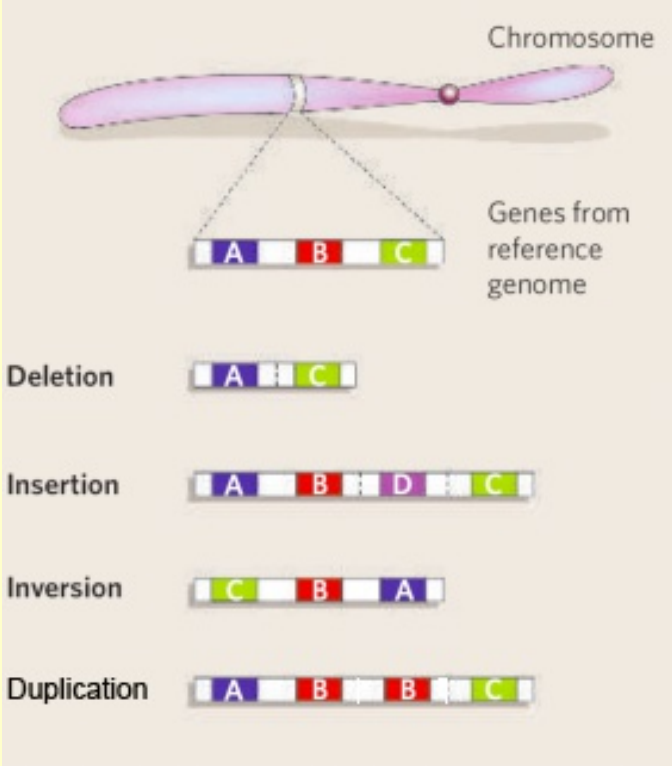
Genomics & Medicine

http://biochem118.stanford.edu/

Structural Variants in the Human Genome

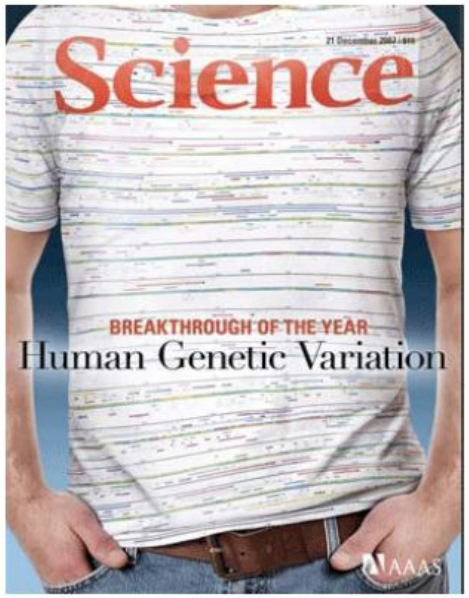


Doug Brutlag
Professor Emeritus of Biochemistry & Medicine
Stanford University School of Medicine

Human Genetic Variation
2007 Scientific Breakthrough of the Year

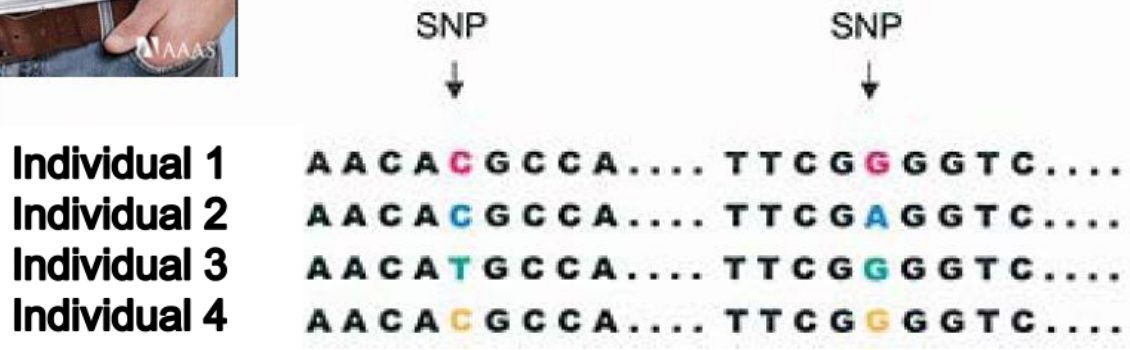
2007 SCIENTIFIC BREAKTHROUGH OF THE YEAR

Science Magazine, December 21, 2007



"It's all about me!"

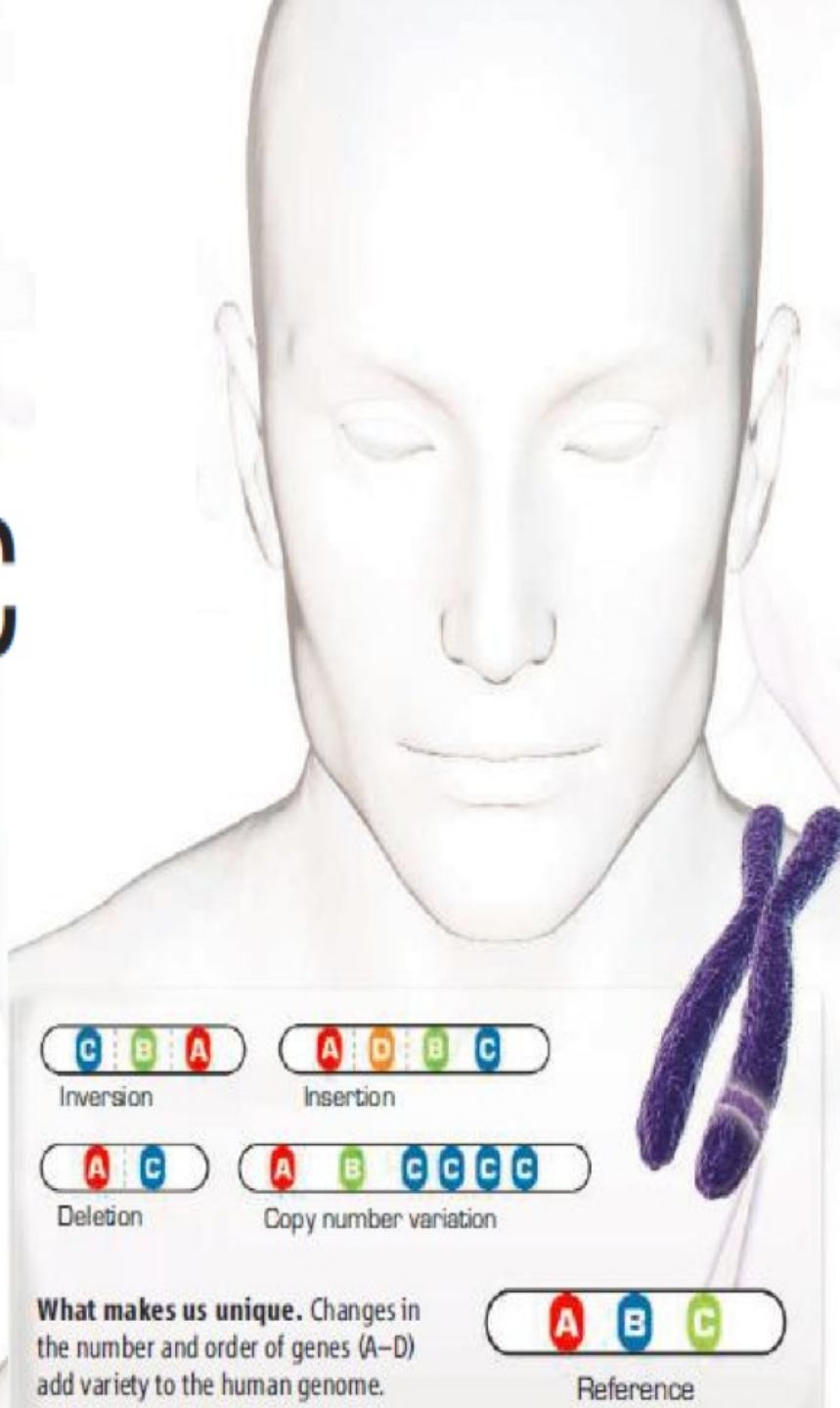
Simple Nucleotide Polymorphisms (SNPs)



BREAKTHROUGH OF THE YEAR

Human Genetic Variation

Equipped with faster, cheaper technologies for sequencing DNA and assessing variation in genomes on scales ranging from one to millions of bases, researchers are finding out how truly different we are from one another



What makes us unique. Changes in the number and order of genes (A–D) add variety to the human genome.

Henry Stewart Talks on Copy Number Variations

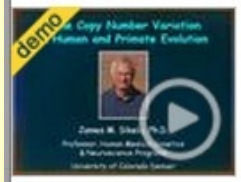
- Henry Stewart Talks http://hstalks.com/
- Copy Number Variation
- Copy Number Variation by Prof. Stephen Scherer
- CNVs in human genomes by Prof. Chris Ponting
- The Future of CNVs: Sequence base resolution and links to human disea
  Professor Evan Eichler – University of Washington
- You will need the Stanford name and password (stanford, member) in order to watch this course off campus.

View the Talks

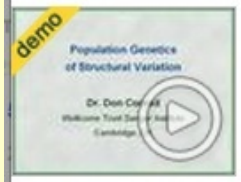
1. Copy number variation (37 mins)
Prof. Stephen W Scherer – Hospital for Sick Children and University of Toronto, Canada

2. Array comparative genomic hybridization to characterize copy number variation in the human genome (17 mins)
Dr. Nigel Carter – The Wellcome Trust Sanger Institute, UK

3. CNVs in human genomes (32 mins)
Prof. Chris Ponting – University of Oxford, UK



4. Gene copy number variation in human and primate evolution (32 mins)
Prof. James Sikela – University of Colorado, Denver, USA



5. Population genetics of structural variation (26 mins)
Dr. Don Conrad – Wellcome Trust Sanger Institute, Cambridge, UK

6. Genomic disorders: mechanisms for copy number variation and clinical implementation of high-resolution genome analysis (64 mins)
Prof. James Lupski – Baylor College of Medicine, USA

7. Databases for CNV in control and disease populations (47 mins)
Dr. Lars Feuk – Uppsala University, Sweden

http://hstalks.com/main/browse_talks.php?r=439&j=757&c=252

Duplications and Deletions in the Human Genome

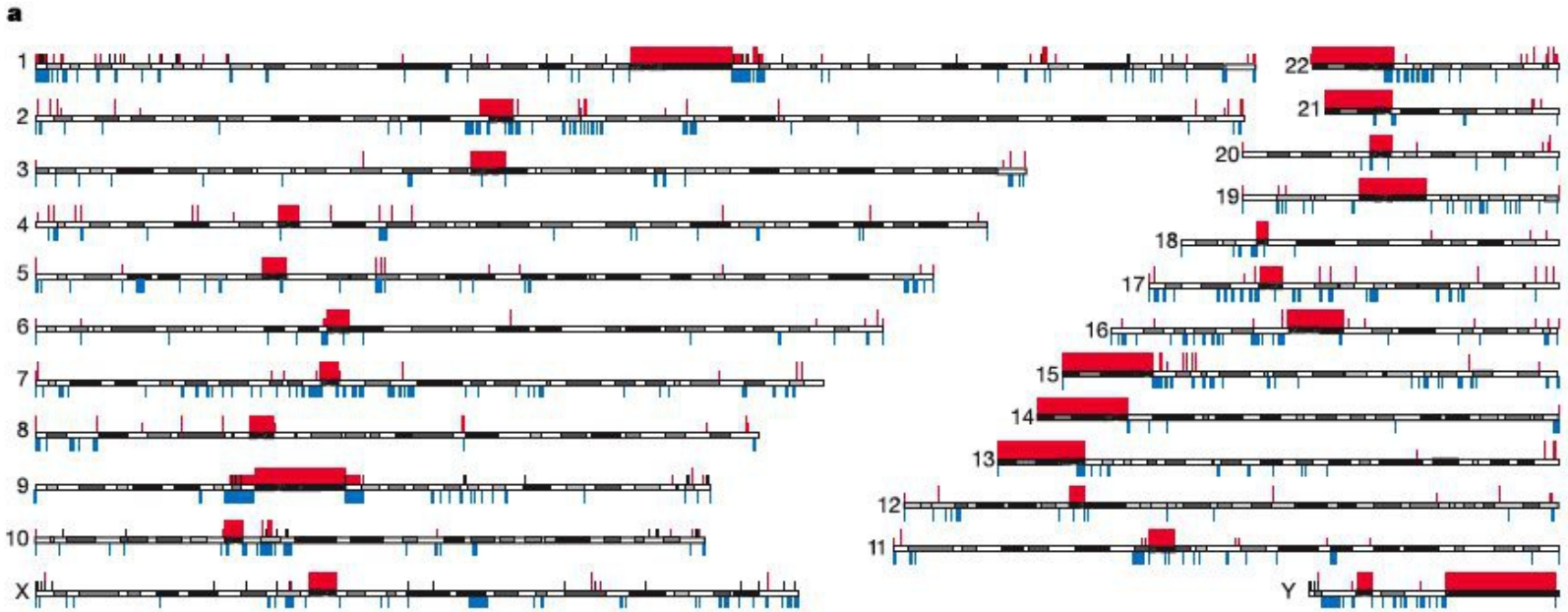
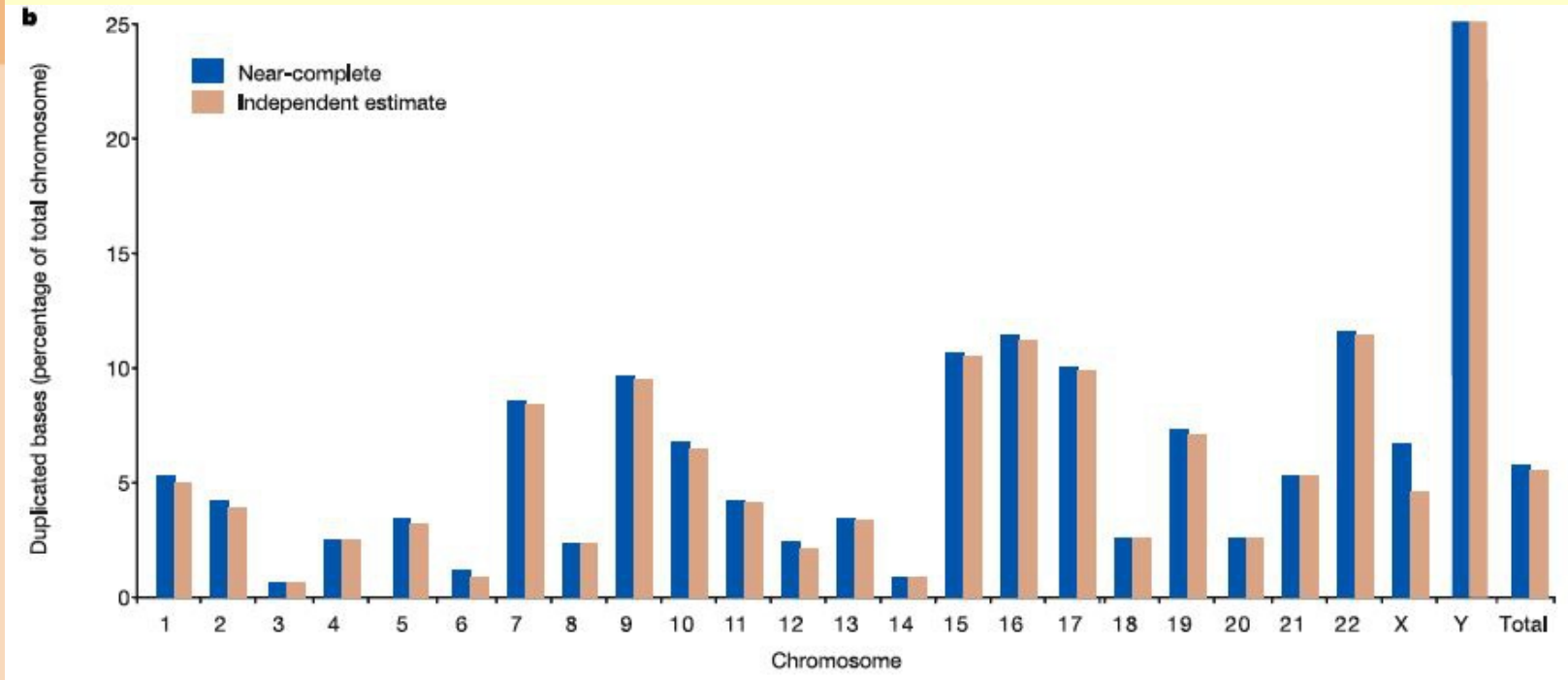


Figure 4 Segmental duplications across the genome. **a**, Segmental duplications and sequence gaps across the genome. Segmental duplications are indicated below the chromosomes in blue (length ≥10 kb and sequence identity ≥95%). Large duplications are shown to approximate scale; smaller ones are indicated as ticks. Sequence gaps are indicated above the chromosomes in red. Large gaps (>300 kb) are shown to approximate scale; smaller gaps are indicated as ticks with those that are 50 kb or smaller shown as shorter ticks. Unfinished clones are indicated as black ticks. **b**, Percentage of

Percentage of Chromosomes Duplicated



The Spectrum of Variations in the Human Genome

Table 1 The spectrum of variation in the human genome

Variation	Rearrangement type	Size range[a]
Single base-pair changes	Single nucleotide polymorphisms, point mutations	1 bp
Small insertions/deletions	Binary insertion/deletion events of short sequences (majority <10 bp in size)	1–50 bp
Short tandem repeats	Microsatellites and other simple repeats	1–500 bp
Fine-scale structural variation	Deletions, duplications, tandem repeats, inversions	50 bp to 5 kb
Retroelement insertions	SINEs, LINEs, LTRs, ERVs[b]	300 bp to 10 kb
Intermediate-scale structural variation	Deletions, duplications, tandem repeats, inversions	5 kb to 50 kb
Large-scale structural variation	Deletions, duplications, large tandem repeats, inversions	50 kb to 5 Mb
Chromosomal variation	Euchromatic variants, large cytogenetically visible deletions, duplications, translocations, inversions, and aneuploidy	~5 Mb to entire chromosomes

Sharp, Cheng & Eichler, Annu. Rev. Genomics Hum. Genet. 2006. 7:407–42

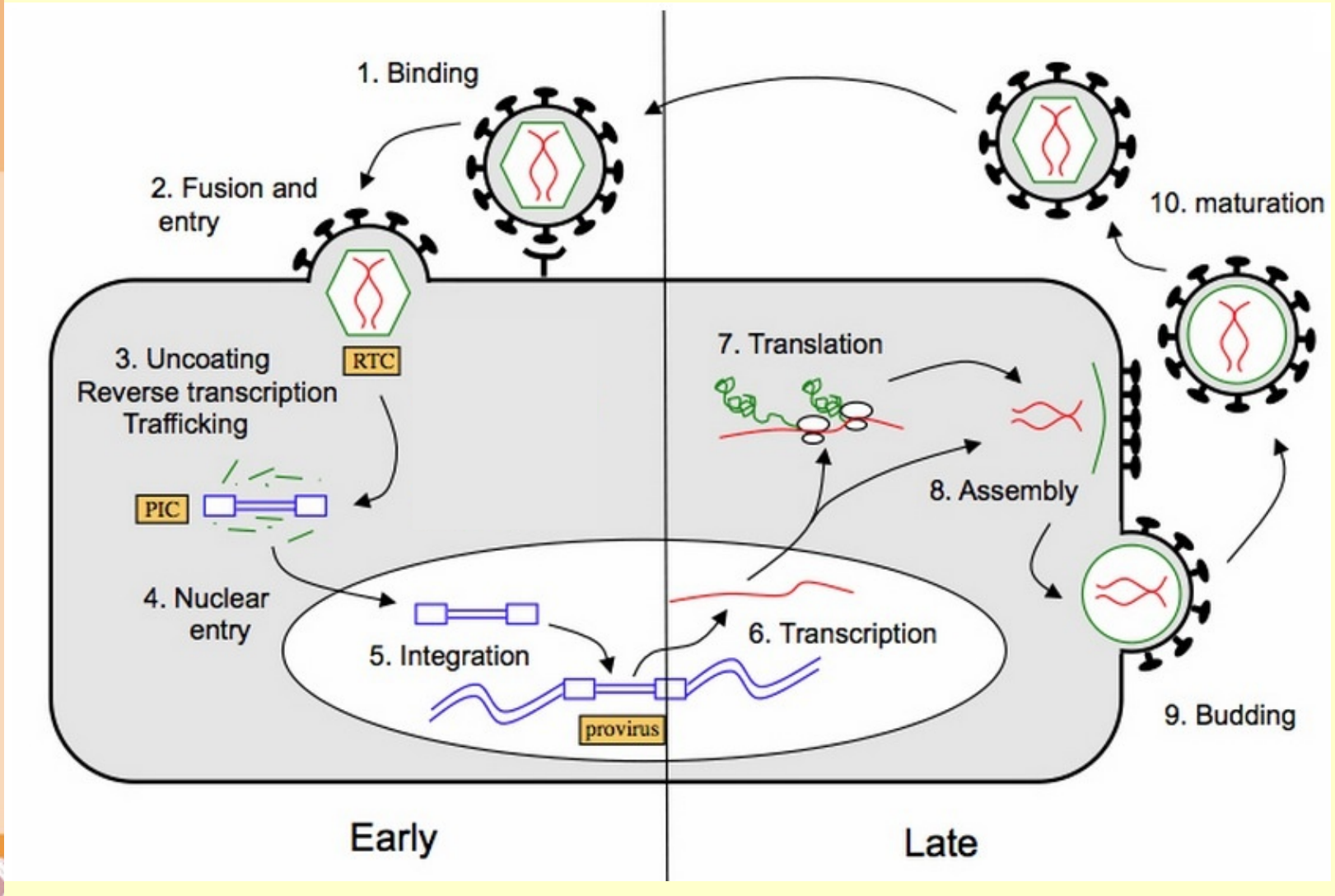
Repeated Elements in the Human Genome ERVs, LINES, SINES and ALUs

- ERVs-Endogenous Retroviruses
  - 10,000 base long RNA genome
  - Converted to DNA and integrate into genome with help of RNA reverse transcriptase and integrase enzymes and long tandem repeats (LTRs)
  - Transcribed into RNA and produce virus (example HIV)

Weiner Curr Opin Cell Biol, 2002 14 (3) 343-50

MRC National Institute for Medical Research

Retroviral Life Cycle



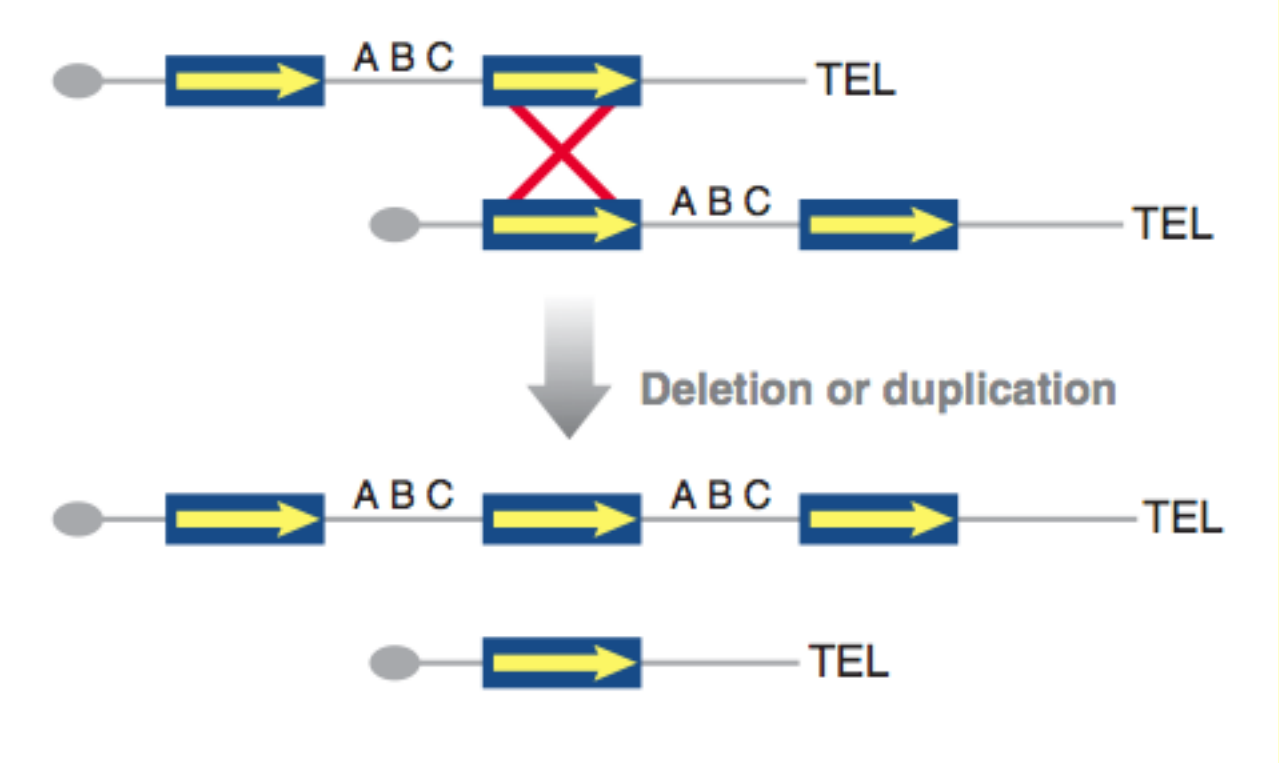
http://www.nimr.mrc.ac.uk/research/kate-bishop/

Repeated Elements in the Human Genome ERVs, LINES, SINES and ALUs

- ERVs-Endogenous Retroviruses
  - 10,000 base long RNA genome
  - Converted to DNA and integrate into genome with help of RNA reverse transcriptase and integrase enzymes and long tandem repeats (LTRs)
  - Transcribed into RNA and produce virus (HIV)
- LINES-Long Interspersed Nuclear Elements
  - About 868,000 in human genome
  - 6,500 base pairs long including LTRs
  - Encode reverse transcriptase and integrase
  - Copy-paste mechanism to insert elsewhere
- SINES-Short Interspersed Nuclear Elements
  - Millions in human genome
  - 100-400 bases long
  - Often contain RNA polymerase III promoters but no genes
- ALUs- The most common SINE
  - 1,500,000 copies = 11% of human genome
  - 350 base pairs in length
  - Contain an RNA Polymerase III promoter, Alu site
  - Appear to evolve from 7S RNA signal recognition particle

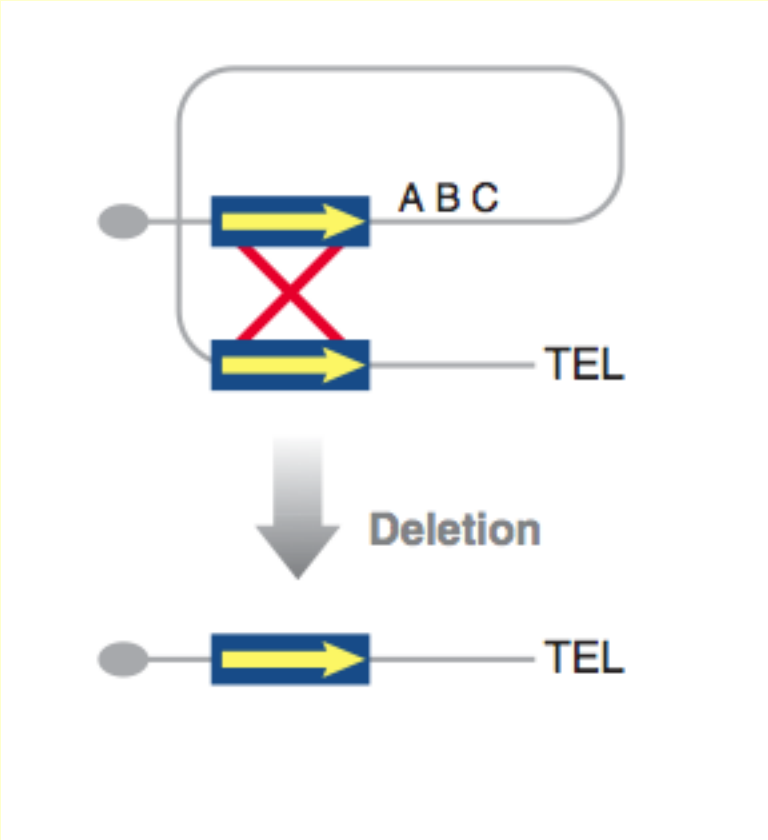
Weiner Curr Opin Cell Biol, 2002 14 (3) 343-50

Unequal Crossing Over Leads to Duplication and Deletion



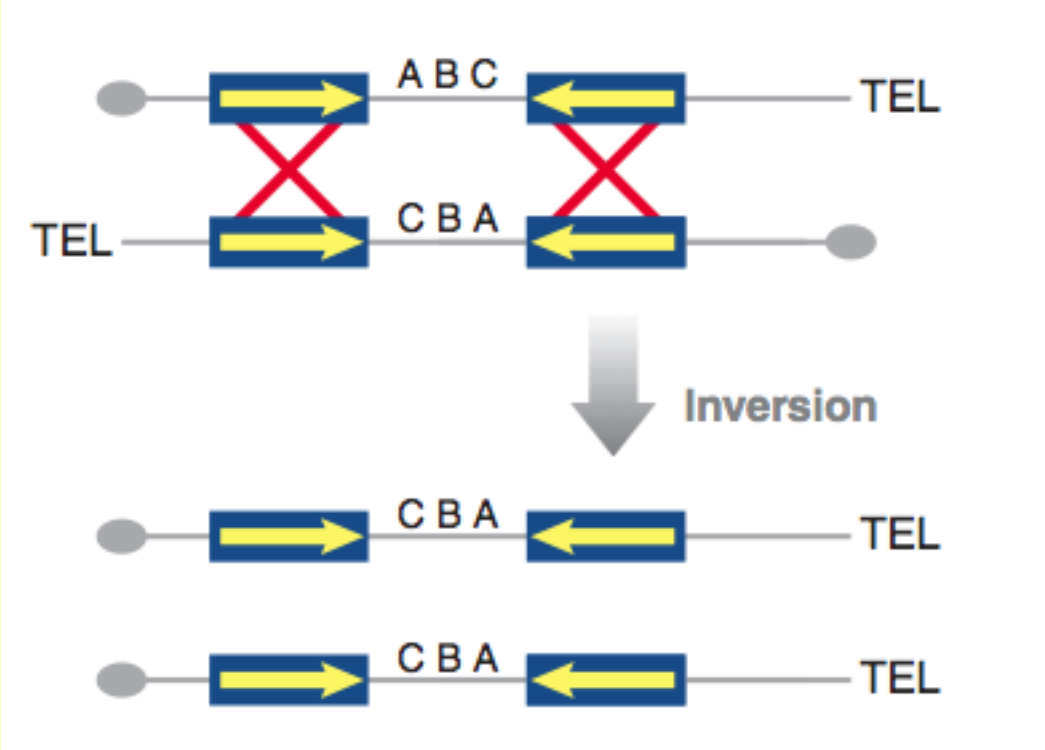
Sharp, Cheng & Eichler, Annu. Rev. Genomics Hum. Genet. 2006. 7:407–42

Intra-Chromosomal Crossing Over Leads to Deletion



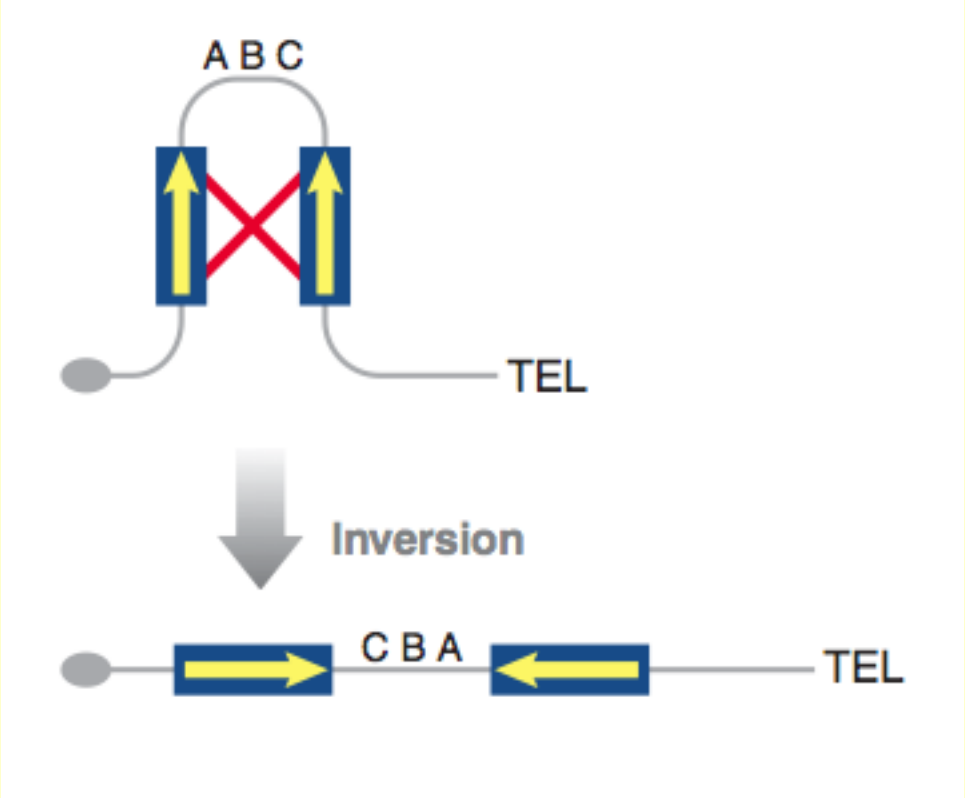
Sharp, Cheng & Eichler, Annu. Rev. Genomics Hum. Genet. 2006. 7:407–42

Inter-Chromosomal Crossing Over Leads to Inversion



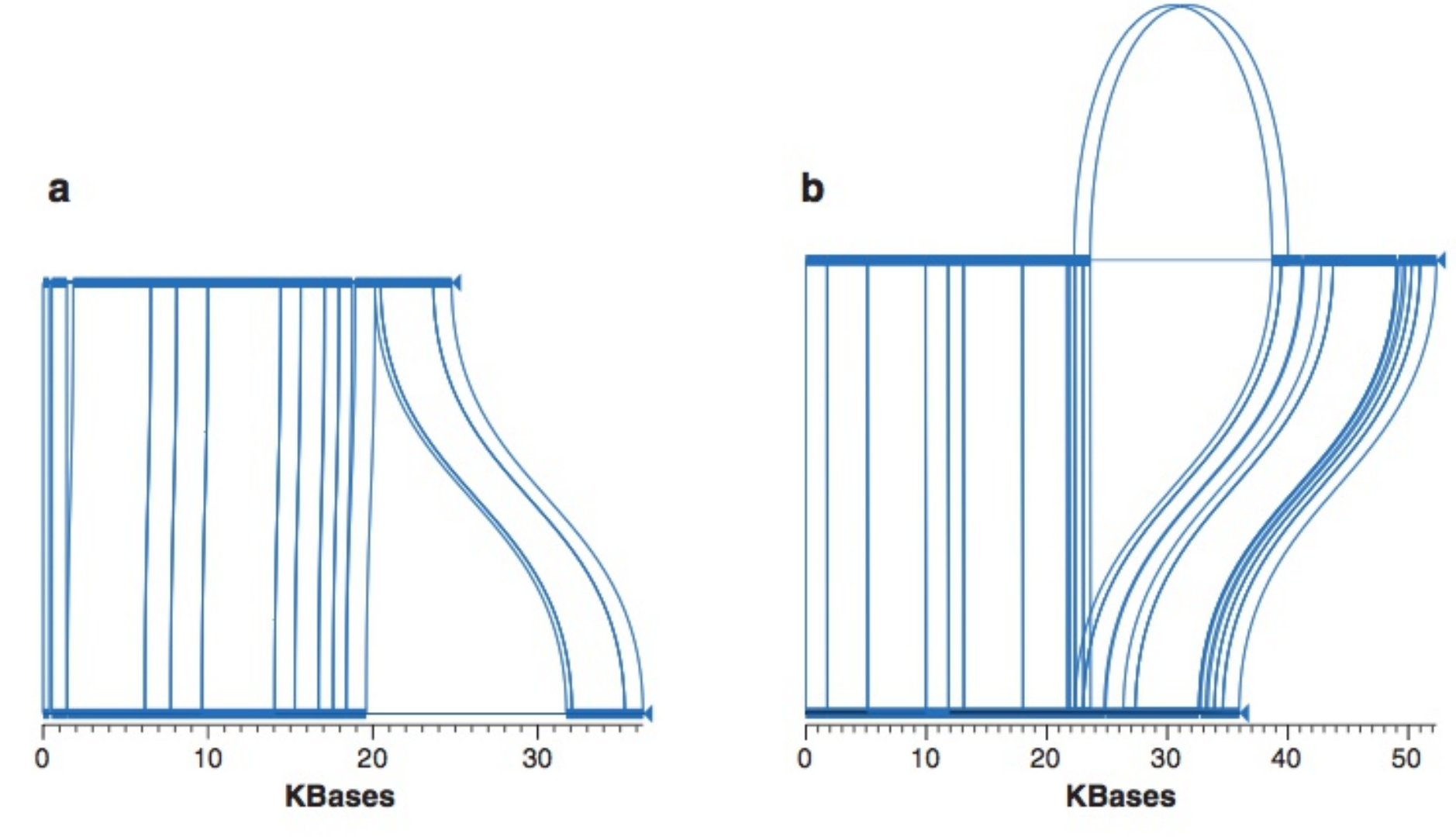
Sharp, Cheng & Eichler, Annu. Rev. Genomics Hum. Genet. 2006. 7:407–42

Intra-Chromosomal Crossing Over Can Also Lead to Inversion



Sharp, Cheng & Eichler, Annu. Rev. Genomics Hum. Genet. 2006. 7:407–42

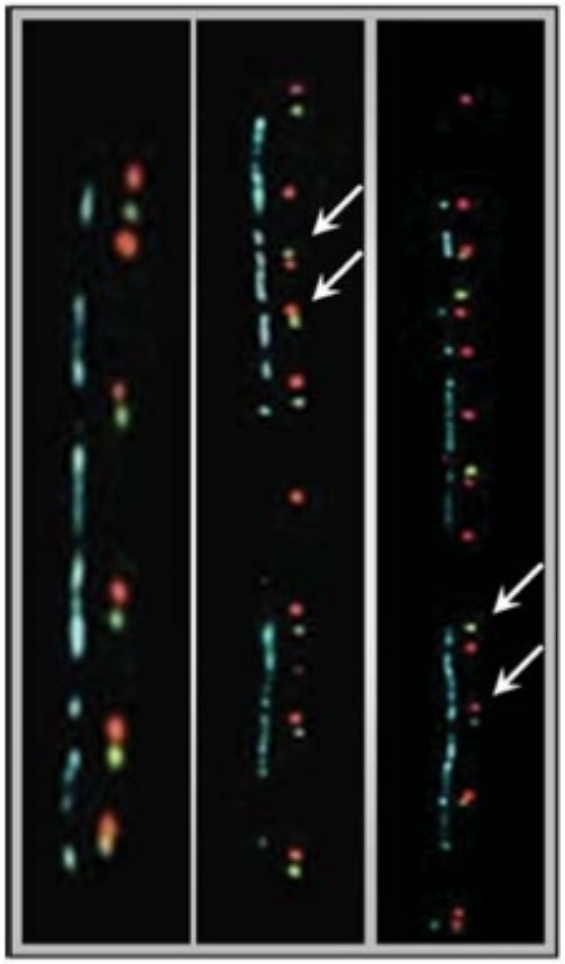
Deletions and Insertions at Repeat Sequences



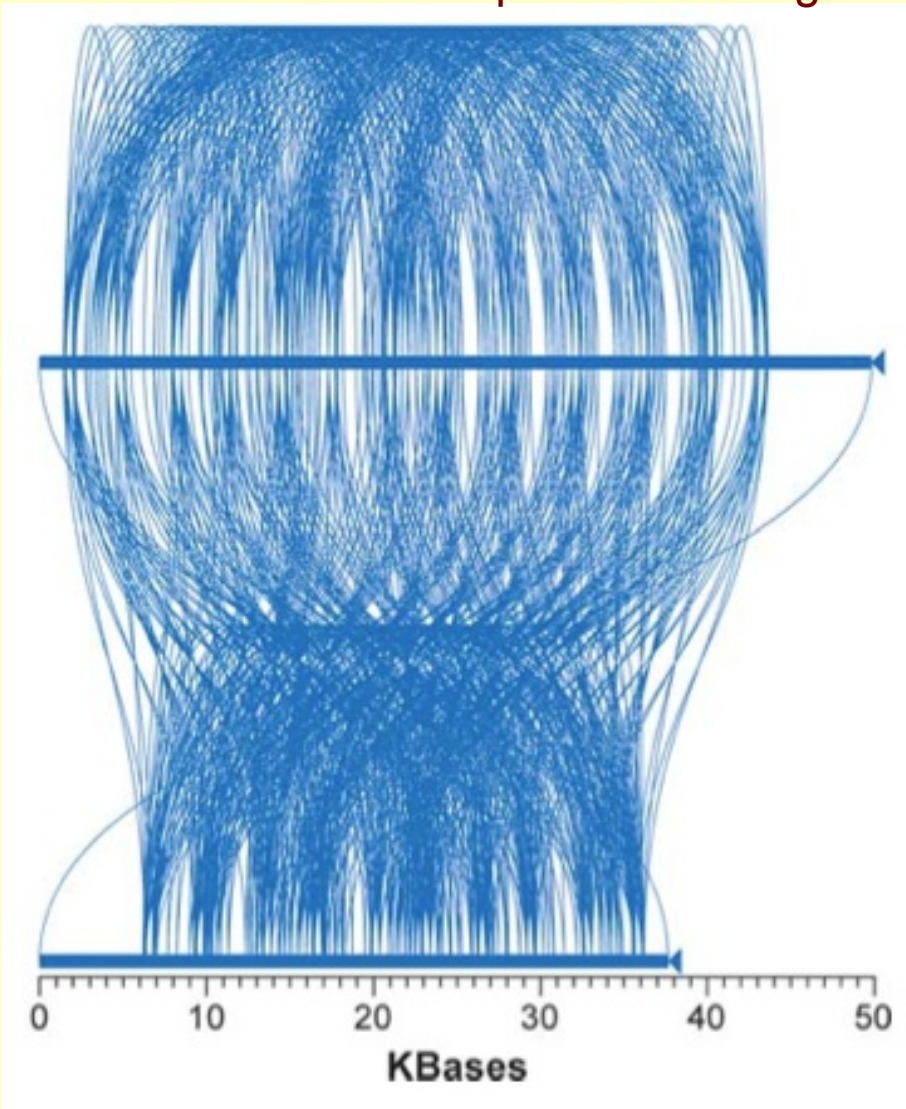
Sharp, Cheng & Eichler, Annu. Rev. Genomics Hum. Genet. 2006. 7:407–42

Variations in Tandem Repeat Arrays
Human α-Amylase Gene Repeats

FISH on DNA

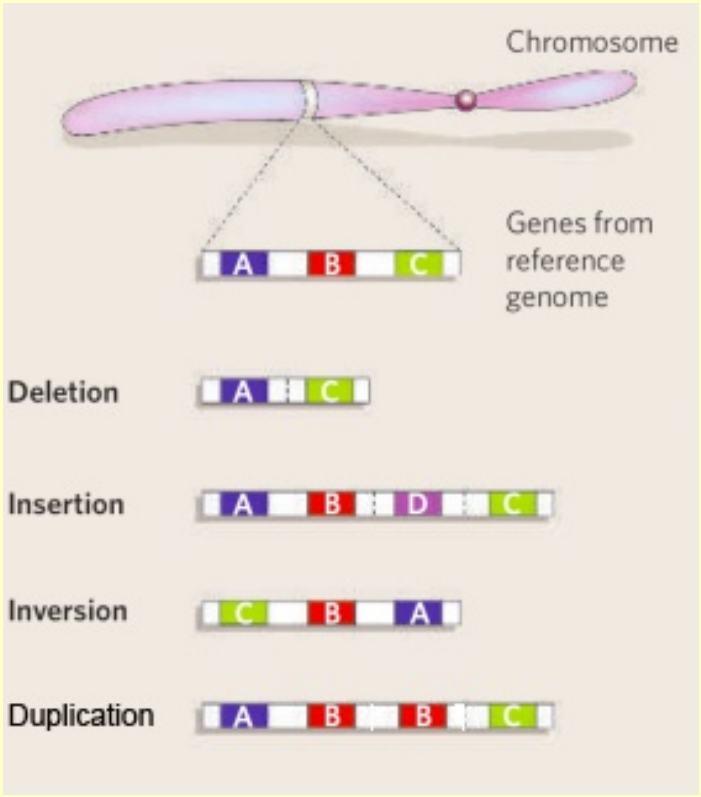


8 or 12 tandem repeats 4 kb long



Sharp, Cheng & Eichler, Annu. Rev. Genomics Hum. Genet. 2006. 7:407–42

Mapping Structural Variation in Humans >1 kb segments



- Structural Variations are Common 40% of the genome

-Structural Variations are involved in phenotype variation and disease

- Until recently most methods for detection were low resolution (>50 kb)




Courtesy of Mike Snyder

Why Study Structural Variation?

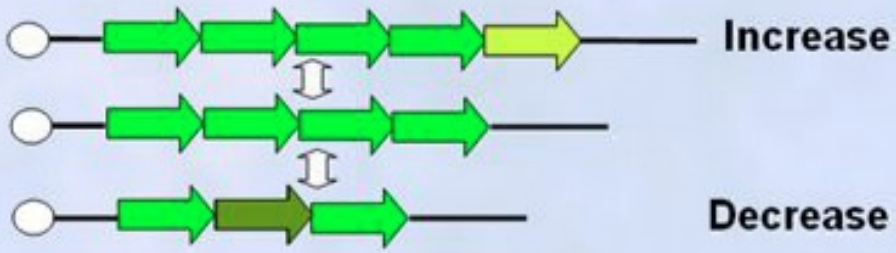
- They are common in "normal" human genomes and they are a major cause of phenotypic variation
- They are common in certain diseases, particularly cancers, behavioral and neurodegenerative diseases
- They are now also showing up in rarer diseases and common behavioral disorders such as autism, schizophrenia, attention deficit, learning disabilities and many other neurological and behavioral disorders

Courtesy of Mike Snyder

HENRY STEWART TALKS

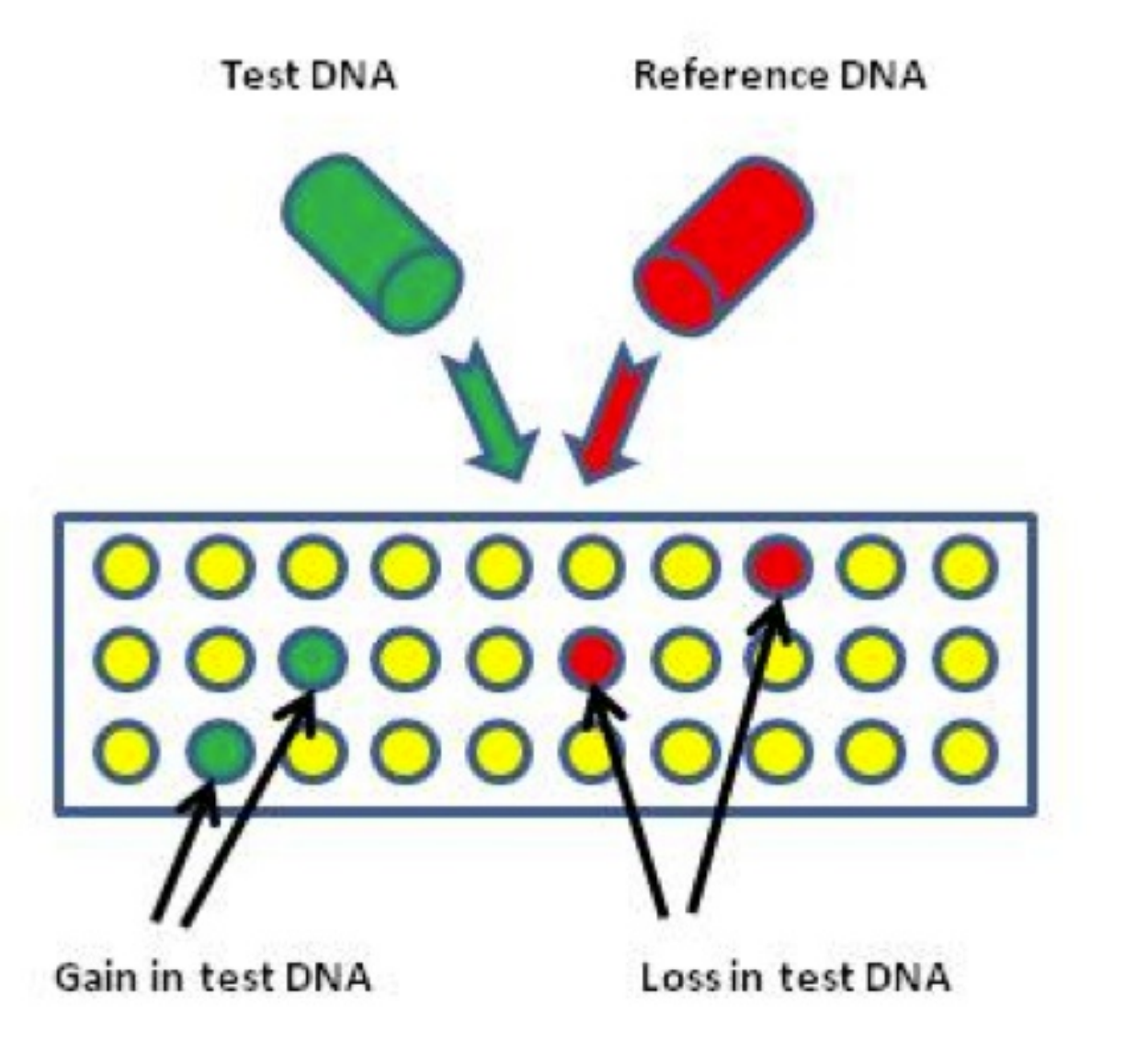
Copy Number Variation and Disease 2002

Gene	Type	Locus	Duplicated Segment	Phenotype
GSTT1	Decrease	22q11.2	54.3 kb	Halothane/epoxide sensitivity
GSTM1	Decrease	1p13.3	18 kb	Toxin resistance, cancer susceptibility
CYP2D6	Increase	22q13.1	5kb	Antidepressant sensitivity
CYP21A2	Increase	6p21.3	35 kb	Congenital adrenal hyperplasia
LPA	Decrease	6q27	5.5*n kb	Coronary heart disease risk
RHD	Decrease	1p36.11	~60 kb	Rhesus blood group sensitivity



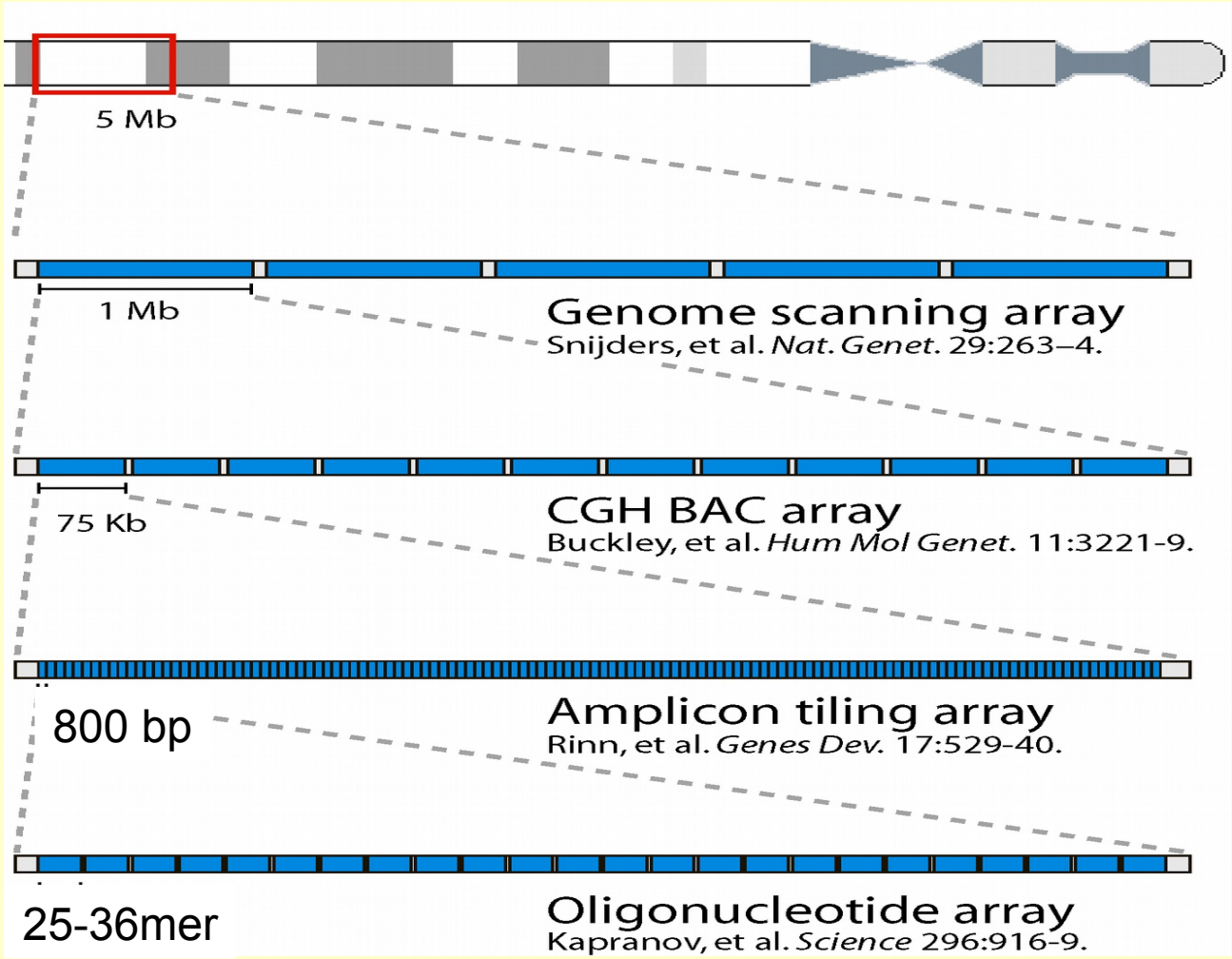
Henry Stewart Talks: Evan Eichler
http://hstalks.com/main/view_talk.php?t=1409&r=439&j=757&c=252

Comparative Genomics Hybridization (CGH)



Courtesy of Mike Snyder

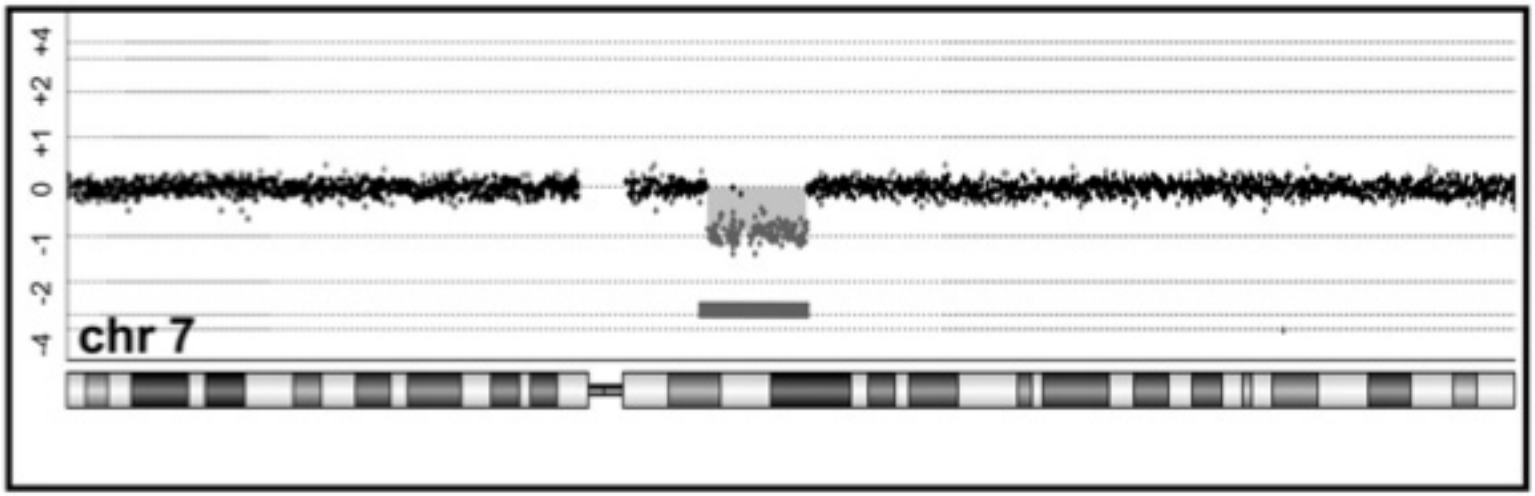
Comparative Micro Arrays (CMA) Using Genome Tiling Arrays

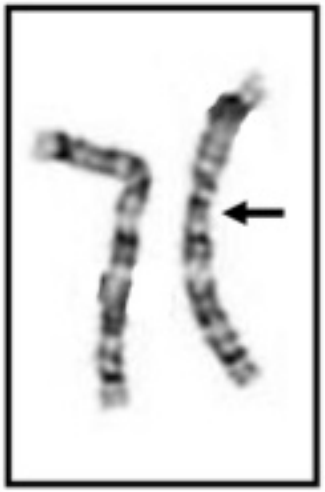


Courtesy of Mike Snyder

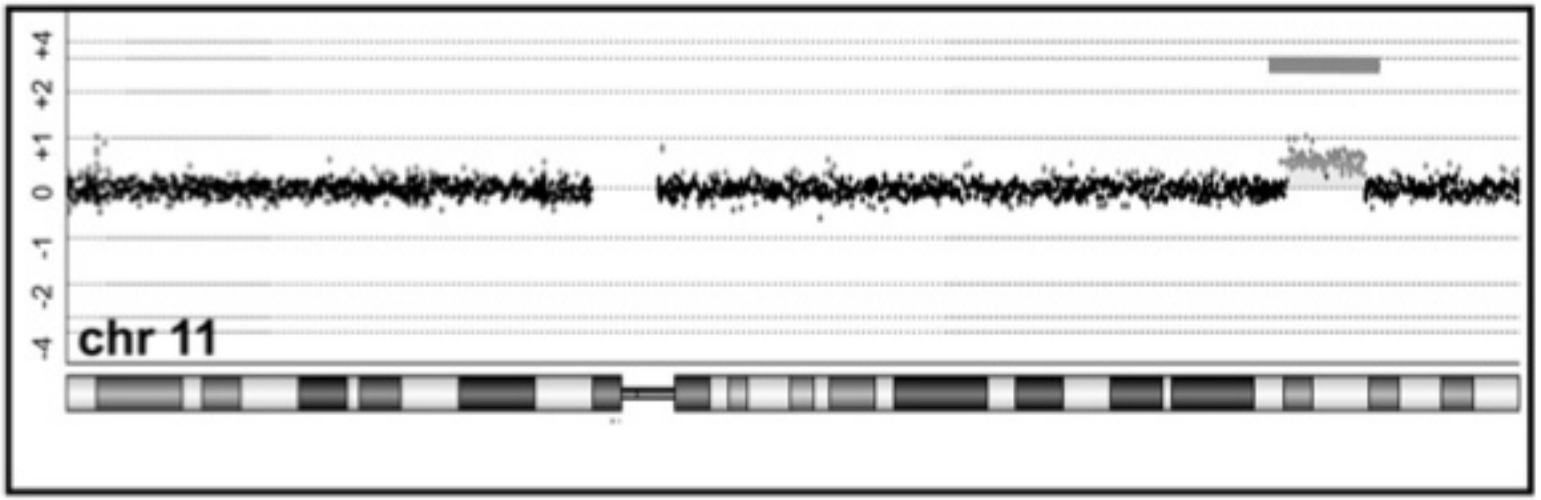
Detection of Duplications and Deletions Using Chromosomal Micro-Arrays

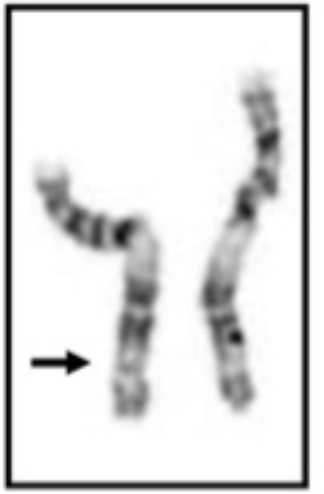
A 10.9 Mbase deletion at 7q11 in Williams-Beuren Syndrome





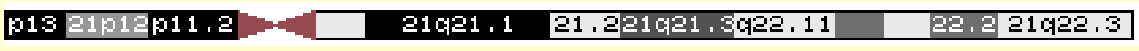
B 7.2 Mbase duplication in 11q

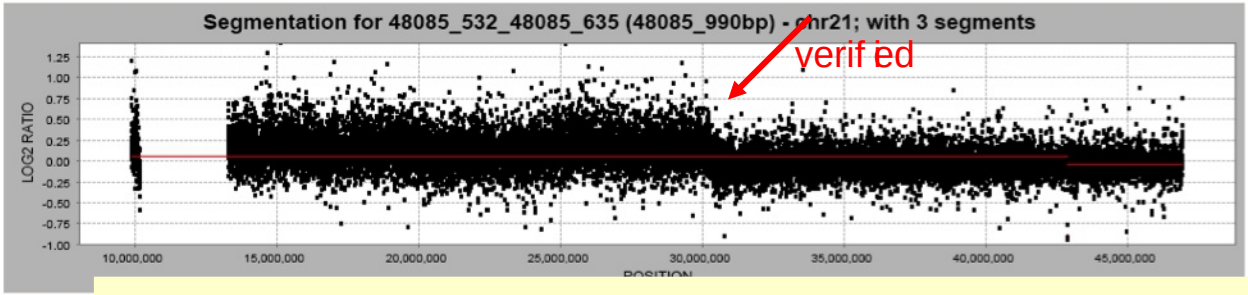


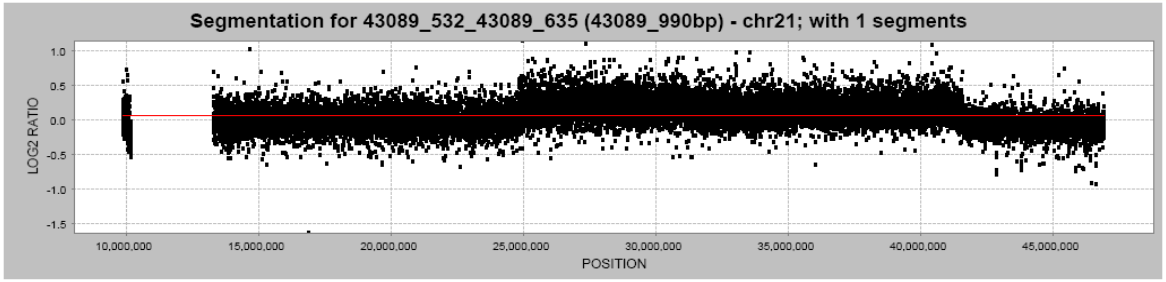


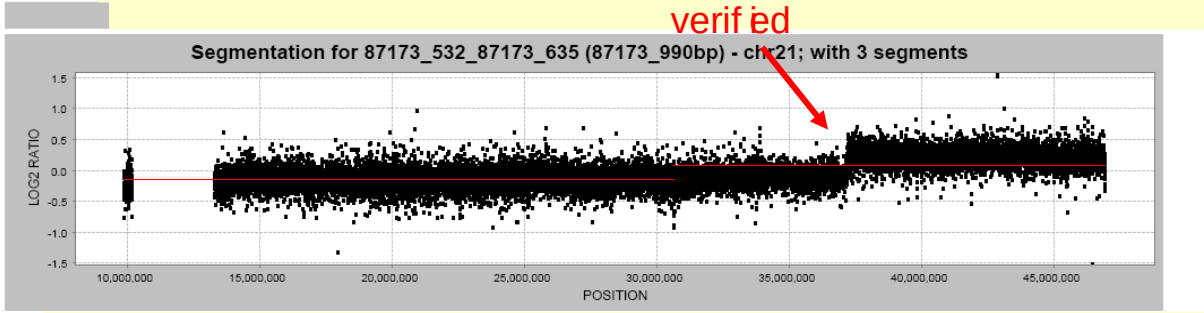
Miller et al., (2010) American Journal of Human Genetics 86, 749-764.

Mapping Breakpoints of Partial Trisomies of Chromosome 21









Courtesy of Mike Snyder

Paired End Mapping (PEM)

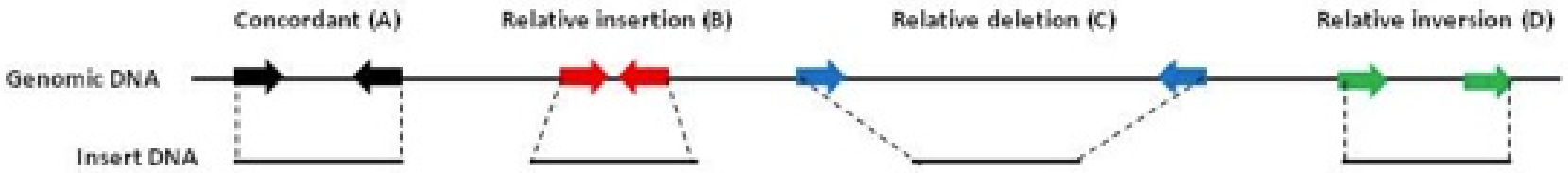
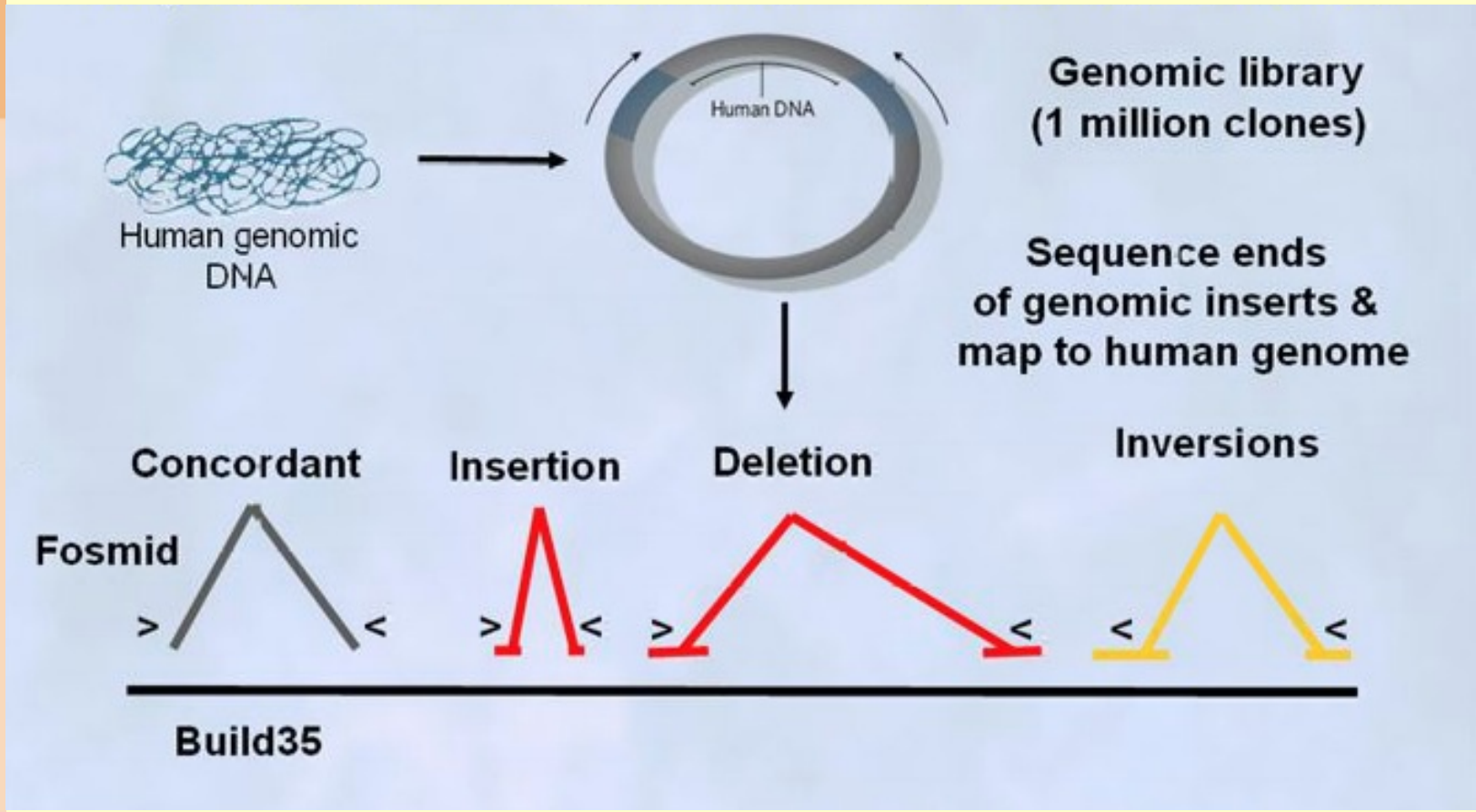


Figure 3: Paired-end mapping (PEM)

A library of known insert size e.g., 40kb fosmid sequences or 3kb DNA fragments is end sequenced and aligned to a genomic assembly.
(A) Ends that map at a similar distance and orientation to the genomic assembly are concordant and do not indicate any structural variation.
(B) Ends that map at a distance significantly less than the insert size on the genomic assembly indicate an insertion in the insert relative to the assembly.
(C) Ends that map at a distance significantly more than the insert size on the genomic assembly indicate an deletion in the insert relative to the assembly.
(D) Ends that map in the same orientation on the genomic assembly indicate an inversion relative to the assembly.

HENRY STEWART TALKS

Sequence Base Resolution of Structural Variation



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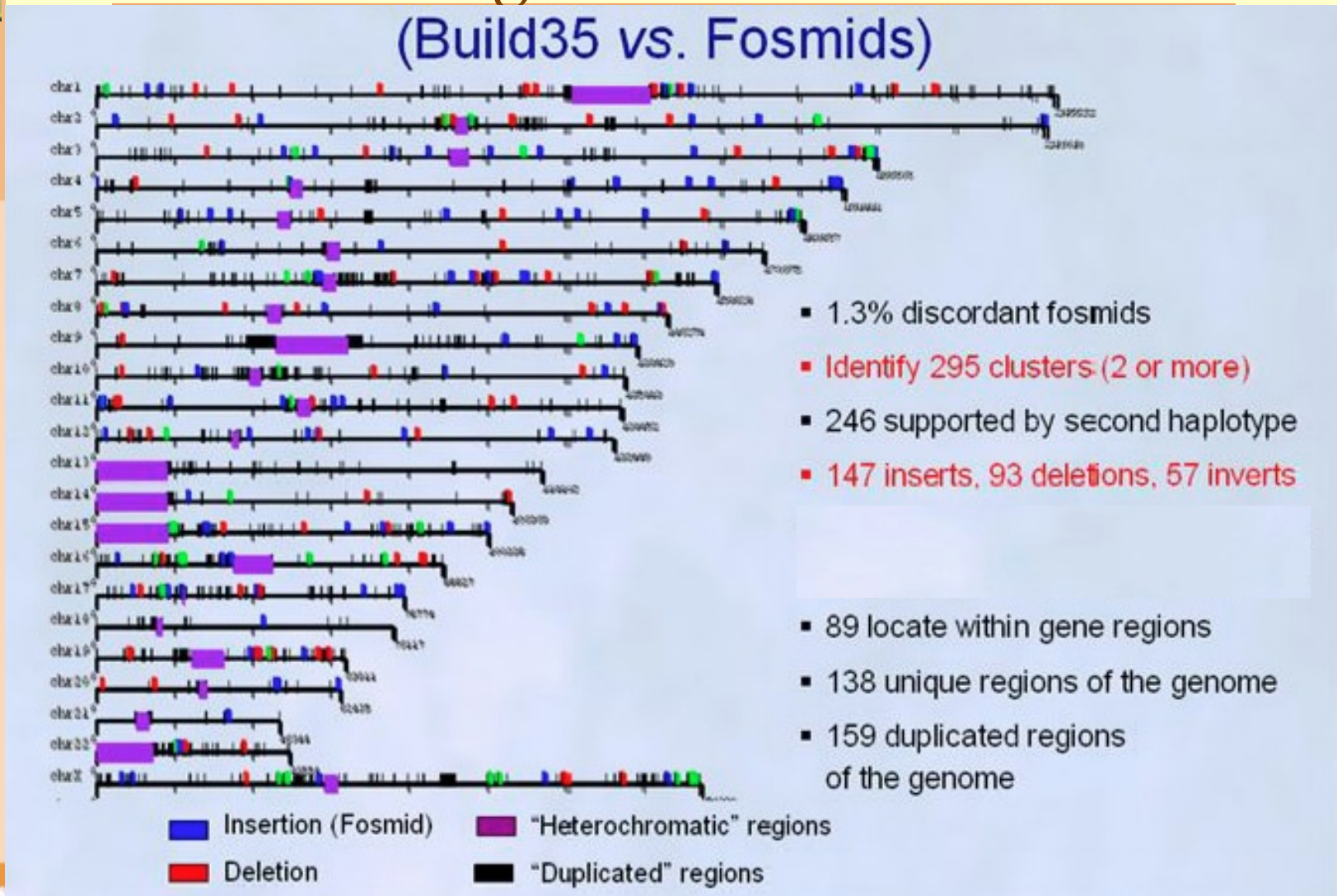
http://hstalks.com/main/view_talk.php?t=1409&r=439&j=757&c=252

HENRY STEWART TALKS

Fine Scale Structural Variation
8.8 x Coverage of a Human Genome



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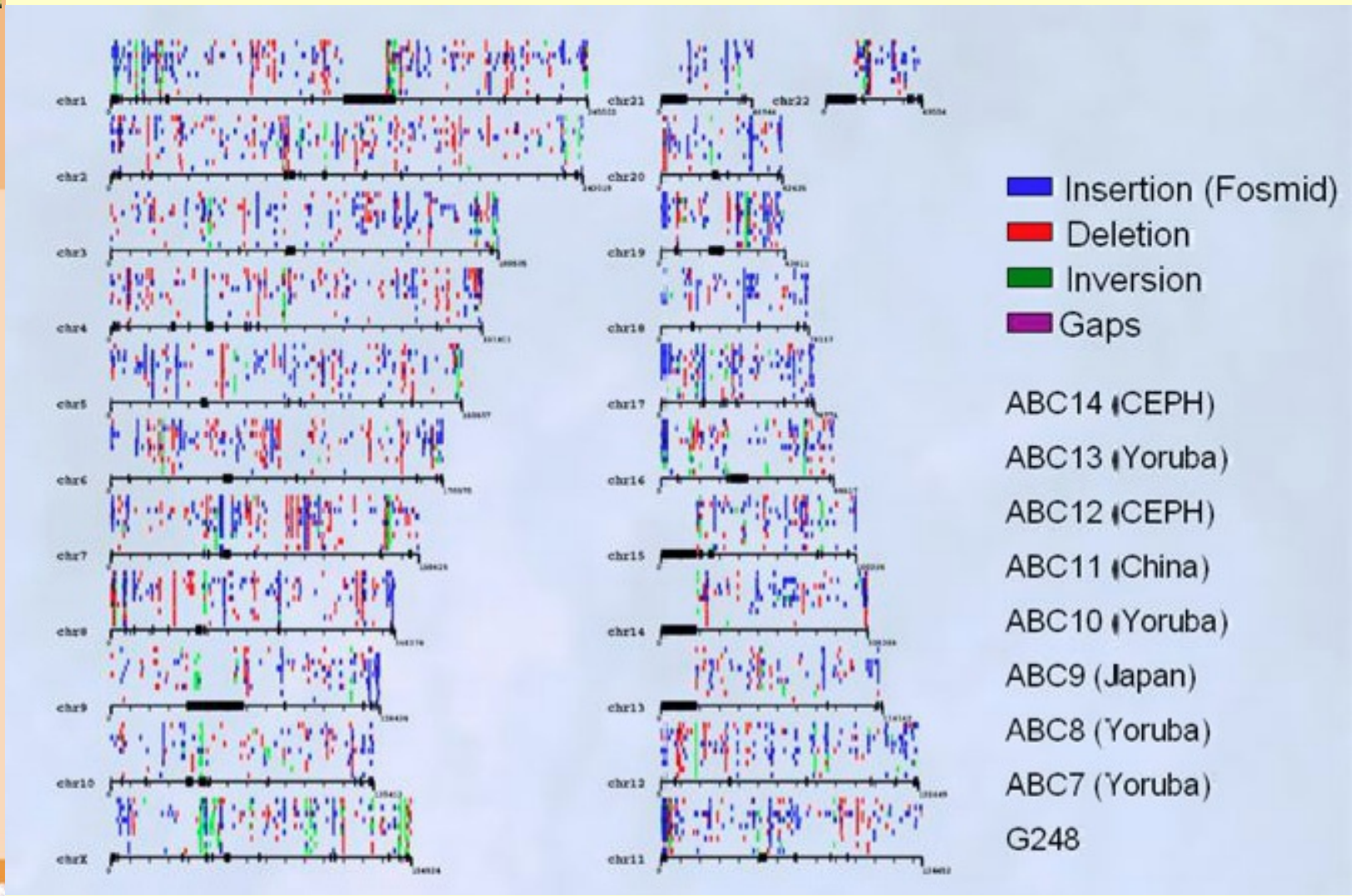
HENRY STEWART TALKS

A Structural Variation Map of Eight Human Genomes



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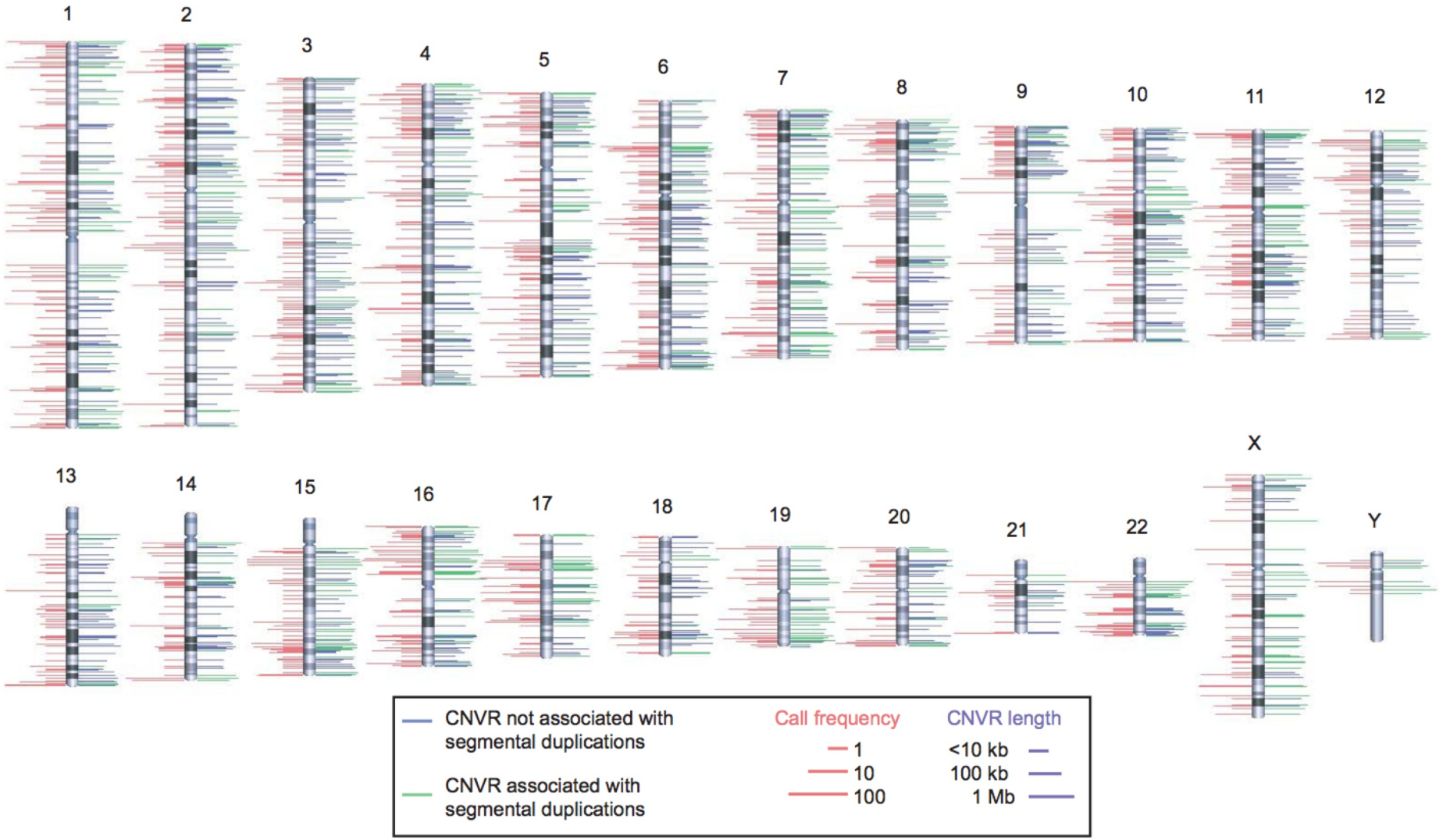
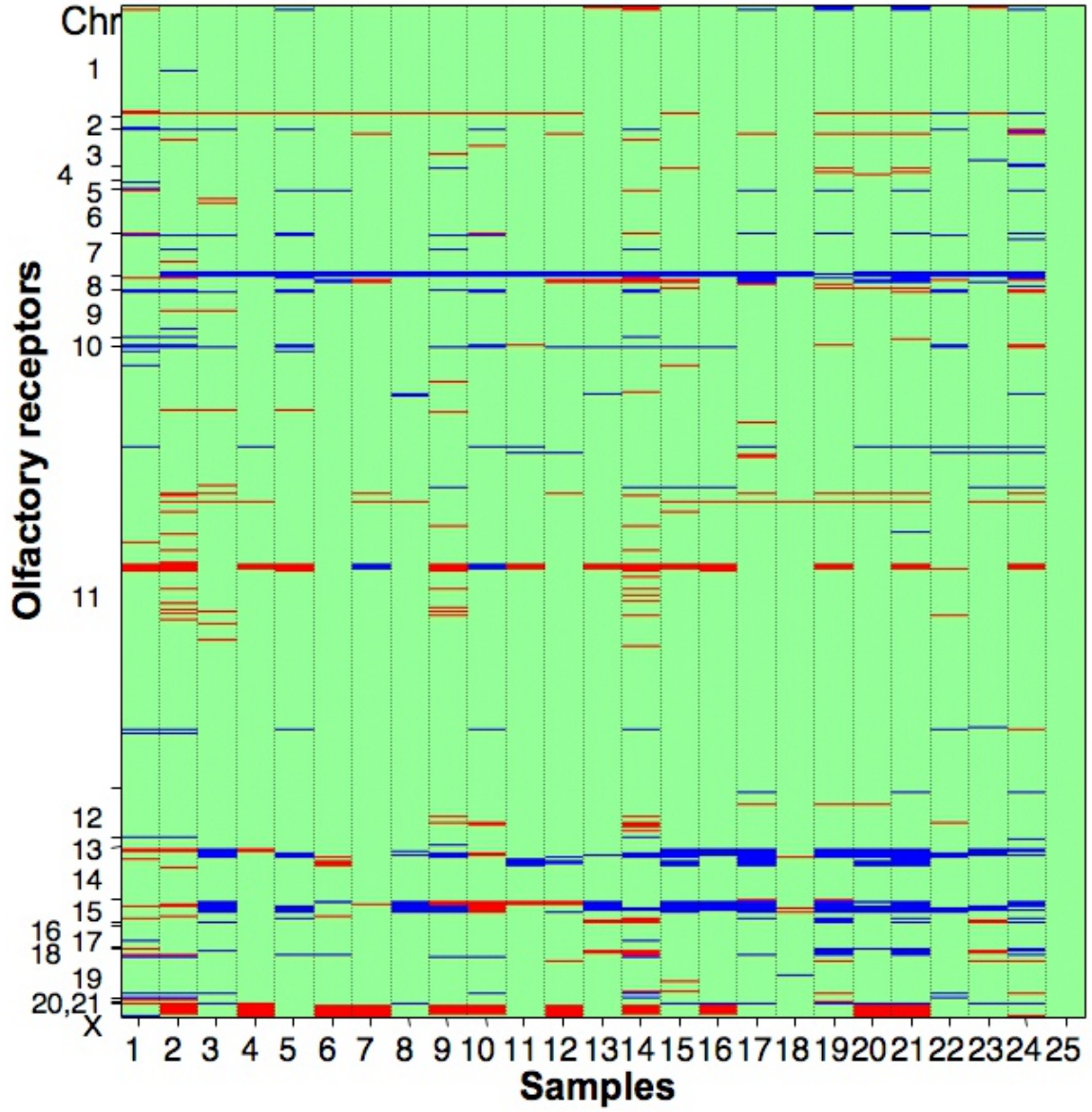
Genomics Distribution of CNV Regions



Courtesy of Mike Snyder

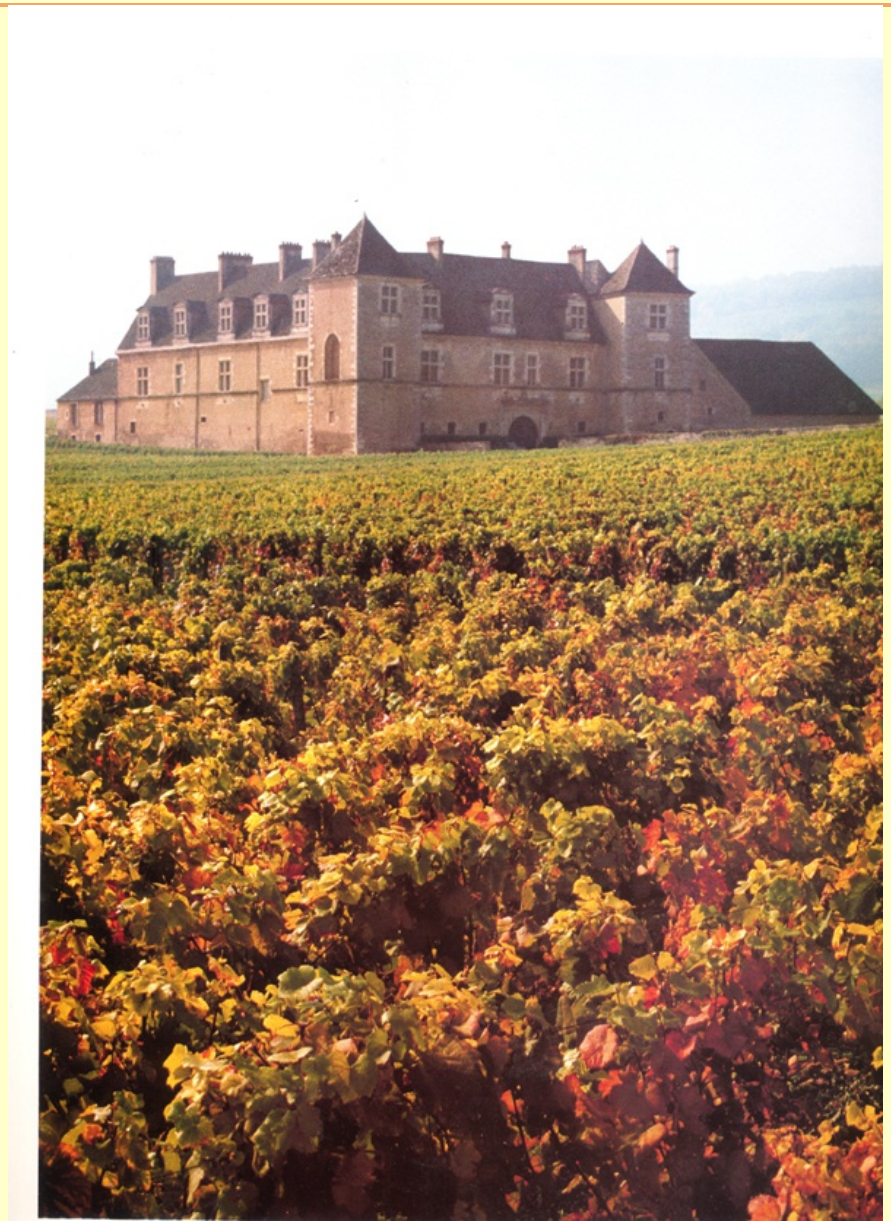
Heterogeneity in Olfactory Receptor Genes

(Examined 851 Olfactory Receptor Loci)



Hasin, ..Snyder, .. Lancet et al. PLoS Genet. 2008 Nov;4(11)

Clos Vougeot in Bourgogne



Chef d'Ordre de la Confrerie des Chevalier du Tastevins

dbVar
Database of genomic structural variation

Charcot-Marie-Tooth Hereditary Neuropathy (CMT1) Disease Results From CNV of PMP22 Gene in 17p11.2-12

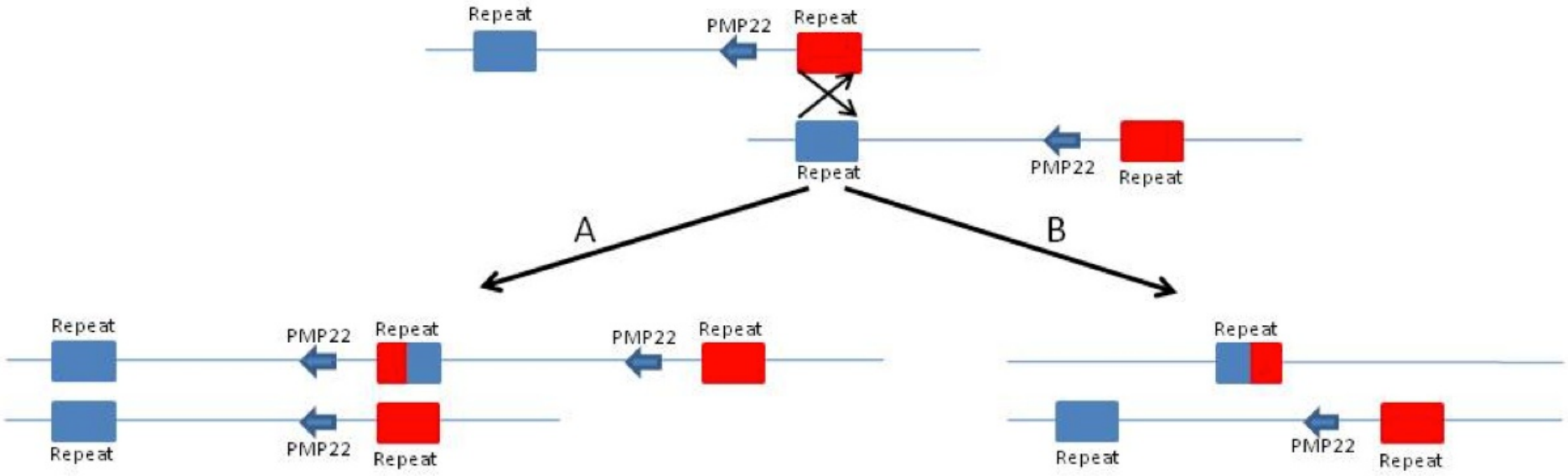
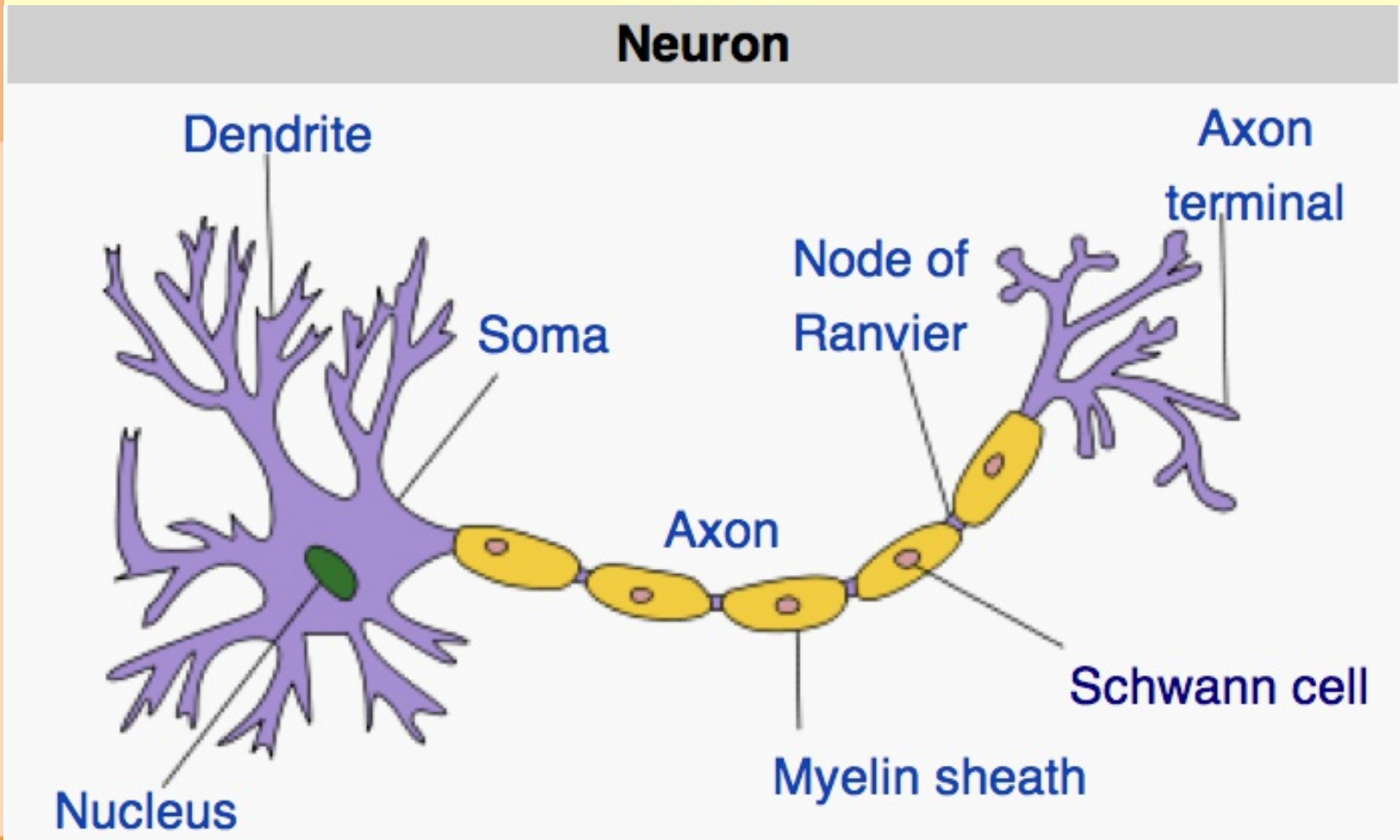


Figure 1: Charcot-Marie Tooth (CMT) disease

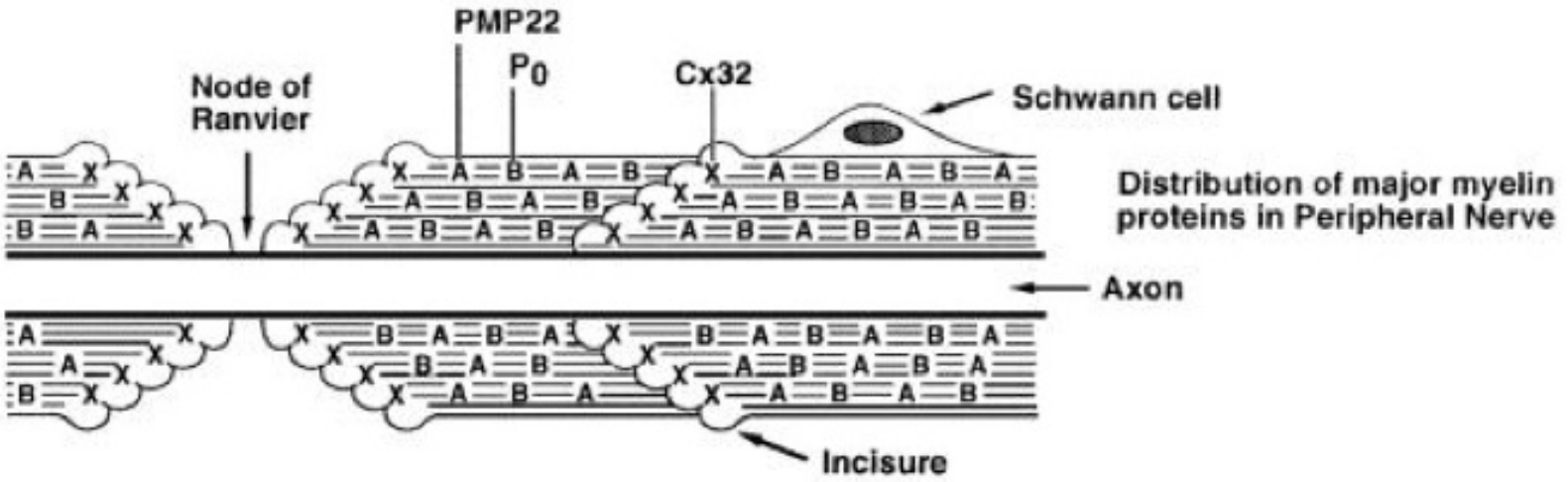
Unequal crossing over between two highly homologous repeats on chromosome 17p12 can result in (A) 3 copies of the PMP22 gene with the CMT1A phenotype or the reciprocal (B) and 1 copy of the PMP22 gene with the HNPP phenotype.

Peripheral Neuropathy, Yuen So, Medical Grand Rounds Jan 16, 2012

Charcot-Marie Tooth Hereditary Peripheral Neuropathy (CMT1) Caused by Abnormal Myelination of Long Axons



Charcot-Marie Tooth Hereditary Peripheral Neuropathy (CMT1) Caused by Abnormal Myelination of Long Axons



Charcot-Marie Tooth Hereditary Neuropathy (CMT1) Disease Genes

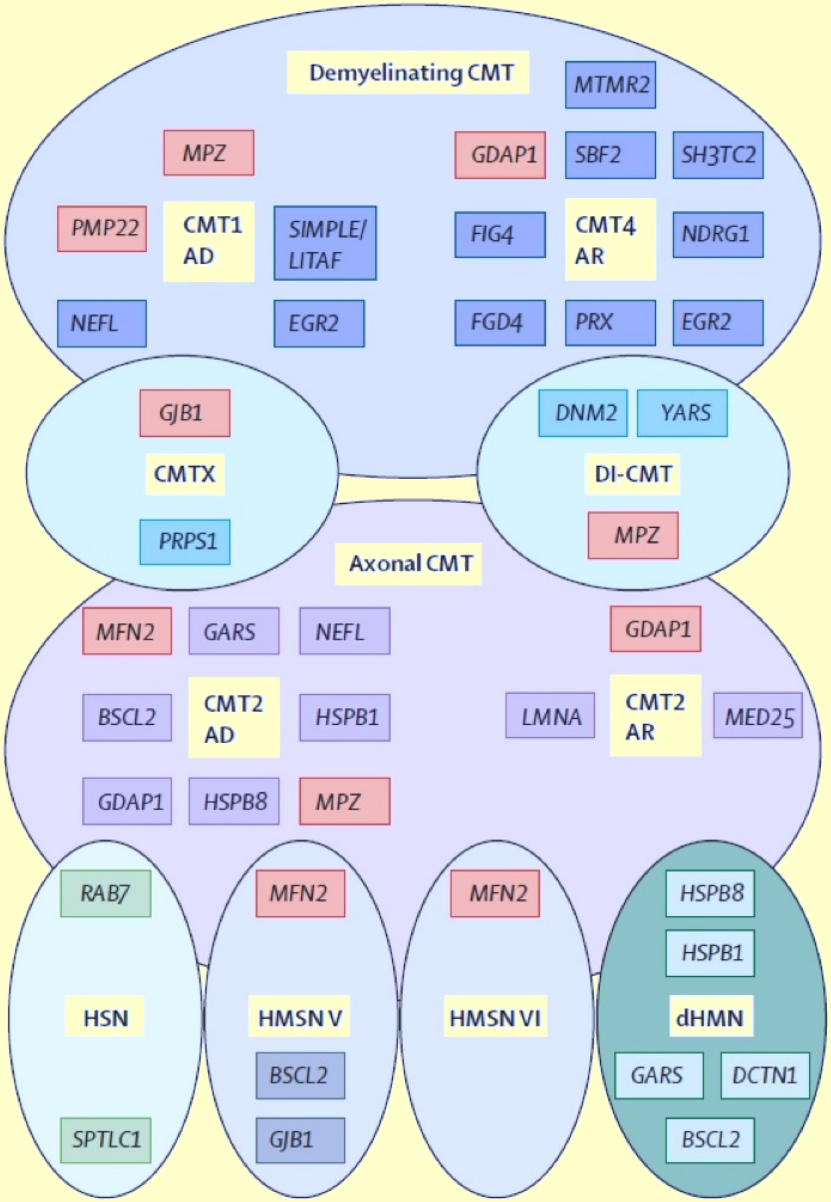
Table 3. CMT1: Molecular Genetics

Locus Name	Proportion of CMT1 (excluding CMTX) [1]	Gene Symbol	Protein Product
CMT1A	70%-80%	*PMP22*	Peripheral myelin protein 22
CMT1B	10%-12%	*MPZ*	Myelin P_0 protein
CMT1C	~1%	*LITAF*	Lipopolysaccharide-induced tumor necrosis factor-alpha factor
CMT1D	Unknown	*EGR2*	Early growth response protein 2
CMT1E	~1%	*PMP22*	Peripheral myelin protein 22 (sequence changes)
CMT1F/2E	Unknown	*NEFL*	Neurofilament light polypeptide

GENEReviews

CMT Hereditary Neuropathy Disease Genes

http://www.ncbi.nlm.nih.gov/books/NBK1358/



Schwann Cell

Attachment proteins

Axon proteins

Axon surface proteins

Gene Reviews
http://www.ncbi.nlm.nih.gov/books/NBK1358/

Structural Variations in Mendelian Disease

Table 3 Summary of common genic structural variations with known phenotypic effect

Gene name(s)	Locus	Population frequency	Diploid copies	Size of variant segment	Associated phenotype
GSTM1	1p13.3	>3%	1–3	18 kb	Altered enzyme activity
RHD	1p36.11	15–20%	0–2	~60 kb	Rhesus blood group sensitivity
SMN2	5q13.2	~60%	1–4	500 kb	Altered severity of spinal muscular atrophy
CYP21A2	6p21.32	1.6%	2–3	35 kb	Congenital adrenal hyperplasia
LPA	6q25.3	94%	2–38	5.5 kb	Altered coronary heart disease risk
α-Defensin gene cluster	8p23.1	~90%	4–14	19 kb	Immune system function
β-Defensin gene cluster	8p23.1	~90%	2–12	240 kb	Immune system function
IGHG1 region	14q32.33	12–74%	1–6	5–170 kb	Immune system function?
CCL3-L1/CCL4-L1	17q12	51%/27%	0–14	>2 kb	Susceptibility to and progression of HIV infection, susceptibility to Kawasaki disease
CYP2A6	19q13.2	1.7%	2–3	7 kb	Altered nicotine metabolism
IGL	22q11.22	28–85%	2–7	5.4 kb	Altered Igκ:Igλ in B lymphocytes
GSTT1	22q11.23	20%	0–2	>50 kb	Altered susceptibility to toxins and cancer
CYP2D6	22q13.1	1–29%	0–13	Undefined	Altered drug metabolism, increased cancer susceptibility
OPN1LW/OPN1MW	Xq28	75%	0–4/0–7	15 kb/13 kb	Defective color vision
Testis-specific genes (*DAZ*, *BPY*, *RBM* families)	Yq11.2	3.2%	0–1	1.6 Mb	Low-penetrance spermatogenic failure

Mendelian CNV mutations (Prof. Joris Veltman in Henry Stewart talks)

Sharp, Cheng & Eichler, Annu. Rev. Genomics Hum. Genet. 2006. 7:407–42

Table 1. Novel Recurrent Copy-Number Changes Associated with Intellectual Disability and Related Disorders.*

Chromosome Region	Coordinates in Mb†	Deletion or Duplication Associated with Disorder	Selected References
1q21.1	Chromosome 1: 145.0–146.35	Deletion: intellectual disability, schizophrenia, multiple congenital anomalies Duplication: intellectual disability, autism	Brunetti-Pierri et al.,[32] Mefford et al.,[33] International Schizophrenia Consortium,[34] Stefansson et al.,[35] Greenway et al.,[36] Haldeman-Englert and Jewett[37]
3q29	Chromosome 3: 197.4–198.9	Deletion: intellectual disability, schizophrenia Duplication: intellectual disability	Ballif et al.,[38] Lisi et al.,[39] Willatt et al.[40]
10q22-q23	Chromosome 10: 81.12–89.07	Deletion: intellectual disability	Balciuniene et al.,[41] van Bon et al.[42]
15q11.2	Chromosome 15: 20.3–20.7	Deletion: intellectual disability, schizophrenia, epilepsy	Stefansson et al.,[35] de Kovel et al.,[43] Mefford et al.,[44] Burnside et al.,[45] Doornbos et al.,[46] Murthy et al.,[47] von der Lippe et al.[48]
15q13.3	Chromosome 15: 28.7–30.2	Deletion: intellectual disability, epilepsy, schizophrenia, autism	Stefansson et al.,[35] Helbig et al.,[49] Sharp et al.,[50] van Bon et al.,[51] Ben-Shachar et al.,[52] Pagnamenta et al.,[53] Miller et al.[54]
15q24	Chromosome 15: 72.2–73.8	Deletion: intellectual disability, autism	Andrieux et al.,[55] Sharp et al.,[56] Mefford et al.,[57] El-Hattab et al.[58]
16p11.2 (a)	Chromosome 16: 29.5–30.1	Deletion: intellectual disability, autism, obesity Duplication: schizophrenia	Weiss et al.,[29] Battaglia et al.,[59] Bijlsma et al.,[60] Hempel et al.,[61] Shinawi et al.,[62] Jacquemont et al.,[63] Walters et al.,[64] McCarthy et al.[65]
16p11.2 (b)	Chromosome 16: 28.7–29.0	Deletion: intellectual disability, obesity	Bachmann-Gagescu et al.,[66] Bochukova et al.[67]
16p12	Chromosome 16: 21.8–22.4	Deletion: intellectual disability	Girirajan et al.[68]
16p13.11	Chromosome 16: 15.4–16.4	Deletion: intellectual disability, epilepsy, autism, schizophrenia Duplication: intellectual disability, ADHD, autism	de Kovel et al.,[43] Mefford et al.,[44] Heinzen et al.,[69] Williams et al.,[70] Ullmann et al.,[71] Kirov et al.[72]
17q12	Chromosome 17: 31.8–33.3	Deletion: intellectual disability, autism, schizophrenia	Moreno-De-Luca et al.,[73] Loirat et al.[74]
17q21.3	Chromosome 17: 41.0–41.7	Deletion: intellectual disability	Koolen et al.,[20] Sharp et al.,[23] Shaw-Smith et al.,[24] Koolen et al.[75]

* The listed recurrent deletions and duplications are those that have been reported since 2006. ADHD denotes attention deficit–hyperactivity disorder.

† The coordinates are based on the National Center for Biotechnology Information (NCBI) build 36.

Next Generation Sequencing to Identify Genes Associated with Learning Diability

Study	Disorder	Presumed Inheritance	Type of Analysis	Genes
Ng et al.[97]	Kabuki syndrome	De novo dominant	Multiple affected	*MLL2*
Hoischen et al.[98]	Schinzel–Giedion syndrome	De novo dominant	Multiple affected	*SETBP1*
Vissers et al.[99]	Nonsyndromic sporadic intellectual disability	De novo dominant	Trio	Multiple
Najmabadi et al.[100]	Recessive intellectual disability	Autosomal recessive, consanguineous families	Targeted recessive	Multiple
Calişkan et al.[101]	Recessive intellectual disability	Autosomal recessive, consanguineous family	Recessive	TECR
O'Roak et al.[102]	Autism	De novo dominant	Trio	*FOXP1, GRIN2B, SCN1A, LAMC3*

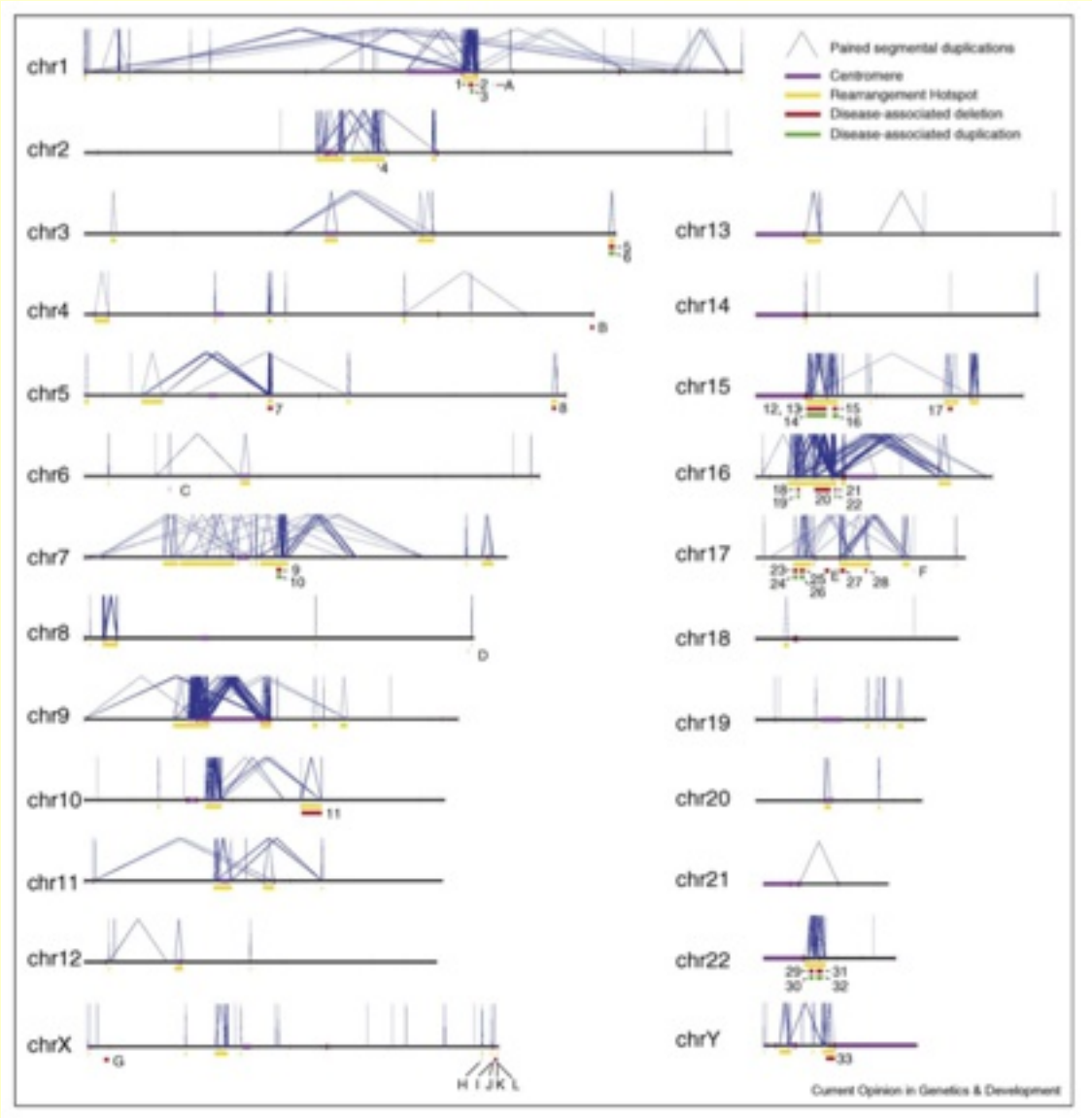
Feero et al. N Engl J Med 2012;366:733-43.

Inversions Lead to Instability & Disease

Table 2 Summary of polymorphic inversions that predispose to further rearrangements

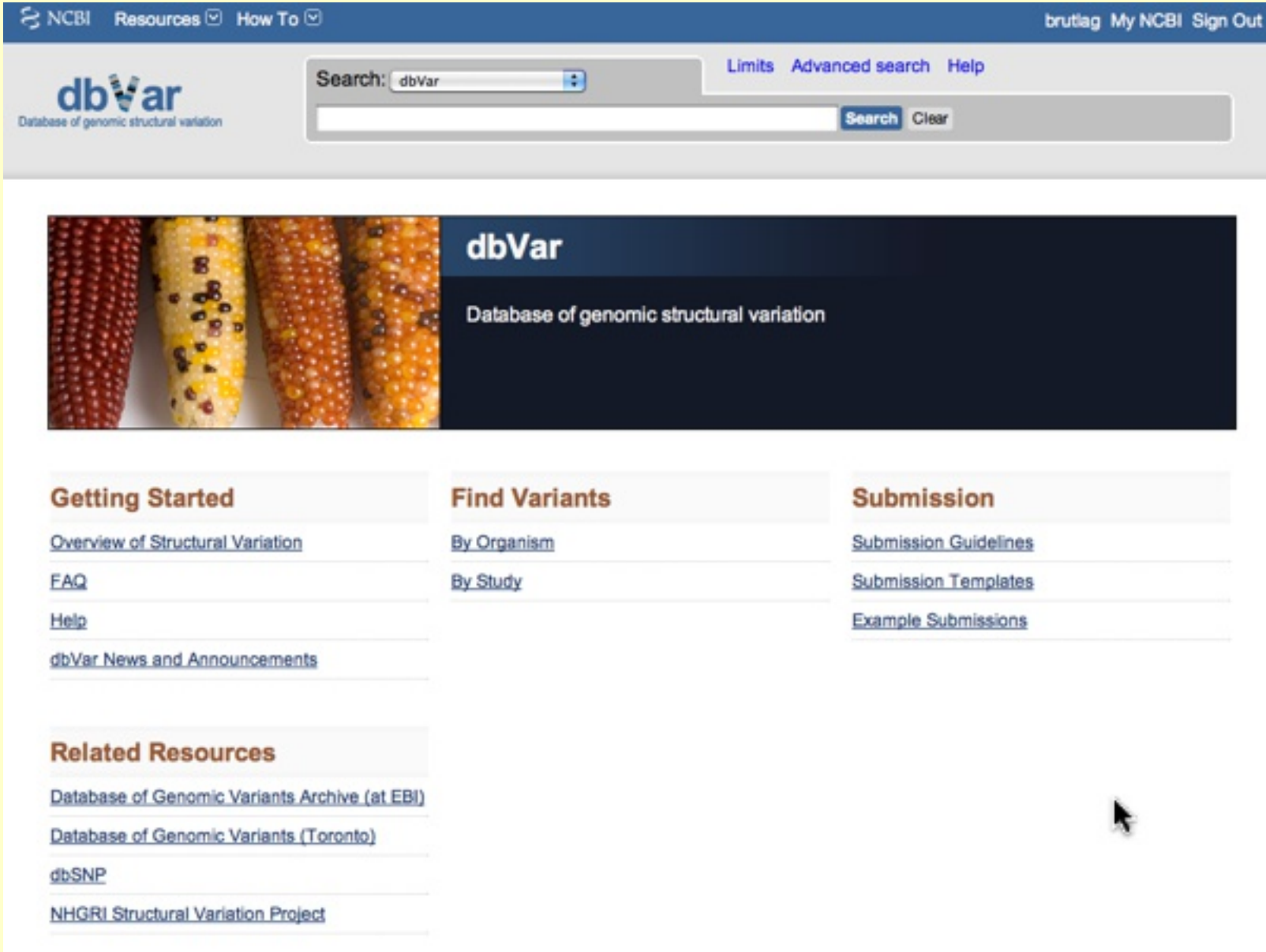
Locus	Cytogenetic location	Population frequency	Size of inversion region	Associated predisposition
OR genes	4p16	12%	~6 Mb	t(4;8)(p16;p23) translocation
Sotos syndrome critical region	5q35	Unknown	2.2 Mb	Deletion of SoS critical region
Williams-Beuren syndrome critical region	7q11.23	Unknown	1.6 Mb	Deletion of WBS critical region (and atypical WBS phenotype?)
OR genes	8p23	26%	4.7 Mb	inv dup(8p), +der(8)(pter-p23.1::p23.2-pter) and del(8)(p23.1;p23.2)
Angelman syndrome critical region	15q11-q13	9%	~4.5 Mb	Deletion of AS critical region
Proximal Yp	Yp11.2	33%	~4 Mb	*PRKX/PRKY* translocation (sex reversal)

Inversion Hot Spots Associated with Disease



dbVAR Database at NCBI

http://www.ncbi.nlm.nih.gov/dbvar



dbVAR Report on PMP22 Gene

http://www.ncbi.nlm.nih.gov/dbvar

dbVar
Database of genomic structural variation

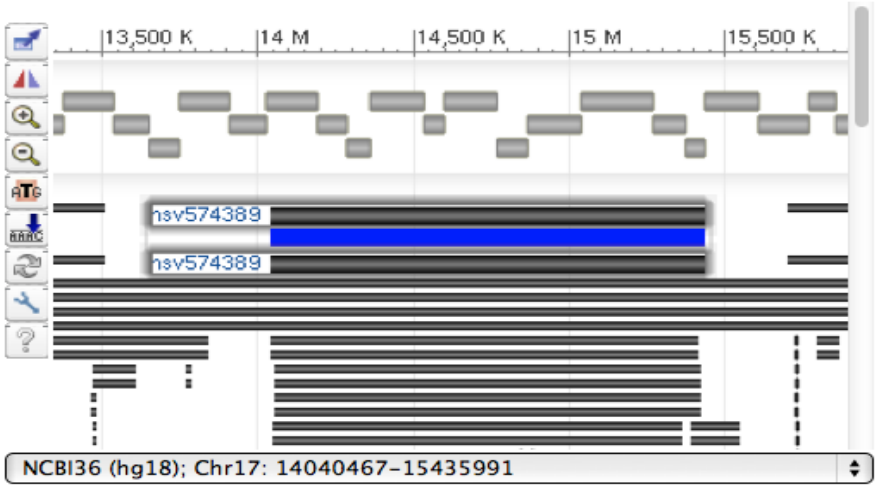
NCBI Resources How To

dbVar dbVar

Limits Advanced

Variant Information

- **Variant accession:** nsv574389
- **Organism:** Human
- **Study:** nstd54
- **Variant Type:** CNV
- **Method type:** SNP array
- **Validation:** Not tested
- **Genomic location:**
- **Submitted:** NCBI36 (hg18); Chr17: 14,040,467 - 15,435,991



Detailed Variant Placement Information

ID	Placement Type	Assembly	Placement	Start	Stop
NC_000017.9	Submitted Genomic	NCBI36 (hg18)	Chr17	14,040,467	15,435,991

Supporting Variants

ID	Type	Allele Length	Sample ID	Subject Phenotype	Assembly	Placement	Start	Stop	Placement Type
nssv867002	Gain	1395524		Not reported	NCBI36 (hg18)	Chr17	14,040,467	15,435,991	Submitted Genomic

Homo sapiens chromosome 17, reference assembly, complete sequence

NCBI Reference Sequence: NC_000017.9

This sequence has been updated. See current version.

GenBank FASTA

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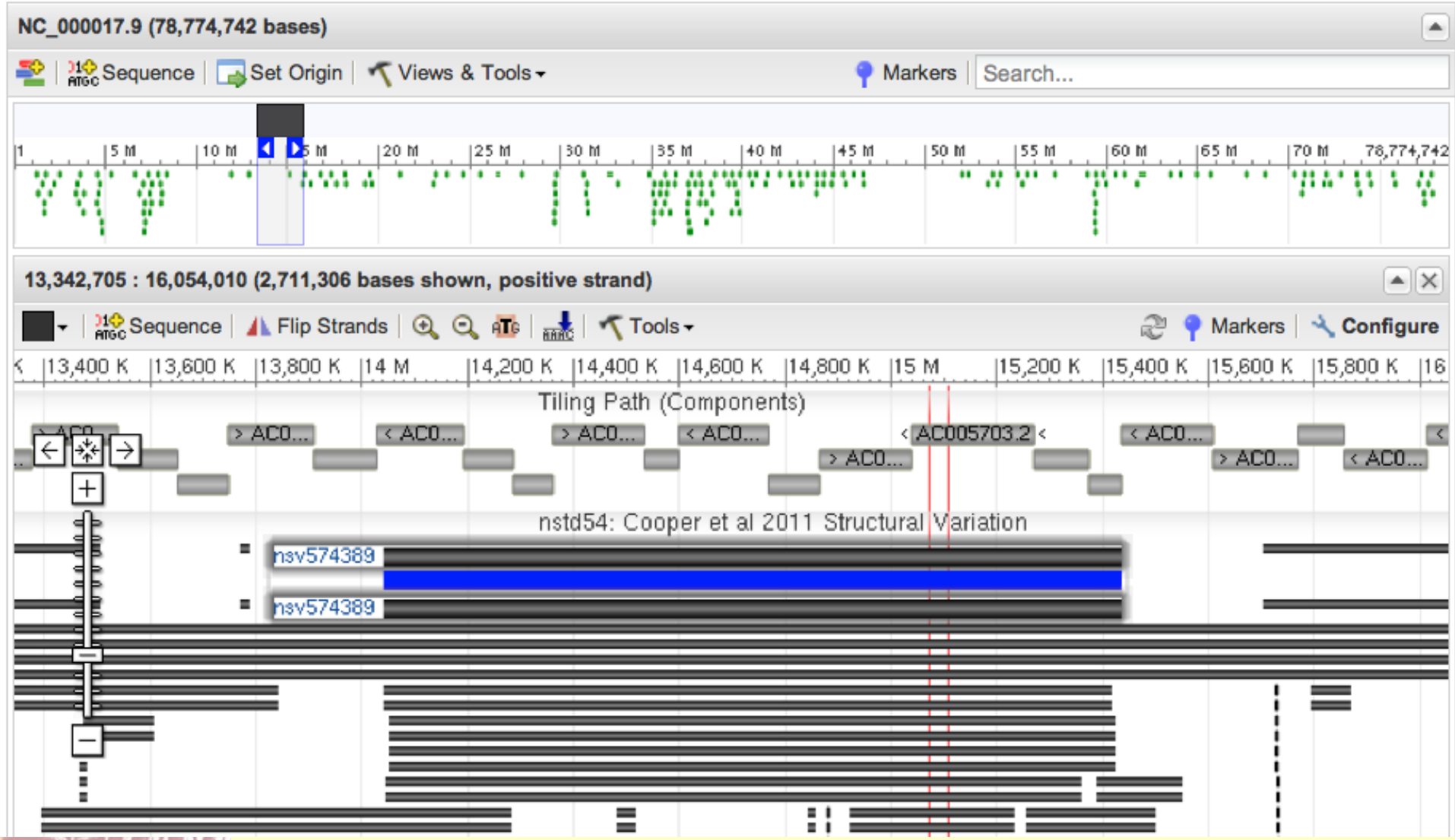

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Database of Genomics Variants

http://dgv.tcag.ca/dgv/app/home

Database of Genomic Variants

A curated catalogue of structural variation in the human genome

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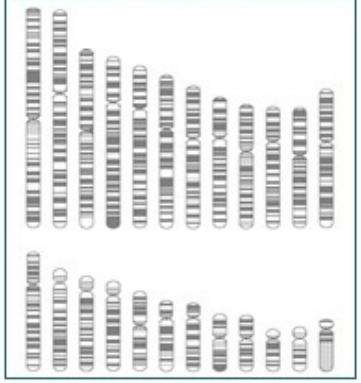
About The Project | Genome Browser | Download | Links | Data Submissions | Email us

Please select genome assembly: Build 36 (Mar. 2006)

View Data by Chromosome

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y All

View Data by Genome



Keyword Search

cmt Search

Exact Match? Yes No

Examples: clone name, accession number, cytoband or gene

BLAT Search

Enter sequence in FASTA format here:

BLAT Search

Summary Statistics

Total entries: 101923 (hg18)
CNVs: 66741
Inversions: 953
InDels (100bp-1Kb): 34229
Total CNV loci: 15963
Articles cited: 42

Last updated: Nov 02, 2010
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The New DGV Beta Site has launched! Access it here

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Applied Genomics

Database of Genomic Variants

A curated catalogue of human genomic structural variation

File Help

Genomic Variants in Human Genome (Build GRCh38: Dec. 2013, hg38): 800 kbp from chr7:71,890,181..72,690,180

Browser | Select Tracks | Custom Tracks | Preferences

Search

Landmark or Region:

chr7:71,890,181..72,690,18 Search

Examples: chr7:71890181..72690180, CFTR, AC108171.3, nsv529033.

Data Source

Genomic Variants in Human Genome (Build GRCh38: Dec. 2013, hg38)

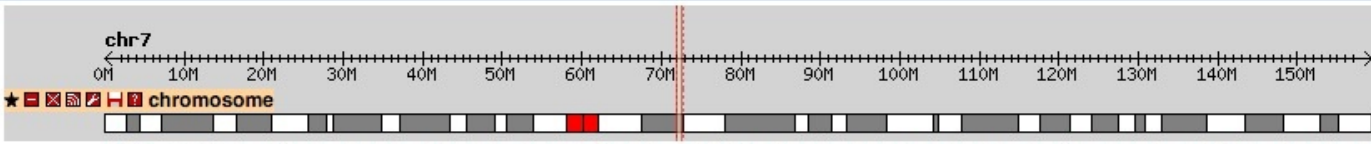
Scroll/Zoom: Show 800 kbp

Filter variants

study = + -

Filter Reset

Overview



Details

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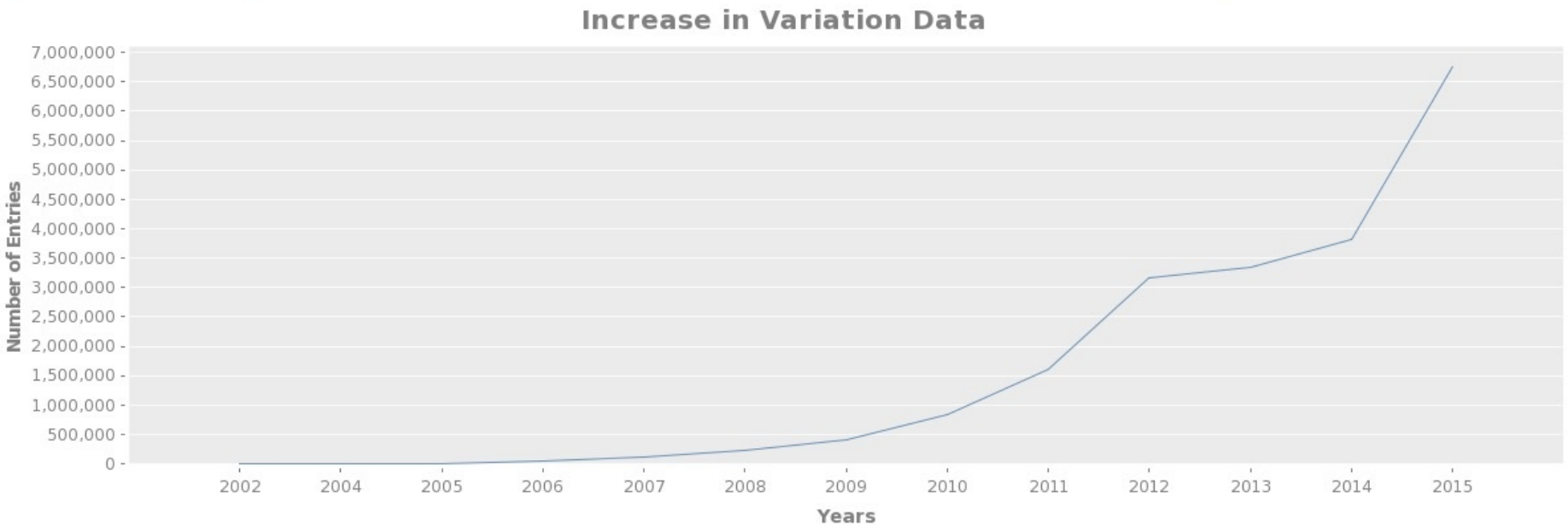
Database of Genomics Variants

http://projects.tcag.ca/variation/

Content Growth

This graph shows the increase in published structural variation data that have been added to the database since its start in 2004; the numbers reflect the year of publication.



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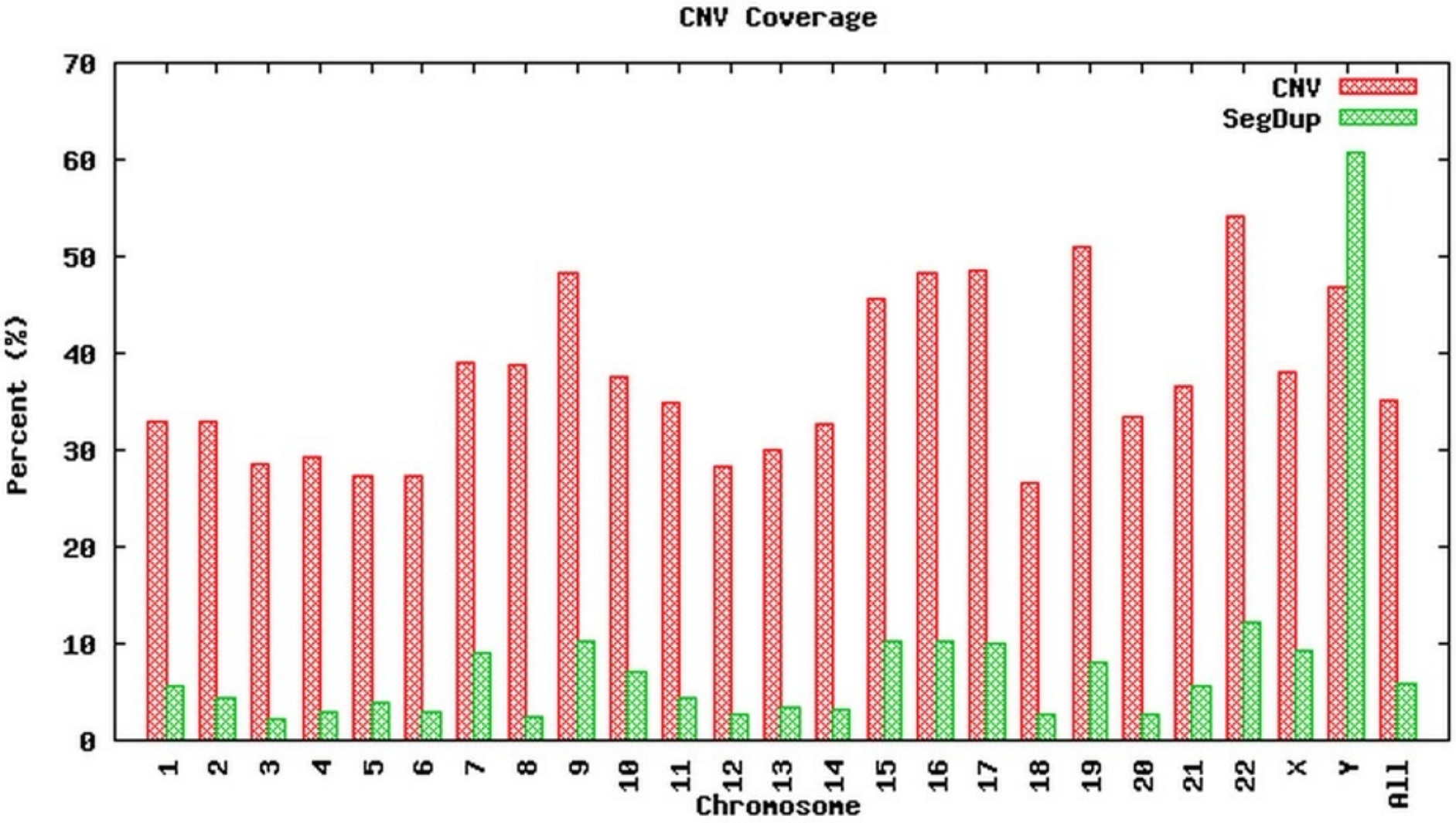
http://projects.tcag.ca/variation/



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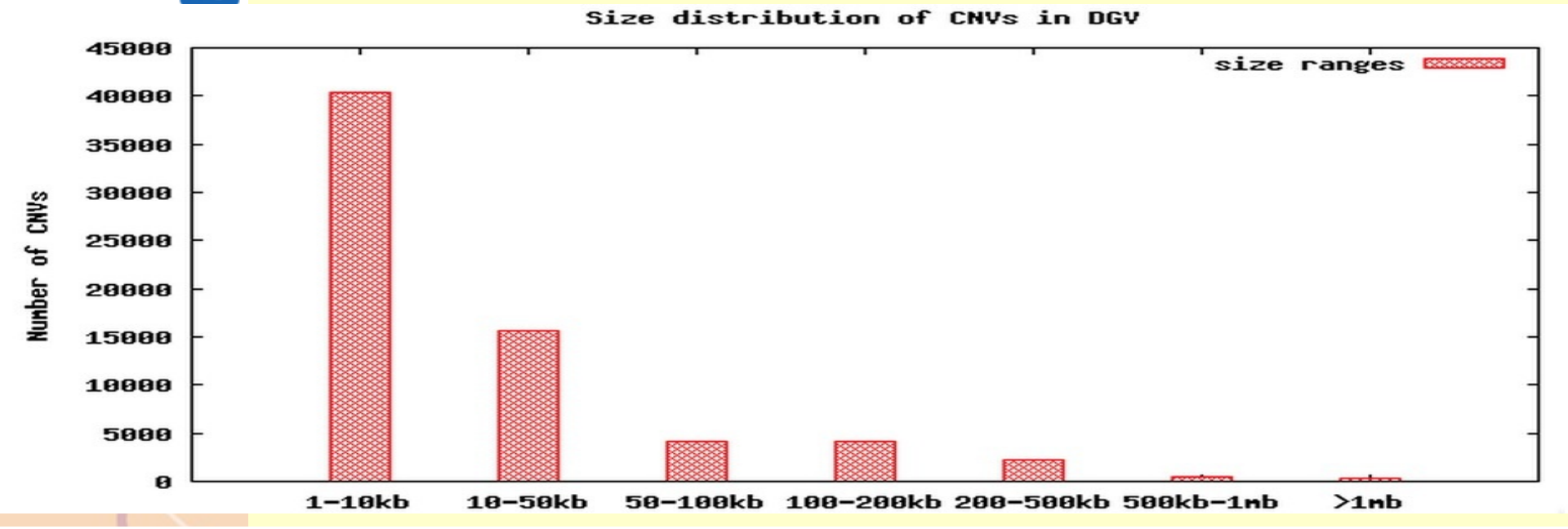
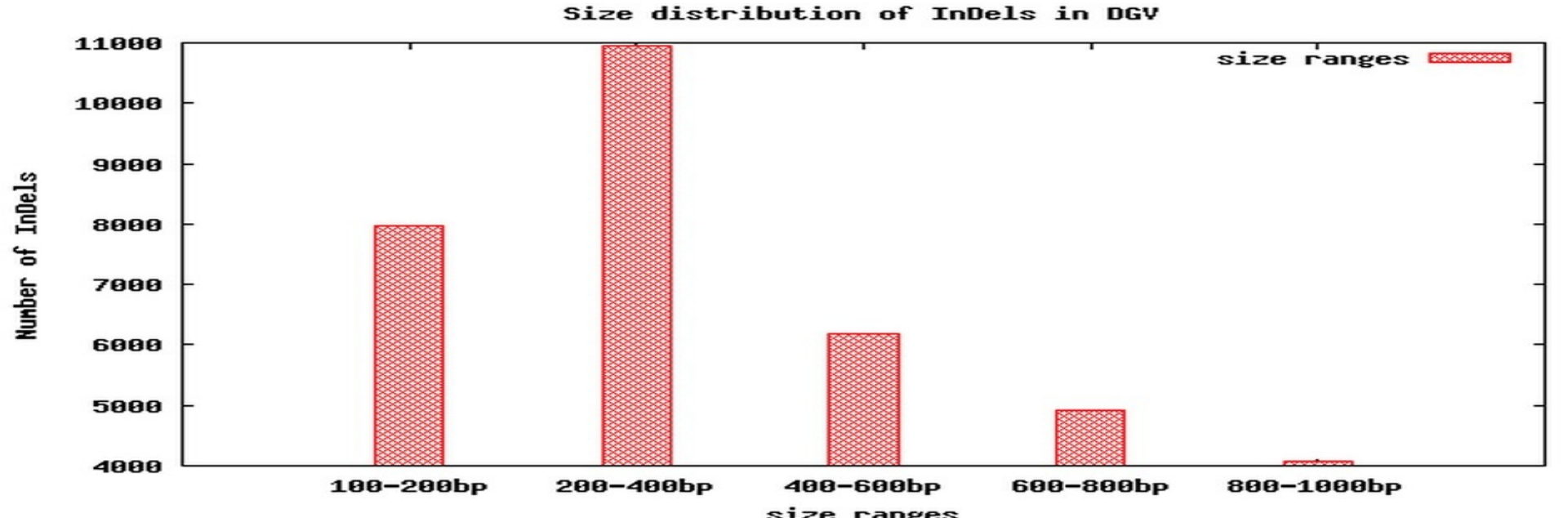
Database of Genomics Variants

http://projects.tcag.ca/variation/project.html





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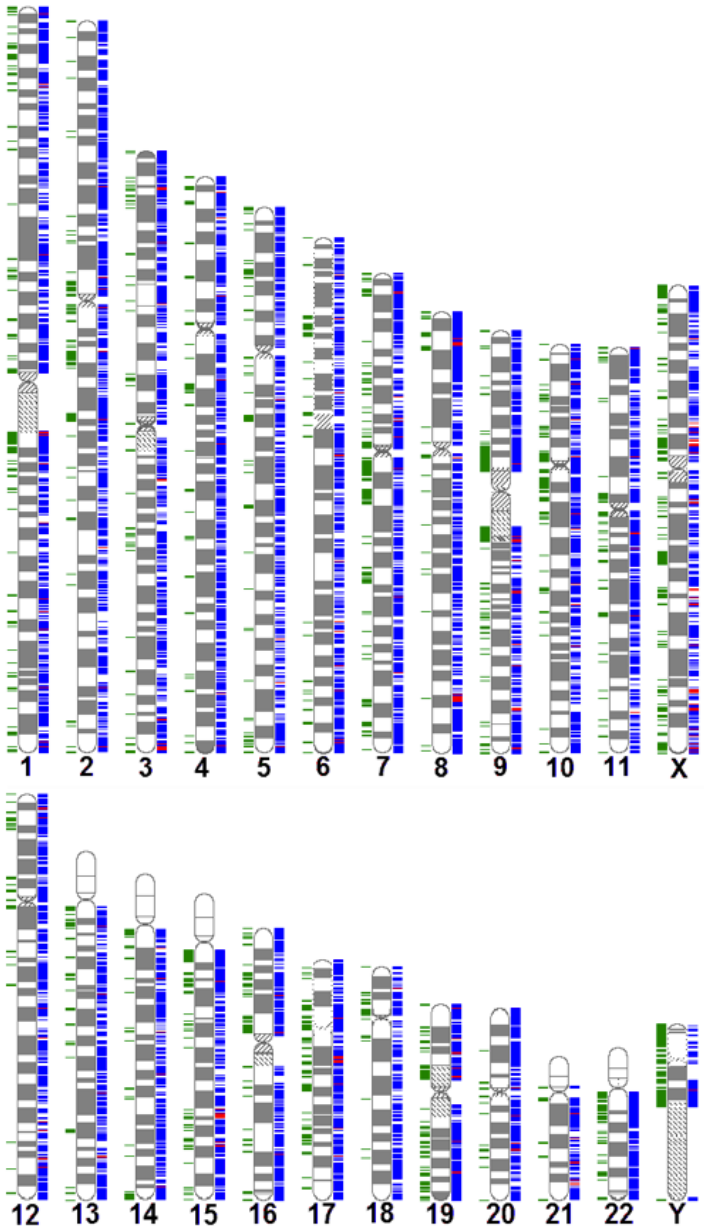
Database of Genomic Variants

Genome-wide view of CNVs

Click on a cytoband to get a list of variants detected within that region



Legend: Blue bars indicate reported CNVs; Red bars indicate reported inversion breakpoints; Green bars to the left indicate segmental duplications.

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Showing 5 Mbp from chr17, positions 12,649,493 to 17,649,492

Instructions
Search using a sequence name, gene name, locus, or other landmark. The wildcard character * is allowed. To center on a location, click the ruler. Use the Scroll/Zoom buttons to change

Examples: chr7:71890181..72690180, CFTR, NM_030798.

[Hide banner] [Bookmark this] [Link to Image] [High-res Image] [Help] [Reset]

Search

Landmark or Region:

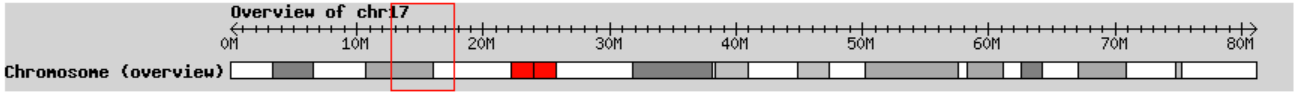
chr17:12649493..1764949 Search

Data Source

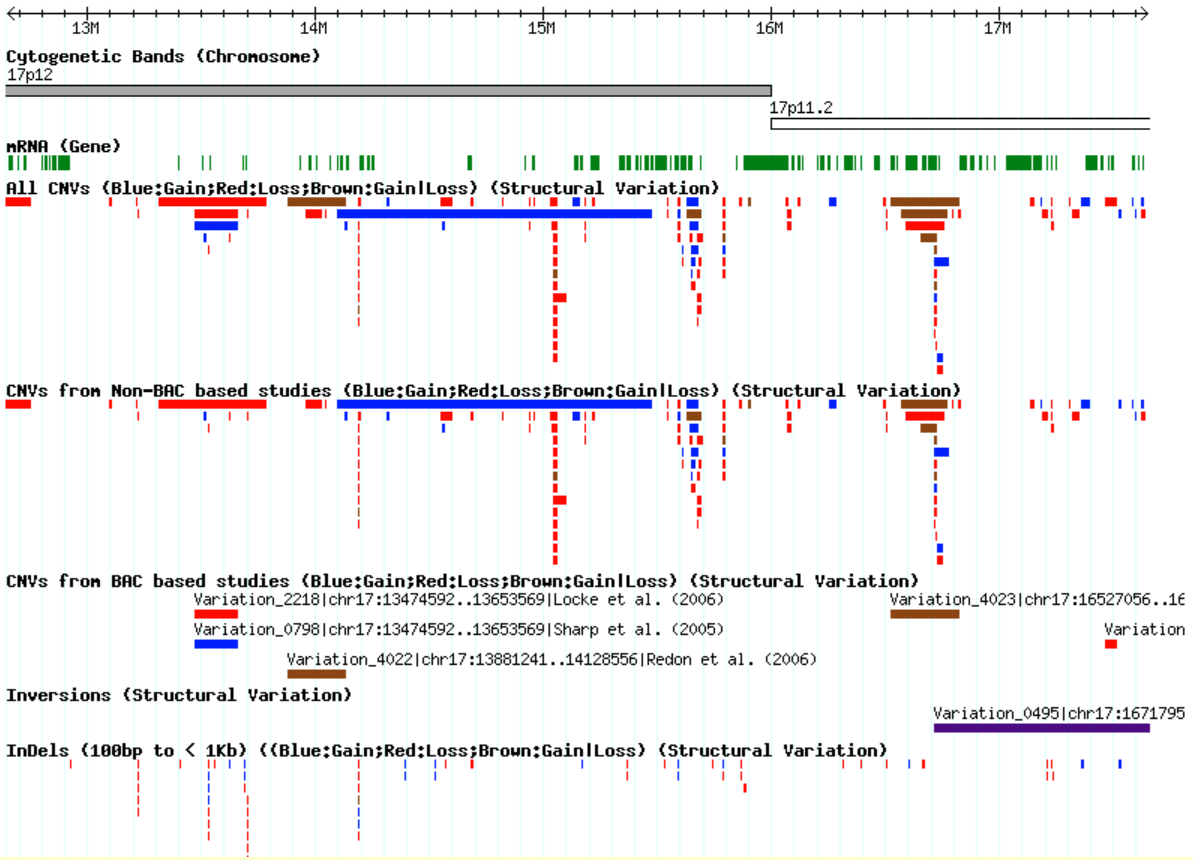
Genomic Variants in Human Genome (GRCh 37: Feb. 2009) (hg19)

Scroll/Zoom: Show 5 Mbp Flip

Overview



Details



NHGRI Structural Variation Project

http://www.ncbi.nlm.nih.gov/projects/genome/StructuralVariation/NHGRIStructuralVariation.shtml

NCBI

NHGRI Structural Variation Clone Viewer | NHGRI | Eichler Lab | White Paper on structural genomics

NHGRI Structural Variation Project

The sequence-based Survey of Human Structural Variation aims to characterize common structural variants that are larger than SNPs, for example, multi-base insertions/deletions, inversions, translocations, and duplications. The approach entails sequencing the ends of fosmids and BACs from multiple individuals. This strategy can be efficiently scaled with current technology and is complementary to efforts to obtain human structural variation information by other technologies. more...

Fosmid library information

HapMap Identifier	Population	Library Name	Status	End sequences submitted to Trace	Full insert sequences submitted to GenBank	Reference
NA15510	N/A	WI2 (G248)	Complete	2,298,885	322	Tuzun et el., 2005
NA18517	Yoruba	ABC7	Complete	2,152,975	115	Kidd et al., 2008
NA18507	Yoruba	ABC8	Complete	3,888,476	169	Kidd et al., 2008
NA18956	Japan	ABC9	Complete	2,084,892	651	Kidd et al., 2008
NA19240	Yoruba	ABC10	Complete	2,121,489	385	Kidd et al., 2008
NA18555	China	ABC11	Complete	1,966,644	313	Kidd et al., 2008
NA12878	CEPH	ABC12	Complete	2,169,280	312	Kidd et al., 2008
NA19129	Yoruba	ABC13	Complete	2,057,345	257	Kidd et al., 2008
NA12156	CEPH	ABC14	Complete	2,089,193	206	Kidd et al., 2008
NA18552	China	JCVI*	Complete	1,992,678		
NA18947	Japan	ABC16	Ongoing	1,546,191	12	
NA18564	China	ABC17	Ongoing	56,944		
NA10847	CEPH	ABC18	Ongoing	1,209,419		
NA18573	China	ABC19	Ongoing	43,351		
NA19102	Yoruba	ABC20	Ongoing	89,566		
NA11993	CEPH	ABC21	Ongoing	684,716		
NA11840	CEPH	ABC22	Ongoing	785,461		
NA18523	Yoruba	ABC23	Ongoing	1,544,982		
NA18502	Yoruba	ABC24	Ongoing	1,388,082	22	
NA11832	CEPH	ABC25	Ongoing	12,286		
NA18861	Yoruba	ABC26	Ongoing	14,559		
NA18942	Japan	ABC27	Ongoing	1,234,412	8	

* The JCVI library is comprised of 4 libraries: COR01, COR02, COR2A and COR03

NHGRI Structural Variation Clone Viewer

http://www.ncbi.nlm.nih.gov/projects/genome/StructuralVariation/NHGRIStructuralVariation.shtml

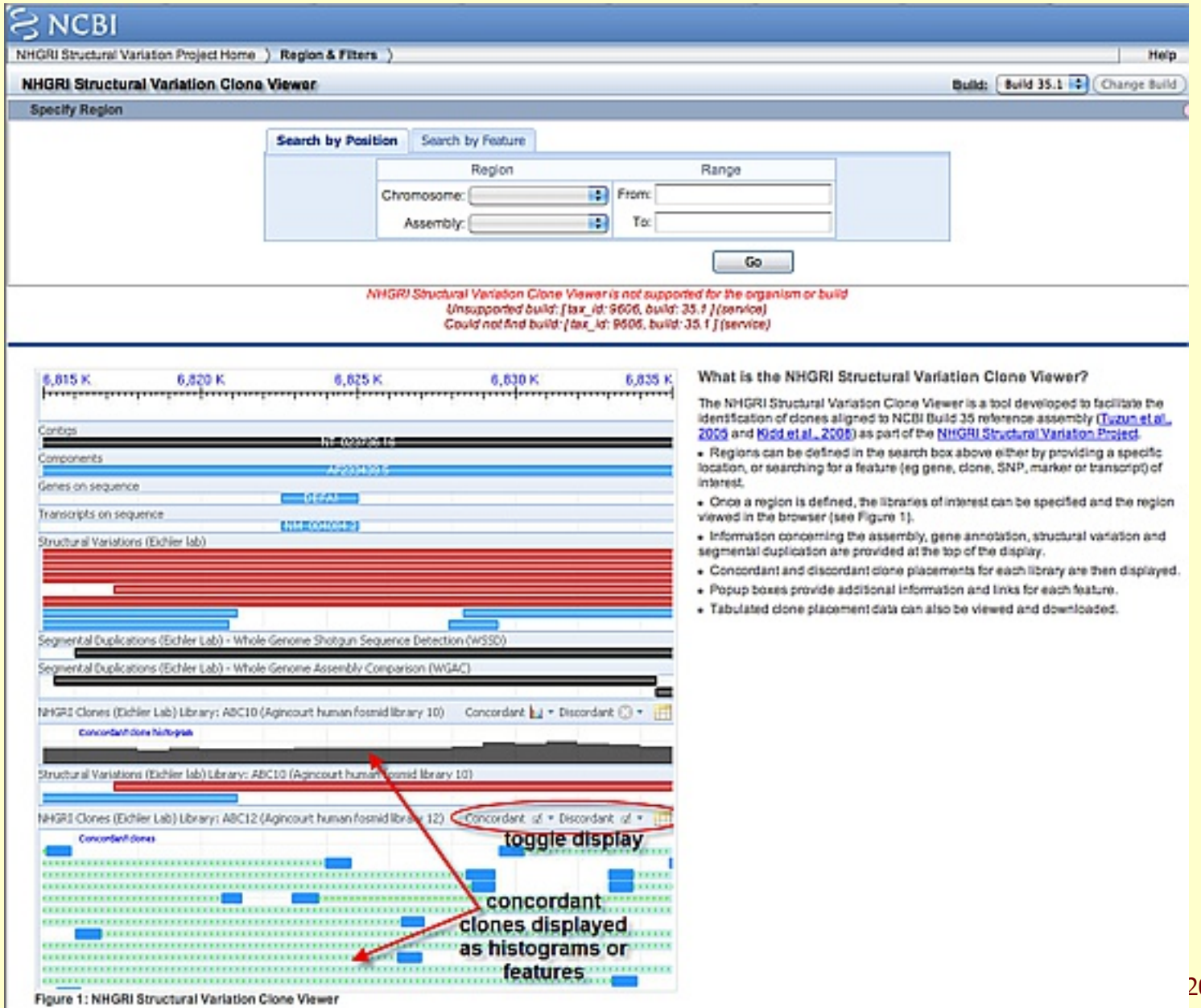
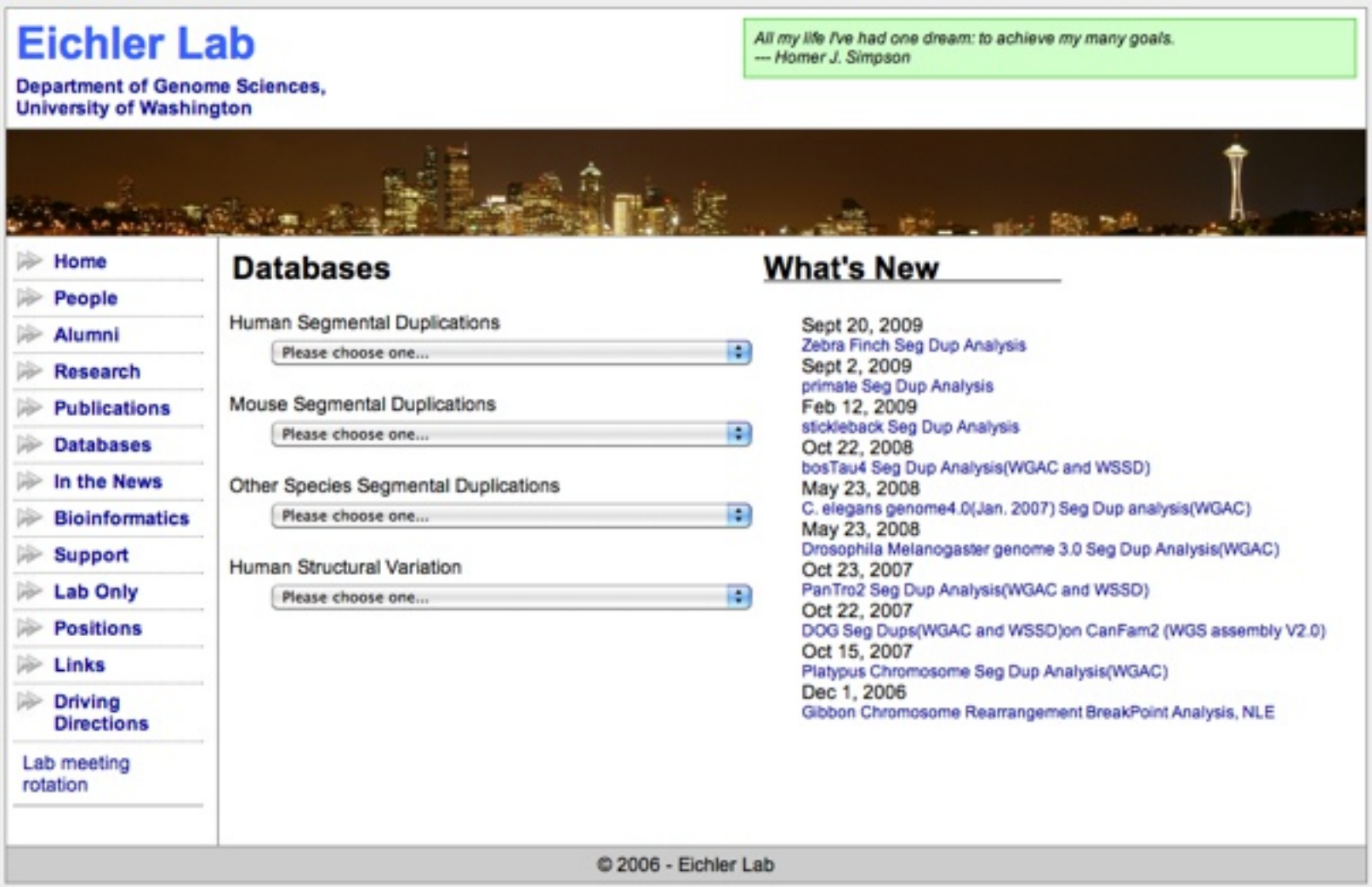


Figure 1: NHGRI Structural Variation Clone Viewer

Eichler Lab

http://eichlerlab.gs.washington.edu/database.html



HENRY STEWART TALKS

Copy Number Variation and Disease 2008

Gene	Type	Duplicated Segment	Disease/Phenotype	
C4A/C4B	Decrease	32.8 kb	Lupus* (SLE)	Yang, 2007
DEFB4.103,104	Increase	310 kb	Psoriasis	Hollox, 2008
	Decrease		Crohn disease, IBD	Fellerman, 2006
CCL3L1	Decrease	64 kb	HIV susceptibility	Gonzalez, 2005
FCGR3B	Decrease	**	Glomeruloneprhitis	Aitman, 2006
				Fanciulli, 2008
IRGM	Deletion	**	Crohn disease	Parkes, 2007

**correspond to more ancient primate segmental duplications

Henry Stewart Talks: Evan Eichler
http://hstalks.com/main/view_talk.php?t=1409&r=439&j=757&c=252

HENRY STEWART TALKS

Copy Number Variation and Disease

Copy number polymorphism in *Fcgr3* predisposes to glomerulonephritis in rats and humans

Timothy J. Aitman[1], Rong Dong[1*], Timothy J. Vyse[2*], Penny J. Norsworthy[1*], Michelle D. Johnson[1], Jennifer Smith[3], Jonathan Mangion[1], Cheri Roberton-Lowe[1,2], Amy J. Marshall[1], Enrico Petretto[1], Matthew D. Hodges[1], Gurjeet Bhangal[3], Sheetal G. Patell[3], Kelly Sheehan-Rooney[3], Mark Duda[1,3], Paul R. Cook[1,3], David J. Evans[3], Jan Domin[3], Jonathan Flint[4], Joseph J. Boyle[5], Charles D. Pusey[5] & H. Terence Cook[5]

Nature, 2006

The Influence of *CCL3L1* Gene–Containing Segmental Duplications on HIV-1/AIDS Susceptibility

Enrique Gonzalez,[1*] Hemant Kulkarni,[1*] Hector Bolivar,[1*†] Andrea Mangano,[2*] Racquel Sanchez,[1‡] Gabriel Catano,[1‡] Robert J. Nibbs,[3‡] Barry I. Freedman,[4‡] Marlon P. Quinones,[1‡] Michael J. Bamshad,[5] Krishna K. Murthy,[6] Brad H. Rovin,[7] William Bradley,[8,9] Robert A. Clark,[1] Stephanie A. Anderson,[8,9] Robert J. O'Connell,[9,10] Brian K. Agan,[9,10] Seema S. Ahuja,[1] Rosa Bologna,[11] Luisa Sen,[2] Matthew J. Dolan,[9,10,12‡] Sunil K. Ahuja[1‡]

Science, 2005, **307**

A Chromosome 8 Gene-Cluster Polymorphism with Low Human Beta-Defensin 2 Gene Copy Number Predisposes to Crohn Disease of the Colon

Klaus Fellermann, Daniel E. Stange, Elke Schaeffeler, Hartmut Schmalzl, Jan Wehkamp, Charles L. Bevins, Walter Reinisch, Alexander Teml, Matthias Schwab, Peter Lichter, Bernhard Radlwimmer, and Eduard F. Stange

The American Journal of Human Genetics, 2006, **79**