consistent with the gene/genomic region, is highly specific, but not necessarily unique to the gene/genomic region.	Confirmed de novo: 0.30 points each Assumed de novo: 0.15 point each *(range: 0 to 0.45)*	
	4C. …the reported phenotype is consistent with the gene/genomic region, but not highly specific and/or with high genetic heterogeneity.	Confirmed de novo: 0.15 point each Assumed de novo: 0.10 point each *(range: 0 to 0.30)*	
Individual case evidence—inconsistent phenotype	**4D**. …the reported phenotype is NOT consistent with what is expected for the gene/genomic region or not consistent in general.	0 points each *(range: 0 to −0.30)*	−0.30 (total)
Individual case evidence—unknown inheritance	**4E**. Reported proband has a highly specific phenotype consistent with the gene/genomic region, but the inheritance of the variant is unknown.	0.10 points each *(range: 0 to 0.15)*	0.30 (total)

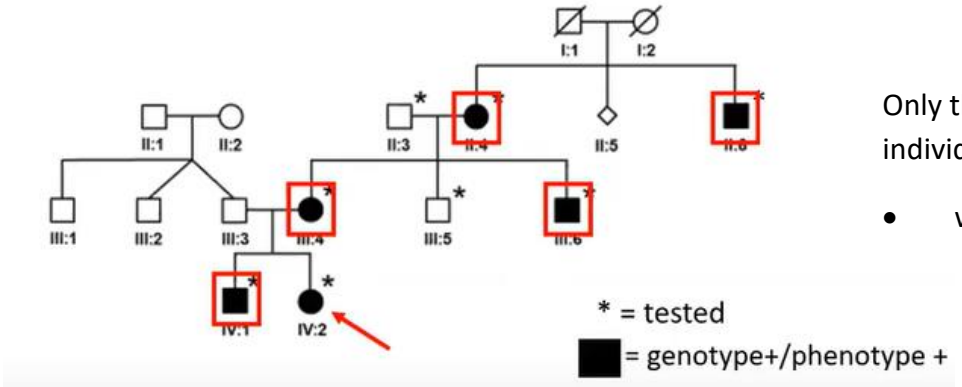
Only used for highly specific phenotypes
- not to be used for ID/autism

Negative point values could be considered with increasing evidence of inconsistency.

- is the case is *de novo*
- how consistent is reported phenotype to what is expected for that gene/region
- how specific is that phenotype in general + how unique it is to the gene/region
- is the *de novo* status confirmed or assumed

Section 4: Detail evaluation of genomic content using literature and databases

Individual case evidence—segregation among similarly affected family members	**4F**. 3–4 observed segregations	0.15	0.45
	4G. 5–6 observed segregations	0.30	
	4H. 7 or more observed segregations	0.45	
Individual case evidence—nonsegregations	**4I**. Variant is NOT found in another individual in the proband's family AFFECTED with a consistent, specific, well-defined phenotype (no known phenocopies).	−0.45 points per family *(range: 0 to −0.45)*	−0.90 (total)
	4J. Variant IS found in another individual in the proband's family UNAFFECTED with the specific, well-defined phenotype observed in the proband.	−0.30 points per family *(range: 0 to −0.30)*	−0.90 (total)
	4K. Variant IS found in another individual in the proband's family UNAFFECTED with the nonspecific phenotype observed in the proband.	−0.15 points per family *(range: 0 to −0.15)*	−0.30 (total)



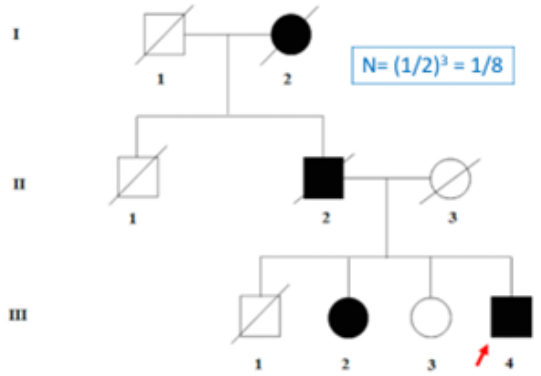
Only those individuals with both the genotype and the phenotype, or individuals who are obligate carriers, can be counted as evidence:

- when counting segregations the proband is not counted
  # of segregations = (# of genotype/phenotype positive) – 1

Difference between guidelines

The CNV guidelines separate case-level segregation (Section 4) and the segregation of the patient/family being studied (Section 5)

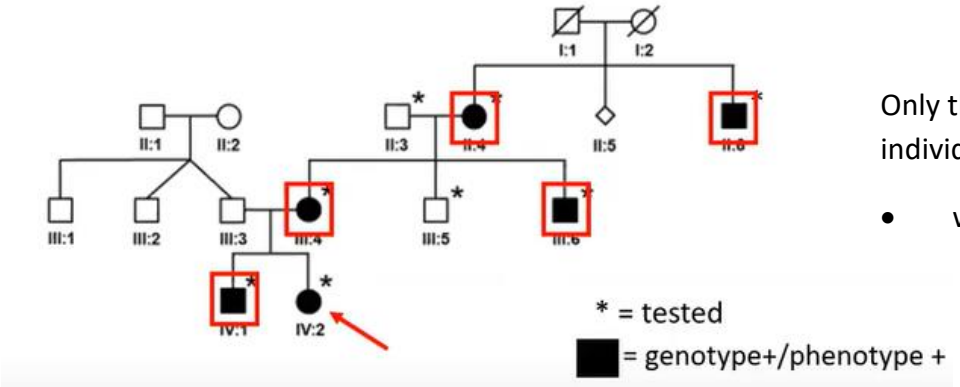
- ≥3 segregations (meiosis) required before any points can be applied
- Frameworks that allow more strength/points to be applied as the segregations increase
- Easier to assign segregations using SNV framework – but CNVs and SNVs are different



SNVs (PP1)	CNVs (4F-4H/5D)
Supporting	**0.15 points**
N is ≤1/8 if 1 family N is ≤1/4 if >1 family	**3-4 segregations**
Moderate	**0.30 points**
N is ≤1/16 if 1 family N is ≤1/8 if >1 family	**5-6 segregations**
Strong	**0.45 points**
N ≤1/32 if 1 family N is ≤1/16 if >1 family	**≥7 segregations**

Section 4: Detail evaluation of genomic content using literature and databases

Individual case evidence—segregation among similarly affected family members	**4F**. 3–4 observed segregations	0.15	0.45
	4G. 5–6 observed segregations	0.30	
	4H. 7 or more observed segregations	0.45	
Individual case evidence—nonsegregations	**4I**. Variant is NOT found in another individual in the proband's family AFFECTED with a consistent, specific, well-defined phenotype (no known phenocopies).	−0.45 points per family *(range: 0 to −0.45)*	−0.90 (total)
	4J. Variant IS found in another individual in the proband's family UNAFFECTED with the specific, well-defined phenotype observed in the proband.	−0.30 points per family *(range: 0 to −0.30)*	−0.90 (total)
	4K. Variant IS found in another individual in the proband's family UNAFFECTED with the nonspecific phenotype observed in the proband.	−0.15 points per family *(range: 0 to −0.15)*	−0.30 (total)



Only those individuals with both the genotype and the phenotype, or individuals who are obligate carriers, can be counted as evidence:

- when counting segregations the proband is not counted
  # of segregations = (# of genotype/phenotype positive) – 1

Section 5: Evaluation of Inheritance Patterns + Phenotype

Section 5: Evaluation of inheritance patterns/family history for patient being studied			
Observed copy-number gain is de novo	**5A**. *Use appropriate category from de novo scoring section in section 4.*	*Use de novo scoring categories from section 4 (4A–4D) to determine score*	0.45
Observed copy-number gain is inherited	**5B**. Patient with a **specific, well-defined phenotype** and no family history. Copy-number gain is inherited from an apparently unaffected parent.	−0.30 *(range: 0 to −0.45)*	−0.45
	5C. Patient with **nonspecific phenotype** and no family history. Copy-number gain is inherited from an apparently unaffected parent.	−0.15 *(range: 0 to −0.30)*	−0.30
	5D. CNV segregates with consistent phenotype observed in the patient's family.	*Use segregation scoring categories from in section 4 (4F–4H) to determine score*	0.45
Observed copy-number gain—nonsegregations	**5E**. *Use appropriate category from nonsegregation section in section 4.*	*Use nonsegregation scoring categories from section 4 (4I–4K) to determine score*	−0.45
	5F. Inheritance information is unavailable or uninformative.	0	0
	5G. Inheritance information is unavailable or uninformative. The patient phenotype is nonspecific, but is consistent with what has been described in similar cases.	0.10 *(range: 0 to 0.15)*	0.15
	5H. Inheritance information is unavailable or uninformative. The patient phenotype is highly specific and consistent with what has been described in similar cases.	0.15 *(range: 0 to 0.30)*	0.30

4A will be either 0.45 (confirmed *dn*) or 0.30 (assumed *dn*)
4B will be either 0.30 (confirmed *dn*) or 0.15 (assumed *dn*)
4C will be either 0.15 (confirmed *dn*) or 0.10 (assumed *dn*)

4F (default points = 0.15): 3-4 segregations
4G (default points = 0.30): 5-6 segregations
4H (default points = 0.45): 7 or more segregations

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5G + 5H: If the patient's phenotype in its entirety is consistent with a specific genetic aetiology, points may be assigned

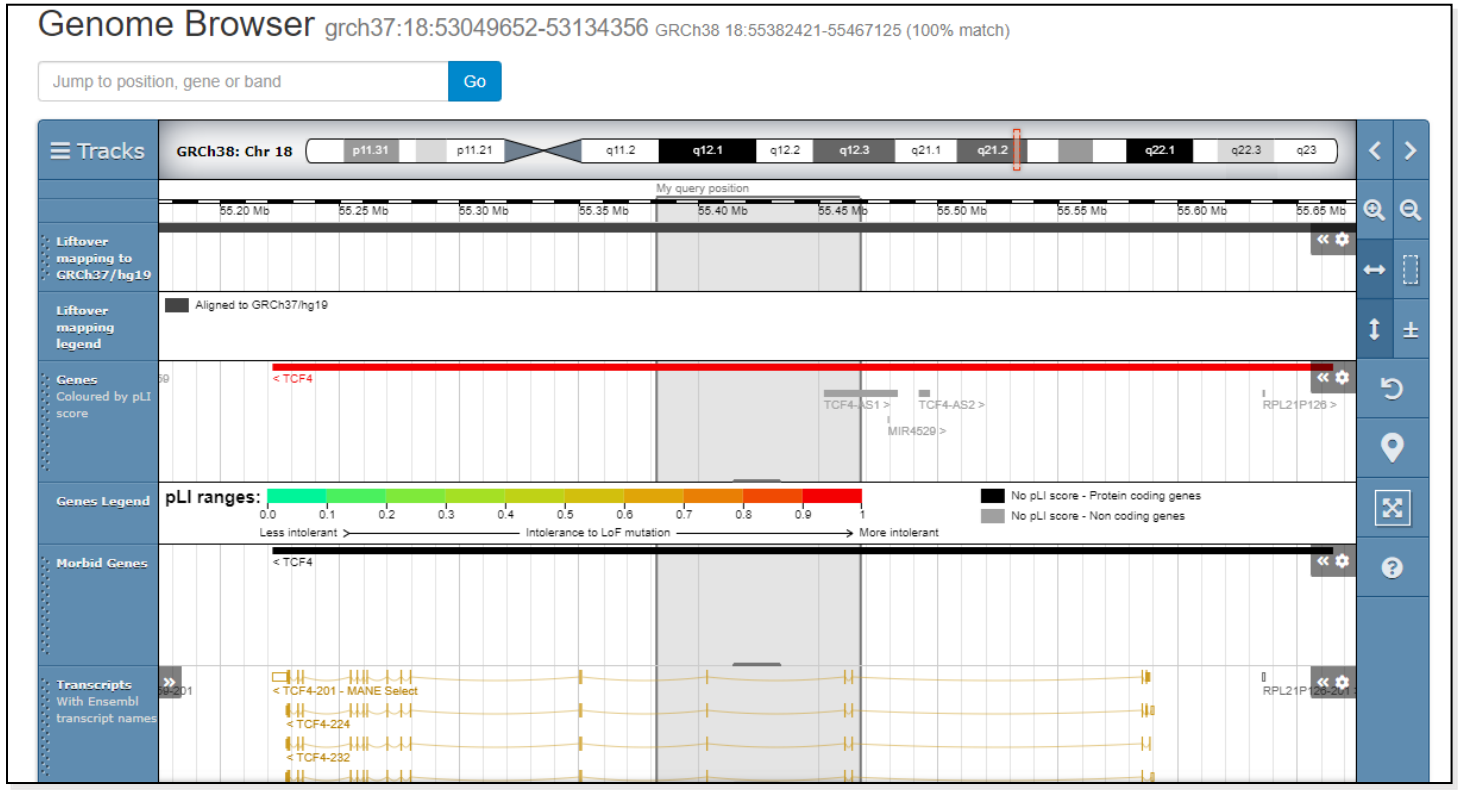
- should be considered equivalent to using PP4 in the sequence variant guidelines at supporting or moderate strength

Example case

- 2yr old, male

- Hypotonia, developmental delay, dysmorphic - prominence of the nose and lower face, unusual breathing patterns, seizures

Results



Intragenic deletion involving TCF4

[GRCh37] 18q21.2(53049652-53134356)x1

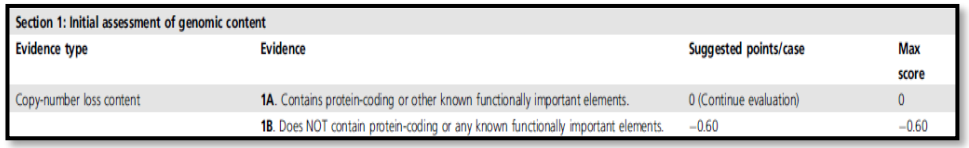
Inheritance unknown - adopted

Scoring

Section 1:

- Would apply category 1A (contains protein-coding or other known functionally important elements) as this deletion includes several exons of a protein-coding gene
- 0 points; continue evaluation

Total = 0 pts



Section 1: Initial assessment of genomic content			
Evidence type	**Evidence**	**Suggested points/case**	**Max score**
Copy-number loss content	**1A**. Contains protein-coding or other known functionally important elements.	0 (Continue evaluation)	0
	1B. Does NOT contain protein-coding or any known functionally important elements.	–0.60	–0.60

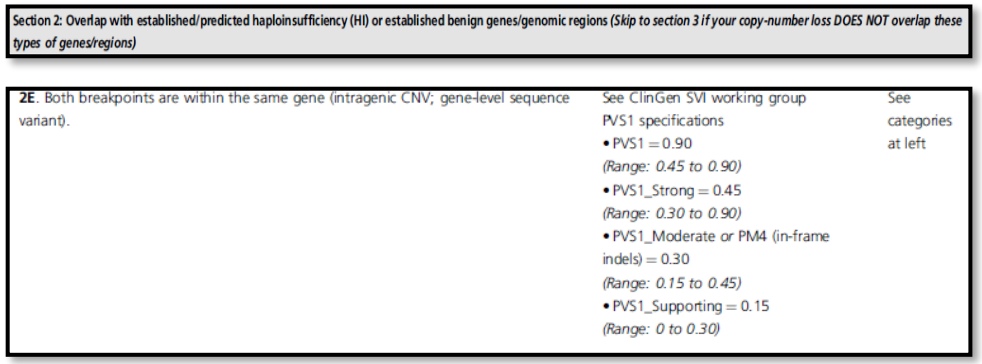
Section 2:

- Intragenic deletion of established HI gene

  TCF4 has a ClinGen DS haploinsufficiency score of 3; is a definitive monoallelic G2P LOF gene; is associated with autosomal dominant Pitt-Hopkins syndrome)

- Would use category 2E

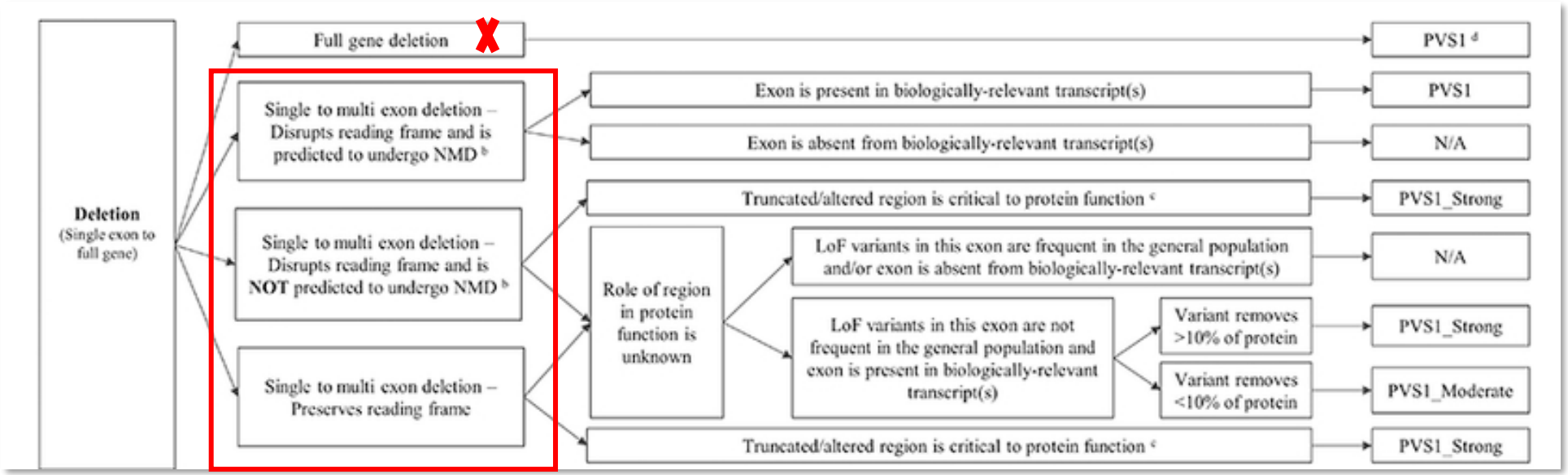
  Both breakpoints are within the same gene…..



Section 2: Overlap with established/predicted haploinsufficiency (HI) or established benign genes/genomic regions *(Skip to section 3 if your copy-number loss DOES NOT overlap these types of genes/regions)*		
2E. Both breakpoints are within the same gene (intragenic CNV; gene-level sequence variant).	See ClinGen SVI working group PVS1 specifications • PVS1 = 0.90 *(Range: 0.45 to 0.90)* • PVS1_Strong = 0.45 *(Range: 0.30 to 0.90)* • PVS1_Moderate or PM4 (in-frame indels) = 0.30 *(Range: 0.15 to 0.45)* • PVS1_Supporting = 0.15 *(Range: 0 to 0.30)*	See categories at left

Scoring

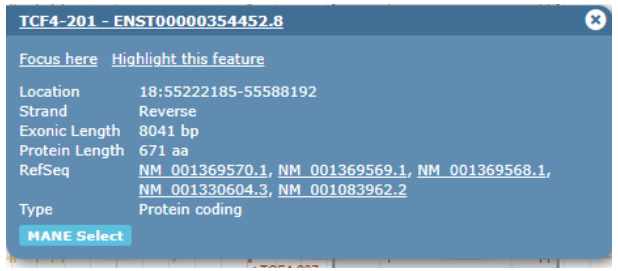
Section 2:



What is the predicted consequence of the deletion?

Scoring

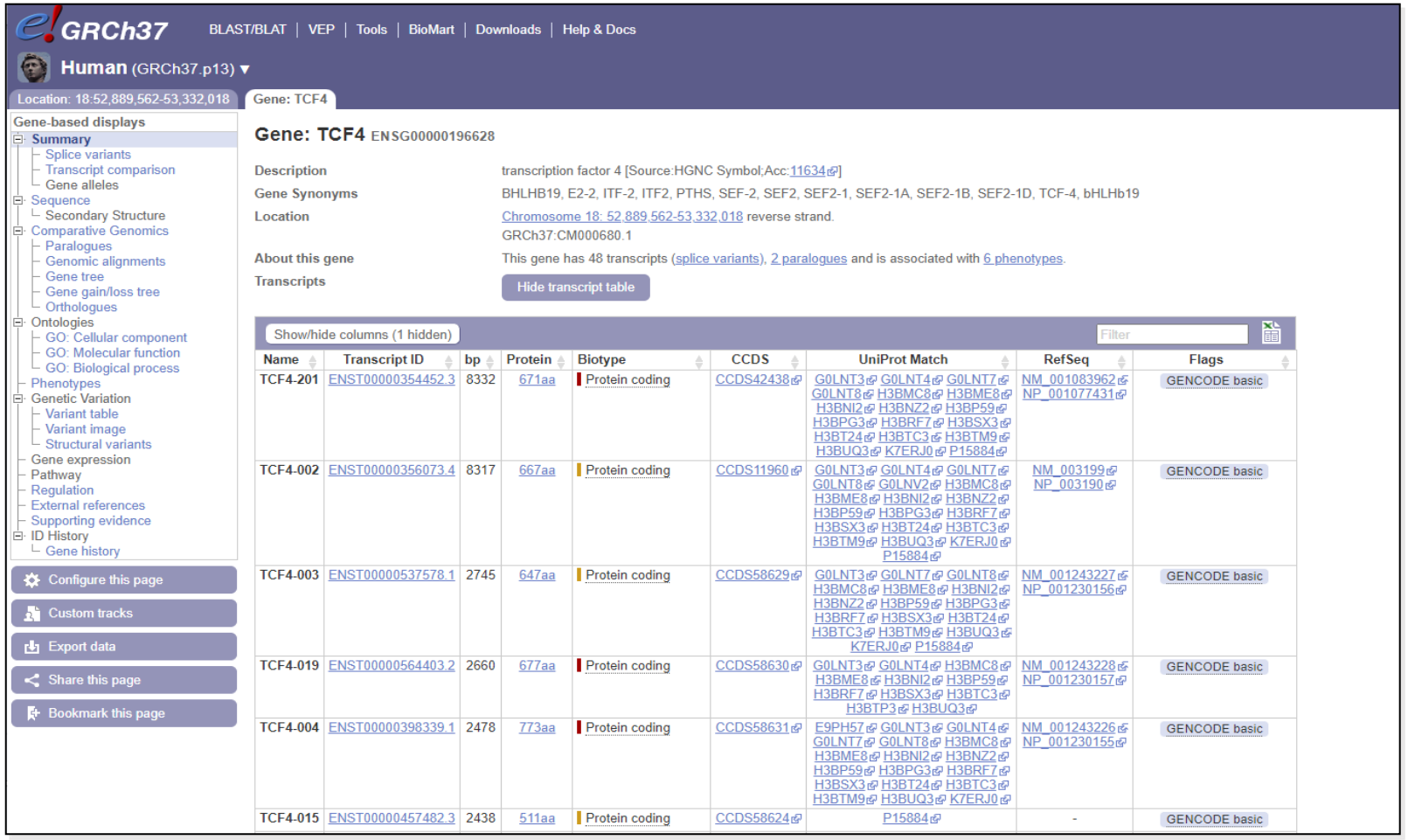
Section 2:



Exons 4-6 of MANE transcript deleted

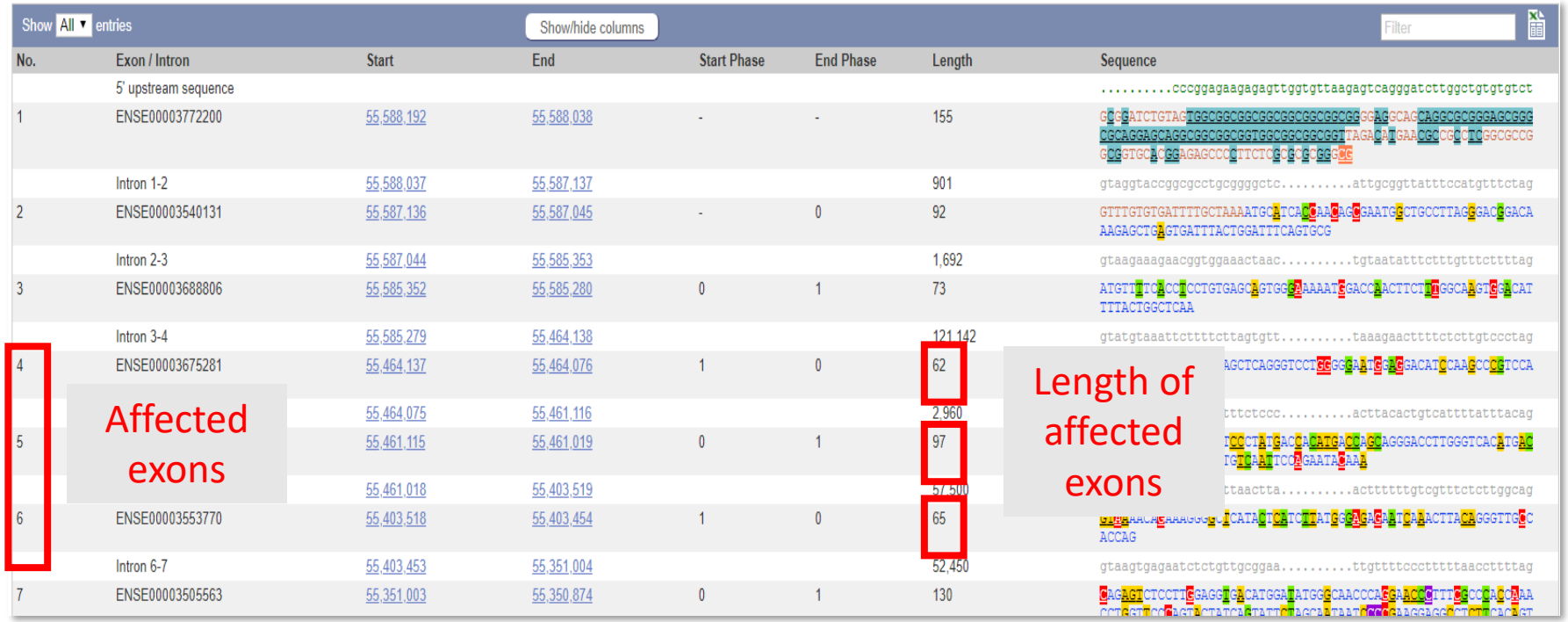
Scoring

Section 2:



Scoring

Section 2:



Show All entries | Show/hide columns | Filter

No.	Exon / Intron	Start	End	Start Phase	End Phase	Length	Sequence
	5' upstream sequence						.....cccggagaagagagttggtgttaagagtcagggatcttggctgtgtgtct
1	ENSE00003772200	55,588,192	55,588,038	-	-	155	GCGGATCTGTAGTGGCGGCGGCGGCGGCGGCGGCGGGAGGCAGCAGGCGCGGGAGCGGG CGCAGGAGCAGGCGGCGGCGGTGGCGGCGGCGGTTAGACATGAACGGCCGCTCGGCGCCG GCGGTGCACGGAGAGCCCCTTCTCGCGCGTGGGCGC
	Intron 1-2	55,588,037	55,587,137			901	gtaggtaccggcgcctgcggggctc.....attgcggttatttccatgtttctag
2	ENSE00003540131	55,587,136	55,587,045	-	0	92	GTTTGTGTGATTTTGCTAAAATGCATCACGAACAGCGAATGGCTGCCTTAGGGACGGACA AAGAGCTGAGTGATTTACTGGATTTCAGTGCG
	Intron 2-3	55,587,044	55,585,353			1,692	gtaagaaagaacggtggaaactaac.....tgtaatatttctttgtttcttttag
3	ENSE00003688806	55,585,352	55,585,280	0	1	73	ATGTTTTCACCTCCTGTGAGCAGTGGGAAAAATGGACCAACTTCTTGGCAAGTGGACAT TTTACTGGCTCAA
	Intron 3-4	55,585,279	55,464,138			121,142	gtatgtaaattcttttcttagtgtt.....taaagaacttttctcttgtccctag
4	ENSE00003675281	55,464,137	55,464,076	1	0	62	AGCTCAGGGTCCTGGGGAATGGAGACATCCAAGCCCCTCCA
		55,464,075	55,461,116			2,960	tttctccc.....acttacactgtcattttatttacag
5		55,461,115	55,461,019	0	1	97	ICCCTATGACCACATGACCAGCAGGGACCTTGGGTCACATGAC TGTCAATTCCAGAATACAAA
		55,461,018	55,403,519			57,500	ttaactta.....acttttttgtcgtttctcttggcag
6	ENSE00003553770	55,403,518	55,403,454	1	0	65	GAAGAACAGAAAGGGCTCATATCCATCTTATGGAGAGAATCAACTTACAGGGTTGCC ACCAG
	Intron 6-7	55,403,453	55,351,004			52,450	gtaagtgagaatctctgttgcggaa.....ttgttttccctttttaacctttag
7	ENSE00003505563	55,351,003	55,350,874	0	1	130	CAGAGTCTCCTTGGAGGTGACATGGATATGGCAACCCAGGAACCCTTTCGCCACACAAA

Affected exons

Length of affected exons

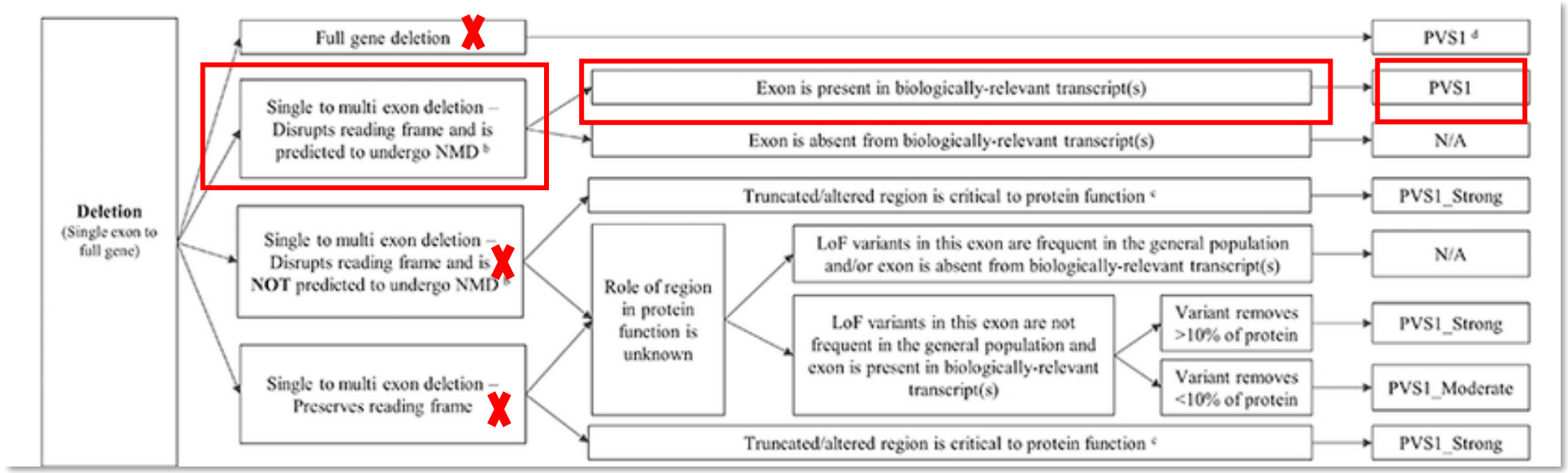
Add the total length of the missing exons and divide by 3

- 62 + 97+ 65 = 224 ÷ 3 = 74.67 (not divisible by 3, predicted to disrupt reading frame)

This gene has 20 exons total; this deletion is not near the end of the gene, and would be expected to undergo NMD

Scoring

Section 2:



Deletion of exons 4-6 in MANE transcript resulting in disruption of reading frame

Would apply category 2E PVS1 = 0.90pts

2E: Both breakpoints are within the same gene (intragenic CNV; gene-level sequence variant).	See ClinGen SVI working group PVS1 specifications • PVS1 = 0.90 *(Range: 0.45 to 0.90)* • PVS1_Strong = 0.45 *(Range: 0.30 to 0.90)* • PVS1_Moderate *or* PM4 (in-frame indels) = 0.30 *(Range: 0.15 to 0.45)* • PVS1_Supporting = 0.15 *(Range: 0 to 0.30)*	See categories at left

Total = 0.90 pts

Scoring

Section 2:

- Should I also award points in category 2H?

  No! This would essentially be double counting

- *TCF4* is a known and established HI gene.

  Category 2H is for genes that have not been curated and are just predicted to be HI

Haploinsufficiency predictors	**2H**. Two or more HI predictors suggest that AT LEAST ONE gene in the interval is HI.	0.15

Section 3:

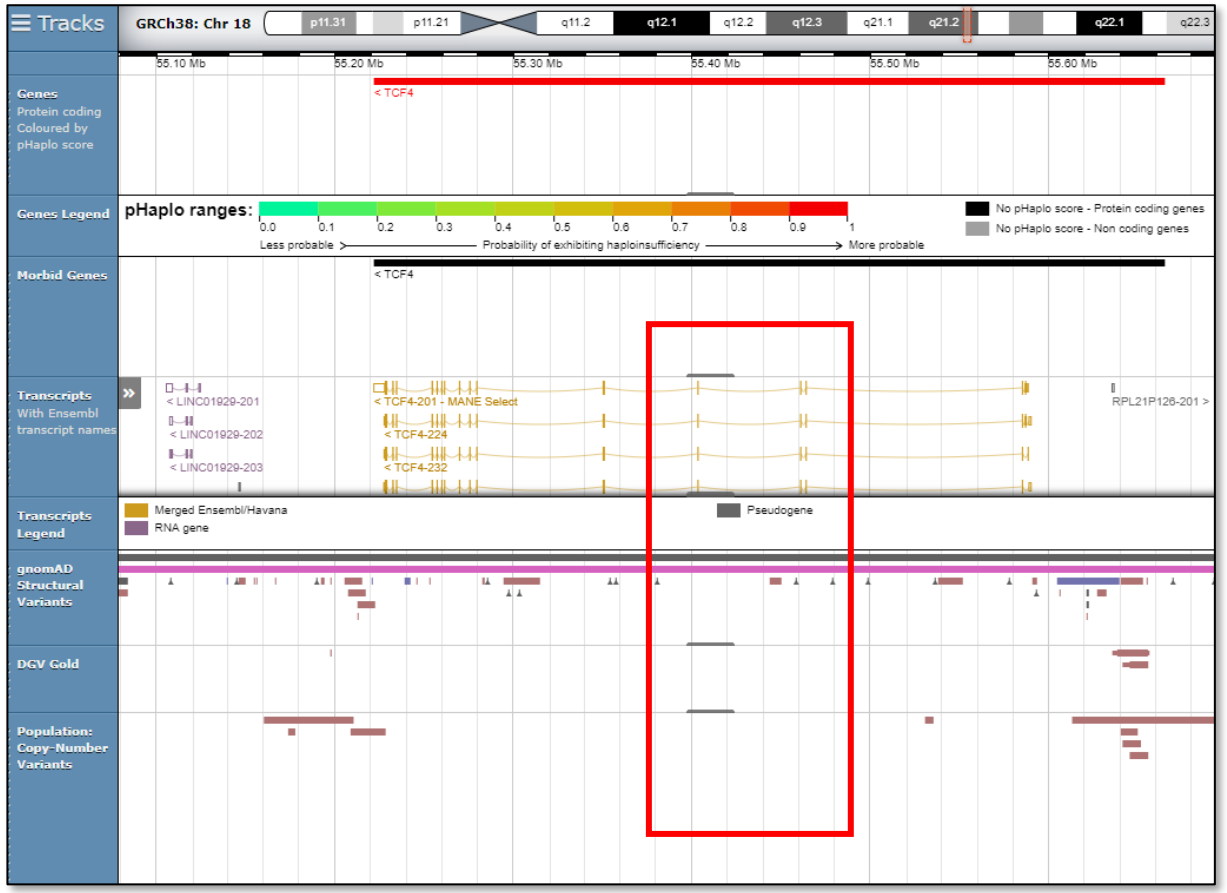
- Single gene involved - intragenic loss
- Would use category 3A, 0 points

Section 3: Evaluation of gene number		
Number of protein-coding RefSeq genes wholly or partially included in the copy-number loss	**3A**. 0–24 genes	0
	3B. 25–34 genes	0.45
	3C. 35+ genes	0.90

Total = 0.90 pts

Scoring

Section 4:



Check the region is not covered by population CNVs

4O. Overlap with common population variation.	*–1 (range: 0 to –1)*

Scoring

Section 4:

- When working with an established HI/LOF gene, you can use Section 4 to gather additional evidence (and accumulate additional points) if you did not reach Pathogenic in Section 2

- In our case, we were able to get to Likely Pathogenic (0.90 points) in Section 2

  - Option 1: use Section 4 to identify other literature cases of intragenic LOF variants in TCF4 to get to Pathogenic

  - Option 2: use our patient's consistent phenotype in Section 5 to get to Pathogenic

Section 4: Detailed evaluation of genomic content using cases from published literature, public databases, and/or internal lab data ***(Skip to section 5 if either your CNV overlapped with an established HI gene/region in section 2, OR there have been no reports associating either the CNV or any genes within the CNV with human phenotypes caused by loss of function [LOF] or copy-number loss)***			
Individual case evidence—de novo occurrences	Reported proband (from literature, public databases, or internal lab data) has either: • A complete deletion of or a LOF variant within gene encompassed by the observed copy-number loss OR • An overlapping copy-number loss similar in genomic content to the observed copy-number loss AND…	See categories below	
	4A. …the reported phenotype is highly specific and relatively unique to the gene or genomic region,	Confirmed de novo: 0.45 points each Assumed de novo: 0.30 points each *(range: 0.15 to 0.45)*	0.90 (total)
	4B. …the reported phenotype is consistent with the gene/genomic region, is highly specific, but not necessarily unique to the gene/genomic region.	Confirmed de novo: 0.30 points each Assumed de novo: 0.15 point each *(range: 0 to 0.45)*	
	4C. …the reported phenotype is consistent with the gene/genomic region, but not highly specific and/or with high genetic heterogeneity.	Confirmed de novo: 0.15 point each Assumed de novo: 0.10 point each *(range: 0 to 0.30)*	
Individual case evidence—inconsistent phenotype	**4D**. …the reported phenotype is NOT consistent with what is expected for the gene/genomic region or not consistent in general.	0 points each *(range: 0 to −0.30)*	−0.30 (total)
Individual case evidence—unknown inheritance	**4E**. Reported proband has a highly specific phenotype consistent with the gene/genomic region, but the inheritance of the variant is unknown.	0.10 points each *(range: 0 to 0.15)*	0.30 (total)

Total = 0.90 pts

Scoring

Section 5:

- Our patient has hypotonia, developmental delay, dysmorphic - prominence of the nose and lower face, unusual breathing patterns, seizures

- This is consistent with the expected phenotype, though relatively non-specific

- Use Category 5G, 0.10 points

Section 5: Evaluation of inheritance patterns/family history for patient being studied			
Observed copy-number gain is de novo	**5A**. *Use appropriate category from de novo scoring section in section 4.*	*Use de novo scoring categories from section 4 (4A–4D) to determine score*	0.45
Observed copy-number gain is inherited	**5B**. Patient with a **specific, well-defined phenotype** and no family history. Copy-number gain is inherited from an apparently unaffected parent.	−0.30 *(range: 0 to −0.45)*	−0.45
	5C. Patient with **nonspecific phenotype** and no family history. Copy-number gain is inherited from an apparently unaffected parent.	−0.15 *(range: 0 to −0.30)*	−0.30
	5D. CNV segregates with consistent phenotype observed in the patient's family.	*Use segregation scoring categories from in section 4 (4F–4H) to determine score*	0.45
Observed copy-number gain—nonsegregations	**5E**. *Use appropriate category from nonsegregation section in section 4.*	*Use nonsegregation scoring categories from section 4 (4I–4K) to determine score*	−0.45
	5F. Inheritance information is unavailable or uninformative.	0	0
	5G. Inheritance information is unavailable or uninformative. The patient phenotype is nonspecific, but is consistent with what has been described in similar cases.	0.10 *(range: 0 to 0.15)*	0.15
	5H. Inheritance information is unavailable or uninformative. The patient phenotype is highly specific and consistent with what has been described in similar cases.	0.15 *(range: 0 to 0.30)*	0.30

Total = 1.0 pts
Pathogenic

Any questions?