Exploring genetic variation in in family studies with GEMINI

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Commands for this session:

https://gist.github.com/arq5x/9e1928638397ba45da2e#file-gemini-intro-sh

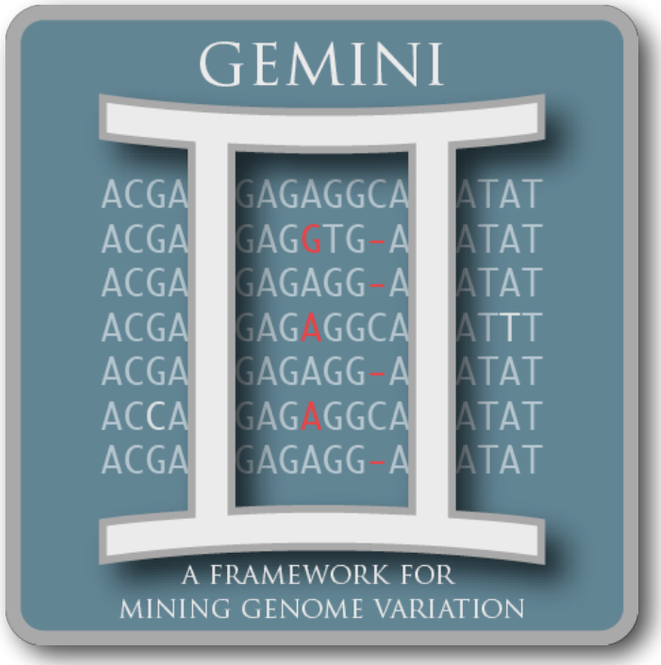
What is GEMINI?

Software package for exploring genetic variation

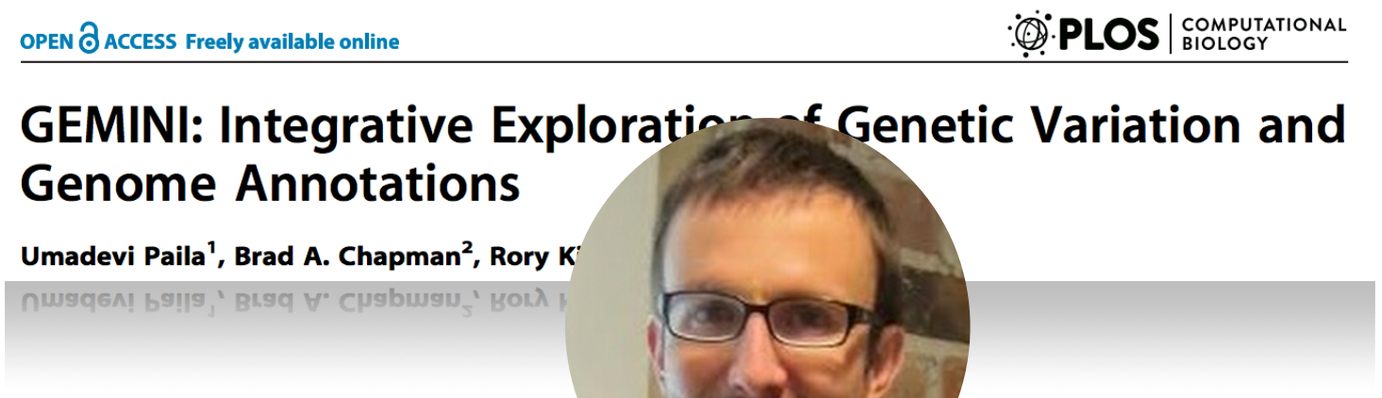
- Integrates annotations from many different sources (ClinVar, dbSNP, ENCODE, UCSC, 1000 Genomes, ESP, KEGG, etc.)

What can you do with Gemini?

- Load a VCF into an "easy to use" database
- Query (fetch data) from database based on annotations or subject genotypes
- Analyze simple genetic models
- More advanced pathway, protein-protein interaction analyses



github.com/arq5x/gemini

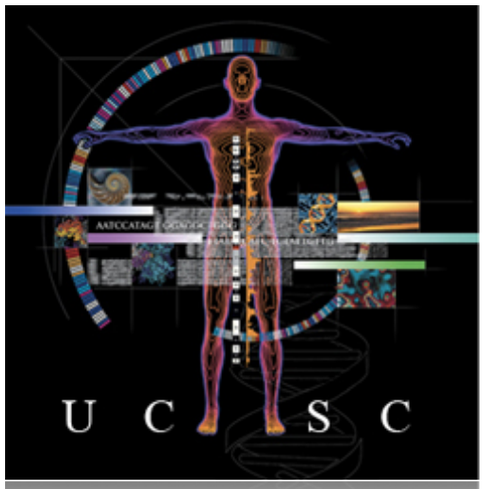


Uma Paila

Brent Pedersen

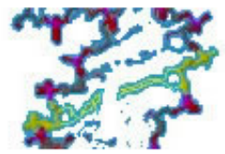
Brad Chapman

What is GEMINI?



Conservation
Repeat elements
Genome Gaps
Cytobands
Gene annotations
“Mappability”
DeCIPHER
ISGA

dbSNP
Short Genetic Variations



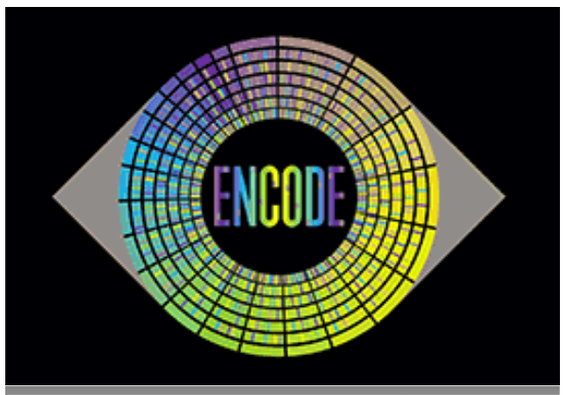
ClinVar

Genetic variation

...CCTCATGCATGGAAA...
...CCTCATGTATGGAAA...
...CCTCATGCATGGAAA...
...CCTCATGCATGGAAA...
...CCTCATGTATGGAAA...
...CCTCATGCATGGAAA...
...CCTCATGTATGGAAA...

OMIM
Online Mendelian Inheritance in Man

1000 Genomes
A Deep Catalog of Human Genetic Variation



Chromatin marks
DNA methylation
RNA expression
TF binding

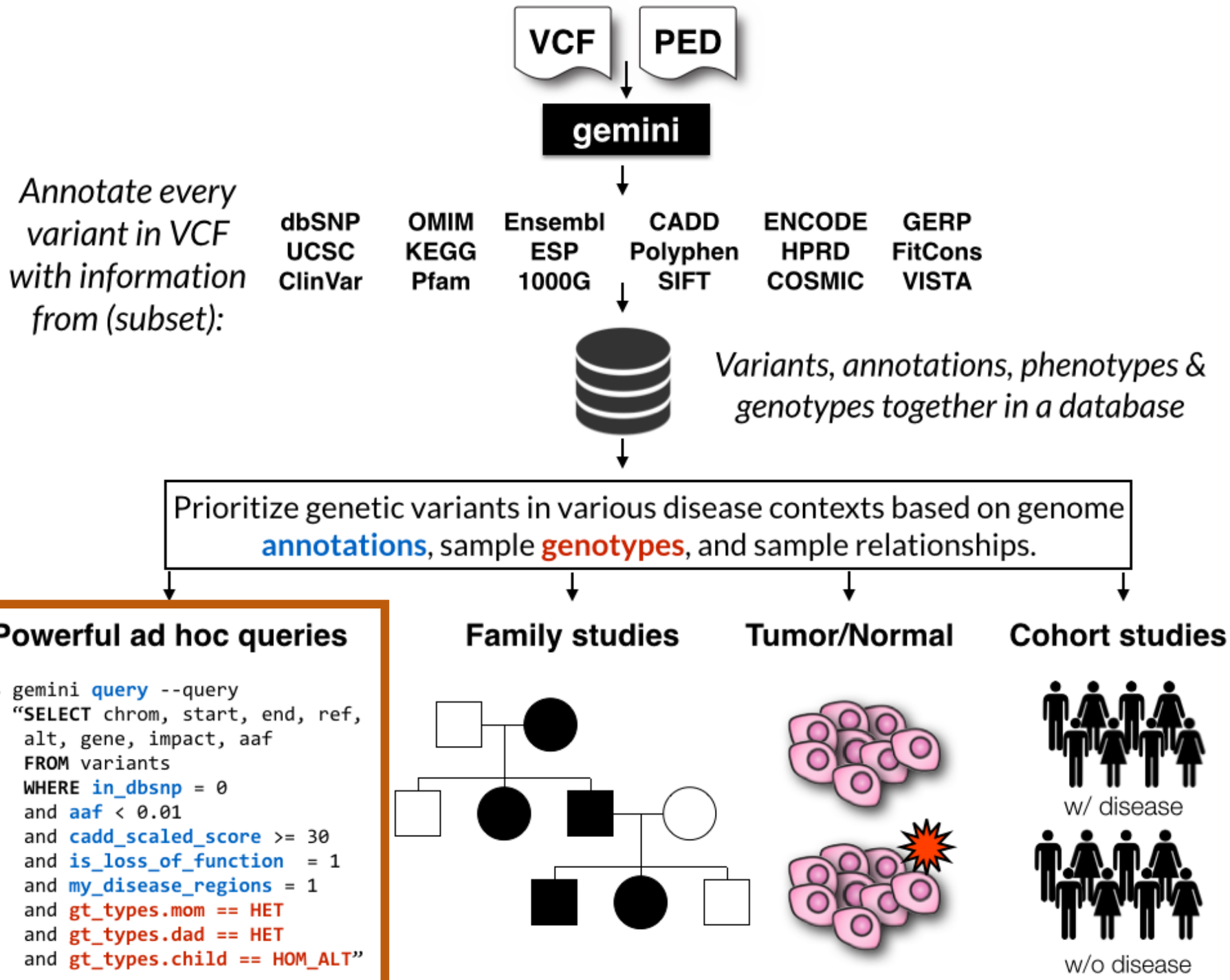
Pfam

KEGG
Kyoto Encyclopedia of Genes and Genomes

HGMD®

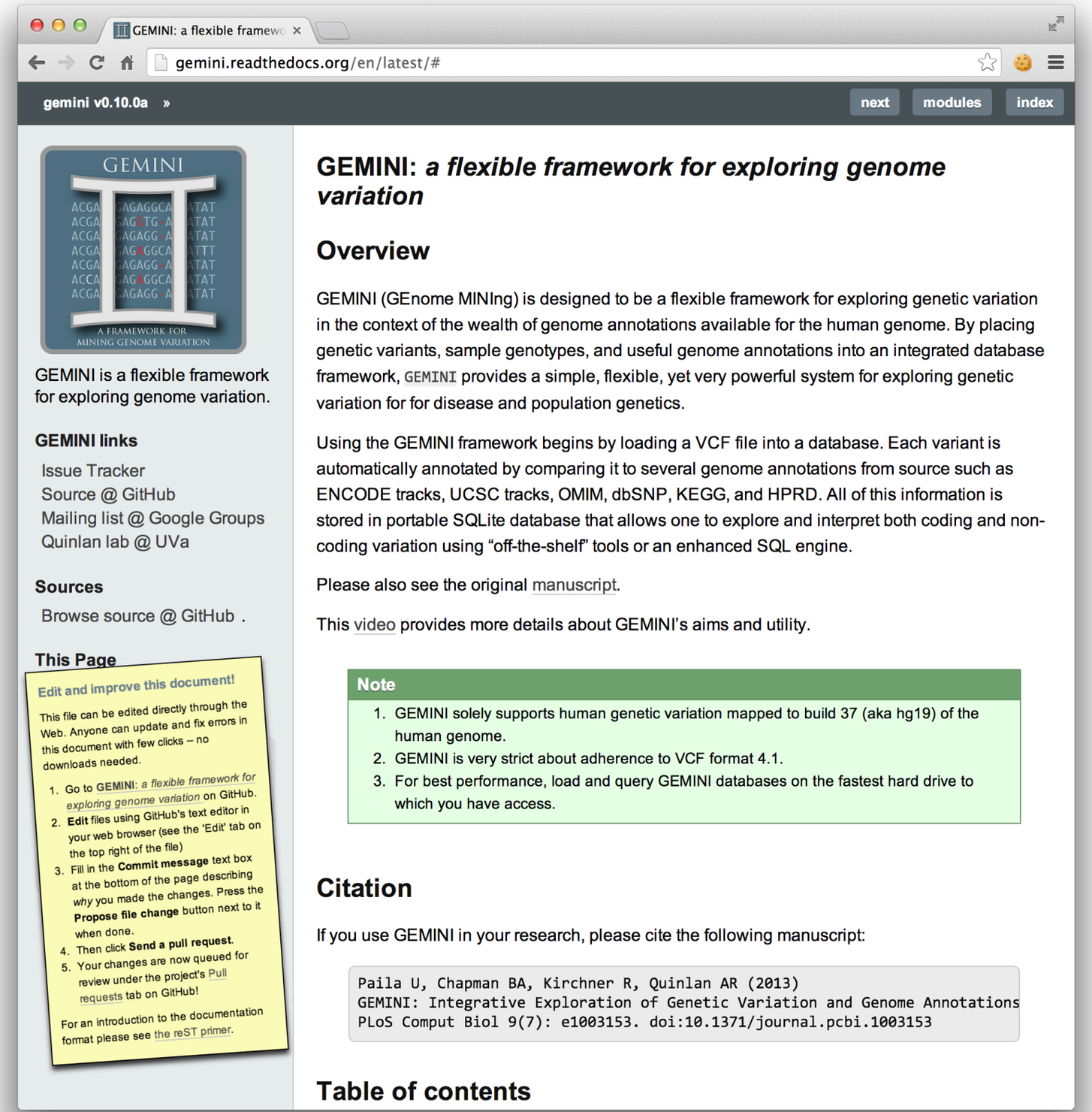
Human Protein Reference Database

GEMINI Framework uses databases and SQL



GEMINI documentation

http://gemini.readthedocs.org



Setup GEMINI exercise

```
# login to AWS

$ mkdir wed

$ cd wed

$ mkdir mydata

$ cd mydata

$ curl https://s3.amazonaws.com/gemini-tutorials/learnSQL.db
> learnSQL.db

$ curl https://s3.amazonaws.com/gemini-tutorials/learnSQL2.db
> learnSQL2.db

$ curl https://s3.amazonaws.com/gemini-tutorials/
chr22.VEP.vcf > chr22.VEP.vcf

$ curl https://s3.amazonaws.com/gemini-tutorials/trio.ped >
trio.ped
```

GEMINI uses a database. Uses SQL to "talk" to it.

- SQL databases to organize genotypes and annotations
- SQL = Structured Query Language
- Data stored in tables

samples							
sample_id	name	family_id	paternal_id	maternal_id	sex	phenotype	ethnicity
1	John	1	Bob	Sue	1	2	CEU
2	Bob	1	0	0	1	1	CEU
3	Mary	1	0	0	2	1	CEU
4	Sue	2	0	0	2	2	YRI

- Query (ask the database) to report data matching your requirements
- Can combine queries, act on results from previous query

Jessica Chong

GEMINI **query** allows one to use SQL to query

samples							
sample_id	name	family_id	paternal_id	maternal_id	sex	phenotype	ethnicity
1	John	1	Bob	Sue	1	2	CEU
2	Bob	1	0	0	1	1	CEU
3	Mary	1	0	0	2	1	CEU
4	Sue	2	0	0	2	2	YRI

```
gemini query -q "SELECT name FROM samples" learnSQL.db
```

John
Bob
Mary
Sue

Filtering rows with the `WHERE (==)` clause

samples							
sample_id	name	family_id	paternal_id	maternal_id	sex	phenotype	ethnicity
1	John	1	Bob	Sue	1	2	CEU
2	Bob	1	0	0	1	1	CEU
3	Mary	1	0	0	2	1	CEU
4	Sue	2	0	0	2	2	YRI

```
gemini query -q "SELECT name FROM samples WHERE phenotype == 2"
                learnSQL.db
```

John
Sue

- phenotype == 2 gets rows where the phenotype value is equal to 2

Filtering rows with the **`WHERE (<>)`** clause

samples							
sample_id	name	family_id	paternal_id	maternal_id	sex	phenotype	ethnicity
1	John	1	Bob	Sue	1	2	CEU
2	Bob	1	0	0	1	1	CEU
3	Mary	1	0	0	2	1	CEU
4	Sue	2	0	0	2	2	YRI

```
gemini query -q "SELECT name FROM samples WHERE phenotype <> 2"
                learnSQL.db
```

Bob
Mary

- phenotype <> 2 gets rows where the phenotype value is NOT equal to 2

Filtering rows with the **`WHERE (<)`** clause

samples							
sample_id	name	family_id	paternal_id	maternal_id	sex	phenotype	ethnicity
1	John	1	Bob	Sue	1	2	CEU
2	Bob	1	0	0	1	1	CEU
3	Mary	1	0	0	2	1	CEU
4	Sue	2	0	0	2	2	YRI

```
gemini query -q "SELECT name FROM samples WHERE sample_id < 3"
                learnSQL.db
```

- Many numeric comparisons possible: <=, >=, >, <

Filtering rows with the **WHERE (NULL)** clause

samples							
sample_id	name	family_id	paternal_id	maternal_id	sex	phenotype	ethnicity
1	John	1	Bob	Sue	1	2	CEU
2	Bob	1	0	0	1	1	CEU
3	Mary	1	0	0	2	1	CEU
4	Sue	2	0	0	2	2	YRI
5	Greg	3	0	0	1	2	

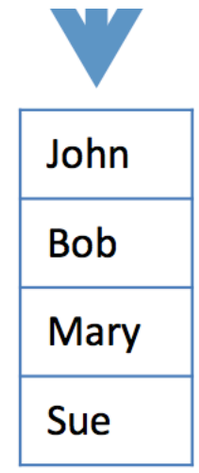
```
gemini query -q "SELECT name FROM samples WHERE ethnicity IS
NULL" learnSQL2.db
```

- When value is missing (empty), it is "NULL"

Filtering rows with the **WHERE (NOT NULL)** clause

samples							
sample_id	**name**	**family_id**	**paternal_id**	**maternal_id**	**sex**	**phenotype**	**ethnicity**
1	John	1	Bob	Sue	1	2	CEU
2	Bob	1	0	0	1	1	CEU
3	Mary	1	0	0	2	1	CEU
4	Sue	2	0	0	2	2	YRI
5	Greg	3	0	0	1	2	

```
gemini query -q "SELECT name FROM samples WHERE ethnicity IS NOT
                NULL" learnSQL2.db
```



The * wildcard

fakevariants				
chrom	**start**	**end**	**rsid**	**in_dbsnp**
chr1	1	2	rs123	1
chr1	3	4		0
chr2	1	2	rs456	1
chr2	3	4		0

```
gemini query -q "SELECT * FROM fakevariants" learnSQL2.db
```

chr1	1	2	rs123	1
chr1	3	4		0
chr2	1	2	rs456	1
chr2	3	4		0

Booleans

- Boolean values are TRUE or FALSE
  - TRUE is equivalent to a value of 1
  - FALSE is equivalent to value of 0

fakevariants				
chrom	**start**	**end**	**rsid**	**in_dbsnp**
chr1	1	2	rs123	1
chr1	3	4		0
chr2	1	2	rs456	1
chr2	3	4		0

Booleans (True)

fakevariants				
chrom	start	end	rsid	in_dbsnp
chr1	1	2	rs123	1
chr1	3	4		0
chr2	1	2	rs456	1
chr2	3	4		0

```
gemini query -q "SELECT chrom,start,end FROM fakevariants
                WHERE in_dbsnp == 1" learnSQL2.db
```

OR

```
gemini query -q "SELECT chrom,start,end FROM fakevariants
                WHERE in_dbsnp" learnSQL2.db
```

chr1	1	2
chr2	1	2

The **COUNT()** operation

fakevariants				
chrom	**start**	**end**	**rsid**	**in_dbsnp**
chr1	1	2	rs123	1
chr1	3	4		0
chr2	1	2	rs456	1
chr2	3	4		0

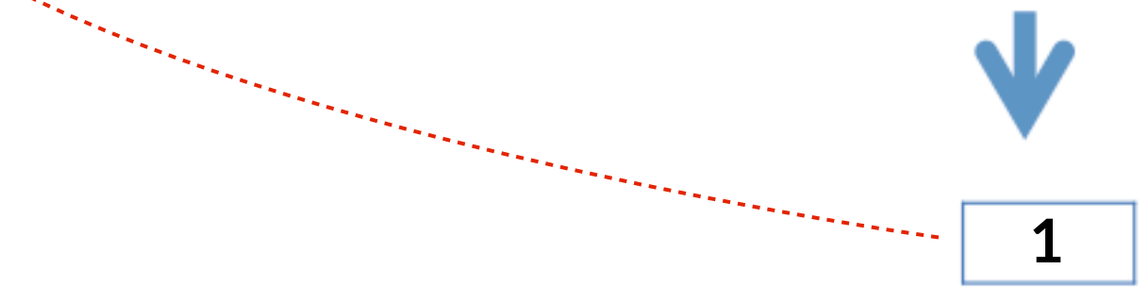
```
gemini query -q "SELECT COUNT(*) FROM fakevariants
      WHERE chrom == 'chr1' " learnSQL2.db
```

2

Multiple **WHERE** clauses

fakevariants				
chrom	**start**	**end**	**rsid**	**in_dbsnp**
chr1	1	2	rs123	1
chr1	3	4		0
chr2	1	2	rs456	1
chr2	3	4		0

```
gemini query -q "SELECT COUNT(*) FROM fakevariants
                 WHERE chrom == 'chr1'
                 AND in_dbsnp == 0 " learnSQL2.db
```



1

Using GEMINI

Annotating genetic variants in the VCF file.

- For gene-based annotations, Gemini supports SnpEff and Variant Effect Predictor (VEP)
- Can add custom annotations as well (e.g. SeattleSeq)
- We will use VEP in this session

VEP webpage: http://uswest.ensembl.org/info/docs/variation/vep/vep_script.html
SeattleSeq: http://snp.gs.washington.edu
SNPEff: http://snpeff.sourceforge.net/

Annotation with VEP (done for you)

```
#perl ~/software/variant_effect_predictor/variant_effect_predictor/
variant_effect_predictor.pl -i chr22.vcf -o chr22.VEP.vcf --vcf \
--cache --dir ~/software/variant_effect_predictor/references \
--sift b --polyphen b --symbol --numbers --biotype --total_length \
--fields
Consequence,Codons,Amino_acids,Gene,SYMBOL,Feature,EXON,PolyPhen,SIFT,Protein_pos
ition,BIOTYPE
```

-i chr22.vcf -o chr22.VEP.vcf	Provide names of input and ouput vcfs
--vcf	Create output in vcf format
--cache --dir data/variant_effect_predictor/references	Use a copy of the VEP database stored locally (faster)
--compress "gunzip -c"	Tells VEP how to uncompress vcf file
--terms so	Style for reporting functional consequence of variants
--sift b --polyphen b	Include **both** score and prediction by SIFT and Polyphen
--hgnc	Include HGNC gene name if available
--numbers	Include number of affected exon/intron
--fields Consequence,Codons,Amino_acids,Gene,HGNC,Feature, EXON,PolyPhen,SIFT	Fields to include in output

Annotation with VEP

Before...

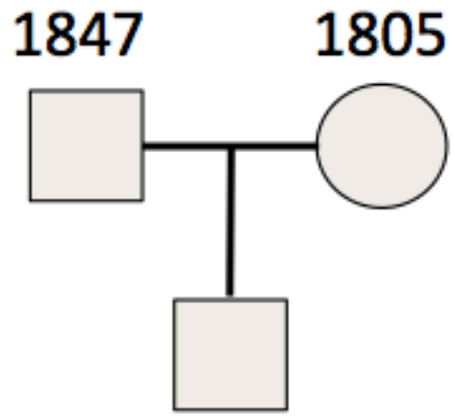
```
22      16157603        .       G       C       382.96  PASS    .       GT:AD:DP:GQ:PL  0/1:4,18:22:0.32:370,0,0         0/1:5,2:7:17.67:46,0,18 ./.:.:.:.:.
22      16157635        .       G       A       15.67   LowQual;QDFilter;QUALFilter     .       GT:AD:DP:GQ:PL  0/0:5,5:10:3:0,3,27      0/1:7,5:12:20.61:47,0,21        ./.:.:.:.:.
22      16157883        .       T       C       104.13  ABFilter;QDFilter       .       GT:AD:DP:GQ:PL  0/1:52,14:66:99:137,0,1177       0/0:88,3:91:99:0,182,2160       ./.:.:.:.:.
22      16159060        .       G       A       11777.6 PASS    .       GT:AD:DP:GQ:PL  1/1:0,49:49:99:1865,144,0       1/1:0,87:87:99:3311,262,0       1/1:3,192:195:99:6602,490,0
22      16255645        .       T       C       235.22  ABFilter;QDFilter       .       GT:AD:DP:GQ:PL  0/1:30,6:36:20.52:155,0,21      0/1:27,7:34:99:119,0,182        0/0:246,1:250:99:0,183,2040
```

After...

```
22      16157603        .       G       C       382.96  PASS    CSQ=C|ENSG00000232775|ENST00000609679|Transcript|intron_variant&nc_transcript_variant|-/552|||||||1/2||1|AP000525.10|Clone_based_vega_gene|||processed_transcript,C|ENSG00000206195|ENST00000437781|Transcript|intron_variant&nc_transcript_variant|-/2398|||||||7/7||-1|AP000525.9|Clone_based_vega_gene|||lincRNA,C|ENSG00000272872|ENST00000608286|Transcript|upstream_gene_variant|-/694|||||||||2837|-1|LL22NC03-N14H11.1|Clone_based_vega_gene|||sense_intronic,C|ENSG00000206195|ENST00000383038|Transcript|downstream_gene_variant|-/1394|||||||||1195|-1|AP000525.9|Clone_based_vega_gene|||processed_transcript,C|ENSG00000206195|ENST00000447898|Transcript|intron_variant&nc_transcript_variant|-/4136|||||||3/3||-1|AP000525.9|Clone_based_vega_gene|||lincRNA,C|ENSG00000206195|ENST00000607933|Transcript|downstream_gene_variant|-/642|||||||||1226|-1|AP000525.9|Clone_based_vega_gene|||processed_transcript,C|ENSG00000232775|ENST00000440946|Transcript|upstream_gene_variant|-/1160|||||||||4463|1|AP000525.10|Clone_based_vega_gene|||processed_transcript,C|ENSG00000206195|ENST00000413768|Transcript|intron_variant&nc_transcript_variant|-/2102|||||||7/7||-1|AP000525.9|Clone_based_vega_gene|||lincRNA      GT:AD:DP:GQ:PL  0/1:4,18:22:0.32:370,0,0         0/1:5,2:7:17.67:46,0,18 ./.:.:.:.:.
22      16157635        .       G       A       15.67   LowQual;QDFilter;QUALFilter     CSQ=A|ENSG00000232775|ENST00000609679|Transcript|intron_variant&nc_transcript_variant|-/552|||||||1/2||1|AP000525.10|Clone_based_vega_gene|||processed_transcript,A|ENSG00000206195|ENST00000437781|Transcript|intron_variant&nc_transcript_variant|-/2398|||||||7/7||-1|AP000525.9|Clone_based_vega_gene|||lincRNA,A|ENSG00000272872|ENST00000608286|Transcript|upstream_gene_variant|-/694|||||||||2869|-1|LL22NC03-N14H11.1|Clone_based_vega_gene|||sense_intronic,A|ENSG00000206195|ENST00000383038|Transcript|downstream_gene_variant|-/1394|||||||||1163|-1|AP000525.9|Clone_based_vega_gene|||processed_transcript,A|ENSG00000206195|ENST00000447898|Transcript|intron_variant&nc_transcript_variant|-/4136|||||||3/3||-1|AP000525.9|Clone_based_vega_gene|||lincRNA,A|ENSG00000206195|ENST00000607933|Transcript|downstream_gene_variant|-/642|||||||||1194|-1|AP000525.9|Clone_based_vega_gene|||processed_transcript,A|ENSG00000232775|ENST00000440946|Transcript|upstream_gene_variant|-/1160|||||||||4431|1|AP000525.10|Clone_based_vega_gene|||processed_transcript,A|ENSG00000206195|ENST00000413768|Transcript|intron_variant&nc_transcript_variant|-/2102|||||||7/7||-1|AP000525.9|Clone_based_vega_gene|||lincRNA      GT:AD:DP:GQ:PL  0/0:5,5:10:3:0,3,27      0/1:7,5:12:20.61:47,0,21        ./.:.:.:.:.
22      16157883        .       T       C       104.13  ABFilter;QDFilter       CSQ=C|ENSG00000232775|ENST00000609679|Transcript|intron_variant&nc_transcript_variant|-/552|||||||1/2||1|AP000525.10|Clone_based_vega_gene|||processed_transcript,C|ENSG00000206195|ENST00000437781|Transcript|intron_variant&nc_transcript_variant|-/2398|||||||7/7||-1|AP000525.9|Clone_based_vega_gene|||lincRNA,C|ENSG00000272872|ENST00000608286|Transcript|upstream_gene_variant|-/694|||||||||3117|-1|LL22NC03-N14H11.1|Clone_based_vega_gene|||sense_intronic,C|ENSG00000206195|ENST00000383038|Transcript|downstream_gene_variant|-/1394|||||||||915|-1|AP000525.9|Clone_based_vega_gene|||processed_transcript,C|ENSG00000206195|ENST00000447898|Transcript|intron_variant&nc_transcript_variant|-/4136|||||||3/3||-1|AP000525.9|Clone_based_vega_gene|||lincRNA,C|ENSG00000206195|ENST00000607933|Transcript|downstream_gene_variant|-/642|||||||||946|-1|AP000525.9|Clone_based_vega_gene|||processed_transcript,C|ENSG00000232775|ENST00000440946|Transcript|upstream_gene_variant|-/1160|||||||||4183|1|AP000525.10|Clone_based_vega_gene|||processed_transcript,C|ENSG00000206195|ENST00000413768|Transcript|intron_variant&nc_transcript_variant|-/2102|||||||7/7||-1|AP000525.9|Clone_based_vega_gene|||lincRNA      GT:AD:DP:GQ:PL  0/1:52,14:66:99:137,0,1177       0/0:88,3:91:99:0,182,2160       ./.:.:.:.:.
22      16159060        .       G       A       11777.6 PASS    CSQ=A|ENSG00000232775|ENST00000609679|Transcript|intron_variant&nc_transcript_variant|-/552|||||||1/2||1|AP000525.10|Clone_based_vega_gene|||processed_transcript,A|ENSG00000206195|ENST00000437781|Transcript|intron_variant&nc_transcript_variant|-/2398|||||||7/7||-1|AP000525.9|Clone_based_vega_gene|||lincRNA,A|ENSG00000272872|ENST00000608286|Transcript|upstream_gene_variant|-/694|||||||||4294|-1|LL22NC03-N14H11.1|Clone_based_vega_gene|||sense_intronic,A|ENSG00000206195|ENST00000383038|Transcript|non_coding_exon_variant&nc_transcript_variant|1132/1394||||||8/8|||-1|AP000525.9|Clone_based_vega_gene|||processed_transcript,A|ENSG00000206195|ENST00000447898|Transcript|intron_variant&nc_transcript_variant|-/4136|||||||3/3||-1|AP000525.9|Clone_based_vega_gene|||lincRNA,A|ENSG00000206195|ENST00000607933|Transcript|non_coding_exon_variant&nc_transcript_variant|411/642||||||1/1|||-1|AP000525.9|Clone_based_vega_gene|||processed_transcript,A|ENSG00000232775|ENST00000440946|Transcript|upstream_gene_variant|-/1160|||||||||3006|1|AP000525.10|Clone_based_vega_gene|||processed_transcript,A|ENSG00000206195|ENST00000413768|Transcript|intron_variant&nc_transcript_variant|-/2102|||||||7/7||-1|AP000525.9|Clone_based_vega_gene|||lincRNA      GT:AD:DP:GQ:PL  1/1:0,49:49:99:1865,144,0      1/1:0,87:87:99:3311,262,0       1/1:3,192:195:99:6602,490,0
22      16255645        .       T       C       235.22  ABFilter;QDFilter       CSQ=C|ENSG00000241838|ENST00000417657|Transcript|non_coding_exon_variant&nc_transcript_variant|833/1123||||||1/1|||-1|LA16c-3G11.7|Clone_based_vega_gene|||processed_pseudogene,C|ENSG00000198062|ENST00000452800|Transcript|downstream_gene_variant|-/1964|-/912|-/303||||||796|-1|POTEH|HGNC|||nonsense_mediated_decay,C|ENSG00000198062|ENST00000343518|Transcript|downstream_gene_variant|-/1928|-/1638|-/545||||||796|-1|POTEH|HGNC|||protein_coding,C|ENSG00000241838|ENST00000339523|Transcript|downstream_gene_variant|-/309|||||||||274|-1|LA16c-3G11.7|Clone_based_vega_gene|||processed_pseudogene      GT:AD:DP:GQ:PL  0/1:30,6:36:20.52:155,0,21      0/1:27,7:34:99:119,0,182        0/0:246,1:250:99:0,183,2040
```

Creating PED files.

- VCF contains genotypes and annotations
- PED file provides family/pedigree, sex, phenotype information
- missing values = 0 or -9



Family ID	Subject ID	Father ID	Mother ID	Sex 1 = male 2 = female	Phenotype 1 = unaffected 2 = affected	Ancestry
1	4805	1847	1805	2	0	CEU
1	1847	0	0	1	0	CEU
1	1805	0	0	2	0	CEU

Loading a VCF file into a GEMINI database

```
gemini load -v chr22.VEP.vcf \
            -p trio.ped \
            -t VEP \
            --cores 2 \
            --skip-gene-tables \
        chr22.db
```

- Use Gemini to load annotated VCF and associated PED file into chr22.db
- Also load per-position GERP scores
- Use 4 cores
  - optional
  - faster, but most laptops have only 2 cores

What is in the database?

```
gemini db_info chr22.db
```

- `table_name` column shows whether information stored applies to:
  - `variants`
  - `variant_impacts`
  - `samples`
- `types` column shows the type of information
  - `text` - just plain text (e.g. "indel" or "SNP")
  - `integer` - a whole number (e.g. "start" position)
  - `float` - a number with decimal places (e.g. "call_rate")
  - `blob` - special data type interpreted by Gemini (genotype data)
  - `bool` - can be true or false (e.g. "in_dbsnp")

Full database details

http://gemini.readthedocs.org/en/latest/content/database_schema.html

Queries of the samples in the database

Which samples/subjects are in your database?

```
gemini query -q "SELECT name FROM samples" --header chr22.db
```

Does the rest of the info match your PED file?

```
gemini query -q "SELECT * FROM samples" --header chr22.db
```

Querying variants. *Basics*.

How many novel (i.e., not in dbSNP) are observed in these samples?

```
gemini query -q "SELECT COUNT(*) \
                 FROM variants \
                 WHERE in_dbsnp == 0" --header chr22.db
```

How many variants passed GATK filters?

```
gemini query -q "SELECT COUNT(*) \
                 FROM variants \
                 WHERE filter is NULL" --header chr22.db
```

Querying variants. ***Basics***.

Let's examine variants with GATK filter PASS in the MLC1 gene

```
gemini query -q "SELECT * FROM variants WHERE
filter is NULL and gene = 'MLC1' " --header chr22.db
```

Let's instead focus the analysis to a specific set of columns

```
gemini query -q "SELECT rs_ids, aaf_esp_ea, impact,
clinvar_disease_name, clinvar_sig
FROM variants
WHERE filter is NULL and gene = 'MLC1' " --header chr22.db
```

Querying variants. *Basics*.

How many variants are rare and in a disease-associated gene?

```
gemini query -q "SELECT COUNT(*) from variants WHERE
clinvar_disease_name is not NULL and aaf_esp_ea <= 0.01" \
chr22.db
```

List the genes

```
gemini query -q "SELECT gene from variants \
WHERE clinvar_disease_name is not NULL and aaf_esp_ea <= 0.01" \
chr22.db
```

Querying variants. ***Sample genotypes***.

For each individual, Gemini gives access to genotype, depth, genotype quality and genotype likelihoods at each variant

`gt_types.subjectID`
  `HOM_REF`
  `HET`
  `HOM_ALT`

`gt_quals.subjectID`
  genotype quality

`gt_depths.subjectID`
  total number of reads in this subject at position

`gt_ref_depths.subjectID`
  number of **reference allele** reads in this subject at position

`gt_alt_depths.subjectID`
  number of **alternate allele** reads in this subject at position

Querying variants. ***Sample genotypes queries***.

At how many sites does subject 1805 have a non-reference allele?

```
gemini query -q "SELECT * from variants" \
             --gt-filter "gt_types.1805 <> HOM_REF" \
             --header \
             chr22.db \
| wc -l
```

At how many sites do subject 1805 ***and*** subject 4805 both have a non-reference allele?

```
gemini query -q "SELECT * from variants" \
             --gt-filter "(gt_types.1805 <> HOM_REF AND \
                          gt_types.4805 <> HOM_REF)" \
             chr22.db \
| wc -l
```

List the genotypes for sample 1805 and 4805

```
gemini query -q "SELECT gts.1805, gts.4805 from variants" \
             --gt-filter "(gt_types.1805 <> HOM_REF and \
                          gt_types.4805 <> HOM_REF)" \
             chr22.db
```

Querying variants. ***Sample genotypes wildcards***.

At which variants are every sample heterozygous?

```
gemini query -q "SELECT chrom, start, end, ref, alt, \
                       gene, impact, (gts).(*) \
                  FROM variants" \
               --gt-filter "(gt_types).(*).(==HET).(all)" \
               --header \
               chr22.db
```

At which variants are all of the female samples reference homozygotes?

```
gemini query -q "SELECT chrom, start, end, ref, alt, \
                       gene, impact, (gts).(*) \
                  FROM variants" \
               --gt-filter "(gt_types).(sex==2).(==HOM_REF).(all)" \
               --header \
               chr22.db
```

Note

The syntax of the wildcard `--gt-filters` is `(COLUMN).(SAMPLE_WILDCARD).(SAMPLE_WILDCARD_RULE).(RULE_ENFORCEMENT).`

Querying variants. ***The "any" wildcard***

At which variants is ***any female*** sample homozygous for the alternate allele?

```
gemini query -q "SELECT chrom, start, end, ref, alt, \
                       gene, impact, (gts).(*) \
                   FROM variants" \
                --gt-filter "(gt_types).(sex==2).(!=HOM_REF).(any)" \
                --header \
                chr22.db
```

Querying variants. *The "none" wildcard*

At which variants are ***none of the female*** samples homozygous for the reference allele?

```
gemini query -q "SELECT chrom, start, end, ref, alt, \
                       gene, impact, (gts).(*) \
                    FROM variants" \
                --gt-filter "(gt_types).(sex==2).(==HOM_REF).(none)" \
                --header \
                chr22.db
```

Querying variants. ***The "count" wildcard***

Identify suspicious variants. Cases where at least 2 of the samples have UNKNOWN genotypes

```
gemini query -q "SELECT chrom, start, end, ref, alt, \
                       gene, impact, (gts).(*) \
                   FROM variants" \
                --gt-filter "(gt_types).(*).(==UNKNOWN).(count >= 2)" \
                --header \
                chr22.db
```

Wildcards work on all of the “genotype” columns in GEMINI

Genotype information

gts	BLOB	A compressed binary vector of sample genotypes (e.g., “A/A”, “A|G”, “G/G”) - Extracted from the VCF `GT` genotype tag.
gt_types	BLOB	A compressed binary vector of numeric genotype “types” (e.g., 0, 1, 2) - Inferred from the VCF `GT` genotype tag.
gt_phases	BLOB	A compressed binary vector of sample genotype phases (e.g., False, True, False) - Extracted from the VCF `GT` genotype tag’s allele delimiter e.g., `A/G` means an unphased genotype. Value is **FALSE**. e.g., `A|G` means a phased genotype. Value is **TRUE**.
gt_depths	BLOB	A compressed binary vector of the depth of aligned sequence observed for each sample - Extracted from the VCF `DP` genotype tag.
gt_ref_depths	BLOB	A compressed binary vector of the depth of reference alleles observed for each sample - Extracted from the VCF `AD` genotype tag.
gt_alt_depths	BLOB	A compressed binary vector of the depth of alternate alleles observed for each sample - Extracted from the VCF `AD` genotype tag.
gt_quals	BLOB	A compressed binary vector of the genotype quality (PHRED scale) estimates for each sample - Extracted from the VCF `GQ` genotype tag.

http://gemini.readthedocs.org/en/latest/content/database_schema.html#genotype-information

Wildcards can be applied to other genotype columns

Identify variants that are likely to have high quality genotypes
(i.e., aligned depth >=50 for all samples)

```
gemini query -q "SELECT chrom, start, end, ref, alt, \
                       gene, impact, (gts).(*), (gt_depths).(*) \
                FROM variants" \
               --gt-filter "(gt_depths).(*).(>=50).(all)" \
               --header \
               chr22.db
```

Variant statistics

Get some basic statistics on variants in samples

```
gemini stats --gts-by-sample chr22.db | column -t
```

```
sample  num_hom_ref  num_het  num_hom_alt  num_unknown  total
1805    860          1031     496          58           2445
1847    676          1297     418          54           2445
4805    662          1242     478          63           2445
```

Calculate transition/transversion ratio

```
gemini stats --tstv chr22.db | column -t
```

```
ts    tv   ts/tv
1594  698  2.2837
```

Variant statistics --summarize

Add "**`--summarize`**" to summarize genotypes by sample for any custom query

```
gemini stats --summarize \
"SELECT * from variants WHERE in_dbsnp = 0" \
chr22.db | column -t
```

```
sample  total  num_het  num_hom_alt
1805    85     73       12
1847    94     75       19
4805    168    148      20
```

```
gemini stats --summarize \
"SELECT * from variants WHERE in_dbsnp = 1" \
chr22.db | column -t
```

```
sample  total  num_het  num_hom_alt
1805    1442   958      484
1847    1621   1222     399
4805    1552   1094     458
```

References

Resources mentioned in these slides:

VEP webpage:

http://uswest.ensembl.org/info/docs/variation/vep/vep_script.html

SeattleSeq:

http://snp.gs.washington.edu

SNPEff:

http://snpeff.sourceforge.net/

Gemini Documentation:

https://gemini.readthedocs.org

Annotations and information available for Gemini:

https://gemini.readthedocs.org/en/latest/content/database_schema.html

To learn more about SQL on your own:

http://software-carpentry.org/4_0/databases/