### Genomics, Bioinformatics & Medicine http://biochem158.stanford.edu/

### Simple Nucleotide Polymorphisms http://biochem158.stanford.edu/SNPs.html





Doug Brutlag Professor Emeritus of Biochemistry & Medicine Stanford University School of Medicine © Doug Brutlag 2015

# ScienceHuman Genetic VariationMAAS2007 Scientific Breakthrough of the Year

### 2007 SCIENTIFIC BREAKTHROUGH OF THE YEAR



Individual 1 Individual 2 Individual 3 Individual 4 Science Magazine, December 21, 2007

### "It's all about me!"

# Single Nucleotide Polymorphisms (SNPs)





### International HapMap Project http://www.hapmap.org/



### International HapMap Project

Home I About the Project I Data I Publications I Tutorial

#### 中文 | English | Français | 日本語 | Yoruba

The International HapMap Project is a partnership of scientists and funding agencies from Canada, China, Japan, Nigeria, the United Kingdom and the United States to develop a public resource that will help researchers find genes associated with human disease and response to pharmaceuticals. See "About the International HapMap Project" for more information.

Project Information	News
About the Project	2013-06-14: HapMap data conversion tool
HapMap Tutorial HapMap Mailing List	There are several inquires for a conversion tool to convert HapMap data into the VCF format. Please take a look of The Genome Analysis Toolkit (by Broad Institute).
HapMap Project Participants	2012-12-06: Downtime for hardware maintenance
Project Data	From December 15 - 16, Hapmap site will be taken offline for an internal hardware maintenance. Sorry for the inconvenience.
HapMap Genome Browser release #28 ( Phases 1, 2 & 3 - merged genotypes &	2011-06-13: HapMap help desk announcement
frequencies ) HapMap3 Genome Browser release #3 ( Phase 3 - genotypes & frequencies )	There was a problem with the HapMap help desk system. In the past several weeks, emails sent to hapmap- help@ncbi.nlm.nih.gov did not reach the help desk, and thus user requests were not addressed. Please resend your email request if you sent emails to the HapMap help desk in the past several weeks. Sorry for the inconvenience.
HapMap Genome Browser release #27 ( Phase 1, 2 & 3 - merged genotypes &	2011-04-20: Hapmap help desk service interruption notice
frequencies) HapMap3 Genome Browser release #2 (	There will be no help desk support from 05/03/2011 to 05/23/2011. Sorry for the inconvenience.
Phase 3 - genotypes, frequencies & LD )	2011-02-02: Haploview issues with rel 28 data
Phase 1 & 2 - full dataset ) GWAs Karyogram	Recently, there are several questions about Haploview data format errors when users tried to analyze HapMap release 28 data. The current Haploview version (4.2) does not recognize the new individuals in release 28 and the software will generate an error similar to "Hapmap data format error: NA18876" when trying to open the data.
HapMap FTP Bulk Data Download	Haploview is developed and maintained by an organization different from HapMap. Please contact Haploview help desk (haploview@broadinstitute.org) for questions specific to this software.
Data Freezes for Publication ENCODE Project	2011-01-19: HapMap phase II recombination rate on GRCh37
Guidelines For Data Use	The liftover of the HapMap II genetic map from human genome build b35 to GRCh37 is available. Data is available for bulk download.

1000 Genomes A Deep Catalog of Human Genetic Variation

### **Thousand Genomes Project** http://www.1000genomes.org/



### LATEST ANNOUNCEMENTS

#### WEDNESDAY SEPTEMBER 30, 2015 A global reference for human genetic variation

The Phase 3 publication, A global reference for human genetic variation and the Phase 3 Structural variation publication, An integrated map of structural variation in 2,504 human genomes are now available from Nature alongside a celebration of 25 years of the Human Genome Project

The variants from the Phase 3 analysis are available in ftp/release/20130502/ and extended information about the SV dataset can be found in ftp/phase3/integrated\_sv\_map/.

Both these papers are open access and should be free for everyone to read and download.

If you have any questions about the data these papers are based on or how to access it please email info@1000genomes.org

http://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502/

### Recent project announcements

FRIDAY OCTOBER 16, 2015 GRCh38 mapping of the Illumina Platinum Genomes CEU pedigree

#### NAVIGATION

 Frequently Asked Ouestions

LINKS



All Project Announcements



Sample and Project Information



Media Archive



Find the 1000 Genomes Project Publications © Doug Brutlag 2015 1000 Genomes A Deep Catalog of Human Genetic Variation

A Global Reference for Human Genetic Variation http://www.nature.com/nature/journal/v526/n7571/full/nature15393.html

# A global reference for human genetic variation

The 1000 Genomes Project Consortium\*

The 1000 Genomes Project set out to provide a comprehensive description of common human genetic variation by applying whole-genome sequencing to a diverse set of individuals from multiple populations. Here we report completion of the project, having reconstructed the genomes of 2,504 individuals from 26 populations using a combination of low-coverage whole-genome sequencing, deep exome sequencing, and dense microarray genotyping. We characterized a broad spectrum of genetic variation, in total over 88 million variants (84.7 million single nucleotide polymorphisms (SNPs), 3.6 million short insertions/deletions (indels), and 60,000 structural variants), all phased onto high-quality haplotypes. This resource includes >99% of SNP variants with a frequency of >1% for a variety of ancestries. We describe the distribution of genetic variation across the global sample, and discuss the implications for common disease studies.



1000 Genomes A Deep Catalog of Human Genetic Variatio An Integrated Map of Structural Variation in 2,504 Human Genomes

# An integrated map of structural variation in 2,504 human genomes

A list of authors and their affiliations appears at the end of the paper.

Structural variants are implicated in numerous diseases and make up the majority of varying nucleotides among human genomes. Here we describe an integrated set of eight structural variant classes comprising both balanced and unbalanced variants, which we constructed using short-read DNA sequencing data and statistically phased onto haplotype blocks in 26 human populations. Analysing this set, we identify numerous gene-intersecting structural variants exhibiting population stratification and describe naturally occurring homozygous gene knockouts that suggest the dispensability of a variety of human genes. We demonstrate that structural variants are enriched on haplotypes identified by genome-wide association studies and exhibit enrichment for expression quantitative trait loci. Additionally, we uncover appreciable levels of structural variant complexity at different scales, including genic loci subject to clusters of repeated rearrangement and complex structural variants with multiple breakpoints likely to have formed through individual mutational events. Our catalogue will enhance future studies into structural variant demography, functional impact and disease association.



### Nature 526, 75-81 (October 1, 2015)



### NHS 100,000 Genomics England Project http://www.genomicsengland.co.uk/





Genomics England, with the consent of participants and the support of the public, is creating a lasting legacy for patients, the NHS and the UK economy through the sequencing of 100,000 genomes: the 100,000 Genomes Project.

Genomics England was set up by the Department of Health to deliver the 100,000 Genomes Project. Initially the focus will be on rare disease, cancer and infectious disease. The project is currently in its pilot phase and will be completed by the end of 2017.

#### Read more...



### **NIH Precision Medicine Initiative** http://www.nih.gov/precisionmedicine/



National Institutes of Health Search Turning Discovery Into Health For Employees Staff Directory En Español Health Information Grants & Funding **Research & Training** About NIH News & Events Institutes at NIH

### PRECISION MEDICINE INITIATIVE

Precision Medicine Initiative

#### What are the near-term goals?

What are the longer-term goals?

How is it different? Who will participate? NIH Workshop



### **Precision Medicine Initiative**

Far too many diseases do not have a proven means of prevention or effective treatments. We must gain better insights into the biology of these diseases to make a difference for the millions of Americans who suffer from them. Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. While significant advances in precision medicine have been made for select cancers, the practice is not currently in use for most diseases. Many efforts are underway to help make precision medicine the norm rather than the exception. To accelerate the pace, President Obama has now unveiled the Precision Medicine Initiative a bold new enterprise to revolutionize medicine and generate the scientific evidence needed to move the concept of precision medicine into every day clinical practice.



#### **Email Updates**

To sign up for updates please enter your e-mail address.





#### Related Links

NEJM Perspective: A New Initiative on Precision Medicine

White House Precision Medicine Web Page

White House Fact Sheet: President **Obama's Precision Medicine Initiative** 

Precision Medicine Initiative and Cancer Research

Single Nucleotide Polymorphisms (SNPs) in the Human Genome

> GCTGTATGAC**T**AGAAGATCGAT GCTGTATGAC**G**AGAAGATCGAT

- About 38 million sites in the human genome where sequence variations have occurred
- About 15 million sites where variation exceeds 1% of a particular population (MAF > 1%)
- Each ethnicity has its own distribution of SNPs
- About 3 million sites where any individual varies from the consensus human genome.
- Each person differs from others in 3 million places (about 0.1% of the genome)



### Single Nucleotide Polymorphisms (SNPs) in the Human Genome

GCTGTATGAC**T**AGAAGATCGAT GCTGTATGAC**G**AGAAGATCGAT

- SNPs can be used for identifying individuals and forensics
- SNPs are used for mapping & genome-wide association studies of complex diseases
- SNPs are used for ancestry tracking & family relationships
- SNPs are used to predict risk of common genetic diseases
- SNPs are used for classifying patients in clinical trials
- SNPs are used to predict drug sensitivity an adverse reactions
- SNPs are used for personalized medicine & pharmacogenomics
- While SNPs are linked with disease, they do not cause disease
- In short, SNPs are used as genetic markers

### S ncbi The dbSNP Database http://www.ncbi.nlm.nih.gov/books/NBK21088/pdf/ch5.pdf

# The NCBI Handbook The National Library of Medicine **NCBI Handbook**

#### Chapter 5: The Single Nucleotide Polymorphism Database (dbSNP) of Nucleotide Sequence Variation

Adrienne Kitts

Stephen Sherry

#### Summary

Sequence variations exist at defined positions within genomes and are responsible for individual phenotypic characteristics, including a person's propensity toward complex disorders such as heart disease and cancer. As tools for understanding human variation and molecular genetics, sequence variations can be used for gene mapping, definition of population structure, and performance of functional studies.

The Single Nucleotide Polymorphism database (dbSNP) is a public-domain archive for a broad collection of simple genetic polymorphisms. This collection of polymorphisms includes single-base nucleotide substitutions (also known as single nucleotide polymorphisms or SNPs), small-scale multi-base deletions or insertions (also called deletion insertion polymorphisms or DIPs), and retroposable element insertions and microsatellite repeat variations (also called short tandem repeats or STRs). Please note that in this chapter, you can substitute any class of variation for the term SNP. Each dbSNP entry includes the sequence context of the polymorphism (i.e., the surrounding sequence), the occurrence frequency of the polymorphism (by population or individual), and the experimental method(s), protocols, and conditions used to assay the variation.

dbSNP accepts submissions for variations in any species and from any part of a genome. This document will provide you with options for finding SNPs in dbSNP, discuss dbSNP content and organization, and furnish instructions to help you create your own (local) copy of dbSNP.

#### Introduction

The dbSNP has been designed to support submissions and research into a broad range of biological problems. These include physical mapping, functional analysis, pharmacogenomics, association studies, and evolutionary studies. Because dbSNP was developed to complement GenBank, it may contain nucleotide sequences (Figure 1) from any organism.

The NCBI Handbook

The NCBI Handbook





# The dbSNP Database

### http://www.ncbi.nlm.nih.gov/books/NBK174586/

#### NCBI Bookshelf

The Database of Short Genetic Variation (dbSNP) The NCBI Handbook [Internet]. 2nd edition

### ? 0 🔳

#### The Database of Short Genetic Variation (dbSNP)

Kitts A, Phan L, Ward M, et al.

#### Scope

Tey

Page 1 of 31

Sequence variation is of scientific interest to population geneticists, genetic mappers, and those investigating relationships among variation and phenotype. These variations can be of several types, from simple substitutions that do not affect sequence length, to those that result in minor length differences, to those that affect multiple genes and multiple chromosomes. Variations can also be categorized with respect to their frequency within a population, from a variation with a single allele to a variation that is highly polymorphic.

Although SNP is the abbreviation for "single nucleotide polymorphism," dbSNP is a public archive of all short sequence variation, not just single nucleotide substitutions that occur frequently enough in a population to be termed polymorphic. dbSNP includes a broad collection of simple genetic variations such as single-base nucleotide substitutions, small-scale multi-base deletions or insertions, and microsatellite repeats. Data submitted to dbSNP can be from any organism, from any part of a genome, and can include genotype and allele frequency data if those data are available. dbSNP accepts submissions for all classes of simple sequence variation, and provides access to variations of germline or somatic origin that are clinically

#### significant.

In order to emphasize the comprehensive nature of dbSNP's content, the full name of the database was changed from "database of Single Nucleotide Polymorphism" to the more inclusive "database of Short Genetic Variation" in July of 2011. The acronym that represents the database will remain "dbSNP" to avoid any confusion that might arise from a complete name change.

Each record in dbSNP includes the sequence context of the variant, the frequency of the polymorphism in a population if available, its zygosity if available, and the experimental method(s), protocols, and conditions used to assay the variation by each submitter. Individual submissions are clustered into dbSNP reference records (rs#) that contain summary data which may include clinical significance from ClinVar, association with phenotype from dbGaP, variation false positive status, allele origin (germline or somatic), and submitter attributes.

The dbSNP has been designed to support submissions and research into a broad range of biological problems that include the identification of genotype-phenotype relationships, genetic and physical mapping, functional analysis, pharmacogenomics, and association studies.

#### **Medical Genetics**

Advances in next-generation sequencing technologies allow

A Primer of Genome Science Chapter 3 Genomic Variation





GREG GIBSON • SPENCER V. MUSE

# Single Nucleotide Polymorphisms (SNPs)

- SNPs are common variations in the genome (minor allele frequency or MAF between 50% and 1%)
- Most SNPs are genetically neutral
  - Used in DNA fingerprints forensics
  - Paternity tests
  - Immigration in the US and United Kingdom
  - Used to track ethnic migrations and ancestry
- Some SNPs reflect distinguishing characteristics
  - Often the basis for racial & genetic discrimination or other stigma
- Rarer variations cause disease. Unlike SNPs, these variations are rare, often called mutations.
- Some SNPs linked to predisposition to disease
- SNPs can serve as genetic markers for other traits
  - Clinical trials associate SNPs with drug efficacy
  - Clinical trials associate SNPs adverse drug reactions
  - Personal genomics associate SNPs with traits

# Types of SNPs

http://www.ncbi.nlm.nih.gov/sites/entrez?db=snp

- Non protein coding SNPs
  - Promoters
  - 5′ UTR
  - 3' UTR
  - Introns
  - Intergenic Regions
  - Pseudogenes
  - Regulatory
    - Splicing
    - Transcriptional regulation (promoter & transcription factor binding sites)
    - Translational regulation (initiation or termination)
    - Regulatory miRNA target sites
- Coding SNPs
  - Synonymous SNPs (third position variation)
  - Replacement SNPs (change Amino acid)
    - Functional SNPs (acceptable amino acid replacement)
    - Non-functional SNPs (traits & diseases)

### Human Promoter SNPs



© Gibson & Muse, A Primer of Genome Science

### Human β-Hemoglobin Gene http://www.ncbi.nlm.nih.gov/gene/3043

Entrez Gen	Search: Gase     Limits Advanced	d search Help
Genes and mapped phenotypes	Se	arch Clear
Display Settings: 🖂 Fu	I Report Send to: ♡	Table of contents
HBB hemoglobin	beta [ Homo saniens ]	Summary
Cone ID: 2042 undate	d on 24 Oct 2010	Genomic regions, transcripts, and proc
serie ID. 3043, update	0 011 24-0Ct-2010	Genomic context
Summany	\$ 7	Bibliography
Summary		Phenotypes
Official Symbol	HBB provided by HGNC	Interactions
Official Full Name	hemoglobin, beta provided by HGNC	General gene info
Primary source	HGNC:4827	General protein info
See related	Ensembl:ENSG00000223609; HPRD:00786; MIM:141900	Reference sequences
RefSeg status	REVIEWED	Related sequences
Organism	Homo sapiens	Additional links
Lineage	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	Autonal Inks
Also known as	CD113t-C; beta-globin; HBB	Linke
Summary	The alpha (HBA) and beta (HBB) loci determine the structure of the 2 types of	Order oDNA close
	polypeptide chains in adult hemoglobin, Hb A. The normal adult hemoglobin	Distance by Case terret
	tetramer consists of two alpha chains and two beta chains. Mutant beta globin	BioAssay, by Gene target
	thalassemia. Reduced amounts of detectable beta clobin causes beta-plus-	BioSystems
	thalassemia. The order of the genes in the beta-globin cluster is 5'-epsilon	Books
	gamma-G gamma-A delta beta3'. [provided by RefSeq]	cobs
		Conserved Domains

### Human β-Hemoglobin Gene http://www.ncbi.nlm.nih.gov/gene/3043



Full text in PMC **GEO Profiles** Genome HomoloGene Map Viewer Nucleotide OMIM Peptidome Probe Protein PubChem Compound PubChern Substance PubMed PubMed (GeneRIF) PubMed (OMIM) RefSeg Proteins RefSeq RNAs RefSeqGene SNP SNP: GeneView SNP: Genotype SNP: VarView Taxonomy UniSTS

### Human β-Hemoglobin Gene SNPs http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?locusId=3043

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	about dbSNP? Try	The SNF or GRCh	<sup>2</sup> GeneVie 138, and v	ew page vill repla	only reports	human va View late	ariation on G er this vear. I	RCh3 Please	88. A ne e visit t	w <u>Va</u> he H	ariation V elp Page	<u>viewer</u> is available or YouTube for a	e to view available	v the gen e features	e HBB v s and se	variations in <u>(</u> and your com	GRCh37p13 ments and
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### Human β-Hemoglobin Variation Viewer http://www.ncbi.nlm.nih.gov/variation/view/

SNCBI Resources 🖂 How To 🖂	brutlag My NCBI Sign Out												
Variation Viewer	Homo sapiens: GRCh38 (GCF_000001405.26)         Chr 11 (NC_000011.10): 5.225M - 5.227M         You Tube           Reset All         Share this page         FAQ         Help         Version 1.2												
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History	HBB												
<ul> <li>Region Details</li> </ul>	NP_0005091 ClinVar Short Variations based on dbSNP 142 (Homo sapiens Annotation Release 106)												
Features of Interest Other sequence representations - None	4 2         + + + + + 3 2 1 2 2 3           dbVar ClinVar Large Variations         *												
<u>1 GRC issue</u> in this view. <u>Add Track</u>													
	dbSNP 142 (Homo sapiens Annotation Release 106) all data												
Variation Data													

S NCBI

Filter by ? 4	1 th	Download	Edit columns			Items 1 - 30	of 669 << First < Prev	Page 1	of 23 Next >	Last >>
Source database dbSNP (632)		Variant ID	Location	Variant type	Gene	Molecular consequences	Worst clinical significance	1000G MAF	GO-ESP MAF	Publications
🔲 dbVar (37)	•	nsv931147	<u>61,793 - 10,727,969</u>	copy number variation	PNPLA2 and 268 more		Pathogenic			1
In ClinVar Sec (378)	•	nsv915986	<u> 196,855 - 5,321,874</u>	copy number variation	PNPLA2 and 153 more		Pathogenic			1
🔲 No (291)		nsv984845	<u> 198,510 - 135,074,876</u>	copy number variation	SPTBN2 and 1515 more					1
Worst clinical significance Pathogenic (109)	•	nsv532276	202,758 - 31,726,224	copy number variation	TRIM5 and 387 more		Pathogenic			1
Likely pathogenic (11) drug response (0)	•	nsv1054121	205,983 - 6,415,299	copy number variation	TRIM5 and 192 more					1
<ul> <li>other (248)</li> <li>risk factor (0)</li> </ul>	•	nsv1048536	205,983 - 17,160,103	copy number variation	TRIM5 and 304 more					1
More	•	nsv1037023	205,983 - 30,840,538	copy number	TRIM5 and 382 more					1

variation

### β-Hemoglobin Gene SNP rs111645889 http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs=111645889

#### Reference SNP(refSNP) Cluster Report: rs111645889

Allele	HGVS Names
Variation Class: SNP:	
single nucleotide polymorphism	
RefSNP Alleles: C/T	
Ancestral Allele: C	
Clinical Association: unknown	
	Allele Variation Class: SNP: single nucleotide polymorphism RefSNP Alleles: C/T Ancestral Allele: C Clinical Association: unknown

SNP Details are organized in the following sections:

Mo

Created/Upda Map to Ge

<u>GeneView</u>	Map	Submission	Fasta	Resource	Diversity	Validation

Integrated Maps (Hint: click on 'Chr Pos' or 'Contig Pos' column value to see variation in NCBI sequence viewer)

Genome - Build	Chr +	Chr Pos 💠	Contig ¢	Contig Pos	SNP to Chr	Contig allele	Contig to ¢ Chr	Group term	Group label
37.1	11	5365554	NW 925006.1	865878	-	G	+	Cista	Celera
37.1	11	4906056	NW_001838021.1	875431	-	G	+	HuRef	HuRef
37.1	11	5246883	NT_009237.18	5186883		G	+	GRCh37	GRCh37

#### GeneView

#### GeneView via analysis of contig annotation: HBB hemoglobin, beta

- View more variation on this gene (click to hide).
- Include clinically associated: 
  in gene region 
  CSNP 
  has frequency 
  double hit 
  Go

Assembly	SNP to Chr	Chr	Chr position	Contig	Contig position	Allele
GRCh37	-	11	5246883	NT_009237.18	<u>5186883</u>	G
RefSeq0	Gene	Gene (	ID)	SNP to RefSeqGene	Position	Allele
NG_000007.3		HBB (30	(43)	+	71963	С

Function		mRNA		Protein				
	SNP to mRNA	Accession	Position	Allele change	Accession	Position	Residue change	
missense	+	NM 000518.4	439	GCC → GTC	NP_000509.1	130	A [Ala] → V [Val]	

### β-Hemoglobin Gene SNP rs111645889 http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs=111645889

S NCBI

Submitter r	records for this F	RefSNP Cluste	ər				1		
The submission	on ss212960479 h	has the longest	t flanking seque	nce of all clus	ter members and was used to insta	antiate sequence for rs111645889 during	BLAST analy	sis for the	e current
NCBI Assay ID	Handle Submitt ID	er <u>Validatio</u> <u>Status</u>	n <u>orientation</u> /Strand	Alleles	5' Near Seq 30 bp	3' Near Seq 30 bp	Entry Date	Update Date	Build Added
<u>ss212960479</u>	RSG_UW HBB- 3419		fwd/B	C/T gca	aagaattcaccccaccagtgcaggct	tg ctatcagaaagtggtggctggtgtgg	taa 04/02/10	04/02/10	132
Fasta sequ	ence (Legend)						1		
gnl dbSNP rs	111645889 allele	Pos=256 totalL	en=511 taxid=9	606 snpclass=	=1 alleles='C/T' mol=Genomic build=	=132			
TGCATATAA AGCAGCTAC TTCTGAGTC AGCTCCTGG CACCAGTGC Y CTATCAGAA CTTTCTTGC TGGGGGGATA TCATTGCAA GTCAGTGCA	A TATTTCTGCA A ATCCAGCTAC C AAGCTAGGCC G CAACGTGGCTG A GGCTG T GTCGATGCTG T GTCCAATTTC T TATGAAGGGC T GATGTATTTA T TTAAA	TATAAATTGT CATTCTGCTA CTTTTGCTAA GTCTGTGTGTGC GTGTGGCTAA TATTAAAGGT CTTGAGCATC AATTATTTCT	AACTGATGTA TTATTTTATG TCATGTTCAT TGGCCCATCA TGCCCTGGCC TCCTTTGTTC TGGATTCTGC GAATATTTTA	AGAGGTTTCJ GTTGGGATAJ ACCTCTTATC CTTTGGCAAJ CACAAGTATC CCTAAGTCCJ CTAATAAAAJ CTAAAAAGGO	A TATTGCTAAT A GGCTGGATTA C TTCCTCCCAC A GAATTCACCC C ACTAAGCTCG A ACTACTAAAC A ACATTTATTT G AATGTGGGAG				
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Population	Diversity						1		
There is no fre	equency data.								
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#### **1000 Genomes** A Deep Catalog of Human Genetic Variation

# Thousand Genomes Browser

http://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/

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#### 1000 Genomes A Deep Catalog of Human Genetic Variation

### Thousand Genomes Browser http://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/

<ul> <li>Genotypes</li> </ul>		Drag ruler or use the arrow buttons to scroll the visible range. Click or Shift-click the ruler to select a column. Alt-click or Shift-Alt-click to show on sequence.									Hide populations with unchecked samples						
Go to	Selecti	tion Scroll Region	5,246,840 336020563	5,246,870 rs113082294	5,246,883	5,246,923 rs34049764	5,246,958	5,246,975 rs191535077	5,247,001 rs140033163	5,247,035 rs181743523	5,247,135 rs185607297	5,247,141 rs1609812	5,247,329 rs78815705	5,247,427 rs190369729	5,247,430 rs182729393	5,247,543 rs187507944	5,247 rs1131
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► CEU	Uta	ah Residents (CEPH	G=1.0000	<b>C=0.9882</b> G=0.0118	G=1.0000 A=0.0000	G=1.0000 A=0.0000	T=1.0000 C=0.0000	A=1.0000 T=0.0000	C=1.0000 G=0.0000	<b>C=1.0000</b> T=0.0000	T=1.0000 G=0.0000	G=0.1412 <b>A=0.8588</b>	<b>G=0.9647</b> T=0.0353	<b>A=1.0000</b> G=0.0000	G=1.0000 A=0.0000	G=1.0000 C=0.0000	G=1.0 A=0.0
► CHB	Har	n Chinese in Bejin	G=1.0000	<b>C=1.0000</b> G=0.0000	G=1.0000 A=0.0000	<b>G=1.0000</b> A=0.0000	T=1.0000 C=0.0000	<b>A=1.0000</b> T=0.0000	<b>C=0.9948</b> G=0.0052	<b>C=1.0000</b> T=0.0000	<b>T=0.9948</b> G=0.0052	G=0.4794 <b>A=0.5206</b>	<b>G=1.0000</b> T=0.0000	A=1.0000 G=0.0000	<b>G=1.0000</b> A=0.0000	G=1.0000 C=0.0000	G=1.0 A=0.0
► CHS	Sou	uthern Han Chinese	<b>3=1.0000</b> A=0.0000	<b>C=1.0000</b> G=0.0000	G=1.0000 A=0.0000	<b>G=1.0000</b> A=0.0000	T=1.0000 C=0.0000	<b>A=1.0000</b> T=0.0000	<b>C=0.9900</b> G=0.0100	<b>C=0.9950</b> T=0.0050	<b>T=0.9950</b> G=0.0050	<b>G=0.5300</b> A=0.4700	G=1.0000 T=0.0000	A=1.0000 G=0.0000	G=1.0000 A=0.0000	G=1.0000 C=0.0000	G=1.0 A=0.0
▶ CLM	Col	lombians from Mede	S=1.0000	C=1.0000 G=0.0000	G=1.0000 A=0.0000	G=1.0000 A=0.0000	T=1.0000 C=0.0000	A=1.0000 T=0.0000	C=1.0000 G=0.0000	<b>C=1.0000</b> T=0.0000	T=1.0000 G=0.0000	G=0.2083 A=0.7917	<b>G=0.9667</b> T=0.0333	A=1.0000 G=0.0000	<b>G=1.0000</b> A=0.0000	G=1.0000 C=0.0000	G=1.0 A=0.0
► FIN	Finni	ish in Finland	S=1.0000 A=0.0000	C=1.0000 G=0.0000	G=1.0000 A=0.0000	<b>G=1.0000</b> A=0.0000	T=1.0000 C=0.0000	<b>A=1.0000</b> T=0.0000	<b>C=1.0000</b> G=0.0000	<b>C=1.0000</b> T=0.0000	<b>T=1.0000</b> G=0.0000	G=0.2366 <b>A=0.7634</b>	<b>G=0.9624</b> T=0.0376	<b>A=0.9946</b> G=0.0054	G=1.0000 A=0.0000	G=1.0000 C=0.0000	G=0.9
► GBR	Brit	tish in England a…	S=1.0000 A=0.0000	C=0.9944 G=0.0056	G=1.0000 A=0.0000	<b>G=1.0000</b> A=0.0000	T=1.0000 C=0.0000	<b>A=0.9888</b> T=0.0112	C=1.0000 G=0.0000	<b>C=1.0000</b> T=0.0000	<b>T=1.0000</b> G=0.0000	G=0.1854 <b>A=0.8146</b>	<b>G=0.9831</b> T=0.0169	A=1.0000 G=0.0000	G=1.0000 A=0.0000	G=1.0000 C=0.0000	G=1.0 A=0.0
▶ IBS	Iberi	ian population i	S=1.0000 A=0.0000	<b>C=0.9643</b> G=0.0357	G=1.0000 A=0.0000	<b>G=1.0000</b> A=0.0000	T=1.0000 C=0.0000	A=1.0000 T=0.0000	C=1.0000 G=0.0000	<b>C=1.0000</b> T=0.0000	<b>T=1.0000</b> G=0.0000	G=0.1786 <b>A=0.8214</b>	G=1.0000 T=0.0000	A=1.0000 G=0.0000	G=1.0000 A=0.0000	G=1.0000 C=0.0000	G=1.( A=0.(
▶ JPT	Japa	anese in Tokyo, J	S=1.0000 A=0.0000	C=1.0000 G=0.0000	G=1.0000 A=0.0000	G=1.0000 A=0.0000	T=1.0000 C=0.0000	<b>A=1.0000</b> T=0.0000	<b>C=0.9607</b> G=0.0393	<b>C=1.0000</b> T=0.0000	<b>T=0.9888</b> G=0.0112	<b>G=0.5112</b> A=0.4888	G=1.0000 T=0.0000	<b>A=1.0000</b> G=0.0000	G=1.0000 A=0.0000	G=1.0000 C=0.0000	G=1.( A=0.(
► LWK	Luh	hya in Webuye, Ken	<b>3=0.9948</b> A=0.0052	<b>C=1.0000</b> G=0.0000	G=1.0000 A=0.0000	G=1.0000 A=0.0000	<b>T=1.0000</b> C=0.0000	<b>A=1.0000</b> T=0.0000	C=1.0000 G=0.0000	<b>C=1.0000</b> T=0.0000	<b>T=1.0000</b> G=0.0000	G=0.0625 <b>A=0.9375</b>	G=1.0000 T=0.0000	A=1.0000 G=0.0000	G=1.0000 A=0.0000	G=1.0000 C=0.0000	<b>G=0.</b> A=0.0
▶ MXL	Me	xican Ancestry fro	G=1.0000	C=1.0000 G=0.0000	G=1.0000 A=0.0000	<b>G=1.0000</b> A=0.0000	T=1.0000 C=0.0000	A=1.0000 T=0.0000	<b>C=1.0000</b> G=0.0000	<b>C=1.0000</b> T=0.0000	T=1.0000 G=0.0000	G=0.3047 <b>A=0.6953</b>	<b>G=0.9688</b> T=0.0313	A=1.0000 G=0.0000	<b>G=0.9922</b> A=0.0078	G=1.0000 C=0.0000	G=1.0 A=0.0
▶ PUR	Pue	erto Ricans from P	S=1.0000 A=0.0000	C=0.9909 G=0.0091	G=1.0000 A=0.0000	<b>G=1.0000</b> A=0.0000	T=1.0000 C=0.0000	A=1.0000 T=0.0000	C=1.0000 G=0.0000	<b>C=1.0000</b> T=0.0000	T=1.0000 G=0.0000	G=0.2091 A=0.7909	G=0.9909 T=0.0091	<b>A=1.0000</b> G=0.0000	G=1.0000 A=0.0000	G=0.9909 C=0.0091	G=1.0 A=0.0
▶ TSI	Tosc	cani in Italia	G=1.0000	<b>C=1.0000</b> G=0.0000	G=1.0000 A=0.0000	<b>G=1.0000</b> A=0.0000	T=1.0000 C=0.0000	<b>A=1.0000</b> T=0.0000	<b>C=1.0000</b> G=0.0000	<b>C=1.0000</b> T=0.0000	T=1.0000 G=0.0000	G=0.1378 <b>A=0.8622</b>	<b>G=0.9898</b> T=0.0102	A=1.0000 G=0.0000	G=1.0000 A=0.0000	G=1.0000 C=0.0000	G=1.0 A=0.0
▶ YRI	Yoru	uba in Ibadan, Ni	S=1.0000	C=1.0000 G=0.0000	<b>G=0.9943</b> A=0.0057	<b>G=1.0000</b> A=0.0000	<b>T=1.0000</b> C=0.0000	<b>A=1.0000</b> T=0.0000	<b>C=1.0000</b> G=0.0000	<b>C=1.0000</b> T=0.0000	<b>T=1.0000</b> G=0.0000	G=0.1080 <b>A=0.8920</b>	<b>G=1.0000</b> T=0.0000	<b>A=1.0000</b> G=0.0000	G=1.0000 A=0.0000	G=1.0000 C=0.0000	G=0.9
		and the second se															



# Origin of Haplotypes



## Linkage Disequilibrium and Recombination Rate





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# Linkage Disequilibrium (LD) Across the Human LPL Gene









7q21

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Recombination hotspots are widespread and account for linkage disequilibrium structure





## Consensus binding site for PRDM9





Baudet et al, PRDM9 and Meiotic Recombination Science 237. 836.

# Initiation of Meiotic Recombination by PRDM9





# **Observation of Haplotypes**

SNPs	SNP	SNP	SNP			
	↓	↓	↓			
Individual 1 Individual 2 Individual 3 Individual 4	A A C A C G C C A A A C A C G C C A A A C A T G C C A A A C A T G C C A A A C A C G C C A	T T C G G G G T C T T C G A G G T C T T C G G G G T C T T C G G G G T C	AGTCGACCG AGTCA ACCG AGTCA ACCG AGTCGACCG			



а





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# SNPs in Populations



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# Sequence and Distance-Based Phylogenies (evolutionary trees)

- Sequence-Based Methods (Parsimony)
  - Assigns mutations to branches
  - Minimize number of changes
  - Topology maximizes similarity of neighboring leaves
- Distance-based methods
  - Branch lengths = D(i,j)/2 for sequences i, j
  - Distances must be metric
  - Distances can reflect time or number of changes
  - Distances must be relatively constant per unit branch length

# nature A Haplotype Map of the Human Genome

http://www.nature.com/nature/journal/v437/n7063/full/nature04226.html



rancis Collins, 2008



### National Human Genome Research Institute http://www.genome.gov/



### genome.gov National Human Genome Research Institute

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#### Highlights 🔊 RSS



### International gathering highlights opportunities in genomic medicine

At the Global Leaders in Genomic Medicine meeting, held Jan. 8-9 at the National Academy of Sciences in Washington, D.C., attendees learned how both large and small countries are creating innovative programs and plans for implementing genomic medicine. The two-day meeting was sponsored by NHGRI. <u>Read more</u>

#### Genomics in Medicine: Genome and Transcriptome Dynamics in Cancer Cells

Join us Friday, February 7th at 8:00 a.m. for our next Genomics in Medicine lecture, part of the 2013-2014 series, featuring Thomas Ried, M.D., senior investigator and chief of the Cancer Genomics Section, National Cancer Institute, NIH. His talk, *Genome and Transcriptome Dynamics in Cancer Cells*, will focus on malignant cells that carry two specific and concurrent alterations of the cellular transcriptome. <u>Read</u> <u>more</u>



TCGA bladder cancer study reveals potential drug targets, similarities to several cancers January 29, 2014

3

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<u>NIH study links family</u> <u>structure to high blood</u> <u>pressure in African-</u> <u>American men</u> December 12, 2013

With new study, aquatic comb jelly floats into new evolutionary position December 12, 2013

NIH deposits first batch of genomic data for Alzheimer's disease December 2, 2013



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The American Society of Human Genetics

### Apply for NHGRI-ASHG's new education fellowship for genetics professionals

To help cultivate an educated citizenry, the American Society of Human Genetics (ASHG) and NHGRI have teamed up to sponsor the new Genetics and Education Fellowship. Every year, one genetics professional will receive comprehensive training and experience to help prepare him or her for a career in genetics and genomics education. <u>Read more</u>



### Centers for Mendelian Genomics http://mendelian.org/

Centers for Mendelian Genomics

Finding the genes underlying human Mendelian conditions

### MANY PEOPLE INFINITE POSSIBILITIES

Understanding the genetic basis of Mendelian conditions.

The Centers for Mendelian Genomics will apply next-generation sequencing and computational approaches to discover the genes and variants that underlie Mendelian conditions.

Our vision is to discover new genes that cause Mendelian conditions. As a result, we will expand our understanding about their biology to facilitate their diagnosis, and potentially indicate new treatments.

Disorders currently being investigated



Yale Center for Mendelian Genomics





Baylor-Johns Hopkins Center for Mendelian Genomics

If you are interested in working with the Centers for Mendelian Genomics to discover the genetic basis of a Mendelian condition, please contact us at gmendel@mendelian.org.

#### More Information

Haploinsufficiency of SF3B4, a Component of the Pre-mRNA Spliceosomal Complex, Causes Nager Syndrome. Online 26 April 2012 | AJHG 90, 925-933 (2012) | doi:10.1016/j.ajhg.2012.04.004

The Centers for Mendelian Genomics: A new large-scale initiative to identify the genes underlying rare Mendelian conditions Online 24 May 2012 I AJMG 158A, 1523-5 (2012) I doi: 10.1002/ajmg.a.35470

The first clinical uses of whole-genome sequencing show just how challenging it can be.

Online 5 October 2011 | Nature 478, 22-24 (2011) | doi:10.1038/478022a

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### Centers for Mendelian Genomics http://mendelian.org/

### INVITED COMMENT



### The Centers for Mendelian Genomics: A New Large-Scale Initiative to Identify the Genes Underlying Rare Mendelian Conditions

Michael J. Bamshad,<sup>1,2,3</sup>\* Jay A. Shendure,<sup>2</sup> David Valle,<sup>4</sup> Ada Hamosh,<sup>4</sup> James R. Lupski,<sup>5,6,7,8</sup> Richard A. Gibbs,<sup>5,8</sup> Eric Boerwinkle,<sup>8,9</sup> Richard P. Lifton,<sup>10</sup> Mark Gerstein,<sup>11</sup> Murat Gunel,<sup>10,12</sup> Shrikant Mane,<sup>10</sup> and Deborah A. Nickerson<sup>2</sup>

#### on behalf of the Centers for Mendelian Genomics

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<sup>12</sup>Department of Neurosurgery, Yale University School of Medicine, New Haven, Connecticut

Manuscript Received: 2 April 2012; Manuscript Accepted: 19 April 2012

# Portrait of a Glitch

- Revere La Noue, MFA, Stanford, 2005
- What is this film about?
- What classes of glitches are mentioned?
- What do these glitches cause?
- Why did I show this film?

