Clinical Exome Sequencing

Pinar Bayrak-Toydemir, M.D., Ph.D.
Rong Mao, M.D.

Outline

1- Exome Sequencing Methodology

2- Guidelines / Recommendations

3- Real Life Experience

"Every dollar we spent to map the human genome has returned $140 to our economy -- $1 of investment, $140 in return."

--President Obama April 2, 2013
Remarks by the President on the BRAIN Initiative and American Innovation**,**

History

1953 Discovery of DNA structure

1977 Discovery of Sanger sequencing

1985 Development of PCR

1999 First human chromosome sequenced- ch 22

2004 Development of next generation sequencing (NGS)

2008 First individual genome sequenced using NGS

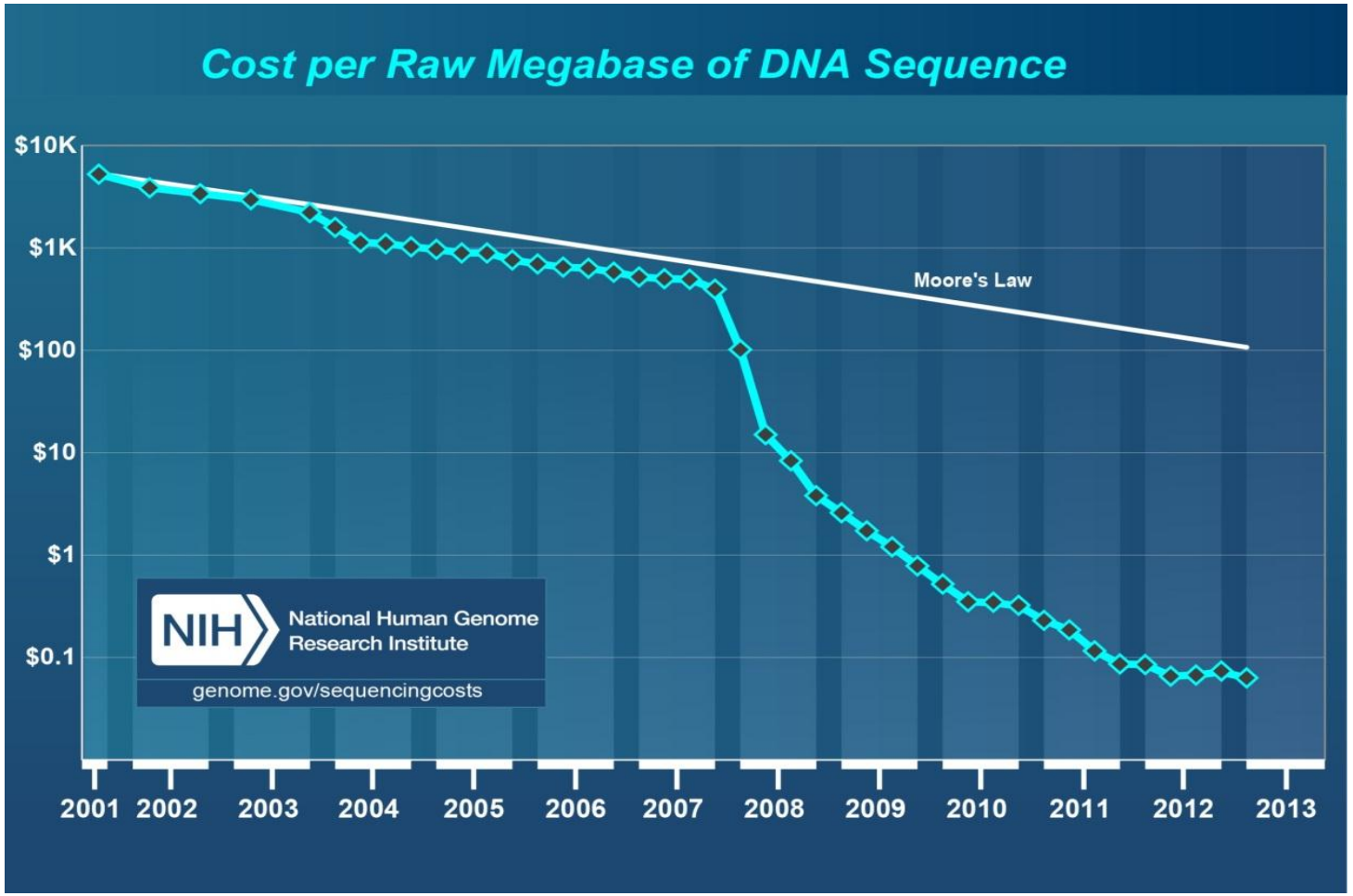
Exome sequencing

A powerful tool for gene discovery

Over 200 genes have been discovered in a couple of years

Now a powerful diagnostic tool !

Next Generation Sequencing Cost Dropping



Cost per base is in free-fall !

http://www.genome.gov/sequencingcosts/

Clin Genet. 2013 May;83(5):457-461. doi: 10.1111/j.1399-0004.2012.01951.x. Epub 2012 Sep 11.

Exploring the utility of whole-exome sequencing as a diagnostic tool in a child with atypical episodic muscle weakness.

Hanchard N, Murdock D, Magoulas P, Bainbridge M, Muzny D, Wu Y, Wang M, McGuire A, Lupski J, Gibbs R, Brown C.

Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA; Texas Children's Hospital, Houston, TX, USA.

Neurology. 2012 Jul 10;79(2):123-6. doi: 10.1212/WNL.0b013e31825f047a. Epub 2012 Jun 6.

Exome sequencing as a diagnostic tool in a case of undiagnosed juvenile-onset GM1-gangliosidosis.

Pierson TM, Adams DA, Markello T, Golas G, Yang S, Sincan M, Simeonov DR, Fuentes Fajardo K, Hansen NF, Cherukuri PF, Cruz P, Teer JK, Mullikin JC; NISC Comparative Sequencing Program, Boerkoel CF, Gahl WA, Tifft CJ.

NIH Undiagnosed Diseases Program, NIH Office of Rare Diseases Research, Neurogenetics Branch, Bethesda, MD, USA. Tyler.Pierson@cshs.org

Ann Neurol. 2012 Jan;71(1):5-14. doi: 10.1002/ana.22647.

Exome sequencing: dual role as a discovery and diagnostic tool.

Ku CS, Cooper DN, Polychronakos C, Naidoo N, Wu M, Soong R.

Cancer Science Institute of Singapore, National University of Singapore, Singapore. csikcs@nus.edu.sg

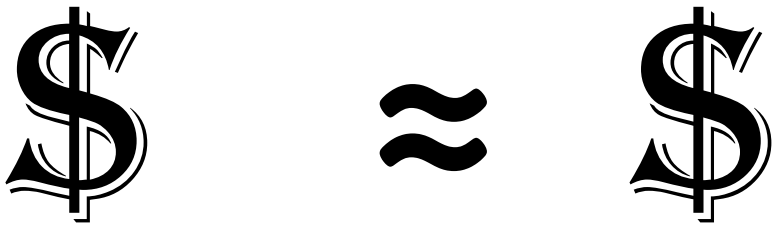
Hum Mutat. 2013 Apr 8. doi: 10.1002/humu.22332. [Epub ahead of print]

Targeted Next-Generation Sequencing can Replace Sanger Sequencing in Clinical Diagnostics.

Sikkema-Raddatz B, Johansson LF, de Boer EN, Almomani R, Boven LG, van den Berg MP, van Spaendonck-Zwarts KY, van Tintelen P, Sijmons RH, Jongbloed JD, Sinke RJ.

Department of Genetics, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands.

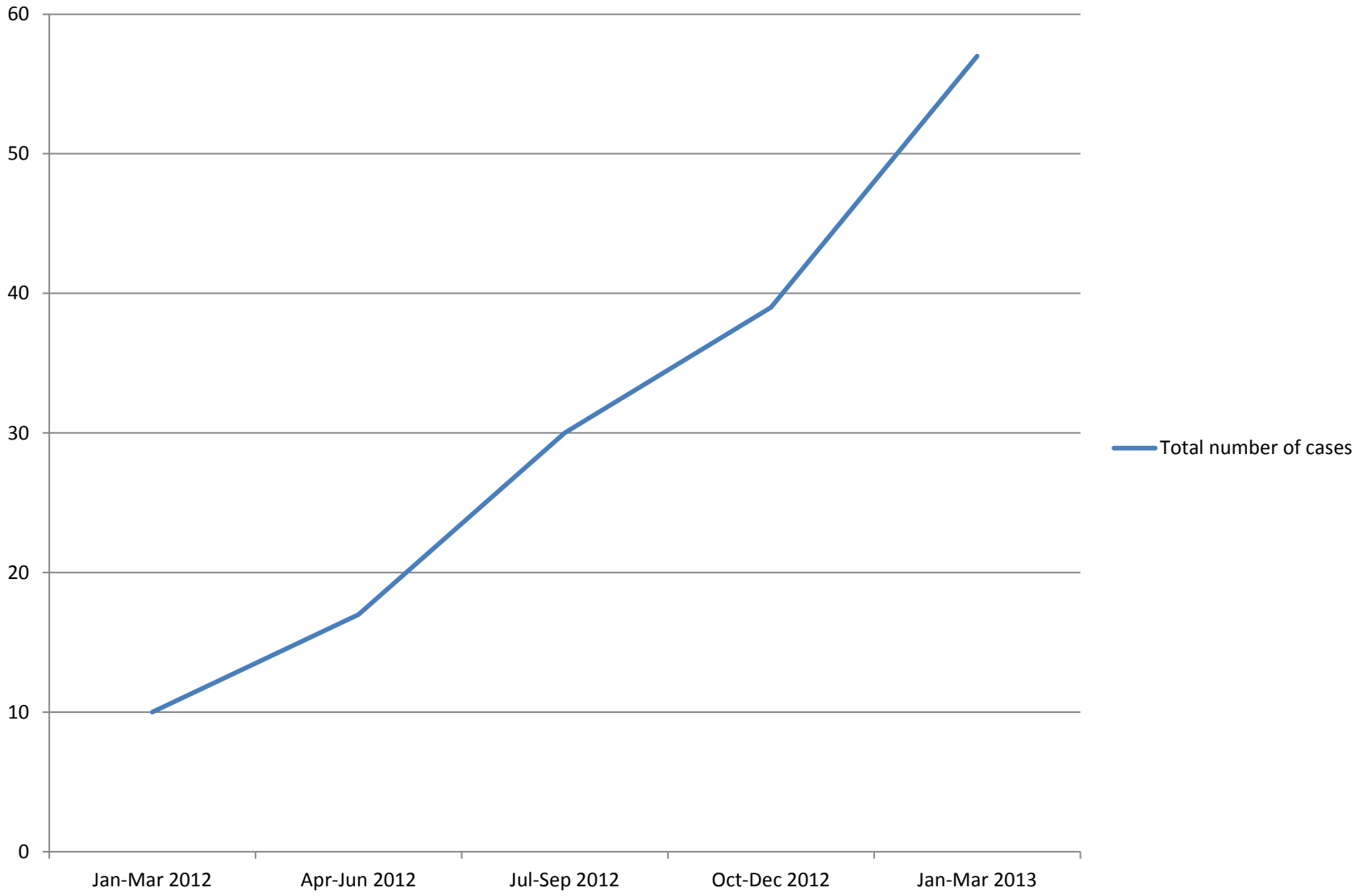
Cost driven test ordering change



FBN1
Sanger sequencing

Aortapathy (Marfan and Marfan like syndromes)
10 gene NGS panel

Total Number of Cases in ARUP Next Generation Sequencing Lab



What is Exome sequencing ?

The sequence of all exons of the genome

What is missing?

Some protein coding genes
Some exons of some genes
Non-genic control elements
Copy number changes
Structural changes
mtDNA
Some microRNA genes

Why Exome Sequencing?

Focuses on the part of the genome we understand best, the exons of the genes

Exons comprise 1% of the genome

~85% of all known disease causing mutations are located on exons

Exome sequencing costs 1/6 of the cost of whole genome sequencing

Diagnostic Yield

Based on the NIH Undiagnosed Diseases Program clinical sensitivity of exome sequencing is around 20%

Possibly selection of “best” cases

Gahl et al., Vol14 (1) Jan 2012 | **Genetics in medicine**

Diagnostic Odyssey

Multiple congenital abnormalities

Intellectual disability

Unexplained developmental delay or declining

Preanalytic Considerations

Patient specific:

- well defined findings
- good evidence for a genetic basis

Family specific:

- affected family members
- inheritance pattern

Analytic Considerations

Limitations of exome testing

- capturing efficiency

Bioinformatic aspects

- variant calling
- filtering
- analyzing genes only in Human Genome

Mutation Database or OMIM

- analyzing genes on mandatory reporting

Postanalytic Considerations

Reporting

- negative, positive, uncertain for primary patient finding

Ethical and counseling issues

Patient consent

Education of consumers (patients, clinicians, payers)

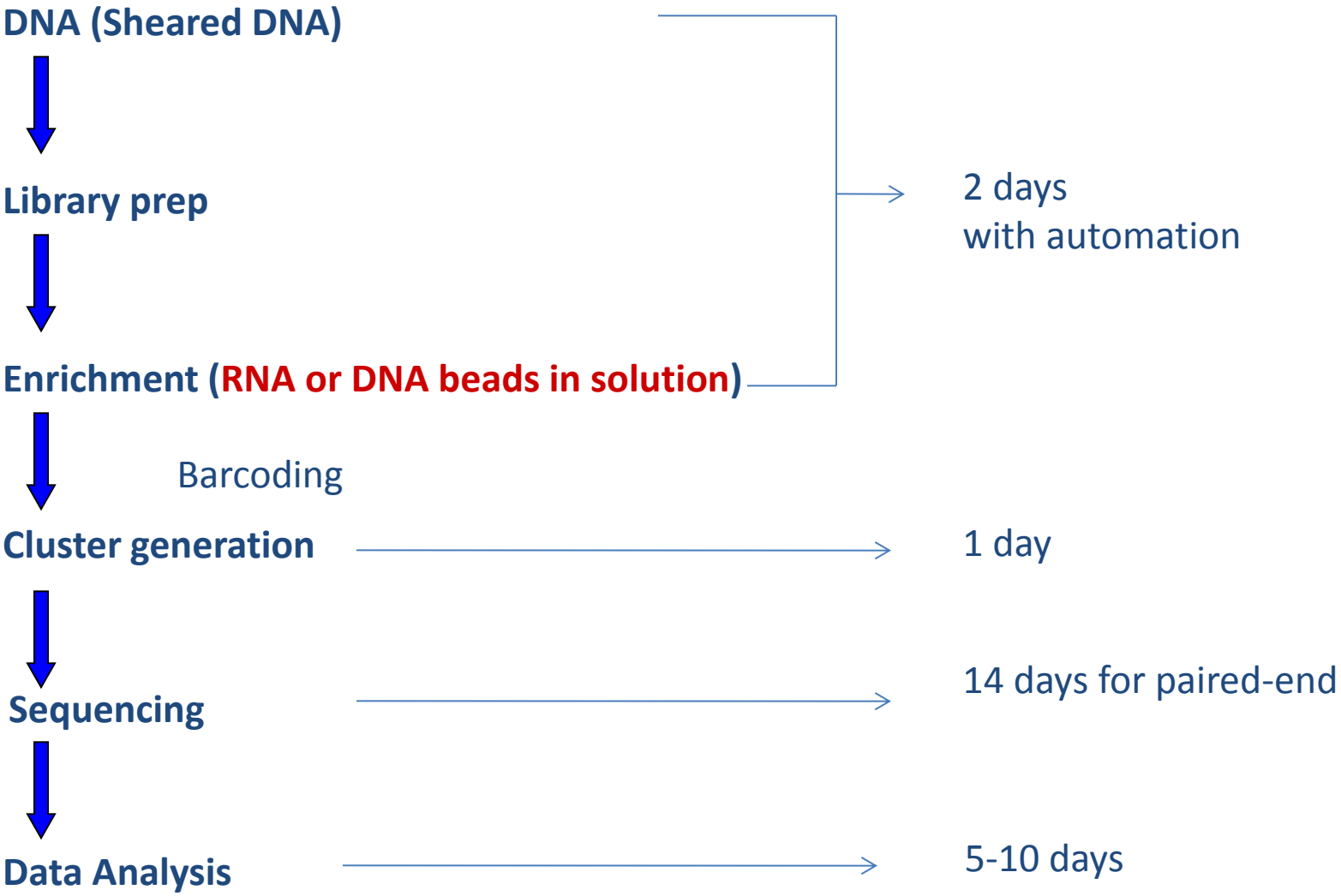
Clinical Exome Sequencing

- Agilent and Nimblegen liquid capturing
- Indexing of samples (barcoding)
- Illumina HiSeq 2000
- Alignment / Variant calling / Phenotype scoring
- Candidate mutation list
- Interpretation

CLINICAL EXOME SEQUENCING

Work flow :

Time Frame:



CLINICAL EXOME SEQUENCING

Work flow :

DNA (Sheared DNA)

Library prep

Enrichment

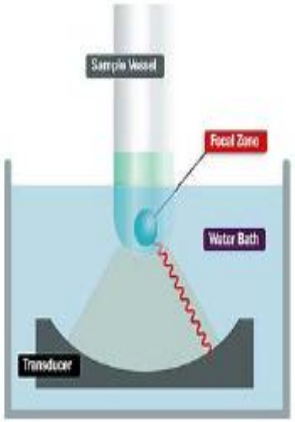
Barcoding

Cluster generation

Sequencing

Data Analysis

1. Shear 3 µg genomic DNA to ~200 bp fragments using sound waves.



Setting	Value
Duty Cycle	10%
Intensity	5
Cycles per Burst	200
Time	6 cyles of 60 seconds each
Set Mode	Frequency sweeping
Temperature	4°C

**Fast, easy to use, reproducible, "tune-in" size range.

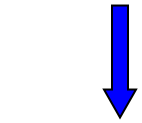
2. Assess fragmentation using a Bioanalyzer.

CLINICAL EXOME SEQUENCING

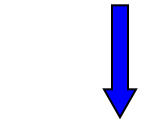
Work flow :

DNA (Sheared DNA)

Library prep

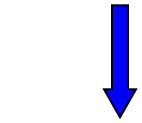


Enrichment

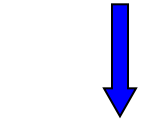


Barcoding

Cluster generation

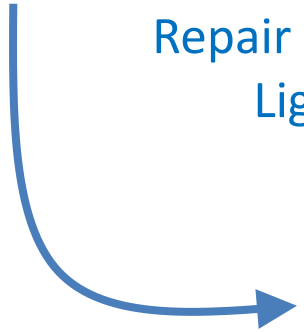


Sequencing



Data Analysis

DNA fragments



Repair and prepare ends
Ligate adapters

Adapters attach flow cells for cluster formation

CLINICAL EXOME SEQUENCING

Work flow :

DNA (Sheared DNA)

Library prep

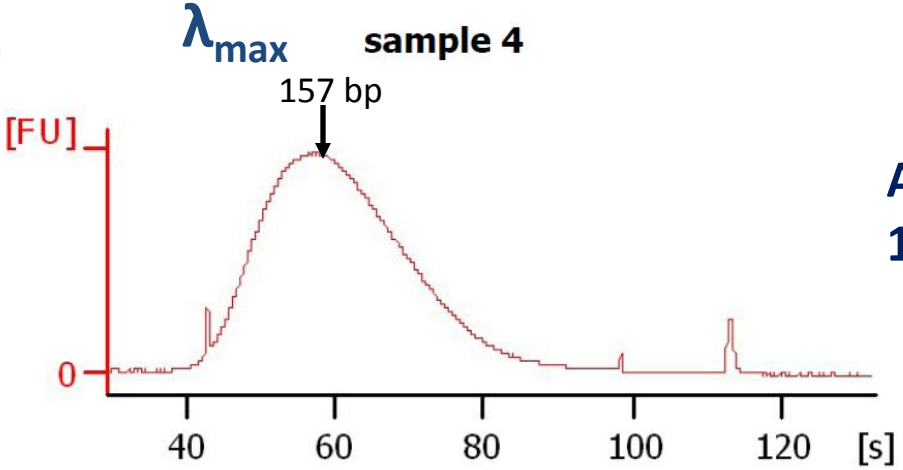
Enrichment

Barcoding

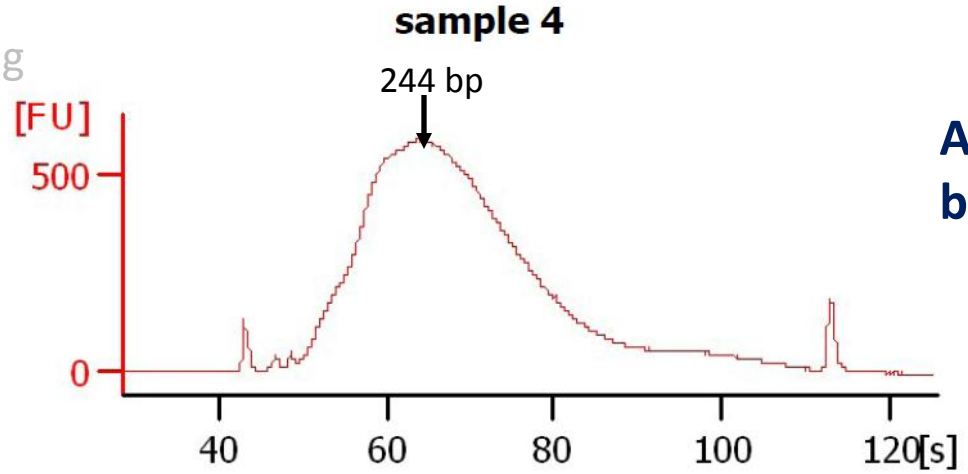
Cluster generation

Sequencing

Data Analysis



After Sonication
150-200 bp desired



After adapter binding

Peak shift indicates successful library generation

CLINICAL EXOME SEQUENCING

Work flow :

DNA (Sheared DNA)

Library prep

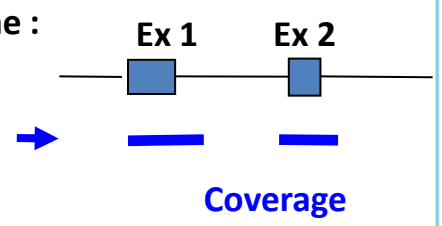
Enrichment

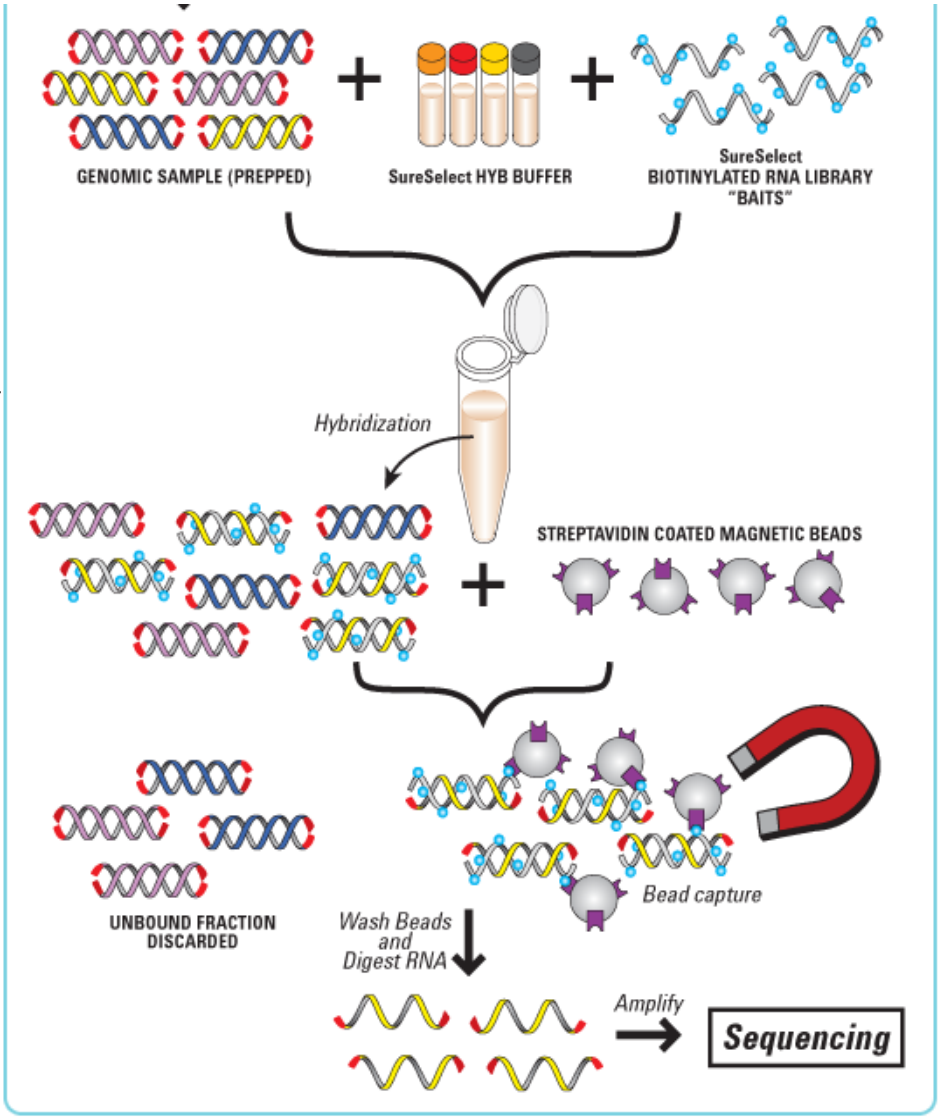
Barcoding

Cluster generation

Sequencing

Data Analysis





Biotinylated RNA library baits covers all exons annotated in the consensus CDS database as well as flanking sequence for each targeted region and small non-coding RNAs

CLINICAL EXOME SEQUENCING

Work flow :

DNA (Sheared DNA)

Library prep

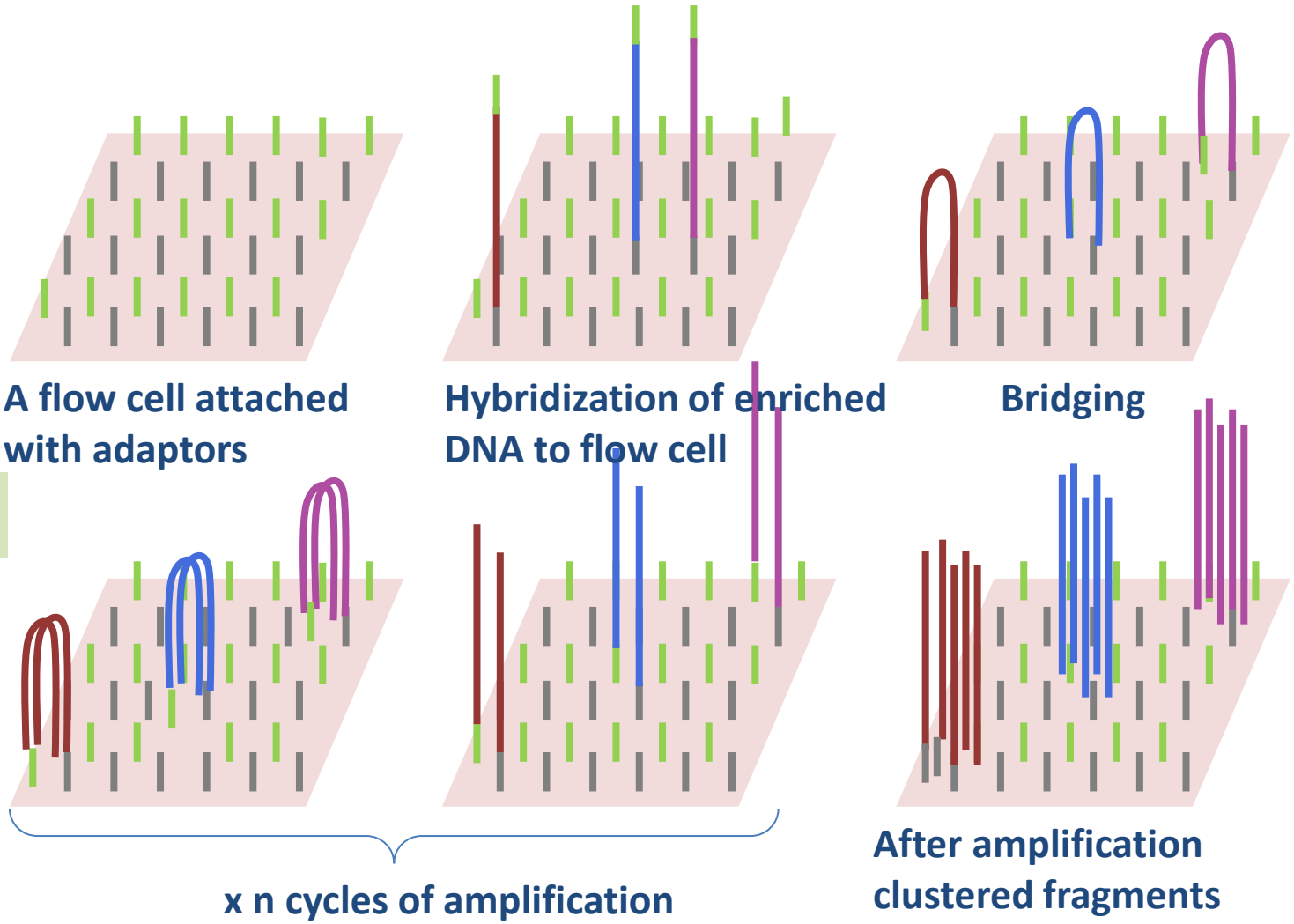
Enrichment

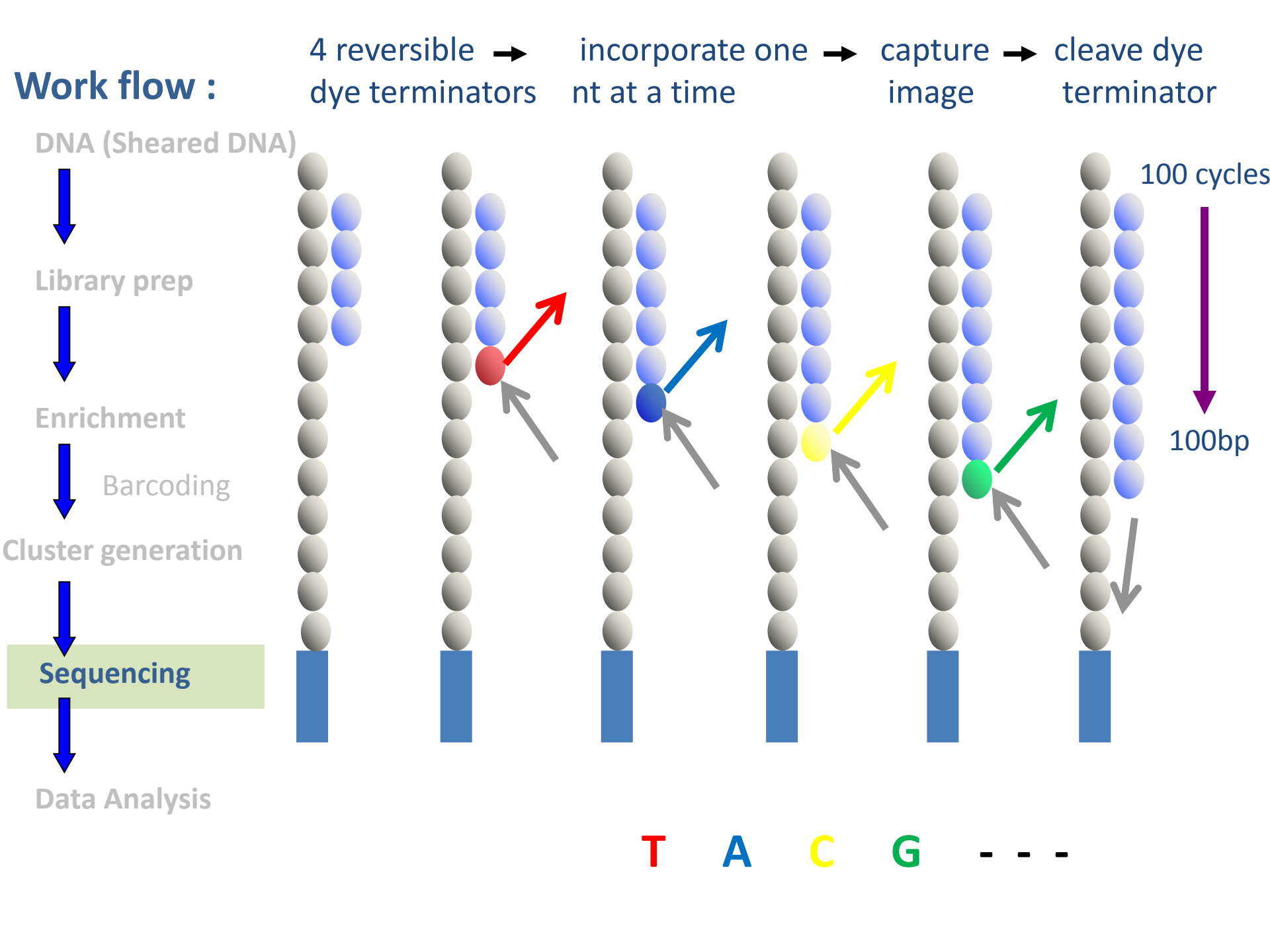
Barcoding

Cluster generation

Sequencing

Data Analysis




Work flow :
4 reversible dye terminators
incorporate one nt at a time
capture image
cleave dye terminator
DNA (Sheared DNA)
Library prep
Enrichment
Barcoding
Cluster generation
Sequencing
Data Analysis
100 cycles
100bp
T A C G - - -

Work flow :

DNA (Sheared DNA)

Library prep

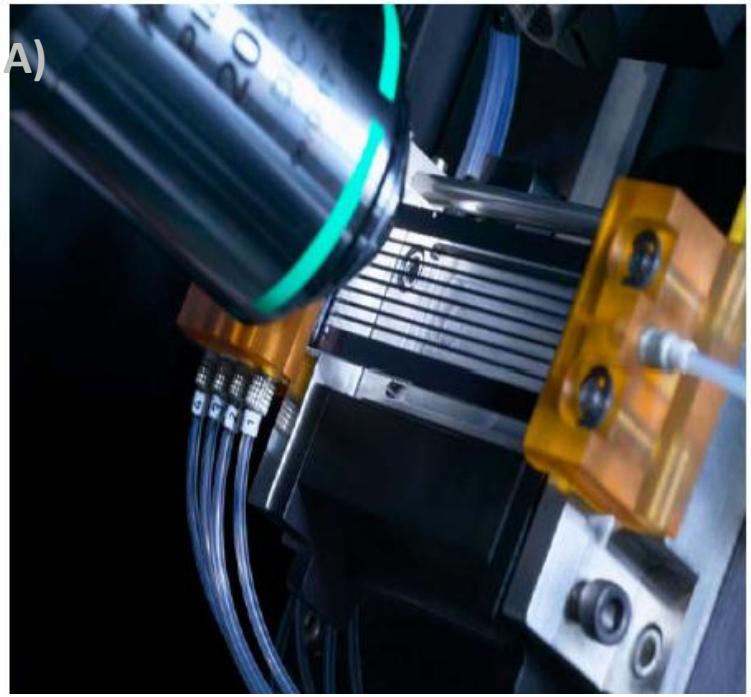
Enrichment

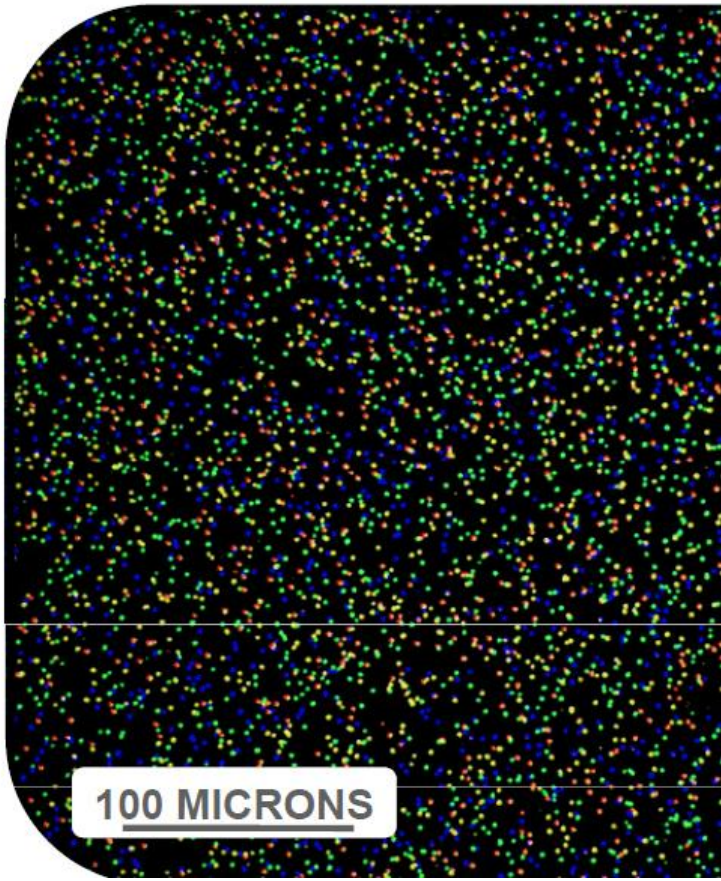
Barcoding

Cluster generation

Sequencing

Data Analysis





T G C A

Image of clusters during sequencing.

Work flow :

DNA (Sheared DNA)

Library prep

Enrichment

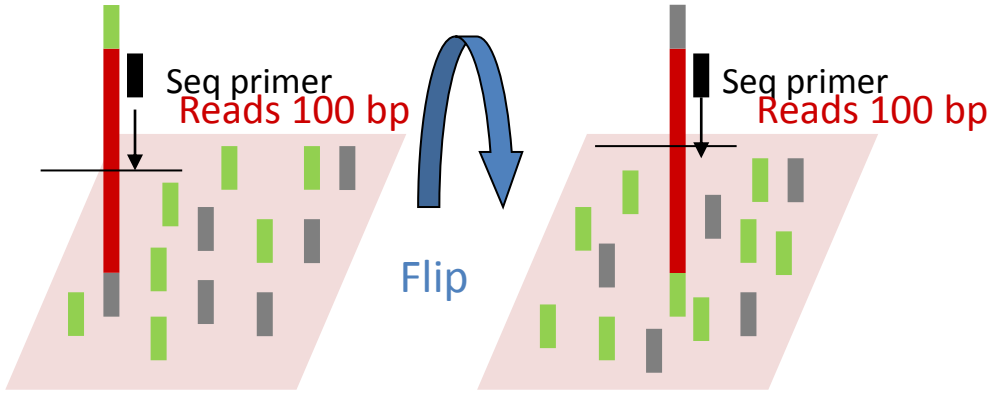
Barcoding

Cluster generation

Sequencing

Data Analysis

Paired-End Reading (2X100 bp)



Paired end reads

- **Increase read coverage per cluster**
- **More accurate reading and alignment**
- **Detect small and large insertions, deletions, inversions, and other rearrangements**

Work flow : Sequencing Data, Exon Coverage of a Gene

DNA (Sheared DNA)

Library prep

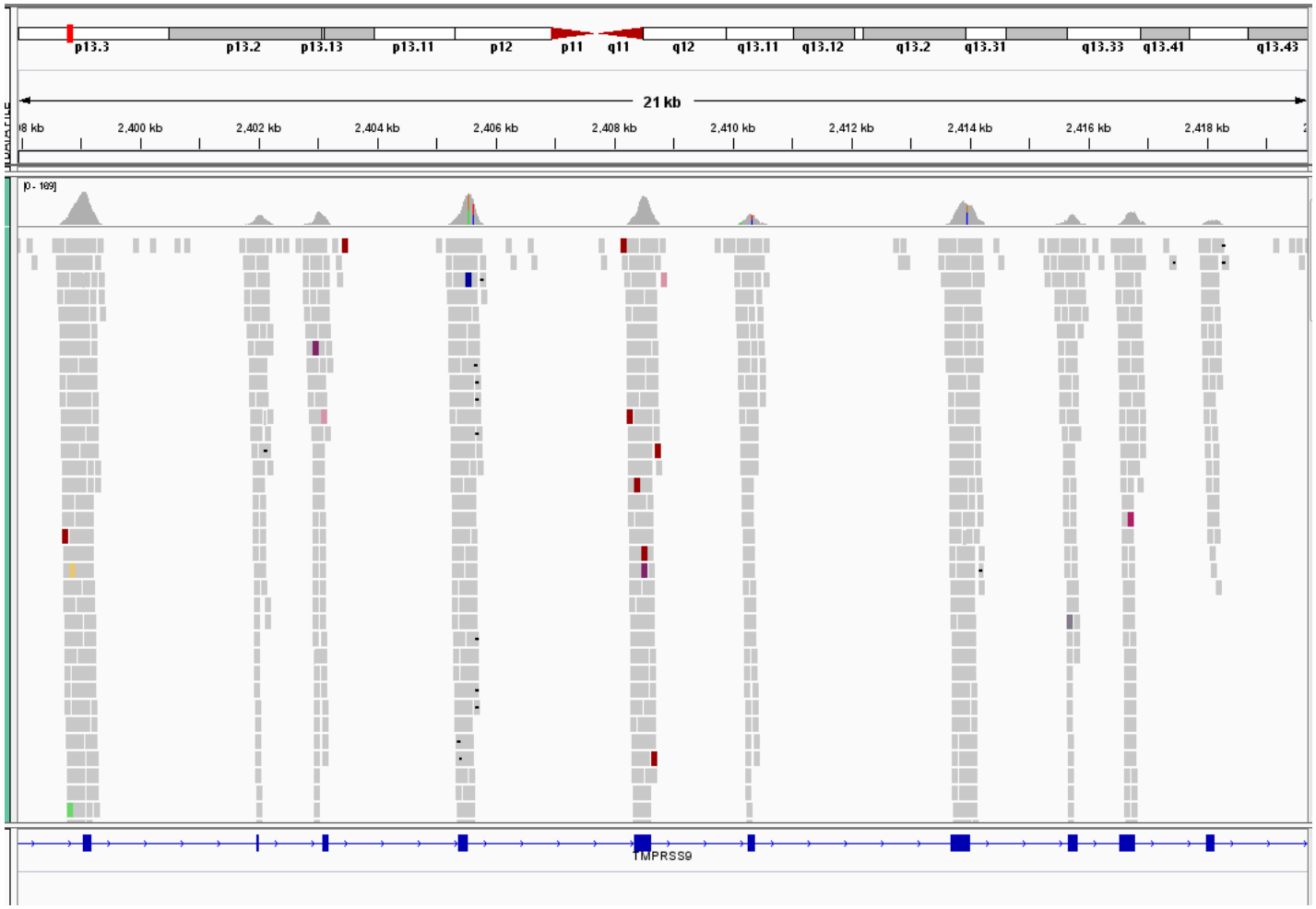
Enrichment

Barcoding

Cluster generation

Sequencing

Data Analysis



Work flow :

DNA (Sheared DNA)

Library prep

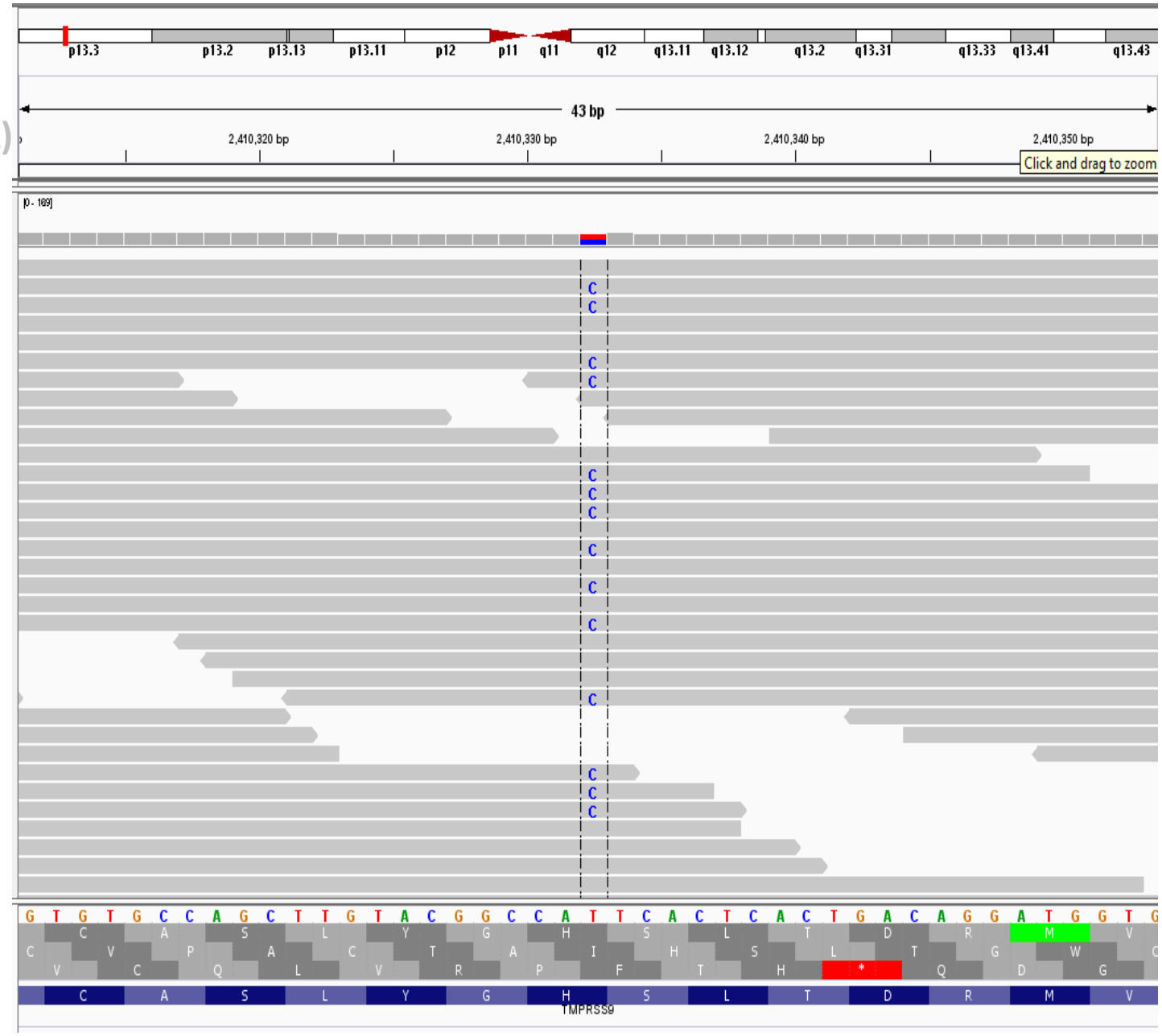
Enrichment

Barcoding

Cluster generation

Sequencing

Data Analysis



GUIDELINES/REGULATIONS
CLIA/CAP/ACMG

Next Generation Sequencing

Next Generation Sequencing (NGS) incorporates two processes: (1) the analytical wet bench process of sample and library preparation and sequence generation and (2) the bioinformatics process or pipeline of sequence alignment, annotation and variant calling. These two processes are inextricably linked as the output from each process supports the optimization of the other. The large volumes of data produced by NGS platforms put substantial demands on laboratories in terms of the requirements for documentation, validation, quality control and assurance, monitoring, data storage, as well as assessment and implementation of new technology and software releases.

Inspector Instructions:

READ	• Sampling of next generation sequencing policies and procedures • Records of wet bench processing and bioinformatics process validation • QM program records with corrective action for component failure • Sampling of exception log records

Guide validation of samples, analysis and reporting

Clinical Laboratory Standards for Next Generation Sequencing

Heidi L. Rehm, PhD[1,2], Sherri J Bale, PhD[3], Pinar Bayrak-Toydemir, PhD[4], Jonathan S Berg, MD[5], Kerry K Brown, PhD[6], Joshua L Deignan, PhD[7], Michael J Friez, PhD[8], Birgit H Funke, PhD[1,2], Madhuri R Hegde, PhD[9], Elaine Lyon, PhD[5], A Working Group of the American College of Medical Genetics and Genomics Laboratory Quality Assurance Committee

Clinical Laboratory Improvement Amendments

Assuring the Quality of Next-Generation Sequencing in Clinical Laboratory Practice

Next-generation Sequencing: Standardization of Clinical Testing (Nex-StoCT) Workgroup Principles and Guidelines

Supplementary Guidelines

American College of Medical Genetics and Genomics

ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

Robert C. Green, MD, MPH[1,2], Jonathan S. Berg, MD, PhD[3], Wayne W. Grody, MD, PhD[4-6], Sarah S. Kalia, ScM, CGC[1], Bruce R. Korf, MD, PhD[7], Christa L. Martin, PhD, FACMG[8], Amy McGuire, JD, PhD[9], Robert L. Nussbaum, MD[10], Julianne M. O'Daniel, MS, CGC[11], Kelly E. Ormond, MS, CGC[12], Heidi L. Rehm, PhD, FACMG[2,13], Michael S. Watson, MS, PhD, FACMG[14], Marc S. Williams, MD, FACMG[15], Leslie G. Biesecker, MD[16]

Direct laboratories to return with each genomic sequencing order results from 57 genes in which mutations greatly increase risk of 24 serious, but treatable diseases, even if clinicians do not suspect patients have them.

What are incidental findings?

Variants found by exome/genome sequencing , which are unrelated to the disease of interest

- majority of them are benign
- a small number of them (between 1-5) might be well-described, disease-associated mutations

Incidental Findings

The ACMG Working Group recommended that the laboratory **actively search** for the specified types of mutations in the specified genes listed in these recommendations.

Mandatory reporting known mutations for the disorders:
- Hereditary cancers,
- Marfan syndrome,
- Long QT syndrome,
- Brugada syndrome,
- Certain cardiomypathies

Patient Autonomy?

the ACMG Working Group did not favor offering the patient a preference as to whether or not to receive the minimum list of incidental findings described in these recommendations.

This may be seen to violate existing ethical norms regarding the patient's autonomy and "right not to know" genetic risk information.

Returning incidental findings in children

Recommendations for seeking and reporting incidental findings not be limited by the age of the person being sequenced.

The ethical concerns about providing children with genetic risk information about adult-onset diseases were outweighed by the potential benefit to the future health of the child and the child's parent of discovering an incidental finding where intervention might be possible.

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

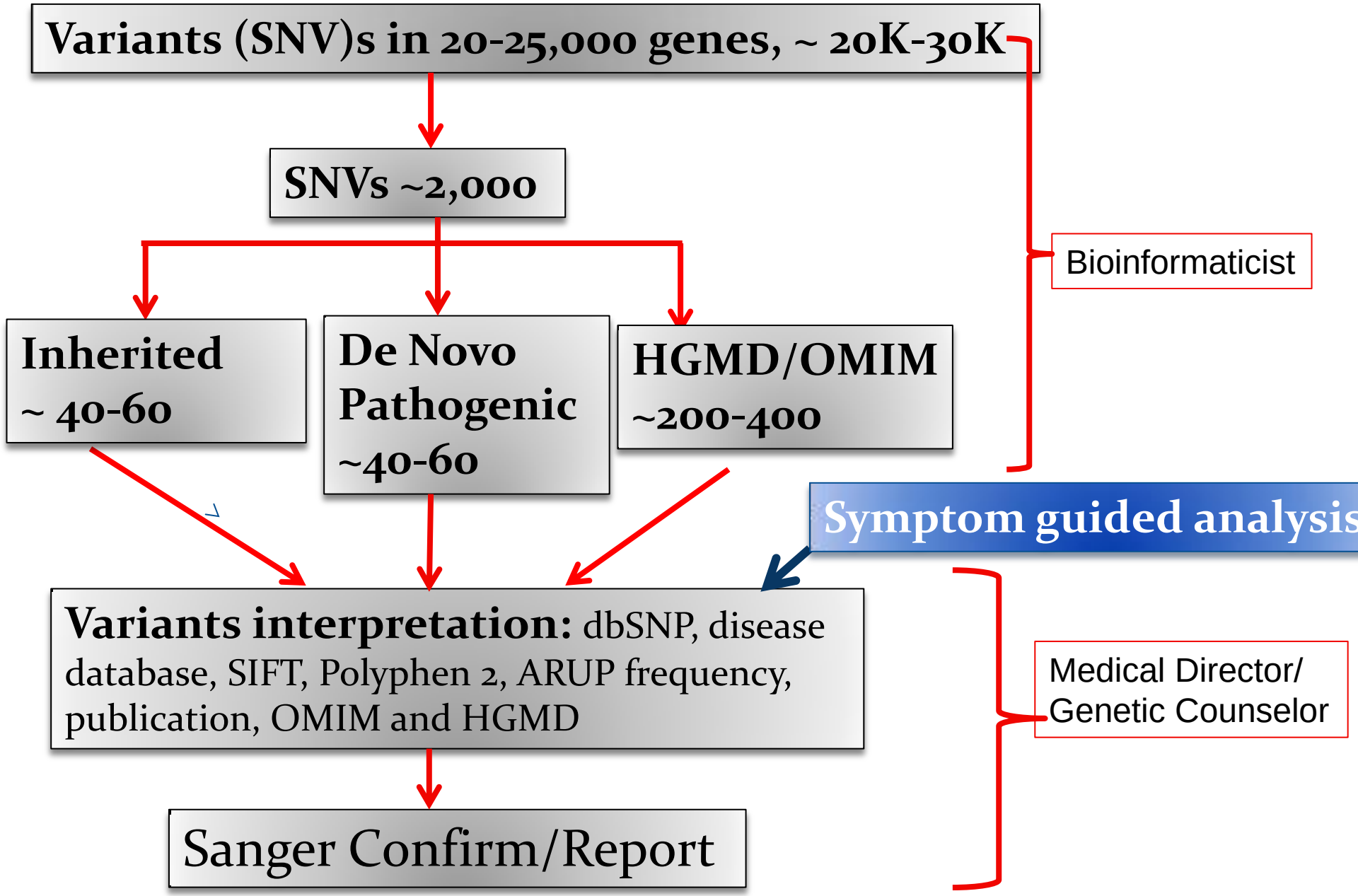
Practices and Policies of Clinical Exome Sequencing Providers: Analysis and Implications

Seema M. Jamal,[1] Joon-Ho Yu,[1] Jessica X. Chong,[1] Karin M. Dent,[2] Jessie H. Conta,[3] Holly K. Tabor,[1,4] and Michael J. Bamshad[1,5]*

	Ambry	ARUP	Baylor	Emory	GeneDx	UCLA
Name of test	Clinical Diagnostic Exome™	Exome Sequencing With Symptom-Guided Analysis	Whole Exome Sequencing	EmExome: Clinical Whole Exome Sequencing	XomeDx	Clinical Exome Sequencing
Began offering	09/2011	04/2012	10/2011	06/2012	01/2012	01/2012
Turn around time (weeks)	8–16	12–16	15	15	12–16	11–12
Method (exome capture)	Agilent SureSelect	Agilent SureSelect, NimbleGen SeqCap	NimbleGen (custom designed) VCRome 2.1	NimbleGen SeqCap	Agilent SureSelect	Agilent SureSelect
Coverage: (mean depth of coverage)	90–100X	>100X	>100X	100X	100-120X	>100X
Coverage (% target bases covered at 10)	90%	95%	>95%	96%	90–95%	95%
Variant confirmation	+ Only primary	+ Only primary	+ Primary, some secondary results	+ Primary, all secondary results	+ Only primary	+ Only primary

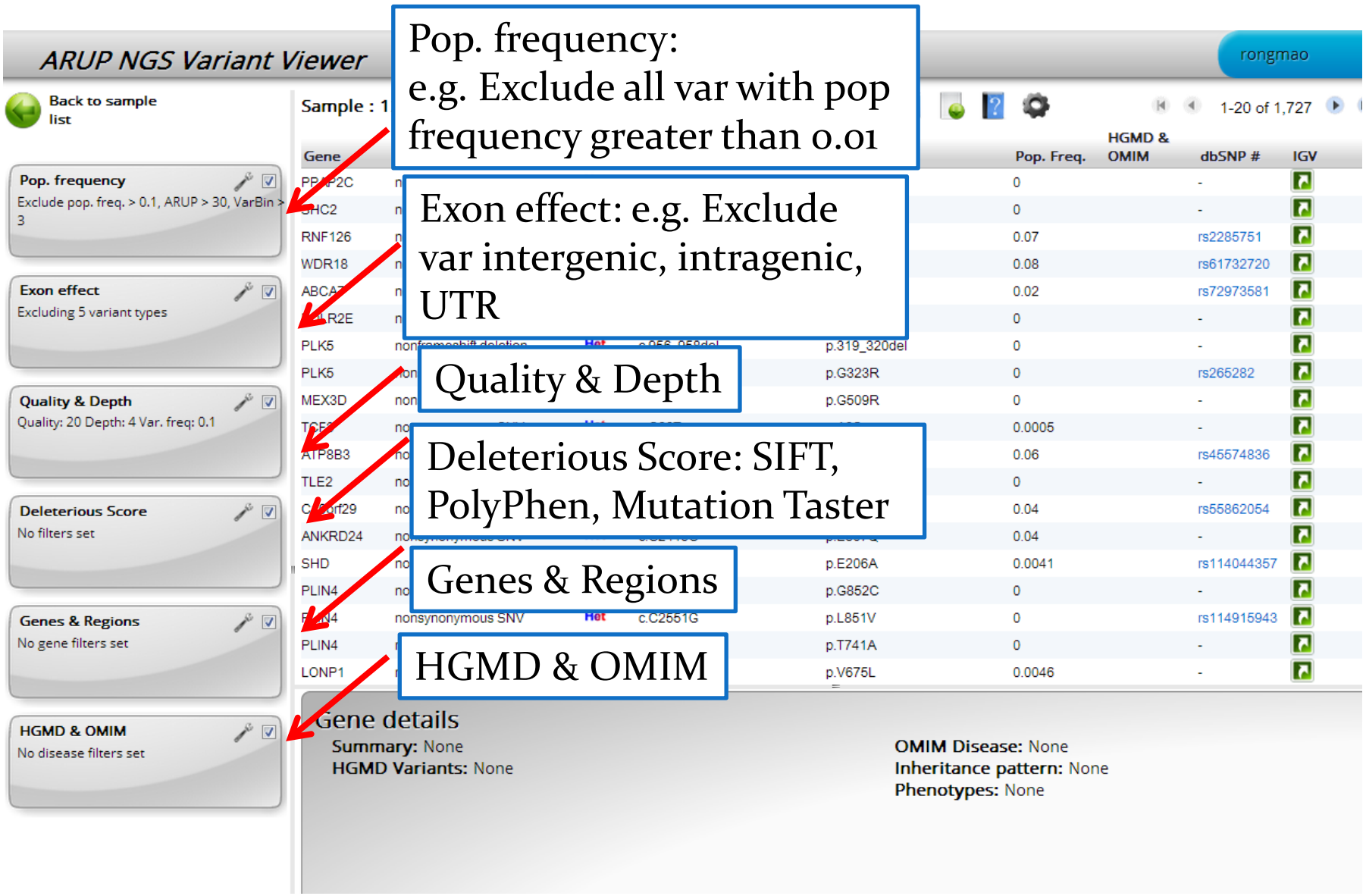
Jamal SM, Yu J-H, Chong JX, Dent KM, Conta JH, Tabor HK, Bamshad MJ. 2013. Practices and policies of clinical exome sequencing providers: Analysis and implications. Am J Med Genet Part A 9999:1–16

Exome Interp Algorithm: weekly meeting

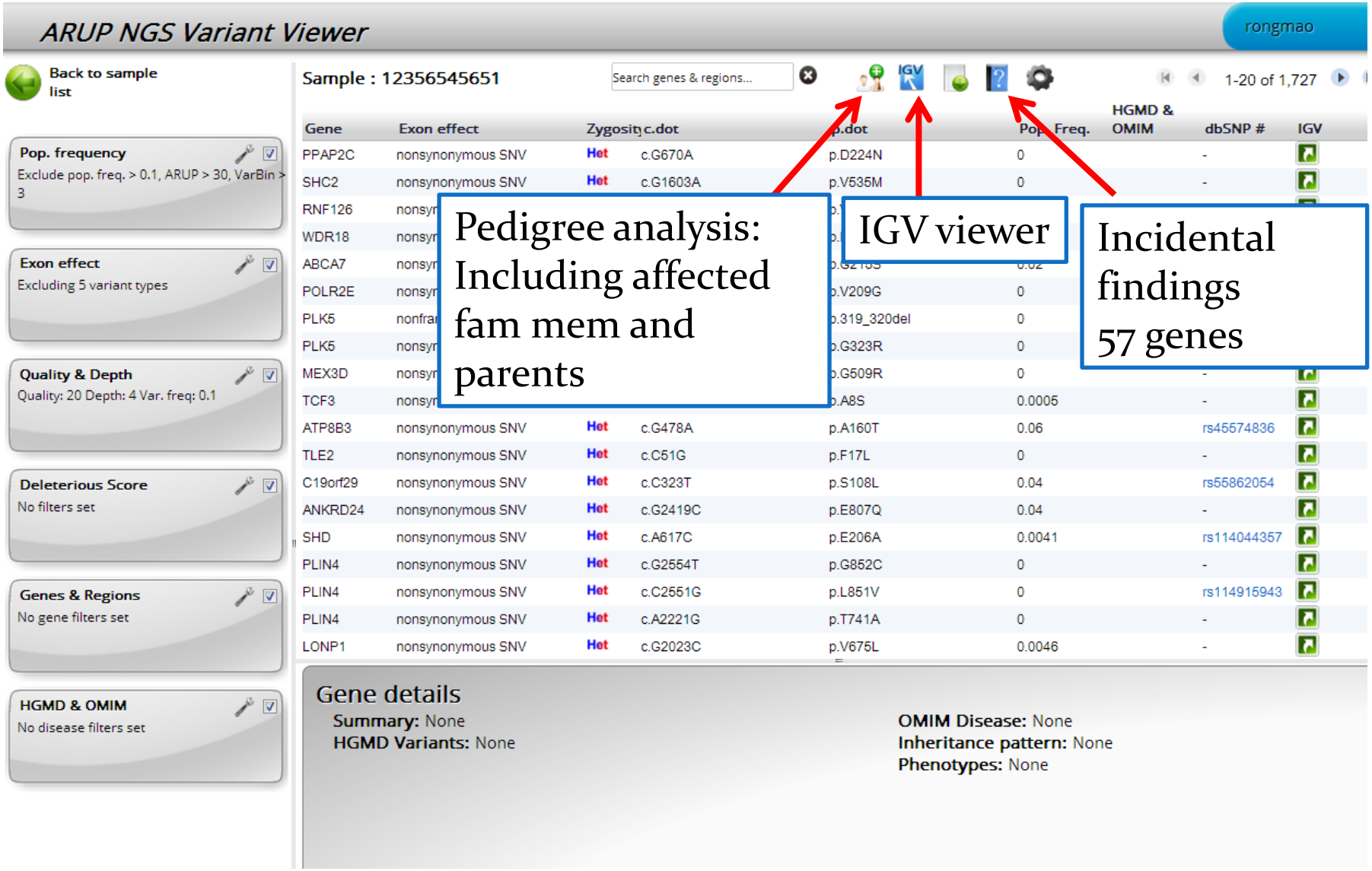


Bioinformatics Pipeline: NGS Variant Viewer

Brendan O'Fallon: Bioinformaticist at ARUP

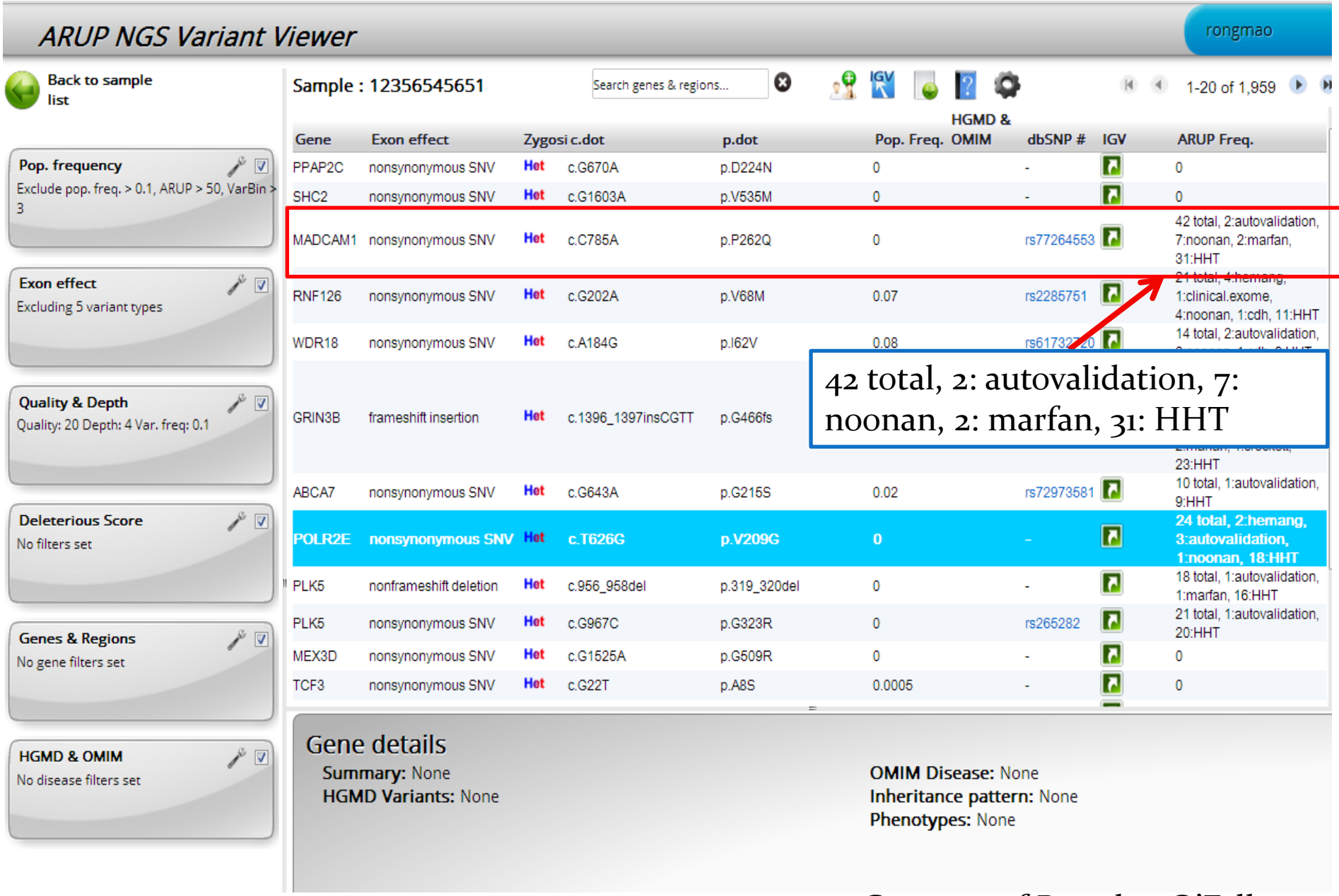


Courtesy of Brendan O'Fallon



Courtesy of Brendan O'Fallon

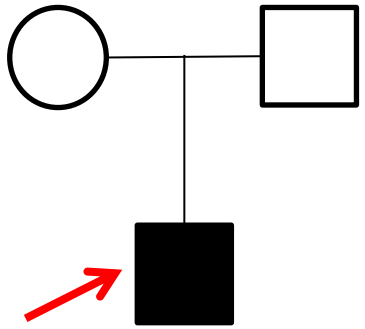
ARUP frequency:



42 total, 2: autovalidation, 7: noonan, 2: marfan, 31: HHT

Courtesy of Brendan O'Fallon

Case 1: trio



- 9 mos. boy
- Postnatal growth failure, global DD, hypotonia
- Mildly distinctive craniofacial features, dysphagia, sleep disturbance
- No fam Hx

Physical exam: global DD
Neuro/muscular
EEG, Echo
Brain MRI, Upper GI
Microarray
Metabolic evaluation
CF Panel

} Normal

Case 1: bioinformatics

Bioinformatics Data Analysis:

- Overall: 44,760
- Initial filtering criteria:
  - Remove var homo in parents: 19,688
  - Remove var freq >5%: 4,755
  - Remove synonymous and deep intronic var

- Initial filtering yielded
  - 781 missense mutations
  - 105 exonic insertions / deletions
  - 30 potential splice site variants
  - 18 stop gains / losses
  - Total: 934

Case 1: variants review

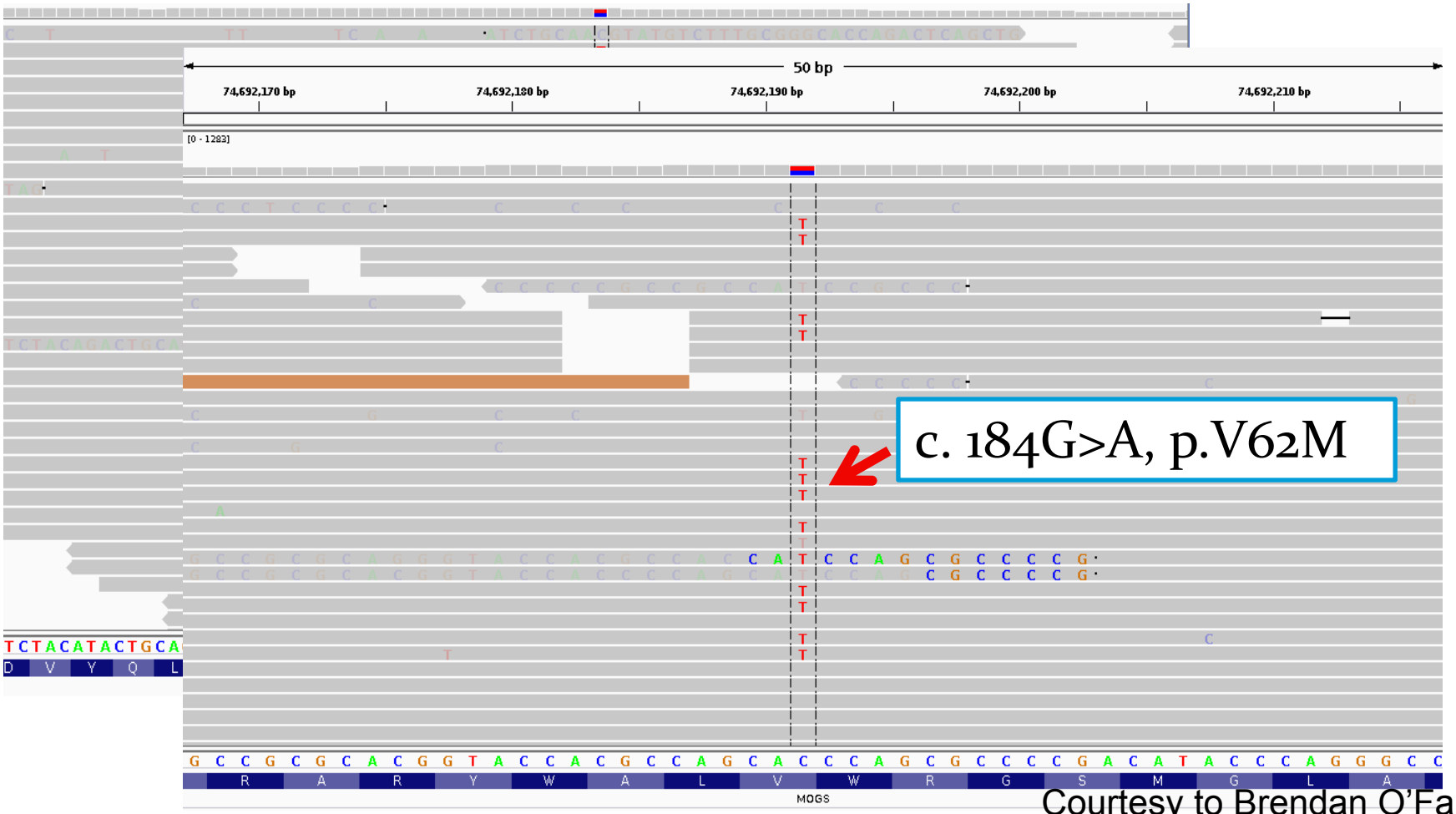
Bioinformatics Data Analysis:

- Inheritance: autosomal recessive, X-linked, de novo
- Clinical Information: patient symptoms included hypotonia and fail to thrive
- HGMD genes, Variant Ranking (Brendan O'Fallon)
- Yield: 381

- Two medical directors review the variants

Case 1: candidate gene/mutation

- MOGS gene: two missense variants V62M and V567I/Sanger confirmed, parents: Het



Courtesy to Brendan O'Fallon

Case 1: MOGS

- Autosomal Recessive
- Mutation causing Congenital glycosylation disorder type IIb
- phenotype: affect neonatal, severe hypotonia, dysmorphic features
- Biochemical assay: elevated oligosaccharides (urine)

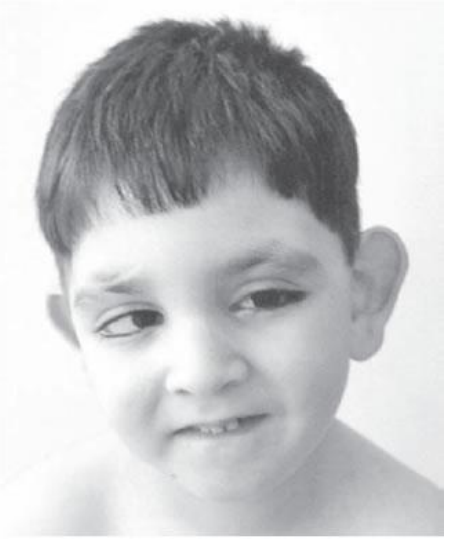
- Consultation with Dr. Longo : not likely
  - Typical features of CDG: FTT (Has), strabismus (not listed), abnormal cerebellum (not listed), inverted nipples (not listed), abnormal fat pads in the buttocks (not listed) but abnormal in the fingers.

Case 1: MOGS

- Variant c.184G>A (p.V62M): in dbSNP 2.9% freq
  - Emory University Genetics Mutation database: benign
    http://genetics.emory.edu/egl/emvclass/emvclass.php
  - classification: Benign
- Variant c.1699G>A (p.V567I): 0.9% freq, not in literature
  - SIFT: deleterious, Polyphen2: damage
  - Classification: Variant of unknown significant (VUS)

Case 1: MLL2

- De novo variant: c. 6664C>T, p. Q2222X (22X coverage)
- Kabuki syndrome
  - distinctive facial features “peculiar face”
  - Skeletal anomalies: brachydactyly, spinal deformity
  - Mild-moderate mental retardation
  - Postnatal growth deficiency



- Sanger sequencing: failed confirmation

Case 1: report

- No pathogenic mutation detected by symptom-guided analysis
- One VUS found in MOGS , V567I
- Follow up: Oligosaccharides and transferrin normal
- Lesson learned: clinical phenotype plays important role for data analysis

Case 2: Proband only

Clinical Information:

- 3 year-old female with intractable epilepsy, hypotonia, and developmental regression.

- aCGH performed at the University of Florida detected UPD9. One mutation detected in Tpp1 gene. Physician interested in evaluating "neuro" genes on Chromosomes 9 and X.

- Parental samples were not submitted.

Case 2: Bioinformatics

Bioinformatics Data Analysis:

- Initial filtering yielded
  - 1093 missense mutations
  - 93 exonic Insertions / deletions
  - 916 potential splice site variants
  - 26 stop gains / losses
  - Total: 2128

- No relatives available for filtering
- Clinical Information: Patient symptoms included epilepsy, intractable seizures, hypotonia and developmental delay
- HGMD genes, Variant Ranking (Brendan O'Fallon): Yield: 291

Case2: Alexander Disease?

- Varian in GFAP:

Gene	Variant	Inheritance	Phenotype
GFAP	c. 469G>A, p. Asp157Asn (D157N), Missense	Autosomal Dominant	Alexander Disease

- Alexander disease: AD, early onset seizures, psychomotor impairment, developmental delay, macrocephaly Dx: Brain MRI
- Contact MD, normal MRI
- Variant also in 0.5% population

Case2: Report

- 2 mutations and 1 VUS detected

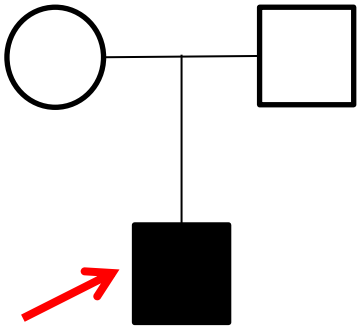
Gene	Var.	Zygosity	Inheritance	Var. Category	Phenotype
GRIA3	c.381_382insG p.GLy127 fs	Homo	X-linked	Pathogenic	X-linked developmental delay
TPP1	c.196C>T p.Q66X	Hetero	Recessive	Pathogenic	Neuronal ceroid lipofuscinosis type 2
GABRG2	c.1204G>A p.A402T	Hetero	Dominant	Variant of unknown significant	Neuortransmitter Generalized epilepsy and febrile seizures

Case2: Follow up

- Parental specimens received:
  - GRIA3c.381_382insG (p.GLy127 fs): Homo- mother and hemi-father : not causative for patient pheno
  - TPP1 c.196C>T (p.Q66X): Het-father
  - GABR2 c.1204G>A (p. A402T): Het-father, AD not causative

- Lesson learned: proband only will be difficult for data analysis/interpretation and lower the positive yield

Case 3: trio



- 11 yrs. male
- Globe DD, short stature, feeding problem require G-tube, hypotonia, hypoplastic genitalia, pectus carinatum, behavioral problems, broad deviated thumbs and great toes, dysmorphic facial features including a flat face, posteriorly rotated ears
- Fam history, NO

CMA SNP
FISH for DiGeorge, Prader-Willi, subtelomeric rearrangements, 16p for Rubinstein-Taybi
Metabolic screening wit UOA/AA, urine MPSs
Karyotype , 46, XY
EEG and Brain MRI

Normal

Case 3: Bioinformatics/Variant review

Bioinformatics Data Analysis:

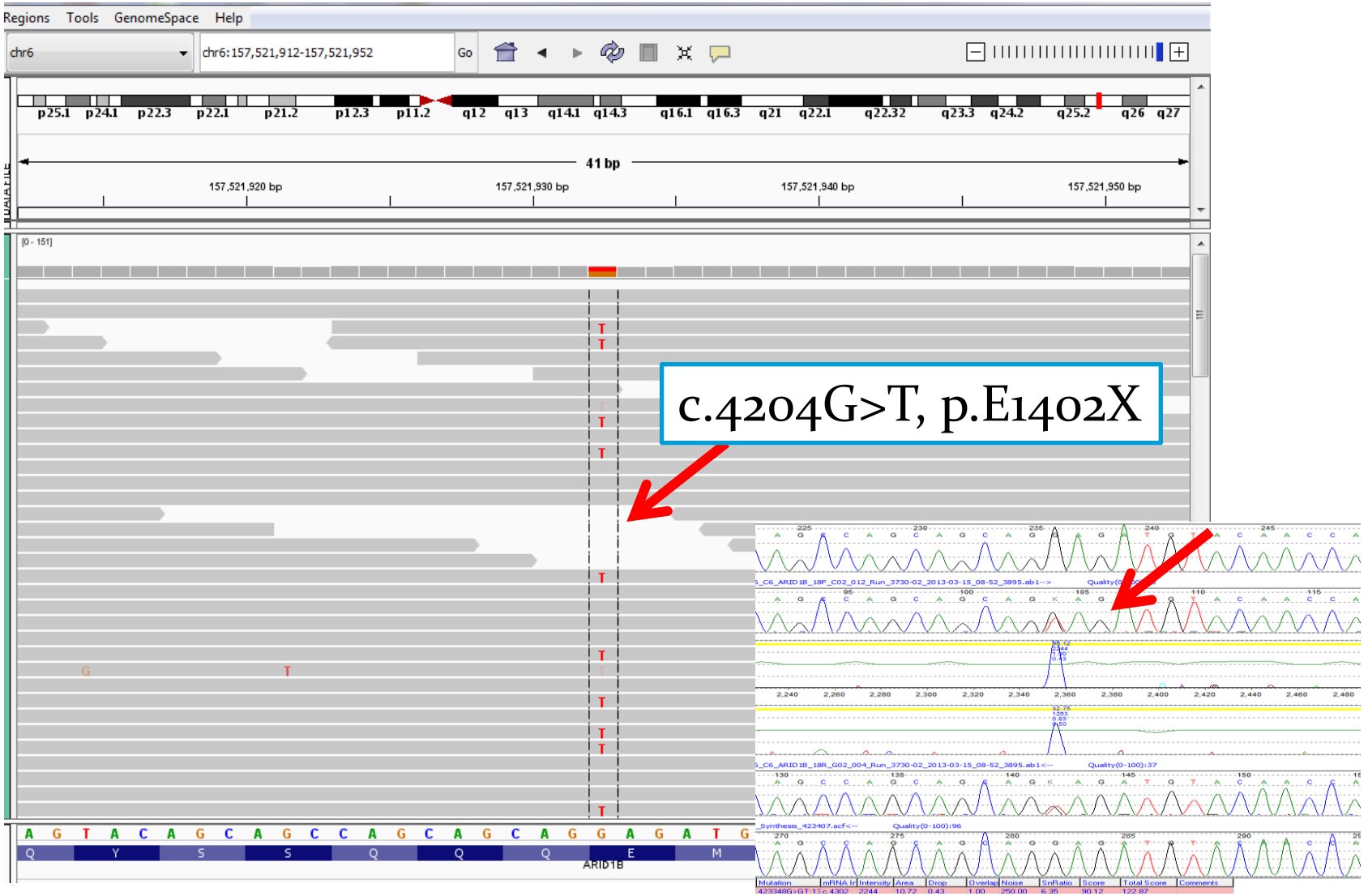
- Same initial filtering criteria used

- Inheritance: autosomal recessive, X-linked, de novo
- Clinical Information: patient symptoms included Globe DD, short stature, feeding problem, hypotonia, hypoplastic genitalia, behavioral problems, broad deviated thumbs and great toes, flat face, posteriorly rotated ears

- HGMD genes, Variant Ranking (Brendan O'Fallon)

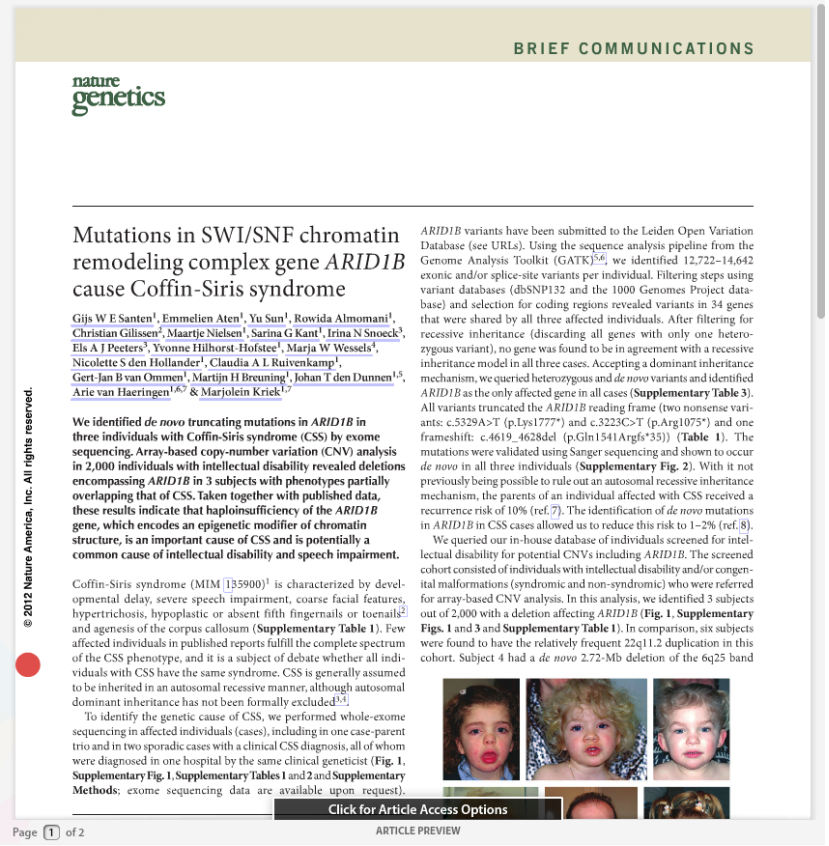
Case 3: Candidate Gene/mutation

- ARID1B gene: de novo variant, c.4204G>T, p.E1402X



Case 3: ARID1B

- ARID1B: At-rich interaction domain-containing protein 1B



BRIEF COMMUNICATIONS

nature genetics

Mutations in SWI/SNF chromatin remodeling complex gene *ARID1B* cause Coffin-Siris syndrome

Gijs W E Santen[1], Emmelien Aten[1], Yu Sun[1], Rowida Almomani[1], Christian Gilissen[2], Maartje Nielsen[1], Sarina G Kant[1], Irina N Snoeck[3], Els A J Peeters[3], Yvonne Hilhorst-Hofstee[1], Marja W Wessels[4], Nicolette S den Hollander[1], Claudia A L Ruivenkamp[1], Gert-Jan B van Ommen[1], Martijn H Breuning[1], Johan T den Dunnen[1,5], Arie van Haeringen[1,6,7] & Marjolein Kriek[1,7]

© 2012 Nature America, Inc. All rights reserved.

We identified *de novo* truncating mutations in *ARID1B* in three individuals with Coffin-Siris syndrome (CSS) by exome sequencing. Array-based copy-number variation (CNV) analysis in 2,000 individuals with intellectual disability revealed deletions encompassing *ARID1B* in 3 subjects with phenotypes partially overlapping that of CSS. Taken together with published data, these results indicate that haploinsufficiency of the *ARID1B* gene, which encodes an epigenetic modifier of chromatin structure, is an important cause of CSS and is potentially a common cause of intellectual disability and speech impairment.

Coffin-Siris syndrome (MIM 135900)[1] is characterized by developmental delay, severe speech impairment, coarse facial features, hypertrichosis, hypoplastic or absent fifth fingernails or toenails[2] and agenesis of the corpus callosum (**Supplementary Table 1**). Few affected individuals in published reports fulfill the complete spectrum of the CSS phenotype, and it is a subject of debate whether all individuals with CSS have the same syndrome. CSS is generally assumed to be inherited in an autosomal recessive manner, although autosomal dominant inheritance has not been formally excluded[3,4].

To identify the genetic cause of CSS, we performed whole-exome sequencing in affected individuals (cases), including in one case-parent trio and in two sporadic cases with a clinical CSS diagnosis, all of whom were diagnosed in one hospital by the same clinical geneticist (**Fig. 1**, **Supplementary Fig. 1**, **Supplementary Tables 1** and **2** and **Supplementary Methods**; exome sequencing data are available upon request). *ARID1B* variants have been submitted to the Leiden Open Variation Database (see URLs). Using the sequence analysis pipeline from the Genome Analysis Toolkit (GATK)[5,6], we identified 12,722–14,642 exonic and/or splice-site variants per individual. Filtering steps using variant databases (dbSNP132 and the 1000 Genomes Project database) and selection for coding regions revealed variants in 34 genes that were shared by all three affected individuals. After filtering for recessive inheritance (discarding all genes with only one heterozygous variant), no gene was found to be in agreement with a recessive inheritance model in all three cases. Accepting a dominant inheritance mechanism, we queried heterozygous and *de novo* variants and identified *ARID1B* as the only affected gene in all cases (**Supplementary Table 3**). All variants truncated the *ARID1B* reading frame (two nonsense variants: c.5329A>T (p.Lys1777*) and c.3223C>T (p.Arg1075*) and one frameshift: c.4619_4628del (p.Gln1541Argfs*35)) (**Table 1**). The mutations were validated using Sanger sequencing and shown to occur *de novo* in all three individuals (**Supplementary Fig. 2**). With it not previously being possible to rule out an autosomal recessive inheritance mechanism, the parents of an individual affected with CSS received a recurrence risk of 10% (ref. 7). The identification of *de novo* mutations in *ARID1B* in CSS cases allowed us to reduce this risk to 1–2% (ref. 8).

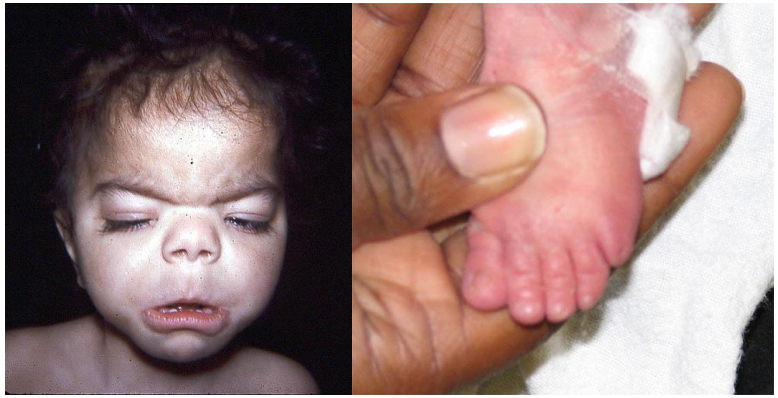
We queried our in-house database of individuals screened for intellectual disability for potential CNVs including *ARID1B*. The screened cohort consisted of individuals with intellectual disability and/or congenital malformations (syndromic and non-syndromic) who were referred for array-based CNV analysis. In this analysis, we identified 3 subjects out of 2,000 with a deletion affecting *ARID1B* (**Fig. 1**, **Supplementary Figs. 1** and **3** and **Supplementary Table 1**). In comparison, six subjects were found to have the relatively frequent 22q11.2 duplication in this cohort. Subject 4 had a *de novo* 2.72-Mb deletion of the 6q25 band

Click for Article Access Options

Santen et al, 2012, Nature Genetics:

"de novo truncated mutations in ARID1B gene in three individuals with Coffin-Siris syndrome"

Case 3: Coffin-Siris



- Globe developmental delay
- Short stature
- Feeding difficulties
- Hypotonia
- Moderate to severe learning difficulties
- Broad thumbs and toes
- Posterior rotated ears

- Mostly AR, can also be sporadic or AD

Case 3: Report

- One pathogenic mutation that is predicted to be causative to the patient's symptoms was detected

Gene	Var.	Zygosity	Inheritance	Var. Category	Phenotype
ARID1B	c.4204G>T p.E1402X	Hetero	De novo	Pathogenic	Coffin Siris syndrome

Conclusion

- Clinical exome sequencing has a great potential for diagnosing diseases of unknown etiology; possible leading to improve treatment and patient care.
- Quality control measures, data analysis and reporting of incidental findings will continue to evolve and improve.
- Exome interpretation is optimally performed by including bioinformaticians, geneticists and clinicians

Acknowledgement

ARUP R&D

- Whitney Donahue
- Shale Dames
- Brendan O'Fallon

University of Utah

- Nicola Longo
- Alan Rope

ARUP Genomics Lab

- Ana Hooker
- Jennifer Stocks
- Tyler Wayman
- Marc Singleton
- Lisa Robles
- Josh Raney

ARUP Genetics Counselors

- Chris Miller
- Patti Krautscheid

ARUP Institute for Clinical & Experimental Pathology

ARUP Laboratories