Today's Attendance URL and QR code:

Reminders

Please log attendance!

https://tinyurl.com/AttendanceJan23

- Register for this series:
  - ***https://tinyurl.com/CNVRegistration***
- Recorded webinars will be posted (slides also available)
  - ***www.clinicalgenome.org***
- Call participants are MUTED upon entry
- Questions?
  - Ask "live" using the Q&A box (must be signed into webinar)
  - Please list your full name with your question so we can send you an answer
    - Some questions will be saved for the Q&A session on March 12th
  - Email: clingen@clinicalgenome.org

ClinGen
Clinical Genome Resource

Defining the clinical relevance of genes & variants for precision medicine and research...

Constitutional CNV Technical Standards Web Series:

Use of the ClinGen Dosage Sensitivity Map

www.ncbi.nlm.nih.gov/projects/dbvar/clingen/

Erica Andersen, PhD, FACMG

ARUP Laboratories, University of Utah

(On behalf of the ClinGen Dosage Sensitivity Curation (DSC) Working Group)

ClinGen Curation Activities

Access education materials, access tools, and view results for each of our curation activities by clicking the boxes below.

Browse All ClinGen's Curated Genes

Browse All ClinGen's Curated Variants

Learn about Activities

Gene-Disease Validity

Can variation in this gene cause disease?

Learn More | Browse Curations

Variant Pathogenicity

Which changes in the gene cause disease?

Learn More | Browse Curations

Clinical Actionability

Are there actions that could be taken to improve outcomes for patients with this genetic risk?

Learn More | Browse Curations

Dosage Sensitivity

Does loss or gain of a copy of this gene or genomic region result in disease?

Learn More | Browse Curations

Somatic Variant

Somatic Cancer Working Group curates the clinical significance of genomic anomalies associated with different cancer types within the following diseases specific taskforces - pediatric cancers, pancreatic cancer, lung cancer and genitourinary cancers

Learn More | Interface

Send Feedback

clinicalgenome.org/curation-activities/

Dosage Sensitivity Documents

Dosage Sensitivity | Training Materials | Documents | Interface | Browse Curations

The following are documents and announcements related to Dosage Sensitivity.

Publications 1

Towards an evidence-based process for the clinical interpretation of copy number variation

publications - November 19, 2011

Dosage Sensitivity Curation

clinicalgenome.org/curation-activities/dosage-sensitivity/documents/

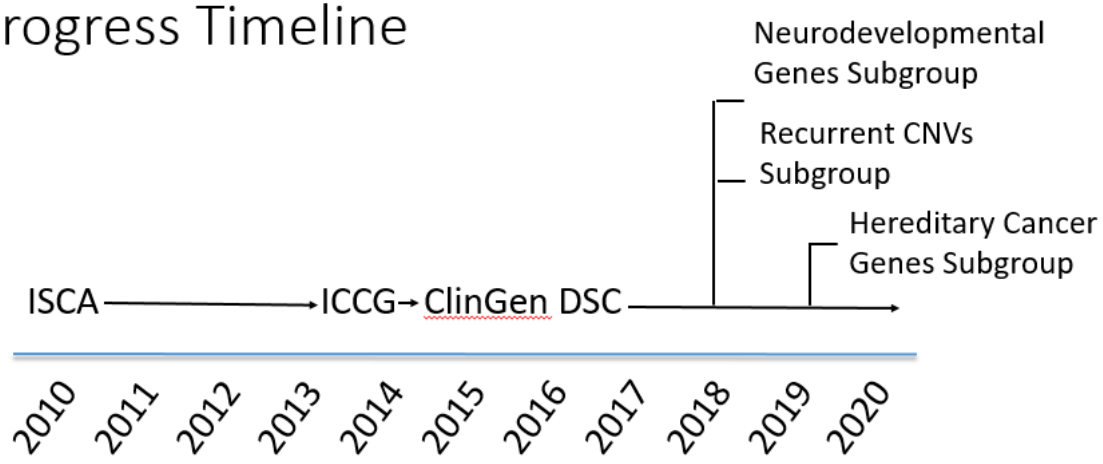
CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Towards an evidence-based process for the clinical interpretation of copy number variation

ER Riggs, DM Church, K Hanson, VL Horner, EB Kaminsky, RM Kuhn, KE Wain, ES Williams, S Aradhya, HM Kearney, DH Ledbetter, ST South, EC Thorland, CL Martin

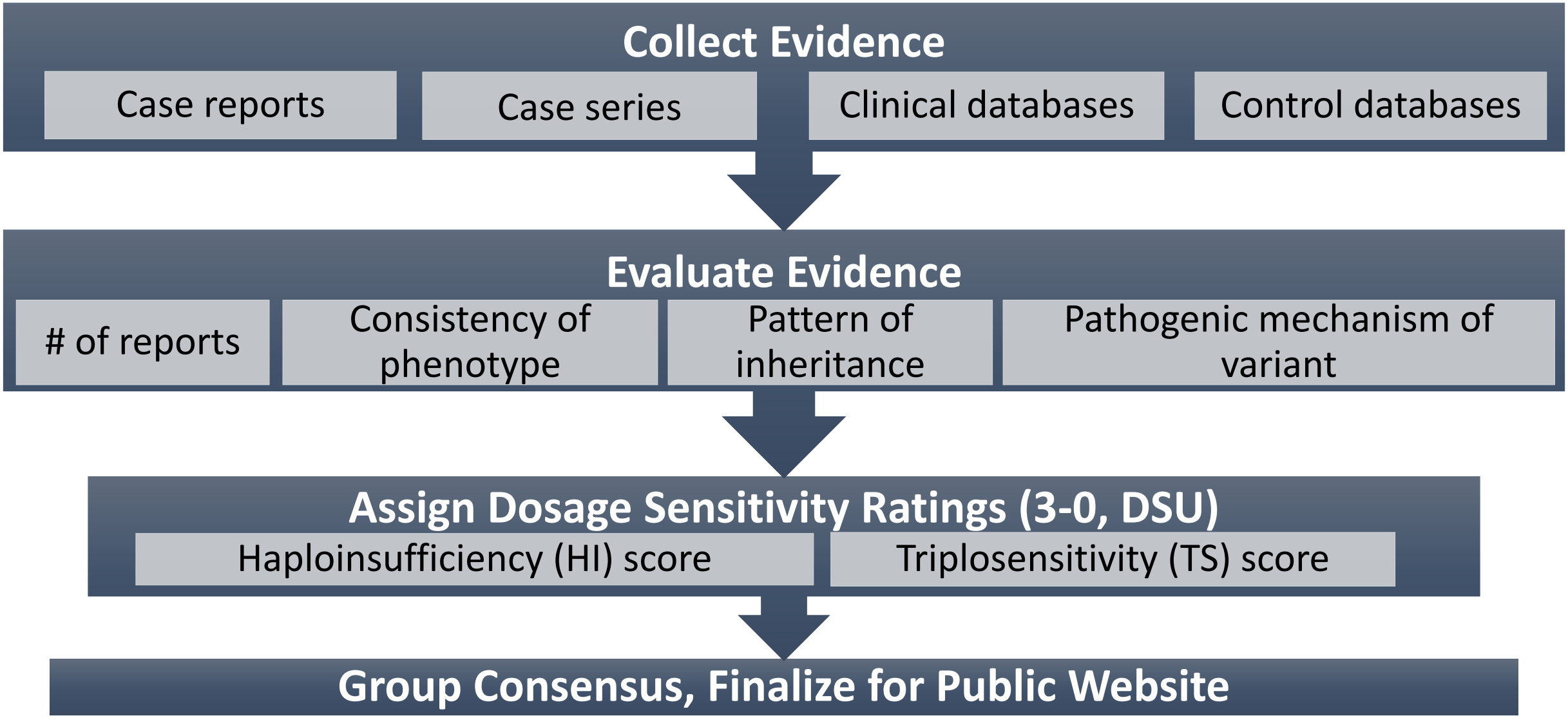
First published: 19 November 2011 | https://doi.org/10.1111/j.1399-0004.2011.01818.x | Cited by: 46

Progress Timeline

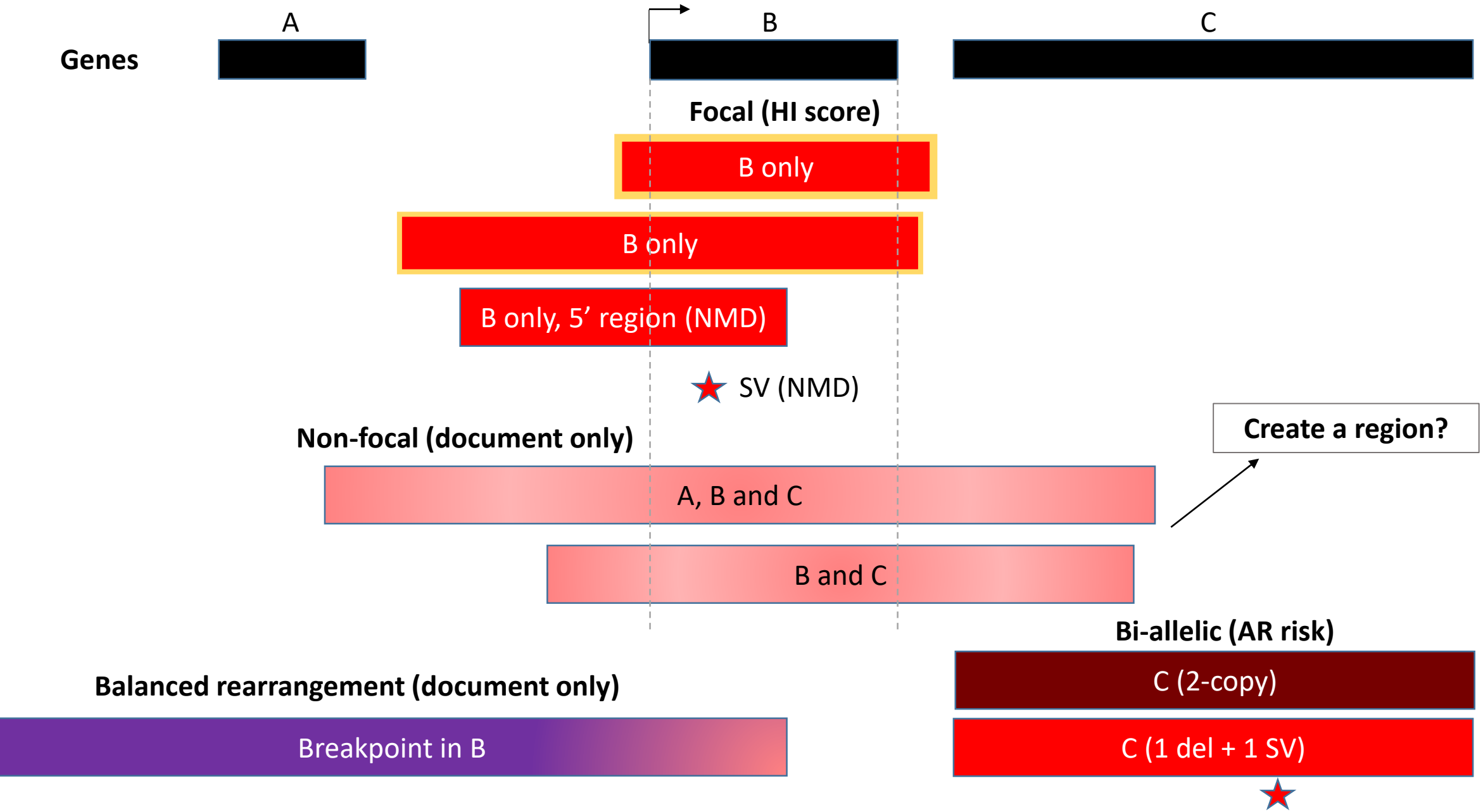


Current Dosage Sensitivity Curation (DSC) Process

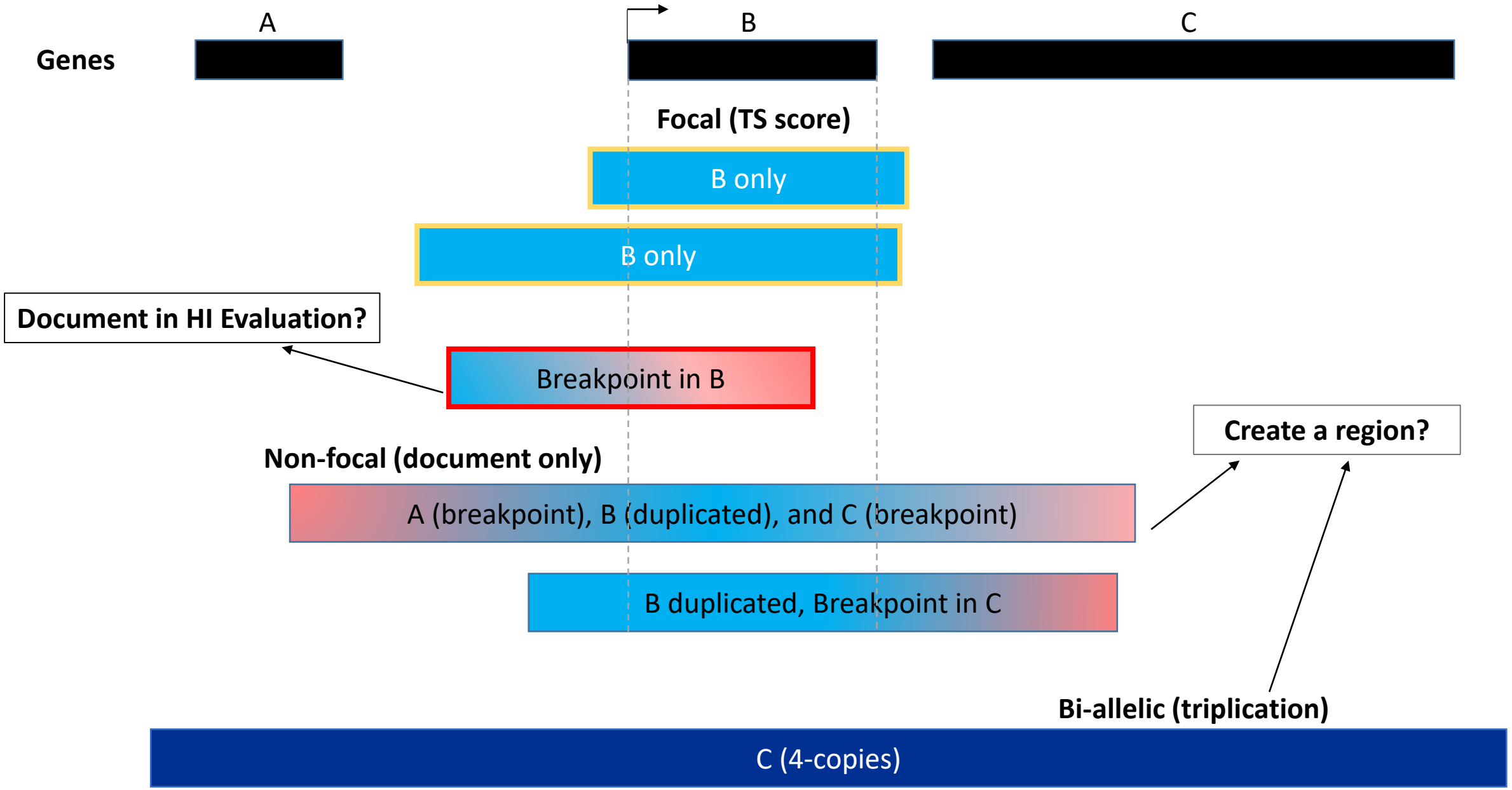
- Does loss or gain of a copy of this gene or genomic region result in a clinical phenotype?



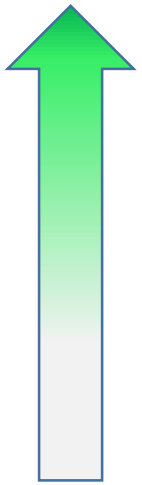
HI Evaluation



TS Evaluation



Dosage Sensitivity Ratings



Score	Strength of Evidence	Potential Clinical Classification
3	Sufficient Evidence	Pathogenic
2	Emerging/Some Evidence	Likely Pathogenic or Uncertain
1	Little/Limited Evidence	Uncertain
0	No/Insufficient Evidence	Uncertain or Likely Benign
40 (DSU)	Dosage Sensitivity Unlikely	Benign
30 (AR)	Autosomal Recessive	Autosomal Recessive

Modified from Riggs et al., *Clin Genet* (2012)

New Single Genes DSC Metric Preview

Evidence Type	Evidence	Suggested Points/Case
Individual Case Evidence: *de novo* occurrences	A. The reported phenotype is highly specific and relatively unique to the gene.	Confirmed *de novo*: 0.45 points each Assumed *de novo*: 0.30 points each *(Range: 0.15-0.45 each)*
	B. The reported phenotype is consistent, specific, but not necessarily unique to the gene.	Confirmed *de novo*: 0.30 points each Assumed *de novo*: 0.15 points each *(Range: 0-0.45 each)*
	C. The reported phenotype is consistent, but not highly specific and/or has high genetic heterogeneity.	Confirmed *de novo*: 0.15 points each Assumed *de novo*: 0.10 points each *(Range: 0-0.30 each)*
	D. The reported phenotype is NOT consistent.	0 points each *(Range: 0 to -0.30 each)*
Individual Case Evidence: Unknown Inheritance	E. Reported proband has a highly specific phenotype consistent with what is expected for the gene, but inheritance of the variant is unknown.	0.10 points each (*Range*: *0-0.15 each)*
Individual Case Evidence: Segregation Among Similarly Affected Family Members	F. 3-4 observed segregations	0.15 points
	G. 5-6 observed segregations	0.30 points
	H. 7 or more observed segregations	0.45 points
Individual Case Evidence: Apparent Non-Segregations	I. 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)*
	J. 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)*
	K. Variant IS found in another individual in the proband's family UNAFFECTED with the non-specific phenotype observed in the proband.	-0.15 points per family *(Range: 0 to -0.15)*

DRAFT

New Regions (Recurrent CNVs) DSC Metric Preview

		Suggested Points	
Evidence Type	**Evidence**	**Default**	**Range**
1) Number of unrelated probands. Variant is rare (never or rarely observed in controls).	More than 2 families reported? (yes =1, no=0). If "no," SKIP to 4	1 or 0	-
2) Phenotype (SKIP to 4 if <two unrelated probands)	a) Specific, well-defined OR	4	3->5
	b) Non-specific (0=phenotypes lack consistency)	1	0->2
3) Inheritance/ segregation	a) CNV is most often de novo OR	4	3->5
	b) CNV is most often inherited, from an *affected* parent/ CNV segregates with phenotype OR	2	1->2
	c) Inheritance is unknown OR	0	-
	d) CNV is most often inherited, from an *unaffected* parent/ CNV does not segregate with phenotype	-2	-2->0
4) Ethnic stratification and/or ascertainment bias	If present, accounted for or corrected? If "no," SKIP sections 5 and 6	-	-
5) p-value	p-value <0.05? (yes=1, no=0). If infinite LR, but below 1/2000	1 or 0	-
6) Effect Size	a) LR or OR: Lower 95% CI is greater than 1.00 (+1), 2.00 (+2), or 5.00 (+3)? OR	3, 2, 1, or 0	-
	b) Control frequency exceeds 0.1% OR the case frequency? Yes (-1)	-1	-
	Bonus point: LR or OR: Exceeds 5 and lower 95% CI does not include 1? (yes= 1, no= 0)	1 or 0	-
7) Contains an established haploinsufficient/ triplosensitive gene	Dosage sensitivity scoring has found that an individual gene within the region is either haploinsufficient or triplosensitive	1 or 0	-
8) Gene count	Loss: 25-34 genes (+1); 35+ genes (+2); Gain: 35-49 genes (+1); 50+ genes (+2)	0, 1 or 2	-
9) Control Frequency (DGV GS and gnomAD)	>0.1% (-1); >1% (-2)	0, -1, or -2	-

DRAFT

➢Updates are coming!

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All data are shown in GRCh37 and GRCh38 coordinates.

Search By Gene Name

Symbol:

Or click on the following examples: ZEB2, PTEN, MAPT

Go

Search By Location (GRCh37)

Location:

example: chr2:44,000,000-45,500,000, 2p21-2p16.2

Go

Links

- ClinGen Home Page
- Help with this site
- FAQ
- Contact Us
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- Curation of the ACMG 59 Genes
- FTP

ncbi.nlm.nih.gov/projects/dbvar/clingen/

Genes/Regions Recently Reviewed

Gene/Region name	Haploinsufficiency score	Triplosensitivity score	Date reviewed
ZNF462	3	0	2020-01-16
SIN3A	3	0	2020-01-13
15q24 recurrent region (C-D) (includes SIN3A)	3	0	2020-01-13
HMBS	3	0	2020-01-08
CHEK2	3	0	2020-01-08
15q24 recurrent region (A-C)	3	1	2020-01-03
BAP1	3	0	2019-12-27
ALK	0	0	2019-12-20
POLE	1	0	2019-12-16
TBX4	3	0	2019-12-11
PAK3	2	0	2019-12-09
ARX	3	0	2019-12-05
FBN1	3	0	2019-12-04
CNKSR2	2	0	2019-12-04
DLG3	2	0	2019-11-20
DMD	3	0	2019-11-20
13q12.12 recurrent region (includes SACS and SGCG)	30: Gene associated with autosomal recessive phenotype	0	2019-11-03
16p12.2 recurrent region (includes OTOA) (distal region)	30: Gene associated with autosomal recessive phenotype	40: Dosage sensitivity unlikely	2019-11-03

Genes/Regions with Updated Scores

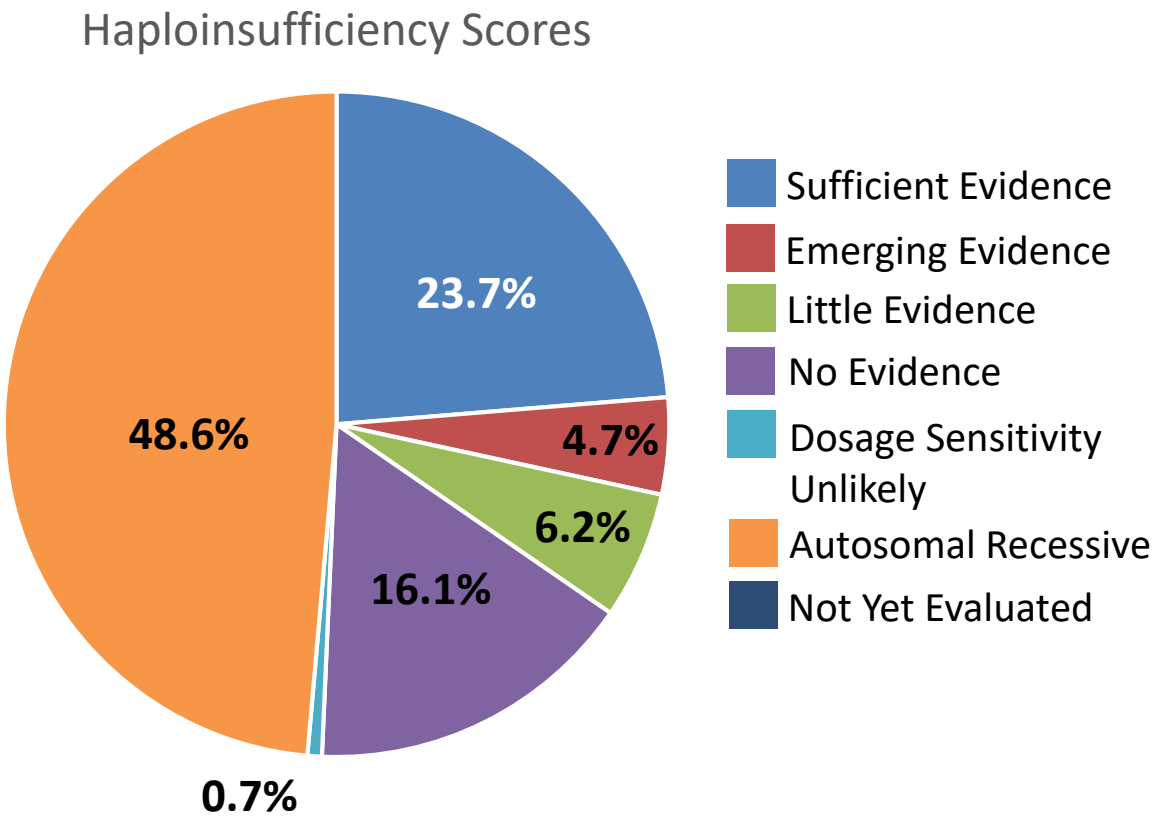
No scores were updated in the last 13 weeks

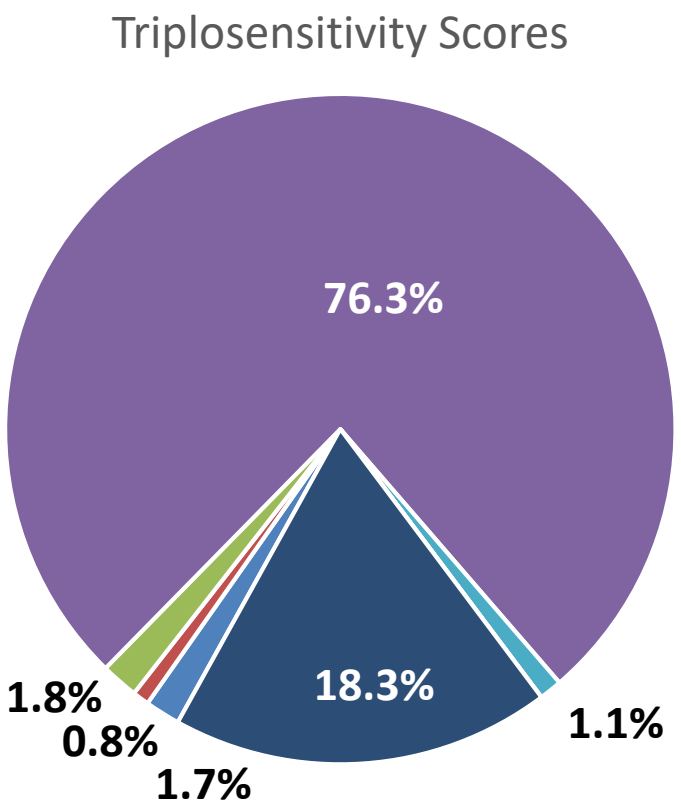
Gene/Region Curation Stats

Review Complete	1,483
Under Primary Review	102
Under Secondary Review	19
Under Group Review	21

Current Progress

- 76 region issues complete
- 1398 single gene issues complete





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All data are shown in GRCh37 and GRCh38 coordinates.

Search By Gene Name

Symbol: SHANK

Or click o B2, PTEN, MAPT

SHANK1
SHANK2
SHANK2-AS1
SHANK2-AS3
SHANK3

Go

Search By Location (GRCh37)

Location:

example: chr2:44,000,000-45,500,000, 2p21-2p16.2

Go

Links

- ClinGen Home Page
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- FAQ
- Contact Us
- Pathogenic CNV regions
- Curation of the ACMG 59 Genes
- FTP

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Links

- ClinGen Curation Home Page
- ClinGen Home Page
- Help with this site
- FAQ
- Contact Us
- Pathogenic regions (nstd45)
- Curation of the ACMG 59 Genes
- FTP
- Report information on a gene

SHANK3

Curation Status: Complete

id: ISCA-3097

Date last evaluated: 2018-08-14

Issue Type: ClinGen Gene Curation

Gene type: protein-coding

Entrez Gene: https://www.ncbi.nlm.nih.gov/gene/85358

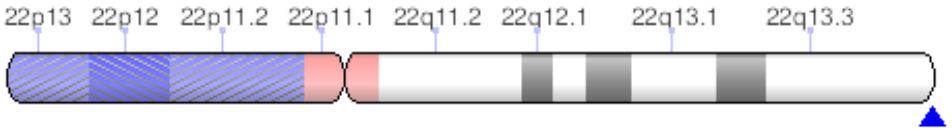
OMIM: https://omim.org/entry/606230

Gene Reviews: https://www.ncbi.nlm.nih.gov/books/NBK1116/?term=SHANK3%5Bgenesymbol%5D

ClinGen Haploinsufficiency Score: 3

ClinGen Triplosensitivity Score: 0

ExAC pLI score: 1.0



Location Information

22q13.33

GRCh37/hg19 chr22: 51,113,070-51,171,640

View: NCBI | Ensembl | UCSC

GRCh38/hg38 chr22: 50,674,642-50,733,212

View: NCBI | Ensembl | UCSC

ncbi.nlm.nih.gov/projects/dbvar/clingen/clingen_gene.cgi?sym=SHANK3&subject=

Genome View | Evidence for Haploinsufficiency Phenotypes | Evidence for Triplosensitive Phenotypes

Haploinsufficiency score: 3
Strength of Evidence (disclaimer): Sufficient evidence for dosage pathogenicity
Haploinsufficiency Phenotype: PHELAN-MCDERMID SYNDROME; PHMDS

Evidence for haploinsufficiency phenotype

PubMed ID	Description
23758760	Soorya et al (2013) reported 22q13 deletions ranging in size from 101 kb to 8.45 Mb and including the gene SHANK3 in 30 individuals. Deletions were confirmed to be de novo in 23 cases. In 6 additional cases, three fathers and three mothers were studied, and did not carry SHANK3 deletions. All parents were healthy, suggesting a de novo origin.
21984749	Sarasua et al (2011) identified highly variable 22q13 deletions ranging from 0.22 to 9.22 Mb with no common breakpoints in 71 patients using a custom-designed high-resolution aCGH platform with a resolution of 100 bp. No inheritance information was available. The authors noted a correlation between increased deletion size and the severity of phenotypes in this cohort.
21779178	Bonaglia et al (2011) described 2 unrelated individuals with developmental delay, speech delay, facial dysmorphisms, and intellectual disability and heterozygous for deletions involving SHANK3. The first patient was a 23 year old female with a 73.8 kilobase deletion that removes exons 1-17 of SHANK3. The second patient was a 6 year old male with a 38.9 kilobase deletion that removes exons 1-9 of SHANK3.

Haploinsufficiency phenotype comments:

Deletions and loss-of-function mutations in SHANK3 are causative for the majority of clinical findings observed in 22q13.3 deletion syndrome (Phelan-McDermid syndrome). This syndrome is characterized by neonatal hypotonia, global developmental delay, absent to severely delayed speech, moderate to profound intellectual disability, normal to accelerated growth, autistic features, and additional variable findings. Patients with sequence-level mutations and intragenic deletions may have a less severe clinical presentation compared to patients with large, non-focal SHANK3 deletions.

Additional relevant literature is summarized below:

PMID 17173049: Durand et al (2007) describe 2 brothers with autism, severely impaired speech, and intellectual disability who are heterozygous for a 1-bp insertion in exon 21 of SHANK3. The insertion creates a frameshift and premature truncation of the protein. The mutation was not found in an unaffected brother or parents (de novo).

PMID 20385823: Gauthier et al (2010) describe 3 brothers with schizophrenia and mild to moderate intellectual disability who are heterozygous for a de novo nonsense mutation in SHANK3, R1117X. This mutation was not found in 285 unaffected controls.

PMID 20186804: Dhar et al. (2010) reported 13 patients with 22q13.33 deletions ranging from 95 kb to 8.5 Mb identified using 244K aCGH. No inheritance information was available. About 90 genes were deleted in the largest sized deletion, whereas the smallest deletion segment contained the three genes, SHANK3, ACR, and RABL2B. The authors discuss the phenotypic contribution of deleted genes (besides SHANK3), including ARSA (AR; metachromatic leukodystrophy), TYMP (AR; mitochondrial neuro-gastrointestinal encephalomyopathy), MLC1 (AR; megalencephalic leukoencephalopathy with subcortical cysts), ALG12 (congenital disorders of glycosylation 1g), and ATXN10 (AD; cerebellar ataxia).

PMID: 11431708: Bonaglia et al (2001) describe a 4.5 year old boy with all the features of 22q13.3 deletion syndrome with a de novo balanced translocation between chromosomes 12 and 22. The breakpoints localize to chromosome 22 within exon 21 of SHANK3 and to chromosome 12 within an intron of APPL2. The translocation does not result in a loss of genetic material. The gene APPL2 is an effector of the small GTPase Rab5, which is involved in a signal transduction pathway required for cell proliferation. Although translocations do not count as primary evidence for dosage sensitivity scoring, this translocation involving SHANK3 provides additional supportive evidence for a role of SHANK3 in Phelan-McDermid syndrome.

Genome View | Evidence for Haploinsufficiency Phenotypes | Evidence for Triplosensitive Phenotypes

Triplosensitivity score: 0
Strength of Evidence (disclaimer): No evidence for dosage pathogenicity

Triplosensitivity phenotype comment:

There are currently no reports of focal duplications involving only SHANK3, therefore the current triplosensitivity score is 0.

Additional relevant literature is summarized below:

PMID 24153177: Han et al (2013) describe two unrelated patients with hyperkinetic neuropsychicatric disorders and small 22q13 duplications involving SHANK3, identified by clinical exon-targeted aCGH testing. The first patient was an 11-year old girl with ADHD, seizures, hyperactivity, poor attention, auditory overstimulation, hyperphagia and kleptomania and a duplication ranging in size between 64 kb to 240 kb (uncertain if focal). The second patient was a 35-year old male with bipolar disorder and epilepsy and a duplication ranging in size between 115 kb and 302 kb (uncertain if focal). Inheritance information was unavailable.

PMID 17975801: Okamoto et al (2007) described two unrelated patients with non-focal duplications in 22q13 including the gene SHANK3. Common clinical findings included infantile hypotonia, developmental delay and growth deficiency. Patient 1 had a de novo ~6 Mb duplication. Patient 2 showed a paternally inherited unbalanced translocation resulting in 17p deletion and 22q13 gain (>2 Mb) father: t(17;22)(p13;q13).

See also additional reports of non-focal, larger 22q13 duplications: PMID 31254375 (Bitar et al 2019), PMID 27846046 (Chen et al 2017), PMID 17539913 (Failla et al 2007), PMID 17173049 (Durand et al 2007).

Example: arr[GRCh37] 22q13.33(50239255_51248495)x1

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Search By Gene Name

Symbol:

Or click on the following examples: ZEB2, PTEN, MAPT

Go

Search By Location (GRCh37)

Location: *chr22:50239255-51248495*

example: chr2:44,000,000-45,500,000, 2p21-2p16.2

Go

Links

- ClinGen Home Page
- Help with this site
- FAQ
- Contact Us
- Pathogenic CNV regions
- Curation of the ACMG 59 Genes
- FTP

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Links
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Location Search Results

Submitted location: chr22:50,239,255-51,248,495

"N/A" indicates that this gene has not yet been evaluated

Gene Issues (44) | Region Issues (0)

Sort by…

Location search results

Items 1 - 20 of 44 << First < Prev Page 1 of 3 Next > Last >>

Gene Symbol	Haploinsufficiency score	Triplosensitivity score	Curation Status	Region Location (GRCh37)	ExAC pLI	OMIM	Relationship to Submitted Location	ISCA ID
ZBED4	N/A	N/A	Awaiting Review	chr22:50,247,497-50,283,726	0.99	612552	Contained	ISCA-917
ALG12	30: Gene associated with autosomal recessive phenotype	0	Complete	chr22:50,296,852-50,312,106	0.008	607144	Contained	ISCA-31851

Gene Issues (44) | Region Issues (0)

Location search results

Items 1 - 20 of 44 << First < Prev Page 1 of 3 Next > Last >>

Gene Symbol	Haploinsufficiency score	Triplosensitivity score	Curation Status	Region Location (GRCh37)	ExAC pLI	OMIM	Relationship to Submitted Location	ISCA ID
SHANK3	3	0	Complete	chr22:51,113,070-51,171,640	1.0	606230	Contained	ISCA-3097
ALG12	30: Gene associated with autosomal recessive phenotype	0	Complete	chr22:50,296,852-50,312,106	0.008	607144	Contained	ISCA-31851
MLC1	30: Gene associated with autosomal recessive phenotype	Not yet evaluated	Complete	chr22:50,497,820-50,524,358	0.0	605908	Contained	ISCA-23102
TUBGCP6	30: Gene associated with autosomal recessive phenotype	0	Complete	chr22:50,656,118-50,683,400	0.0	610053	Contained	ISCA-32792
TYMP	30: Gene associated with autosomal recessive phenotype	Not yet evaluated	Complete	chr22:50,964,181-50,968,514	0.0	603041	Contained	ISCA-28356
CHKB	30: Gene associated with autosomal recessive phenotype	0	Complete	chr22:51,017,387-51,021,428	0.001	612395	Contained	ISCA-34928
ARSA	30: Gene associated with autosomal recessive phenotype	0	Complete	chr22:51,061,182-51,066,601	0.0	607574	Contained	ISCA-31588
ZBED4	N/A	N/A	Awaiting Review	chr22:50,247,497-50,283,726	0.99	612552	Contained	ISCA-917
CRELD2	N/A	N/A	Awaiting Review	chr22:50,312,278-50,321,188	0.0	607171	Contained	ISCA-14047
PIM3	N/A	N/A	Awaiting Review	chr22:50,354,143-50,357,720	0.937	610580	Contained	ISCA-14499

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ncbi.nlm.nih.gov/projects/dbvar/clingen/

Index of /pub/dbVar/clingen

[parent directory]

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ClinGen_gene_curation_list_GRCh38.tsv	198 kB	1/15/20, 1:00:00 AM
ClinGen_haploinsufficiency_gene.bed	0 B	2/25/18, 5:00:00 PM
ClinGen_haploinsufficiency_gene_GRCh37.bed	44.1 kB	1/15/20, 1:00:00 AM
ClinGen_haploinsufficiency_gene_GRCh38.bed	44.0 kB	1/15/20, 1:00:00 AM
ClinGen_recurrent_CNV_V1.0-hg19.aed	32.0 kB	10/8/18, 6:00:00 PM
ClinGen_recurrent_CNV_V1.0-hg19.bed	12.5 kB	10/8/18, 6:00:00 PM
ClinGen_recurrent_CNV_V1.0-hg38.aed	21.3 kB	4/2/19, 6:00:00 PM
ClinGen_recurrent_CNV_V1.0-hg38.bed	12.2 kB	4/2/19, 6:00:00 PM
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ClinGen_region_curation_list_GRCh38.tsv	15.7 kB	1/15/20, 1:00:00 AM
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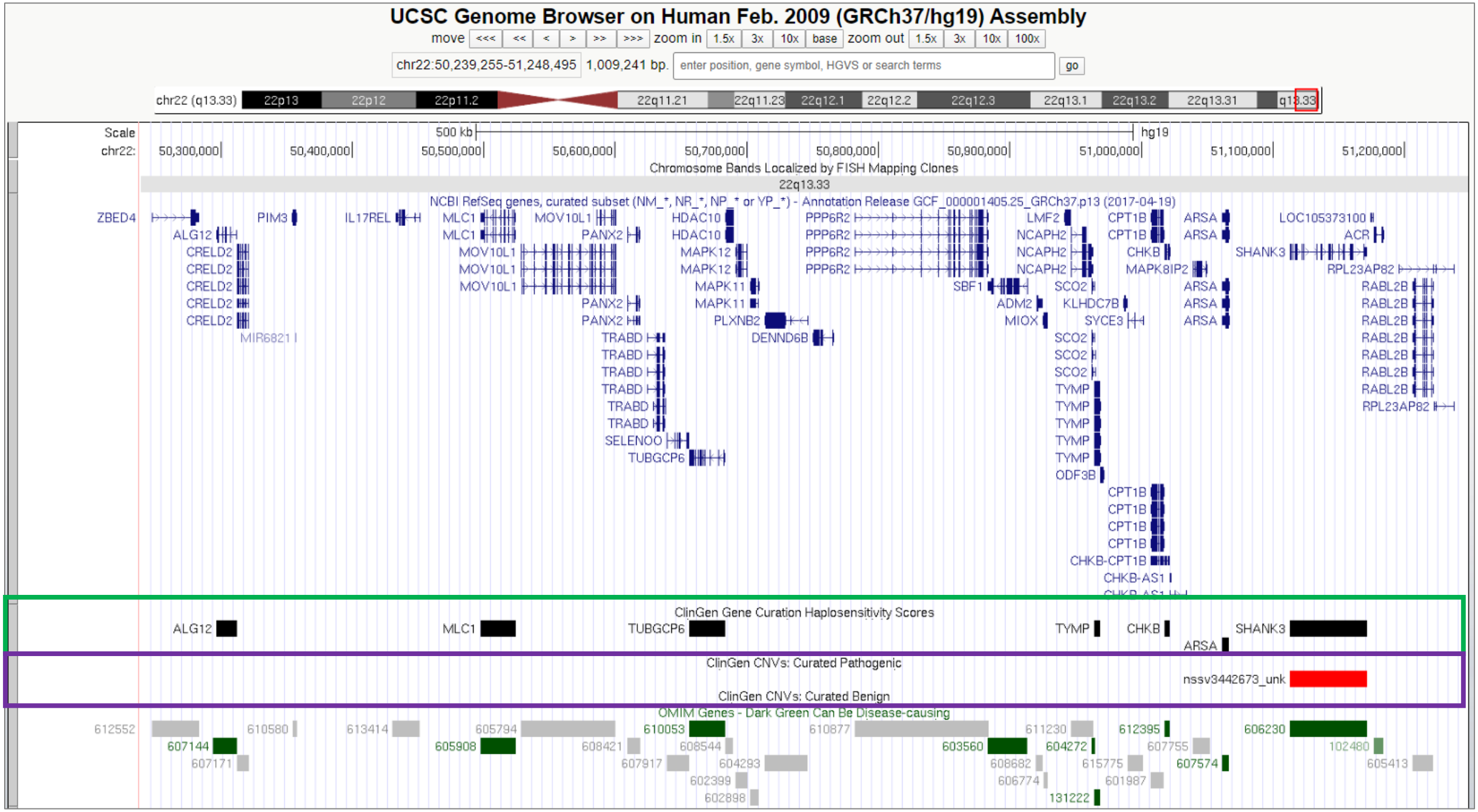
ftp://ftp.ncbi.nlm.nih.gov/pub/dbVar/clingen


UCSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) Assembly
move <<< << < > >> >>> zoom in 1.5x 3x 10x base zoom out 1.5x 3x 10x 100x
chr22:50,239,255-51,248,495 1,009,241 bp.
enter position, gene symbol, HGVS or search terms
go
chr22 (q13.33)
22p13 22p12 22p11.2 22q11.21 22q11.23 22q12.1 22q12.2 22q12.3 22q13.1 22q13.2 22q13.31 q13.33
Scale
500 kb
hg19
chr22:
50,300,000 50,400,000 50,500,000 50,600,000 50,700,000 50,800,000 50,900,000 51,000,000 51,100,000 51,200,000
Chromosome Bands Localized by FISH Mapping Clones
22q13.33
NCBI RefSeq genes, curated subset (NM_*, NR_*, NP_* or YP_*) - Annotation Release GCF_000001405.25_GRCh37.p13 (2017-04-19)
ZBED4
ALG12
CRELD2
MIR6821
PIM3
IL17REL
MLC1
MOV10L1
PANX2
TRABD
SELENOO
TUBGCP6
HDAC10
MAPK12
MAPK11
PLXNB2
DENND6B
PPP6R2
SBF1
ADM2
MIOX
LMF2
NCAPH2
SCO2
KLHDC7B
SYCE3
TYMP
ODF3B
CPT1B
CHKB
MAPK8IP2
CHKB-CPT1B
CHKB-AS1
ARSA
LOC105373100
ACR
SHANK3
RPL23AP82
RABL2B
ClinGen Gene Curation Haplosensitivity Scores
ALG12 MLC1 TUBGCP6 TYMP CHKB SHANK3 ARSA
ClinGen CNVs: Curated Pathogenic
nssv3442673_unk
ClinGen CNVs: Curated Benign
OMIM Genes - Dark Green Can Be Disease-causing
612552 610580 613414 605794 610053 610877 611230 612395 606230
607144 605908 608421 608544 603560 604272 607755 102480
607171 607917 604293 608682 615775 607574 605413
602399 606774 601987
602898 131222

Index of /pub/dbVar/clingen

[parent directory]

Name	Size	Date Modified
ClinGen_gene_curation_list.tsv	0 B	2/25/18, 5:00:00 PM
ClinGen_gene_curation_list_GRCh37.tsv	198 kB	1/15/20, 1:00:00 AM
ClinGen_gene_curation_list_GRCh38.tsv	198 kB	1/15/20, 1:00:00 AM
ClinGen_haploinsufficiency_gene.bed	0 B	2/25/18, 5:00:00 PM
ClinGen_haploinsufficiency_gene_GRCh37.bed	44.1 kB	1/15/20, 1:00:00 AM
ClinGen_haploinsufficiency_gene_GRCh38.bed	44.0 kB	1/15/20, 1:00:00 AM
ClinGen_recurrent_CNV_V1.0-hg19.aed	32.0 kB	10/8/18, 6:00:00 PM
ClinGen_recurrent_CNV_V1.0-hg19.bed	12.5 kB	10/8/18, 6:00:00 PM
ClinGen_recurrent_CNV_V1.0-hg38.aed	21.3 kB	4/2/19, 6:00:00 PM
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ClinGen_region_curation_list_GRCh38.tsv	15.7 kB	1/15/20, 1:00:00 AM
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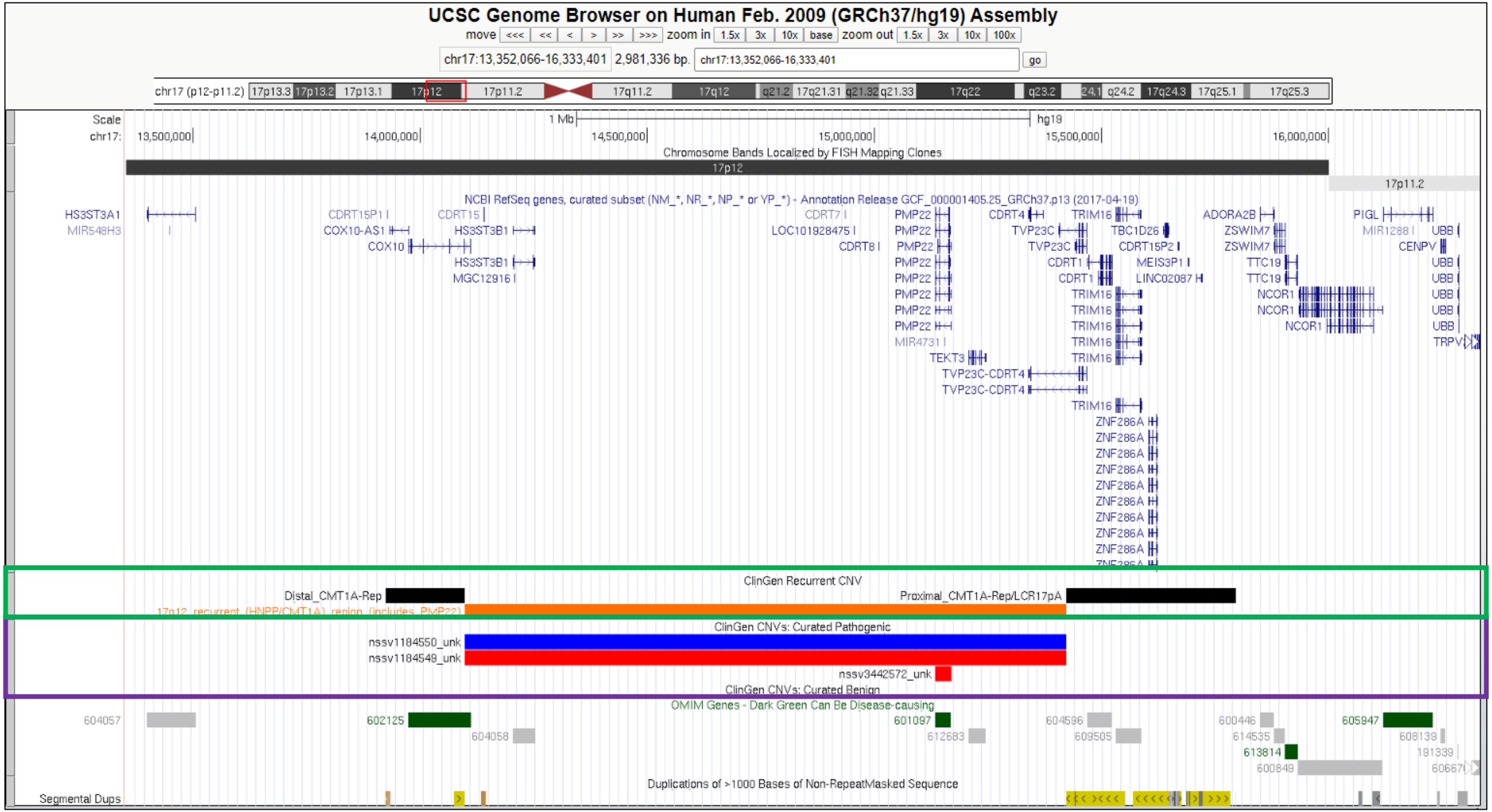
ClinGen_triplosensitivity_gene_GRCh38.bed	47.5 kB	1/15/20, 1:00:00 AM
README	7.8 kB	4/1/19, 6:00:00 PM
all_clinical_significance/		4/10/17, 6:00:00 PM

ftp://ftp.ncbi.nlm.nih.gov/pub/dbVar/clingen


UCSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) Assembly
move <<< << < > >> >>> zoom in 1.5x 3x 10x base zoom out 1.5x 3x 10x 100x
chr17:13,352,066-16,333,401 2,981,336 bp. chr17:13,352,066-16,333,401 go
chr17 (p12-p11.2) 17p13.3 17p13.2 17p13.1 17p12 17p11.2 17q11.2 17q12 q21.2 17q21.31 q21.32 q21.33 17q22 q23.2 24.1 q24.2 17q24.3 17q25.1 17q25.3
Scale
chr17:
1 Mb
hg19
13,500,000
14,000,000
14,500,000
15,000,000
15,500,000
16,000,000
Chromosome Bands Localized by FISH Mapping Clones
17p12
17p11.2
NCBI RefSeq genes, curated subset (NM_*, NR_*, NP_* or YP_*) - Annotation Release GCF_000001405.25_GRCh37.p13 (2017-04-19)
HS3ST3A1
MIR548H3
CDRT15P1
CDRT15
COX10-AS1
HS3ST3B1
COX10
HS3ST3B1
MGC12916
CDRT7
LOC101928475
CDRT8
PMP22
MIR4731
TEKT3
TVP23C-CDRT4
CDRT4
TVP23C
CDRT1
TRIM16
ZNF286A
ADORA2B
TBC1D26
CDRT15P2
MEIS3P1
LINC02087
ZSWIM7
TTC19
NCOR1
PIGL
MIR1288
UBB
CENPV
TRPV
ClinGen Recurrent CNV
Distal_CMT1A-Rep
Proximal_CMT1A-Rep/LCR17pA
17p12 recurrent (HNPP/CMT1A) region (includes PMP22)
ClinGen CNVs: Curated Pathogenic
nssv1184550_unk
nssv1184549_unk
nssv3442572_unk
ClinGen CNVs: Curated Benign
OMIM Genes - Dark Green Can Be Disease-causing
604057
602125
604058
601097
612683
604596
609505
600446
614535
613814
600849
605947
608139
191339
606671
Duplications of >1000 Bases of Non-RepeatMasked Sequence
Segmental Dups

ClinGen Dosage Sensitivity Curation Page

PMP22

Curation Status: Complete

id: ISCA-27257

Date last evaluated: 2012-07-12

Issue Type: ClinGen Gene Curation

Gene type: protein-coding

Entrez Gene: https://www.ncbi.nlm.nih.gov/gene/5376

OMIM: https://omim.org/entry/601097

Gene Reviews: https://www.ncbi.nlm.nih.gov/books/NBK1116/?term=PMP22%5Bgenesymbol%5D

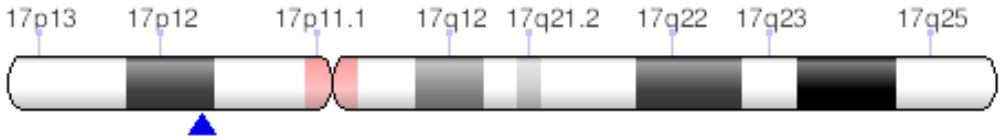
ClinGen Haploinsufficiency Score: 3

ClinGen Triplosensitivity Score: 0

ExAC pLI score: 0.833

See related regions:

17p12 recurrent (HNPP/CMT1A) region (includes PMP22)



Location Information

17p12

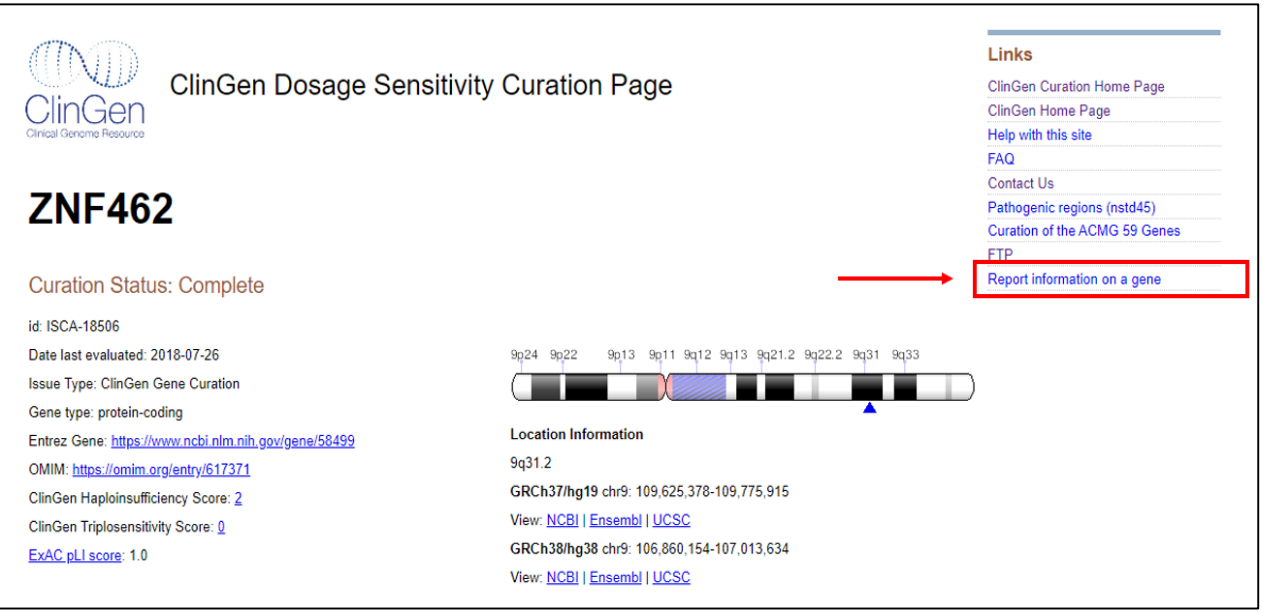
GRCh37/hg19 chr17: 15,133,094-15,168,690

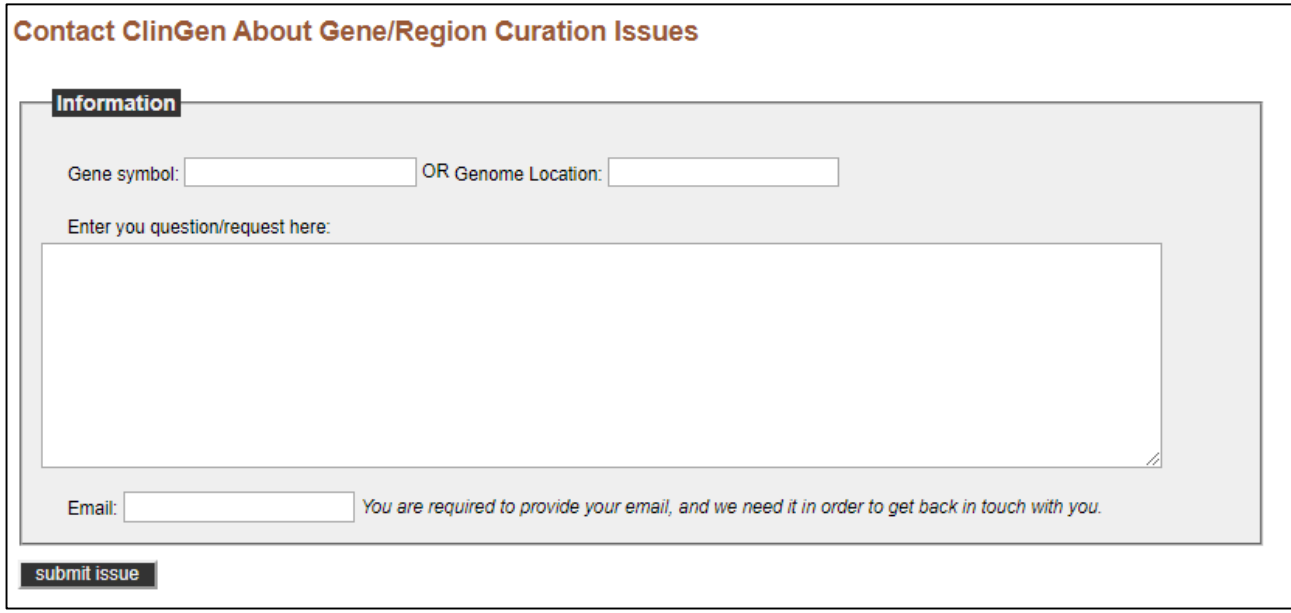
View: NCBI | Ensembl | UCSC

GRCh38/hg38 chr17: 15,229,777-15,265,373

View: NCBI | Ensembl | UCSC

Got feedback/questions? Let us know!





https://www.ncbi.nlm.nih.gov/projects/dbvar/clingen/contact.shtml

The DSC Team (Acknowledgements)

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- Angela Lager
- Benjamin Clyde
- Benjamin Hilton
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- Deborah Ritter
- Diogo Lovato
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- Erik Thorland*
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- George Burghel
- Guang Li
- Hiba Risheg
- Hutton Kearney
- John Herriges*
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- Vaidehi Jobanputra
- Wahab Khan
- Yang Cao
- Yiping Shen
- Zoe Lewis

*DSC Leadership

CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Towards an evidence-based process for the clinical interpretation of copy number variation

ER Riggs, DM Church, K Hanson, VL Horner, EB Kaminsky, RM Kuhn, KE Wain, ES Williams, S Aradhya, HM Kearney, DH Ledbetter, ST South, EC Thorland, CL Martin

First published: 19 November 2011 | https://doi.org/10.1111/j.1399-0004.2011.01818.x | Cited by: 46

Human Mutation Variation, Informatics, and Disease HGV

RESEARCH ARTICLE

Copy number variant discrepancy resolution using the ClinGen dosage sensitivity map results in updated clinical interpretations in ClinVar

Erin R. Riggs, Tristan Nelson, Andrew Merz, Todd Ackley, Brian Bunke, Christin D. Collins, Morag N. Collinson, Yao-Shan Fan, McKinsey L. Goodenberger, Denae M. Golden, Linda Haglund-Hazy, Danijela Krgovic, Allen N. Lamb, Zoe Lewis, Guang Li, Yajuan Liu, Jeanne Meck, Whitney Neufeld-Kaiser, Cassandra K. Runke, Jennifer N. Sanmann, Dimitri J. Stavropoulos, Emma Strong, Meng Su, Marwan K. Tayeh, Nadja Kokalj Vokac, Erik C. Thorland, Erica Andersen, Christa L. Martin ... See fewer authors

First published: 10 August 2018 | https://doi.org/10.1002/humu.23610 | Cited by: 1

Funding information: This work is supported by the National Human Genome Research Institute (NHGRI) through grant U41HG006834.
For the ClinGen/ClinVar Special Issue

2011

ACMG POLICY STATEMENTS, STANDARDS AND GUIDELINES

American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants

Hutton M. Kearney, PhD[1], Erik C. Thorland, PhD[2], Kerry K. Brown, PhD[3], Fabiola Quintero-Rivera, MD[4], and Sarah T. South, PhD[5], A Working Group of the American College of Medical Genetics (ACMG) Laboratory Quality Assurance Committee

© American College of Medical Genetics and Genomics

ACMG STANDARDS AND GUIDELINES | Genetics inMedicine

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf of the ACMG Laboratory Quality Assurance Committee

© American College of Medical Genetics and Genomics

ACMG TECHNICAL STANDARDS | Genetics inMedicine

Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen)

Erin Rooney Riggs, MS, CGC[1], Erica F. Andersen, PhD[2,3], Athena M. Cherry, PhD[4], Sibel Kantarci, PhD[5], Hutton Kearney, PhD[6], Ankita Patel, PhD[7], Gordana Raca, MD, PhD[8], Deborah I. Ritter, PhD[9], Sarah T. South, PhD[10], Erik C. Thorland, PhD[6], Daniel Pineda-Alvarez, MD[11], Swaroop Aradhya, PhD[4,11] and Christa Lese Martin, PhD[1]

Received: 1 May 2018 | Revised: 15 July 2018 | Accepted: 23 August 2018

DOI: 10.1002/humu.23626

SPECIAL ARTICLE

WILEY | HGVS HUMAN GENOME VARIATION SOCIETY

Recommendations for interpreting the loss of function PVS1 ACMG/AMP variant criterion

Ahmad N. Abou Tayoun[1,2]* | Tina Pesaran[3] | Marina T. DiStefano[4] | Andrea Oza[4] | Heidi L. Rehm[4,5,6] | Leslie G. Biesecker[7] | Steven M. Harrison[4] |

ClinGen Sequence Variant Interpretation Working Group (ClinGen SVI)

2020

Section 2: Overlap with Established DS Genes/Genomic Regions

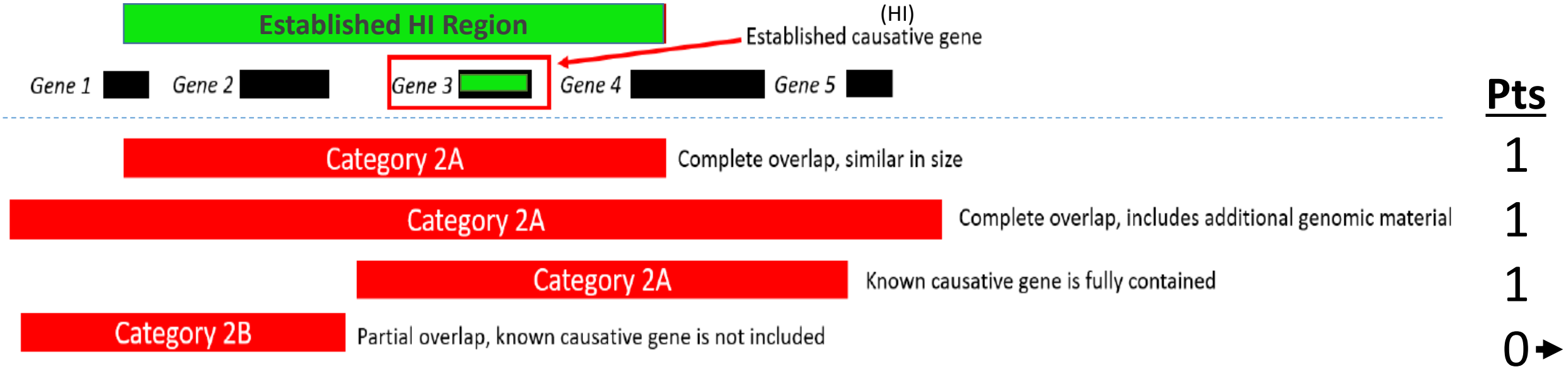
Evidence type	Evidence	Suggested points/case	Max score
Overlap with ESTABLISHED DS genes or genomic regions and consideration of reason for referral	**2A**. Complete overlap of an established DS gene/genomic region.	1.00	1.00
	2B. Partial overlap of an established DS genomic region • The observed CNV does NOT contain the known causative gene or critical region for this established DS 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 DS genomic region	0 (Continue evaluation)	0

- "Established dosage sensitive" (DS) genes or genomic regions are those with sufficient evidence for HI and/or TS (i.e., a score of 3)
- A list of genes and regions that have been evaluated using these criteria is updated daily and can be accessed at https://www.ncbi.nlm.nih.gov/projects/dbvar/clingen/

➢ LOSS

Points	Proposed Classification
0.99 or more	Pathogenic
0.90 to 0.98	Likely Pathogenic
0.89 to -0.89	Uncertain
-0.90 to -0.98	Likely Benign
-0.99 or less	Benign

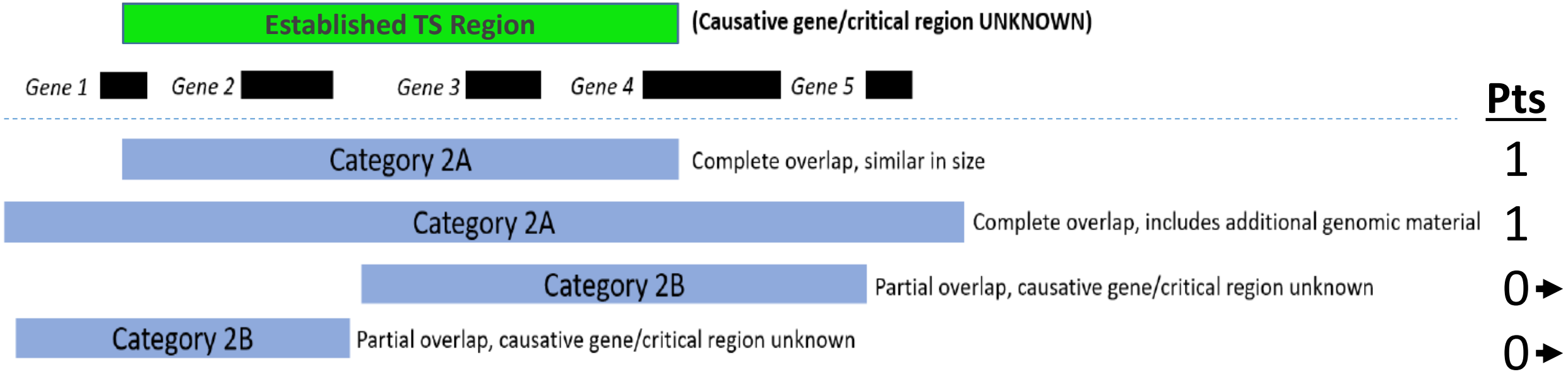
Section 2:



GAIN

Points	Proposed Classification
0.99 or more	Pathogenic
0.90 to 0.98	Likely Pathogenic
0.89 to -0.89	Uncertain
-0.90 to -0.98	Likely Benign
-0.99 or less	Benign

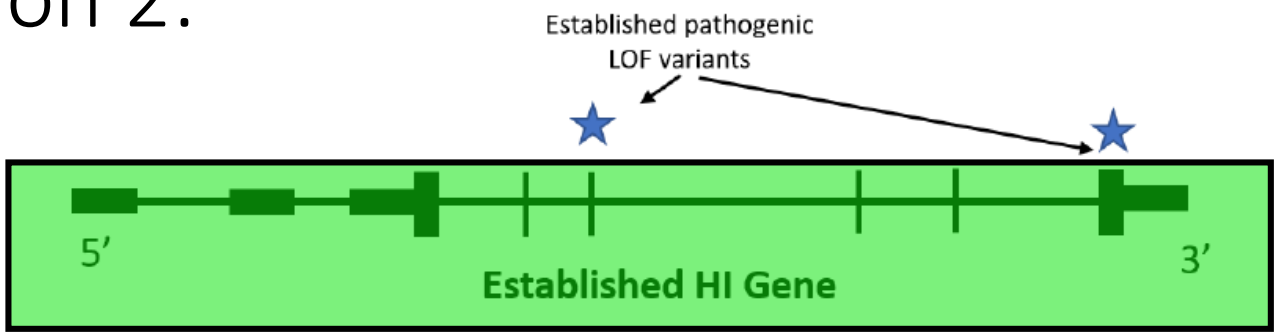
Section 2:



GENE-LEVEL

More on Feb 6!

Section 2:



Category 2C-1 — Overlap with 5' end, coding sequence involved

Category 2C-2 — Only 5' UTR is involved

Category 2D-1 — Only 3' UTR is involved

Category 2D-2 — Only the last exon is involved; other established pathogenic variants have been reported in this exon

Category 2D-4 — Overlap with 3' end; includes other exons in addition to the last exon; nonsense-mediated decay expected to occur

Category 2E — Both breakpoints are within the HI gene

Category 2H — HI gene fully contained within observed copy number gain

Category 2I — Both breakpoints are within the HI gene

Category 2J or 2K — One breakpoint within the HI gene

Section 2: Overlap with Established BENIGN Genes/Genomic Regions

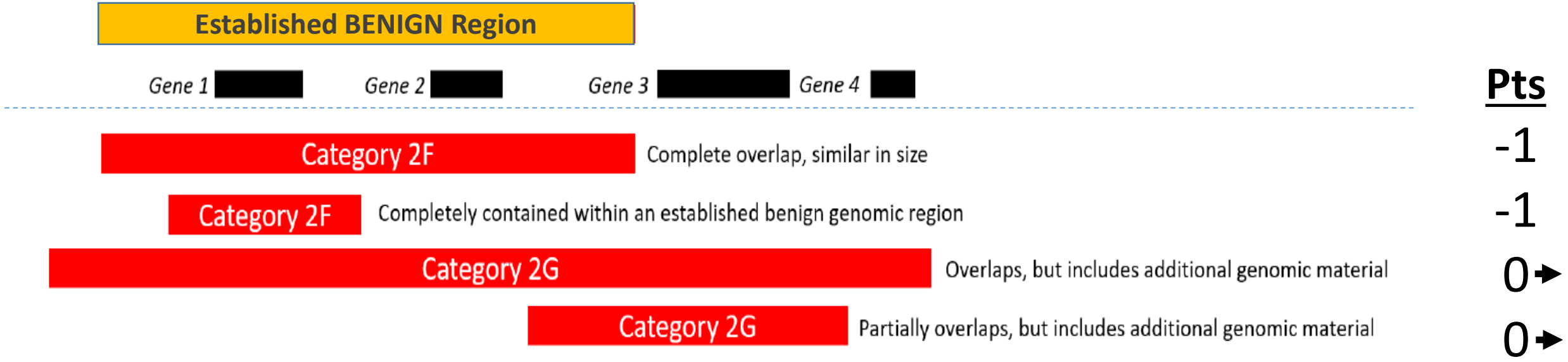
Evidence type	Evidence	Suggested points/case	Max score
Overlap with ESTABLISHED benign genes or genomic regions	**2F**. Completely contained within an established benign CNV region.	−1	−1
	2G. Overlaps an established benign CNV, but includes additional genomic material.	0 (Continue evaluation)	0

- “Established benign” genes or genomic regions are those classified as “dosage sensitivity unlikely” per the ClinGen Dosage Sensitivity Map
- In general, these are CNVs that occur at high frequency in the general population (1% or higher), are not known to be more frequent in cases compared to controls, and are not associated with any consistent phenotype

➢ LOSS

Points	Proposed Classification
0.99 or more	Pathogenic
0.90 to 0.98	Likely Pathogenic
0.89 to -0.89	Uncertain
-0.90 to -0.98	Likely Benign
-0.99 or less	Benign

Section 2:



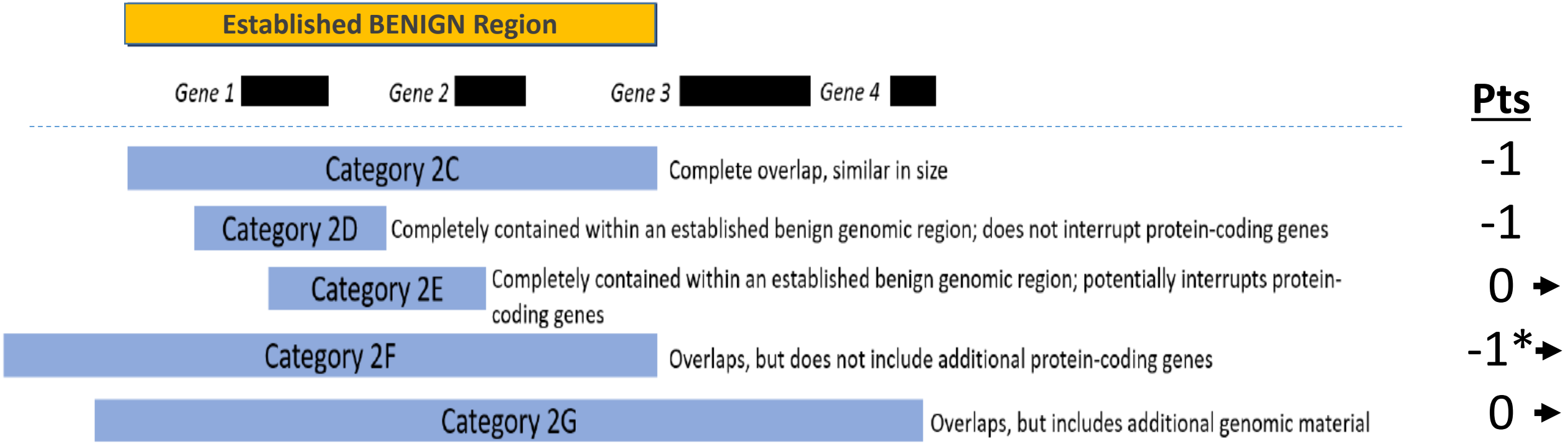
Section 2: Overlap with Established BENIGN Genes/Genomic Regions

Evidence type	Evidence	Suggested points/case	Max score
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

GAIN

Points	Proposed Classification
0.99 or more	Pathogenic
0.90 to 0.98	Likely Pathogenic
0.89 to -0.89	Uncertain
-0.90 to -0.98	Likely Benign
-0.99 or less	Benign

Section 2:



*(range: 0 to -1.00)

CNVs overlapping “established” genes/regions…

- In general, if a CNV reaches a 1 or -1 score due to complete overlap with an established dosage sensitive gene or region, users of these metrics may not need to proceed further
- However, for some CNVs, particularly those with incomplete penetrance and/or variability expressivity, additional evaluation may be necessary, and caution is recommended before interpreting a CNV based on this information alone
- When reviewing ClinGen DS scores, it is important to note the date of last evaluation, as curations reflect a temporally static assessment. New evidence may have emerged since the date of last evaluation, either supporting or refuting the original assessment

ClinGen
Clinical Genome Resource

Acknowledgements

Today's Attendance URL and QR code:

Please log attendance!

https://tinyurl.com/AttendanceJan23

- Erin Rooney Riggs
- Christa Lese Martin
- Daniel Pineda Alvarez
- Swaroop Aradhya
- Erica Andersen
- Athena Cherry
- Sibel Kantarci
- Hutton Kearney
- Ankita Patel
- Gordana Raca
- Deborah Ritter
- Sarah South
- Erik Thorland
- Outside Reviewers (11)
- ClinGen Genomic Variant and Sequence Variant Interpretation Working Groups
- Ronak Patel and ClinGen Baylor team for CNV calculator

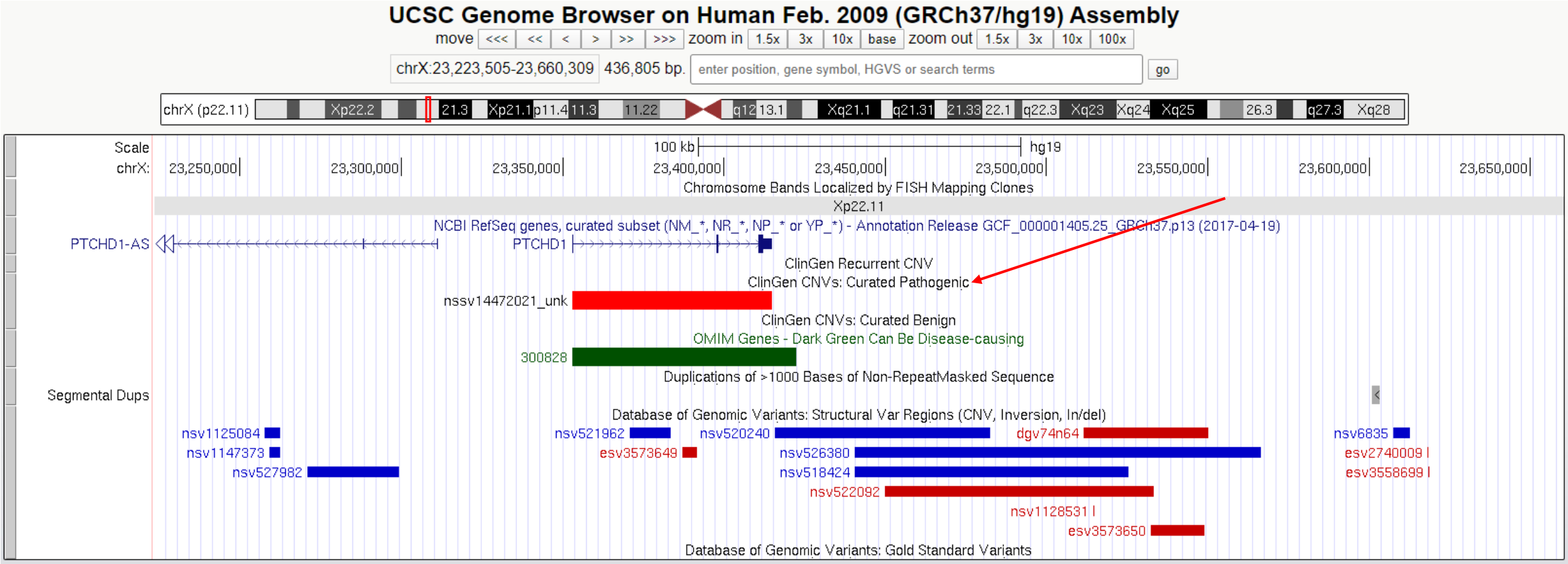
ClinGen is primarily funded by the National Human Genome Research Institute (NHGRI), through the following three grants:U41HG006834, U41HG009649, U41HG009650

Case V

arr[GRCh37] Xp22.11(23223505_23660309)x1 mat

3 year-old female referred for genomic microarray testing due to postnatal growth deficiency, VSD, scoliosis, hand anomalies, hearing loss, craniofacial dysmorphism

CNV is maternally inherited


UCSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) Assembly
move <<< << < > >> >>> zoom in 1.5x 3x 10x base zoom out 1.5x 3x 10x 100x
chrX:23,223,505-23,660,309 436,805 bp. enter position, gene symbol, HGVS or search terms go
chrX (p22.11) Xp22.2 21.3 Xp21.1 p11.4 11.3 11.22 q12 13.1 Xq21.1 q21.31 21.33 22.1 q22.3 Xq23 Xq24 Xq25 26.3 q27.3 Xq28
Scale 100 kb hg19
chrX: 23,250,000 23,300,000 23,350,000 23,400,000 23,450,000 23,500,000 23,550,000 23,600,000 23,650,000
Chromosome Bands Localized by FISH Mapping Clones
Xp22.11
NCBI RefSeq genes, curated subset (NM_*, NR_*, NP_* or YP_*) - Annotation Release GCF_000001405.25_GRCh37.p13 (2017-04-19)
PTCHD1-AS
PTCHD1
ClinGen Recurrent CNV
ClinGen CNVs: Curated Pathogenic
nssv14472021_unk
ClinGen CNVs: Curated Benign
OMIM Genes - Dark Green Can Be Disease-causing
300828
Duplications of >1000 Bases of Non-RepeatMasked Sequence
Segmental Dups
Database of Genomic Variants: Structural Var Regions (CNV, Inversion, In/del)
nsv1125084
nsv1147373
nsv527982
nsv521962
esv3573649
nsv520240
nsv526380
nsv518424
nsv522092
dgv74n64
nsv1128531
esv3573650
nsv6835
esv2740009
esv3558699
Database of Genomic Variants: Gold Standard Variants

ClinGen Clinical Genome Resource

ClinGen Dosage Sensitivity Curation Page

Links

- ClinGen Curation Home Page
- ClinGen Home Page
- Help with this site
- FAQ
- Contact Us

Location Search Results

Submitted location: chrx:23,223,505-23,660,309

"N/A" indicates that this gene has not yet been evaluated

Gene Issues (3) | Region Issues (0)

Location search results

Gene Symbol	Haploinsufficiency score	Triplosensitivity score	Curation Status	Region Location (GRCh37)	ExAC pLI	OMIM	Relationship to Submitted Location	ISCA ID
PTCHD1-AS	N/A	N/A	Awaiting Review	chrx:22,211,122-23,311,263			Overlap	ISCA-43098
PTCHD1	3	0	Complete	chrx:23,352,985-23,414,918	0.947	300828	Contained	ISCA-33627
LOC100217367	N/A	N/A	Awaiting Review	chrx:23,369,112-23,369,771			Contained	ISCA-8162

ClinGen Dosage Sensitivity Curation Page

PTCHD1

Curation Status: Complete

id: ISCA-33627

Date last evaluated: 2018-02-28

Issue Type: ClinGen Gene Curation

Gene type: protein-coding

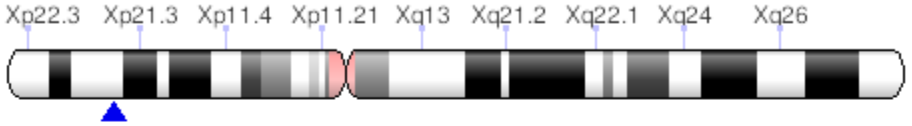
Entrez Gene: https://www.ncbi.nlm.nih.gov/gene/139411

OMIM: https://omim.org/entry/300828

ClinGen Haploinsufficiency Score: 3

ClinGen Triplosensitivity Score: 0

ExAC pLI score: 0.947



Location Information

Xp22.11

GRCh37/hg19 chrX: 23,352,985-23,414,918

View: NCBI | Ensembl | UCSC

GRCh38/hg38 chrX: 23,334,370-23,404,374

View: NCBI | Ensembl | UCSC

Print Full Report

Genome View | Evidence for Haploinsufficiency Phenotypes | Evidence for Triplosensitive Phenotypes

Haploinsufficiency score: 3
Strength of Evidence (disclaimer): Sufficient evidence for dosage pathogenicity
Haploinsufficiency Phenotype: AUTISM, SUSCEPTIBILITY TO, X-LINKED 4; AUTSX4

Evidence for haploinsufficiency phenotype

PubMed ID	Description
25131214	Chaudhry et al. 2015 studied 23 individuals from 16 families with PTCHD1 deletions or truncating mutations along with detailed phenotypic descriptions, concluding that PTCHD1 disruptions are highly penetrant genetic risk factors for NDD's. Of the 16 families three families had truncating mutations in exon 3; five families had exon 1 deletions; seven families had whole gene deletions; and one family had a deletion of exon 2 and 3. All mutations were maternally inherited except for two de novo mutations that resulted in a truncating mutation in one individual and a whole gene deletion in another individual. Four of these families had deletions that included the gene DDX53; the authors conclude that this gene is "an unlikely candidate for contribution to the ASD/ID phenotype because its expression has not been seen in adult or fetal brains." Consistent neurological findings in the solely PTCHD1 haploinsufficient cohort are orofacial hypotonia, mild motor incoordination, ASD, GDD, and severe ID. The authors posit that "hemizygous PTCHD1 LOF causes an X-linked neurodevelopmental disorder with a strong propensity to autistic behavior.?
20844286	Noor et. al 2010 discovered mutations within PTCHD1 in 7 families with ASD and 3 families with ID. A 167 Kb microdeletion spanning exon 1 was found in two brothers: one with ASD and the other with a learning disability and ASD features. A 90 Kb deletion encompassing the entire PTCHD1 gene and 5? exons of the ncRNAS was found in three males with ID in one family. The deletion was validated using qPCR revealing that the deletion was maternally inherited in two affected brothers and their affected uncle. Equivalent changes were not found in male control individuals (p=1.2 x10-5). Functional studies were performed in mice and found to statistically inhibit transcription via the Hedgehog signaling pathway. Microdeletions in the gene, 5? region, and 3? region were identified that disrupted the PTCHD1 gene in males leading to either ASD, ID or learning disability; suggesting involvement of this locus in ~1% of ASD and ID individuals. Gene was found to be expressed in human cortex and cerebellum as well as in mice and drosophila brain.
25533962	Fitzgerald et. al 2015 as a part of the Deciphering Developmental Disorders Study used a genotype driven approach to identify 1,133 children (median age 5.5 yrs) with severe undiagnosed developmental disorder and their parents using a combination of exome sequencing and array-based detection of chromosomal rearrangements. A population-based control dataset of un-transmitted diplotypes was generated using the un-transmitted haplotypes from the parents of the affected probands in 1,080 non-consanguineous trios. To define the rarity of each indel, only CNVRs sharing less than 80% if their boundaries with an CNVE of the same type observed at less than 1% population frequency were classified as rare; no LOF variants in PTCHD1 were found in controls. One male proband with no family history of developmental disorders had a De Novo SNV at Chromosome X g.23411706>T, hemizygous genotype, leading to a nonsense mutation (R>*) validated by DNM and LOF phenotype? blue sclerae, deeply set eye, wide mouth, long philtrum, global developmental delay. One male proband with no family history, had an indel on ChrX g.23411077delC, hemizygous genotype (AC>A), leading to a de novo frameshift mutation ? Global Developmental Delay, abnormal facial shape, sleep disturbance, aggressive behavior, constipation, eczema, drooling, gait disturbance.

The loss-of-function and triplosensitivity ratings for genes on the X chromosome are made in the context of a male genome to account for the effects of hemizygous duplications or nullizygous deletions. In contrast, disruption of some genes on the X chromosome causes male lethality and the ratings of dosage sensitivity instead take into account the phenotype in female individuals. Factors that may affect the severity of phenotypes associated with X-linked disorders include the presence of variable copies of the X chromosome (i.e. 47,XXY or 45,X) and skewed X-inactivation in females.

#300830
Table of Contents

MIM Entry

Phenotypic Series

300830

AUTISM, SUSCEPTIBILITY TO, X-LINKED 4; AUTSX4

INHERITANCE
- X-linked recessive

HEAD & NECK

Eyes
- Visual problems, mild

Mouth
- Orofacial hypotonia

MUSCLE, SOFT TISSUES
- Hypotonia (in some patients)

NEUROLOGIC

Central Nervous System
- Global development delay
- Intellectual disability
- Learning disability
- Motor tics

Behavioral Psychiatric Manifestations
- Autism spectrum disorder
- Attention deficit-hyperactivity disorder
- Impulsivity
- Aggressive behavior

MISCELLANEOUS
- Onset in infancy
- Variable severity
- Nonspecific subtle dysmorphic facial features may be present
- Most patients have contiguous gene deletion syndrome involving Xp22

MOLECULAR BASIS
- Caused by mutation in the patched domain-containing protein 1 gene (PTCHD1, 300828.0001)

Creation Date: Cassandra L. Kniffin : 9/22/2015
Edit History: joanna : 10/23/2015

Our Patient (Case V)

? 3 year-old
? Female
X Postnatal growth deficiency
X VSD
X Scoliosis
X Hand anomalies
X Hearing loss
? Craniofacial dysmorphism

Print Full Report

Genome View | Evidence for Haploinsufficiency Phenotypes | Evidence for Triplosensitive Phenotypes

Haploinsufficiency score: 3
Strength of Evidence (disclaimer): Sufficient evidence for dosage pathogenicity
Haploinsufficiency Phenotype: AUTISM, SUSCEPTIBILITY TO, X-LINKED 4; AUTSX4

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Chaudhry et al.

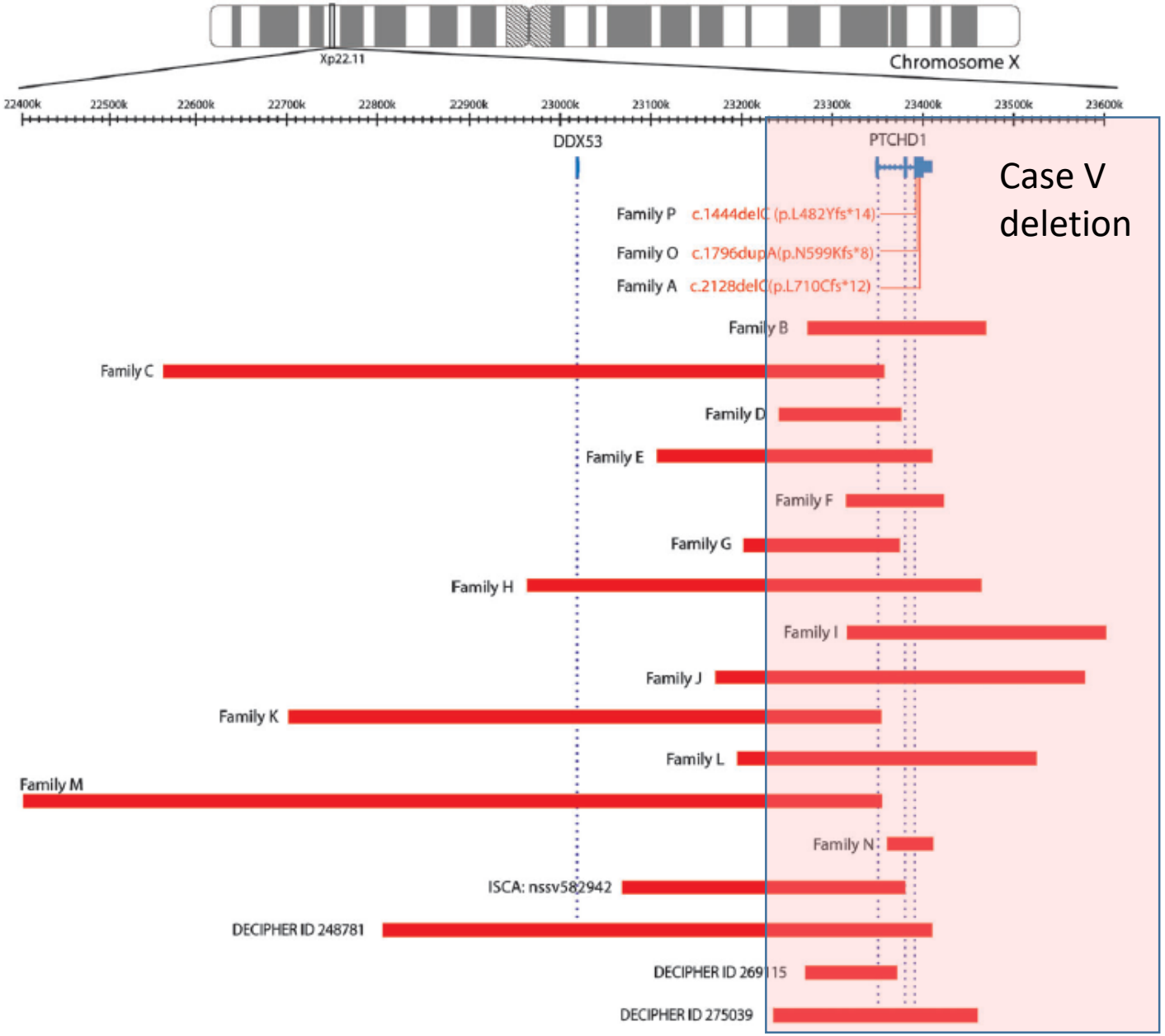

Fig. 1. Schematic of deletion sizes for families and individuals in our study. Horizontal bars represent the deleted region. Vertical dotted lines correspond to exons. Genomic coordinates correspond to build hg19.

- 23 individuals (16 families) with a truncating mutation or deletion
- PTCHD1 disruptions in males are associated with neurodevelopmental disorders of varying severity, with a prominence of ASD and other behavioral characteristics
- “We did not have detailed information on female carriers (mothers, sisters and grandmothers of the probands) but they were reported to have no major problems with intellect and daily functioning.”
- More studies are needed in females to clarify whether carrier status and X-inactivation pattern may have subtle effects on phenotype

Table 1. Continued

ID	Deletion/mutation (deletion coordinates hg 19)	Age at last assessment (years)	Sex	Ethnicity	Dysmorphic features	Growth abnormalities	Developmental/ cognitive functioning	Psychiatric/ behavioral disorders	Neurological features
F1	90 kb whole-gene deletion (chrX:23,329,087–23,419,289)	44	M	Caucasian	Not reported	Relative macrocephaly	Moderate ID	Excessive alcohol intake	None
F2	90 kb whole-gene deletion (chrX:23,329,087–23,419,289)	22	M	Caucasian	Tall forehead, downturned corners of mouth	Relative macrocephaly (HC 99th percentile)	GDD, mild to moderate ID	Conduct problems	Hypotonic face
F3	90 kb whole-gene deletion (chrX:23,329,087–23,419,289)	9.7	M	Caucasian	Prominent forehead, relatively small ears prominent central upper incisors, tented upper lip	Early FTT	GDD, mild ID, g motor delay r prominent tha cognitive dela		
G1	167 kb deletion, Includes entire exon 1 (chrX:23,204,258–23,371,802)	12.5	M	Northern European, Caucasian	Upslanted palpebral fissures	None	GDD, Dyslexia		
G2	167 kb deletion, Includes entire exon 1 (chrX:23,204,258–23,371,802)	12.5	M	Northern European, Caucasian	Upslanted palpebral fissures, double hair whorls	None	GDD, LD		
H1	503 kb whole-gene deletion (chrX:22,960,743–23,463,337)	2.6	M	British/First Nations, Caucasian	Cupped ears, bilateral fifth finger clinodactyly, fetal finger pads, spatulate finger and toenails	None	GDD		
I1	273 kb whole-gene deletion (chrX:23,331,184–23,604,246)	1.25	M	Caucasian	Deep set eyes with hooded lids, left naso-labial flattening	None	Isolated motor d		bilateral increased tone in arms and legs
J1	412 kb whole-gene deletion (chrX:23,164,422–23,576,222)	4	M	Caucasian/ Filipino	Straight eyebrows, epicanthal folds, bifid tongue	Early FTT, macrocephaly	GDD	ASD features	Hypotonic face, hypotonia
K1	643 kb deletion, Includes entire exon 1 (chrX:22,686,771–23,354,655)	5	F	East Indian	None	None	Isolated speech delay	ASD	None

Chaudhry et al.

"The single female subject in our study (K1) has a history of speech delay and a subsequent diagnosis of high-functioning ASD; her unaffected mother also carried the *PTCHD1* deletion. X-inactivation studies in mother and daughter were uninformative. Thus we cannot rule out subtle neurodevelopmental phenotype in carrier females, and more in-depth studies are needed."

Classification: Pathogenic

- Classification of losses involving X-linked recessive genes in females should be based on the predicted impact in a male

	Evidence	Score	Notes
1A	Protein-coding gene?	0	Yes
2A	Complete overlap with established HI gene?	1	Yes, an XLR gene (can stop here)
OR			
3A	Gene count: 0-24 genes	0	1 protein-coding gene
4C	Individual case evidence: “de novo” inheritance**, phenotype non-specific	0.9	>10 cases (0.1 points for each, 0.90 points max)
2H	HI predictors (%HI AND pLI)	0.1**	PTCHD1 (X-linked gene)
4L-O	Case-control, population evidence		Limited data available (X CNV)
5B	Maternal inheritance (unaffected), proband with specific phenotype	0	XLR, inheritance not informative
	Total points	1	

**Modified for X-linked gene (more guidance coming from the ClinGen DSC)

Clinical Significance?

- Given the significant reproductive risk to female carriers of X-linked conditions, we recommend reporting these variants because it provides the opportunity for the patient and relevant family members to pursue additional testing/counseling as needed.
- Additionally, females may manifest symptoms in many X-linked disorders; these variants may ultimately have an impact on their medical management.

Example Report 6: X-linked finding in a female

Patient Name: Jane Doe
DOB: 01/01/2010
Laboratory ID: 1234567
Test ordered: Chromosomal Microarray

Include any other important header information, such as: relevant dates, additional patient demographics, ordering provider information, sample information, etc.

Reason For Referral (RFR): Jane Doe is 9 year old female referred for hearing loss.

Don't stop here

Report Summary: This test did not identify any variants that can explain the patient's reported clinical features at this time. However, a maternally inherited, PATHOGENIC 124 kb deletion of Xq21.1 (involving the *ATP7A* gene) was identified. Hemizygous loss of function variants in this gene have been associated with Menkes disease in MALES; as Jane Doe is a FEMALE, this finding likely represents CARRIER STATUS for Menkes disease. Female carriers of pathogenic *ATP7A* variants are typically asymptomatic, though unfavorably skewed X-inactivation could result in clinical findings related to this disorder. Genetic counseling and clinical correlation are recommended to discuss the potential reproductive implications of this finding and to determine if additional testing is warranted to identify a genetic etiology for Jane Doe's hearing loss.

Copy Number Variant (CNV): 124 kb Xq21.1 Deletion

ISCN	Type	Size	Inheritance	Zygosity	Classification
arr [GRCh37] Xq21.1 (77226076-77350000) x 1	Deletion	124 kb	Maternal	Heterozygous	Pathogenic

Relevant Genomic Content:
This deletion includes a single gene relevant to this report:

Gene	*Disease*	*Mode of Inheritance*	*Relevance Category*	*Notes*
ATP7A	Menkes disease	X-linked	Carrier Status	Female heterozygous carriers of pathogenic variants in *ATP7A* TYPICALLY DO NOT display overt clinical features of Menkes syndrome, an X-linked condition affecting predominantly males. This finding DOES NOT explain the patient's reported clinical features. Clinical correlation is recommended to determine if additional testing is warranted.

ATP7A
Include a more detailed description of ATP7A, Menkes disease, and the evidence supporting this classification, including any appropriate references.

Include any other relevant report information, such as methods, quality metrics, disclaimers, resources, etc.

Today's Attendance URL and QR code:

Questions?

https://tinyurl.com/AttendanceJan23

- Register for this series:
  - ***https://tinyurl.com/CNVRegistration***
- Recorded webinars will be posted (slides also available)
  - ***www.clinicalgenome.org***
- Call participants are MUTED upon entry
- Questions?
  - Ask "live" using the Q&A box (must be signed into webinar)
  - Please list your full name with your question so we can send you an answer
    - Some questions will be saved for the Q&A session on March 12th
  - Email: clingen@clinicalgenome.org