ClinGen Dosage Sensitivity Map (and other CNV-related topics)

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ClinGen
Clinical Genome Resource

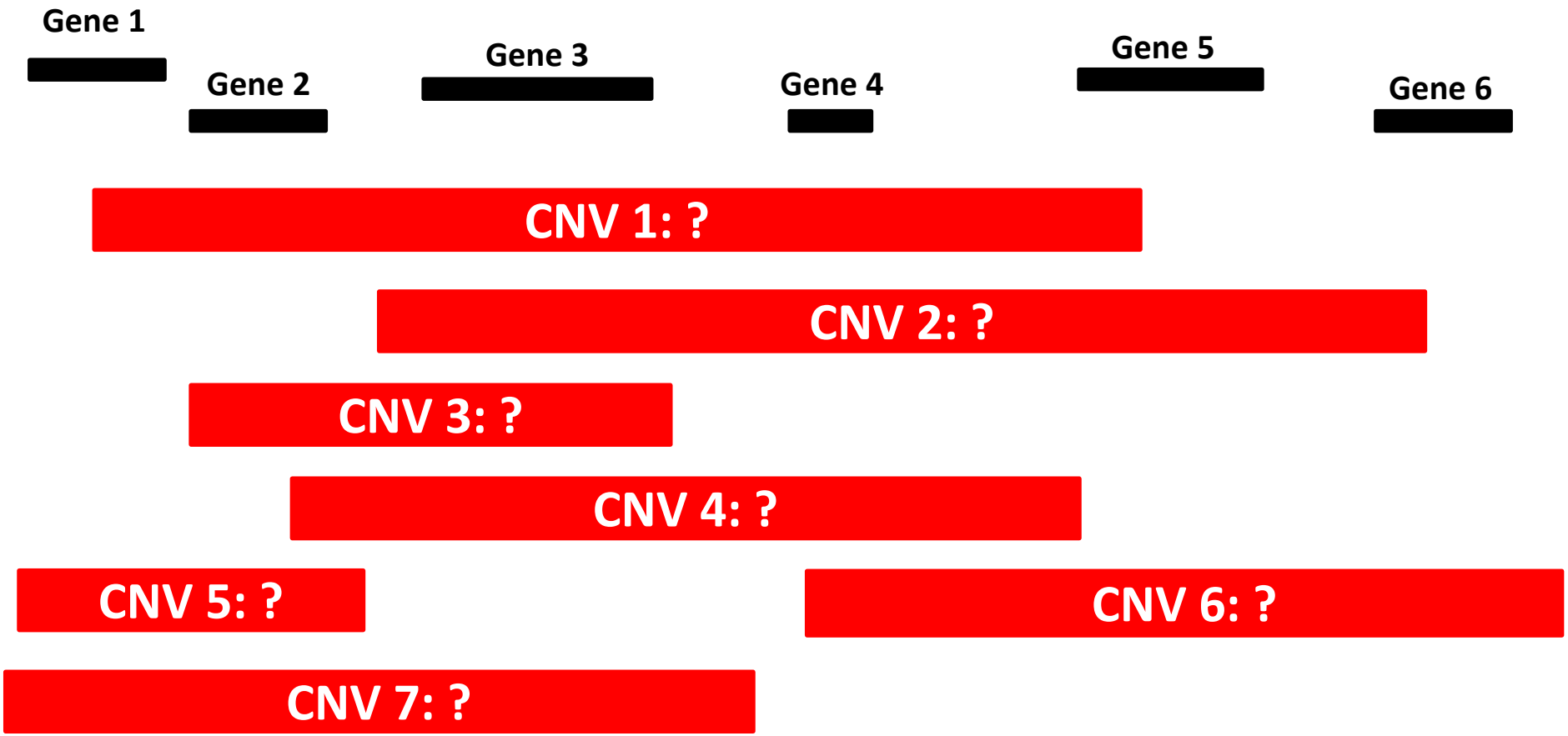
Agenda

- ClinGen Dosage Sensitivity
- Utilizing CNVs/Dosage Information in Gene-Disease Validity Classifications
- Locating CNVs in ClinVar

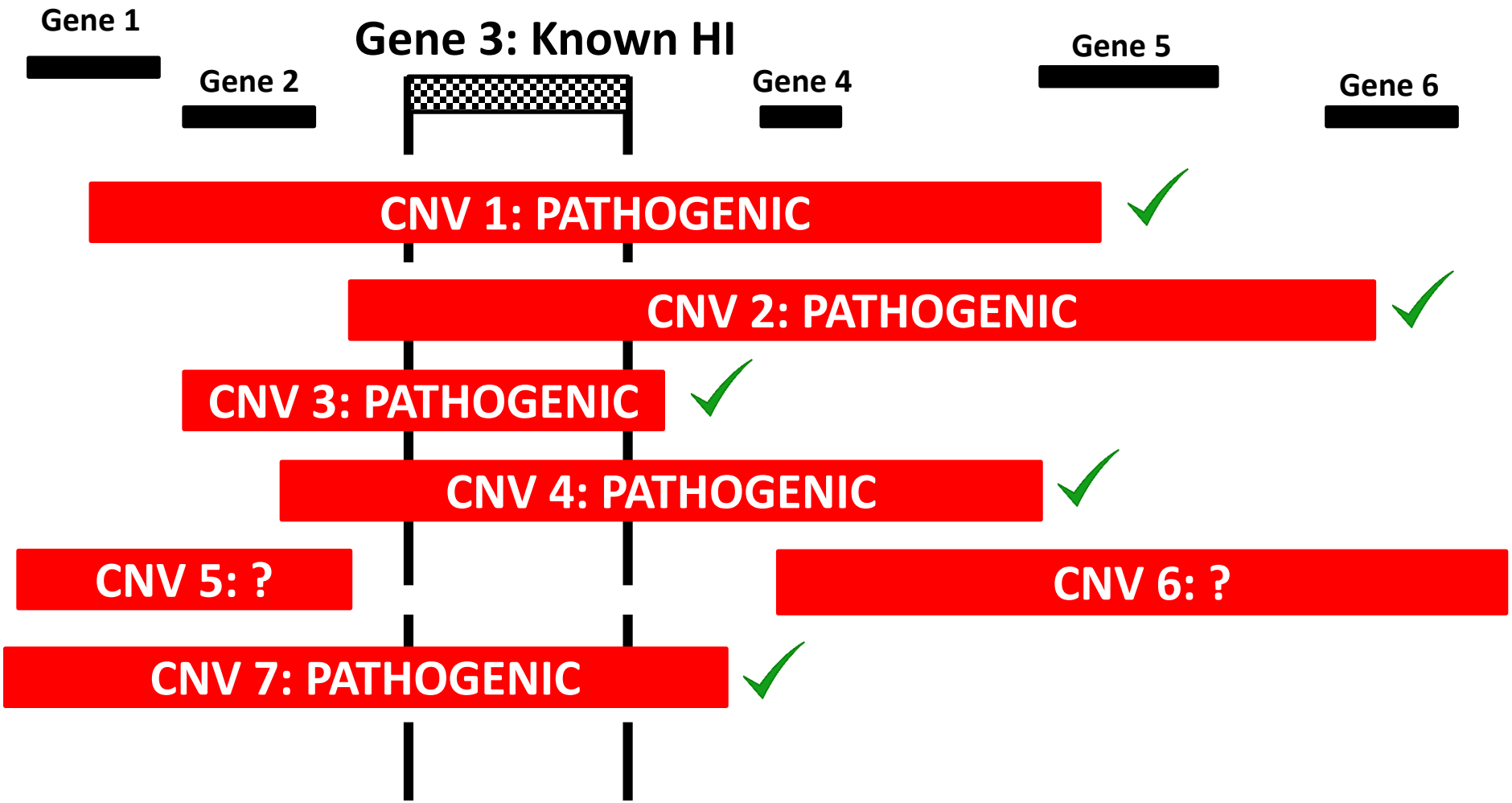
Evolution of the Dosage Sensitivity Map

- Dosage Sensitivity (DS) curation has been ongoing since 2011 (ISCA)
  - Chromosomal microarray (CMA) coming in to wide clinical use
- Many of the copy number variants (CNVs) being identified were unique and not well described in the clinical literature
- How to interpret these?
  - Assess genomic content and correlate with established clinical literature
- DS curation process developed to facilitate this process and promote classification consistency

ClinGen Dosage Map can inform the process of CNV classification



ClinGen Dosage Map can inform the process of CNV classification



Curation Focus

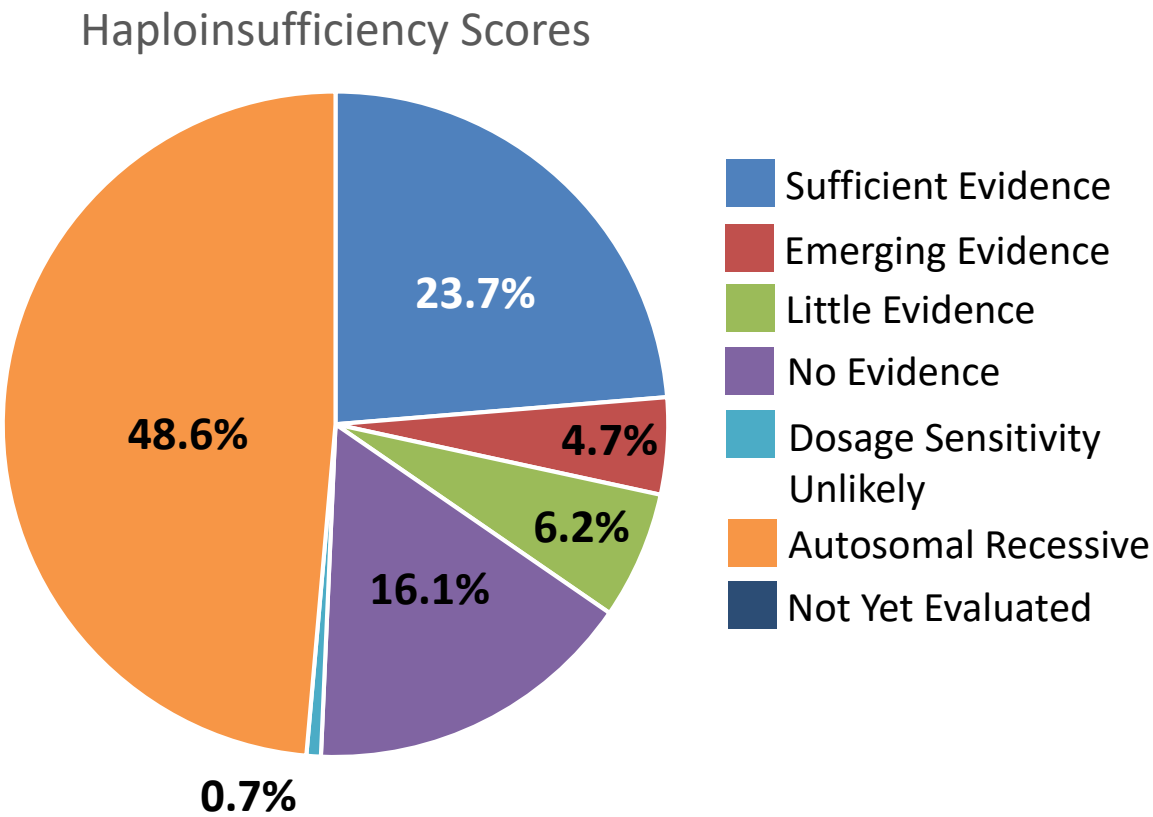
- Initial focus: genes with targeted coverage on ISCA 180K array design
  - Similar to the approach today's GCEPs take with evaluating multi-gene panels in their disease areas
- Transition into focus on neurodevelopmental disorders, as these are common reasons for CMA referral
- Current efforts:
  - Neurodevelopmental subgroup
    - Evaluating dosage sensitivity of genes implicated in neurodevelopmental disorders (NDDs), such as ID, autism, seizures, etc.
  - Recurrent regions subgroup
    - Developing additional considerations for the evaluation of recurrent CNVs, including regions associated with low penetrance
  - Hereditary Cancer subgroup
    - Evaluating dosage sensitivity of genes implicated in hereditary cancer

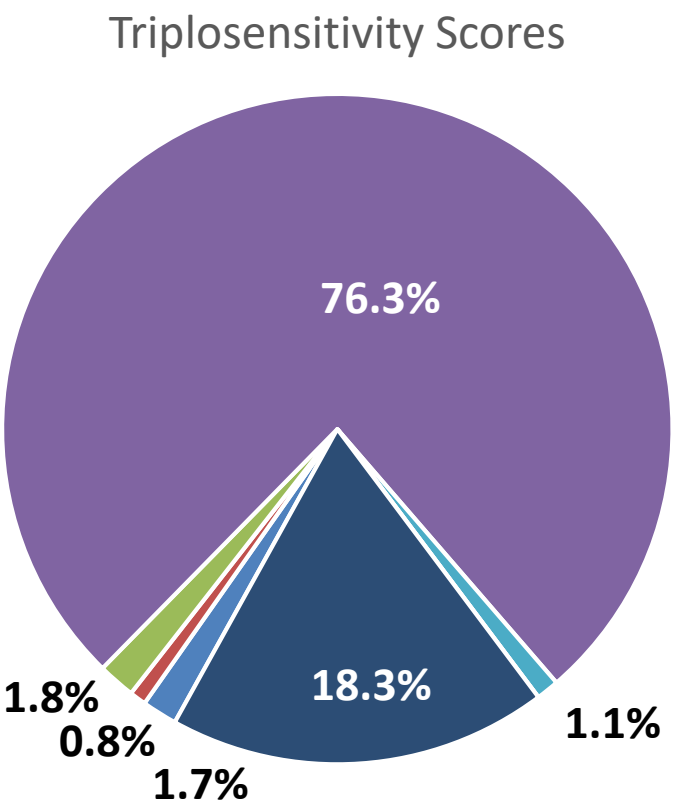
Dosage Sensitivity Evaluations

- 2 types of dosage sensitivity “records”
  - Single Gene
  - Genomic Region
    - Typically recurrent regions (such as those mediated by segmental duplications) or other commonly observed, clinically relevant regions
- Each record is evaluated for BOTH haploinsufficiency and triplosensitivity
  - Separate scores are assigned for each

Current Progress

- 76 region issues complete
- 1398 single gene issues complete





Transitional Period for Dosage Sensitivity

- The types of evidence available to us and the ways in which we evaluate and apply that evidence has changed since we first started curating for Dosage Sensitivity in 2011.
- Currently in the process of updating our scoring procedures to be more consistent with those put forth in the new ACMG/ClinGen CNV technical standards (Riggs et al. 2019)
  - New single-gene scoring procedures in place since February 2019

Each gene or region gets both a haploinsufficiency (HI) and triplosensitivity (TS) "score"

Score	Meaning	ORIGINAL Clinical Interpretation/Comments (2011 – February 2019)	PROPOSED NEW Clinical Interpretation/Comments (February 2019 - present)
3	Sufficient Evidence	Pathogenic	Pathogenic
2	Emerging Evidence	Likely Pathogenic OR Uncertain	Likely Pathogenic ←
1	Little Evidence	Uncertain	Uncertain
0	No Evidence	Uncertain OR Likely Benign	Uncertain ←
40	Dosage Sensitivity Unlikely	Likely Benign OR Benign	Likely Benign OR Benign
30	Gene Associated with AR Condition	Gene Associated with AR Condition	Gene Associated with AR Condition
-1	Will not evaluate	Programmatically applied to genes we will not evaluate, such as pseudogenes	Programmatically applied to genes we will not evaluate, such as pseudogenes

Riggs et al. *Clin Genet* 2012

Dosage Sensitivity Questions

- When this [gene or genomic region] is LOST, does it result in a consistent phenotype? (Haploinsufficiency score)
- When there is an EXTRA COPY of this [gene or genomic region], does it result in a consistent phenotype? (Triplosensitivity score)

Assigning Haploinsufficiency (HI) and Triplosensitivity (TS) Scores

- Primary evidence = case data from humans
- Haploinsufficiency
  - Looking for evidence of loss of function (LOF), including:
    - Single gene deletions
    - Exonic deletions within a single gene
    - Putative LOF sequence variants (for example, nonsense) believed to undergo nonsense-mediated decay
    - Other sequence variants may be considered IF there is strong functional evidence suggesting loss of function
- Triplosensitivity
  - Whole gene duplications ONLY

Assigning HI and TS Scores

- IN GENERAL, we take a conservative approach:
  - For gene evaluations, only evidence involving that gene ALONE is considered
  - The following are typically considered supporting evidence, not primary evidence*
    - Smallest region of overlap as sufficient evidence that a gene is a "causative" gene
    - Evidence from translocation cases (unless both breakpoints have been mapped, functional evidence suggests no effect of second breakpoint)
    - Unpublished evidence
  - Functional evidence, such as evidence from animal models, may be used to upgrade a particular evidence score

**These data are still useful pieces of information, and are noted in the gene record, but do not contribute to the overall score(s).*

Original Scoring Guidelines

- 3: There are at least 3 documented variants demonstrating LOF (HI score) or duplications of a single whole gene (TS score) from at least 2 independent publications
  - If all of the variants are coming from a single group, the score is typically 2, exceptions may apply
- Score of 2 = 2 probands, 1= 1 proband, 0 = no evidence, etc.
- Score "Dosage Sensitivity Unlikely" ONLY if there is valid evidence against dosage sensitivity
- Score "Gene Associated with AR disorder" in the HI score section when applicable, comment on the mechanism of the disorder if known

The main change to this approach removing the concept of a specific, set number of probands driving the score. The other concepts still apply!

New Single Gene Process: Consistent with Category 4 of CNV Technical Standards

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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]

Genet Med. 2019 Nov 6. doi: 10.1038/s41436-019-0686-8. [Epub ahead of print]

New Single Gene Process: Consistent with Category 4 of CNV Technical Standards

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)

New Single Gene Process: Consistent with Category 4 of CNV Technical Standards

- Points are still awarded per proband, but the amount differs based on:
  - Inheritance
    - *De novo*
    - Unknown inheritance
    - Segregation among similarly affected family members
    - Apparent non-segregations
  - Phenotype
    - Highly specific, relatively unique
    - Consistent, specific, but not necessarily unique
    - Consistent, but not highly specific and/or with high genetic heterogeneity
- A suggested number of points is provided for each category
  - A range is also provided to give you the ability to upgrade for compelling pieces of evidence, and downgrade for evidence of lesser quality

Points for each piece of evidence will be tallied to reach the final HI/TS Score

Evidence Points	HI/TS Score	Suggested Clinical Classification
0.99 or higher	3	Pathogenic
0.90-0.98	2	Likely Pathogenic
0.10-0.89	1	VUS
0	0	VUS
No evidence to evaluate	0	VUS
0 to -0.89	0	VUS
-0.90 to -0.98	Dosage Sensitivity Unlikely	Likely Benign
Fewer than -0.99	Dosage Sensitivity Unlikely	Benign

De novo probands

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)*

- Highly specific, relatively unique:
  - Fixed, dilated pupils (Gillespie syndrome)
  - Fetal adrenocortical cytomegaly (Beckwith-Wiedemann)
- Highly specific, not necessarily unique
  - Early infantile epileptic encephalopathy (68 entries in OMIM)
  - Spastic paraplegia (68 entries in OMIM)
- Not highly specific, and/or with high genetic heterogeneity
  - Developmental delay/intellectual disability
  - Autism

What if the phenotype isn't consistent (D)?

- Need to consider whether this actually represents "anti" evidence
- Negative point values could be considered with increasing evidence of inconsistency.
- Example 1: *De novo* deletion of a particular gene reported twice in the literature - once in a 7yo with developmental delay, and once in a newborn with a congenital anomaly (0 points)
- Example 2: *De novo* deletion reported 5 times in the literature - all in well-phenotyped, older individuals - 1 with intellectual disability, 1 with a history of cardiac defect and normal development, 1 with a history of genitourinary anomalies and normal development, and 2 in general population individuals (-0.30 points)

Unknown Inheritance

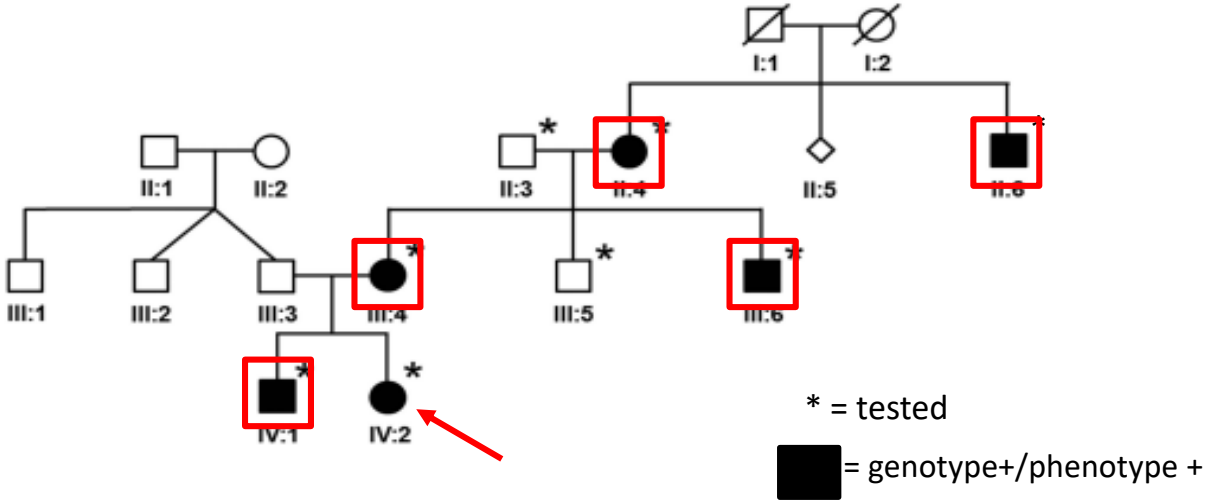
Individual Case Evidence: Unknown Inheritance	E. Reported proband has a highly specific phenotype consistent with what is expected for the gene, but inheritance of the variant is unknown.	0.10 points each (*Range: 0-0.15 each)*

- Use ONLY when the phenotype is specific
  - Do NOT use in non-specific phenotypes such as ID/Autism
- Example: use when evaluating a relatively specific, adult-onset condition where getting parental samples is particularly difficult

Segregation In Affected Family Members

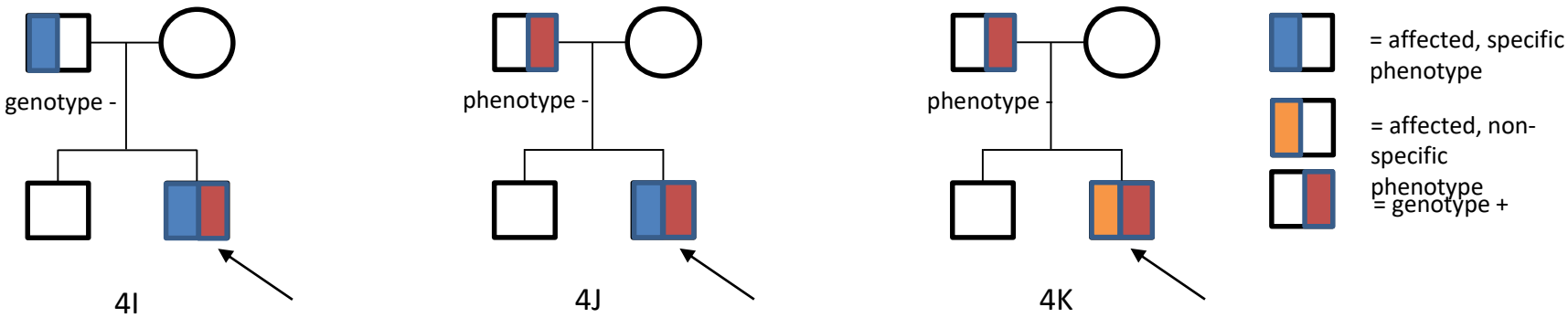
Individual case evidence – segregation among similarly affected family members[13]	**4F**. 3-4 observed segregations	0.15	0.45	
	4G. 5-6 observed segregations	0.30		
	4H. 7 or more observed segregations	0.45		

- For simplicity, count only genotype +/phenotype + individuals, and/or obligate carriers



Case evidence, apparent non-segregation

Individual case evidence - Non-Segregations[14]	**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[2]: 0 to -0.45)
	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[2]: 0 to -0.30)
	4K. 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[2]: 0 to -0.15)



Other factors to consider…

- HI predictors
  - gnomAD pLI score is >0.90 AND DECIPHER HI index is <10%
  - This information can be use to bump up (or bump down!) genes that are “on the fence”
  - Use judgement to decide if this is appropriate
    - Genes associated with adult-onset conditions may have lower pLI scores as reproductive fitness is not impacted
    - LOF variants observed in the general population may be in a different area of the gene than the LOF variants in affected individuals
    - Potential false positives, etc.

Other factors to consider…

- Common variation
  - Frequency of 1% or greater – could consider awarding up to -0.90 points
  - Observed at a lower frequency but still relatively common? Could consider downgrading.
- Case-control data
  - Consider the quality of the study before awarding a score - methods, potential sources of bias/confounding, etc.

Proposed Recurrent Region Process

Evidence Type	Evidence	Default	Range	Max Score
1) Number of unrelated probands	More than 2 families reported? (yes =1, no=0). If "no," SKIP to 4	1 or 0	-	1
2) Phenotype (SKIP to 4 if <two unrelated probands)	a) Specific, well-defined OR	4	3->5	5
	b) Non-specific	1	0->2	2
3) Inheritance/ segregation	a) CNV is most often de novo	4	3->5	5
	b) CNV is most often inherited, from an *affected* parent/ CNV segregates with phenotype OR	2	1->2	2
	c) Inheritance is unknown OR	0	-	0
	d) CNV is most often inherited, from an *unaffected* parent/ CNV does not segregate with phenotype	-1	-1->0	-1
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)	1 or 0	-	1
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	-	3
	b) Control frequency exceeds 0.1% OR the case frequency? Yes (-1)	-1	-	-1
	Bonus point: LR or OR: Exceeds 5 and lower 95% CI does not include 1? (yes= 1, no= 0)	1 or 0	-	1
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	-	1

Dosage Sensitivity	Points Range
Sufficient Evidence (3)	10->17
Emerging Evidence (2)	5->9
Little Evidence (1)	1->4
No Evidence (0)	0
Dosage Sensitivity Unlikely	-2->-1
CNV is Autosomal Recessive	n/a

Single Gene Example: *ZNF462*

- Weiss *et al.* 2017 (PMID:28513610):
  - Describe probands from 6 families (8 total individuals) with predicted LOF variants in *ZNF462*
  - Per the authors: "Shared features include metopic ridging or lambdoid craniosynostosis (5/8), dysgenesis of the corpus callosum (3/8), ptosis (7/8), and developmental delay with or without autistic features (4/8). In addition, we identified overlapping dysmorphic features in most subjects such as arched eyebrows, down slanting palpebral fissures, epicanthal folds, wide philtrum, and a short upturned nose with a bulbous tip."

Weiss *et al.* 2017

Proband/Family	Variant	Method of Detection	Key Features	Other variants?	Comments
Family 1 (proband, sister, father, pat GM; variable expressivity)	c.3787C>T (p.Arg1263*)	WES	Metopic ridge, ptosis, +/- dysmorphic features, normal development	"No rare variants in genes previously associated with craniosynostosis or ACC."	
Proband 2	c.2979_2980delinsA (p.Val994Trpfs*147) *de novo*	Trio WES	Metopic ridge, ptosis, dysmorphic features; ASD	None reported.	
Proband 3	c.4263delA p.(Glu1422Serfs*6) *de novo*	WES	Lambdoid synostosis/metopic ridge; hypotonia; ptosis; dysmorphic features; transposition of the great arteries; developmental delay	Pat VUS in *FOXP2* (c.776-5T>G, NM_014491.3); mito VUS (m.14787T>C p.(I14T), NC_012920.1) in *MT-CYB* at 30% heteroplasmy	Consider not counting. Effects of other variants cannot be ruled out.
Proband 4	Chr9:108940763-110561397x 1(hg19) *de novo*	CMA	Hypotonia; dysgenesis of the corpus callosum; ptosis; dysmorphic features; normal development	Includes *RAD23B* and *KLF4*	Looking for evidence of *ZNF462* HI – effects of losing other genes cannot be ruled out
Proband 5	Chr9:108464368-110362345 x1 (hg19) *de novo*	CMA	Mild ID; ASD; ADD; OCD; hx of ventricular septal defect; no evidence of craniosynostosis; no metopic ridge; no ptosis	Includes *TMEM38B*, *RAD23B* and *KLF4;* pat inherited 374 kb dup at 6q22.31 (classified as VUS)	Looking for evidence of *ZNF462* HI – effects of losing other genes cannot be ruled out
Proband 6	c.5145delC p.(Tyr1716Thrfs*28) *de novo*	Trio WES	Developmental delay; hypotonia; facial asymmetry; dysmorphic features.	None reported.	

What type of phenotype is this?

- Based on the first paper: the first 6 probands reported had a variable phenotype including a number of nonspecific features (ID, dev delay, ASD, hypotonia) and some slightly more specific (but not unique) features (ptosis, metopic ridge)
  - Unclear if this is a consistent but variable constellation of findings, or unrelated
  - Additional cases may help clarify
- Conservative approach:
  - 1 3-segregation family (0.15 points thus far)
  - 2 *de novo* LOF variants, parental relationships confirmed (trio-based WES) (0.15 points x 2 = 0.30 points)

Total: 0.45 points

Cosemans *et al.* 2018 (PMID: 29427787)

- *De novo* balanced translocation (t(9; 13)(q31.2; q22.1)) in a patient with ID, ASD, metopic craniosynostosis, dysgenesis of the corpus callosum, and ptosis
- Translocation breakpoints were mapped to *KLF12* on chr13 and *ZNF462* on chr9
  - HI of *ZNF462* was assumed (due to previous clinical reports) but not functionally demonstrated
  - No functional studies of *KLF12* → cannot rule out effect of this gene
- Of note, another translocation case was reported by Talisetti *et al.* in 2003; features overlap with those reported here plus those associated with the other gene involved
- While compelling, this type of evidence should not scored
  - These and the unused cases from Weiss et al. could be used as an argument for upgrading if on the border between 2 classifications at the end.

Total: 0.45 points

Kruszka *et al.* 2019 (PMID:31361404)

- Describes 14 additional individuals with LOF variants in *ZNF462*
  - Total of 24 individuals including those from Weiss and the translocation cases
- Sheds additional light on phenotypic spectrum:
  - Developmental delay: 79%
  - ASD: 33%
  - Ptosis: 83%
  - Down-slanting palpebral fissures 58%
  - Metopic ridging or craniosynostosis: ~33%
  - Dysgenesis of the corpus callosum: ~25%
  - Structural heart defects: 21%

Summary of variants in Kruszka *et al.*

- 13/14 detected by exome sequencing; 1/14 by genome sequencing
  - All putative LOF
  - 10 *de novo*; no comment on confirmation of parental relationships (trio-based WES vs. WES on proband with Sanger confirmation in parents)
  - 2 unknown inheritance
  - 1 paternally inherited with + paternal family hx (father with ptosis requiring surgery)
  - 1 maternally inherited, mosaic

Putting everything together…

- Even if we were being extremely conservative…
  - …and counting this as a non-specific phenotype
  - …and assuming parental relationships were not confirmed if not explicitly stated
  - …and not using cases where other variants were identified/effects of other genes were not ruled out
  - …we'd still have:
    - Category 4C: *De novo* LOF variant, non-specific phenotype
      - Parental relationships confirmed – 2 cases (Weiss) → 0.15 x 2 = 0.30
      - Parental relationships assumed – 10 cases (Kruszka) → 0.10 x 10 = 1.0
    - Category 4F: 4 total observed segregations (1 family in Weiss, 1 family in Kruszka)→ 0.15 points

Total: >1.0 points

Sufficient evidence to suggest *ZNF462* is a haploinsufficient gene

Evidence Points	HI/TS Score	Suggested Clinical Classification
0.99 or higher	3	Pathogenic
0.90-0.98	2	Likely Pathogenic
0.10-0.89	1	VUS
0	0	VUS
No evidence to evaluate	0	VUS
0 to -0.89	0	VUS
-0.90 to -0.98	Dosage Sensitivity Unlikely	Likely Benign
Fewer than -0.99	Dosage Sensitivity Unlikely	Benign

How do I access Dosage Sensitivity Curations?

- Available through the Dosage Sensitivity Map website
  - Includes single genes, recurrent regions
  - Ability to search by gene name or coordinates
  - Current URL: https://www.ncbi.nlm.nih.gov/projects/dbvar/clingen/
  - Will be redirecting at the end of the month to a ClinGen-controlled server
- Single gene information currently available on www.clinicalgenome.org
  - Regions and coordinate search will be available in the future
- Genes/regions with scores of 3 or 40 are added to the NCBI study "nstd45" on a quarterly basis
  - Populates tracks in both UCSC and NCBI's Variation Viewer

NCBI http://www.ncbi.nlm.nih.gov/projects/dbvar/clingen/

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Clinical Genome Resource

ClinGen Dosage Sensitivity Map

The Clinical Genome Resource (ClinGen) consortium is curating genes and regions of the genome to assess whether there is evidence to support that these genes/regions are dosage sensitive and should be targeted on a cytogenomic array.

All data are shown in GRCh37 coordinates.

Search By Gene Name

Symbol:

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

Go

Search By Location

Location:

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

Go

Genes/Regions with Updated Scores

Gene/Region Name	Old score	New score	Date changed
SF3B4	Haploinsufficiency score: 2	Haploinsufficiency score: 3	07/15/2014
MBD5	Triplosensitivity score: 1	Triplosensitivity score: 0	09/24/2014
NOTCH2	Haploinsufficiency score: 3	Haploinsufficiency score: 0	07/17/2014

Gene/Region Curation Stats

Review Complete	667
Under Primary Review	10
Under Secondary Review	16
Under Group Review	12
Awaiting Review	34,453

Links

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Curation Team

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Using the Dosage Sensitivity Map Site

ClinGen
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Search Results

Gene Issues (9) | Region Issues (1)

Location search results

ISCA ID	Curation Status	Region Location	Region Name	Relationship to Submitted Location
ISCA-37440	Complete	chr2:44,410,272-44,589,641	2p21 region involving PREPL and SLC3A1	Contained

Gene Issues (9) | Region Issues (1)

Location search results

ISCA ID	Curation Status	Region Location	Gene Symbol	Relationship to Submitted Location
ISCA-791	Awaiting Review	chr2:44,001,178-44,037,149	DYNC2LI1	Contained
ISCA-35806	Awaiting Review	chr2:44,039,611-44,065,958	ABCG5	Contained
ISCA-12332	Awaiting Review	chr2:44,066,103-44,105,605	ABCG8	Contained
ISCA-25314	Awaiting Review	chr2:44,113,363-44,223,144	LRPPRC	Contained
ISCA-26721	Awaiting Review	chr2:44,396,000-44,461,742	PPM1B	Contained
ISCA-10238	Awaiting Review	chr2:44,497,672-44,498,296	RPL12P19	Contained
ISCA-29498	Complete	chr2:44,502,597-44,547,963	SLC3A1	Contained
ISCA-23484	Complete	chr2:44,544,746-44,589,001	PREPL	Contained
ISCA-19054	Awaiting Review	chr2:44,589,043-44,999,729	CAMKMT	Contained

ClinGen Genome Curation Page

SH2B1

Curation Status: Complete

id: ISCA-11221

Date last evaluated: 2014-09-11

Issue Type: ClinGen Gene Curation

Gene type: protein-coding

Entrez Gene: http://www.ncbi.nlm.nih.gov/gene/25970

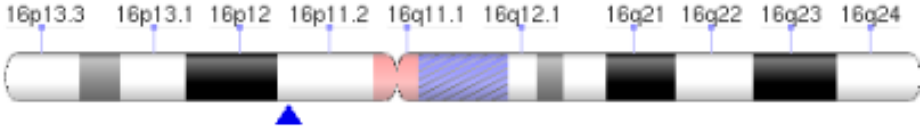
OMIM: http://omim.org/entry/608937

ClinGen Haploinsufficiency Score: 2

ClinGen Triplosensitivity Score: 0

See related regions:

Distal 16p11.2 region, 220 kb, includes SH2B1



Location Information

16p11.2

GRCh37/hg19 chr16: 28,875,078-28,885,534

View: NCBI | Ensembl | UCSC

SH2B1

Curation Status: Complete

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

Haploinsufficiency score: 2
Strength of Evidence (disclaimer): Some evidence for dosage pathogenicity

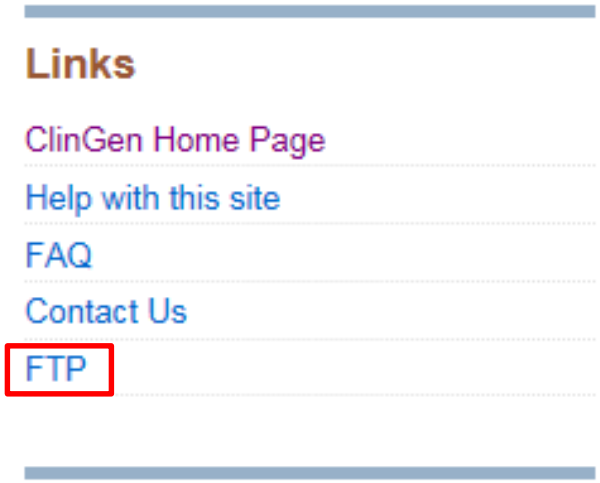
Evidence for haploinsufficiency phenotype

PubMed ID	Description
23160192	Doche et al. 2013: Describes 4 heterozygous variants (1 frameshift and 3 missense) in SH2B1 detected in 5 apparently unrelated individuals of mixed European descent amongst a cohort of 300 individuals with severe, early-onset obesity with a disproportionate degree of insulin resistance for their obesity. Mutations in genes causing known monogenic obesity syndromes had been excluded in these patients. All variants were inherited from overweight/obese parents. Individuals with SH2B1 variants were reported to have delayed speech development and aggressive behavior, but no formal psychiatric/behavioral observation was performed. The variants and the reported behavioral abnormalities were not detected amongst 500 control subjects. Subsequent functional studies demonstrated loss-of-function in assays of GH/NGF-mediated signaling.

Haploinsufficiency phenotype comments: Of note, Pearce et al. (2014) (PMID: 24971614) describe 4 additional SH2B1 variants in 500 additional individuals from the same cohort of severe early-onset individuals used in the Doche et al. (2013) paper referenced above. Of these 4 new variants, only 1, T546A, lies within the same N-terminal region common to all 4 SH2B1 isoforms as the variants described in Doche et al. This variant was found in a single individual who was described as also having mild developmental delay. The other 3 variants are in the C-terminal tail of SH2B1 alpha; individuals with these variants were not reported to have neurodevelopmental phenotypes, and 2 of them have been observed in publically available exome databases (though BMI information is not available on these reportedly normal individuals). The authors suggest that "SH2B1 contains a spectrum of common and rare alleles that contribute to BMI and obesity predisposition with a broad range of penetrance, from low to more highly penetrant rare alleles." They also point out the "need to determine, at the mechanistic level, whether the behavioral phenotype results from disruption of a specific SH2B1 isoform (eg, SH2B1Î²) or a function emanating from the 1â€“631 region shared by all 4 isoforms." PMID: 17235396 Ren et al (2007) generated Sh2b1-knockout mice that developed hyperlipidemia, leptin resistance, hyperphagia, obesity, hyperglycemia, insulin resistance, and glucose intolerance. Neuron-specific restoration of Sh2b1 corrected the metabolic disorders in the knockout mice and improved leptin signaling and leptin regulation of orexigenic neuropeptide expression in the hypothalamus. Neuron-specific overexpression of Sh2b1 dose-dependently protected against high fat diet-induced leptin resistance and obesity. They suggested that neuronal SH2B1 regulates energy balance, body weight, peripheral insulin sensitivity, and glucose homeostasis at least in part by enhancing hypothalamic leptin.

Other Resources

- The results of our curation efforts can be bulk downloaded by anyone, anytime
  - File updated daily



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

Knowledge Base

ClinGen Curated | Share Information

SH2B1

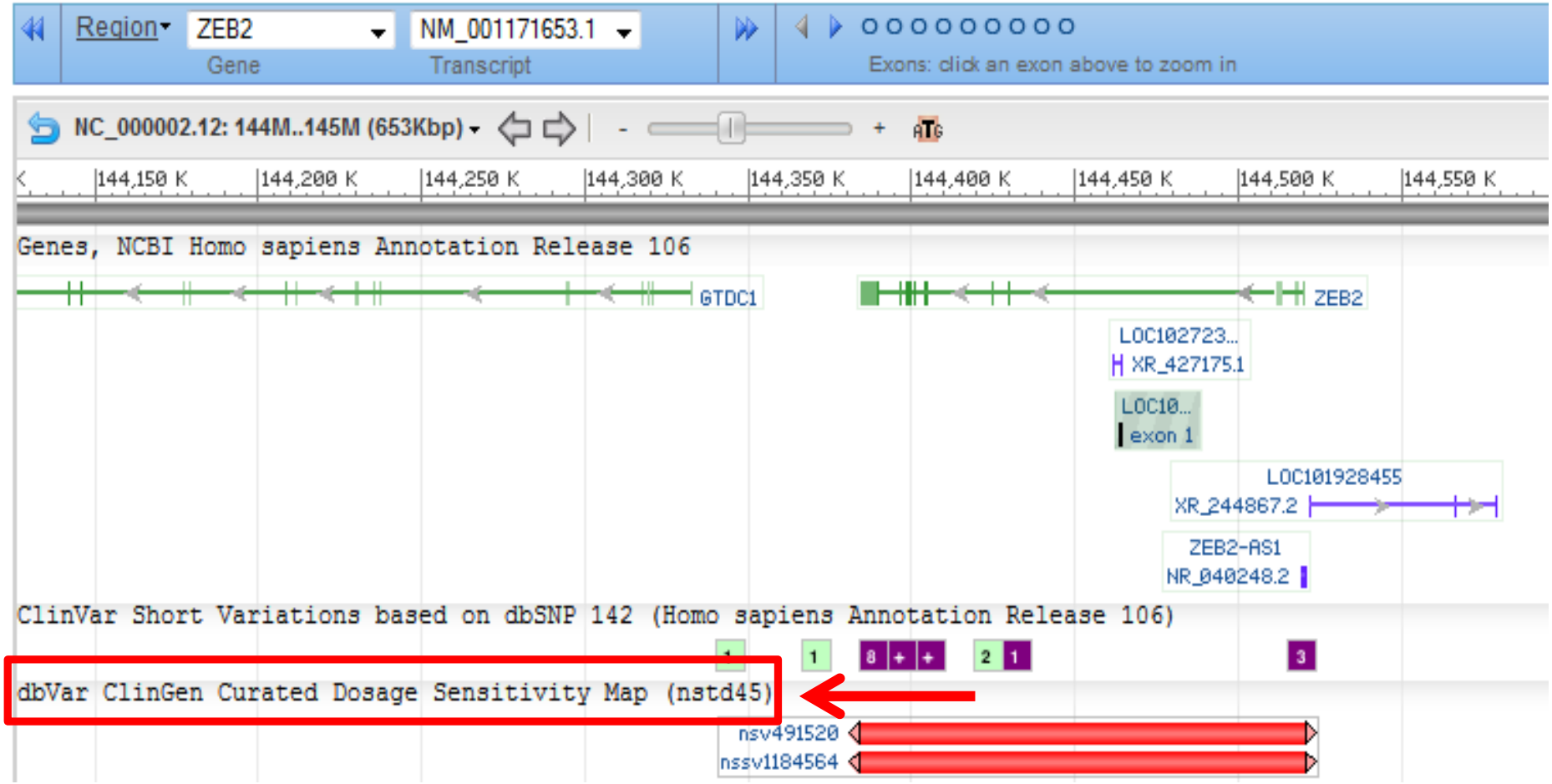
Name	SH2B1	External Resources	View external resources
HGNC ID	HGNC:30417	ClinVar Variants	View ClinVar Variants
Cytogenetic Location	16p11.2	GeneReviews®	View GeneReviews
Haploinsufficiency	Some Evidence		
Triplosensitivity	No Evidence		

ClinGen's Curation Summaries | External Genomic Resources | ClinVar Variants

SH2B1

Curated by	Classification	Date	Report
Gene Dosage Sensitivity	**Some Evidence for Haploinsufficiency**	05/31/2017	View report
Gene Dosage Sensitivity	**No Evidence for Triplosensitivity**	05/31/2017	View report

Other Resources



Genes/regions with scores of “3” are added to our curated study in dbVar (nstd45) on a quarterly basis

Utilizing CNVs/Dosage Information in Gene-Disease Validity Classifications

Dosage and other ClinGen Curations

- Dosage evaluations can be used as a starting point for any other ClinGen curation activity that may find this type of information useful
- Example: Gene-Disease Validity
  - Dosage information may be a good source of case data → direct the curators to useful articles
  - May help establish mechanism of disease (loss of function or triplosensitivity)

Using CNVs as Evidence

- As in the dosage evaluations, only intragenic CNVs (or those otherwise involving only a single gene) can be considered “countable” evidence
  - If you cannot rule out the possibility that other involved genes may affect the observed phenotype, do not count
  - May still be useful to note large events as supporting evidence without scoring

Entering CNVs into Curation Interfaces

- To enter any variant into either the Gene or Variant Curation databases, an ID is required
  - If your CNV is in ClinVar – great! Use this ID.
  - If your CNV is NOT in ClinVar:
    - Will need to obtain an identifier from the ClinGen Allele Registry
    - Previously: Allele registry would not accept variants over 10kb in size.
    - Currently: Allele registry working on supporting real-time registration of CNVs, GCI/VCI working on be able to accept new Allele Registry CNV IDs.

What if I want to count a CNV as part of my gene curation NOW?

- If there is enough evidence to reach Definitive without the CNV(s), there may not be a need to include them
  - If they are a frequent variant type, may want to mention this in the free text evidence summary.
- If the CNVs are required to maximize scoring:
  - Describe in the free text evidence blurb
  - Keep a mental note of the points each is worth
  - Adjust the final classification at the end (if warranted); provide rationale behind the change.

Evidence Summary

NRXN1 – complex neurodevelopmental disorder – *Autosomal dominant inheritance*

Classification owner: Intellectual Disability and Autism
Calculated classification: Limited
Modified classification: Definitive
Reason for modified classification:
Due to the size of the deletions observed (>10kb), unable to enter variants on Gene Curation Interface (preventing ability to score). See Evidence Summary for a complete description of scoring for all cases, which brings the total score into the Definitive range (15.6 points).
SOP: Gene Clinical Validity Standard Operating Procedures (SOP), Version 6

Classification status: APPROVED PUBLISHED
Date classification saved: 2019 Jul 10, 8:30 am
Date classification published: 2019 Aug 21, 10:27 am
Replication Over Time: Yes
Contradictory Evidence? Proband: **No**, Experimental: **No**
Disease: complex neurodevelopmental disorder

Evidence Summary

Variants in NRXN1 have been associated with a variety of different neurodevelopmental conditions, including intellectual disability, epilepsy, and autism spectrum disorder. At least 118 pathogenic or likely pathogenic variants have been reported in ClinVar (most being deletions, SNVs, or duplications), with the first reported NRXN1 deletion observed by The Autism Genome Project Consortium in 2007 (PMID: 17322880). Here, we report several cases that have led to a definitive classification between the curated disease entity, complex neurodevelopmental disorder (MONDO:0100038), and NRXN1. Zahir et al., 2008 (PMID: 18057082) report a 12yo male proband with ID, autistic features, and severe language and motor impairments; this individual had a heterozygous de novo deletion of ~320kb in NRXN1 (chr2:50,799,281-51,120,644 (hg18)), and was given 2 points. Another case report from Zehra et al., 2008 (PMID: 26438105) presented a 28yo female proband with ID, developmental delay, language delay, and impaired social interactions (heterozygous de novo deletion of ~455 kb (chr2:51,020,477-51,476,031 (hg19)) – this individual was given 1.5 points, as the effect of this variant on protein function was not clear. A family study by Wisniowiecka-Kowalnik et al., 2010 (PMID: 20162629) outlined three families (only two scored). Family 1 received a score of 1.5 points for an ~380 kb deletion in NRXN1 that was observed in all five affected members (chr2:50,034,351-50,413,346 (hg18)). Family 2 also received a score of 1.5 points for an inherited tandem duplication, found in all three affected individuals (chr2:50,011,487-50,195,746 (hg18)). Two final studies were assessed, both of which presented a number of unrelated individuals. In a paper from Gregor et al., 2011 (PMID: 21827697), four probands were scored (N1, N2, N5, and N6). All four were given defaults scores of 0.5 points for their NRXN1 deletions (chr2:50,806,393-51,208,000 (hg18); chr2:50,270,203-51,357,206 (hg17); chr2:50,861,527-51,090,563 (hg17); chr2:51,033,865-51,496,143 (hg17)). Finally, Ching et al., 2010 (PMID: 20468056) present twelve individuals, eight of which were scored. Patient 2 received a full score of 2 points for a 3923kb de novo deletion (chr2:50,128,256-54,050,713 (hg18)). Patient 3 received a downgraded score of 0.1 point for a 315kb deletion chr2:50,897,002-51,212,385 (hg18)) in light of a very mild neurodevelopmental disorder phenotype. Patients 4, 5, 6, 7, and 9 all received scores of 0.5. Patients 4, 6, 7, and 9 all had inherited deletions (chr2:50,936,914-51,167,934; chr2:51,059,410-51,316,396; chr2: 51,090,504-51,212,385; chr2:50,689,280-50,853,329 (hg18)), while patient 5 had a de novo deletion (chr2:50,920,082-51,059,469 (hg18)), but was downgraded due to a mild phenotype. The variant observed in patient 10 (chr2:50,714,927-50,853,329 (hg18)) only impacted intronic regions and was given a score of zero since at this time, only exonic NRXN1 variants are known to be pathogenic.. In total, 13.1 points were awarded for genetic evidence (note that more evidence is available, but not assessed given that this is above the 12 point cut-off), and 4 points for experimental evidence (max allowed for non-human model organisms), bringing the NRXN1-complex NDD classification into the definitive range (replicated over time) – 16 points.

NRXN1 – complex neurodevelopmental disorder – *Autosomal dominant inheritance*

Classification owner: Intellectual Disability and Autism
Calculated classification: Limited
Modified classification: Definitive
Reason for modified classification:
Due to the size of the deletions observed (>10kb), unable to enter variants on Gene Curation Interface (preventing ability to score). See Evidence Summary for a complete description of scoring for all cases, which brings the total score into the Definitive range (15.6 points).
SOP: Gene Clinical Validity Standard Operating Procedures (SOP), Version 6

Classification status: APPROVED PUBLISHED
Date classification saved: 2019 Jul 10, 8:30 am
Date classification published: 2019 Aug 21, 10:27 am
Replication Over Time: Yes
Contradictory Evidence? Proband: **No**, Experimental: **No**
Disease: complex neurodevelopmental disorder

ClinVar and
Copy Number Variants (CNVs)

Yes, ClinVar accepts and displays CNVs!

- There are currently >51,000 CNVs in ClinVar
- These include CNVs previously submitted via the International Standards for Cytogenomic Arrays (ISCA) Consortium
  - Legacy cases
  - Submitters often designated as “ISCA Site 1,” “ISCA Site 2,” etc.
- Also includes direct submissions to ClinVar

Identifying CNVs in ClinVar: Genomic Coordinates

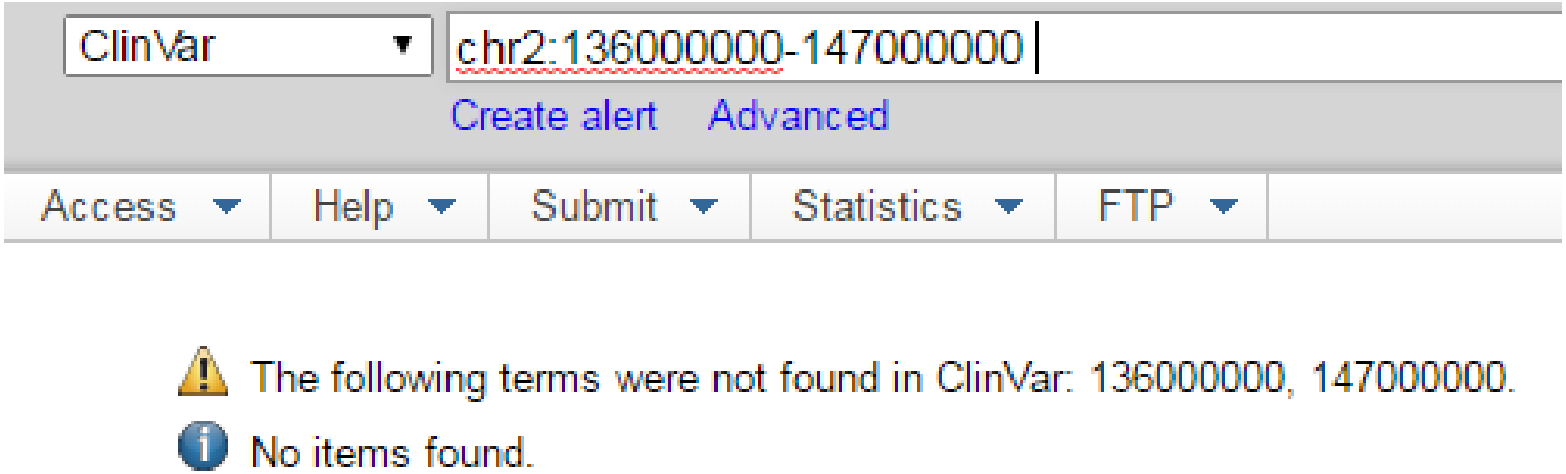
- Searching for a CNV in ClinVar IS NOT THE SAME as searching in UCSC or other genome browsers
- Entering genomic coordinates alone into the ClinVar search box will only search for EXACT MATCHES
- Must use structured language or advanced search to return overlapping results

Identifying CNVs in ClinVar: Genomic Coordinates

- Search syntax for genomic coordinates:
  - Information specific to your search in red
  - Syntax in blue
- Chromosome Number [chr] AND Genomic Coordinate 1:Genomic Coordinate 2 [chrpos37]

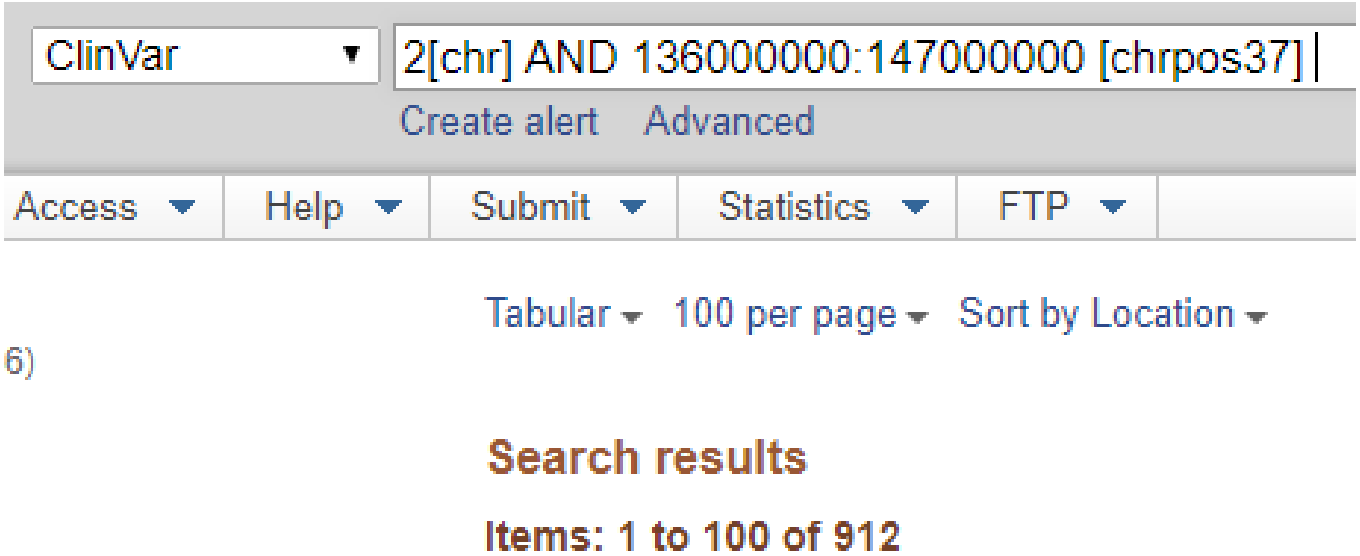
This represents the assembly – edit the number depending on the assembly you are looking for (using the GRCh numbering system)

Example: Searching for chr2:136000000-147000000 (GRCh37)



- Searching with traditional syntax yields no results
- ClinVar does not recognize the coordinates without the proper syntax!

Example: Searching for chr2:136000000-147000000 (GRCh37)



- Using the proper syntax, our search has yielded 912 results
  - Doesn't matter if you put spaces between your info and the bracketed items, or after the colon, but you must put a space before and after "AND"
- Note that this method will also include sequence variants in this interval– you can exclude many of these by using the filters on the left hand side of the screen

Results

NCBI Resources How To

ClinVar

ClinVar | 2[chr] AND 136000000:147000000 [chrpos37] | Search

Create alert Advanced

Home About Access Help Submit Statistics FTP

Clinical significance
Conflicting interpretations (36)
Benign (128)
Likely benign (246)
Uncertain significance (237)
Likely pathogenic (30)
Pathogenic (189)
Risk factor (1)

Molecular consequence
Frameshift (94)
Missense (261)
Nonsense (60)
Splice site (7)
ncRNA (19)
Near gene (0)
UTR (94)

Variation type
Deletion (155)
Duplication (73)
Indel (5)
Insertion (42)
Single nucleotide (660)

Variant length
Less than 51 bp (797)
Between 51 and 1000 bp (3)
Between 1 and 50 kb (3)
Between 50 and 500 kb (14)
Between 500 kb and 1 Mb (7)
Between 1 and 5 Mb (11)
Greater than 5 Mb (6)

Review status
Practice guideline (0)
Expert panel (0)
Multiple submitters (88)
Single submitter (621)
At least one star (745)
Conflicting interpretations (36)

Tabular 100 per page Sort by Location

You can narrow your search using filters on the left.

Search results

Items: 1 to 100 of 912

<< First < Prev

	Variation *Location*	Gene(s)	Protein change	Condition(s)	Clinical significance (Last reviewed)
1.	GRCh38/hg38 2q14.3-22.1(chr2:123445762-140592538)x1 *GRCh37:* Chr2:124203338-141350107 *GRCh38:* Chr2:123445762-140592538	BIN1, CCNT2, DARS1, ERCC3, GPR17, GPR39, GYPC, HNMT, LCT, MCM6, MGAT5, MYO7B, POLR2D, PROC, CXCR4, HS6ST1, MAP3K2, NXPH2, RAB3GAP1, UBXN4, R3HDM1, PTPN18, C2orf27A, ARHGEF4, LRP1B, PLEKHB2, WDR33, SMPD4, IWS1, LIMS2, CFC1, UGGT1, SAP130, MZT2B, MAP3K19, THSD7B, TMEM163, AMMECR1L, ZRANB3, RAB6C, CCDC115, SFT2D3, CCDC74A, ...more		See cases	Pathogenic (Oct 1, 2010)
2.	GRCh38/hg38 2q21.3(chr2:134950277-135611818)x3 *GRCh37:* Chr2:135707847-136369388 *GRCh38:* Chr2:134950277-135611818	CCNT2, RAB3GAP1, R3HDM1, MAP3K19, ZRANB3, SNORA40B, LOC111562379		See cases	Uncertain significance (Aug 2, 2011)
3.	GRCh38/hg38 2q21.3(chr2:135479205-135518855)x1 *GRCh37:* Chr2:136236775-136276425 *GRCh38:* Chr2:135479205-135518855	ZRANB3		See cases	Likely benign (Apr 30, 2011)
4.	NM_002299.4(LCT):c.*442_*443GT[1] *GRCh37:* Chr2:136545449-136545450 *GRCh38:* Chr2:135787879-135787880	LCT		Congenital lactase deficiency, Lactose intolerance	Likely benign (Jun 14, 2016)
5.	NM_002299.4(LCT):c.*429A>C *GRCh37:* Chr2:136545465 *GRCh38:* Chr2:135787895	LCT		Congenital lactase deficiency, Lactose intolerance	Likely benign (Jun 14, 2016)
6.	NM_002299.4(LCT):c.*325G>C *GRCh37:* Chr2:136545569 *GRCh38:* Chr2:135787999	LCT		Congenital lactase deficiency, Lactose intolerance	Uncertain significance (Jun 14, 2016)

Filtering for CNVs: By Size

Search results

Items: 1 to 100 of 912

	Variation *Location*	Gene(s)	Protein change	Condition(s)
1.	GRCh38/hg38 2q14.3-22.1(chr2:123445762-140592538)x1 *GRCh37:* Chr2:124203338-141350107 *GRCh38:* Chr2:123445762-140592538	BIN1, CCNT2, DARS1, ERCC3, GPR17, GPR39, GYPC, HNMT, LCT, MCM6, MGAT5, MYO7B, POLR2D, PROC, CXCR4, HS6ST1, MAP3K2, NXPH2, RAB3GAP1, UBXN4, R3HDM1, PTPN18, C2orf27A, ARH MZT2B, MAP CDC74A, ...more		See cases
2.	GRCh38/hg38 2q21.3(chr2:134950277-135611818)x3 *GRCh37:* Chr2:135707847-136369388 *GRCh38:* Chr2:134950277-135611818	CCN		See cases
3.	GRCh38/hg38 2q21.3(chr2:135479205-135518855)x1 *GRCh37:* Chr2:136236775-136276425 *GRCh38:* Chr2:135479205-135518855	ZRA		See cases
4.	NM_002299.4(LCT):c.*442_*443GT[1] *GRCh37:* Chr2:136545449-136545450 *GRCh38:* Chr2:135787879-135787880	LCT		Congenital lactase deficiency, Lactose intolerance
5.	NM_002299.4(LCT):c.*429A>C *GRCh37:* Chr2:136545465 *GRCh38:* Chr2:135787895	LCT		Congenital lactase deficiency, Lactose intolerance
6.	NM_002299.4(LCT):c.*325G>C *GRCh37:* Chr2:136545569 *GRCh38:* Chr2:135787999	LCT		Congenital lactase deficiency, Lactose intolerance

Variant length

- Less than 51 bp (797)
- Between 51 and 1000 bp (3)
- Between 1 and 50 kb (3)
- Between 50 and 500 kb (14)
- Between 500 kb and 1 Mb (7)
- Between 1 and 5 Mb (11)
- Greater than 5 Mb (6)

Filtering can be used to separate CNVs from SNVs, if desired.

Filtering for CNVs: By Size

- Select the size bins you are interested in (typically, anything 1kb or greater)
- This reduced the results of our original query to 41

Search results

tems: 41

Filters activated: Between 1 and 50 kb, Between 50 and 500 kb, Between 500 kb and 1 Mb, Between 1 and 5 Mb, Greater than 5 Mb. Clear all to show 912 items.

	Variation *Location*	Gene(s)	Protein change	Condition(s)	Clinical significance (Last reviewed)
1.	GRCh38/hg38 2q14.3-22.1(chr2:123445762-140592538)x1 *GRCh37:* Chr2:124203338-141350107 *GRCh38:* Chr2:123445762-140592538	BIN1, CCNT2, DARS1, ERCC3, GPR17, GPR39, GYPC, HNMT, LCT, MCM6, MGAT5, MYO7B, POLR2D, PROC, CXCR4, HS6ST1, MAP3K2, NXPH2, RAB3GAP1, UBXN4, R3HDM1, PTPN18, C2orf27A, ARHGEF4, LRP1B, PLEKHB2, WDR33, SMPD4, IWS1, LIMS2, CFC1, UGGT1, SAP130, MZT2B, MAP3K19, THSD7B, TMEM163, AMMECR1L, ZRANB3, RAB6C, CCDC115, SFT2D3, CCDC74A, CCDC74B, IMP4, TUBA3E, ...more		See cases	Pathogenic (Oct 1, 2010)
2.	GRCh38/hg38 2q21.3(chr2:134950277-135611818)x3 *GRCh37:* Chr2:135707847-136369388 *GRCh38:* Chr2:134950277-135611818	CCNT2, RAB3GAP1, R3HDM1, MAP3K19, ZRANB3, SNORA40B, LOC111562379		See cases	Uncertain significance (Aug 2, 2011)
3.	GRCh38/hg38 2q21.3(chr2:135479205-135518855)x1 *GRCh37:* Chr2:136236775-136276425 *GRCh38:* Chr2:135479205-135518855	ZRANB3		See cases	Likely benign (Apr 30, 2011)
4.	NC_000002.11:g.(?_136707983)_(136875650_?)del *GRCh37:* Chr2:136707983-136875650 *GRCh38:* Chr2:135950413-136118080	DARS1, CXCR4, DARS-AS1		Warts, hypogammaglobulinemia, infections, and myelokathexis	Uncertain significance (Sep 6, 2018)

Filtering for CNVs: Variant-Gene Relationship

- Allows you to filter by the following categories:
  - Single gene: variant is contained within a single gene
    - Consider using this (in conjunction with other filters) if looking for CNVs involving a single gene
  - In overlapping genes: variant is within the region of overlap between genes that are known to overlap (ex: *MYH7* and *MHRT*)
  - Spans multiple genes: variant spans multiple genes
    - Consider using this if looking for larger CNVs
  - Multiple genes: In general, the combination of the "In Overlapping Genes" and "Spans Multiple Genes" categories

- Note: selecting "spans multiple genes" will filter out intragenic events, and selecting "single gene" will exclude larger, multi-gene CNVs

Filtering for CNVs: Variation Type

- The filter “variation type” can be used to narrow your search to common variation types, including:
  - Deletion
  - Duplication
  - Indel
  - Insertion
  - Single nucleotide
- Additional options are available through advanced search, such as:
  - Copy Number Loss
  - Copy Number Gain

Filtering for CNVs: Variation Type

- The “variation type” of a particular ClinVar variant is chosen by the submitter
- When submitting variants detected by chromosomal microarray (CMA) with fuzzy end points, ClinVar recommends the use of “copy number gain” and “copy number loss”
- HOWEVER, some submitters still select “deletion” or “duplication”
  - These terms also apply to sequence-level variation

Filtering for CNVs: Variation Type

- When using this filter, keep in mind that selecting “deletion” or “duplication” from the commonly used filters on the left may result in some sequence variants remaining in your query

Example: Using Multiple Filters

- Example use case: Are there any other deletions overlapping a gene of interest?
  - Let's use *SCN1A*

Enter Gene of Interest

scn1a[gene] Search

Create alert Advanced

Submit Statistics FTP

Tabular 100 per page Sort by Location

Showing for results for variants in the **scn1a** gene. *Search instead for all ClinVar records that mention **scn1a***

Search results

Items: 1 to 100 of 1745 ← **1745 results**

	Variation *Location*	Gene(s)	Protein change	Condition(s)
1.	GRCh38/hg38 2q24.1-31.1(chr2:154294042-175989372)x3 *GRCh37:* Chr2:155150555-176854100 *GRCh38:* Chr2:154294042-175989372	ACVR1, ATP5MC3, CHN1, CHRNA1, ATF2, DLX1, DLX2, DYNC1I2, DPP4, FAP, GAD1, GALNT3, GCG, GPD2, GRB14, ITGA6, ITGB6, KCNJ3, LRP2, LY75, NR4A2, PDK1, RBMS1, **SCN1A**, SCN2A, SCN3A, SCN7A, SCN9A, SP3, SSB, WIPF1, PKP4, HAT1, SLC25A12, ABCB11, B3GALT1, PPIG, CIR1, CYTIP, TLK1, CD302, TANK, DHRS9, PSMD14, KLHL41, TBR1, RAPGEF4, GALNT5, COBLL1, PLA2R1, GCA, ...more		See cases
2.	GRCh38/hg38 2q24.1-24.3(chr2:154366788-167048902)x3 *GRCh37:* Chr2:155223300-167905412 *GRCh38:* Chr2:154366788-167048902	LOC112806057, LOC114827830, ACVR1, DPP4, FAP, GALNT3, GCG, GPD2, GRB14, ITGB6, KCNJ3, LY75, NR4A2, RBMS1, **SCN1A**, SCN2A, SCN3A, SCN7A, SCN9A, PKP4, CYTIP, CD302, TANK, PSMD14, TBR1, GALNT5, COBLL1, PLA2R1, GCA, BAZ2B, FIGN, SLC4A10, ERMN, IFIH1, MARCHF7, TTC21B, CSRNP3, TANC1, KCNH7, DAPL1, GALNT13, XIRP2, ACVR1C, CCDC148, SLC38A11, ...more		See cases
3.	GRCh38/hg38 2q24.1-24.3(chr2:158382388-166605758)x1 *GRCh37:* Chr2:159238900-167462268 *GRCh38:* Chr2:158382388-166605758	DPP4, FAP, GALNT3, GCG, GRB14, ITGB6, LY75, RBMS1, **SCN1A**, SCN2A, SCN3A, SCN7A, SCN9A, PKP4, CD302, TANK, PSMD14, TBR1, COBLL1, PLA2R1, GCA, BAZ2B, FIGN, SLC4A10, IFIH1, MARCHF7, TTC21B, CSRNP3, TANC1, KCNH7, DAPL1, CCDC148, SLC38A11, WDSUB1, LOC643072, PKP4-AS1, DPP4-DT, SNORA70F, LINC02478, LOC100506124, TTC21B-AS1, LY75-CD302, MIR4785, ...more		See cases

Filter: Variant Type

Variation type

Deletion (228)

Duplication (100)

Indel (15)

Insertion (94)

Single nucleotide (1,388)

Filter: Variant Type

scn1a[gene]

Search

Create alert Advanced

Submit Statistics FTP

Tabular 100 per page Sort by Location

Showing for results for variants in the **scn1a** gene. *Search instead for all ClinVar records that mention **scn1a***

Search results

Items: 1 to 100 of 228

Filter narrows search to 228 variants.

Filters activated: Deletion. Clear all to show 1745 items.

	Variation *Location*	Gene(s)	Protein change	Condition(s)
1.	GRCh38/hg38 2q24.1-24.3(chr2:158382388-166605758)x1 *GRCh37:* Chr2:159238900-167462268 *GRCh38:* Chr2:158382388-166605758	DPP4, FAP, GALNT3, GCG, GRB14, ITGB6, LY75, RBMS1, **SCN1A**, SCN2A, SCN3A, SCN7A, SCN9A, PKP4, CD302, TANK, PSMD14, TBR1, COBLL1, PLA2R1, GCA, BAZ2B, FIGN, SLC4A10, IFIH1, MARCHF7, TTC21B, CSRNP3, TANC1, KCNH7, DAPL1, CCDC148, SLC38A11, WDSUB1, LOC643072, PKP4-AS1, DPP4-DT, SNORA70F, LINC02478, LOC100506124, TTC21B-AS1, LY75-CD302, MIR4785, ...more		See cases
2.	GRCh38/hg38 2q24.3(chr2:163455290-166962322)x1 *GRCh37:* Chr2:164311800-167818832 *GRCh38:* Chr2:163455290-166962322	GALNT3, GRB14, **SCN1A**, SCN2A, SCN3A, SCN7A, SCN9A, COBLL1, FIGN, TTC21B, CSRNP3, XIRP2, SLC38A11, SNORA70F, LOC100506124, TTC21B-AS1, LOC101929633, **SCN1A**-AS1, LOC102724058, LOC110120601, LOC110120677, LOC110120725, LOC111413009, LOC112806057		See cases
3.	GRCh38/hg38 2q24.3-32.1(chr2:163965382-182195062)x1 *GRCh37:* Chr2:164821892-183059789 *GRCh38:* Chr2:163965382-182195062	ATP5MC3, CHN1, CHRNA1, ATF2, DLX1, DLX2, DYNC1I2, GAD1, GALNT3, GRB14, HOXD1, HOXD3, HOXD4, HOXD8, HOXD9, HOXD10, HOXD11, HOXD12, HOXD13, ITGA6, ITGA4, LRP2, NEUROD1, NFE2L2, PDE1A, PDK1, **SCN1A**, SCN2A, SCN3A, SCN7A, SCN9A, SP3, SSB, ITPRID2, TTN, WIPF1, HAT1, AGPS, PRKRA, SLC25A12, ABCB11, B3GALT1, PPIG, CIR1, TLK1, DHRS9, KLHL41, UBE2E3, ...more		See cases
4.	GRCh38/hg38 2q24.3-31.1(chr2:164066038-172097886)x1 *GRCh37:* Chr2:164922548-172962614	DLX1, DYNC1I2, GAD1, GALNT3, GRB14, LRP2, **SCN1A**, SCN2A, SCN3A, SCN7A, SCN9A, SSB, HAT1, SLC25A12, ABCB11, B3GALT1, PPIG, TLK1, DHRS9, KLHL41, COBLL1, GORASP2, STK39, METTL5, SPC25, G6PC2, FASTKD1, TTC21B, METTL8, CYBRD1, CSRNP3, DCAF17, NOSTRIN,		See cases

Additional Filters Would Narrow the Search

Variant length

Less than 51 bp (161)
Between 51 and 1000 bp (3)
Between 1 and 50 kb (5)
Between 50 and 500 kb (3)
Between 500 kb and 1 Mb (1)
Between 1 and 5 Mb (5)
Greater than 5 Mb (4)

Variant-gene relationship

Single gene (121)
In overlapping genes (85)
Spans multiple genes (23)
Multiple genes (107)

Viewing CNVs in Genomic Context

- While many CNVs are cataloged in ClinVar, it is often preferable to view them in genomic context
- This can be done using genome browsers
- Both UCSC and NCBI's Variation Viewer have tracks displaying structural variation in ClinVar
  - In UCSC: "ClinVar Variants" track
  - In Variation Viewer: "dbVar Clinical Structural Variants" (nstd102)

The DSC Team (Acknowledgements)

- Andrea Vaags
- Angela Lager
- Benjamin Clyde
- Benjamin Hilton
- Bradley Coe
- Brynn Levy
- Cassandra Runke
- Cherisse Marcou
- Christa Martin
- Christine Preston
- Con Ngo
- Coumarane Mani
- Dany Pineda-Alvarez
- Deborah Ritter
- Diogo Lovato
- Erica Andersen
- Erik Thorland
- Erin Rooney Riggs
- George Burghel
- Guang Li
- Hiba Risheg
- Hutton Kearney
- John Herriges
- Joo Wook Ahn
- Justin Schleede
- Kristy Lee
- Laura Conlin
- Lei Zhang
- Marsha Speevak
- McKinsey Goodenberger
- Meng Su
- Minjie Luo
- Molly Schroeder
- Natalie Pino
- Oscar Cano
- Prabakaran Paulraj
- Preti Jain
- Ross Rowsey
- Sainan Wei
- Shamini Selvarajah
- Shulin Zhang
- Sibel Kantarci
- Swaroop Aradhya
- Ted Higginbotham
- Tracy Brandt
- Vaidehi Jobanputra
- Wahab Khan
- Yang Cao
- Yiping Shen
- Zoe Lewis

<u>NCBI Team, including:</u>

- Melissa Landrum
- Tim Hefferon
- Chao Chen

<u>ClinGen Web Team, including:</u>

- Scott Goehringer
- Phillip Weller
- Tristan Nelson