

Genetic Data Sharing and Reanalysis of Genomic Test Results: Challenges and Benefits to Implementation

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Financial Disclosure

ARUP receives funding from the NIH to support some of the activities described in this presentation

Objectives

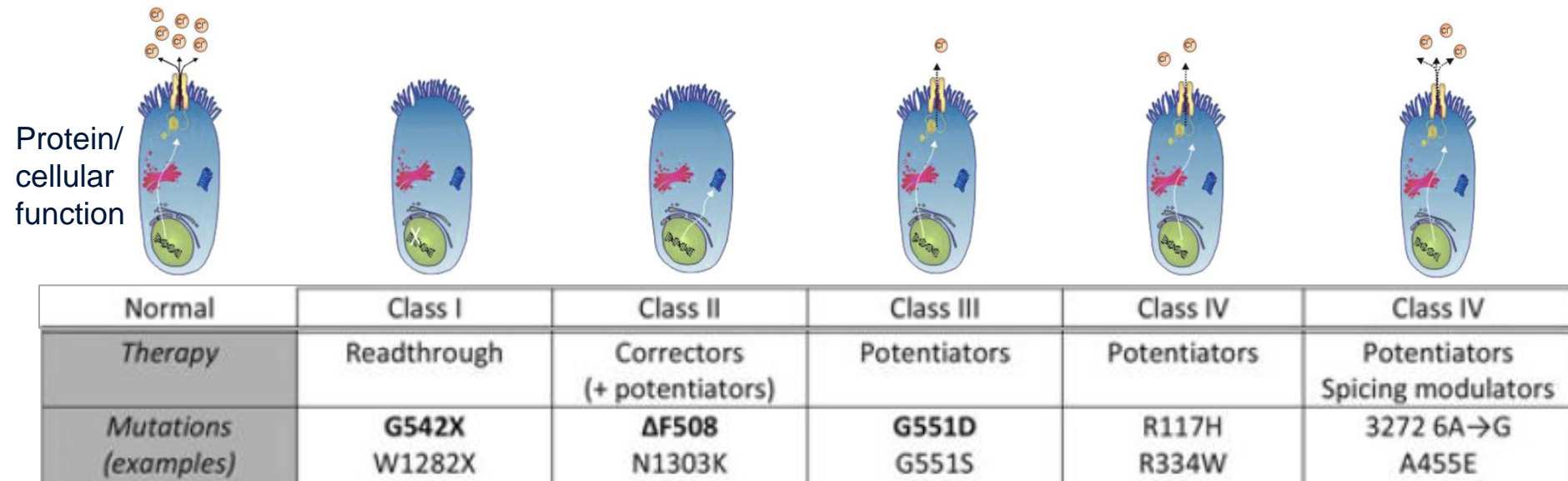
- Review current practices and policies relating to genetic data sharing and case reanalysis/variant reevaluation in clinical laboratories
- Compare and contrast reanalysis/reevaluation processes for common genomic tests, including next generation sequencing and chromosomal microarray
- Describe key aspects of data sharing and reevaluation process implementation through retrospective data review and case presentations

Why Share (and Re-Evaluate) Clinical Genetic Data?

- 5000-7000 rare genetic diseases exist, each with variable frequency and many with considerable clinical variability
- Genetic heterogeneity: multiple disease-causing genes/variants (and background genomic variation) alter clinical presentation, outcomes

Source: ACMG, Genet. Med, 2017

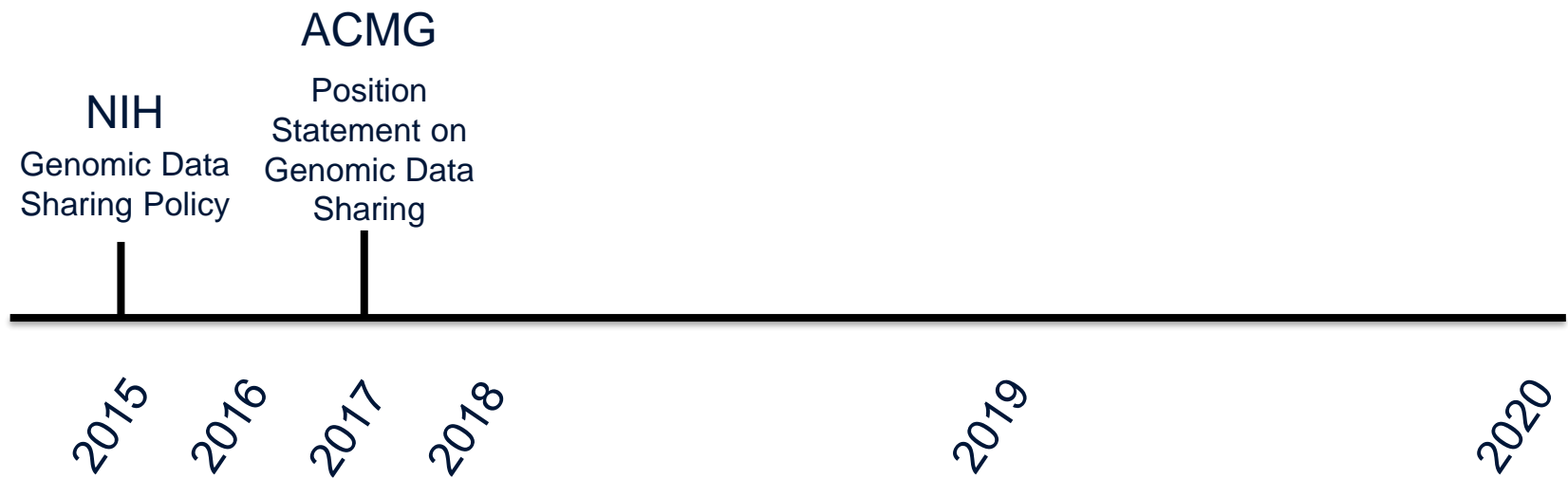
Example: Diverse allelic variants in cystic fibrosis guide therapies



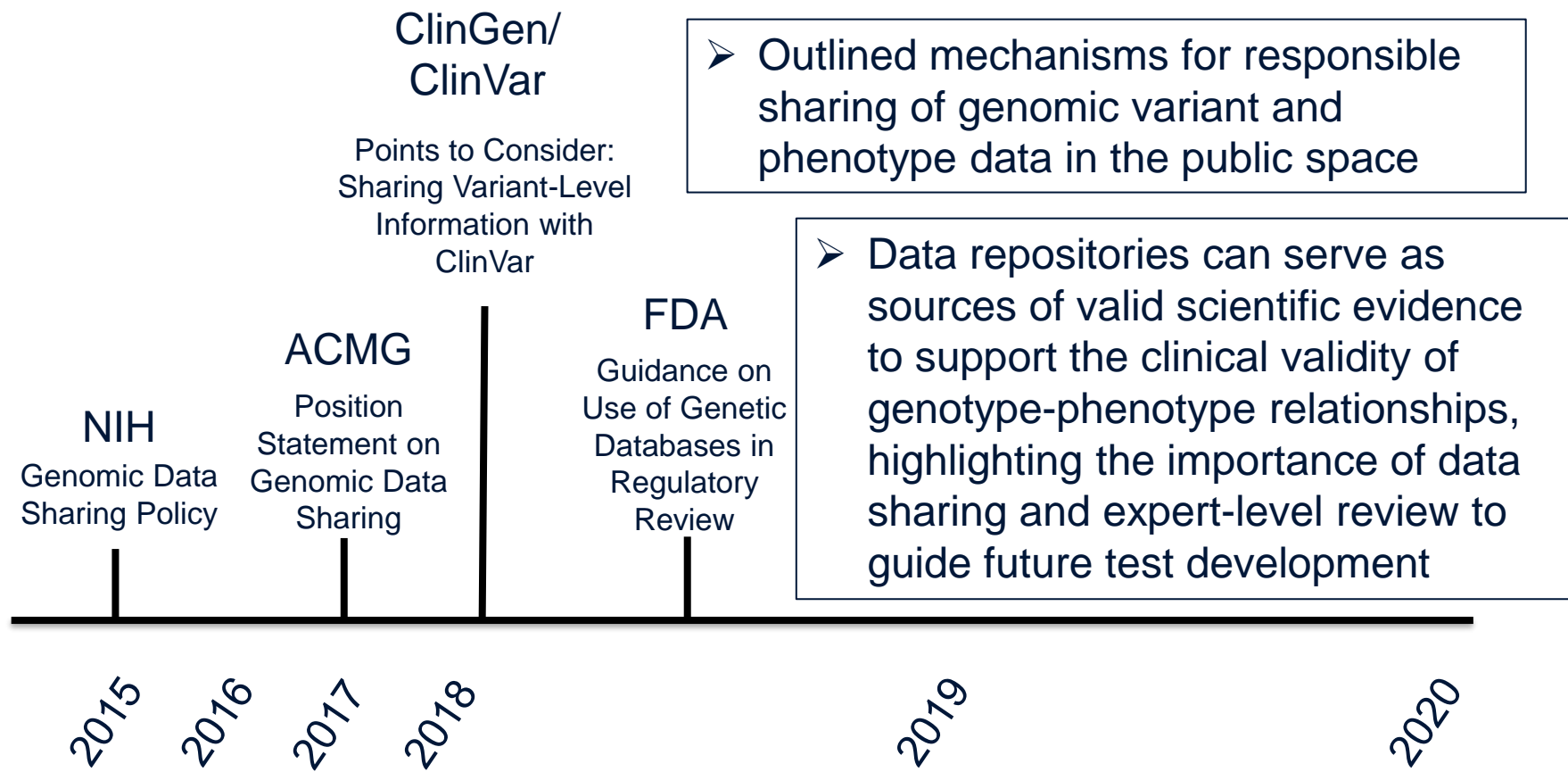
Modified from: Bradbury (2016) CFTR and Cystic Fibrosis: A Need for Personalized Medicine

Increasing Demands on Clinical Genetics Laboratories

- Extensive sharing of laboratory and clinical data from individuals who have undergone genomic testing will provide the robust information necessary to improve clinical care and empower device and drug manufacturers developing tests and treatments for patients



Increasing Demands on Clinical Genetics Laboratories

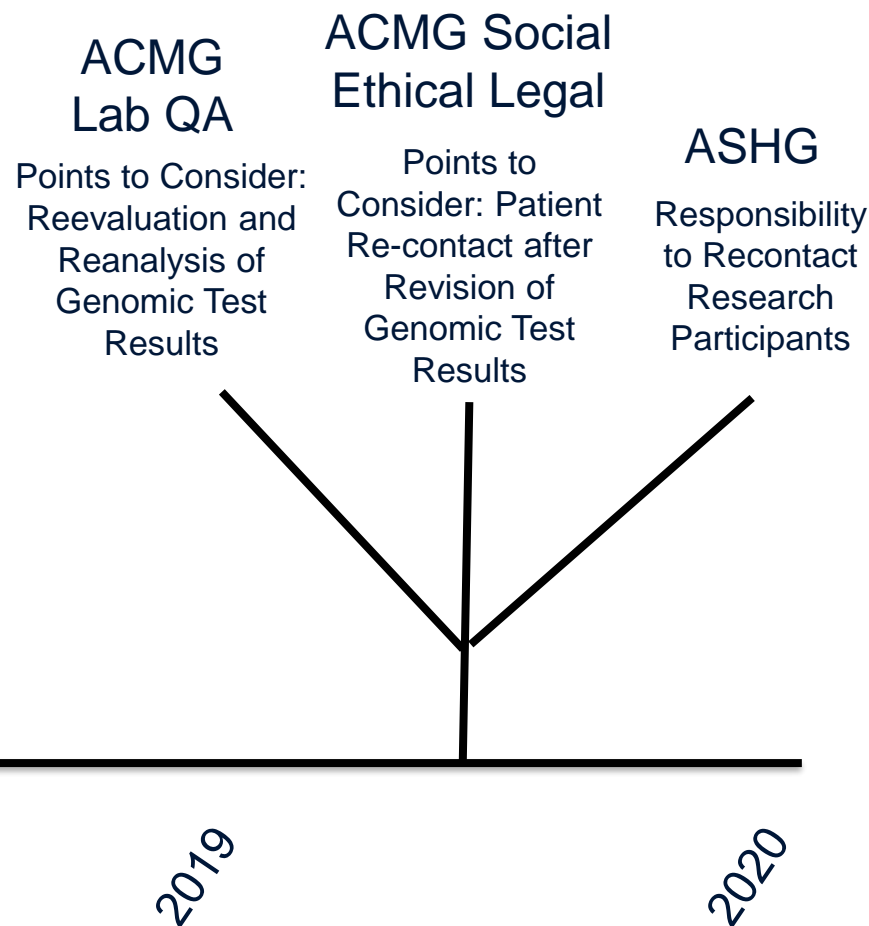


Increasing Demands on Clinical Genetics Laboratories

➤ Laboratories share a responsibility to inform clinicians of variant reclassification or discovery of a new gene–disease relationship

➤ Clinical laboratories should have reanalysis policies and protocols that keep pace with resources used in routine/live case/variant review

➤ Responsibilities apply also the individuals tested in the research setting



Benefits of Sharing Variant Classifications and Evidence with ClinVar



- Improved genetic variant classification within and across laboratories
 - Identify classification differences, work towards consensus
 - Prioritize variants for re-evaluation, update clinicians/patients
 - Standardized nomenclature/descriptions of variants and conditions, classifications/terms for clinical significance
- Compliance with evolving regulatory and medical standards
- Strategic business positioning: preferential ordering from laboratories that share data, selective reimbursement from payers

Source: clinicalgenome.org/docs/benefits-of-sharing-variant-classifications-and-evidence-with-clinvar/

NM_000335.4(SCN5A):c.1604G>A (p.Arg535Gln)

Cite this record

Interpretation: Conflicting interpretations of pathogenicity
Pathogenic(1);Uncertain significance(4)

Review status: ★☆☆☆ criteria provided, conflicting interpretations

Submissions: 6 (Most recent: May 19, 2020)

Last evaluated: Aug 28, 2019

Accession: VCV000067672.3

Variation ID: 67672

Description: single nucleotide variant

FEEDBACK

Variant details

Conditions

Gene(s)

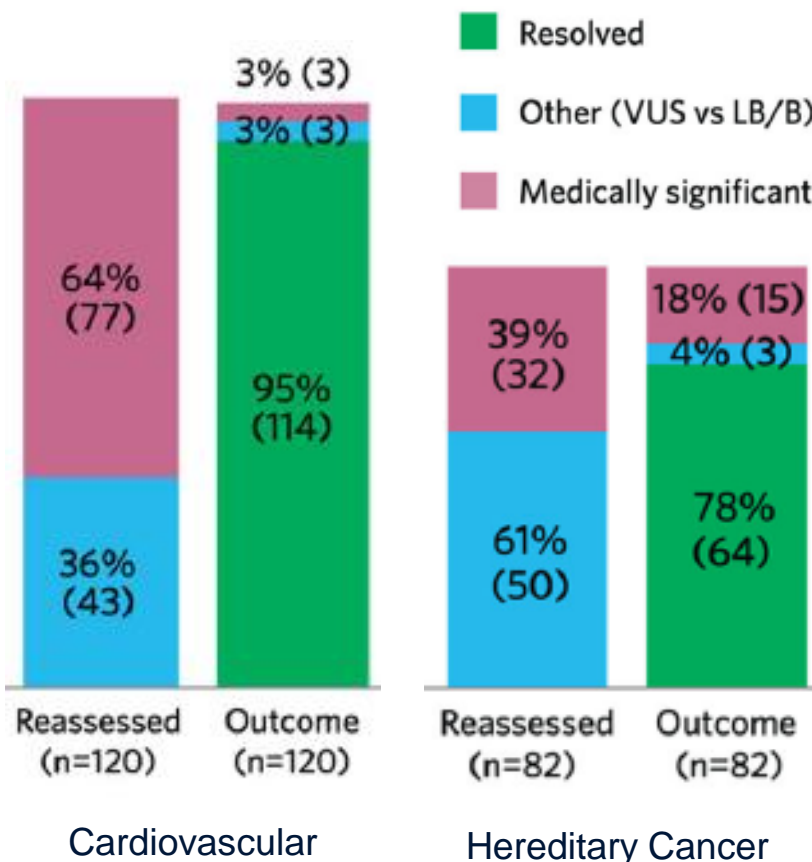
Aggregate interpretations per condition

Interpreted condition	Interpretation	Number of submissions	Review status	Last evaluated	Variation/condition record
Brugada syndrome	Uncertain significance	1	criteria provided, single submitter	Nov 22, 2017	RCV000638649.1
Long QT syndrome 3	Pathogenic	1	criteria provided, single submitter	Aug 3, 2016	RCV000677695.1
Brugada syndrome 1	Uncertain significance	1	criteria provided, single submitter	May 28, 2019	RCV000987228.1
Arrhythmia	Uncertain significance	1	criteria provided, single submitter	Feb 10, 2019	RCV001189141.1
not specified	Uncertain significance	1	criteria provided, single submitter	Aug 28, 2019	RCV001193949.1
Congenital long QT syndrome	not provided	1	no assertion provided	-	RCV000058435.3

Updated example from Landrum et al., *Nucleic Acids Research*, 2020

Benefit: Resolving Inter-laboratory Classification Differences

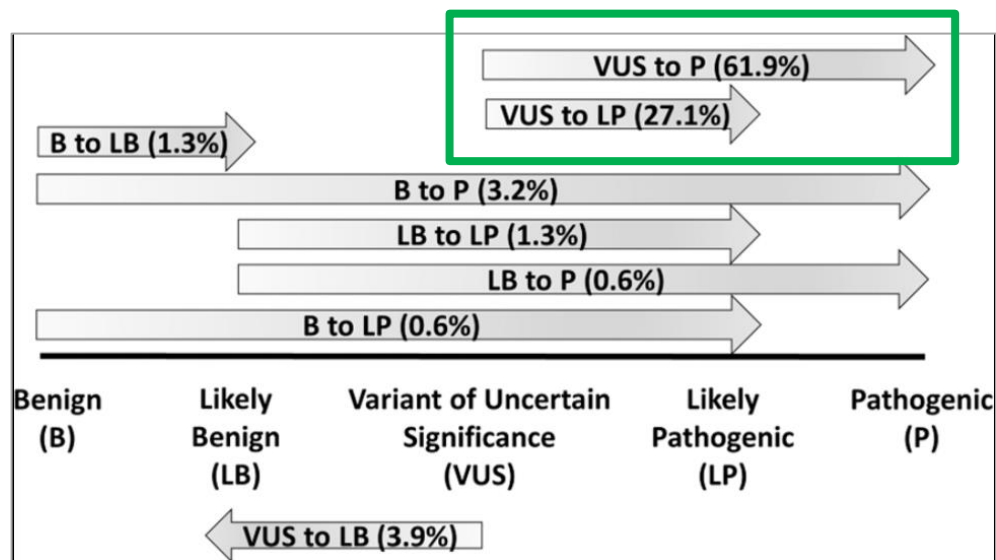
Sequence Variants



Harrison et al., Genet. Med. 2017

Copy Number Variants

- Similarly overlapping CNVs
- CNVs overlapping dosage sensitive genes



Riggs et al., Hum. Mutat. 2018

Clinical Laboratories Meeting Minimum Requirements for Data Sharing to Support Quality Assurance



Laboratory	Meets Requirements	Additional Achievements		
		>95% from past 5 years ¹	Discrepancy resolution ²	Consenting mechanism ³
Ambry				
ARUP	<p>➤ Open and transparent data sharing allows peer-review and knowledge dissemination to ensure the highest quality care of patients</p>			
Athena Diagnostics				
Center for Pediatric Genomic Medicine, Children's Mercy Hospital and Clinics				
Color Genomics, Inc.				
GeneDx				

Source: clinicalgenome.org/tools/clinical-lab-data-sharing-list/ (Accessed 9/6/20, modified)

Practical Challenges

- How to share data: determining which data to share (test type, variant-level vs. case-level), developing consent/opt-out policies
- Data management: ensuring data security, storing and migrating data, ensuring compatibility/interoperability across different databases/systems
- How to reevaluate/reanalyze: determining which data to re-review (test type, variant-level vs. case-level), developing reclassification processes and policies (clinician/patient vs. public database vs. laboratory-initiated), communicating updated information to clinicians/patients, prioritization of result updating
- Resource availability: current vs. retrospective review, manual vs. automated processes, time/financial costs; inadequate reimbursement for reevaluation/reanalysis

Perspectives and Experiences from the Molecular Laboratory

Rong Mao, MD, FACMG

Section Chief, Molecular Genetics and Genomics

Professor, Clinical Pathology

ARUP's Data Sharing and Reevaluation/Reanalysis Practices

Technique	Databases Shared	Reevaluation/Reanalysis Performed		
		Clinician-initiated	Public Database-Initiated	Lab-Initiated
Targeted Variant	N/A	No	Yes	Yes
Single Gene	ClinVar, Locus-Specific	Yes	Yes	Yes
Gene Panel	ClinVar	Yes	Yes	Yes
Whole Exome	ClinVar, GeneMatcher*	Yes	Yes	Yes

*Controlled access database

Limit of detection

Assay type	Average limit of detection
Genome sequencing	~20 – 30%
Exome sequencing	~20 – 30%
NGS-based gene panels	5 – 10%
Sanger sequencing	20%
Single mutation assay	<10%

Farewell, et al. Genetics in Medicine 2015

Why Clinicians order diagnostic exome sequencing

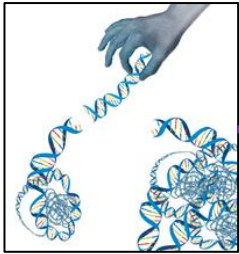
- Rare Disease Facts:
 - 7,000 identified rare diseases
 - 25-30M Americans are affected with a rare disease
 - Up to 25% of pediatric in-patient admissions are attributable to these diseases
 - 80% are genetic in origin with limited diagnostic testing options.
- The Road to Diagnosis:
 - 5-7 years searching for a proper diagnosis
 - Up to 8 physician consults searching for a proper diagnosis
 - 2-3 misdiagnoses prior to proper diagnosis

Iglesia et al. Genetics in Medicine 2014 and Ng et al. Nature Genetics 2009

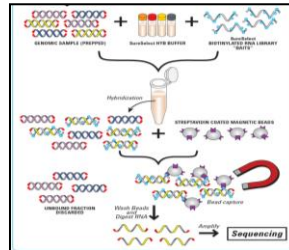
Exome sequencing

- Capture all the exons from all 20,000 genes
- Sequence all in parallel
- Get a complete sequence read-out of all the exons in the genome

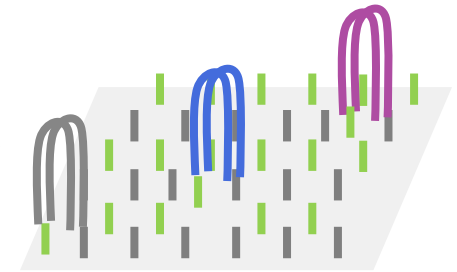
DNA isolation, fragmentation



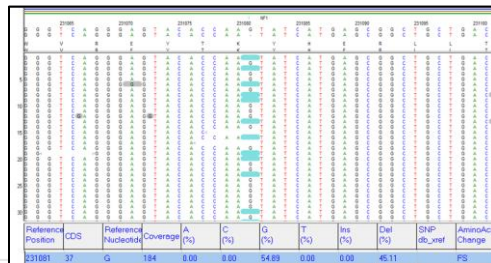
Sequence capture



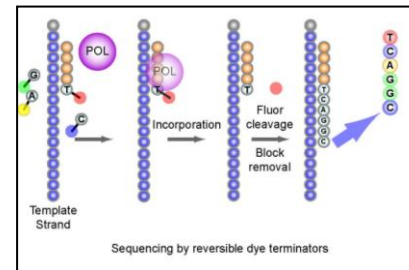
Clonal amplification



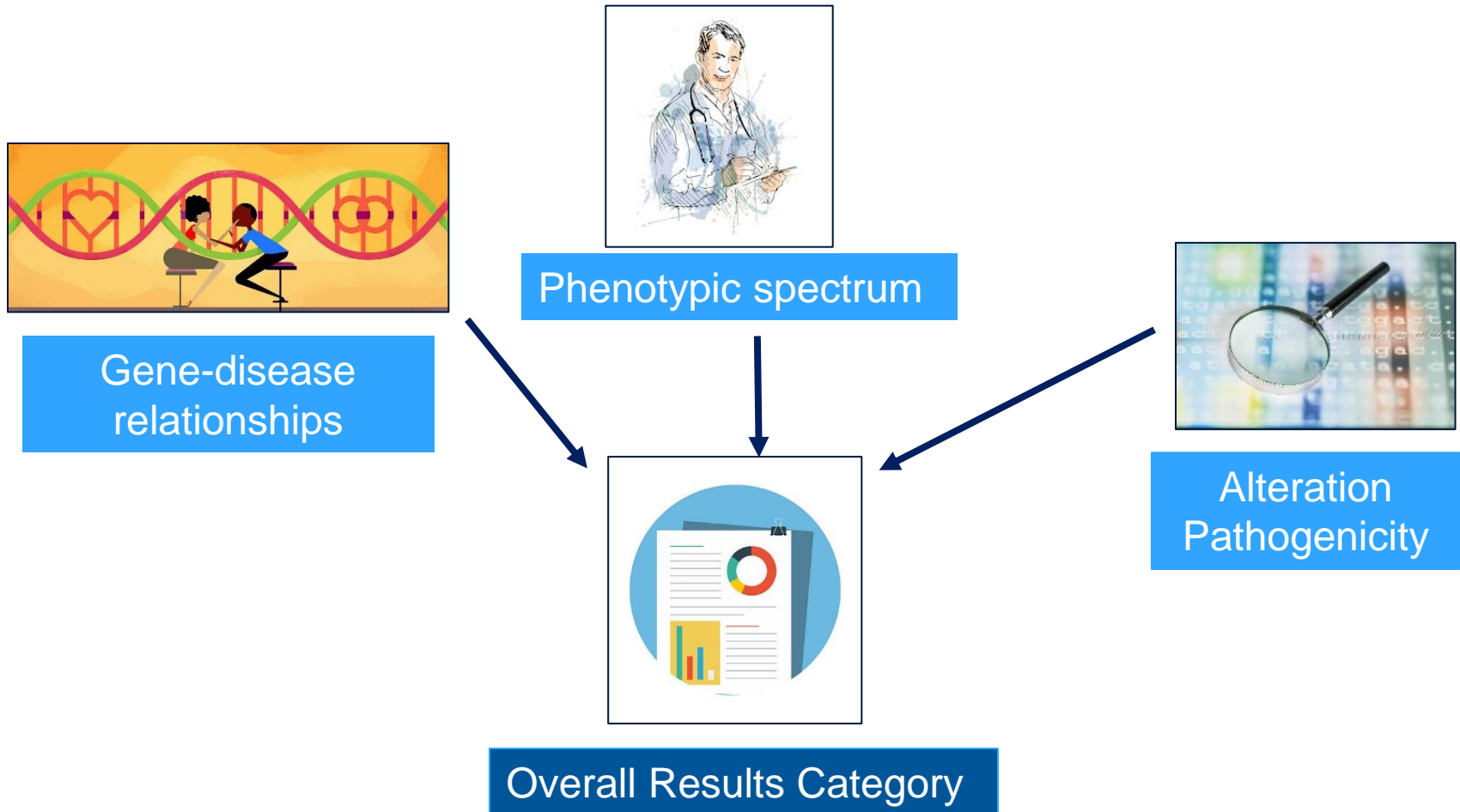
Alignment



Sequencing



Exome results dependent on current knowledge



What we know about genes that are associated with disease



Cooper, et al. Hum Mutat 2010

What is left to discover?



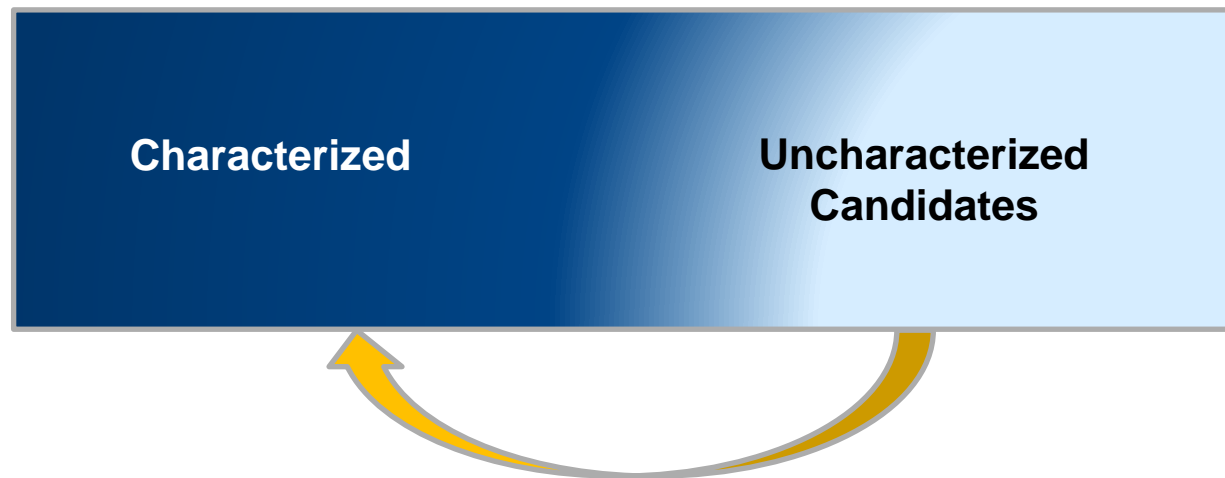
Clinical validity: Strength of evidence associating pathogenic variants in a gene to genetic diseases or syndrome

What is left to discover?



Clinical validity: Strength of evidence associating pathogenic variants in a gene to genetic diseases or syndrome

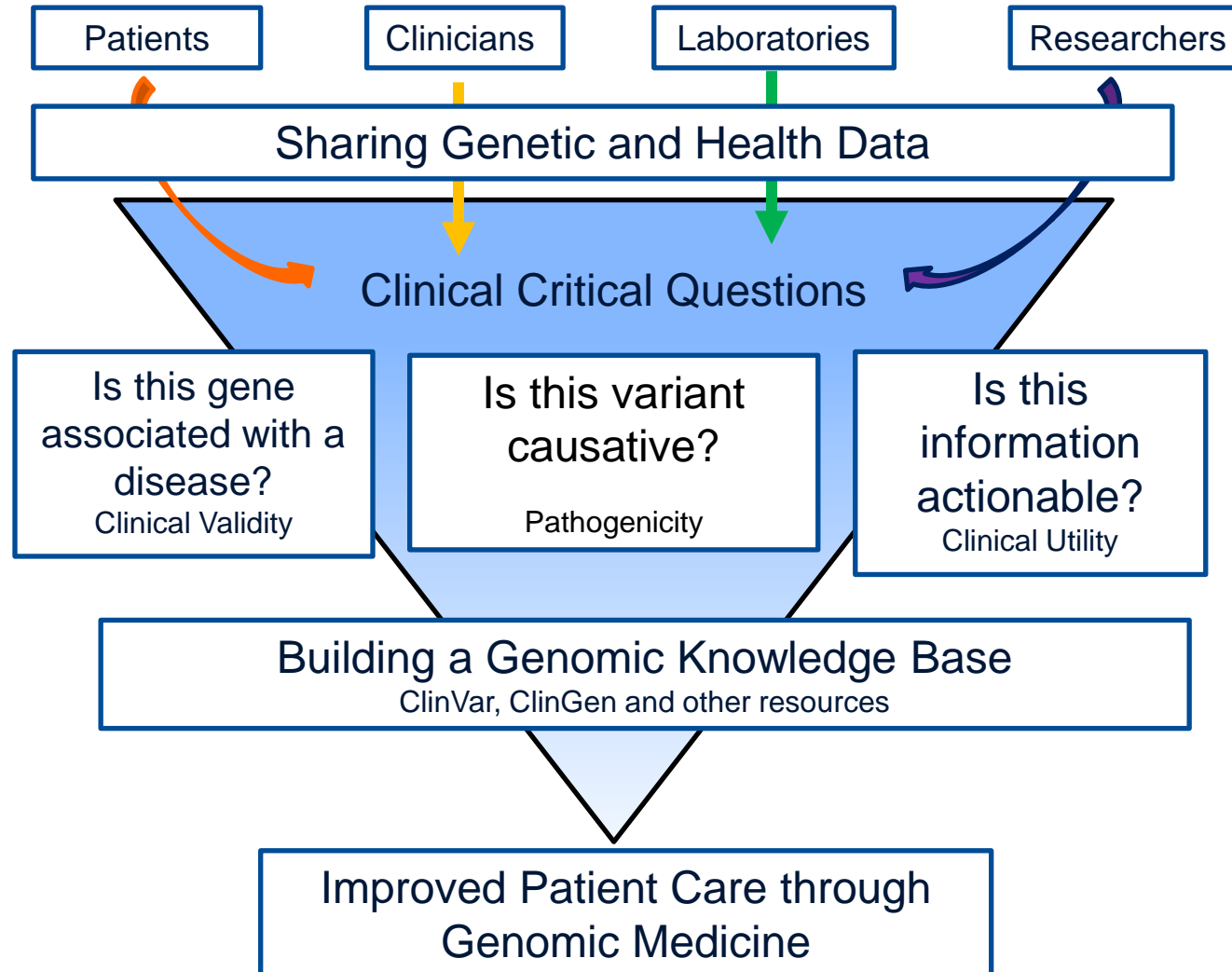
Increasing evidence allows disease-genes to be characterized



Increasing evidence over time leads to higher Clinical Validity

- Published patients and pathogenic variants
- Functional evidence
- Model system evidence

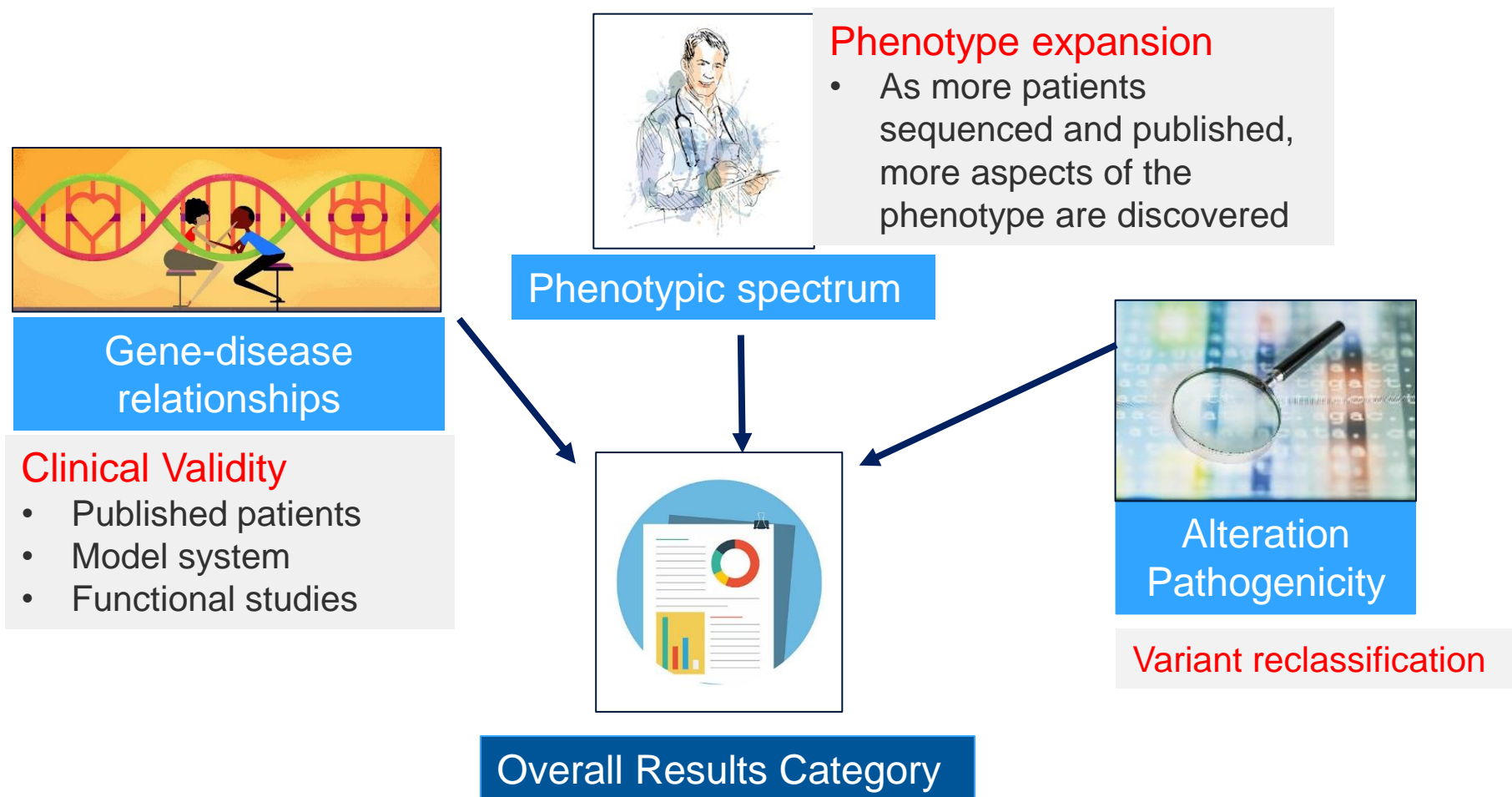
Building a genomic knowledge base to improve patient care



Genomics data sharing resources



Exome Reanalysis dependent on new information



Example of phenotype expansion

Exome case 1:

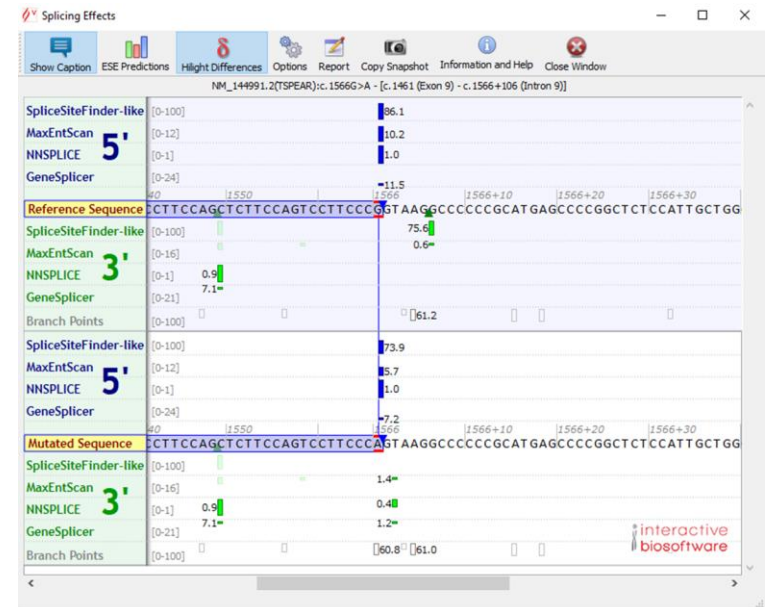
- 4-year-old Caucasian male
- Congenital anomalies including severe lacrimal stenosis, laryngeal web, stenosis of external auditory meatus with conductive hearing loss, and bilateral cataracts
- Teeth problem, slow hair growth, nasal hypoplasia, underdevelopment of tissue around base of thumb

Example of phenotype expansion

Exome sequencing:

Gen	Effect	Variant	Info	Variant Classification
TSPEAR	Coding silent	c.1566G>A p.Pro522=	HGMD HIT, reduced splicing.	VUS
TSPEAR	Nonsense	c.589C>T p.Arg197Ter	Early termination	LP

TSPEAR c.1566G>A p.Pro522=
Reduced splicing



Example of phenotype expansion

TSPEAR

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
21q22.3	?Deafness, autosomal recessive 98	614861	AR	3	TSPEAR	612920

doi:10.1093/hmg/ddc212
Advance Access published on June 7, 2012

Defect in the gene encoding the EAR/EPTP domain-containing protein TSPEAR causes DFNB98 profound deafness

Sedigheh Delmaghani^{1,2,3,†}, Asadollah Aghaie^{2,3,4,†}, Nicolas Michalski^{1,2,3}, Crystel Bonnet^{2,3,4}, Dominique Weil^{1,2,3} and Christine Petit^{1,2,3,4,5,*}

¹Institut Pasteur, Unité de Génétique et Physiologie de l'Audition, Paris, France, ²INSERM UMRS 587, Paris, France, ³

Phenotype-Gene Relationships

Location	Phenotype
21q22.3	Ectodermal dysplasia 14, hair/tooth type with or without hypohidrosis

RESEARCH ARTICLE

Mutations in *TSPEAR*, Encoding a Regulator of Notch Signaling, Affect Tooth and Hair Follicle Morphogenesis

Alon Peled^{1,2*}, Ofer Sarig^{1*}, Liat Samuelov^{1,3}, Marta Bertolini⁴, Limor Ziv⁵, Daphna Weissglas-Volkov⁶, Marina Eskin-Schwartz^{1,2}, Christopher A. Adase³, Natalia Malchin¹, Ron Bochner¹, Gilad Fainberg¹, Ilan Goldberg¹, Koji Sugawara⁷, Avital Baniel¹, Daisuke Tsuruta⁷, Chen Luxenburg⁶, Noam Adir⁸, Olivier Duverger⁹,

Example of gene-disease relationships

Exome case 2:

- 8 yo Hispanic boy
- **Neurologic:** severe global DD, chorea, intractable seizure
- **Brain MRI:** bilateral perisylvian cortical dysplasia, nodular heterotopia
- **Dysmorphic features:** microcephaly, wide-spaced eyes, downturned corners of the mouth, U-shaped contour to the mouth with micrognathia
- **Skeletal:** hip dysplasia
- **EEG:** hypsarrhythmia
- **GI:** dysphagia, constipation
- **Family History:** No

- Proband ONLY

Example of gene-disease relationships

Negative exome:

- No strong candidate gene/variant identified
- Some variants to discuss

Gene	Transcript	Type	Zygoty	DNA alteration	Protein alteration	Inheritance mode	Human disease	Classification
<i>CSTB</i>	NM_000100	nonsense	het	c.C136T	p.Q46X	Autosomal recessive	Progressive myoclonic epilepsy 1A	Pathogenic
<i>POLR3B</i>	NM_018082	missense	het	c.G2158A	p.V720I	Autosomal recessive	Hypomyelinating leukodystrophy-8	VUS
<i>GRID2</i>	NM_001510	missense	het	c.A101G	p.D34G	Autosomal recessive	Spinocerebellar ataxia- 18	VUS
<i>STARD9</i>	NM_020759	missense	het	c.G986A	p.R329Q	Autosomal recessive	Unknown	VUS
	NM_020759	missense	het	c.C6955T	p.R2319W			VUS
<i>TIMM17B</i>	NM_001167947	missense	hemi	c.G304A	p.A102T	X-linked	Unknown	VUS

Example of gene-disease relationships

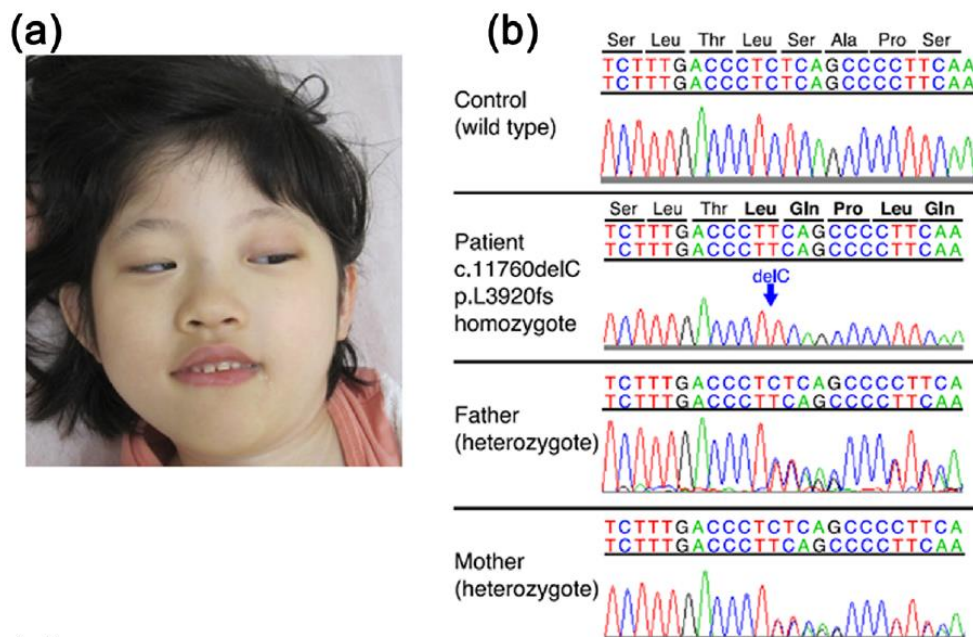
Exome reanalysis, compound Heterozygous Variants in *STARD9*

Gene	Transcript	Type	Zygosity	DNA alteration	Protein alteration	Inheritance mode	Human disease	Classification
<i>STARD9</i>	NM_020759	missense	het	c.G986A	p.R329Q	Autosomal recessive	Okamoto et al 2017 (PMID 28777490)	VUS
	NM_020759	missense	het	c.C6955T	p.R2319W			VUS

- *STARD9* gene encodes a protein that belongs to the kinesin-3 family. It associates with mitotic microtubules and regulates spindle pole assembly (Torres et al., 2011).
- Okamoto, et al., 2017 (PMID 28777490, Epub ahead of print on Aug 4, 2017) identified a homozygous pathogenic frame-shift variant in the *STARD9* gene via WES in one patient with severe intellectual disability, dysmorphic features, generalized tonic seizure, acquired microcephaly, cortical blindness, and sleep apnea.

A novel genetic syndrome with *STARD9* mutation and abnormal spindle morphology

Nobuhiko Okamoto^{1,2} | Yuki Tsuchiya^{3,4} | Fuyuki Miya^{5,6} |
Tatsuhiko Tsunoda^{5,6} | Kumiko Yamashita⁷ | Keith A. Boroevich⁶ |
Mitsuhiro Kato⁸ | Shinji Saitoh⁹ | Mami Yamasaki¹⁰ | Yonehiro Kanemura^{11,12} |
Kenjiro Kosaki¹³ | Daiju Kitagawa^{3,4}



Clinical Report

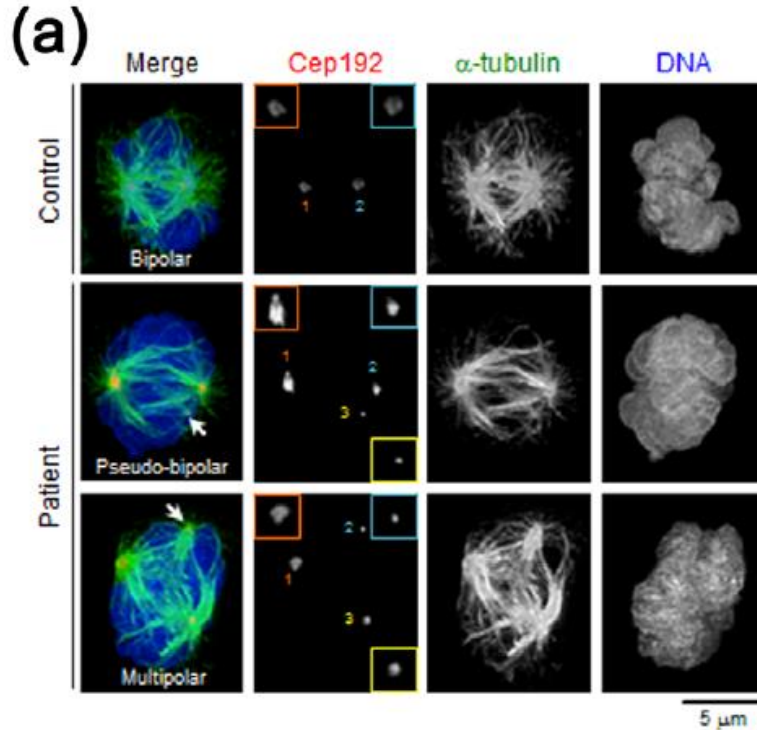
6 yrs female

- **Neurologic:** Severe DD, Seizure, little/no speech, cortical blindness, and sleep apnea
- **Dysmorphic features:** microcephaly, sparse eyebrow, epicanthal fold,
- **Muscle:** hypotonia, deep tendon reflexes were absent
- **Growth parameters:** height 99cm (-4.0SD), weight 11.7kg (-2.8SD), OFC 47.0cm (-2.2SD)
- **GI:** poor feeding
- **MRI:** No structural abnormalities

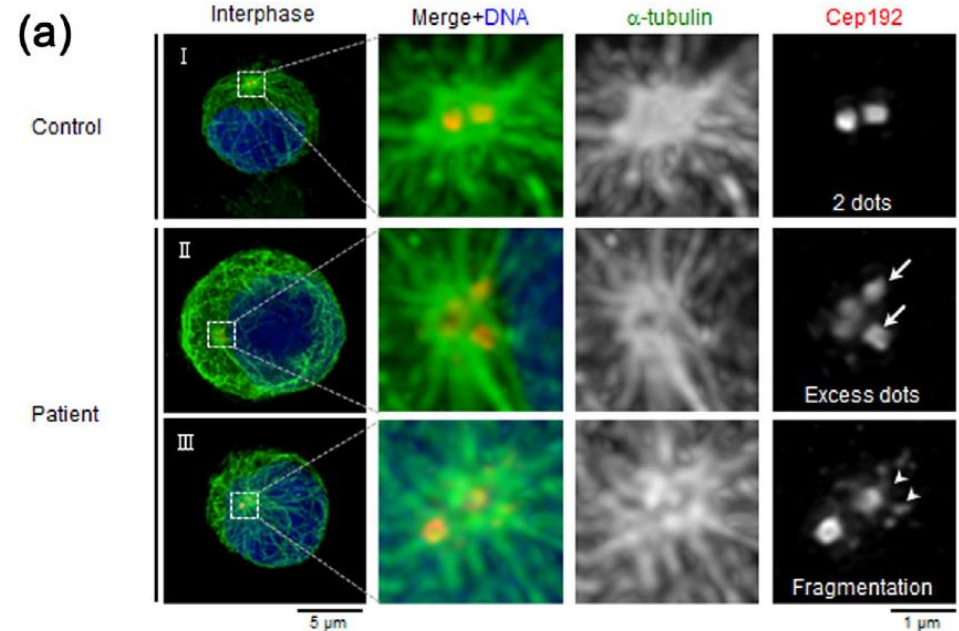
Mutation: homozygous of c.11760delC, p.L3920fs in *STARD9*

Abnormal Spindle Morphology and Increase # of Centrosomes

Abnormal spindle morphology



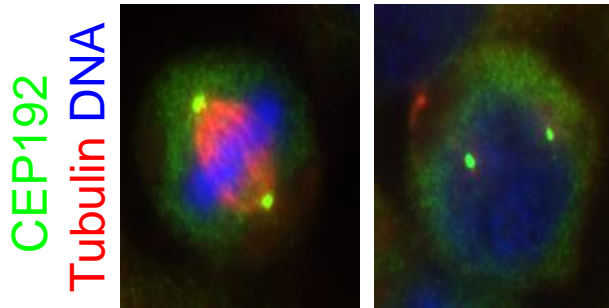
Increased number of centrosomes and fragmentation



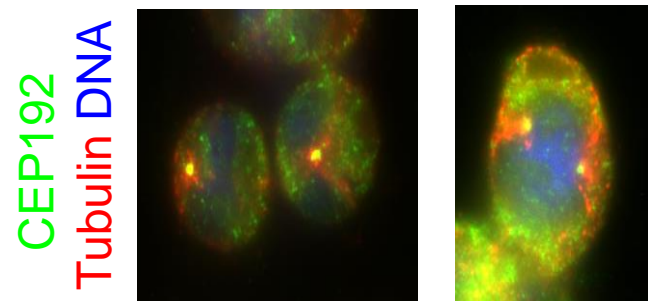
Okamoto et al. 2017

Research Collaboration with Huntsman Cancer Institute

1) Initial antibody test on adherent HeLa cells (no smear gel) – CEP192 antibody works nicely



2) Optimized conditions using trypsinized HeLa cells (to mimic suspension cells) in smear gel:



Drs. Katherine Ullman and Dollie LaJoie

There is obvious value in reanalysis of exome data

- Exome reanalysis is a routine clinical labs practice
- O'Daniel, 2017: “The majority of laboratories indicated that they had reanalyzed case-specific data to provide an updated report at least once (11 of 12 clinical labs). The instances were rare, however, with 7 of 12 labs indicating that reanalysis rarely or never occurred. Only one clinical laboratory routinely reanalyzed every case. When reanalysis was performed, roughly half used the existing variant call format (VCF) file and a half performed new alignment and variant calling. Of the clinical laboratories, six indicated reanalysis would be free of charge, five charge a fee, and one was still developing its policy.”

ARUP exome reanalysis

- By physician request, free of charge
- Systematic reanalysis of clinical exomes yield of additional diagnosis of 10-15%

Raw FASTQ files run through updated pipeline

Variant calling and filtering with current knowledge and population frequency

Clinical/medical review of phenotype updates and variants pathogenicity

Reanalysis report including new relevant findings, variants reclassification communicate to clinician

Example of pipeline improvement and variant reclassification

Exome case 3:

- 1 year old Caucasian/Native American/French Canadian male
- Severe DD, poor growth, microcephaly, hypotonia, cataracts, nystagmus, sensorineural hearing loss, dysmorphic facial features
- Exome sequencing trio was performed in 2015

Example of pipeline improvement and variant reclassification

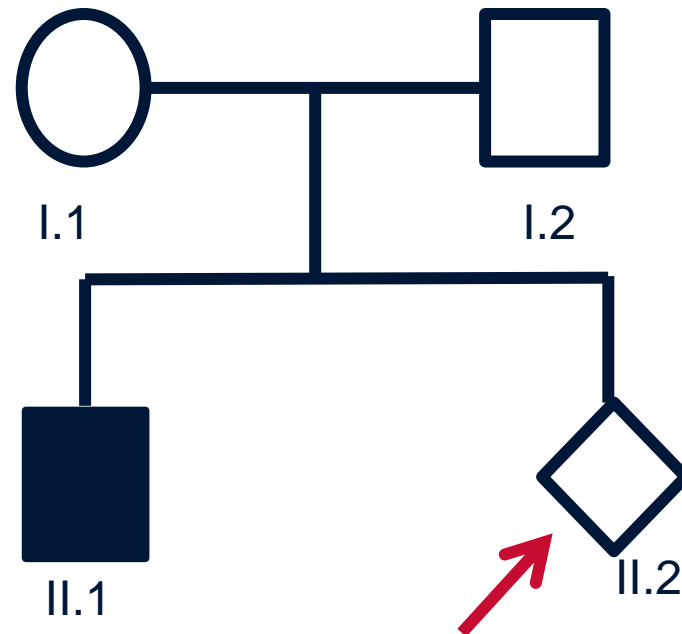
Exome sequencing identified one variant in *ERCC6*

Gen	Effect	Variant	Info	Inheritance	Variant Classification
<i>ERCC6</i>	Nonsense	c.2569T>C, p.Arg857X	Early termination	Paternal	Likely Pathogenic

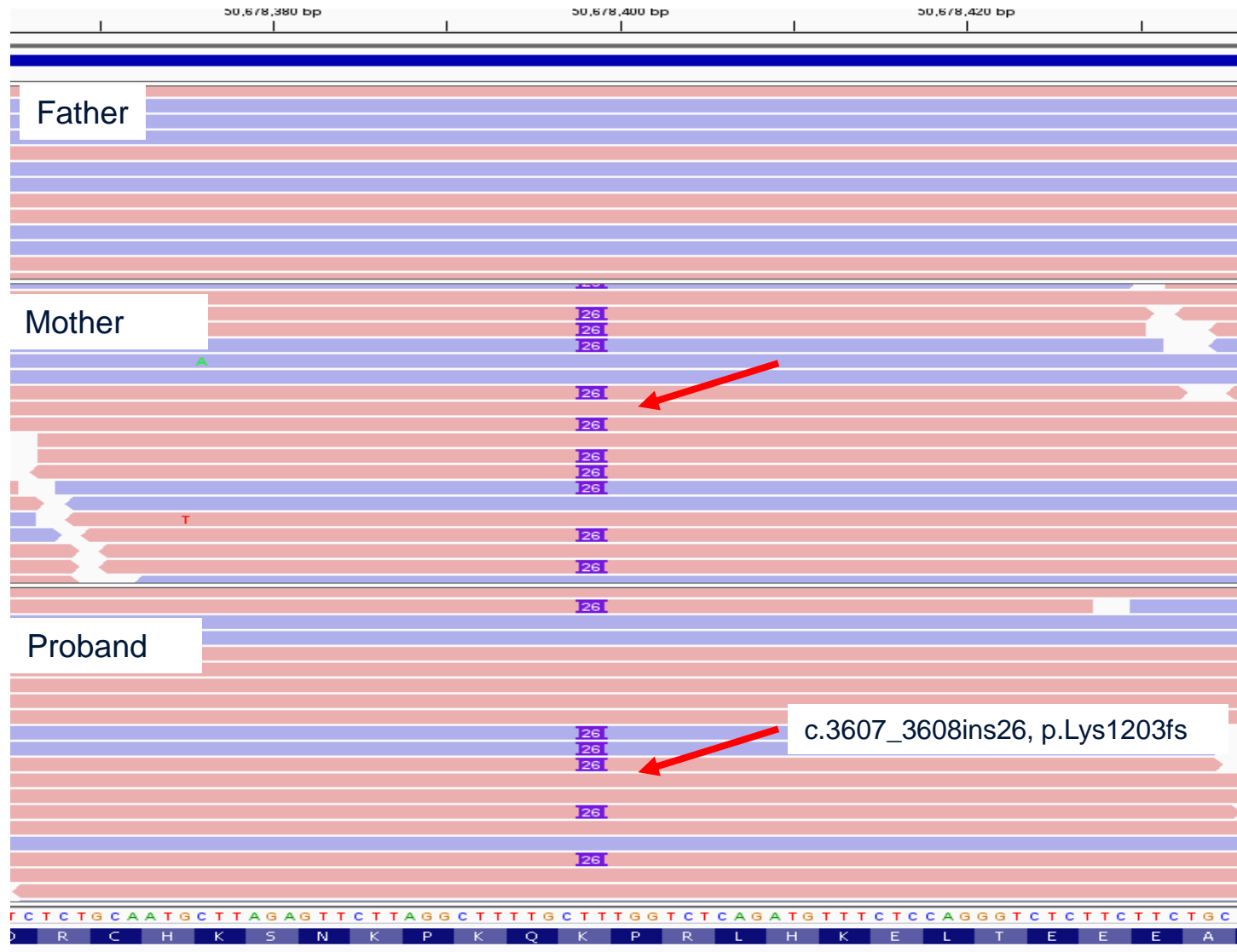
ERCC6 pathogenic variants cause Cockayne syndrome, type B (OMIM#133540), **autosomal recessive**. Affected patients with Cockayne syndrome can have a severe congenital phenotype that includes **failure to thrive, severe developmental delay, congenital cataracts, sensorineural hearing loss, distinctive face** with small deep-set eyes and prominent nasal bridge, kyphosis, and cachectic dwarfism.

Only one pathogenic variant detected.

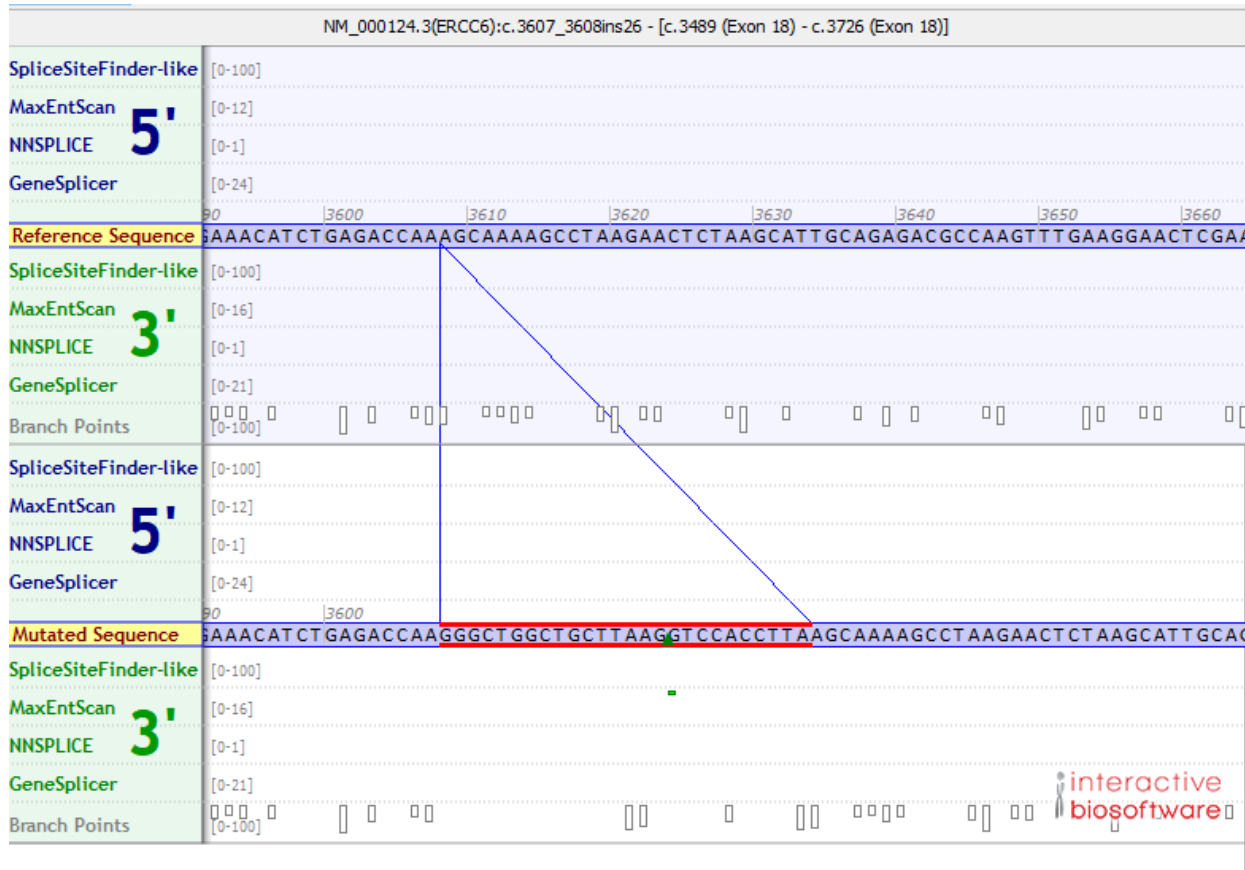
Exome reanalysis requested for recurrence risk



A second pathogenic variant of c.3607_3608ins26 detected in ERCC6



A second pathogenic variant of c.3607_3608ins26 detected in ERCC6



This variant introduces an early termination codon in exon 18 of 21 and is predicted to result in a truncated or absent protein

A second pathogenic variant of c.3607_3608ins26 detected in ERCC6

NM_000124.4(ERCC6):c.3607_3608insGGGCTGGCTGCTTAAGGTCCACCTTA (p.Lys1203fs)

[Follow](#) [Link](#) [Download](#)

[Cite this record](#)

Interpretation: Pathogenic/Likely pathogenic

Review status: ★★☆☆ criteria provided, multiple submitters, no conflicts

Submissions: 2 (Most recent: Jul 10, 2018)

Last evaluated: Dec 6, 2017

Genotype-phenotype correlations

ORIGINAL ARTICLE

Functional and clinical relevance of novel mutations in a large cohort of patients with Cockayne syndrome

Nadege Calmels,¹ Elena Botta,² Nan Jia,³ Heather Fawcett,⁴ Tiziana Nardo,² Yuka Nakazawa,^{3,5,6} Manuela Lanzafranco,² Shinichi Moriwa,⁷ Katsuo Sugita,⁸ Masaya Kubota,⁹ Cathy Obringer,¹⁰ Marie-Aude Spitz,¹¹ Miria Stefanini,² Vincent Laugel,^{10,11} Donata Orioli,² Tomoo Ogi,^{3,5,6} Alan Robert Lehmann⁴

Am. J. Hum. Genet. 62:77–85, 1998

Molecular Analysis of Mutations in the CSB (ERCC6) Gene in Patients with Cockayne Syndrome

Donna L. Mallery,¹ Bianca Tanganelli,² Stefano Colella,² Herdis Steingrimsdottir,^{1,*} Alain J. van Gool,^{3,*} Christine Troelstra,³ Miria Stefanini,² and Alan R. Lehmann¹

¹MRC Cell Mutation Unit, Sussex University, Falmer, Brighton; ²Istituto di Genetica Biochimica ed Evoluzionistica CNR, Pavia, Italy; and ³Department of Cell Biology and Genetics, Erasmus University, Rotterdam

Summary

Cockayne syndrome is a multisystem sun-sensitive ge-

variety of carcinogens, including UV light. Three genetic disorders—xeroderma pigmentosum (XP), Cockayne syndrome (CS), and trichothiodystrophy (TTD)—are as-

Citations for this variant

Title	Author	Journal	Year	Link
Molecular analysis of mutations in the CSB (ERCC6) gene in patients with Cockayne syndrome.	Mallery DL <i>et al.</i>	American journal of human genetics	1998	PMID: 9443879

In ClinVar, this variant has been submitted by multiple clinical laboratories and classified as Pathogenic/Likely Pathogenic

Reclassify the exome report-positive

Gen	Effect	Variant	Info	Inheritance	Variant Classification
ERCC6	Nonsense	c.2569T>C, p.Arg857X	Early termination	Paternal	Pathogenic
ERCC6	Frameshift	c.3607_3608ins26, p.Lys1203fs	Early termination	Maternal	Pathogenic

Confirmed two ERCC6 pathogenic variants detected and Cockayne syndrome, type B (OMIM#133540).

Prenatal diagnosis is available for current pregnancy

Challenges for exome reanalysis

- Cost of reanalysis estimated at 38% relative to the initial analysis, review and reporting
- Difficult to follow-up and request exome reanalysis if patient has moved around or changed healthcare providers
- How this would affect follow-up appointments?

Variant submissions to ClinVar

- ARUP Molecular Genetics and Genomics Laboratories
 - 10,387 sequence variants
 - Individual case
 - Variant curation following ACMG Variant Interpretation Guidelines
 - Assertion criteria:
submit.ncbi.nlm.nih.gov/ft/byid/jucit10y/arup_molecular_germline_variant_investigation_process.pdf
 - Variants have been submitted twice a year, and re-evaluated in six months
- Research and Development (ARUP Laboratories)
 - 1676 sequence variants
 - Publication review and evidence based curation
 - Variants have been reviewed every year
 - Twelve disease specific variant databases
<https://arup.utah.edu/database/index.php>

Perspectives and Experiences from the Cytogenetics Laboratory

Erica Andersen, PhD, FACMG

Section Chief, Cytogenetics and Genomic Microarray

Associate Professor, Clinical Pathology

ARUP's Data Sharing and Reevaluation/Reanalysis Practices

Technique	Databases Shared	Reevaluation/Reanalysis Performed		
		Clinician-initiated	Public Database-Initiated	Lab-Initiated
Targeted Variant	N/A	No	Yes	Yes
Single Gene	ClinVar, Locus-Specific	Yes	Yes	Yes
Gene Panel	ClinVar	Yes	Yes	Yes
Whole Exome	ClinVar, GeneMatcher*	Yes	Yes	Yes
Genomic Microarray (CNVs)	ClinVar, CAGdb*	Yes (increasingly)	Yes	Yes

*Controlled access database

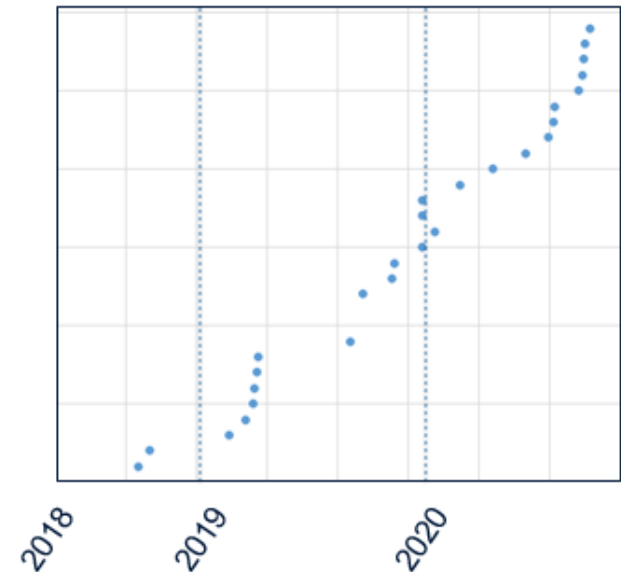
Variant submissions to ClinVar

- ARUP Genomic Microarray Laboratory
 - 1915 copy number variants submitted (postnatal constitutional)
 - Variant-level information (phenotype)
 - IRB approval (consent: opt-out mechanism)
 - Variant classification following ACMG CNV Interpretation Guidelines
 - Assertion criteria:
aruplab.com/files/resources/genetics/ARUP%20Cytogenomic%20Constitutional%20CNV%20Assertion%20Criteria_final.pdf
 - In process: Implement updated numerical-based CNV-scoring system (Riggs *et al.*, 2019 Genet. Med)

CNV Reevaluations (Clinician-Initiated, Past 2 years)

- How frequent?
 - Requests are increasing recently (several per quarter) compared to historically (handful per year)
 - Developed a process to manage, tracking requests for resource management
 - Lessons learned: good record keeping/databasing is essential
 - Expect case-level requests as exome/genome CNV calling is implemented broadly

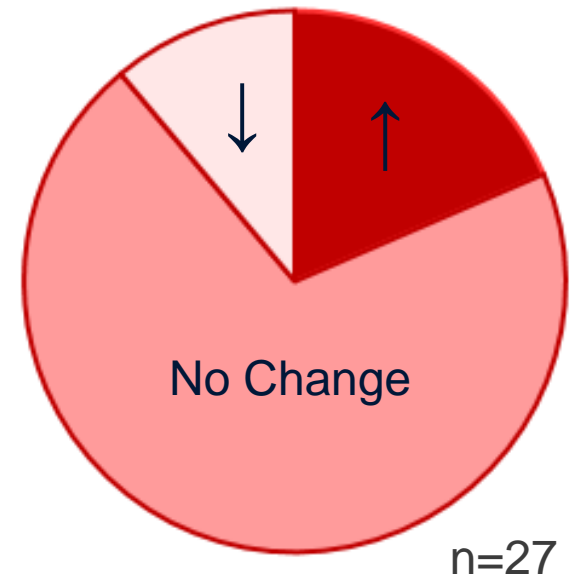
Request Frequency



CNV Reevaluations (Clinician-Initiated, Past 2 years)

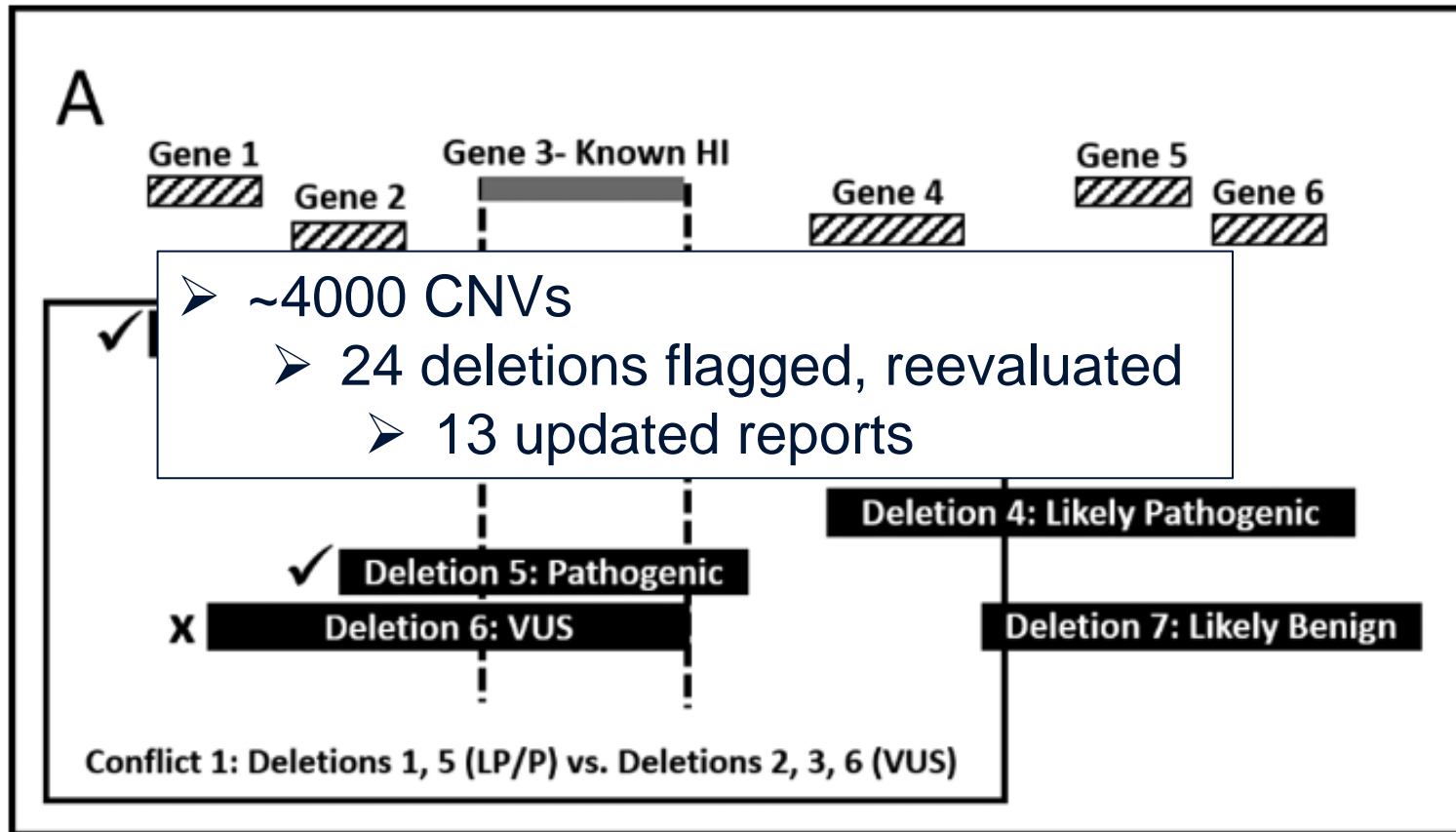
- Who asks? Clients/clinicians vary
- How soon? Avg. time-frame = 3.4 years (range: 0.5-9 years)
- Why? Majority VUS, to manage clinical follow-up
- Utilization is broad, appropriate
- Which reports are updated?
 - Any upgrade to likely pathogenic/pathogenic
 - Any downgrade to likely benign/benign

Changes to CNV Classification



CNV Reevaluations (ClinVar / Internally-Initiated)

Method: Haploinsufficient (HI) Gene Overlap



Riggs et al., Hum Mutat. 2018

CNV Case 1: VUS to Pathogenic Reclassification

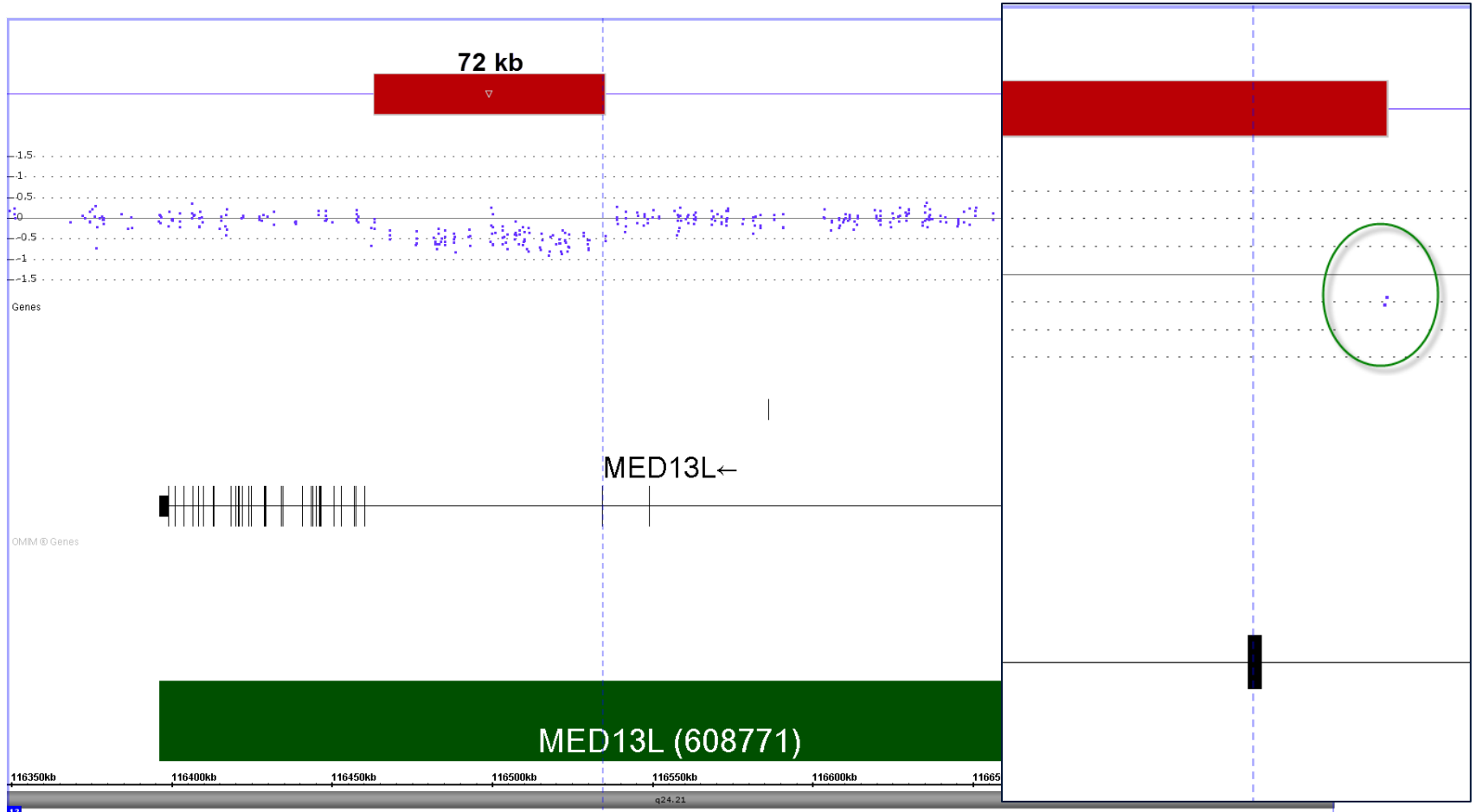
- 10 y/o male (age 13 at reevaluation), with indication: unspecified intellectual disability
- 2q36.3q37.1 loss involving 13 protein-coding genes including TRIP12, now a curated HI gene
 - TRIP12 HI: autosomal dominant intellectual disability, behavioral anomalies, additional clinical findings in some patients
- Inheritance unknown (not maternal; unaffected), unaffected sibling negative
- Pediatrician contacted upon reclassification, discussed updated clinical significance
- Benefits:
 - Patient now qualifies to receive services
 - Family members can be counseled about their reproductive risks

CNV Case 2: VUS to Pathogenic Reclassification

- Newborn male (age 6 at reevaluation), presenting with minor dysmorphic features
- 1p36.11p35.3 loss involving 14 protein-coding genes, including AHDC1, now a curated HI gene
 - AHDC1 LOF: Xia-Gibbs syndrome: DD, ID, hypotonia, sleep abnormalities, seizures, other variable findings
- Contacted clinician and obtained additional clinical history
 - Patient now has features of Xia-Gibbs (usually de novo-but recommended parental testing for reproductive counseling)
- Benefits:
 - Ends diagnostic odyssey for patient/family
 - Improved medical management, genetic counseling for family

CNV Case 3: No reclassification from VUS

10 y/o female with dysmorphic features



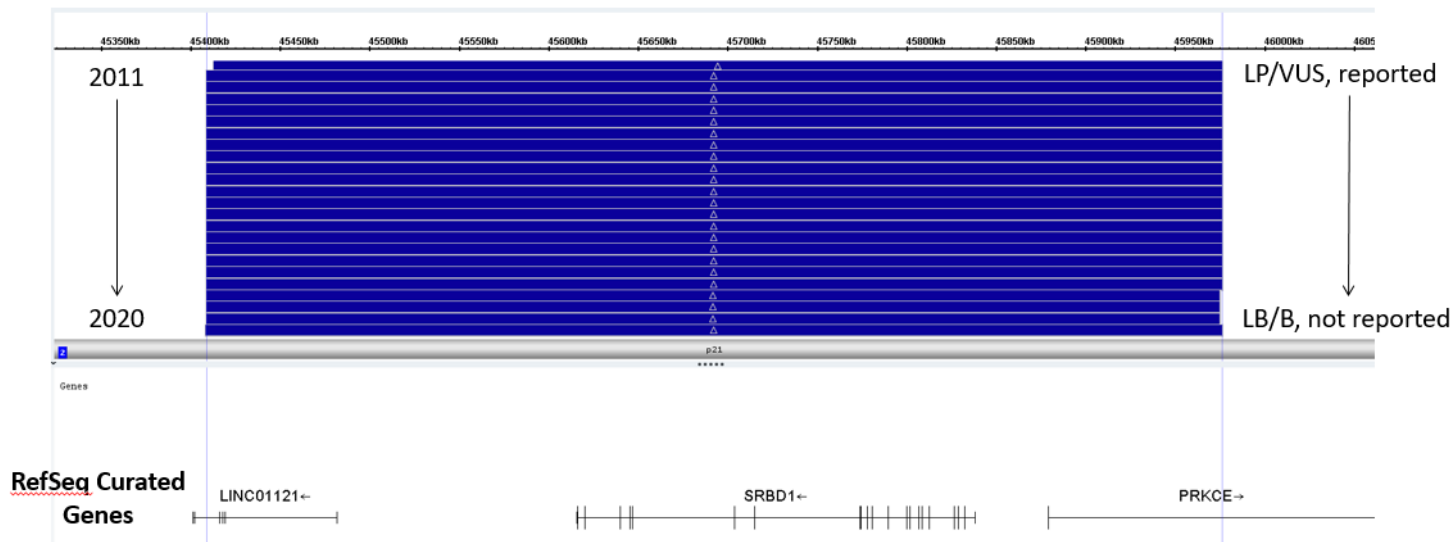
CNV Reevaluations (ClinVar / Internally-Initiated)

Method: “Close-Match” and Recurrent CNVs

- Encountered multiple times
- $\geq 99\%$ overlap & $\geq 99\%$ similarity in size
- Discordant classifications

Example: 2p21 duplication: LP/VUS to LB/B

Numerous dups of this region, phenotypes/indications vary widely



Summary

- Clinical laboratories are now increasingly called upon to share genetic testing data, as well as reevaluate results from previously performed tests for hereditary conditions
- These efforts create unique opportunities and challenges during the diagnostic workup for new and previously tested patients, but ultimately help patients with rare genetic disorders end their diagnostic odyssey and improve their clinical care through personalized medicine
- Clinical laboratories should stay up-to-date on recent and emerging recommendations and policies surrounding genetic data sharing and variant reevaluation, and work to proactively implement these practices in a responsible, practical, and forward-thinking manner

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