GVF: a computable standard for personal genomes data

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Genomics enabled EHRs will need to*:

(1) integrate structured genotype and phenotypic information (for accurate clinical interpretation),

(2) insert genetic/genomic information into the clinical workflow (for streamlined processes)

(3) enable secondary use of the data

** Emerging Landscape of Genomics in the Electronic Health Record for Personalized Medicine* Mollie H. Ullman-Cullere and Jomol P. Mathew. Human mutation 2011

This means that:

- EHR systems need to be adapted for the personalization of medicine enabled through genetics/genomics data.

- As a first step, structured genetic/genomic data must be available within the EHR in a ***computable*** and ***consistent*** format.

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Outline

- GVF – a computable, consistent & clinically orientated data standard for personal genome sequences
- GVF can be used to describe a single variant, a gene's variants, or an entire genome's
- Proof-of-principle whole-genome comparative analyses enable by GVF
- GVF enabled software tools for clinical decision support

Its all in the variant file

- Variant files have become the *de facto* 'standard' for personal genome sequences

- Each variant file contains about 3 million SNVs compared to the reference human genome

Variant files are not standardized
This is a problem.

```
# Soap SNP
chr1    SoapSNP    SNP    4793    4793    25    +    .    ID=YHSNP0128643; status=novel; ref=A; allele=A/G; support1=48; support2=26;
chr1    SoapSNP    SNP    6434    6434    48    +    .    ID=YHSNP0128644; status=novel; ref=G; allele=A/G; support1=10; support2=11;
chr1    SoapSNP    SNP    93896   93896   51    +    .    ID=rs4287120; status=dbSNP; ref=T; allele=C/T; support1=5; support2=4;
                                                          location=MSTB1:LTR/MaLR;
```

```
# Watson Genome SNP
BJW-1117373   chr1   41921   G   C   .   novel          .   2   0   4   het
BJW-1117523   chr1   42101   T   G   Y   rs2691277.1    .   1   0   1   ?
BJW-1119675   chr1   45408   C   T   Y   rs28396308     .   3   0   3   .
```

```
# Venter Genome SNP
1   1103675000013   heterozygous_SNP   556001   556002   .   +   A/C;RMR=0;TR=0   Method1
1   1103675000017   homozygous_SNP   652719   652720   .   +   G/A;RMR=0;TR=1   Method1
1   1103675000019   homozygous_SNP   694229   694230   .   +   T/C;RMR=1;TR=0   Method1
```

```
# Korean Genome SNP
chr10 56397    C    CT    rs12262442   28    C/T    17    11
chr10 61776    T    CT    rs61838967   15    T/C    7     8
chr10 65803    T    CT    KOREFSNP1    27    T/C    19    8
```

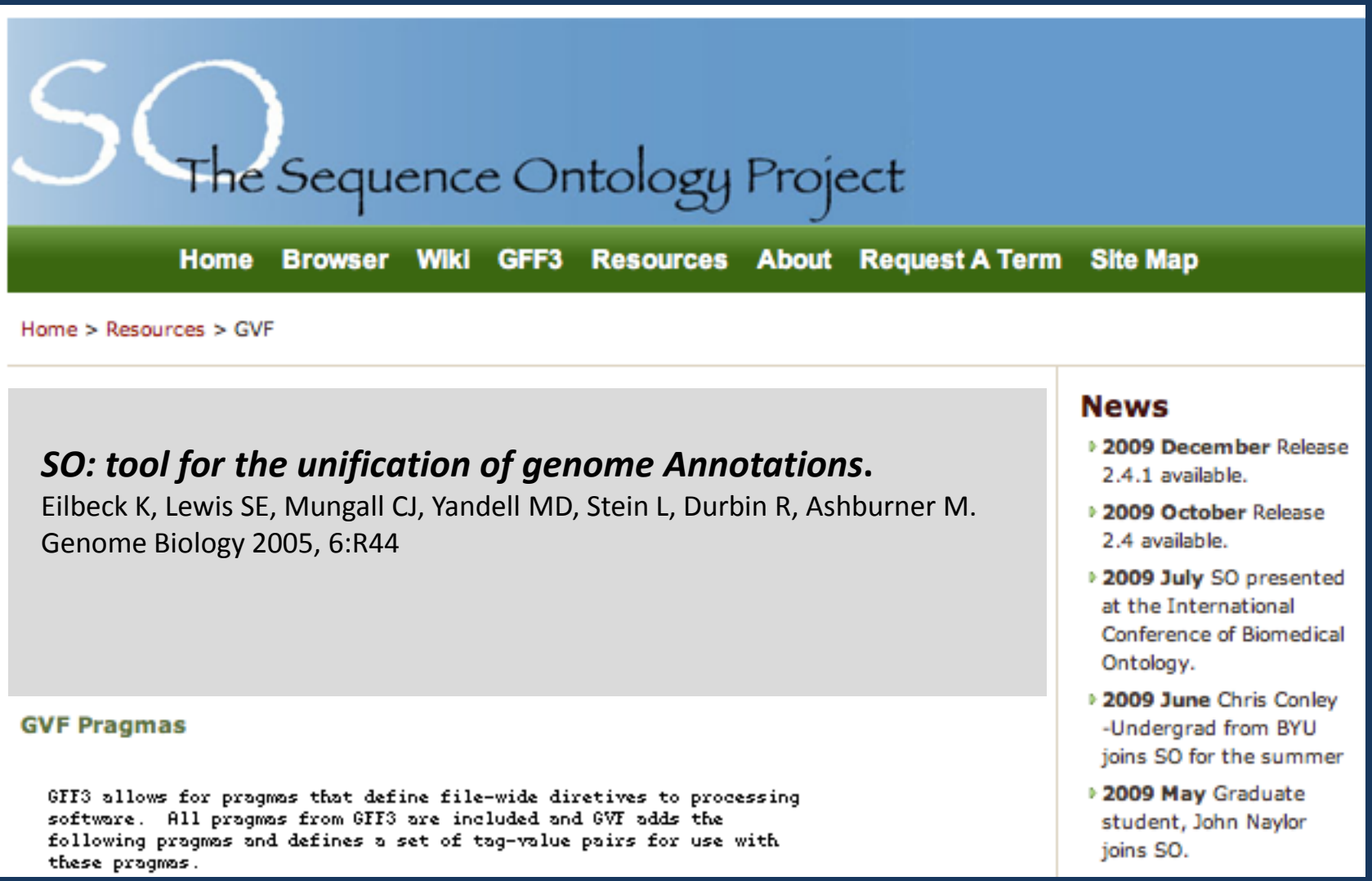
```
# Complete Genomics SNP
6,chr1,31843,31844,snp,snp,A,G,G,235
21,chr1,36532,36533,snp,snp,A,G,G,36
23,chr1,36970,36971,snp,snp,G,C,C,109
```

Badly needed : a standard format

- Currently every sequence provider uses their own idiomatic data format for variant files.
- The first step towards enabling analyses of multiple personal genomes is a standardized data format to facilitate comparisons.
- This is not the first time the genomics community has faced this problem.

This isn't a new problem for genomics

- 1998 onward the model organism community worked together to facilitate genome annotation
  - The Generic Model Organism Database Community
    - Genomic browsers like Apollo and GBrowse
    - Data storage such as Chado relational Schema
    - Data exchange such as GFF3
    - Annotation pipelines such as MAKER
  - One of the main take homes was that an ontology was needed to type fields in both files and databases; hence the Sequence Ontology



This is what a gene annotation looks like naked

GFF3 representation of a gene annotation

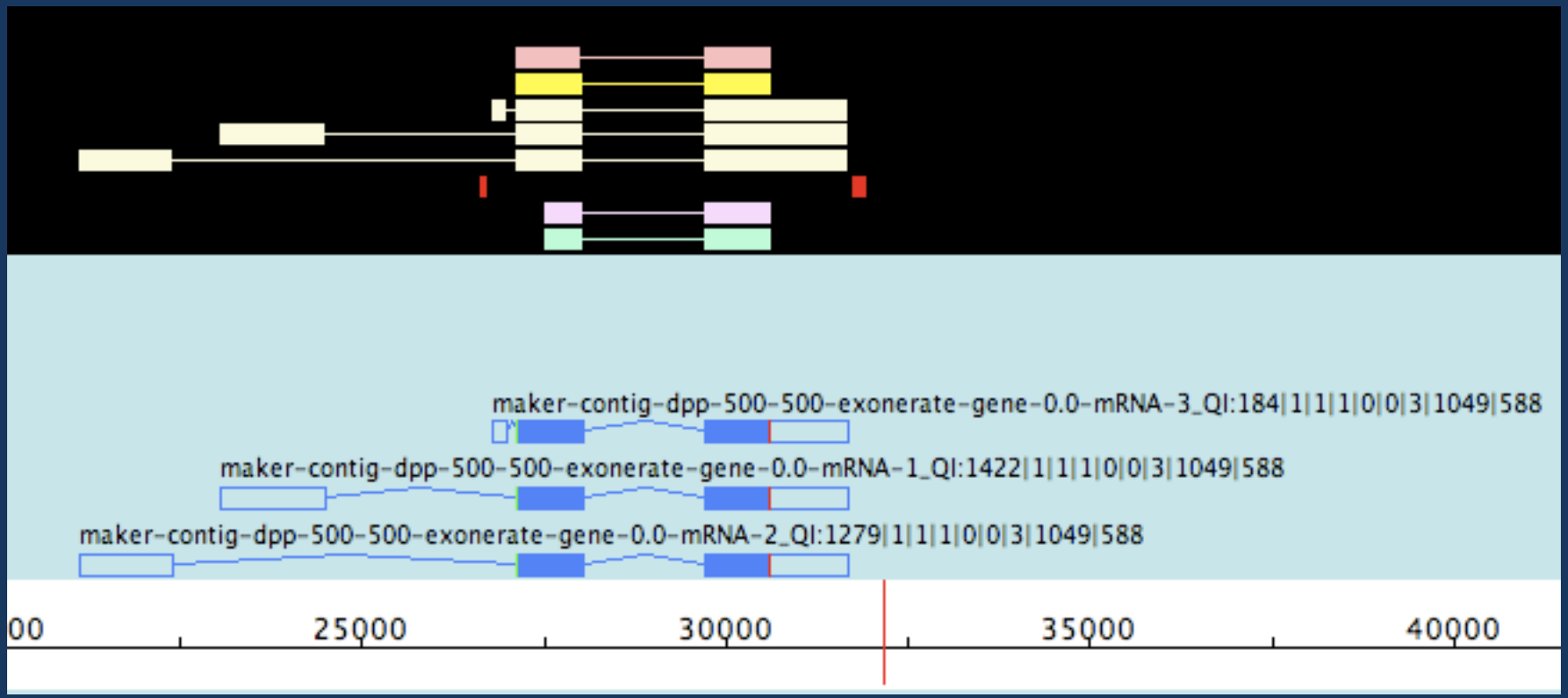
##gff-version3

ID	source	feature	start	stop	score	strand	phase	attributes
chr17	UCSC	**mRNA**	62467934	62469545	.	-	.	ID=A00469;…
chr17	UCSC	**three_prime_UTR`**	62467934	62468038	.	-	.	Parent=A00469
chr17	UCSC	**CDS**	62468039	62468236	.	-	1	Parent=A00469
Chr17	UCSC	**CDS**	62468490	62468654	.	-	2	Parent=A00469
Chr17	UCSC	**CDS**	62468747	62468866	.	-	1	Parent=A00469
chr17	UCSC	**CDS**	62469076	62469236	.	-	1	Parent=A00469
chr17	UCSC	**CDS**	62469497	62469506	.	-	0	Parent=A00469
chr17	UCSC	**five_prime_UTR**	62469507	62469545	.	-	.	Parent=A00469
chr9	UCSC	**mRNA**	90517946	90527968	.	-	.	ID=AB000114;Ontology_term=GO:0007155,GO:0005194,GO:0005578;Dbxref=AFFX-U95:41031_at,Genbank-protein:BAA19055,;
chr9	UCSC	**three_prime_UTR**	90517946	90518841	.	-	.	Parent=AB000114
chr9	UCSC	**CDS**	90518842	90519167	.	-	1	Parent=AB000114
chr9	UCSC	**CDS**	90520309	90521248	.	-	0	Parent=AB000114
chr9	UCSC	**five_prime_UTR**	0521249	90521264	.	-	.	Parent=AB000114
chr9	UCSC	**five_prime_UTR**	90527892	90527968	.	-	.	Parent=AB000114

SO terms

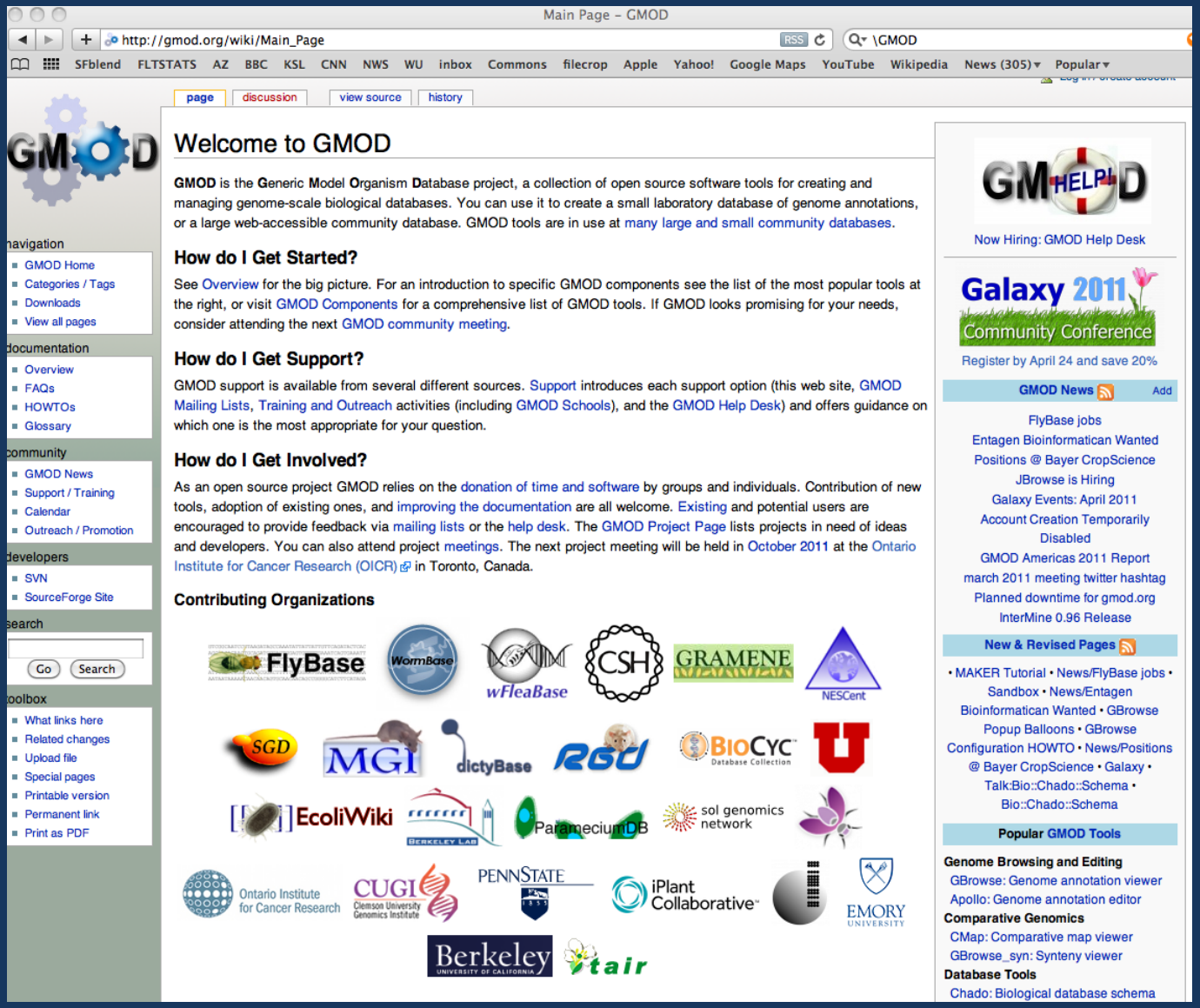
SO relations

Standardized file formats enable downstream software applications for analysis

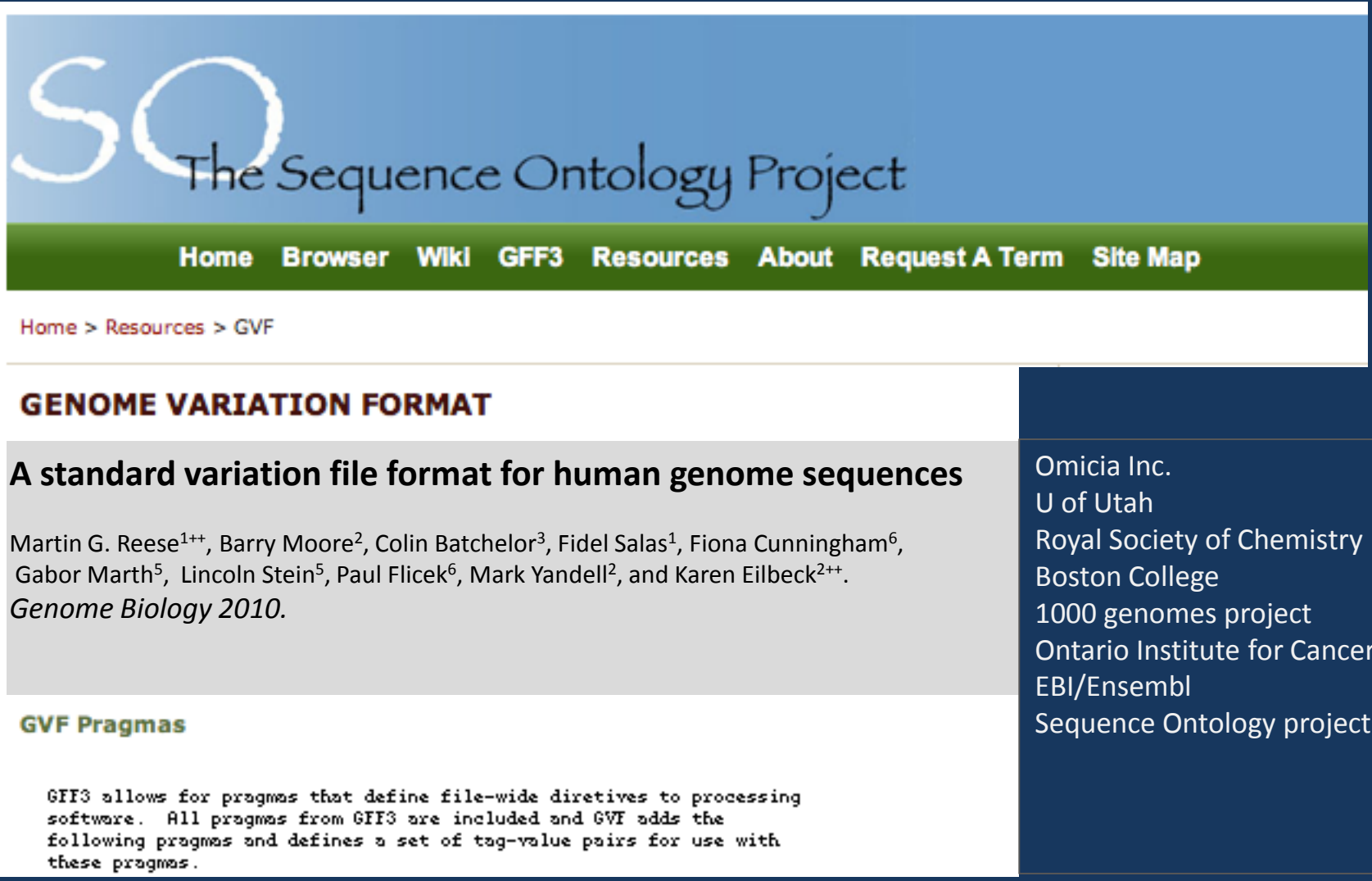


A GFF3 genome annotation visualized in the Apollo Genome Browser

Data standards have great power to unify and enable the community



GVF: a standardized file format for variation files



Omicia Inc.
U of Utah
Royal Society of Chemistry
Boston College
1000 genomes project
Ontario Institute for Cancer Research
EBI/Ensembl
Sequence Ontology project

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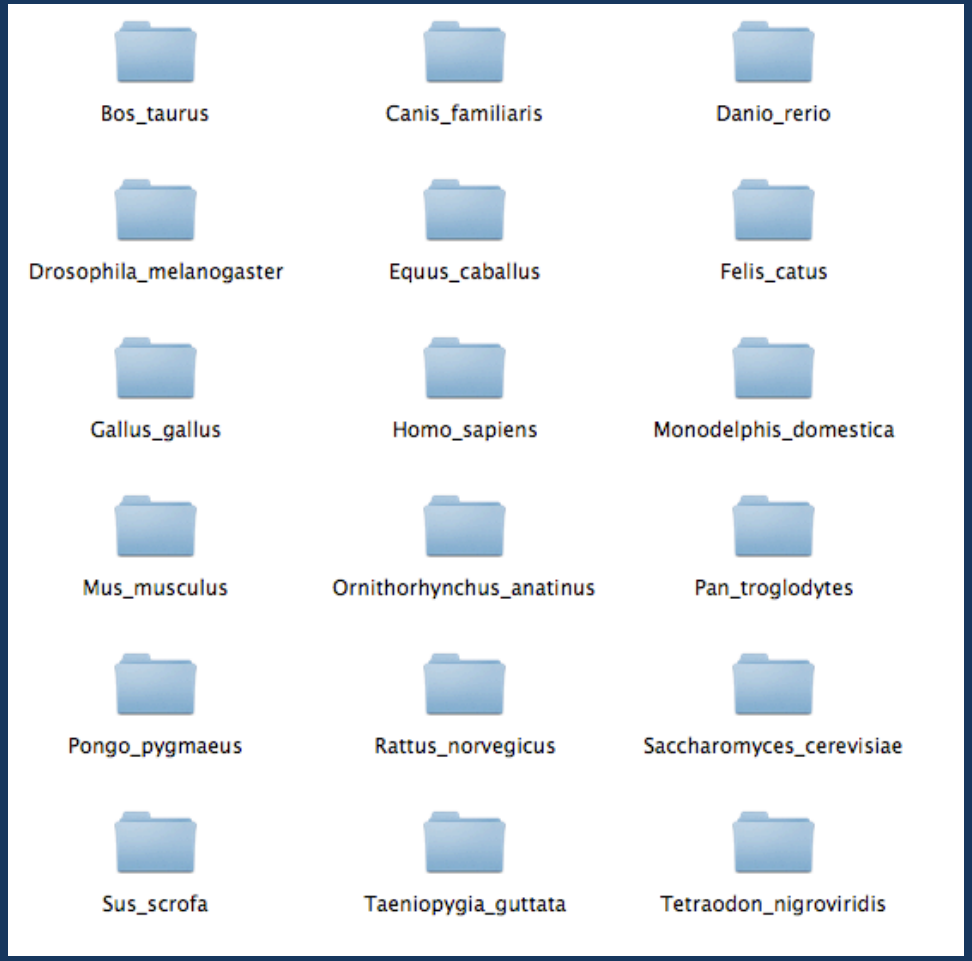
Advantages of GVF

- Describe a personal genome, a population or collection of variants.
- Descriptive terms are Ontology typed. Therefore file can be reasoned over computationally
- Library of existing software for analysis and visualization
- Multiple technologies can be represented
- Permits detailed annotation of physical manifestation of variant

How is GVF different from VCF?

- Descriptive terms typed via the Sequence Ontology.
- Library of existing software for analysis and visualization (GMOD tools)
- Focus is on clinical annotation and functional consequence of variant; e.g. splice junction variant causing exon skipping in DMD.

GVF is now the output of EBI variant annotation pipeline



ftp://ftp.ensembl.org/pub/current/variation/

10Gen Dataset

http://www.sequenceontology.org/resources/10Gen.html

Genome	Individual	Ethnicity	Platform	Reference
0	NA19240	African	ABI SOLiD	De la Vega, et al. 2009
1	NA18507	African	Illumina	Bentley et al. 2008
2	NA18507	African	ABI SOLiD	McKernan, et al. 2009
3	Chinese	Asian	Illumina	Wang et al. 2008
4	Korean	Asian	Illumina	Ahn et al. 2009
5	Venter	Caucasian	Sanger	Levy et al. 2007
6	Watson	Caucasian	Roche 454	Wheeler et al. 2007
7	NA07022	Caucasian	CGenomics	Drmanac, et al. 2009
8	NA12878	Caucasian	ABI SOLiD	De la Vega, et al. 2009
9	Quake	Caucasian	Helicos	Pushkarev et al. 2009

A standard variation file format for human genome sequences Martin G. Reese[1++], Barry Moore[2], Colin Batchelor[3], Fidel Salas[1], Fiona Cunningham[6], Gabor Marth[5], Lincoln Stein[5], Paul Flicek[6], Mark Yandell[2], and Karen Eilbeck[2++].
Genome Biology 2010.

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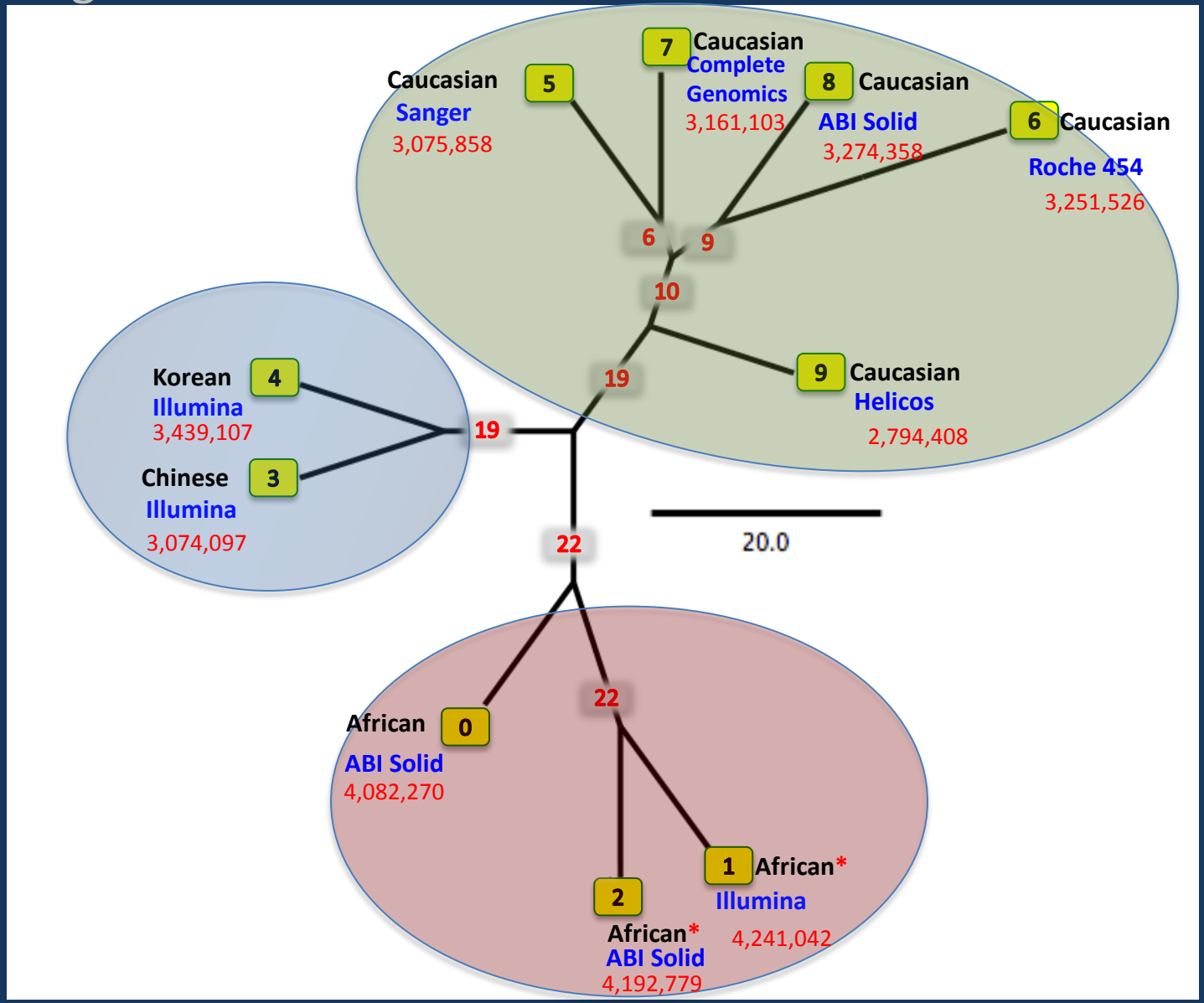
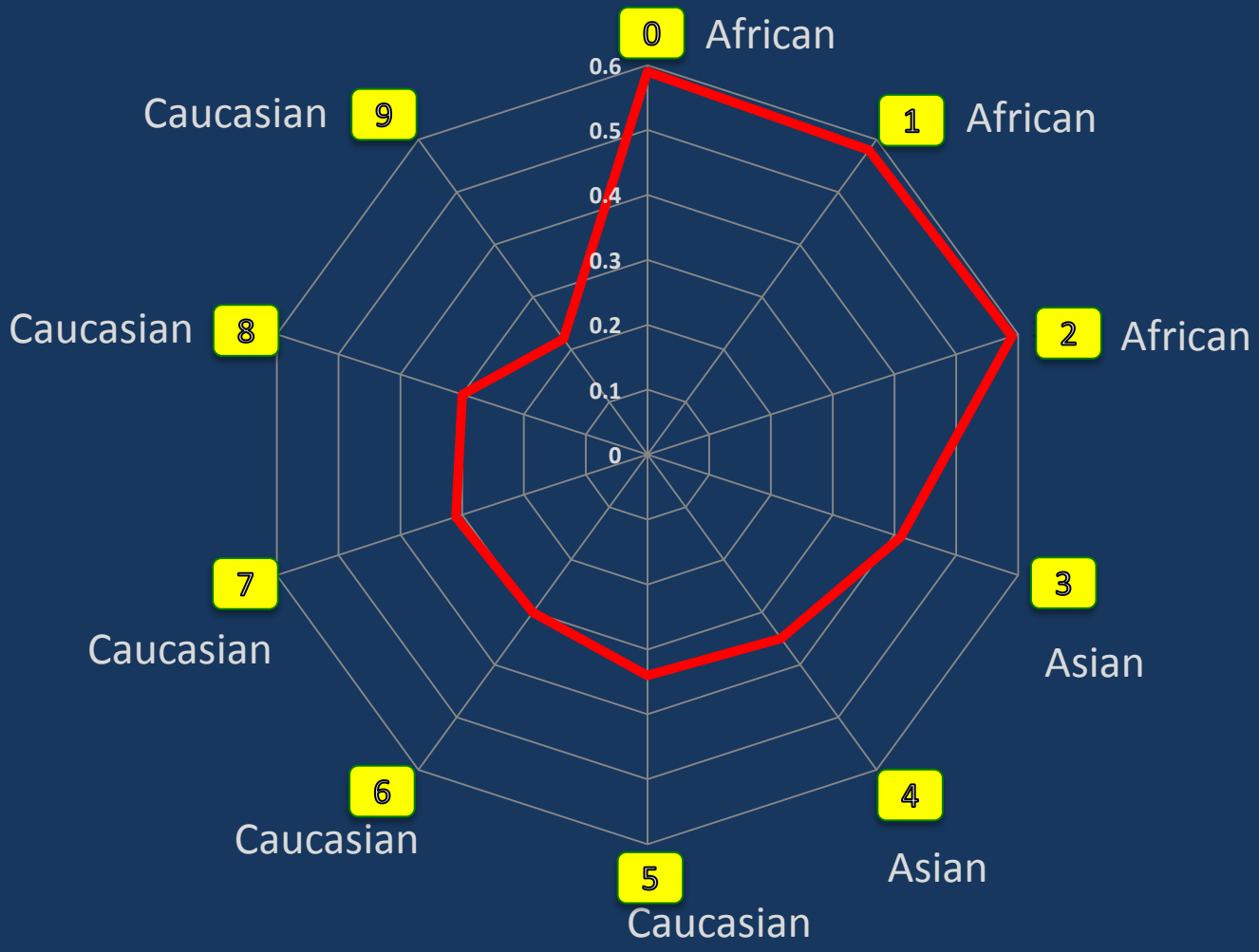
Standards enable comparative genomics of people, platforms and variant calling methods



Global analysis of disease-related DNA sequence variation in 10 healthy individuals: Implications for whole-genome-based clinical diagnostics. Barry Moore, Hao Hu, Marc Singleton, Martin G. Reese, and Mark Yandell. Genetics in Medicine 2011

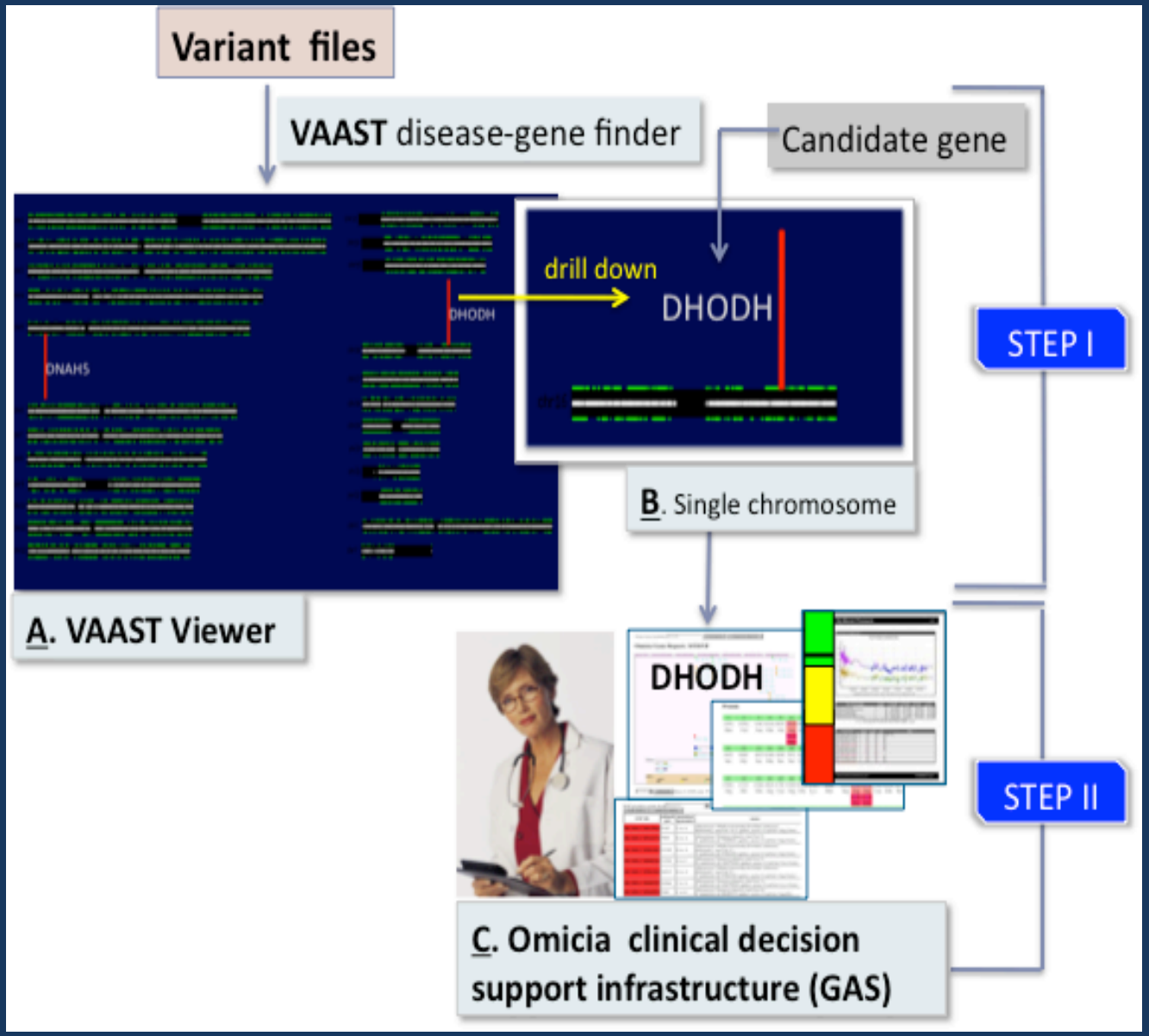
African Genomes Are Generally Homozygous For More OMIM Alleles*



*Ratio homozygous/heterozygous positions

Global analysis of disease-related DNA sequence variation in 10 healthy individuals: Implications for whole-genome-based clinical diagnostics.
Barry Moore, Hao Hu, Marc Singleton, Martin G. Reese, and Mark Yandell. Genetics in Medicine 2011

Standards enable tools for clinical decision support



VAAST

Omicia Tools

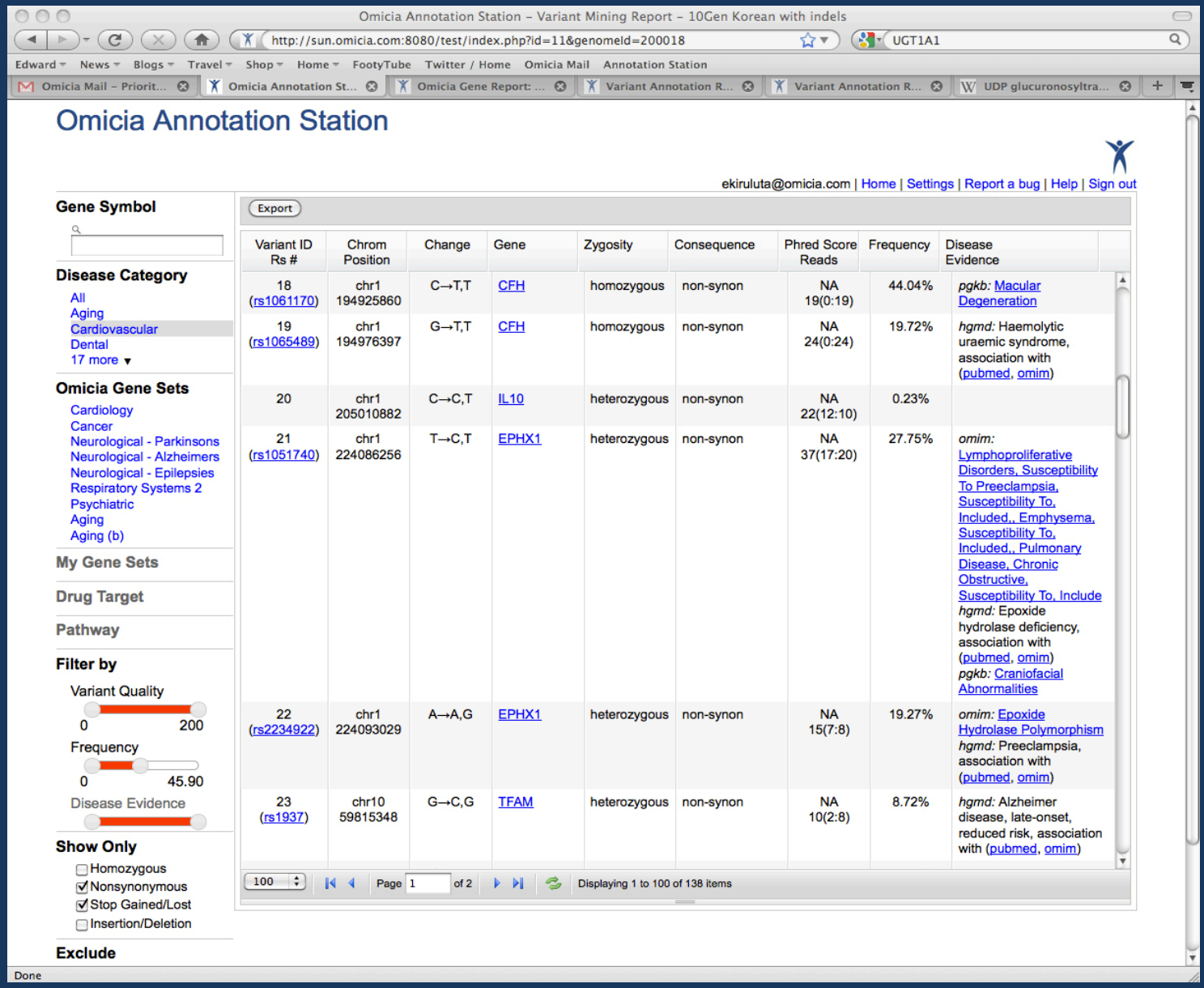
GVF is input to the Omicia Inc. Genome Annotation Station

Disease categories

Known disease genes

Support

Kind of alteration



GVF is the input for VAAST*

- A Probabilistic disease-gene finder for personal genomes
- Rapidly search personal genome sequences for genes having significant differences in variant frequencies vs. controls
- Identify novel disease-causing genes & their variants
- Can be used to hunt for both rare and common disease genes and their causative alleles
- Determine the statistical significance of candidate genes

***A probabilistic disease-gene finder for personal genomes** Mark Yandell, Chad Huff, Hao Hu, Marc Singleton, Barry Moore, Jinchuan Xing, Lynn Jorde and Martin G. Reese. Manuscript under review.

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VAAST rhymed with BLAST

BLAST	VAAST
query	target genomes
database	background genomes
hits	hits
Expect	P-value
Fast	Fast

BLAST searches for statistically significant *similarity* between sequences.

VAAST searches for statistically significant *dissimilarity* between sequences.

A Test Case: MILLER SYNDROME

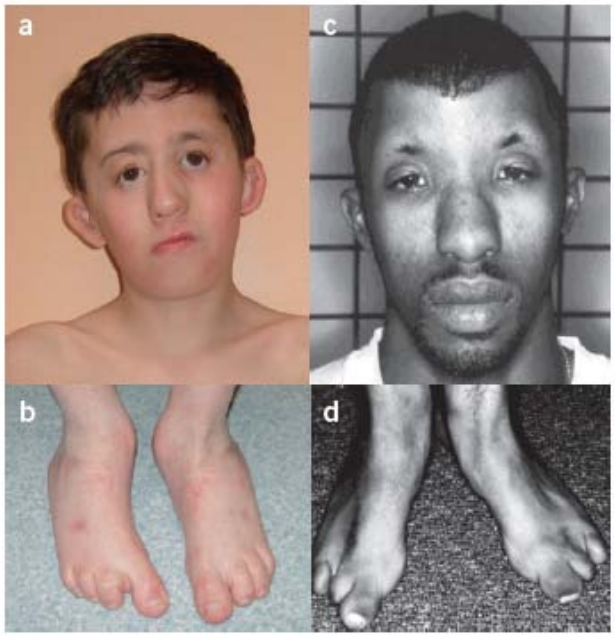

Figure 1 Clinical characteristics of an individual with Miller syndrome and an individual with methotrexate embryopathy. (a,b) A 9-year-old boy with Miller syndrome caused by mutations in *DHODH*. Facial anomalies (a) include cupped ears, coloboma of the lower eyelids, prominent nose, micrognathia and absence of the fifth digits of the feet (b). (c,d) A 26-year-old man with methotrexate embryopathy. Note the cupped ears, hypertelorism, sparse eyebrows and prominent nose (c) accompanied by absence of the fourth and fifth digits of the feet (d). c and d are reprinted with permission from ref. 30.

ARTICLES

nature genetics

Exome sequencing identifies the cause of a mendelian disorder

Sarah B Ng[1,10], Kati J Buckingham[2,10], Choli Lee[1], Abigail W Bigham[2], Holly K Tabor[2,3], Karin M Dent[4], Chad D Huff[5], Paul T Shannon[6], Ethylin Wang Jabs[7,8], Deborah A Nickerson[1], Jay Shendure[1] & Michael J Bamshad[1,2,9]

Science

AAAS

Analysis of Genetic Inheritance in a Family Quartet by Whole-Genome Sequencing

Jared C. Roach, *et al.*
Science **328**, 636 (2010);
DOI: 10.1126/science.1186802

Analysis of Genetic Inheritance in a Family Quartet by Whole-Genome Sequencing

Jared C. Roach,[1*] Gustavo Glusman,[1*] Arian F. A. Smit,[1*] Chad D. Huff,[1,2*] Robert Hubley,[1] Paul T. Shannon,[1] Lee Rowen,[1] Krishna P. Pant,[3] Nathan Goodman,[1] Michael Bamshad,[4] Jay Shendure,[5] Radoje Drmanac,[3] Lynn B. Jorde,[2] Leroy Hood,[1†] David J. Galas[1†]

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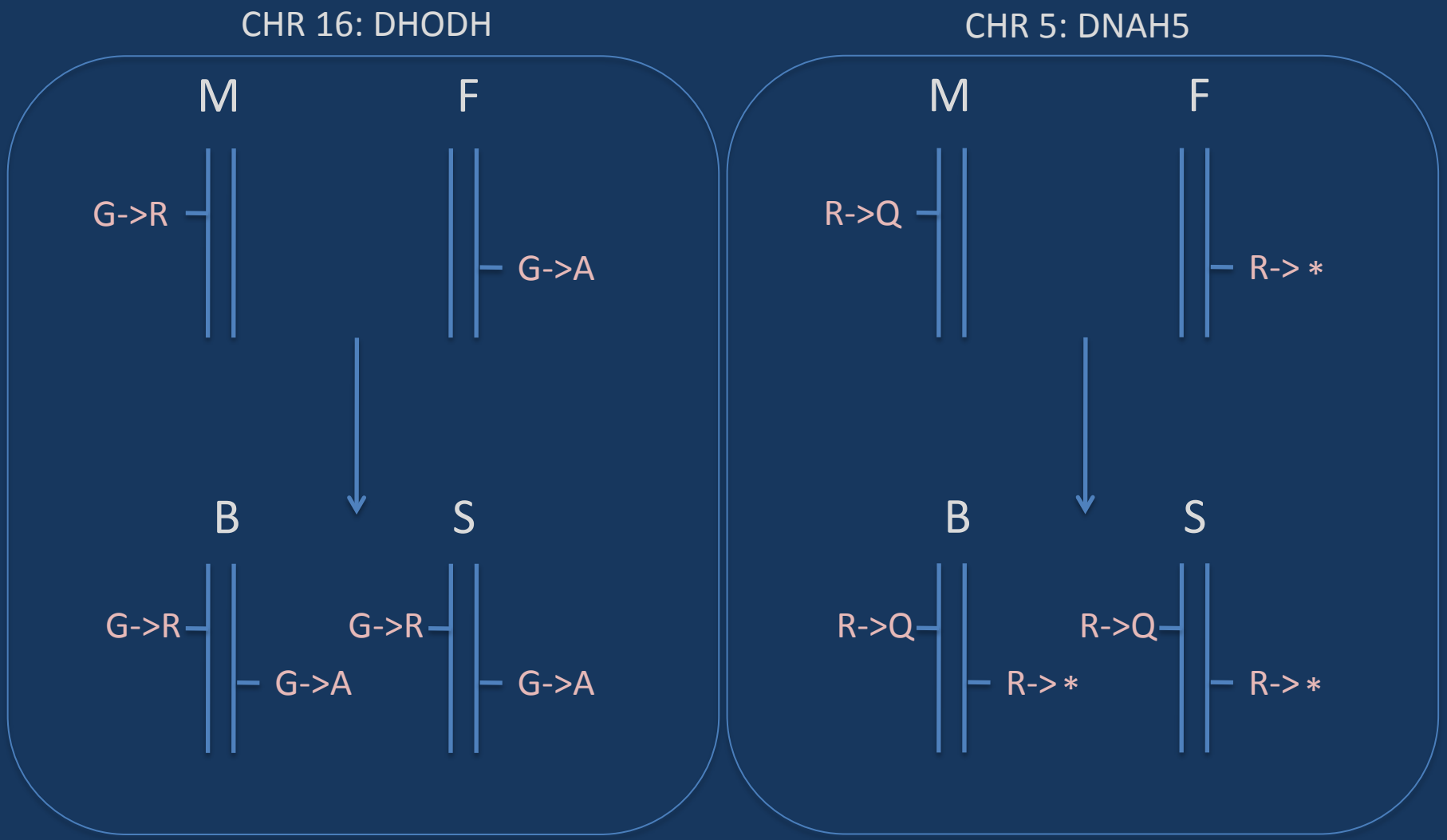
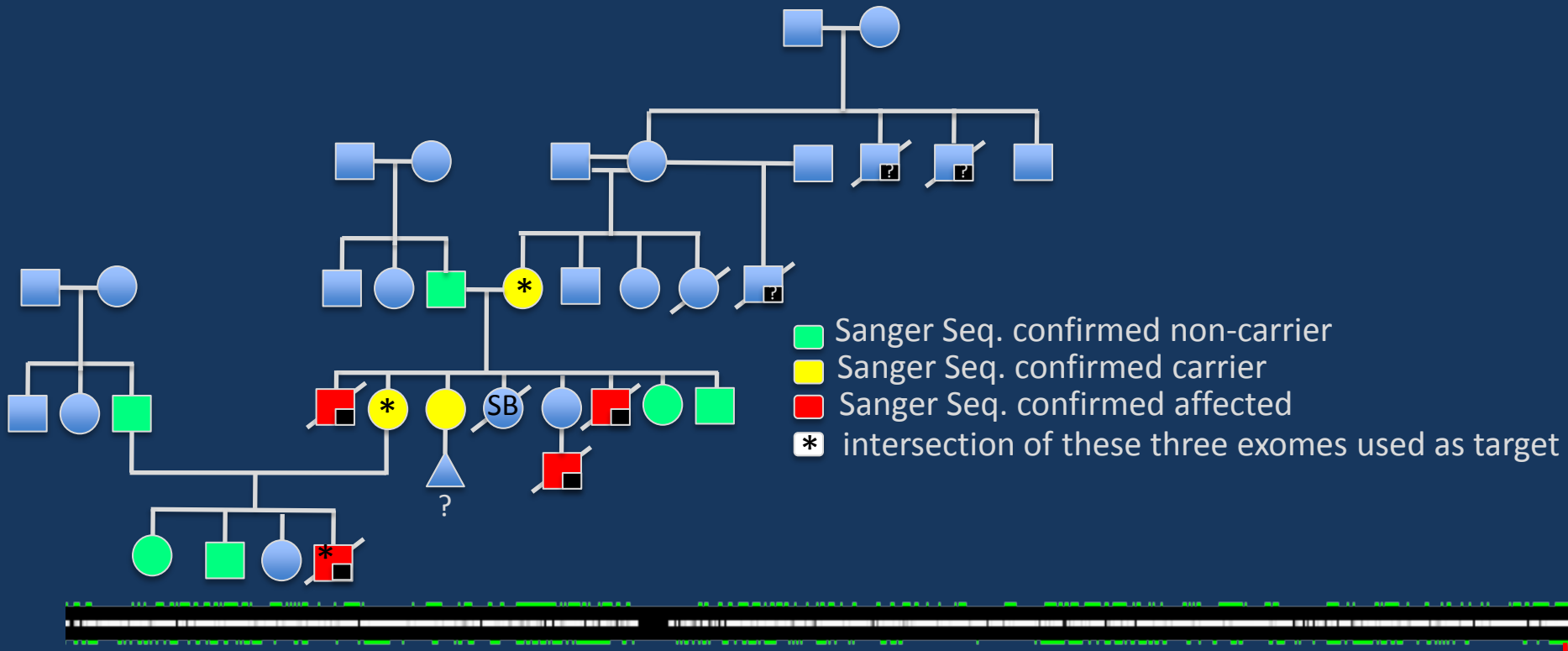
Alleles Responsible for MILLER SYNDROME in Utah Kindred*



- Ng *et al,* Nature Genetics 42, 30–35 (2010) doi:10.1038/ng.499
- Roach, *et al*, Science , 328 636, 2101

Schematic of VAAST Analysis of MILLER Kindred 1 using a single quartet : *only two candidate genes*

10/20/2010: VAAST identifies its first new human genetic disease



High-throughput sequencing identifies an infantile lethal disorder caused by protein N-terminal acetyltransferase deficiency

N-α-acetyltransferase 10

$P < 1X10^{-8}$

Alan F. Rope, Kai Wang, Rune Evjenth, Jinchuan Xing, Jennifer J. Johnston Jeffrey J Swensen, W. Evan Johnson, Barry Moore, Chad D. Huff, Lynne M. Bird, John C. Carey, John M. Opitz, Catherine A. Stevens, Christa Schank, Heidi Deborah Fain, Reid Robison, Brian Dalley, Steven Chin, Sarah T. South, Theodore J. Pysher, Lynn Jorde, Hakon Hakonarson, Johan R. Lillehaug, Leslie G. Biesecker, Mark Yandell, Thomas Arnesen, Gholson J. Lyon; submitted

Next Steps for GVF

- Expand support for phenotype and clinical annotation
- Flesh out representation of single gene diagnostic descriptions (Collaboration with K. Voelkerding, ARUP)
- Develop HL7 compliant XML DTD for embedding GVF in EHRs

Acknowledgements (SO)

- **P41** – NHGRI (PI Blake)
  - Supports the development of The Sequence Ontology & The Gene Ontology
- **R01** – NHGRI (PI Eilbeck)
  - Supports the development of ontology enabled software
- **SBIR** – NLM (multi PI Reese & Eilbeck)
  - Supports variant/disease annotation

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OMIM Alleles Are Distributed Along Ethnic Lines