ISCA: Sharing data for knowledge generation and improved clinical care

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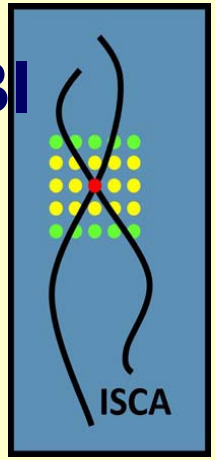
ISCA Consortium
(International Standards for Cytogenomic Arrays)

- Established in 2007 and now includes >150 clinical laboratories worldwide
- The goals of the ISCA Consortium include:
  - standardization for genotype and phenotype data
  - create evidence-base for data interpretation
  - publicly available databases through NCBI for research and clinical communities
- Goal >200,000 cases by 2012

http://iscaconsortium.org/



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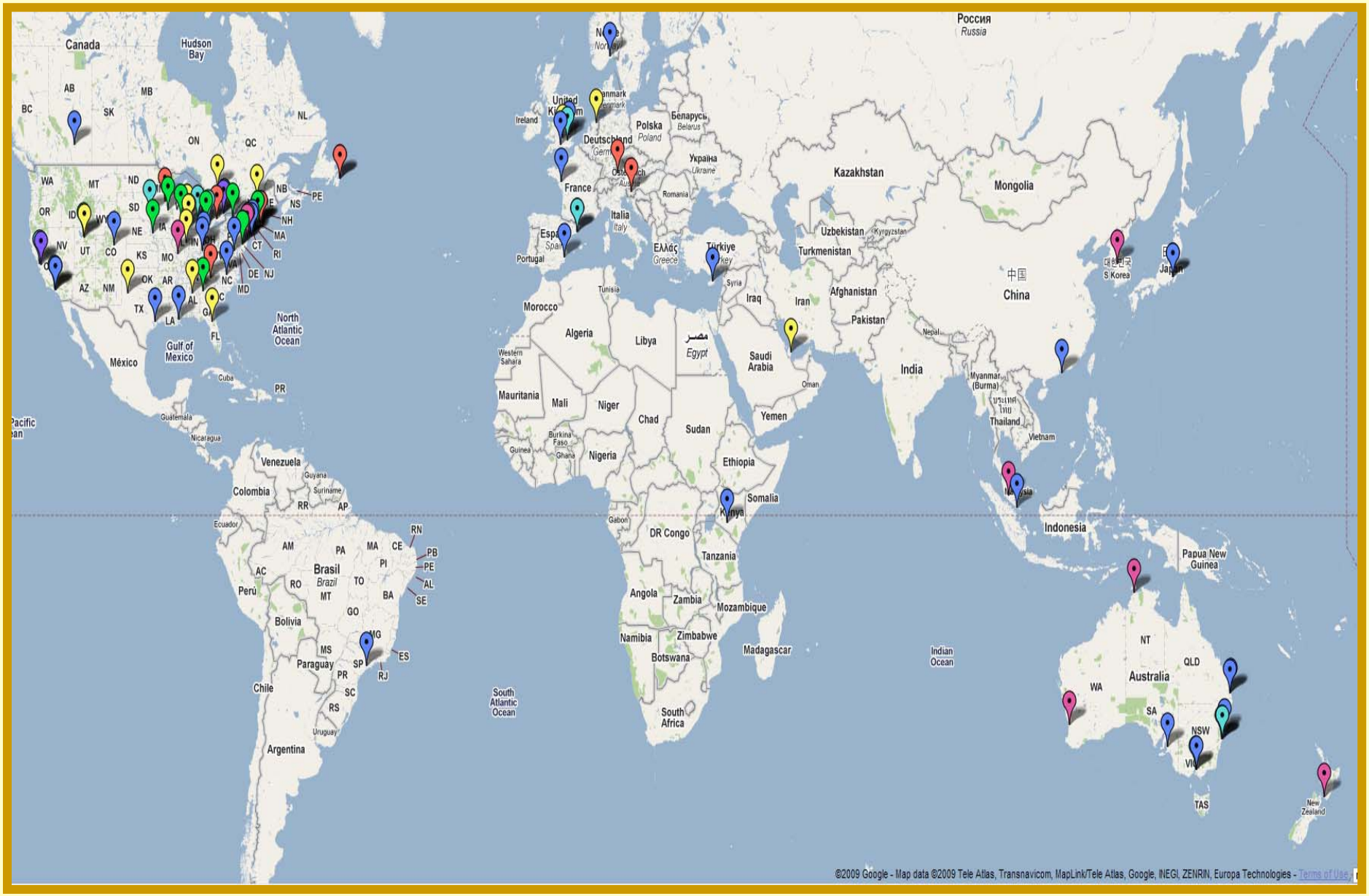
>150 International ISCA Laboratories



Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies

David T. Miller,[1,*] Margaret P. Adam,[2,3] Swaroop Aradhya,[4] Leslie G. Biesecker,[5] Arthur R. Brothman,[6] Nigel P. Carter,[7] Deanna M. Church,[8] John A. Crolla,[9] Evan E. Eichler,[10] Charles J. Epstein,[11] W. Andrew Faucett,[2] Lars Feuk,[12] Jan M. Friedman,[13] Ada Hamosh,[14] Laird Jackson,[15] Erin B. Kaminsky,[2] Klaas Kok,[16] Ian D. Krantz,[17] Robert M. Kuhn,[18] Charles Lee,[19] James M. Ostell,[8] Carla Rosenberg,[20] Stephen W. Scherer,[21] Nancy B. Spinner,[17] Dimitri J. Stavropoulos,[22] James H. Tepperberg,[23] Erik C. Thorland,[24] Joris R. Vermeesch,[25] Darrel J. Waggoner,[26] Michael S. Watson,[27] Christa Lese Martin,[2] and David H. Ledbetter[2,*]

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"Our recommendation based on current evidence is to offer CMA as the first-tier genetic test, in place of G-banded karyotype, for patients with unexplained DD/ID, ASD, or MCA." ISCA Consortium

Yield for clinically significant CNVs is 15-20%.
May impact prognosis, identify and *direct management of medical co-morbidities*, recurrence risk counseling).

Published September 2010

Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities

Melanie Manning, MD, MS FACMG[1] and Louanne Hudgins, MD, FACMG[1]
For the Professional Practice and Guidelines Committee

Recommendations:

1. Cytogenetic microarray (CMA) testing for copy number variation (CNV) is recommended as a first-line test in the initial postnatal evaluation of individuals with the following:
   A. Multiple anomalies not specific to a well-delineated genetic syndrome
   B. Apparently non-syndromic developmental delay/intellectual disability
   C. Autism spectrum disorders
2. Further determination of the use of CMA testing for the evaluation of the child with growth retardation, speech delay, and other less-well studied indications is recommended, particularly via prospective studies and aftermarket analysis.
3. Appropriate follow up is recommended in cases of chromosome imbalance identified by CMA, to include cytogenetic/FISH studies of the patient, parental evaluation, and clinical genetic evaluation and counseling.

CNV data from routine Clinical Testing

- 10s-100s thousands cases analyzed/year on routine, fee-for-service basis (reimbursed by healthcare payors)
- More CNV data generated during the course of routine patient care (for free!) than in all research studies (although lower resolution)
  - same could be true for DNA sequencing data in near future
- How do we capture and leverage this data for knowledge generation re: functional and clinical significance of CNVs?

Pathogenic vs. Benign Imbalances

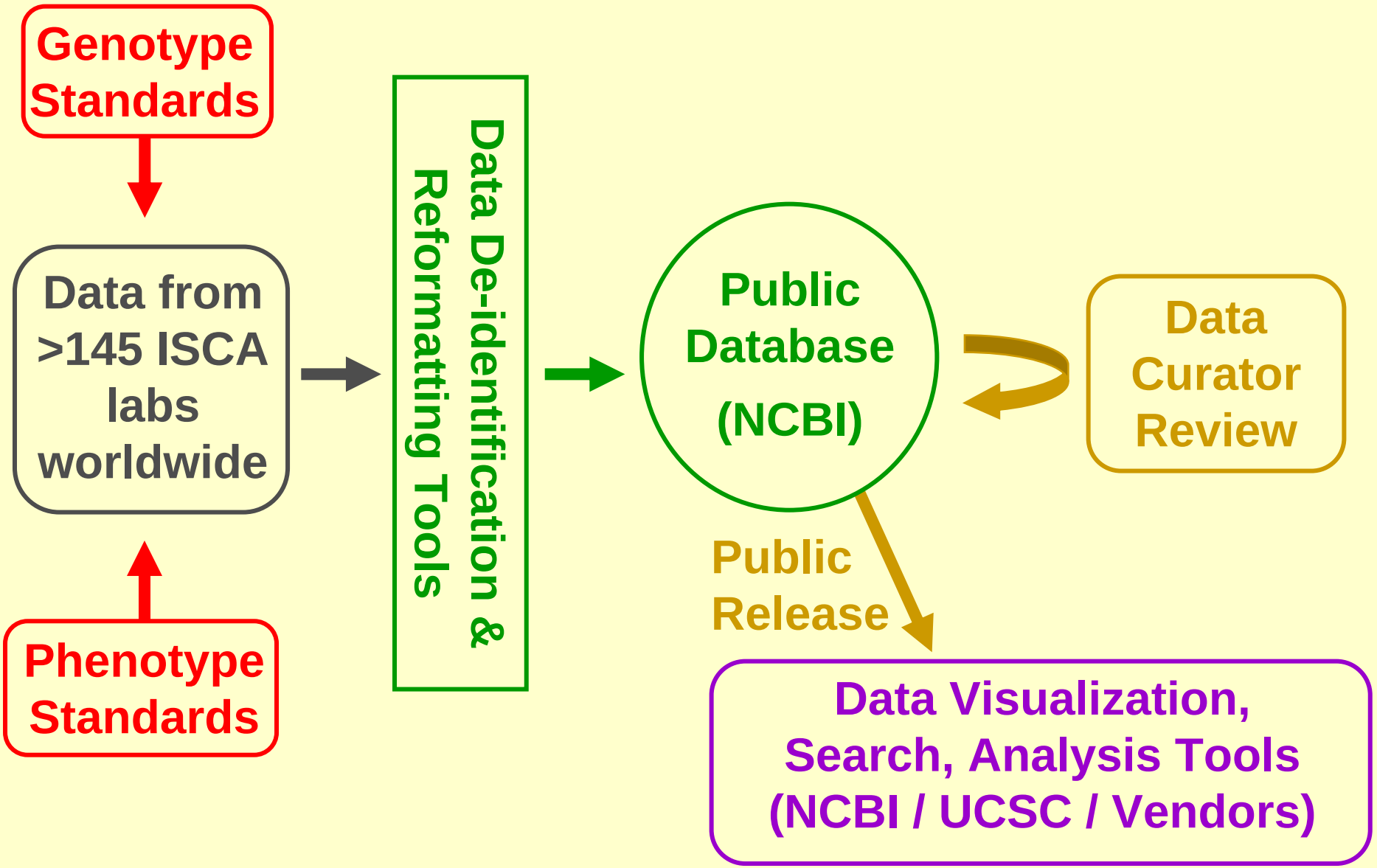
1. **Evidence from literature/databases**
   - known del/dup or Mendelian disorders
     OMIM, DECIPHER
   - known CNV in normal population
     DGV, dbVar
   - comparison with patient population data, case reports
     PubMed, DECIPHER, ISCA

Need a lot more data!!!

2. **Genomic/Gene Content**
   - correlates with size and location
     UCSC, Ensembl
3. **Inherited or *de novo***

Clinical Judgment (significant variability)

CNV Atlas for Human Development
(NICHD GO Grant 10/1/09 - 9/30/11)



The International Standards For Cytogenomic Arrays Consortium

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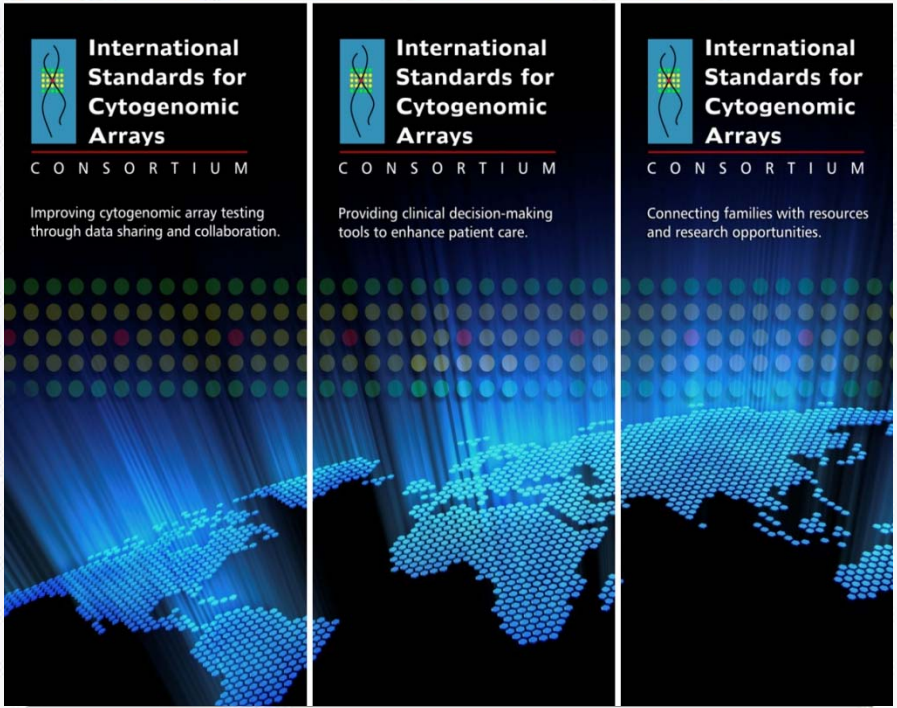
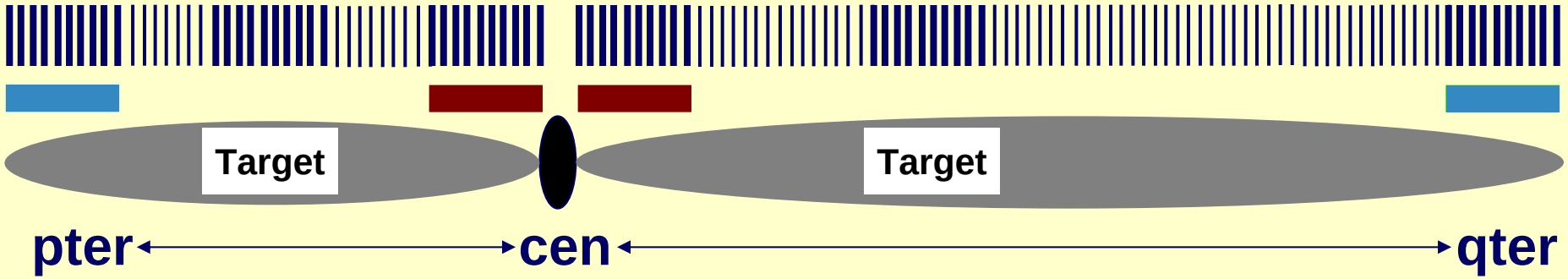
ISCA Consortium and Public Database

The International Standards for Cytogenomic Arrays (ISCA) Consortium is a rapidly growing group of clinical cytogenetics and molecular genetics laboratories committed to improving quality of patient care related to clinical genetic testing using new molecular cytogenetic technologies including array comparative genomic hybridization (aCGH) and quantitative SNP analysis by microarrays or bead chip technology.

The ISCA database contains whole genome array data from a subset of the ISCA Consortium clinical diagnostic laboratories. Array analysis was carried out on individuals with phenotypes including intellectual disability, autism, and developmental delay.



Whole-genome plus Targeted Array Design



Resolution

- Telomere FISH clone
- Unique centromere FISH clone
- Known clinically relevant targets

~20 - 50 kb

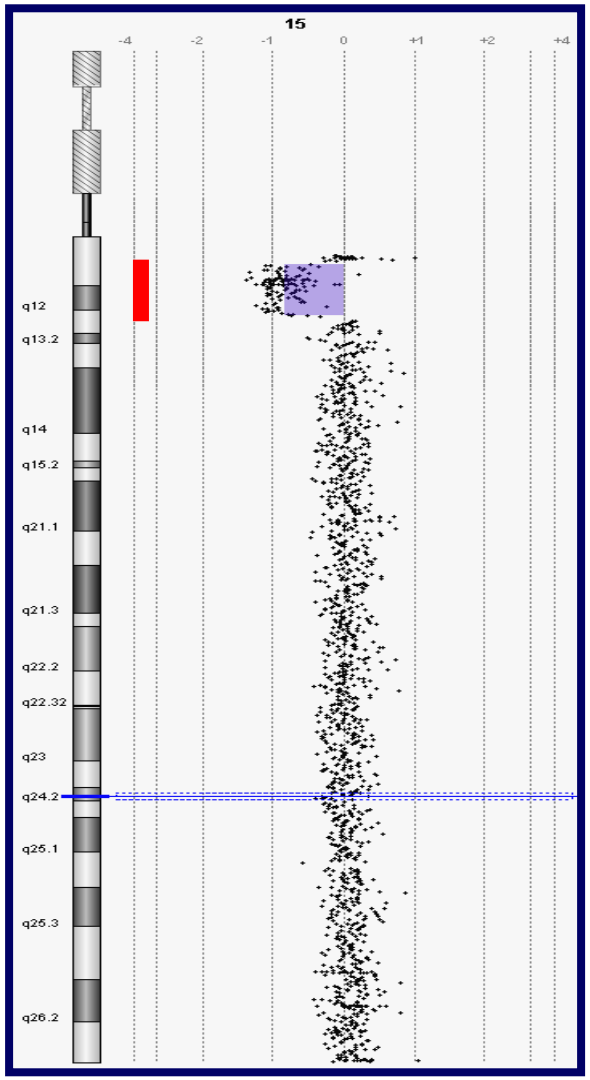
- ~25, 35 or 75 kb interval backbone (corresponds to 180K, 105K, 44K)

~100 - 250 kb

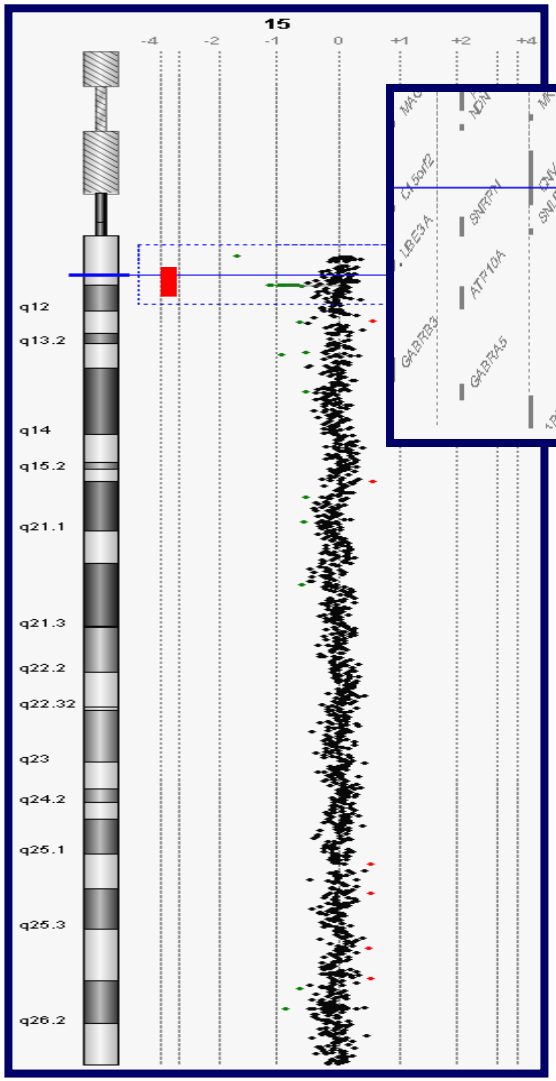
Baldwin et al., Genet Med 2008

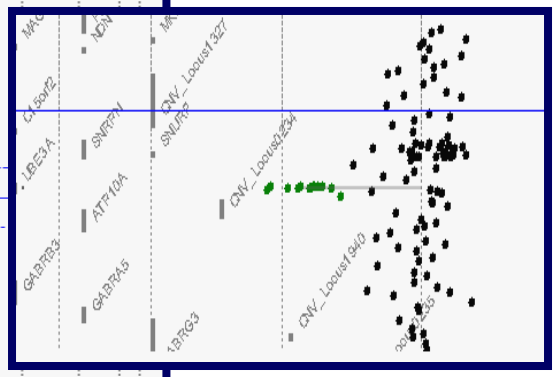
Targeted Coverage: PWS/AS Region

PWS/AS deletion



Atypical deletion

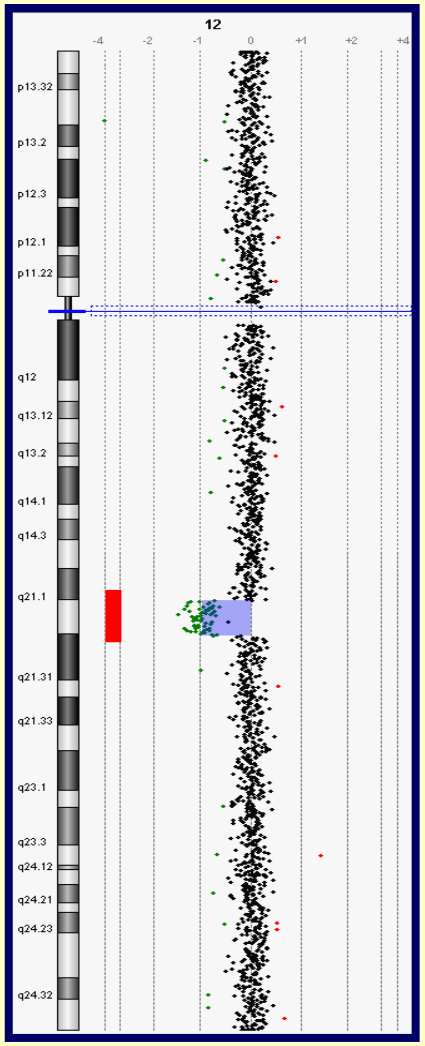




UBE3A
45 kb loss

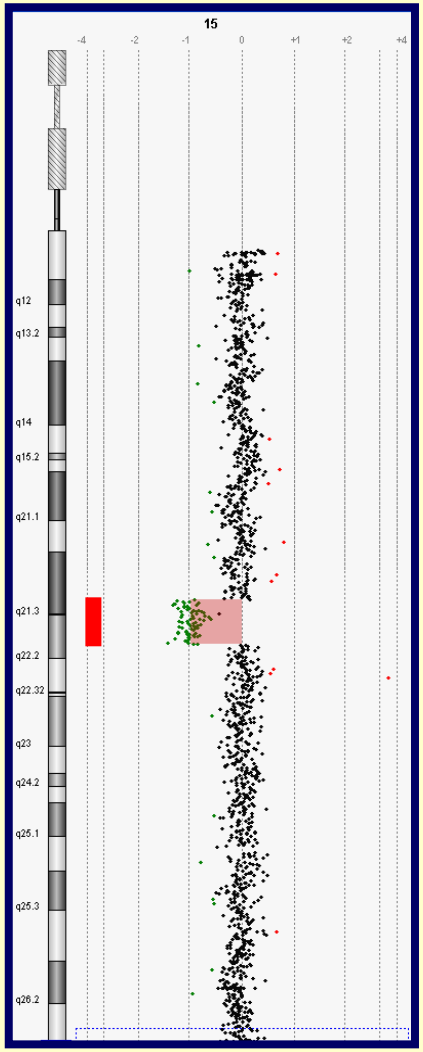
Whole Genome Coverage

Case 1



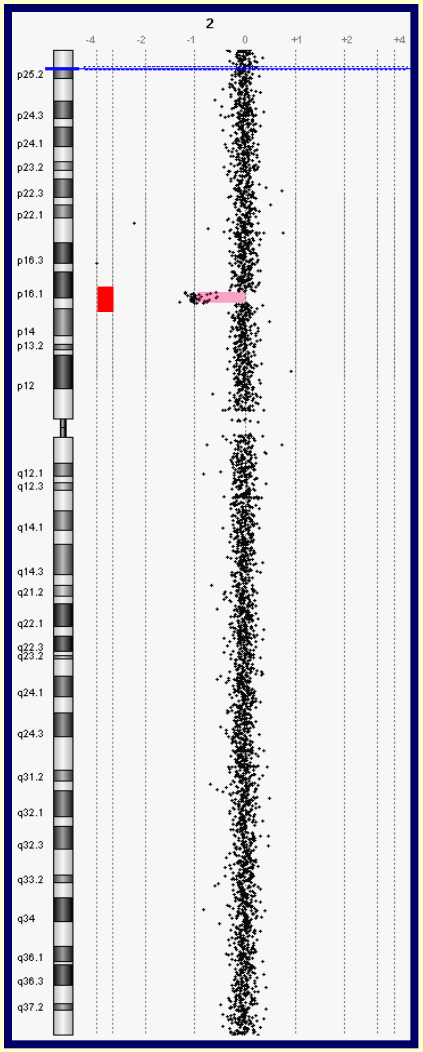
12q: 4.7 Mb deletion
~11 known genes

Case 2



15q: 4.5 Mb deletion
~21 known genes

Case 3



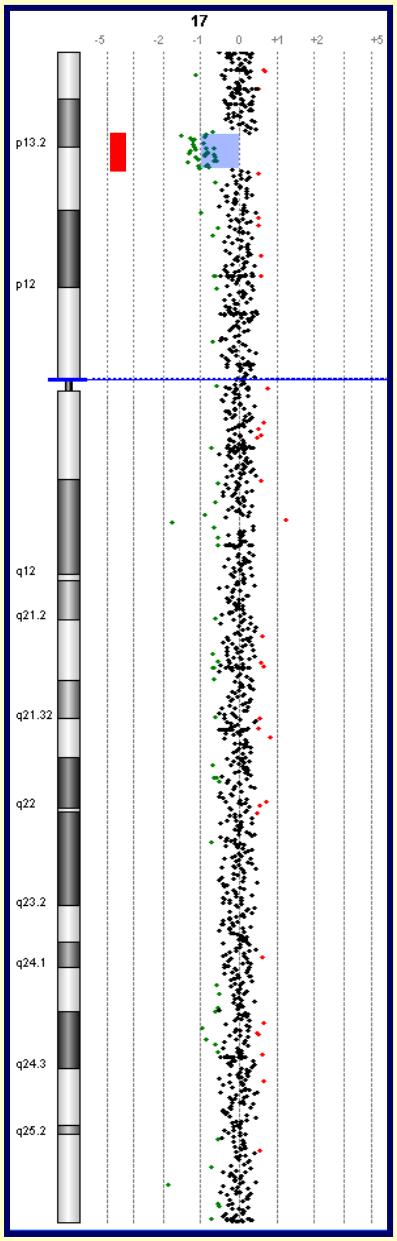
2p: 3.0 Mb deletion
~ 12 known genes

Case 11

Referring Dx:

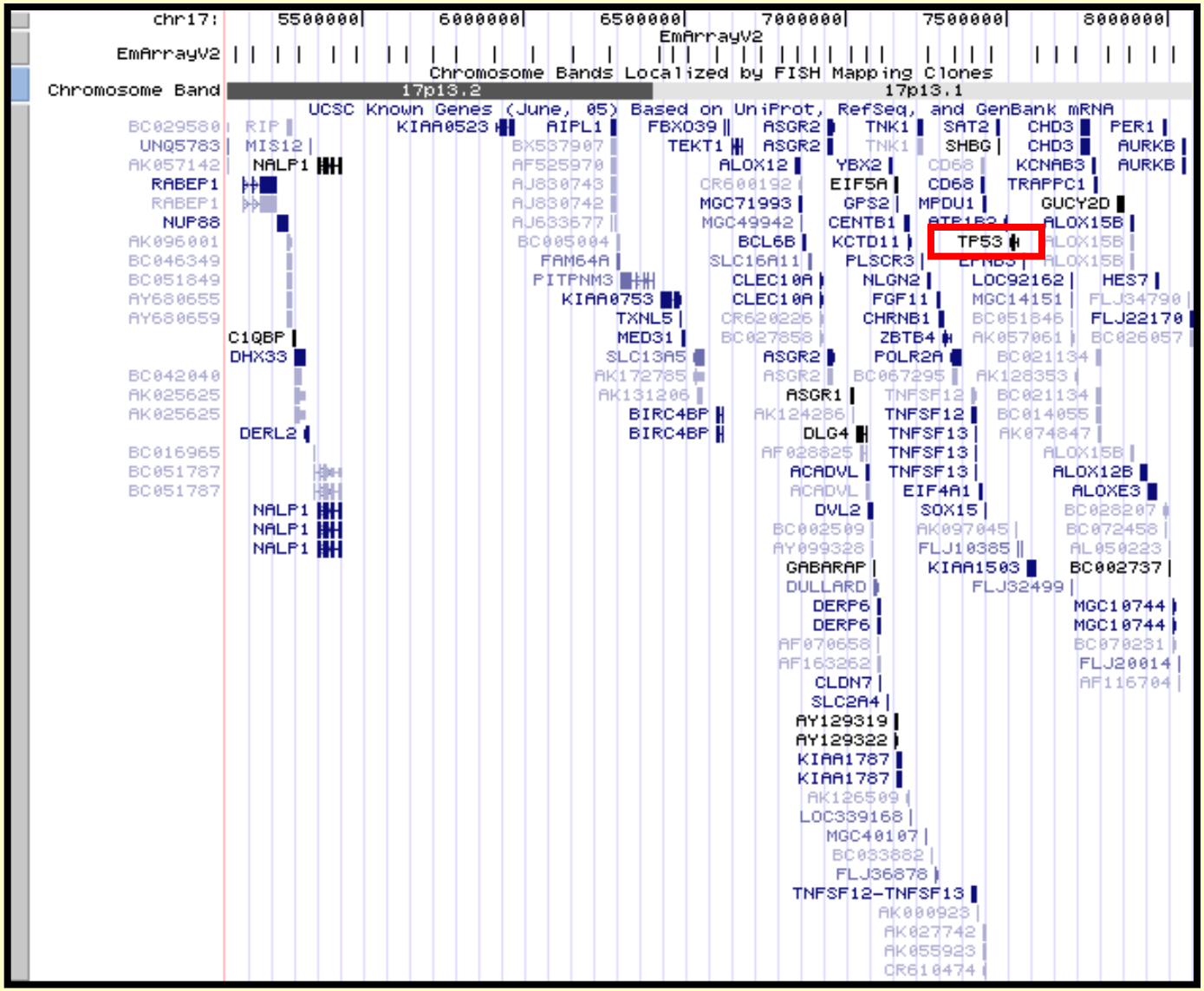
Dysmorphic features
Developmental delay
Hypotonia
Hypoplastic penis

17p: 2.3 Mb deletion



Case 11

Loss of 17p13.2p13.1: ~2.3Mb

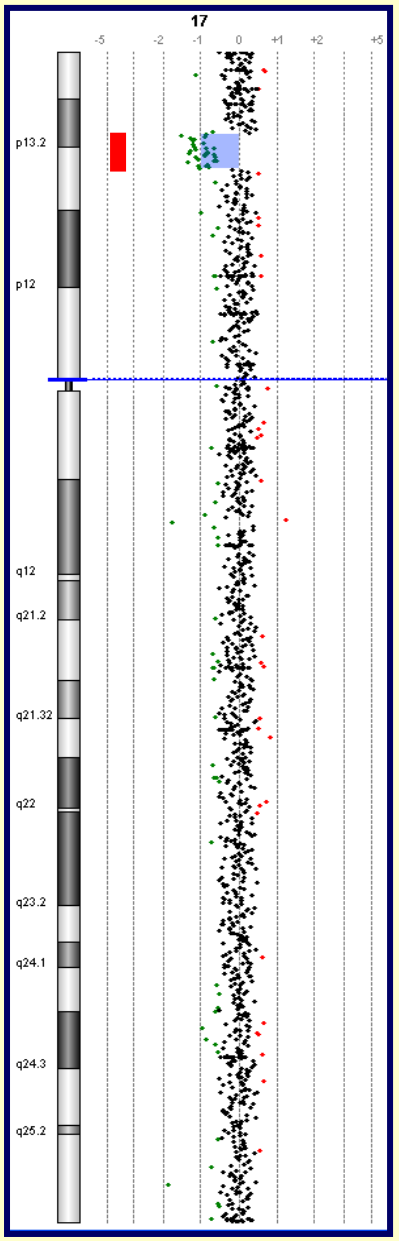


Cancer Susceptibility

Referring Dx:
Dysmorphic features
Developmental delay
Hypotonia
Hypoplastic penis

17p: 2.3 Mb deletion

p53 loss = Li-Fraumeni syndrome, high cancer risk



Adam et al., J Ped, 2009
Other cases: *RB1*, *VHL*, Peutz-Jeghers

Chromosomal Microarray (CMA): Clinical Testing

- **Whole genome analysis not only identifies cause/recurrence risk for family, but often reveals "incidental findings" leading to life-saving interventions, medical management (although insufficient published evidence on frequency and clinical value)**
- **Children with developmental disabilities now early beneficiaries of truly predictive, personalized medicine.**

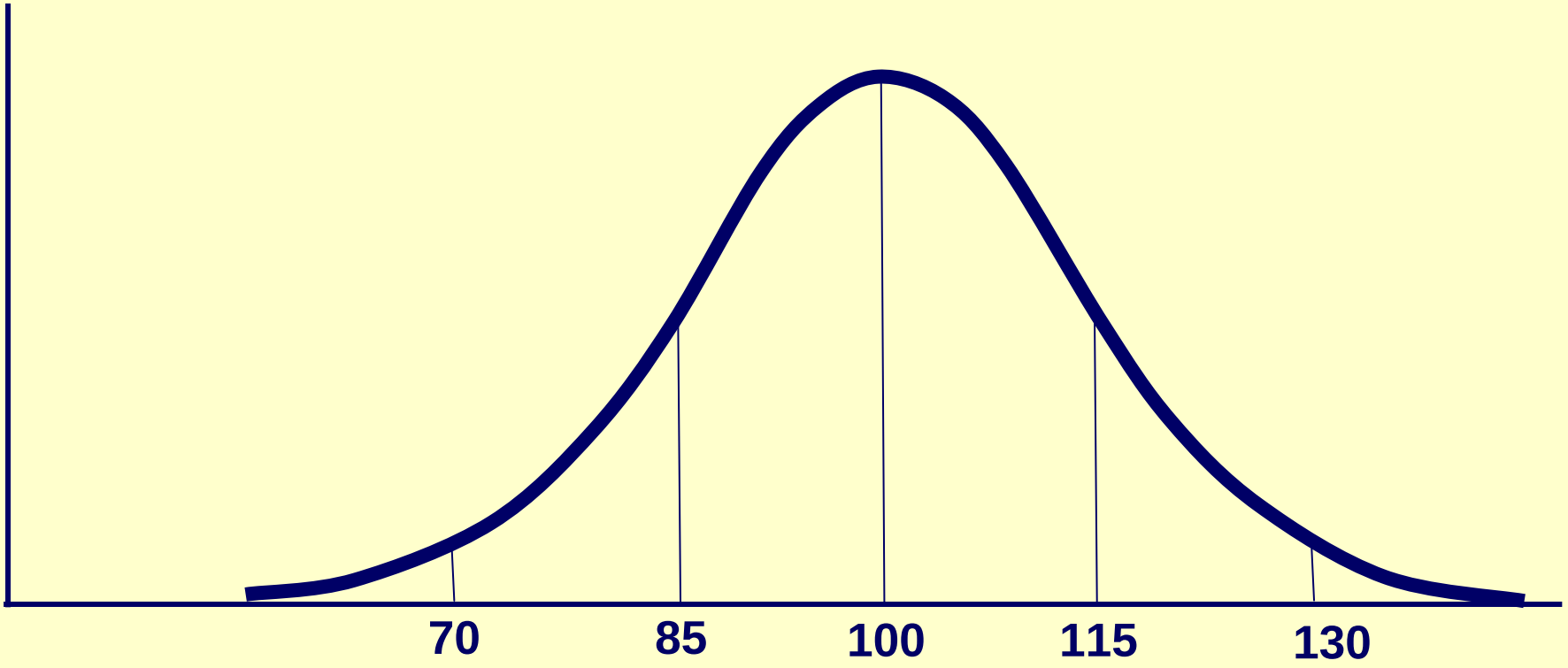
Next challenge: put genomic data into electronic health record (EHR) in a clinically useful way and dynamically update clinical interpretation.

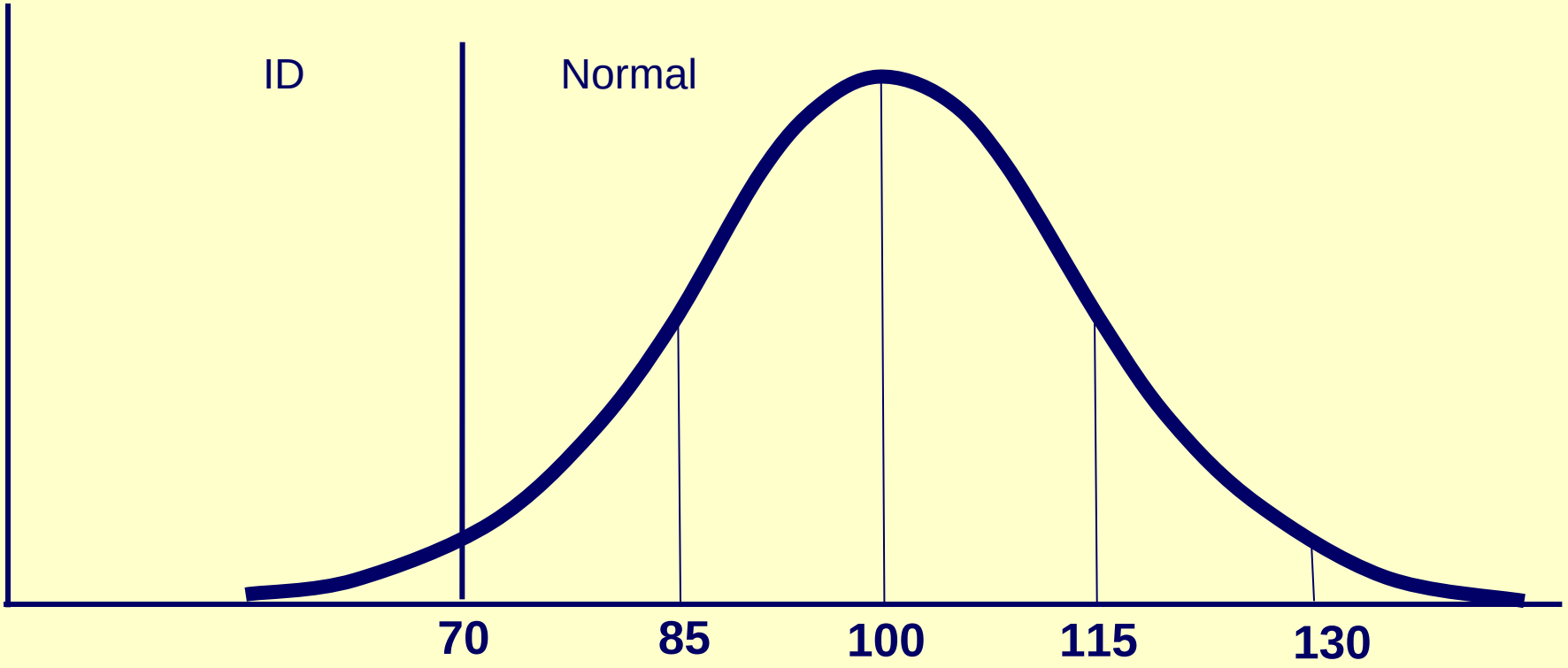
Pathogenic vs. Benign Imbalances

1. **Clinical Significance**
   - known del/dup or Mendelian disorders
     OMIM, DECIPHER (Sanger)
   - known CNV
     DGV
   - comparison with other cases
     PubMed, DECIPHER

2. **Genomic/Gene Content**
   - correlates with size and location
     UCSC, Ensembl (Sanger)

3. **Inherited or *de novo***


70
85
100
115
130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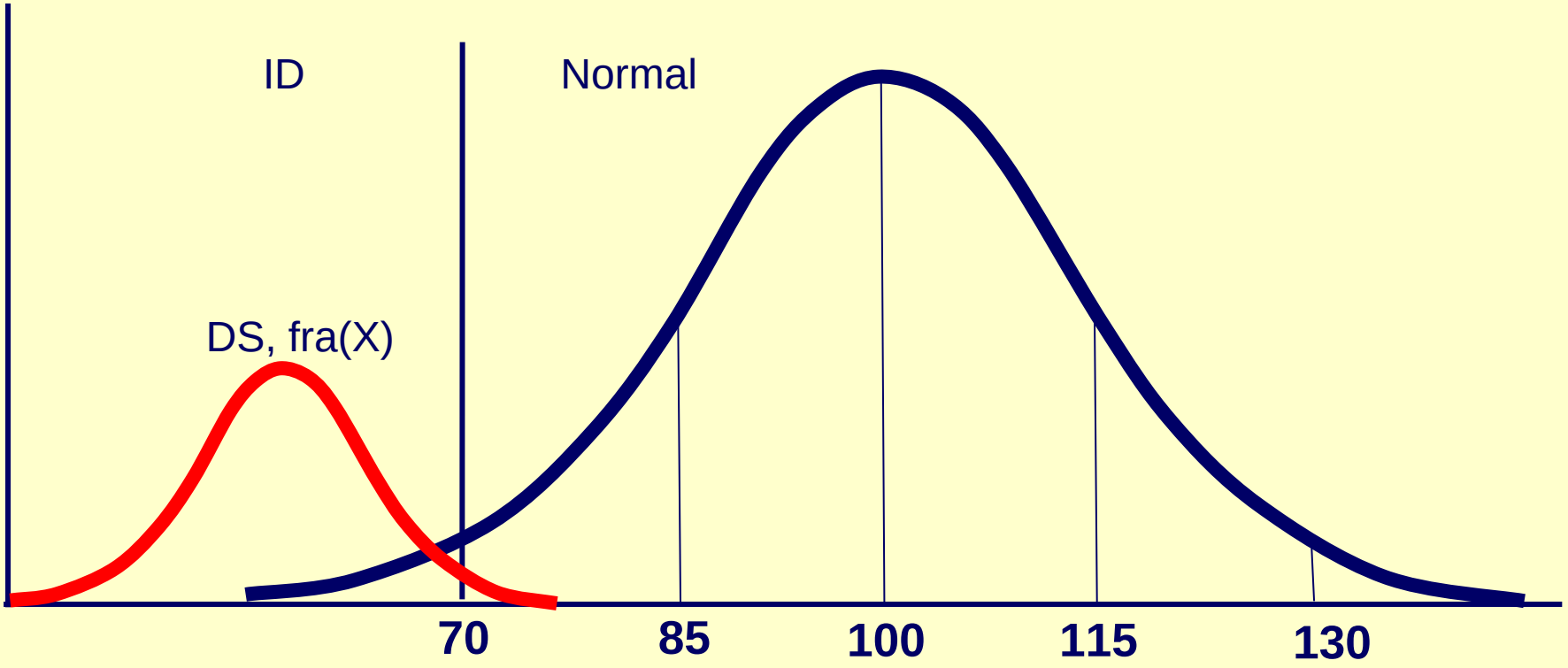
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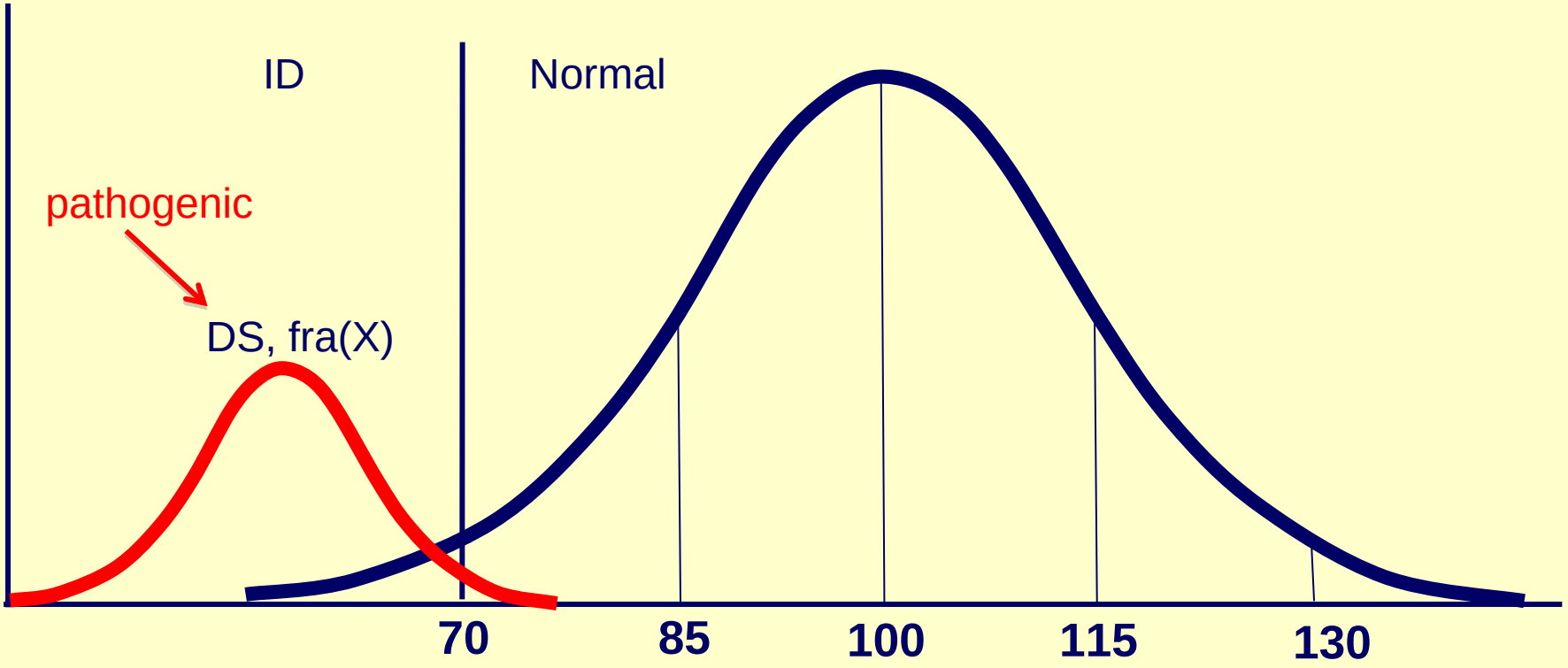
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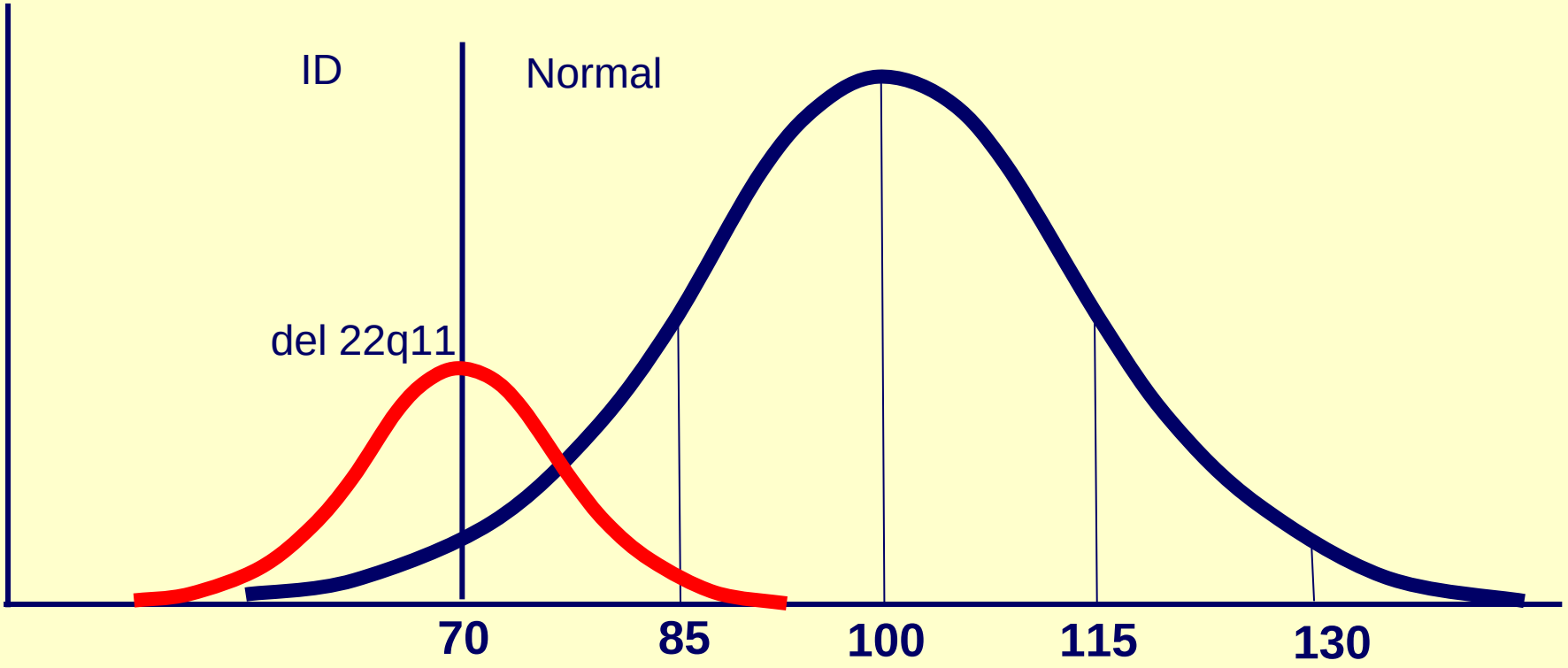
ID
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del 22q11
70
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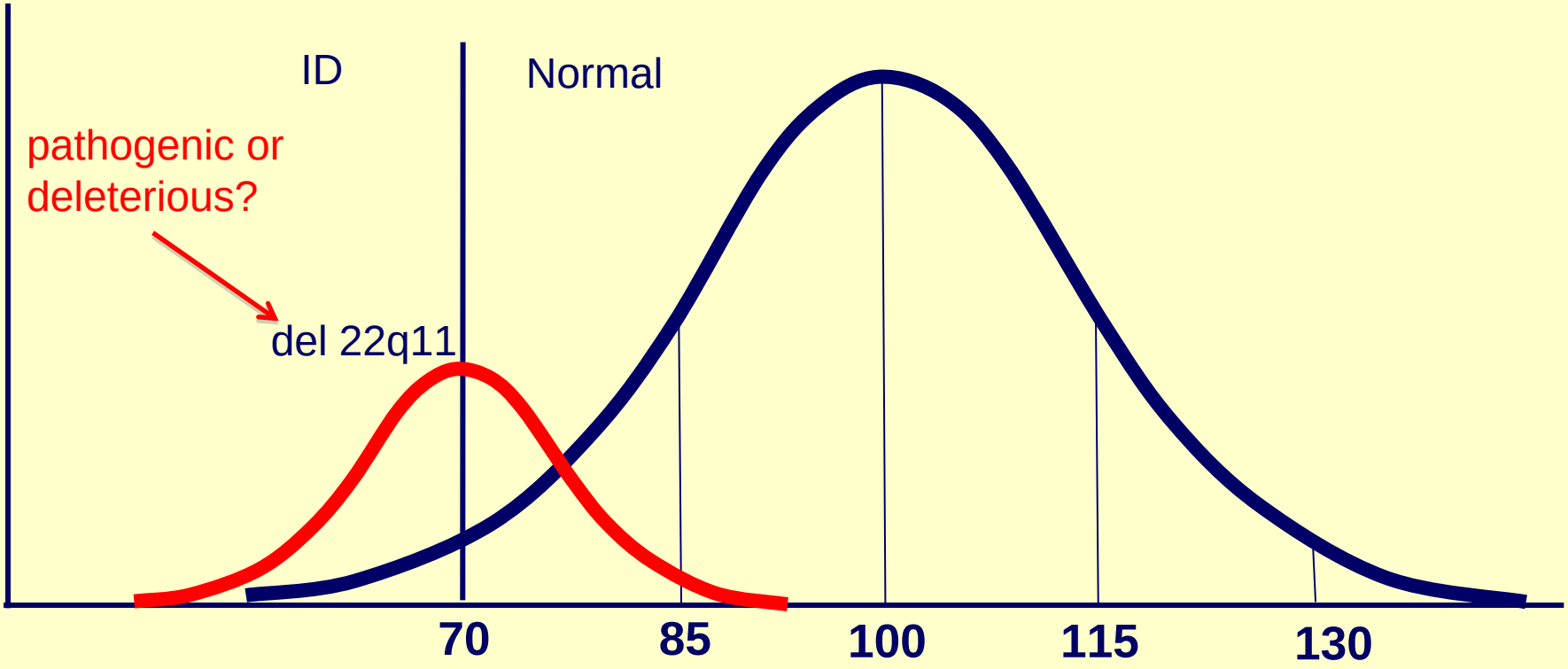

ID
Normal
pathogenic or
deleterious?
del 22q11
70
85
100
115
130

Deleterious vs. Benign Imbalances

1. **Clinical Significance**
   - known del/dup or Mendelian disorders
     OMIM, DECIPHER (Sanger)
   - known CNV
     DGV
   - comparison with other cases
     PubMed, DECIPHER

2. **Genomic/Gene Content**
   - correlates with size and location
     UCSC, Ensembl (Sanger)

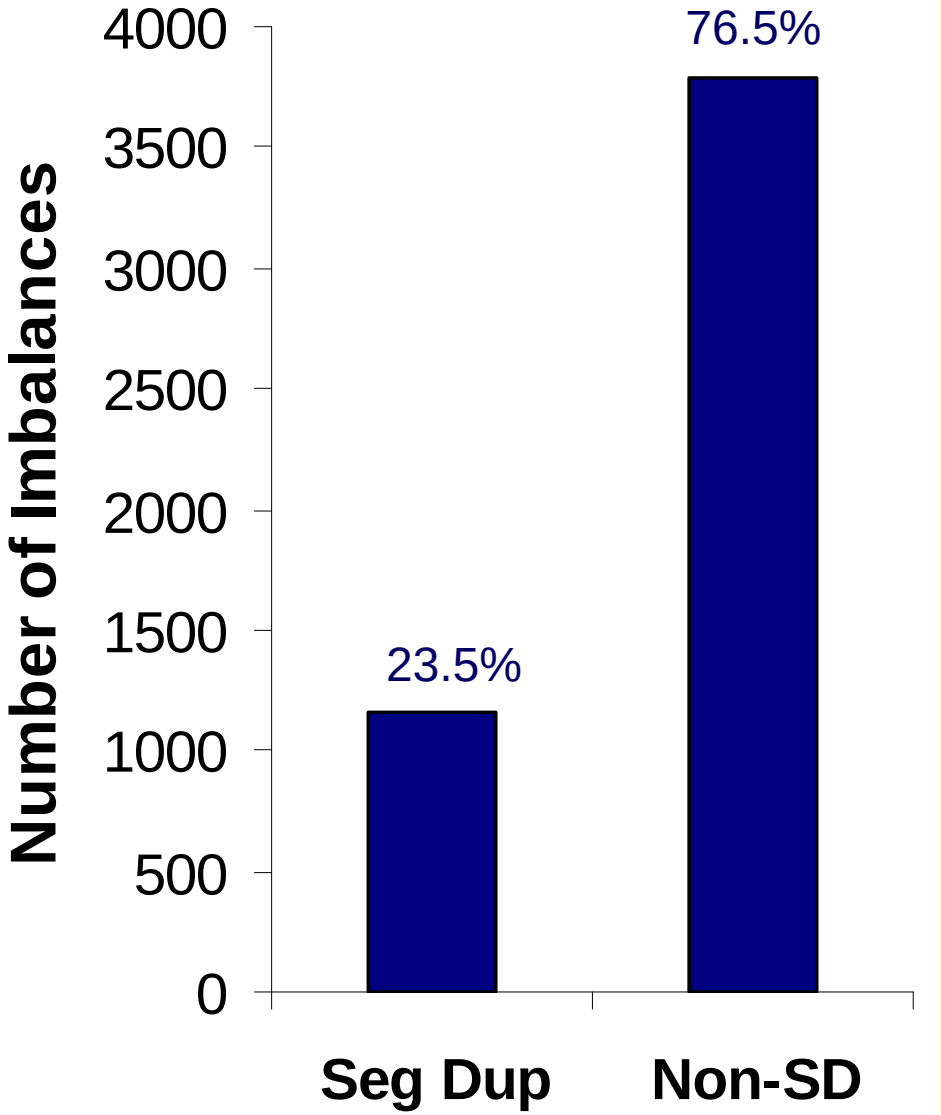
3. **Inherited or *de novo***

Pathogenic/Deleterious CNVs

15,753 arrays from 7 ISCA groups

- **pCNV = 2,766 (17.6% of total arrays)**
  - **Size of pCNVs:**
    - **Median: 2.7 Mb**
  - **Median number of genes: 44**
  - **Deletions - 63.6% vs. Duplications - 36.4%**

Mechanism of Chromosomal Imbalances



Seg dup regions (hotspots) only represent ~8% of the genome, but >20% of CNVs involve these regions.

The majority of CNVs do not involve seg dups.

Most Frequent Recurrent Deletions

CNV Loss	Cases (n=15,749)	Controls (n=10,118)	OR	p-value
22q11.2	93	0	∞	9.15E-21
16p11.2	67	5	8.6	6.34E-10
1q21.1	55	3	11.8	5.38E-09
15q13.2-q13.3 (BP4-5)	46	0	∞	1.44E-10
15q11.2-q13 (BP1/2-3)	41	0	∞	2.77E-09

Recurrent Deletions

Deleted CNV	Syndrome/Phenotype	Initial Call	Final Call	Cases	Ctrls	OR	p-value
22q11.2	22q11.2 Deletion syndrome	pCNV	pCNV	93	0	∞	9.15E-21
16p11.2	Autism	pCNV	pCNV	67	5	8.6	6.34E-10
1q21.1	ID/Microcephaly	pCNV	pCNV	55	3	11.8	5.38E-09
15q13.2-q13.3	ID/Epilepsy (BP4-5)	pCNV	pCNV	46	0	∞	1.44E-10
15q11.2-q13	PW/Angelman (BP1/2-3)	pCNV	pCNV	41	0	∞	2.77E-09
7q11.23	Williams syndrome	pCNV	pCNV	34	0	∞	8.49E-08
16p13.11	Autism/ID/Schizophrenia	pCNV	pCNV	22	3	4.7	0.0063
17q21.31	17q21 deletion syndrome	pCNV	pCNV	22	0	∞	2.49E-05
17q12	RCAD, autism & SCH	pCNV	pCNV	18	0	∞	0.00015
1q21	TAR syndrome	pCNV	pCNV	17	1	10.9	0.0026
17p11.2	Smith-Magenis syndrome	pCNV	pCNV	16	0	∞	0.00045
3q29	3q29 deletion syndrome	pCNV	pCNV	10	0	∞	0.0084
8p23.1	8p23.1 deletion syndrome	pCNV	pCNV	10	0	∞	0.0084
5q35	Sotos syndrome	pCNV	pCNV	8	0	∞	0.026
17p12	HNPP	pCNV	pCNV	3	2	0.96	1.00

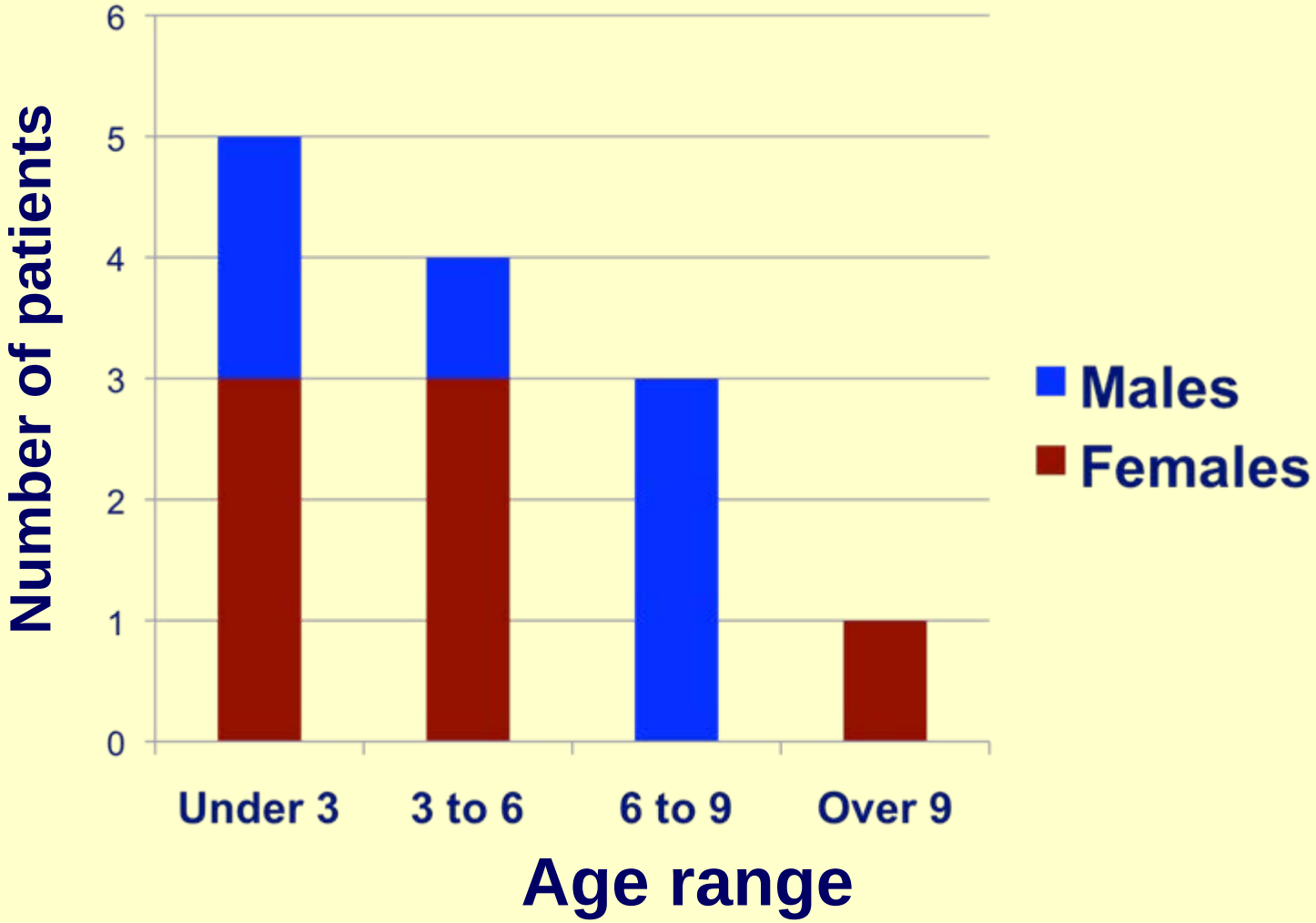
Recurrent Duplications

Duplicated CNV	Syndrome/ Phenotype	Initial Call	Final Call	Cases	Ctrls	OR	p-value
16p13.11	Variable phenotype	VOUS	VOUS	45	20	1.5	0.203
16p11.2	Autism	VOUS	pCNV	39	4	6.3	2.50E-05
15q11.2-q13	Autism (BP1/2-3)	pCNV	pCNV	35	0	∞	4.57E-08
22q11.2	Variable phenotype; LD	pCNV	pCNV	32	5	4.1	0.0011
1q21.1	ID/Autism	pCNV	pCNV	28	3	6.0	0.0004
17q12	Epilepsy	pCNV	pCNV	21	4	3.4	0.022
7q11.23	Autism	pCNV	pCNV	16	1	10.3	0.0046
17p11.2	Potocki-Lupski syndrome	pCNV	pCNV	15	0	∞	0.0008
15q13.2-q13.3	Psychiatric disease (BP4-5)	VOUS	VOUS	14	3	3.0	0.083
17p12	CMT1A	pCNV	pCNV	9	7	0.8	0.80
3q29	Variable phenotype	pCNV	pCNV	8	1	5.1	0.100
8p23.1	Variable phenotype	pCNV	pCNV	6	0	∞	0.088
1q21	TAR region	VOUS	bCNV	5	12	0.3	0.011
5q35	Short stature, microcephaly	pCNV	pCNV	2	0	∞	0.52
17q21.31	Behavioral problems	N/A	N/A	0	0	nd	nd

Frequency of Seg Dup-Mediated Deletions

Region	Syndrome	Number of Cases	Frequency in 15,753 Samples
22q11.2	22q11.2 deletion syndrome (1.5 and 3.0 Mb)	93	1 in 169
16p11.2	Autism, DD/ID	63	1 in 250
1q21.1	MR / Microcephaly / Cardiac / Cataracts	54	1 in 292
15q13.2-q13.3	MR / Epilepsy	44	1 in 358
15q11.2-q13	Prader-Willi/Angelman (BP1-BP3)	39	1 in 404
7q11.23	Williams syndrome	34	1 in 463
17q21.31	17q21 deletion syndrome	22	1 in 716
16p13.11	Autism / MR / Schizophrenia (1.5 and 3.0 Mb)	21	1 in 750
17q12	Renal cysts / Diabetes	18	1 in 875
1q21	TAR syndrome	14	1 in 1125
3q29	3q29 deletion syndrome	10	1 in 1575
8p23.1	8p23.1 deletion syndrome	10	1 in 1575
17p11.2	Smith-Magenis syndrome	10	1 in 1575
17p12	HNPP	3	1 in 5251

del 16p11.2: clinical aCGH cases



SIMONS VIP CONNECT

VARIATION IN INDIVIDUALS PROJECT

- **Two components:**
  - **Online community**
    - **Facilitate communication among families**
    - **Family matching service**
    - **Provide access to cutting edge clinical and research information**
  - **Research study**
    - **Characterize the range of medical, cognitive, and behavioral features of individuals with 16p11.2 deletions and duplications**
    - **Collect detailed clinical information and blood samples on 200 families**

CNV Atlas of dev. brain disorders

- **Goal of >200,000 patients in next 2 years.**
- **Allows early diagnosis, opportunities for natural history and clinical research to identify "triggers" for autism, epilepsy, schizophrenia.**
- **What interventions/therapeutic approaches work best for each genetic subtype of autism, epilepsy, schizophrenia (Simons Foundation initiating major new prospective research project and patient registry).**

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Andres Moreno de Luca, M.D.

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