ClinGen
Clinical Genome Resource

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

Copy Number Variant Interpretation and Dosage Sensitivity Curation

Erica Andersen, PhD, FACMG
ARUP Laboratories, University of Utah

(On behalf of the ACMG/ClinGen CNV Interpretation Guidelines and ClinGen Dosage Sensitivity Curation (DSC) Working Groups)

Start here: clinicalgenome.org/tools/h3africa-rdwg-workshop/copy-number-variant-interpretation-dosage-sensitivity-curation/

H3Africa Rare Disease Working Group and ClinGen Resource Workshop

This workshop will provide an overview of clinical genomic interpretation for rare disease, with a focus on assessing gene-disease associations (gene curation) and assessing variant pathogenicity (variant curation).

H3Africa

Overview | Workshop Agenda | Educational Resources | Get Involved

The recording will be available a few days after the presentation.

Copy Number Variant Interpretation/Dosage Sensitivity Curation

Erica Andersen, PhD
ARUP Laboratories

Description

Review the 2020 ACMG/ClinGen technical standards for classifying constitutional copy number (CNV) variants, and learn how ClinGen's process for evaluating haploinsufficiency and triplosensitivity informs the CNV classification process.

Recommended Audience

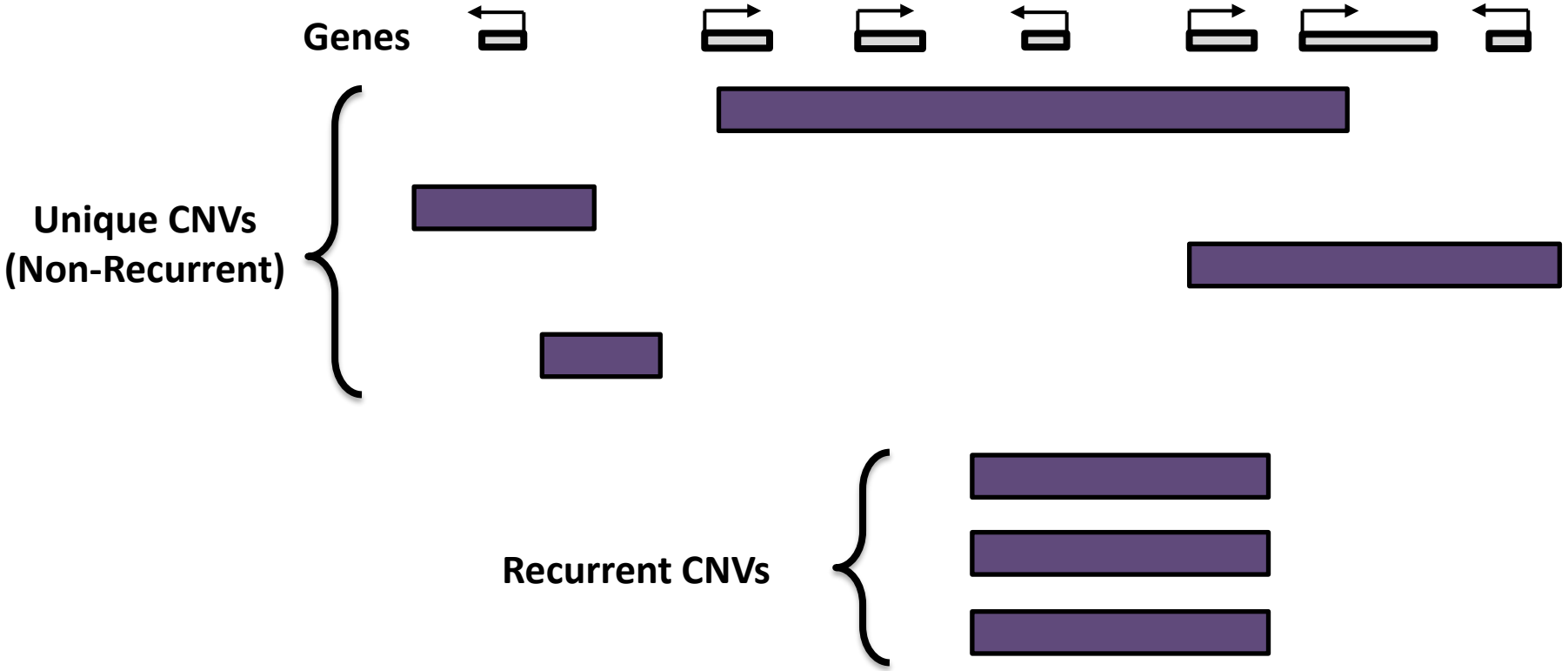
All learners are welcome to attend. This session will introduce resources available to assist and standardize clinical CNV interpretation, including a short tutorial of the ClinGen Dosage Sensitivity Map website and use of the new metrics for CNV classification through example cases.

Share on Twitter

- **ClinGen CNV Interpretation Guidelines WG Page**
- **CNV Technical Standards Web Series**
- **ClinGen Dosage Sensitivity Map Website**
- **CNV Calculator**

Challenges with CNV Interpretation

- Most CNVs are unique: variable breakpoints, gene content
  - Recurrent CNVs: many with variable clinical findings, reduced penetrance



Needs

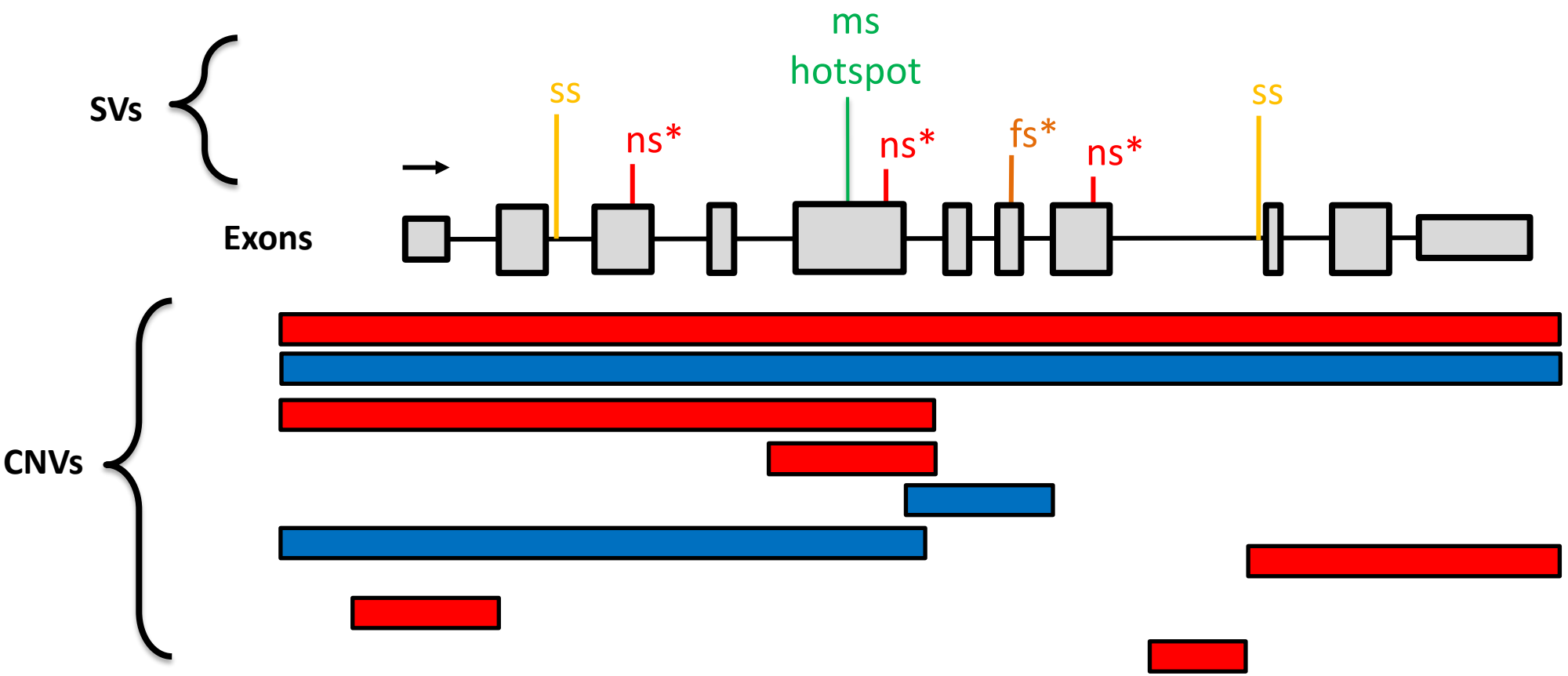
- Compiling evidence from different resources
- Standardized classification processes
- Tailored clinical reports

Needs

- Standardized classification processes and reporting
- Appropriate clinical counseling

Challenges with CNV Interpretation

- Genes that are disease-associated may do so by mechanisms other than deletion/duplication (dosage sensitivity)



Needs

- Compiling evidence from different resources
- Technical and functional understanding
- Standardized classification processes

2011

Evolving CNV Interpretation

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

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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

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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]

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)

2021

➢ Standardize: across labs, across technologies, across specialties

New Change: Officially Adopt the 5-Tier Variant Classification System

Former

- Pathogenic
- Uncertain Clinical Significance
  - Uncertain, Likely Pathogenic
  - Uncertain (VUS)
  - Uncertain, Likely Benign
- Benign

****New***

- Pathogenic
- Likely Pathogenic
- Uncertain Significance (VUS)
- Likely Benign
- Benign

**These are the standardized classification categories that should be used. Using other terms causes confusion for clinicians and families – additional information can be provided in the report to further explain the result*

New Change: Numerical Scoring System for Deletions and Duplications

Key Features

- Start at VUS=0
- Points used to up- or down-grade CNV classification
- Points values for each piece of evidence correspond to sequence variant evidence categories (ClinGen SVI, ACMG/AMP)

Evidence category	Points
Very Strong	+/- 0.90
Strong	+/- 0.45
Moderate	+/- 0.30
Supporting	+/- ≤0.15

- Default values provided for all, ranges included for many evidence categories

Key Evidence Types for CNV Classification

- Evidence types separated out, scored independently

1) Gene/exon/regulatory element content
2) Overlap with established DS and Benign genes/regions
   - Rules for intragenic CNV evaluation
   - HI Predictors for deletions
3) Gene count (protein-coding genes, gene families)
   - Different values for deletions vs. duplications
4) Literature and database review
   - Phenotype specificity
   - Inheritance patterns
   - Common variation and case-control data
5) Inheritance patterns/family history for patient being studied

New Change: Numerical Scoring System for Deletions and Duplications

Key Features

- Scores are summed to a total value and assigned a corresponding classification
- Total point values correspond to confidence levels that a particular CNV is disease-causing or benign
  - Greater than 99% certainty of Pathogenic and Benign
  - Greater than 90% certainty for LP and LB

Points	Classification
0.99 or more	Pathogenic (P)
0.90 to 0.98	Likely Pathogenic (LP)
0.89 to -0.89	Uncertain (VUS)
-0.90 to -0.98	Likely Benign (LB)
-0.99 or less	Benign (B)

Case 1

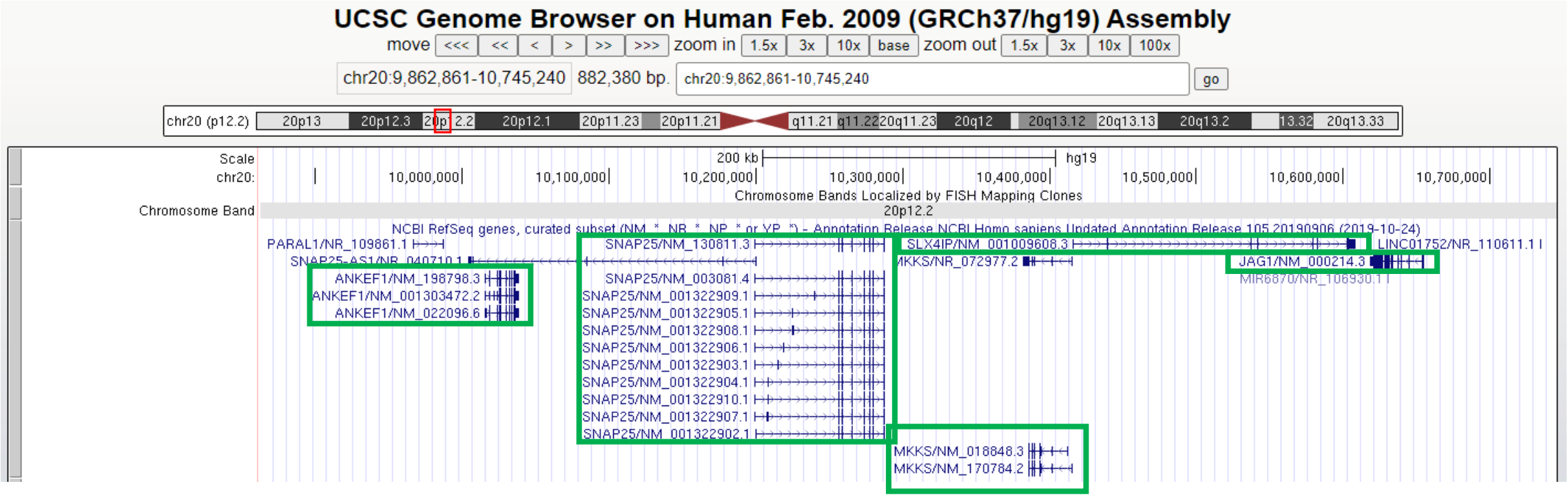
Newborn male with poor feeding, small for gestational age

Cytogenomic Nomenclature (ISCN):
arr[GRCh37] 20p12.2(9,862,861_10,745,240)x1 dn

- An 882 kb de novo deletion

Input format: chr20:9,862,861-10,745,240 (use GRCh37/hg19)

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



NCBI RefSeq genes

Protein Coding? "NM_" = mRNA (coding) "NR_" = noncoding RNA More: en.wikipedia.org/wiki/RefSeq

Section 2: Overlap with Established DS/Benign Genes/Regions

Evidence	Suggested points/case	Max score
2A. Complete overlap of an established HI gene/genomic region.	1.00	1.00
2F. Completely contained within an established benign CNV region.	−1	−1

- “The ClinGen Dosage Sensitivity Map specifically annotates and scores genes and genomic regions in relation to dosage sensitivity, and should be used to interrogate most CNVs”

Riggs et al., *Genetics in Medicine* (2019)

About Us...

Dosage Sensitivity

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

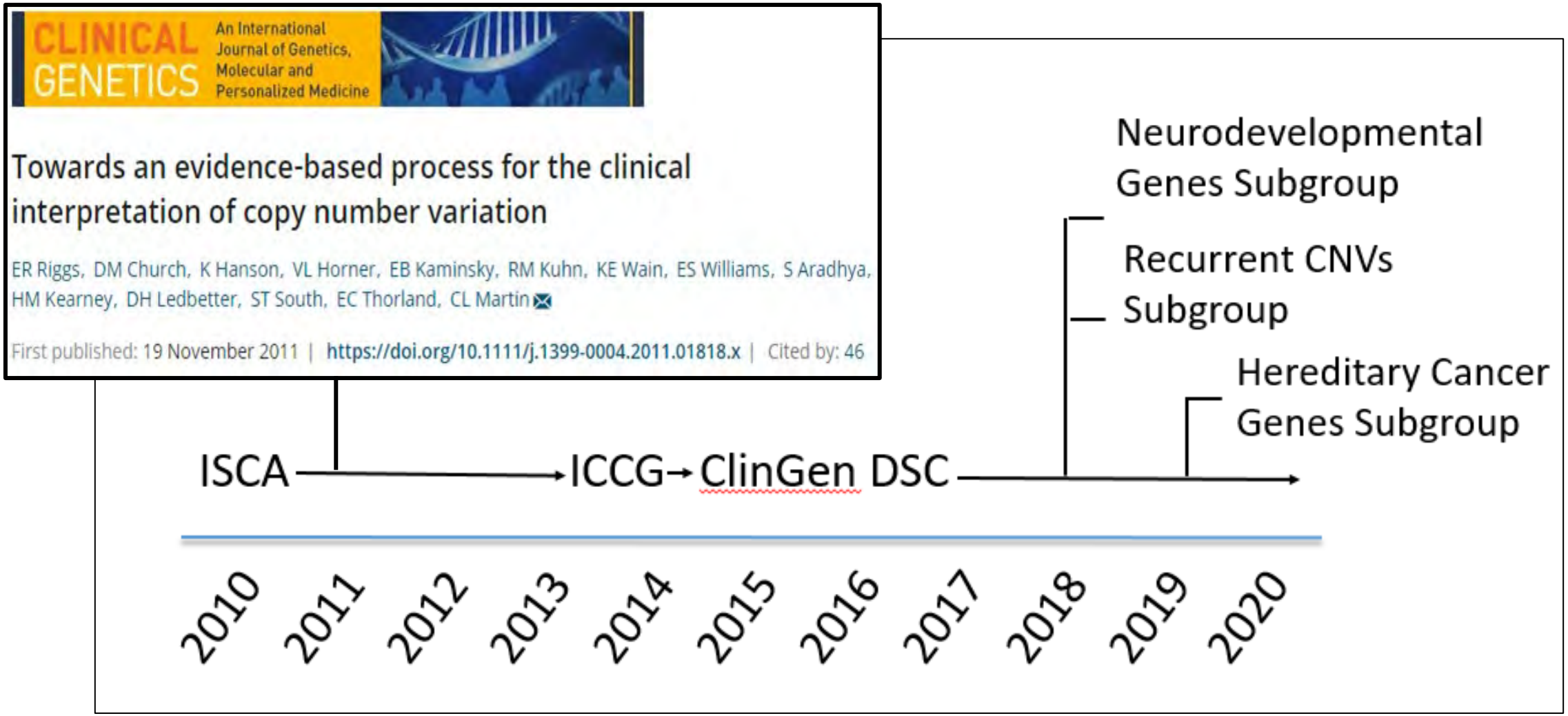
- https://clinicalgenome.org/curation-activities/dosage-sensitivity/

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)

About Us…


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
Neurodevelopmental Genes Subgroup
Recurrent CNVs Subgroup
Hereditary Cancer Genes Subgroup
ISCA
ICCG→ ClinGen DSC
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020

JAG1

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: ALAGILLE SYNDROME 1; ALGS1

Evidence for haploinsufficiency phenotype

PubMed ID	Description
9585603	Krantz et al. (1998) tested 54 Alagille syndrome (AGS) patients and their families for for the frequency of variants in JAG1. They found mutations/deletions in 75% of the patients, including 3 whole-gene deletions, 19 small deletions and insertions, and 9 nonsense mutations. Some of the identified variants were de novo and some were inherited from parents with clinical features consistent with JAG1 or an AGS microform (meaning they had some physical features consisted with AGS but not enough to establish clinical diagnosis).
12497640	Ropke et al. (2003) tested a series of probands with Alagille syndrome for mutations in JAG1. They identified 36 new variants in JAG1, including 23 truncating variants (these included deletions, insertions, complex and nonsense variants). Some of the identified variants were de novo and some were determined to be inherited.
16575836	Warthen et al. (2006) tested 247 probands with diagnosis of Alagille syndrome and found JAG1 mutations in 94% of patients, including over 40 different truncating variants.

Haploinsufficiency phenotype comments:

Haploinsufficiency of JAG1 is associated with Alagille syndrome. Alagille syndrome is an autosomal dominant disorder variably affecting multiple organ systems including the liver, heart, vertebra, kidneys, vasculature, eye and face. Genotype-phenotype correlation studies suggest deletions including JAG1 and smaller than approximately 4-5 Mb do not result in additional clinical findings as compared to patients with isolated JAG1 disruption.

Section 2: Overlap with Established DS Genes/Genomic Regions

Evidence	Suggested points/case	Max score
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

Pathogenic
Total score:
1

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ClinGen CNV Pathogenicity Calculator

Switch to CNV-Gain

CNV Interpretation Scoring Rubric: Copy Number LOSS

Section 1: Initial Assessment of Genomic Content				
Evidence Type	**Evidence**	**Suggested points**	**Max Score**	**Points Given**
Copy number loss content (For intragenic variants, use section 2E)	☑ 1A. Contains protein-coding or other known functionally important elements	0 (Continue Evaluation)	0	
	☐ 1B. Does NOT contain protein-coding or any known functionally important elements ℹ	-0.60	-0.60	Assigned points: 0
Section 2 : Overlap with Established/Predicted HI or Established Benign Genes/Genomic Regions *(Skip to Section 3 if your copy number loss DOES NOT overlap these types of genes/regions)*				
	☑ 2A. Complete overlap of an established HI gene/genomic region	1	1	Assigned points: 1

- In general, if a CNV reaches a 1 or -1 score due to complete overlap with an established dosage sensitive or benign gene or region, users of these metrics may not need to proceed further

Classification: Pathogenic

	Evidence	Score	Notes
1A	Protein-coding gene?	0	Yes
2A	Complete overlap with established HI gene?	1	Yes, JAG1
	Total points	**1**	

- Section 4 (lit review) may be helpful to evaluate additional genes in the interval, genotype-phenotype correlation

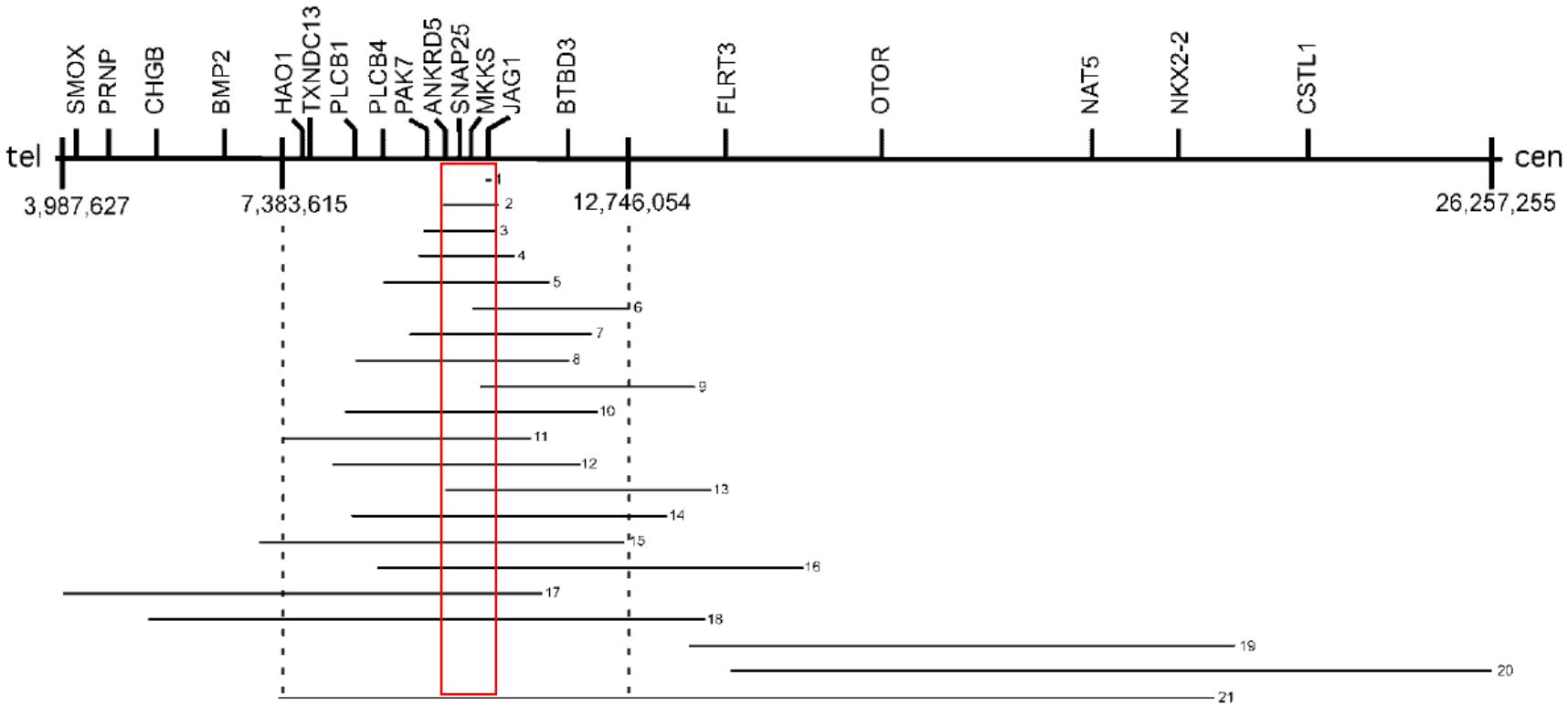

Figure 3. Map of the 20p deletions from each of the patients studied. A map of selected genes from 20p is presented along the top, and the extent of the deletions is represented by a line. The dotted lines indicate the boundaries of the "Alagille only" critical region. Deletions that are fully within these boundaries do not appear to be associated with clinical features outside of those seen in AGS.

Kamath et al., Hum Mutat. 2009

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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 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
- Pathogenic CNV regions
- Curation of the ACMG 59 Genes
- FTP

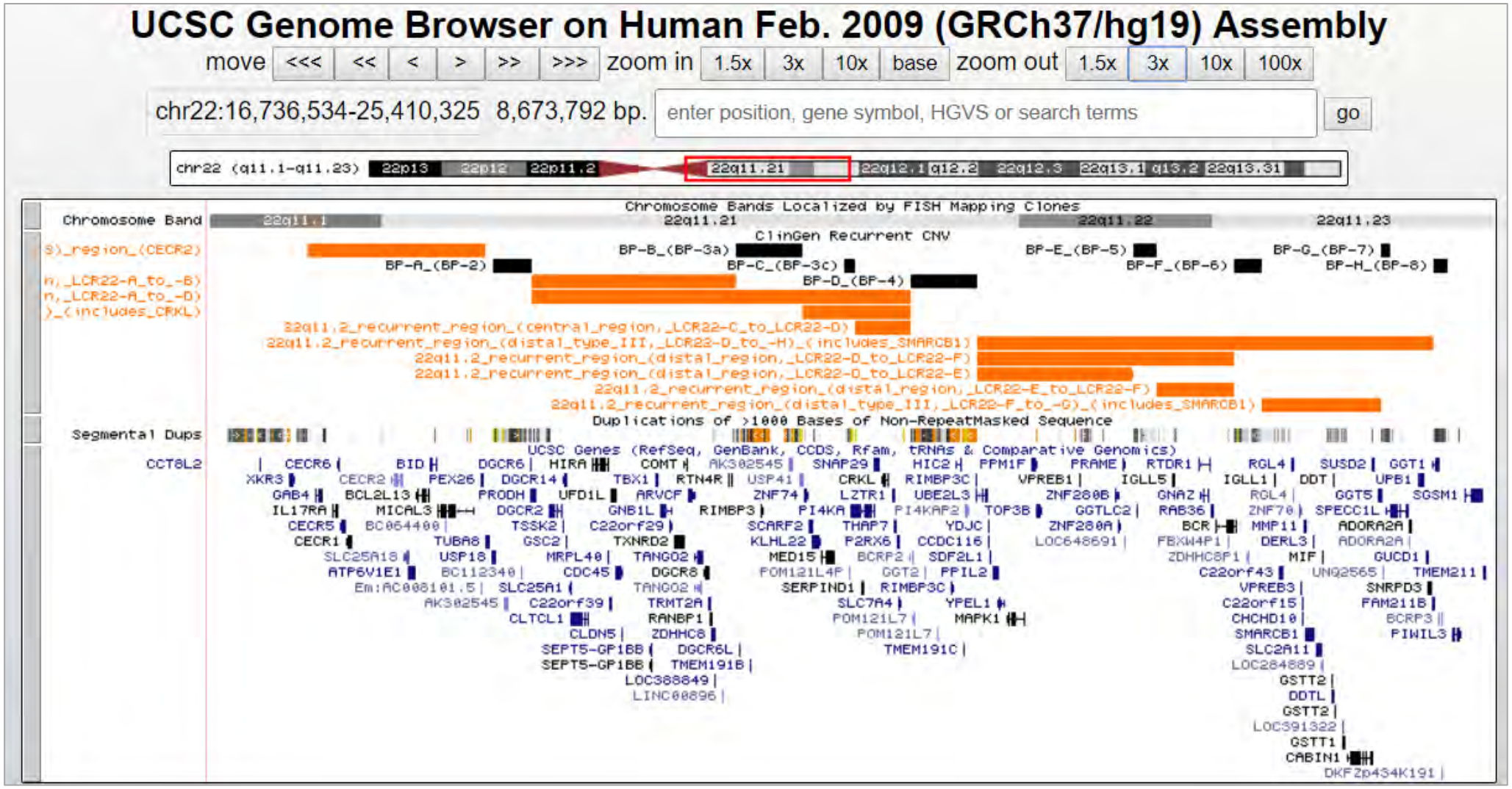
Useful files: https://ftp.clinicalgenome.org/

Index of /

Name	Last modified	Size	Description
ClinGen_gene_curation_list_GRCh37.tsv	2021-02-01 03:29	160K	
ClinGen_gene_curation_list_GRCh38.tsv	2021-02-01 03:29	160K	
ClinGen_haploinsufficiency_gene_GRCh37.bed	2021-02-01 03:29	45K	
ClinGen_haploinsufficiency_gene_GRCh38.bed	2021-02-01 03:29	45K	
ClinGen_region_curation_list_GRCh37.tsv	2021-02-01 03:29	16K	
ClinGen_region_curation_list_GRCh38.tsv	2021-02-01 03:29	16K	
ClinGen_triplosensitivity_gene_GRCh37.bed	2021-02-01 03:29	36K	
ClinGen_triplosensitivity_gene_GRCh38.bed	2021-02-01 03:29	36K	
ClinGen recurrent CNV .aed file V1.1-hg19.aed	2020-03-03 13:14	31K	
ClinGen recurrent CNV .aed file V1.1-hg38.aed	2020-03-03 13:14	20K	
ClinGen recurrent CNV .bed file V1.1-hg19.bed	2020-03-03 13:14	12K	
ClinGen recurrent CNV .bed file V1.1-hg38.bed	2020-03-03 13:14	12K	
README	2020-03-03 13:16	2.4K	
archive/	2021-02-01 03:29	-	

Apache/2.4.29 (Ubuntu) Server at ftp.clinicalgenome.org Port 443

Annotation file-available on our FTP site



New Change: “Uncouple” Variant Classification from Clinical Significance

- Two different concepts:
  - CNV Classification: Is there enough evidence that this CNV causes disease?
  - Clinical Significance: Is this CNV causing *my particular patient’s* phenotype?

- Examples:
  - Deletion of 17p12 (PMP22 gene) causing autosomal dominant HNPP, observed in a newborn patient referred for MCA or an adult with foot drop
  - Deletion of Xp22.31 (STS gene) causing X-linked recessive ichthyosis in males, observed in a 10 y/o female referred for dysmorphism and severe ID/DD

Classification vs. Clinical Significance

- In both scenarios, the CLASSIFICATION of the variant should remain the same
  - The evidence supporting these classifications (at the same point in time) is the same
  - Therefore, the variant should receive the same CLASSIFICATION (P, LP, VUS, LB, or B) regardless of the context in which it is observed
- In each scenario, the CLINICAL SIGNIFICANCE of the variant could be different
  - In scenario 1 (later-onset), the variant could represent a incidental finding in one patient but explain the indication for testing in another
  - In scenario 2 (X-linked), the variant could be disease-causing in a hemizygous male, but represent a carrier state in a heterozygous female
- Clearly labeled sections on a report delineating findings related to the RFR, findings that may be incidental, and findings that may represent carrier status could be utilized to clarify these situations

Example Report: Pathogenic CNV, Incidental Finding

Reason For Referral (RFR): Jane Doe is 9 year old female referred for developmental delay and autism spectrum disorder.

Report Summary: **This test did not identify any variants that can explain the patient's reported clinical features at this time.** However, a PATHOGENIC 1.4 Mb deletion of 3q11.2 involving 10 protein-coding genes, including Gene Y, was identified. Heterozygous loss of function (LOF) variants in Gene Y have been identified in individuals with autosomal dominant progressive sensorineural hearing loss (see discussion of Gene Y below). Jane Doe was not reported to have hearing loss; this may represent an incidental finding, or a cause for a phenotype that was not reported or that may be observed in the future. Clinical correlation and genetic counseling are recommended.

Copy Number Variant (CNV): 1.4 Mb 3q11.2 Deletion

ISCN	Type	Size	Inheritance	Zygosity	Classification
arr [GRCh37] 3q11.2 (XXXXXXX-XXXXXXX) x 1	Deletion	1.4 Mb	*De Novo*	Heterozygous	Pathogenic

Relevant Genomic Content:

This deletion includes 10 protein-coding genes, including the following, which are relevant to this report:

Gene	*Disease*	*Mode of Inheritance*	*Relevance Category*	*Notes*
Gene Y	Progressive sensorineural hearing loss (SNHL)	AD	Incidental Finding	Though Jane Doe was not reported to have hearing loss, she is thought to be at risk to develop hearing loss given this finding. Clinical correlation and genetic counseling are recommended.

Riggs et al., *Genetics in Medicine* (2019), Supp 4

Updated: Secondary/Incidental Findings

- A CNV may be identified that involves a DS gene unrelated to the patient's reason for referral:
  - e.g. a large 17q deletion causing syndromic features in a child that also includes the cancer risk gene BRCA1
  - e.g. focal BRCA1 gene deletion identified in a fetal specimen referred for ultrasound anomalies
- If the mechanism of disease is consistent with haploinsufficiency or triplosensitivity, these CNVs should be reported
  - *Be sure to consider the mechanism for pathogenicity (not all due to DS)*
- Resource: genes listed on the ACMG SF list curated by ClinGen Dosage Sensitivity Curation Working Group:
  (Go to dciw.clinicalgenome.org/acmg.shtml)

New Change: CNV Reporting Criteria for Prenatal Testing

- The CNV (del and dup) metrics and evaluation process should be used in the same manner for prenatal and postnatal testing
- Laboratories offering prenatal CNV testing should clearly outline which CNVs they will report, for example:
  - Only likely pathogenic and pathogenic variants
  - Only VUS larger than a specific size threshold

New Resource: CNV Technical Standards Web Series

➢ Go to... clinicalgenome.org/tools/cnv-webinar/

Recorded Jan-March 2020

Date	Topic	Presenter
January 16, 2020	Overview: Updated Technical Standards for Constitutional CNVs	Erin Rooney Riggs (Geisinger)
January 23, 2020	Use of the ClinGen Dosage Sensitivity Map	Erica Andersen (ARUP)
January 30, 2020	Scoring Case-Level Data	Erin Rooney Riggs (Geisinger)
February 6, 2020	Special Considerations in the Evaluation of Intragenic CNVs	Daniel Pineda-Alvaraz (Invitae)
February 13, 2020	Understanding Case-Control Data	Bradley Coe (BC Children's and BC Women's Hospitals)
February 20, 2020	Resources for Population CNV Data: gnomAD SV	Ryan Collins (Broad Institute)
February 27, 2020	Resources for Population CNV Data: Database of Genomic Variants (DGV)	Jeff MacDonald (The Hospital for Sick Children)
March 5, 2020	Uncoupling Variant Classification from Clinical Significance: Considerations for Reporting	Christa Lese Martin (Geisinger)
March 12, 2020	General Questions and Answers	All

New Recorded Nov 2020

CNV Implementation Webinar Video- Mayo Clinic

CNV Implementation Webinar Video- ARUP

CNV Implementation Webinar Video- Quest Diagnostics

CNV Implementation Webinar Video- Invitae

Case 2

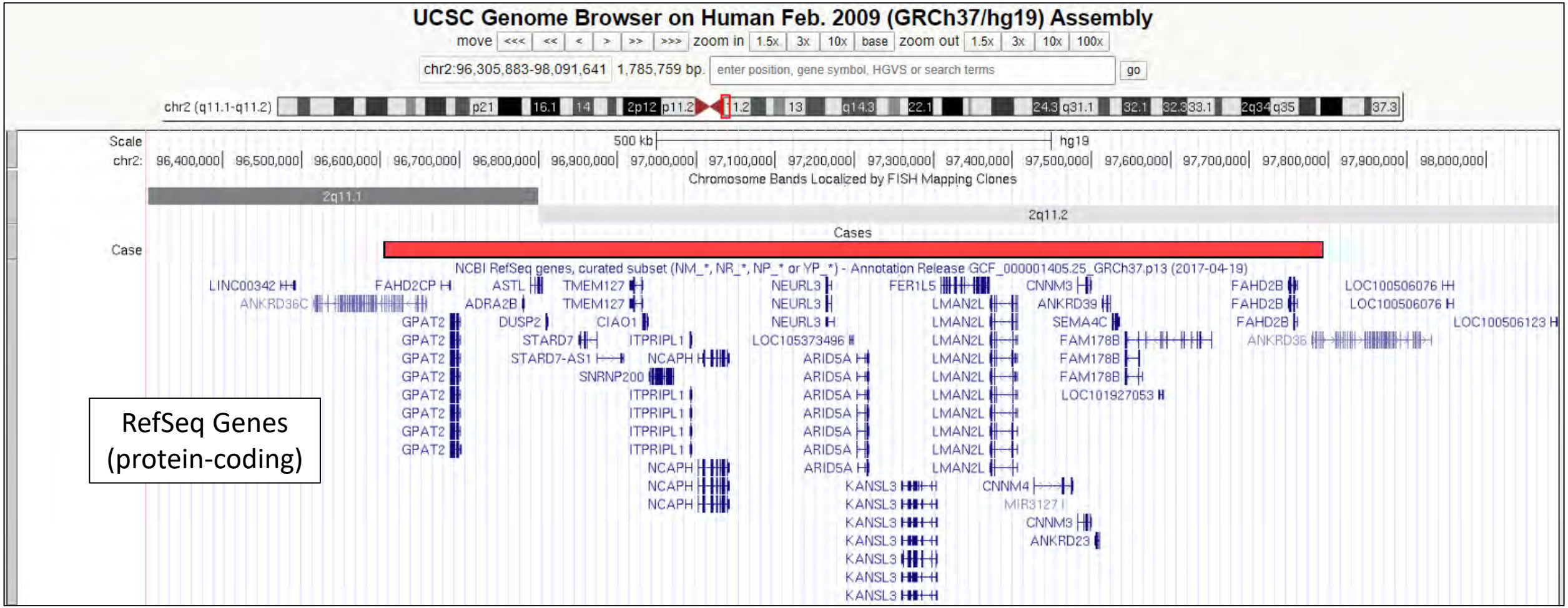
arr[GRCh37] 2q11.2(96603509_97794149)x1

3 y/o male referred for genomic microarray testing for DD

Inheritance unknown

- https://cnvcalc.clinicalgenome.org/cnvcalc/cnv-loss

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



Section 2: Overlap with Established DS/Benign Genes and Regions

Overlap with ESTABLISHED HI genes or genomic regions and consideration of reason for referral	**2A**. Complete overlap of an established HI gene/genomic region.	1.00	1.00
	2B. Partial overlap of an established HI genomic region • The observed CNV does NOT contain the known causative gene or critical region for this established HI genomic region OR • Unclear if known causative gene or critical region is affected OR • No specific causative gene or critical region has been established for this HI genomic region	0 (Continue evaluation)	0
	2C. Partial overlap with the 5′ end of an established HI gene (3′ end of the gene not involved)...	See categories below	
	2C-1. ...and coding sequence is involved	0.90 *(range: 0.45 to 1.00)*	1.00
	2C-2. ...and only the 5′ UTR is involved	0 *(range: 0 to 0.45)*	0.45
	2D. Partial overlap with the 3′ end of an established HI gene (5′ end of the gene not involved)...	See categories below	
	2D-1. ...and only the 3′ untranslated region is involved.	0 (Continue evaluation)	0
	2D-2. ...and only the last exon is involved. Other established pathogenic variants have been reported in this exon.	0.90 *(range: 0.45 to 0.90)*	0.90
	2D-3. ...and only the last exon is involved. No other established pathogenic variants have been reported in this exon.	0.30 *(range: 0 to 0.45)*	0.45
	2D-4. ...and it includes other exons in addition to the last exon. Nonsense-mediated decay is expected to occur.	0.90 *(range: 0.45 to 1.00)*	1.00
	2E. Both breakpoints are within the same gene (intragenic CNV; gene-level sequence variant).	See ClinGen SVI working group PVS1 specifications • PVS1 = 0.90 *(Range: 0.45 to 0.90)* • PVS1_Strong = 0.45 *(Range: 0.30 to 0.90)* • PVS1_Moderate *or* PM4 (in-frame indels) = 0.30 *(Range: 0.15 to 0.45)* • PVS1_Supporting = 0.15 *(Range: 0 to 0.30)* • N/A = No points, but continue evaluation	See categories at left
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

Contact Us

Location Search Results

Submitted location: chr2:96,603,509-97,794,149

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

Gene Issues (37) | Region Issues (1)

No HI Genes

Location search results

Items 1 - 20 of 37 < Prev Page 1 of 2 Next >

Gene Symbol	Haploinsufficiency score	Triplosensitivity score	Curation Status	Region Location (GRCh37)	ExAC pLI	OMIM	Relationship to Submitted Location	ISCA ID
CNNM4	30: Gene associated with autosomal recessive phenotype	Not yet evaluated	Complete	chr2:97,426,639-97,477,628	0.0	607805	Contained	ISCA-21038
ANKRD36C	N/A	N/A	Awaiting Review	chr2:96,515,296-96,658,068			Overlap	ISCA-25651
RN7SL210P	N/A	N/A	Awaiting Review	chr2:96,670,311-96,670,598			Contained	ISCA-43121
FAHD2CP	N/A	N/A	Awaiting Review	chr2:96,676,299-96,688,884			Contained	ISCA-31499

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

DECIPHER GRCh37 About Browse DDD(UK) Search DECIPHER Join Login

Search results for 'position:2:96739012-97671429' (Refine Search)

Open-access patients 50 | CNV Syndromes 0 | DDD Research Variants 2 | Genes 23

Results | Browser

Genes: 1 to 20 of 20 (out of 23 total)

Show: OMIM Morbid DDG2P Protein coding Filter...

Name	Location	Description	OMIM	Morbid	DDG2P	%HI	pLI	Links
SNRNP200	2 96940074 96971297	small nuclear ribonucleoprotein U5 subunit 200	✔	✔	-	19.63	1.00	View
SEMA4C	2 97525453 97536494	semaphorin 4C	✔	-	-	42.72	1.00	View

https://decipher.sanger.ac.uk/

https://gnomad.broadinstitute.org/

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

DECIPHER GRCh37 About Browse DDD(UK) Search DECIPHER Join Login

Search results for 'position:2:96739012-97671429' (Refine Search)

Open-access patients 50 | CNV Syndromes 0 | DDD Research Variants 2 | Genes 23

Results | Browser

Genes: 1 to 20 of 20 (out of 23 total)

Show: ☐ OMIM ☐ Morbid ☐ DDG2P ☑ Protein coding Filter...

Name	Location	Description	OMIM	Morbid	DDG2P	%HI	pLI	Links
SNRNP200	2 96940074 96971297	small nuclear ribonucleoprotein U5 subunit 200	✔	✔	-	19.63	1.00	View
SEMA4C	2 97525453 97536494	semaphorin 4C	✔	-	-	42.72	1.00	View

Section 4: Detailed Evaluation of Genomic Content Using Published Literature, Public Databases, and/or Internal Lab Data

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	Confirmed de novo: 0.30	
Individua inconsiste			0.30 otal)
Individua unknown			.30 otal)
Individual case evidence—segregation among similarly affected family members	**4F**. 3–4 observed segregations	0.15	0.45
	4G. 5–6 observed segregations	0.30	
	4H. 7 or more observed segregations	0.45	
Individual case evidence—nonsegregations	**4I**. Variant is NOT found in another individual in the proband's family AFFECTED with a consistent, specific, well-defined phenotype (no known phenocopies).	−0.45 points per family *(range: 0 to −0.45)*	−0.90 (total)
	4J. Variant IS found in another individual in the proband's family UNAFFECTED with the specific, well-defined phenotype observed in the proband.	−0.30 points per family *(range: 0 to −0.30)*	−0.90 (total)
	4K. Variant IS found in another individual in the proband's family UNAFFECTED with the nonspecific phenotype observed in the proband.	−0.15 points per family *(range: 0 to −0.15)*	−0.30 (total)

- De novo or Inherited?
- Segregating?
- Phenotype specific or nonspecific?
- Common?

Contact Us

Location Search Results

Submitted location: chr2:96,603,509-97,794,149

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

Gene Issues (37) | Region Issues (1)

Location search results

Region Name	Haploinsufficiency score	Triplosensitivity score	Curation Status	Region Location (GRCh37)	ExAC pLI	OMIM	Relationship to Submitted Location	ISCA ID
2q11.2 recurrent region (includes ARID5A, LMAN2L)	1	1	Complete	chr2:96,739,012-97,671,429			Contained	ISCA-37495

ClinGen Dosage Sensitivity Curation Page

2q11.2 recurrent region (includes ARID5A, LMAN2L)

Curation Status: Complete

id: ISCA-37495

Date last evaluated: 2020-02-28

Issue Type: ClinGen Region Curation

ClinGen Haploinsufficiency Score: 1

ClinGen Triplosensitivity Score: 1

Location Information

2q11.2

GRCh37/hg19 chr2: 96,739,012-97,671,429

View: NCBI | Ensembl | UCSC

GRCh38/hg38 chr2: 96,073,264-97,005,692

View: NCBI | Ensembl | UCSC

https://dosage.clinicalgenome.org/clingen_region.cgi?id=ISCA-37495

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

Haploinsufficiency score: 1
Strength of Evidence (disclaimer): Little evidence for dosage pathogenicity

Evidence for haploinsufficiency phenotype

Literature summary (up to 3 references)

PubMed ID	Description
26227573	Riley et al. (2015) report four new cases (five individuals total), three unrelated individuals (Subjects 1-3) and two siblings (Subjects 4-5, Family 1), with recurrent 2q11.2 deletions. Deletion of Subject 1 was paternally inherited with the father noted to have ?trouble in school?. The deletion of Subject 2 was de novo. The deletion of Subject 3 was maternally inherited (no phenotypic information available). Subjects 4 and 5 are similarly affected siblings (no parental phenotype information). Clinical findings in common across patients include: speech delay, ADHD, and dysmorphic features.
19443486	Rudd et al. (2009) analyzed array CGH data of 2419 individuals in an effort to identify new syndrome-associated segmental duplication-mediated chromosome rearrangements. This study described one individual (Patient 2, Table 1) with deletion of the recurrent 2q11.2 region. This individual had clinical features that included learning disabilities, ADHD, scoliosis, cafe au lait spots, and aortic coarcation requiring surgical repair. The inheritance was unknown. The deletion was not identified in an unpublished control population, which included 347 unaffected parents of schizophrenia probands and 529 Ashkenazi Jewish patients with Crohn?s disease, dystonia or Parkinson?s disease (n=876).

Haploinsufficiency phenotype comments:

Explanation for dosage score

Evidence in support of the pathogenicity of recurrent 2q11.2 deletion* is limited at this time. Five independent 2q11.2 deletion cases have been reported across two studies. Amongst affected carriers, clinical findings in common are nonspecific. The associated phenotypes include speech delay, ADHD, dysmorphic features and additional variable findings. Inheritance information is not well-understood (known in four cases): one case was de novo, three cases involve inheritance, but parental phenotypes are unknown/not well-characterized. In addition, nominal statistical significance has been observed from case-control comparison (reviewed below): observed deletions in both populations are relatively rare (wide CIs for OR/LR, lower bound <2). Therefore the haploinsufficiency score is 1.

Description of genomic region

*The proximal 2q region contains a cluster of low copy repeats that mediate recurrent copy number changes through non-allelic homologous recombination. This review refers to deletions involving recurrent breakpoints within the 2q11.2 region (ARID5A, LMAN2L included). Note that genes used as landmarks are not necessarily causative of the complete phenotype(s) associated with the region.

Additional relevant literature

Additional literature is summarized below:

Case-control studies

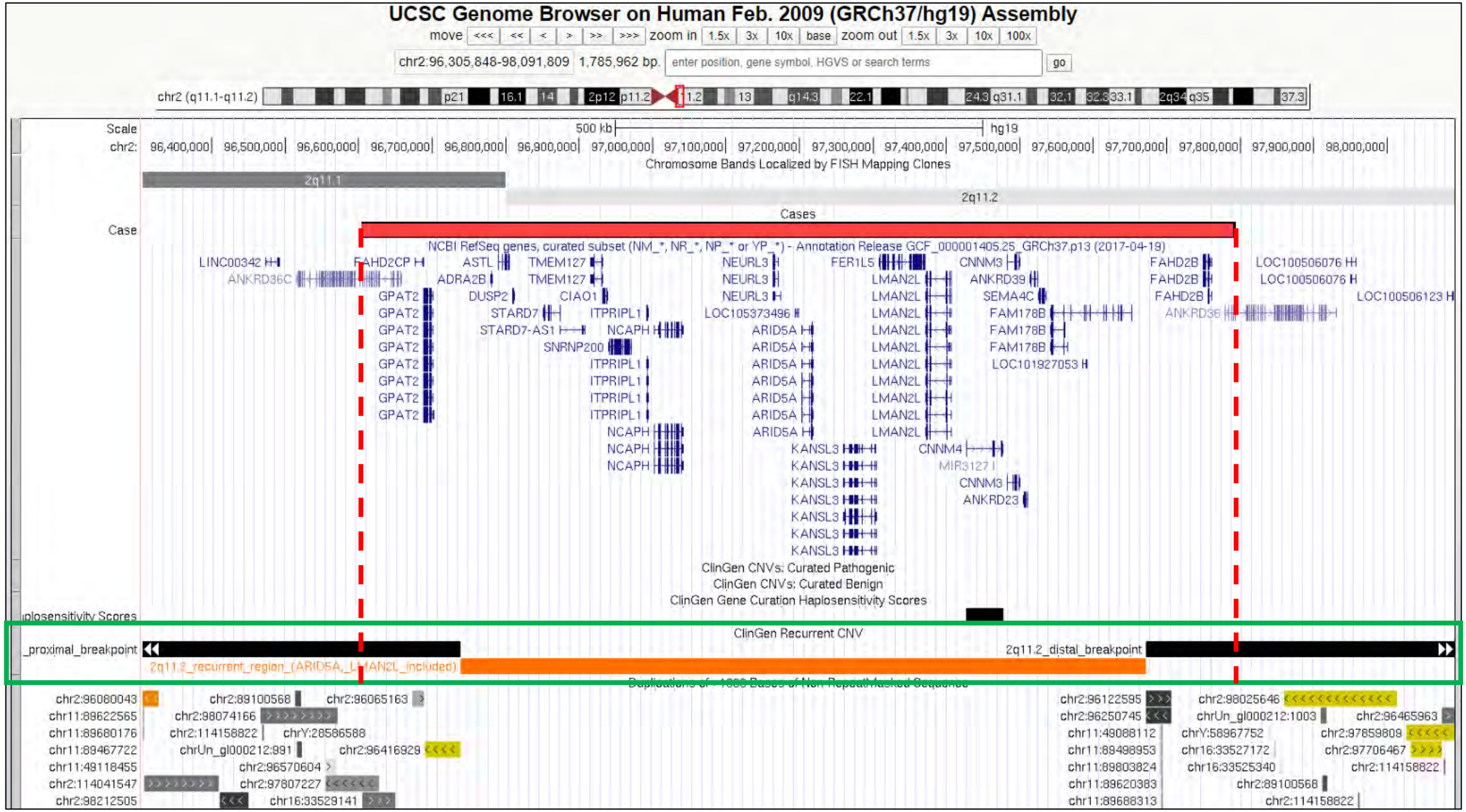
PMID: 25217958:
Coe et al. (2014): In a large-scale case-control comparison study of the relative prevalence of copy number variants in children with ID/DD, MCA, and other developmental phenotypes compared to controls, deletions of the recurrent 2q11.2 (ARID5A, LMAN2L) region were observed in 6/29,085 cases versus 0/19,584 controls (p=0.455; LR: Inf, CI: (1 to Inf)), demonstrating a nominal level of significance in support of enrichment this deletion in the clinical population. See also Cooper et al. (2011), PMID 21841781.

https://dosage.clinicalgenome.org/clingen_region.cgi?id=ISCA-37495

Description of genomic region

*The proximal 2q region contains a cluster of low copy repeats that mediate recurrent copy number changes through non-allelic homologous recombination. This review refers to deletions involving recurrent breakpoints within the 2q11.2 region (ARID5A, LMAN2L included). Note that genes used as landmarks are not necessarily causative of the complete phenotype(s) associated with the region.

https://dosage.clinicalgenome.org/clingen_region.cgi?id=ISCA-37495


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
chr2:96,305,848-98,091,809 1,785,962 bp.
enter position, gene symbol, HGVS or search terms
go
chr2 (q11.1-q11.2)
Scale
500 kb
hg19
chr2:
96,400,000 96,500,000 96,600,000 96,700,000 96,800,000 96,900,000 97,000,000 97,100,000 97,200,000 97,300,000 97,400,000 97,500,000 97,600,000 97,700,000 97,800,000 97,900,000 98,000,000
Chromosome Bands Localized by FISH Mapping Clones
2q11.1
2q11.2
Cases
Case
NCBI RefSeq genes, curated subset (NM_*, NR_*, NP_* or YP_*) - Annotation Release GCF_000001405.25_GRCh37.p13 (2017-04-19)
LINC00342
ANKRD36C
FAHD2CP
GPAT2
ASTL
ADRA2B
DUSP2
STARD7
STARD7-AS1
TMEM127
CIAO1
ITPRIPL1
NCAPH
SNRNP200
NEURL3
LOC105373496
ARID5A
FER1L5
LMAN2L
KANSL3
CNNM4
MIR3127
CNNM3
ANKRD39
SEMA4C
FAM178B
LOC101927053
ANKRD23
FAHD2B
ANKRD36
LOC100506076
LOC100506123
ClinGen CNVs: Curated Pathogenic
ClinGen CNVs: Curated Benign
ClinGen Gene Curation Haplosensitivity Scores
uplosensitivity Scores
ClinGen Recurrent CNV
_proximal_breakpoint
2q11.2_distal_breakpoint
2q11.2_recurrent_region_(ARID5A,_LMAN2L_included)
Duplications of ~1000 Bases of Non-RepeatMasked Sequence
chr2:96080043
chr2:89100568
chr2:96065163
chr11:89622565
chr2:98074166
chr11:89680176
chr2:114158822
chrY:28586588
chr11:89467722
chrUn_gl000212:991
chr2:96416929
chr11:49118455
chr2:96570604
chr2:114041547
chr2:97807227
chr2:98212505
chr16:33529141
chr2:96122595
chr2:98025646
chr2:96250745
chrUn_gl000212:1003
chr2:96465963
chr11:49088112
chrY:58967752
chr2:97859809
chr11:89498953
chr16:33527172
chr2:97706467
chr11:89803824
chr16:33525340
chr2:114158822
chr11:89620383
chr2:89100568
chr11:89688313
chr2:114158822

Are we done yet?

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

- “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”

Riggs et al., *Genetics in Medicine* (2019)

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

Haploinsufficiency score: 1
Strength of Evidence (disclaimer): Little evidence for dosage pathogenicity

Evidence for haploinsufficiency phenotype

Literature summary (up to 3 references)

PubMed ID	Description
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19443486	Rudd et al. (2009) analyzed array CGH data of 2419 individuals in an effort to identify new syndrome-associated segmental duplication-mediated chromosome rearrangements. This study described one individual (Patient 2, Table 1) with deletion of the recurrent 2q11.2 region. This individual had clinical features that included learning disabilities, ADHD, scoliosis, cafe au lait spots, and aortic coarcation requiring surgical repair. The inheritance was unknown. The deletion was not identified in an unpublished control population, which included 347 unaffected parents of schizophrenia probands and 529 Ashkenazi Jewish patients with Crohn?s disease, dystonia or Parkinson?s disease (n=876).

Haploinsufficiency phenotype comments:

Evidence in support of the pathogenicity of recurrent 2q11.2 deletion* is limited at this time. Five independent 2q11.2 deletion cases have been reported across two studies. Amongst affected carriers, clinical findings in common are nonspecific. The associated phenotypes include speech delay, ADHD, dysmorphic features and additional variable findings. Inheritance information is not well-understood (known in four cases): one case was de novo, three cases involve inheritance, but parental phenotypes are unknown/not well-characterized. In addition, nominal statistical significance has been observed from case-control comparison (reviewed below); observed deletions in both populations are relatively rare (wide CIs for OR/LR, lower bound <2). Therefore the haploinsufficiency score is 1.

*The proximal 2q region contains a cluster of low copy repeats that mediate recurrent copy number changes through non-allelic homologous recombination. This review refers to deletions involving recurrent breakpoints within the 2q11.2 region (ARID5A, LMAN2L included). Note that genes used as landmarks are not necessarily causative of the complete phenotype(s) associated with the region.

Additional literature is summarized below:

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https://dosage.clinicalgenome.org/clingen_region.cgi?id=ISCA-37495

2q11.2 Recurrent Deletion- Literature Review

- Five cases across two studies (Riley et al., 2015, Rudd et al., 2009)
- Phenotype: speech delay, ADHD, dysmorphic features, other variable features

Non-specific

- Inheritance:
  - Deletion of Subject 1 was paternally inherited with the father noted to have “trouble in school”
  - The deletion of Subject 2 was de novo
  - The deletion of Subject 3 was maternally inherited (no phenotypic information available)
  - Subjects 4 and 5 are similarly affected siblings (no parental phenotype information)
  - Deletion of patient 2 from Rudd et al (2009) was unknown

Section 4: Detailed Evaluation of Genomic Content Using Published Literature, Public Databases, and/or Internal Lab Data

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)

0.10

2q11.2 Recurrent Deletion- Literature Review

- Phenotype: speech delay, ADHD, dysmorphic features, other variable features

Non-specific

- Inheritance:
  - Deletion of Subject 1 was paternally inherited with the father noted to have “trouble in school”
  - The deletion of Subject 2 was de novo
  - The deletion of Subject 3 was maternally inherited (no phenotypic information available)
  - Subjects 4 and 5 are similarly affected siblings (no parental phenotype information)
  - Deletion of patient 2 from Rudd et al (2009) was unknown

Section 4: Detailed Evaluation of Genomic Content Using Published Literature, Public Databases, and/or Internal Lab Data

Individual case evidence—segregation among similarly affected family members	**4F**. 3–4 observed segregations	0.15	0.45
	4G. 5–6 observed segregations	0.30	
	4H. 7 or more observed segregations	0.45	
Individual case evidence—nonsegregations	**4I**. Variant is NOT found in another individual in the proband's family AFFECTED with a consistent, specific, well-defined phenotype (no known phenocopies).	−0.45 points per family *(range: 0 to −0.45)*	−0.90 (total)
	4J. Variant IS found in another individual in the proband's family UNAFFECTED with the specific, well-defined phenotype observed in the proband.	−0.30 points per family *(range: 0 to −0.30)*	−0.90 (total)
	4K. Variant IS found in another individual in the proband's family UNAFFECTED with the nonspecific phenotype observed in the proband.	−0.15 points per family *(range: 0 to −0.15)*	−0.30 (total)
Case–control and population evidence	**4L**. Statistically significant increase amongst observations in cases (**with a consistent, specific, well-defined phenotype**) compared with controls.	0.45 per study *(range: 0 to 0.45 per study)*	0.45 (total)
	4M. Statistically significant increase amongst observations in cases (**without a consistent, nonspecific phenotype OR unknown phenotype**) compared with controls.	0.30 per study *(range: 0 to 0.30 per study)*	0.45 (total)
	4N. No statistically significant difference between observations in cases and controls.	−0.90 (per study) *(range: 0 to −0.90 per study)*	−0.90 (total)
	4O. Overlap with common population variation.	−1 *(range: 0 to −1)*	−1

X

2q11.2 Recurrent Deletion- Literature Review

- Phenotype: speech delay, ADHD, dysmorphic features, other variable features

Non-specific

- Inheritance:
  - Deletion of Subject 1 was paternally inherited with the father noted to have “trouble in school”
  - The deletion of Subject 2 was de novo
  - The deletion of Subject 3 was maternally inherited (no phenotypic information available)
  - Subjects 4 and 5 are similarly affected siblings (no parental phenotype information)
  - Deletion of patient 2 from Rudd et al (2009) was unknown

Section 4: Detailed Evaluation of Genomic Content Using Published Literature, Public Databases, and/or Internal Lab Data

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)

X

2q11.2 Recurrent Deletion- Literature Review

- Five cases across two studies (Riley et al., 2015, Rudd et al., 2009)
- Phenotype: speech delay, ADHD, dysmorphic features, other variable features

Non-specific

- Inheritance:
  - Deletion of Subject 1 was paternally inherited with the father noted to have “trouble in school” X
  - The deletion of Subject 2 was de novo ✓
  - The deletion of Subject 3 was maternally inherited (no phenotypic information available) X
  - Subjects 4 and 5 are similarly affected siblings (no parental phenotype information) X
  - Deletion of patient 2 from Rudd et al (2009) was unknown X

0.1
(Range:0-0.3)

Section 4: Detailed Evaluation of Genomic Content Using Published Literature, Public Databases, and/or Internal Lab Data

Individual case evidence—segregation among similarly affected family members	**4F**. 3–4 observed segregations	0.15	0.45
	4G. 5–6 observed segregations	0.30	
	4H. 7 or more observed segregations	0.45	
Individual case evidence—nonsegregations	**4I**. Variant is NOT found in another individual in the proband's family AFFECTED with a consistent, specific, well-defined phenotype (no known phenocopies).	−0.45 points per family *(range: 0 to −0.45)*	−0.90 (total)
	4J. Variant IS found in another individual in the proband's family UNAFFECTED with the specific, well-defined phenotype observed in the proband.	−0.30 points per family *(range: 0 to −0.30)*	−0.90 (total)
	4K. Variant IS found in another individual in the proband's family UNAFFECTED with the nonspecific phenotype observed in the proband.	−0.15 points per family *(range: 0 to −0.15)*	−0.30 (total)
Case–control and population evidence	**4L**. Statistically significant increase amongst observations in cases (**with a consistent, specific, well-defined phenotype**) compared with controls.	0.45 per study *(range: 0 to 0.45 per study)*	0.45 (total)
	4M. Statistically significant increase amongst observations in cases (**without a consistent, nonspecific phenotype OR unknown phenotype**) compared with controls.	0.30 per study *(range: 0 to 0.30 per study)*	0.45 (total)
	4N. No statistically significant difference between observations in cases and controls.	−0.90 (per study) *(range: 0 to −0.90 per study)*	−0.90 (total)
	4O. Overlap with common population variation.	−1 *(range: 0 to −1)*	−1

Supplementary Table 2 – Newly Significant Genomic Disorders

				Deletions					
Chr	Start (hg18 Mbp)	End (hg18 Mbp)	Type[a]	Deletion Syndrome	Cases	Controls	p-value	q-value	Likelihood Ratio
1	144	144.34	HS	1q21 prox TAR deletion[23 b] (RBM8A)	25	2	1.63E-04	5.27E-04	8.42 (2.49 to 38.3)
2	96.09	97.04	HS	2q11.2 deletion[25 b,c]	6	0	0.0455	0.0758	Inf (1 to Inf)
2	111.1	112.81	HS	2q13 deletion[25 b]	20	3	0.00483	0.0102	4.49 (1.53 to 15.5)
3	197.2	198.84	HS	3q29 deletion[26 b]	11	0	0.0035	0.00837	Inf (2.21 to Inf)
4	1.84	1.98	MB	Wolf-Hirschhorn deletion[27]	24	0	4.29E-06	1.97E-05	Inf (5.61 to Inf)

Coe et al., Nat Genet. 2014

See also: Rees et al (2016) JAMA Psych SZ: 6 [0.03%] vs 1 [0.004%]; p=0.37, OR= 9.3 (1.03-447.76)

Supplementary Table 2 – Newly Significant Genomic Disorders

p-values show nominal statistical significance, LR/OR CI's are wide…

Chr	St (h Mbp)	Mbp)	Type	Deletion Syndrome	Cases	Controls	p-Value	q-Value	Likelihood Ratio
1	144	144.34	HS	1q21 prox TAR deletion[23 b] (RBM8A)	25	2	1.63E-04	5.27E-04	8.42 (2.49 to 38.3)
2	96.09	97.04	HS	2q11.2 deletion[25 b,c]	6	0	0.0455	0.0758	Inf (1 to Inf)
2	111.1	112.81	HS	2q13 deletion[25 b]	20	3	0.00483	0.0102	4.49 (1.53 to 15.5)
3									to Inf)
4									to Inf)

- "CNVs [counted in this category will be observed at a significantly higher frequency in cases versus controls ($p<0.05$), and with a strong effect size (odds ratio or likelihood ratio >5) and relatively narrow associated 95% confidence interval (lower bound >1)"

Coe et al., Nat Genet. 2014

See also: Rees et al (2016) JAMA Psych SZ: 6 [0.03%] vs 1 [0.004%]; p=0.37, OR= 9.3 (1.03-447.76)

Section 4: Detailed Evaluation of Genomic Content Using Published Literature, Public Databases, and/or Internal Lab Data

Individual case evidence—segregation among similarly affected family members	**4F**. 3–4 observed segregations	0.15	0.45
	4G. 5–6 observed segregations	0.30	
	4H. 7 or more observed segregations	0.45	
Individual case evidence—nonsegregations	**4I**. Variant is NOT found in another individual in the proband's family AFFECTED with a consistent, specific, well-defined phenotype (no known phenocopies).	−0.45 points per family *(range: 0 to −0.45)*	−0.90 (total)
	4J. Variant IS found in another individual in the proband's family UNAFFECTED with the specific, well-defined phenotype observed in the proband.	−0.30 points per family *(range: 0 to −0.30)*	−0.90 (total)
	4K. Variant IS found in another individual in the proband's family UNAFFECTED with the nonspecific phenotype observed in the proband.	−0.15 points per family *(range: 0 to −0.15)*	−0.30 (total)
Case–control and population evidence	**4L**. Statistically significant increase amongst observations in cases (**with a consistent, specific, well-defined phenotype**) compared with controls.	0.45 per study *(range: 0 to 0.45 per study)*	0.45 (total)
	4M. Statistically significant increase amongst observations in cases (**without a consistent, nonspecific phenotype OR unknown phenotype**) compared with controls.	0.30 per study *(range: 0 to 0.30 per study)*	0.45 (total)
	4N. No statistically significant difference between observations in cases and controls.	−0.90 (per study) *(range: 0 to −0.90 per study)*	−0.90 (total)
	4O. Overlap with common population variation.	−1 *(range: 0 to −1)*	−1

(Range:0-0.3)
2x.10=0.20

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

Section 5: Inheritance Pattern/Family History

- "Special considerations that preclude confident inference and may only be well defined after ascertainment of multiple families include the following:
  - Incomplete penetrance: The CNV may be pathogenic but non-penetrant in the carrier parent
  - Variable expressivity: The carrier parent may have subclinical features that will later be shown to be in the spectrum of the disorder caused by the CNV"

Riggs et al., *Genetics in Medicine* (2019)

- “Use of these metrics for recurrent regions other than those with definitive evidence classifications should be performed with caution.”

Riggs et al., *Genetics in Medicine* (2019)

CNV Scoring: 2q11.2 Deletion

	Evidence	Score	Notes
1A	Protein-coding gene(s)?	0	Yes
2A	Complete overlap with established HI gene?	0	No
2H	HI predictors (%HI AND pLI)	0	No
3A	Gene count: 0-24 genes	0	20 protein-coding genes
4C	Individual case evidence: “de novo” inheritance, phenotype nonspecific	0.1	1 case only (others inherited, no parental phenotype/unknown)
4M	Case-control, population evidence	0.2	2 case-control studies, both nominally significant, rare CNV
5F	Inheritance for patient studied	0	Unknown
	Total points	**0.3**	

Classification: VUS

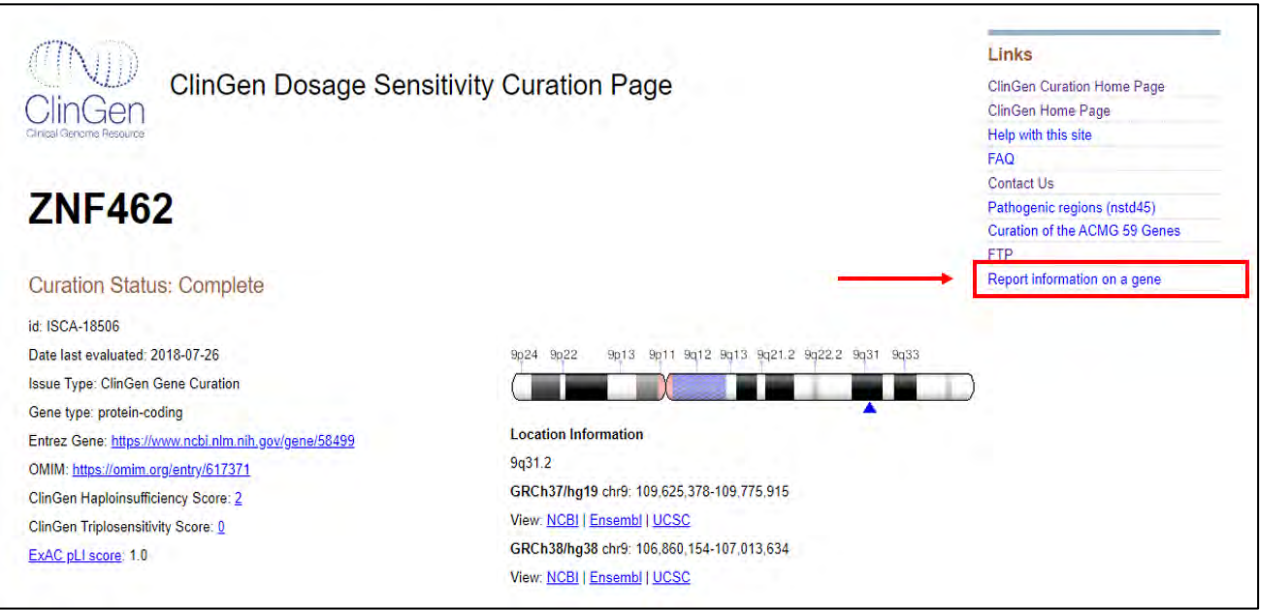
Haploinsufficiency phenotype comments:

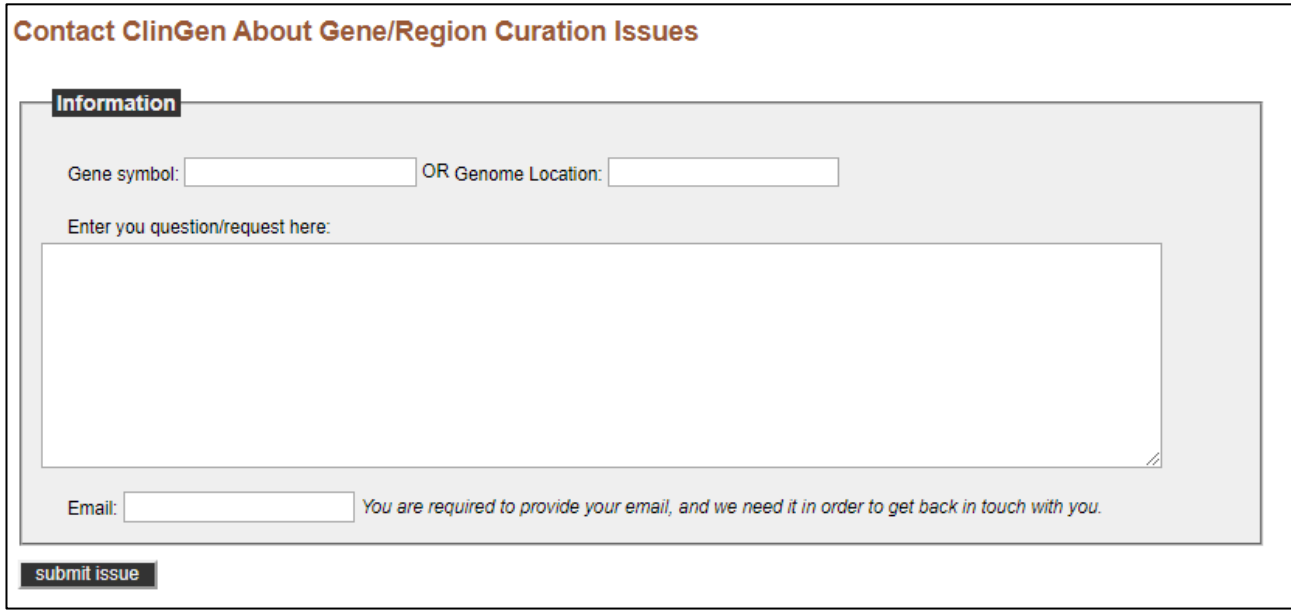
Evidence in support of the pathogenicity of recurrent 2q11.2 deletion* is limited at this time. Five independent 2q11.2 deletion cases have been reported across two studies. Amongst affected carriers, clinical findings in common are nonspecific. The associated phenotypes include speech delay, ADHD, dysmorphic features and additional variable findings. Inheritance information is not well-understood (known in four cases): one case was de novo, three cases involve inheritance, but parental phenotypes are unknown/not well-characterized. In addition, nominal statistical significance has been observed from case-control comparison (reviewed below); observed deletions in both populations are relatively rare (wide CIs for OR/LR, lower bound <2). Therefore the haploinsufficiency score is 1.

https://dosage.clinicalgenome.org/clingen_region.cgi?id=ISCA-37495

Score	Strength of Evidence	Potential Clinical Classification
1	Little/Limited Evidence	Uncertain

Got feedback/questions? Let us know!





https://dosage.clinicalgenome.org/contact.shtml

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- Outside Reviewers (11)
- ClinGen Genomic Variant and Sequence Variant Interpretation Working Groups
- Ronak Patel and ClinGen Baylor team for CNV calculator

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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 HGVS

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

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For the ClinGen/ClinVar Special Issue

ClinGen
Clinical Genome Resource

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

Copy Number Variant Interpretation and Dosage Sensitivity Curation

Questions?

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(On behalf of the ACMG/ClinGen CNV Interpretation Guidelines and ClinGen Dosage Sensitivity Curation (DSC) Working Groups)