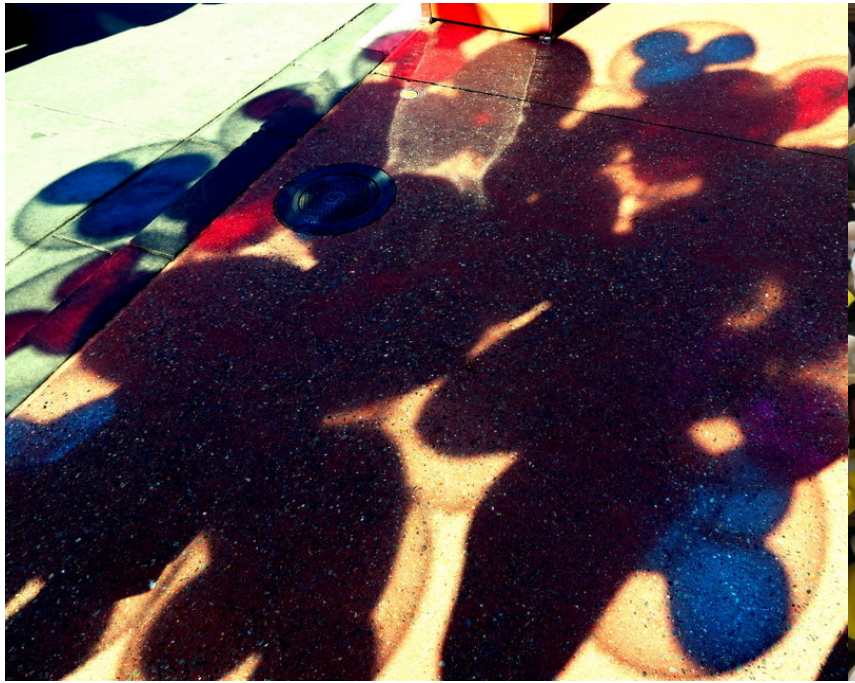
Leveraging Protein Structure & Dynamics for Variant Interpretation in Coding Regions

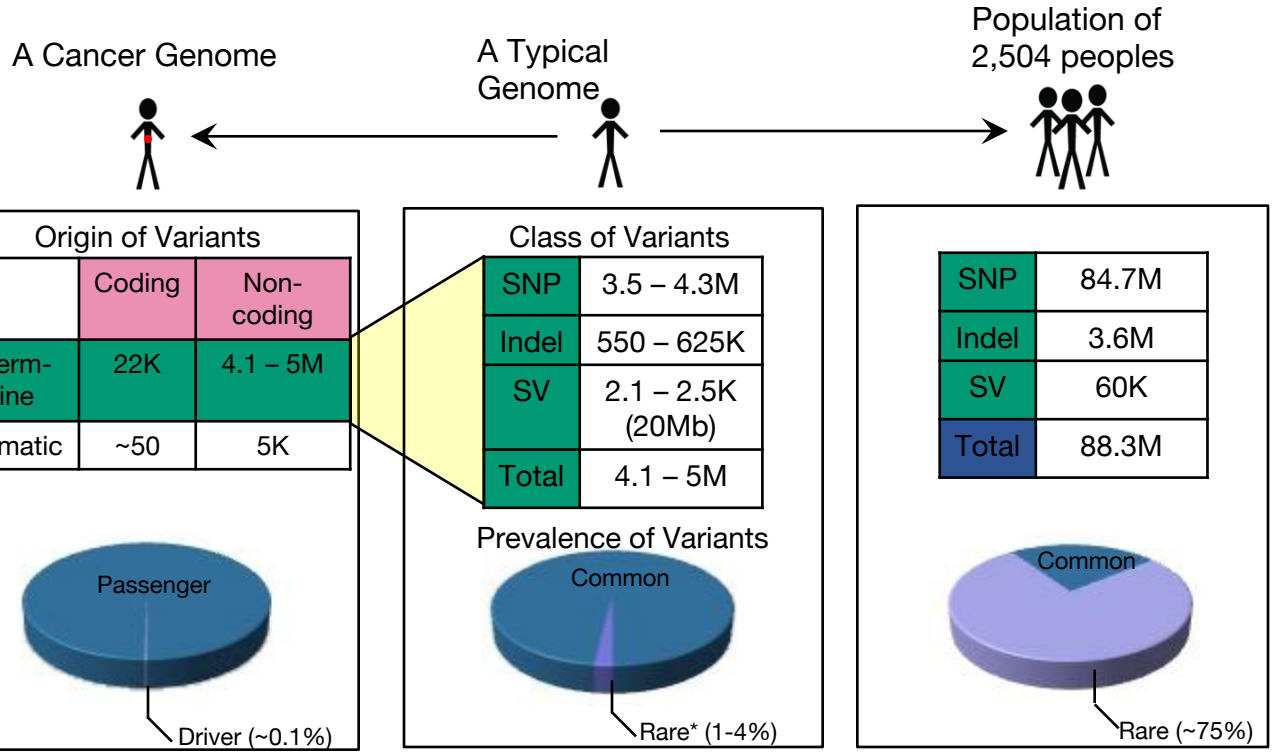


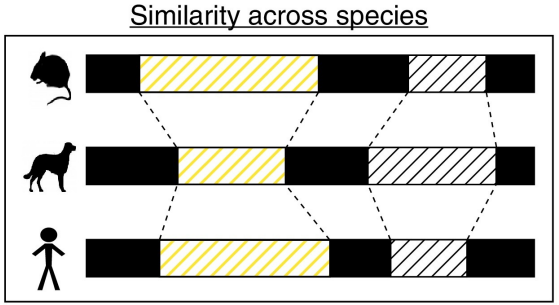
k Gerstein
Yale

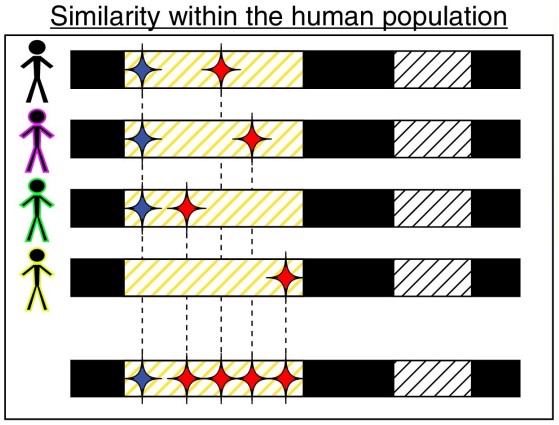
Slides freely downloadable from **Lectures.GersteinLab.org** & “tweetable” (via **@MarkGerstein**).

No Conflicts for this Talk. See last slide for more info.

Human Genetic Variation: the prevalence of rare variants in population studies







[Sethi et al. COSB ('15)]

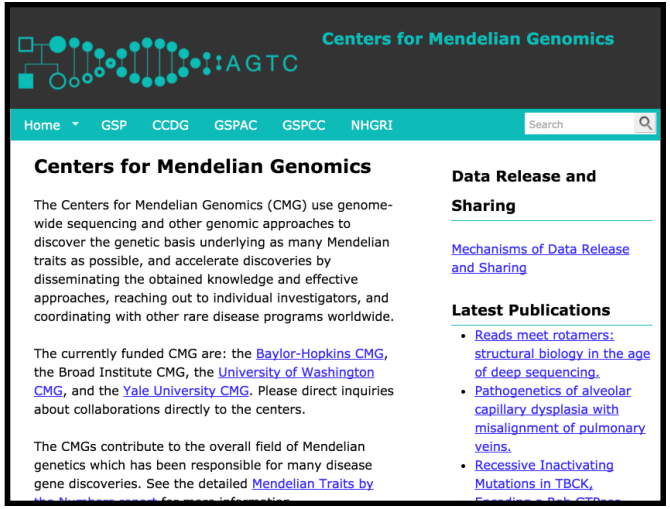
* Variants with allele frequency < 0.5% are considered as rare variants in 1000 genomes project.

The 1000 Genomes Project Consortium, Nature. 2015. 526:68-74
Khurana E. et al. Nat. Rev. Genet. 2016. 17:93-108

Rare variant analysis particularly applicable at the moment because of the many exomes

CMG rare disease variants & TCGA somatic variants

- Main NIH disease genomic project
- Both of these focus on ”rare” variant for which GWAS is not meaningful
- Larger numbers of individual exomes more important than WGS



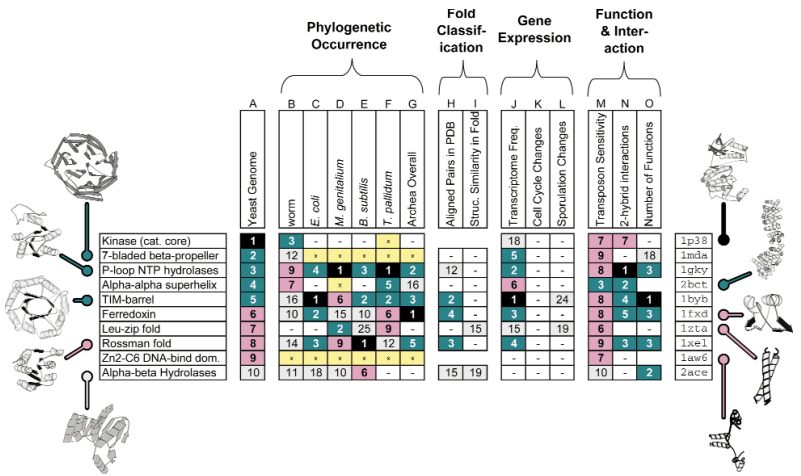
Exomes have the current potential for great scale with the better impact interpretability of coding variants, often in a region of known protein structure

- Scale of EXAC, >60K exomes [Lek et al. ‘16]

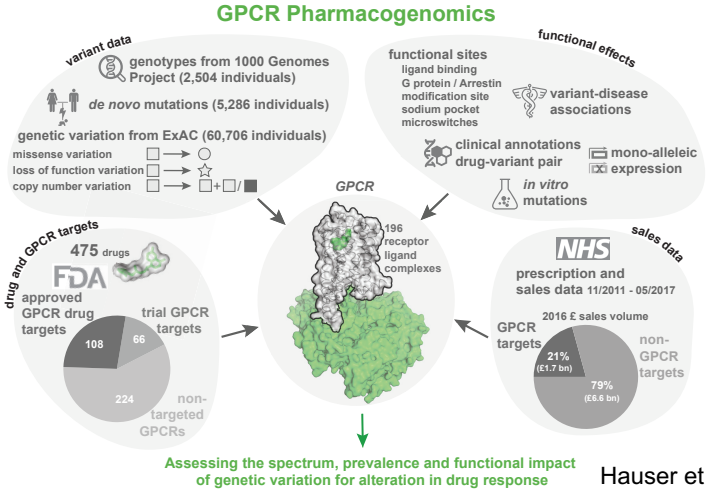
Structure & genomics

Structure particularly useful for interpreting the impact of the many rare variants whose effect can not be found via GWAS

Also, integration of structure data with genomic variants, EHR & drug data will be key for realizing the goal of precision medicine.



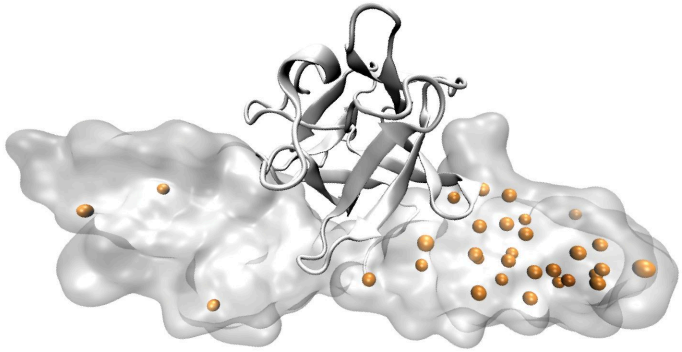
Gerstein et al., Nat. Struct. Bio. 2000



Hauser et al., Cell 2018

Unlike common SNVs, the statistical power with which we can evaluate rare SNVs in case-control studies is severely limited

Protein structures may provide the needed alternative for evaluating rare SNVs, many of which may be disease-associated



Fibroblast growth factor receptor 2 (pdb: 1IIL)

- 1000G & ExAC SNVs (common | rare)
- Hinge residues
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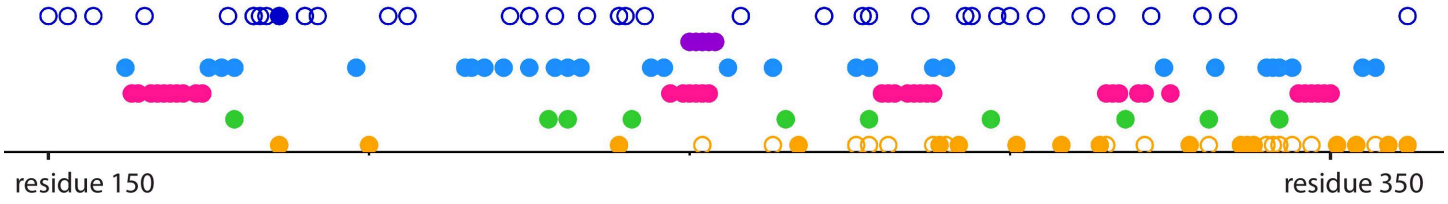

[Sethi et al. COSB ('15)]

Leveraging Protein Structure and Dynamics for Variant Interpretation in Coding Regions

- Background on rare & common variants
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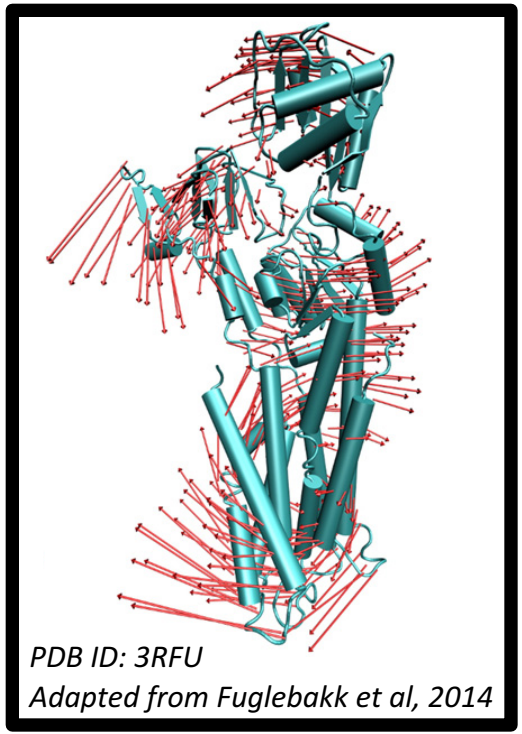
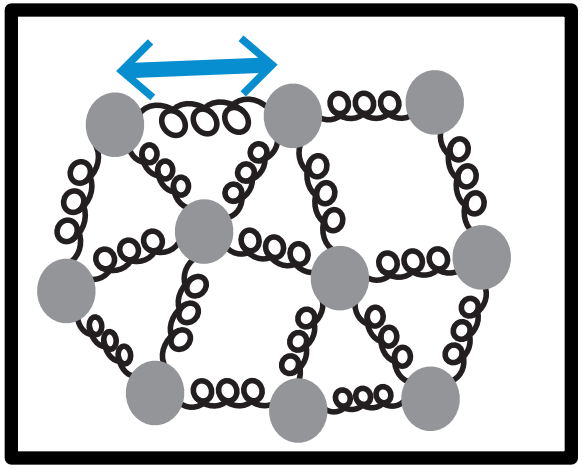
Models of Protein Conformational Change

Motion Vectors from Normal Modes (ANMs)



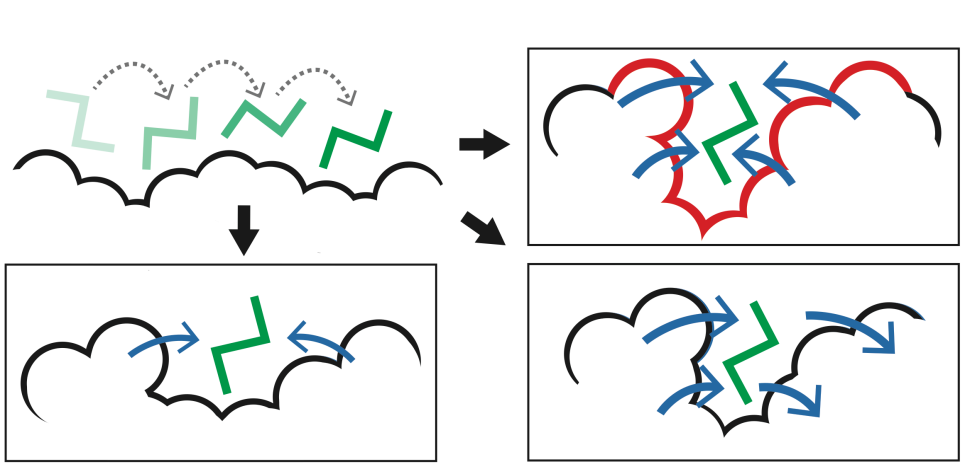
PDB ID: 3RFU
Adapted from Fuglebakk et al, 2014



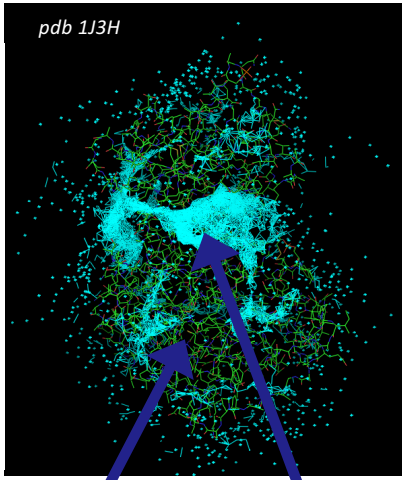
Characterizing uncharacterized variants
<= Finding Allosteric sites
<= Modeling motion

Predicting Allosterically-Important Residues at the Surface

1. MC simulations generate a large number of candidate sites
2. Score each candidate site by the degree to which it perturbs large-scale motions
3. Prioritize & threshold the list to identify the set of high confidence-sites

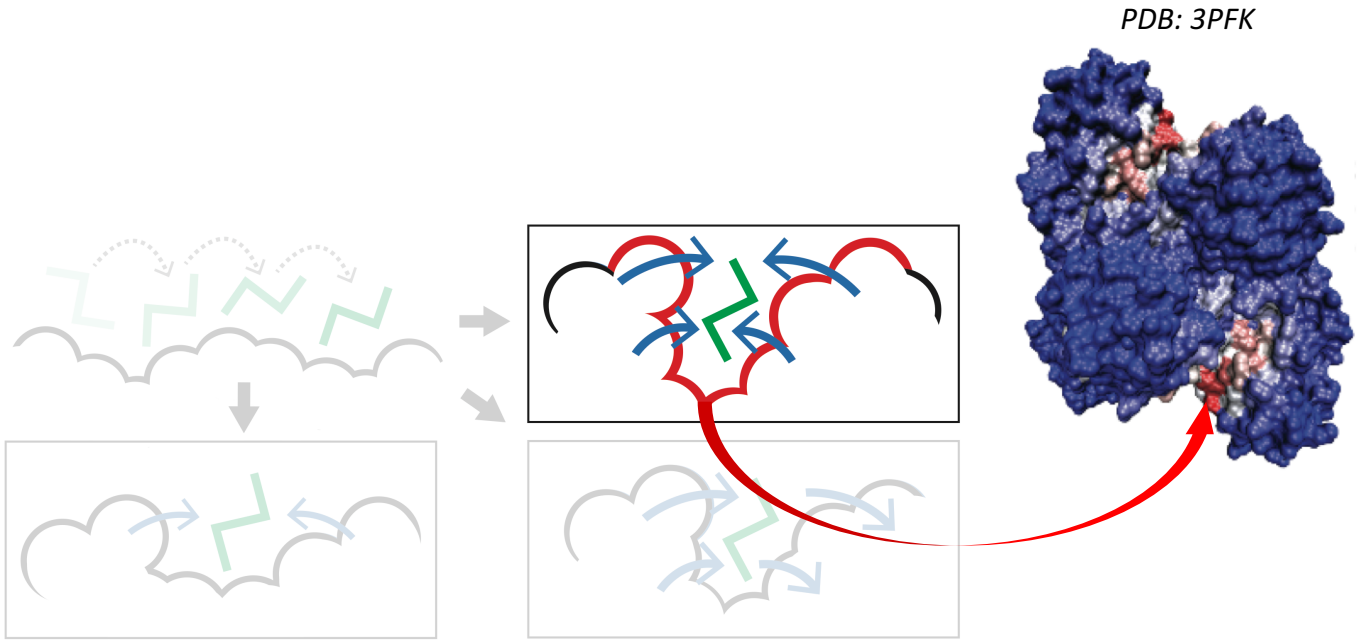


$$\textit{binding leverage} = \sum_{m=1}^{10}\left(\sum_{i}\sum_{j}\Delta d_{ij(m)}^{2}\right)$$



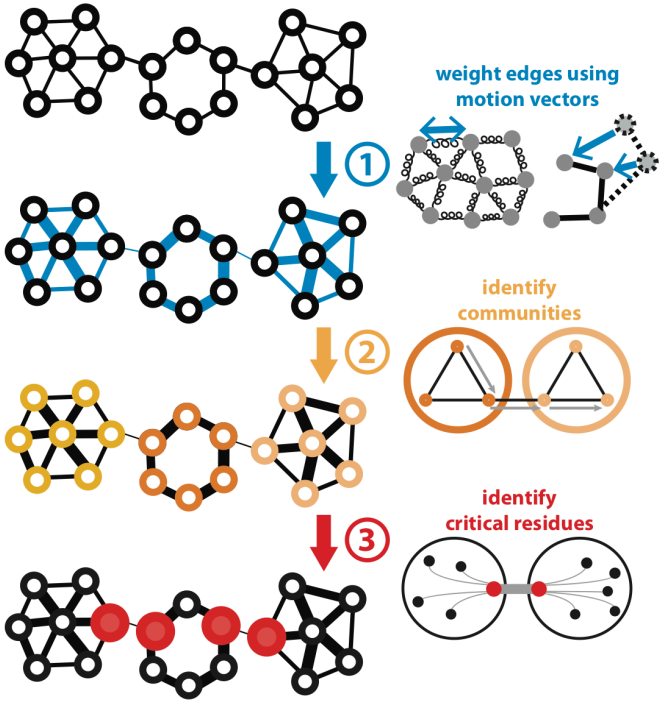
Adapted from Clarke*, Sethi*, et al *('16)*

Predicting Allosterically-Important Residues at the Surface



Adapted from Clarke*, Sethi*, et al *('16)*

Predicting Allosterically-Important Residues within the Interior



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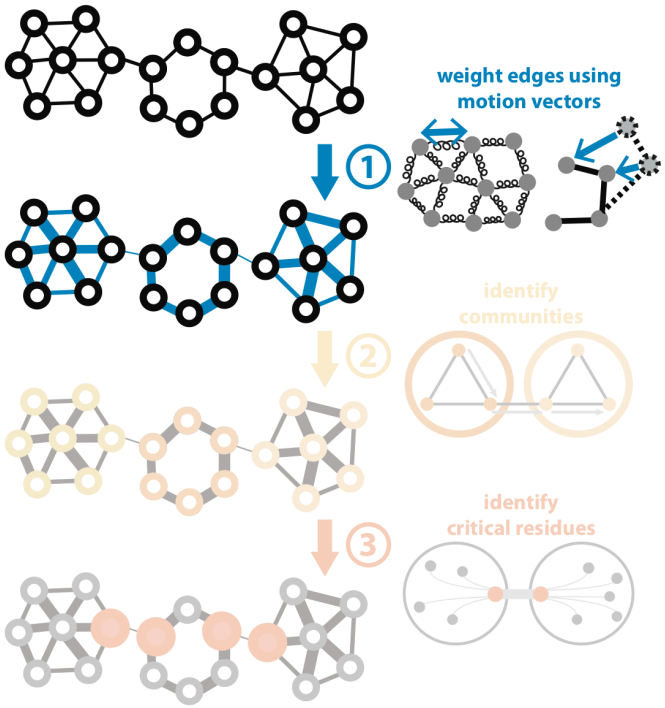


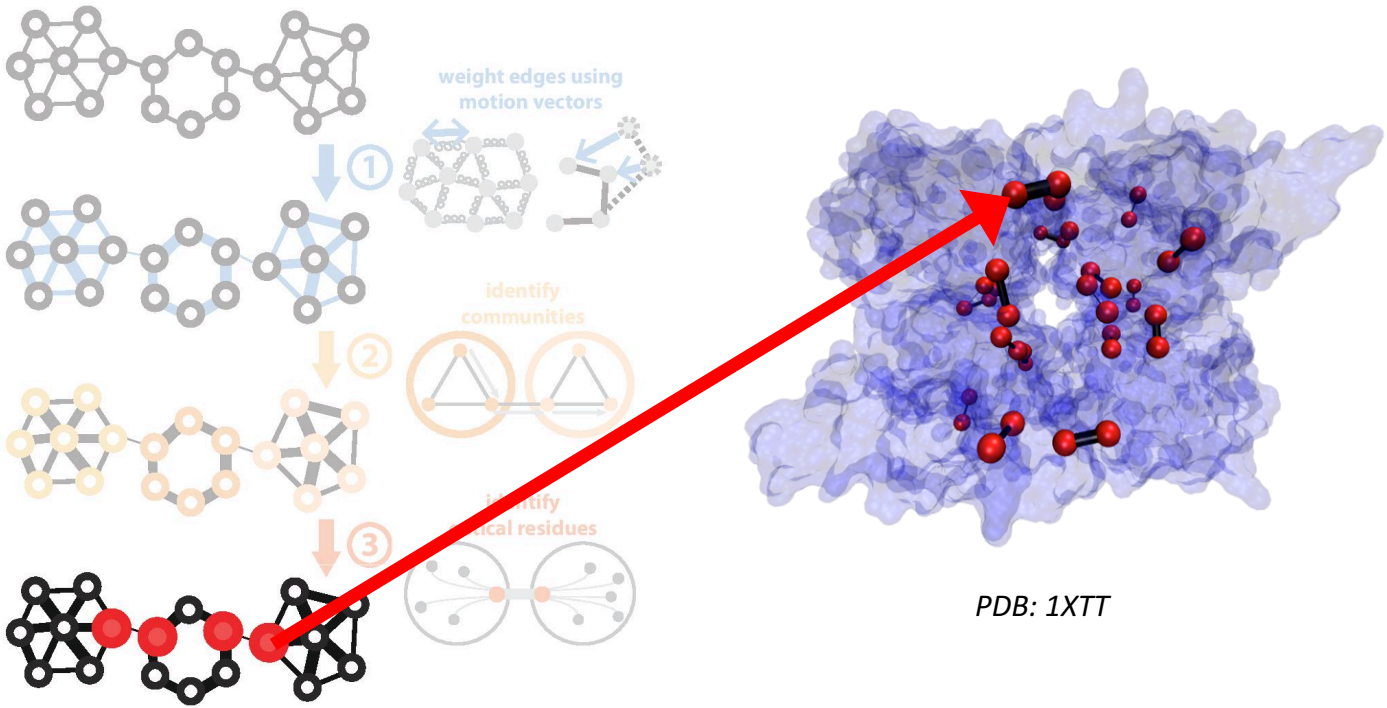
$$Cov_{ij} = \langle \mathbf{r}_i \bullet \mathbf{r}_j \rangle$$

$$C_{ij} = Cov_{ij} \; / \; \sqrt{(\langle \mathbf{r}_i^2 \rangle \langle \mathbf{r}_j^2 \rangle)}$$

$$D_{ij} = -\log(|C_{ij}|)$$

Adapted from Clarke*, Sethi*, et al *('16)*

Predicting Allosterically-Important Residues within the Interior

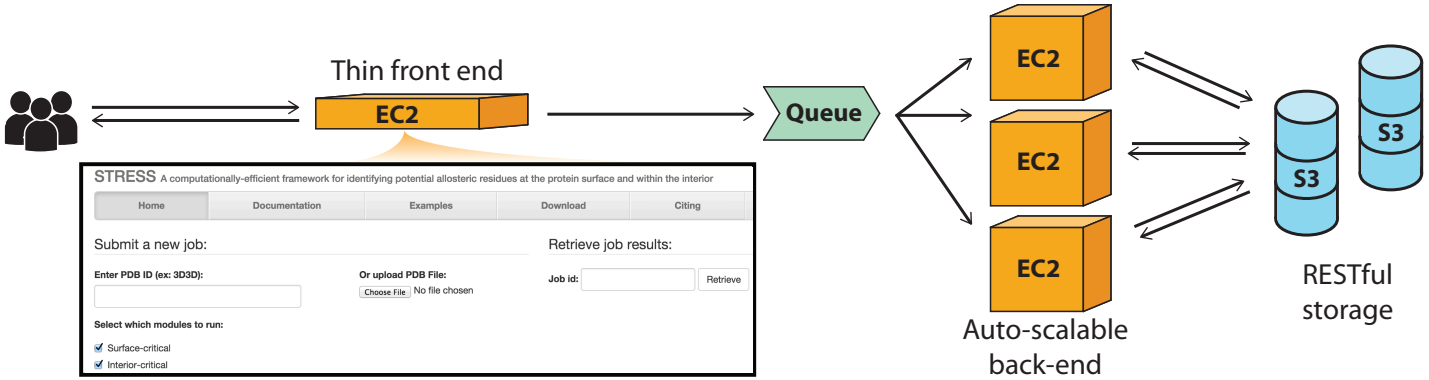


PDB: 1XTT

Adapted from Clarke*, Sethi*, et al *('16)*

STRESS Server Architecture: Highlights

stress.molmovdb.org



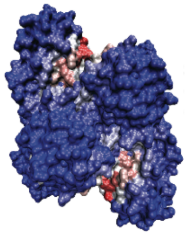
- A light front-end server handles incoming requests, and powerful back-end servers perform calculations.
- Auto Scaling adjusts the number of back-end servers as needed.
- A typical structure takes ~30 minutes on a E5-2660 v3 (2.60GHz) core.
- Input & output (i.e., predicted allosteric residues) are stored in S3 buckets.

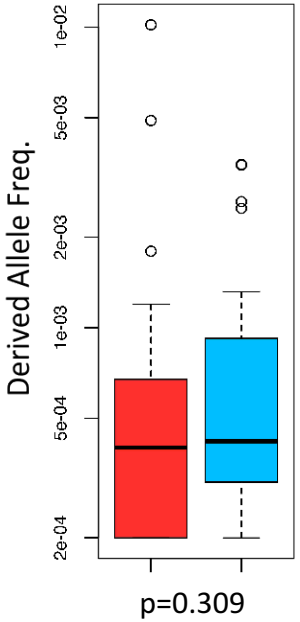
Adapted from Clarke*, Sethi*, et al *('16)*

Intra-species conservation of predicted allosteric residues

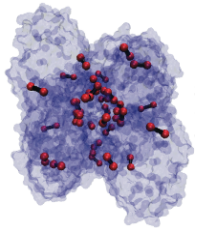
1000 Genomes

Surface



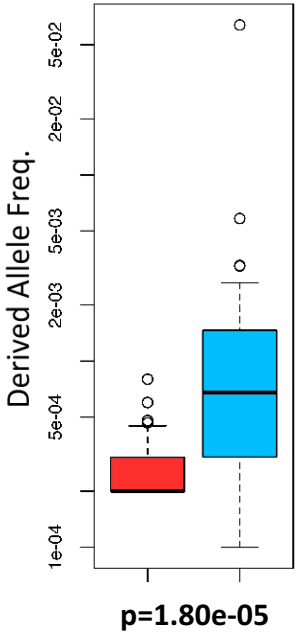


Interior



critical

non-critical



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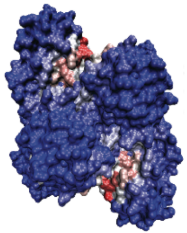
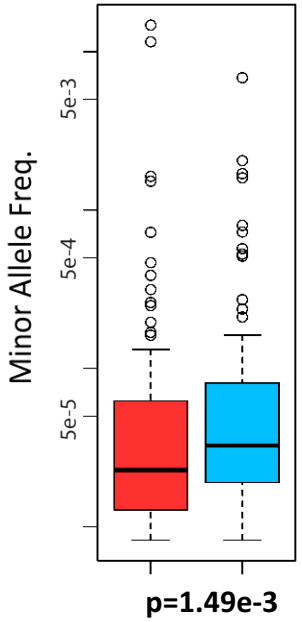
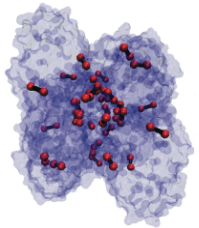
ExAC

Surface







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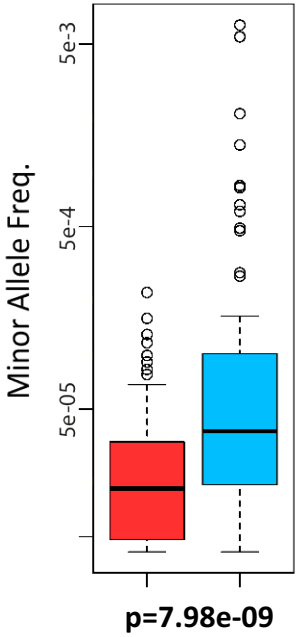

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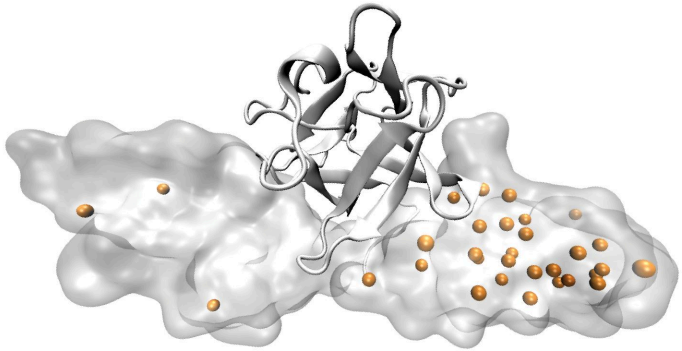

Fibroblast growth factor receptor 2 (pdb: 1IIL)

- 1000G & ExAC SNVs (common | rare)
- Hinge residues
- Buried residues
- Protein-protein interaction site
- Post-translational modifications
- HGMD site (w/o annotation overlap)
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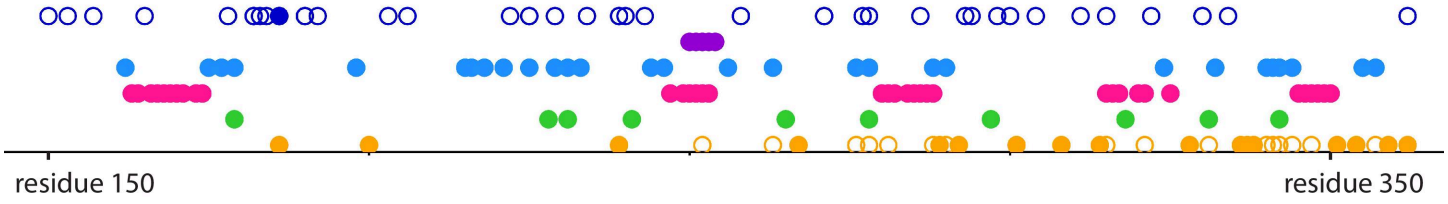

[Sethi et al. COSB ('15)]

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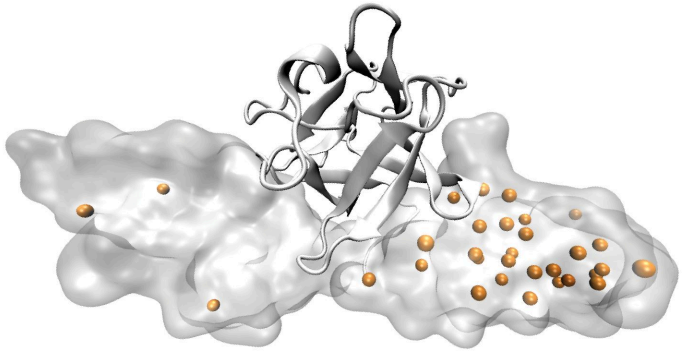
Rationalizing disease variants in the context of allosteric behavior with allostery as an added annotation



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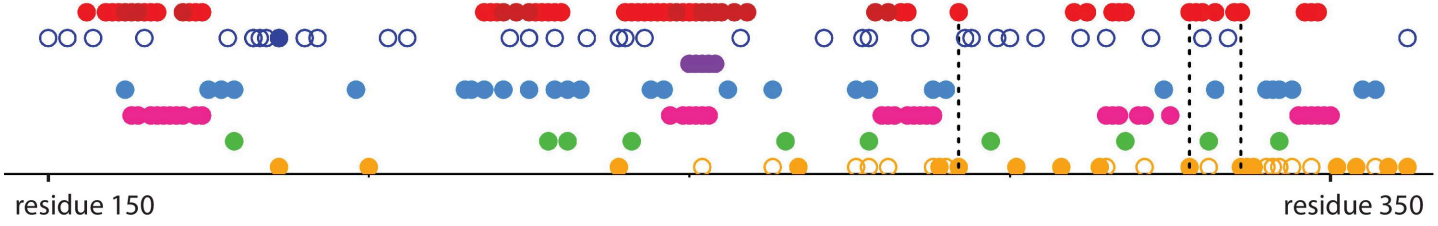

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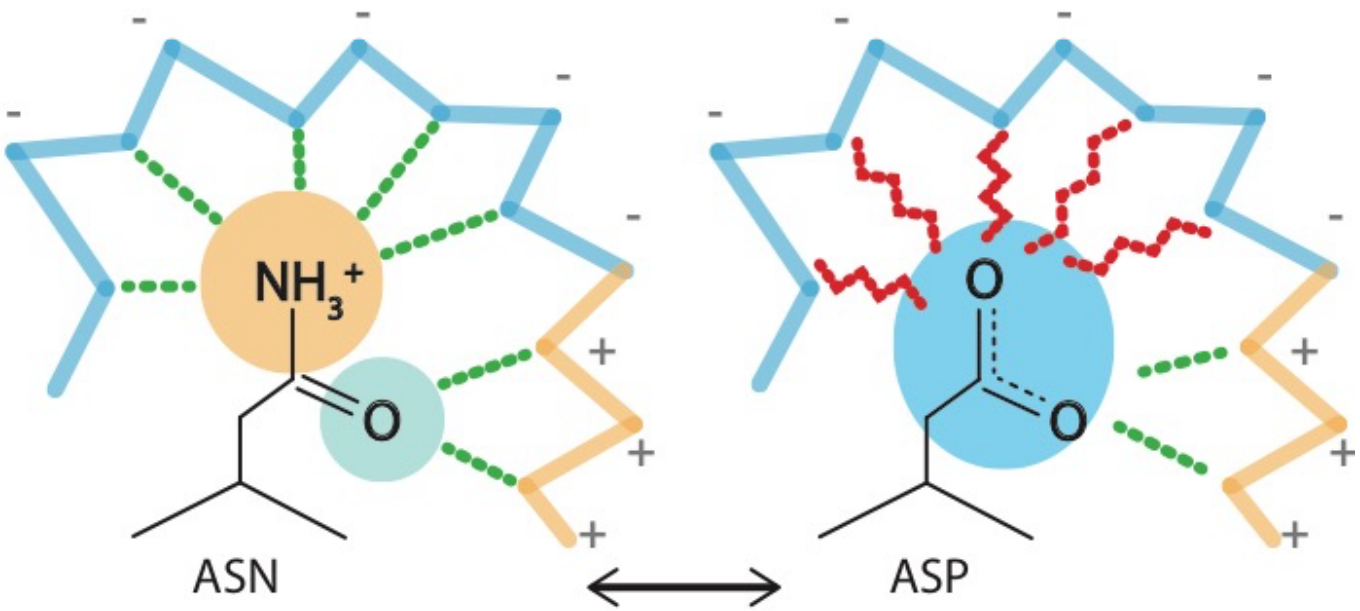
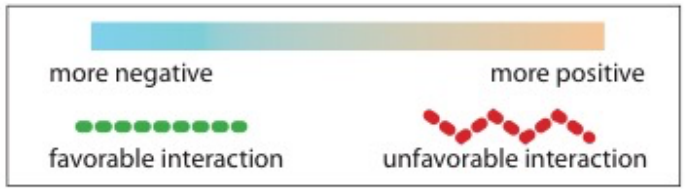
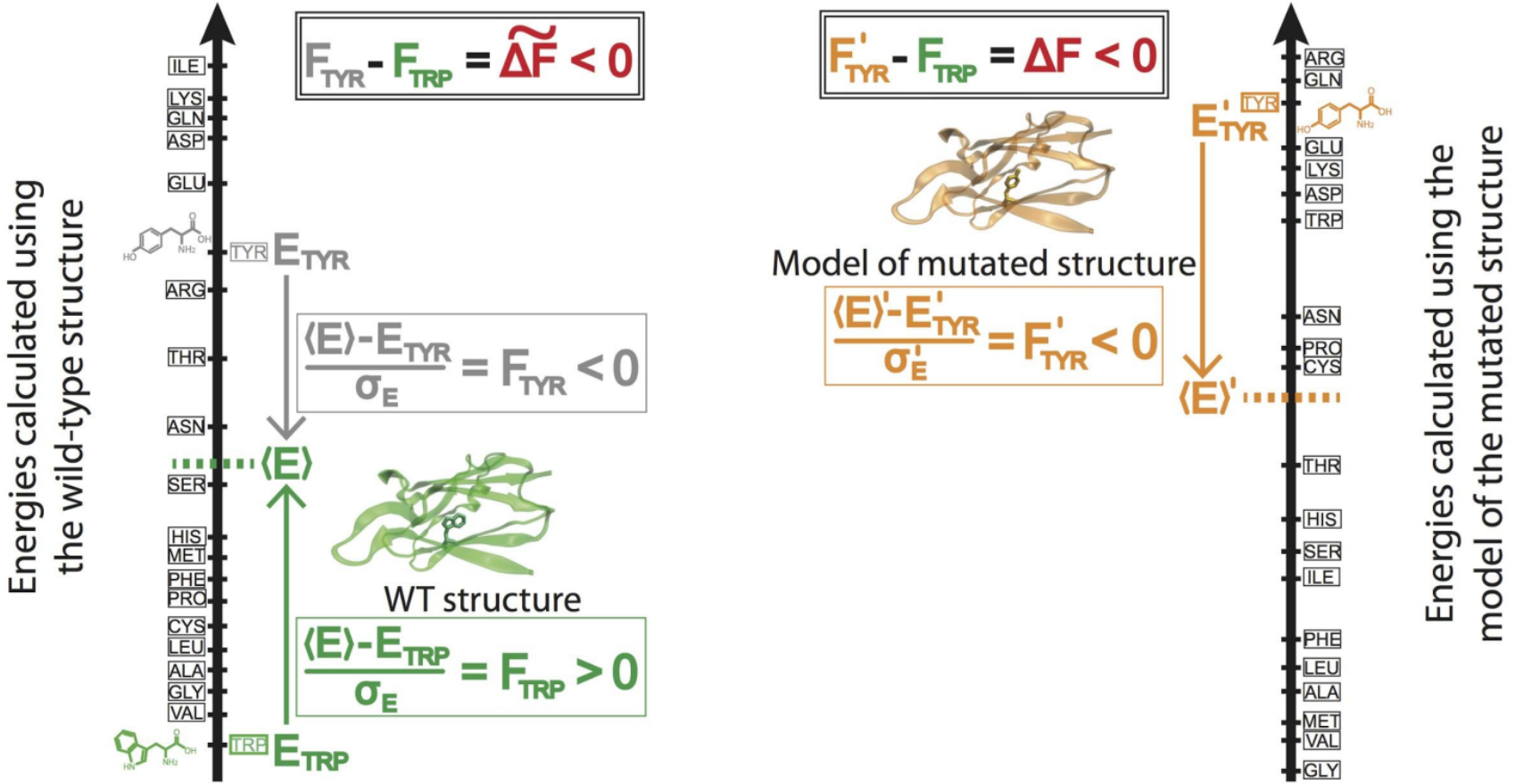




What is localized frustration ?

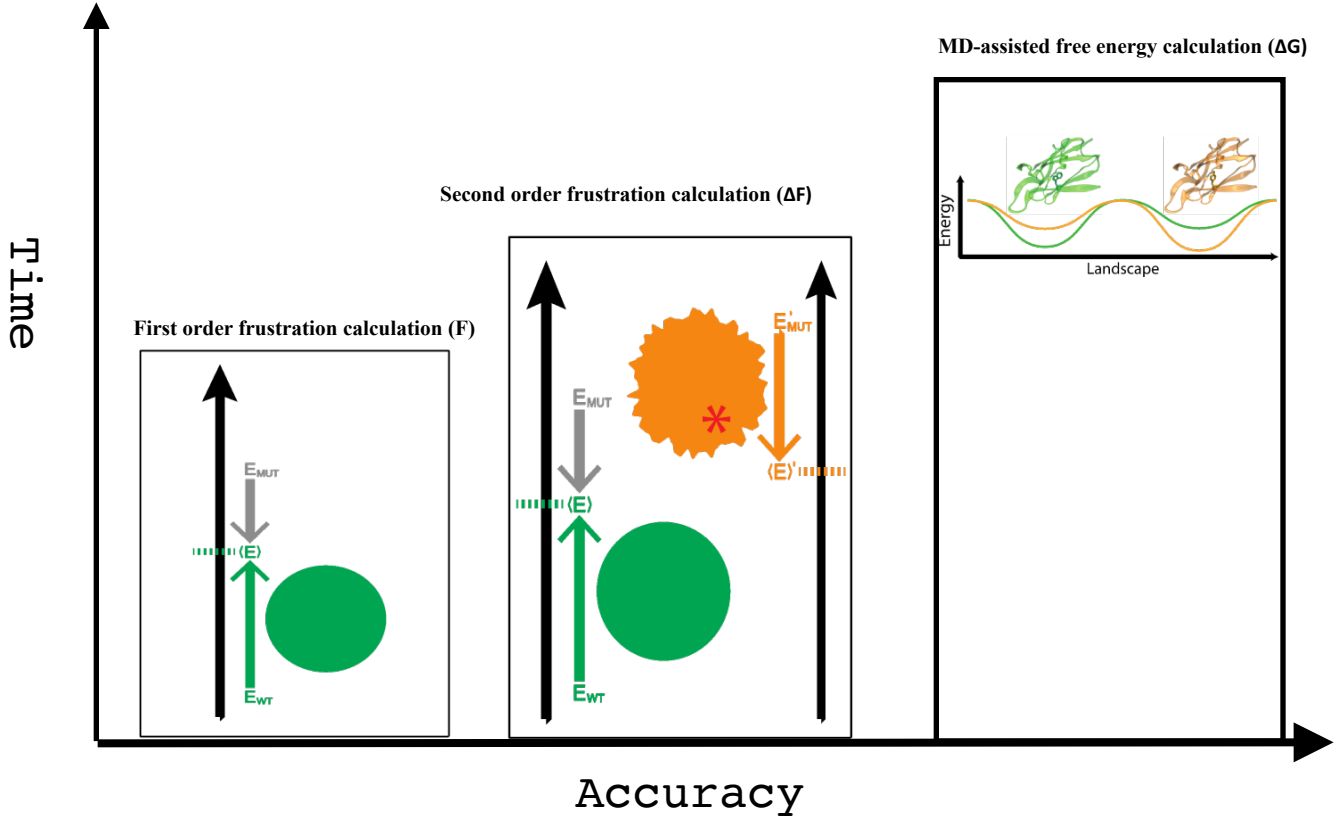
[Ferreiro et al., *PNAS* ('07)]

Workflow for evaluating localized frustration changes (ΔF)

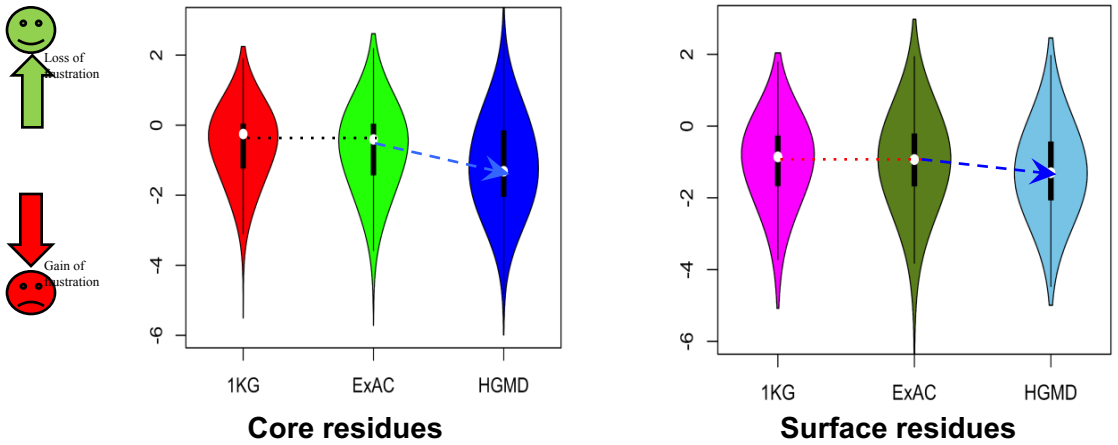


[Kumar et al. *NAR* (2016)]

Complexity of the second order frustration calculation



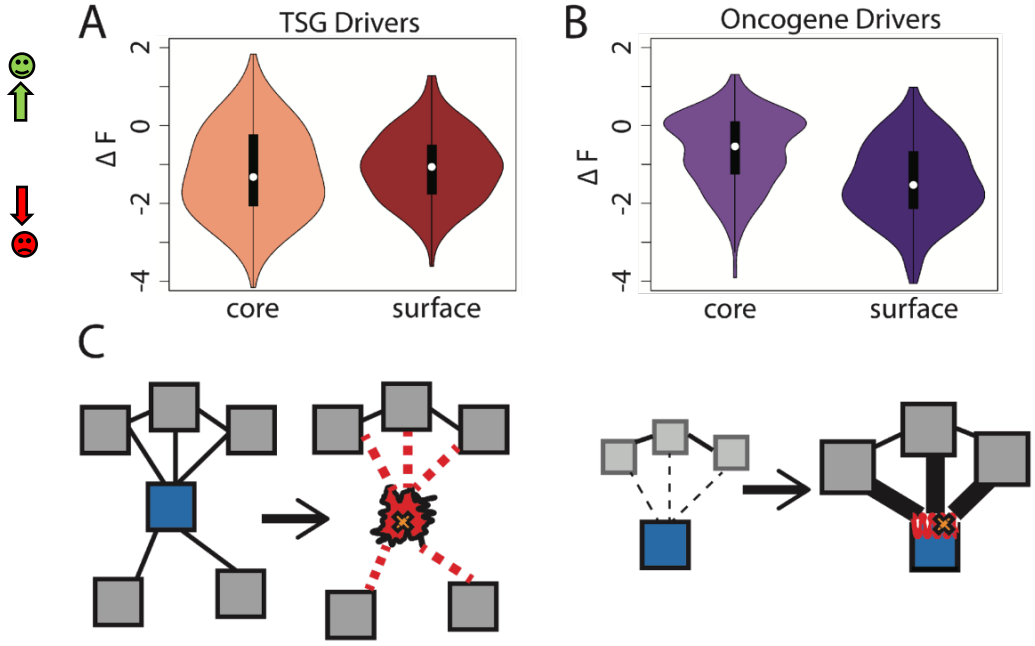
Comparing ΔF values across different SNV categories: disease v normal



Normal mutations (1000G) tend to unfavorably frustrate (less frustrated) surface more than core, but for disease mutations (HGMD) no trend & greater changes

[Kumar et al, *NAR* (2016)]

Comparison between ΔF distributions: TSGs v. oncogenes



SNVs in TSGs change frustration more in core than the surface, whereas those associated with oncogenes manifest the opposite pattern. This is consistent with differences in LOF v GOF mechanisms.

[Kumar et al, *NAR* (2016)]

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Variant Annotation Tool (VAT), developed for 1000G FIG

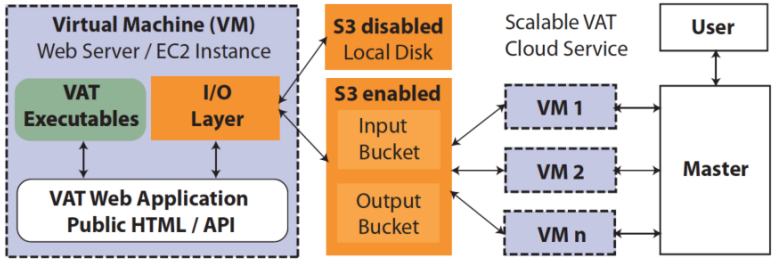
VCF Input

Output:

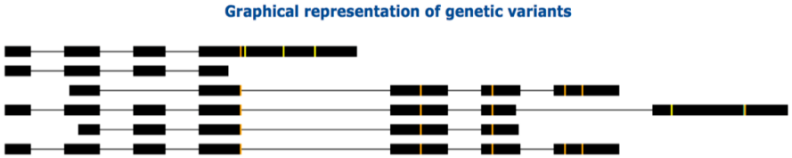
- Annotated VCFs
- Graphical representations of functional impact on transcripts

Access:

- Webserver
- AWS cloud instance
- Source freely available



CLOUD APPLICATION



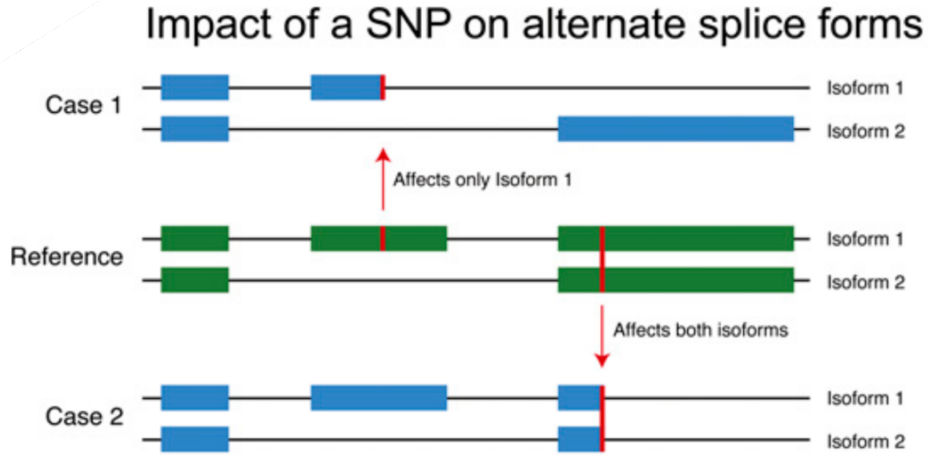
vat.gersteinlab.org

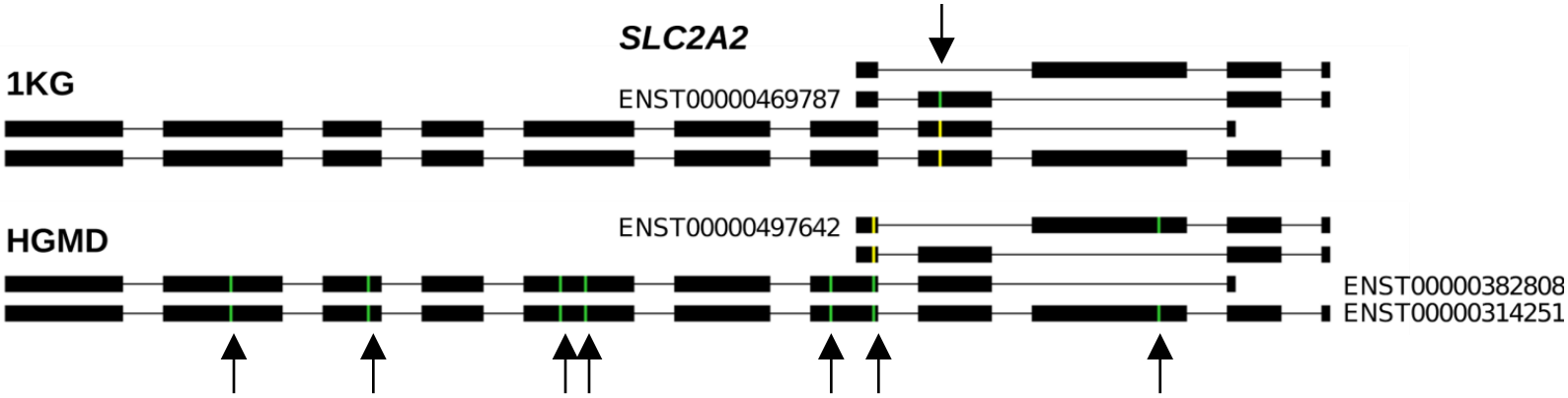
Habegger L., Balasubramanian S.*, et al. Bioinformatics, 2012*

Complexities in LOF annotation

Transcript isoforms,
distance to stop,
functional domains,
protein folding,
etc.

Balasubramanian S. et al., *Genes Dev.,* '11
Balasubramanian S.*, Fu Y.* et al., *NComms.*, '17



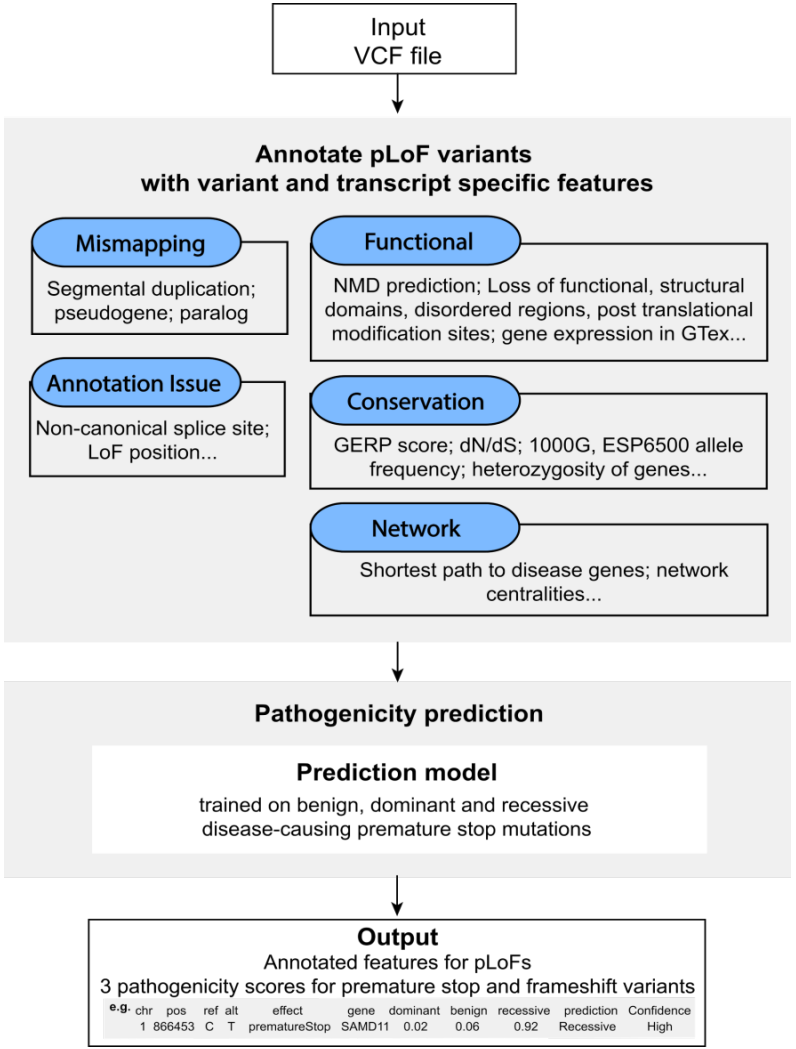


Annotation of Loss-of-Function Transcripts (ALoFT)

Runs on top of VAT

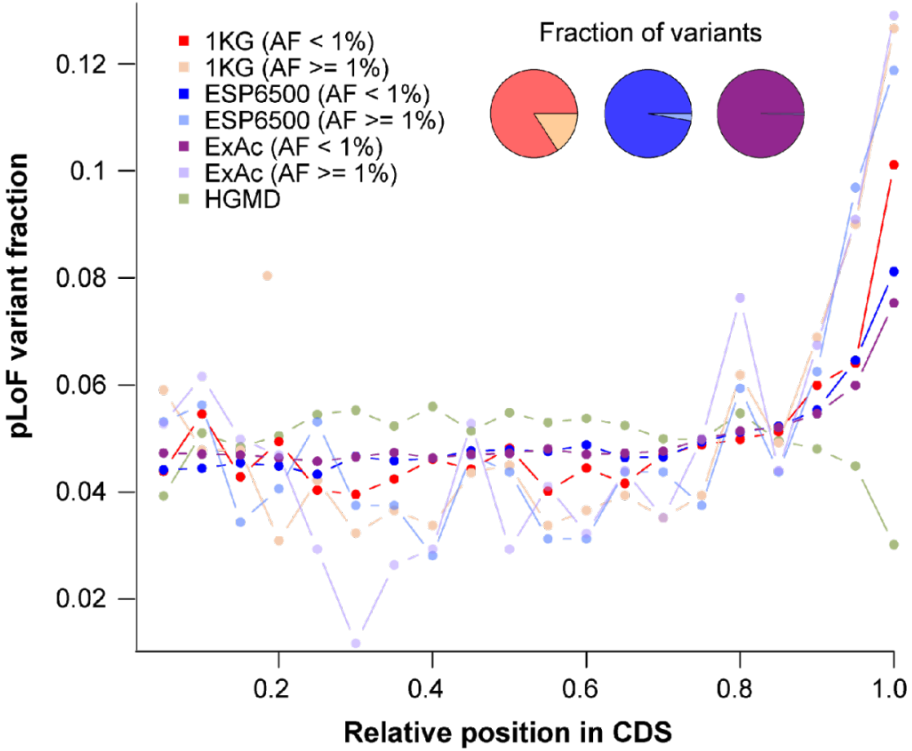
Output:

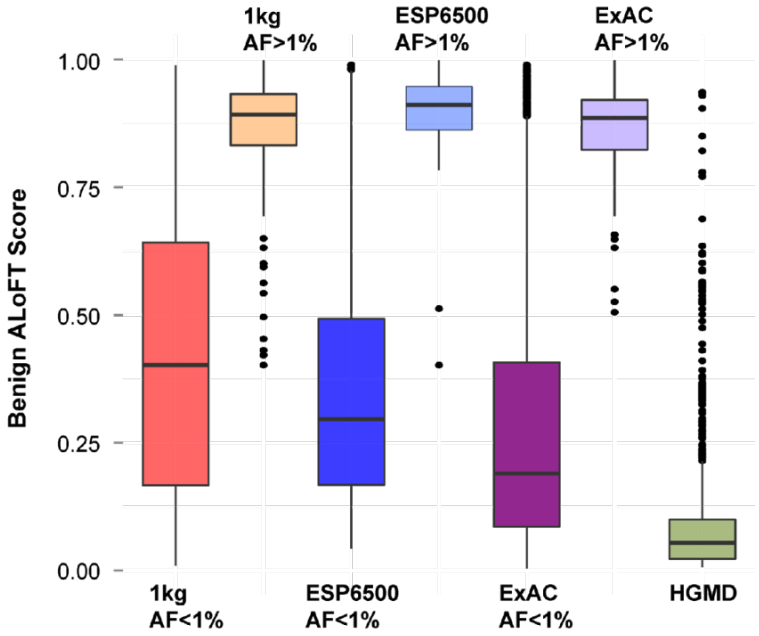
- Impact score: benign or deleterious.
- Decorated VCF.



Balasubramanian S.*, Fu Y.* et al., *NComms.*, '17

LoF distribution varies as expected by mutation set (from healthy people v from disease)





Balasubramanian S.*, Fu Y.* et al., *NComms.*, '17

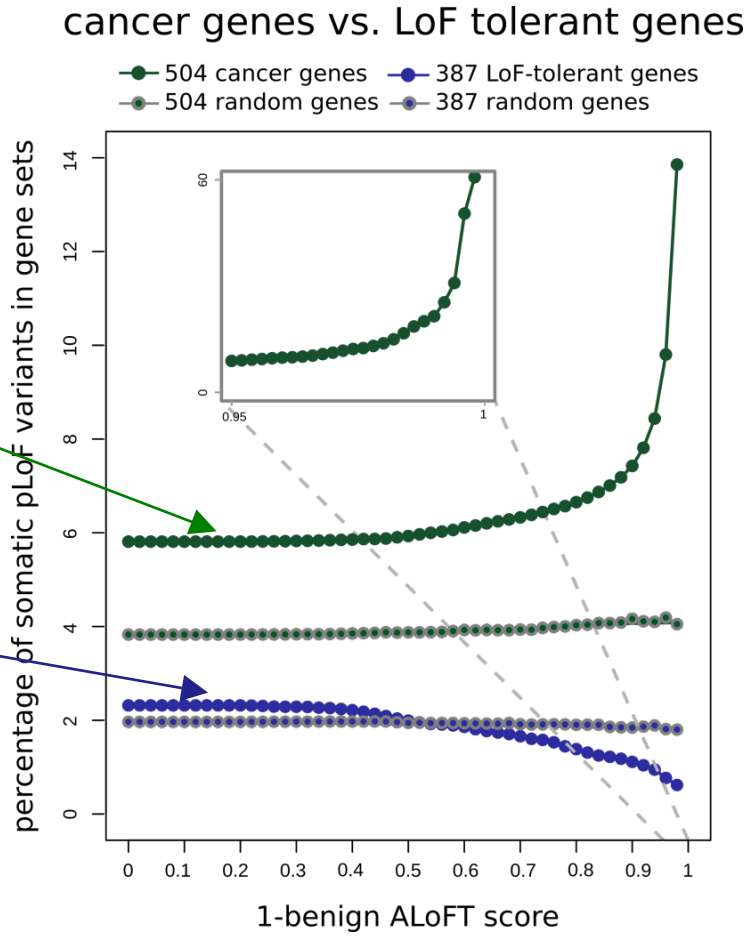
ALoFT identifies deleterious somatic LoF variants

Cancer genes:

- COSMIC consensus.
- *Enriched in deleterious LoFs.*

LoF tolerant genes:

- LoF in the 1KG cohort.
- *Depleted in deleterious LoFs.*



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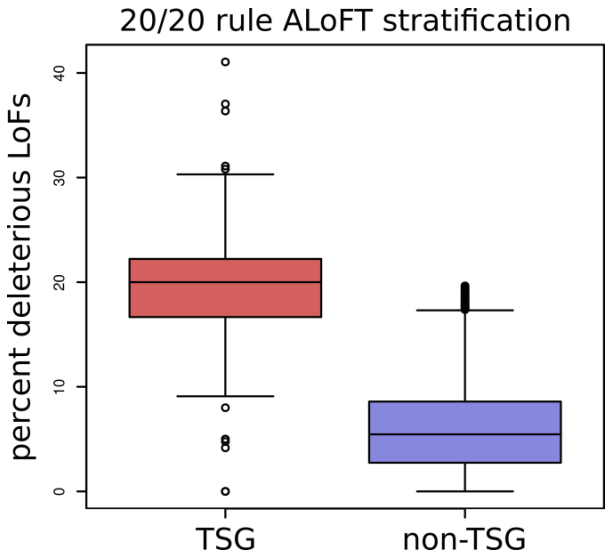
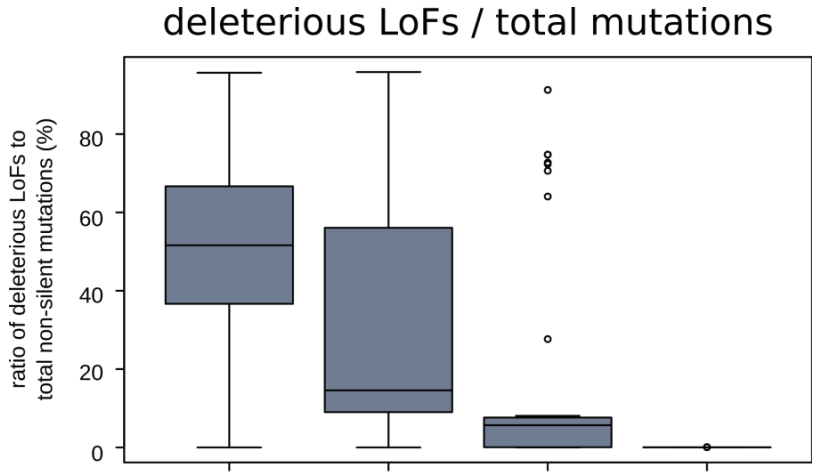
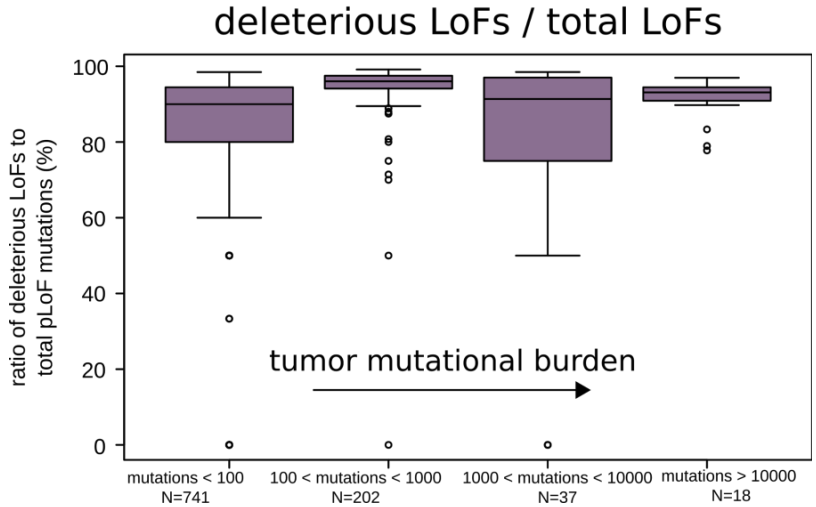
ALoFT refines cancer mutation characterization



Vogelstein et al. '13: if >20% of mutations in gene inactivating → tumor suppressor gene (TSG).

ALoFT further refines 20/20 rule predictions.





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Leveraging Protein Structure and Dynamics for Variant Interpretation in Coding Regions

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- Identifying cryptic allosteric sites with **STRESS**
  - On surface & in interior bottlenecks
- **Frustration** as a localized metric of SNV impact
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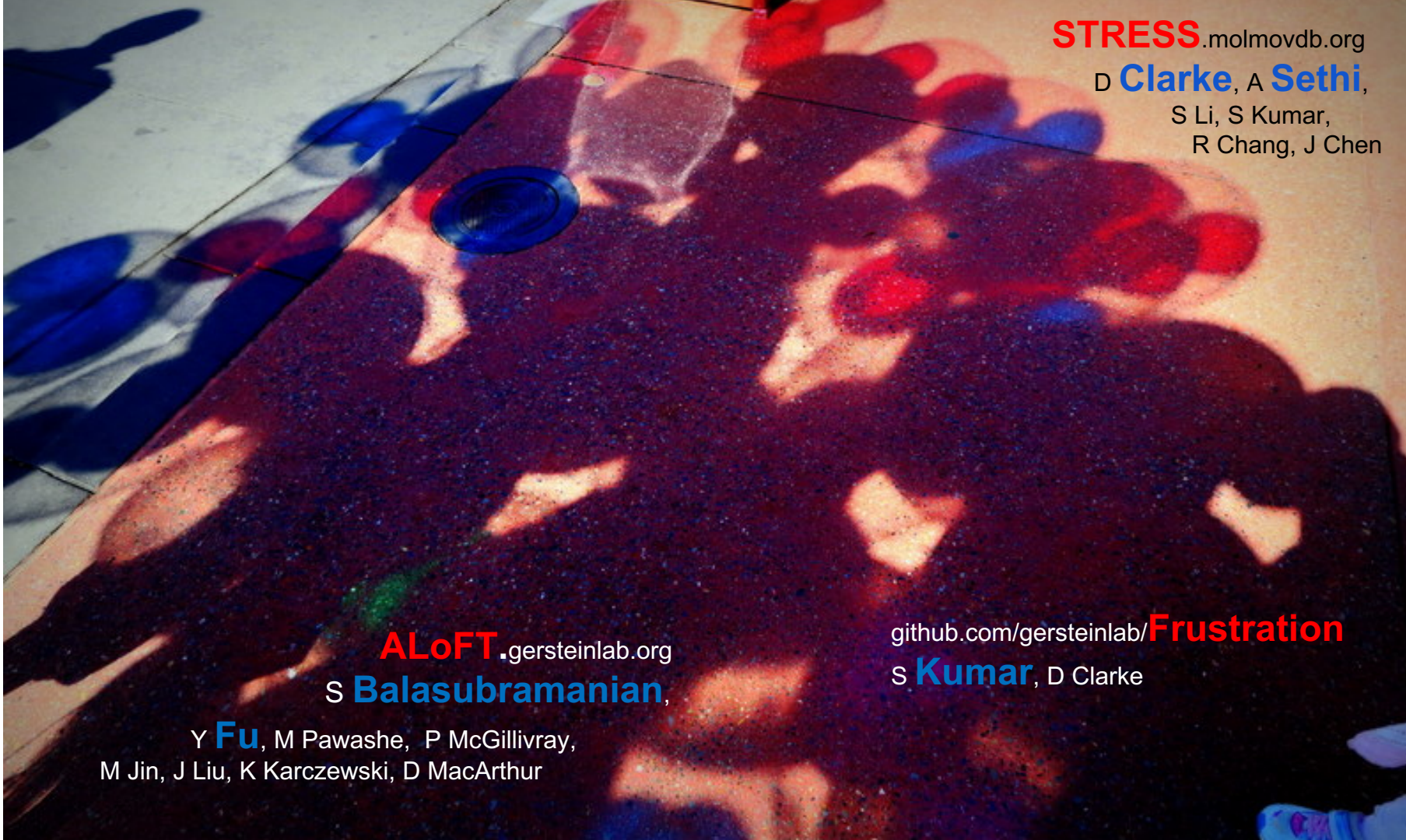

Acknowledgments! Also, Hiring: See **Jobs**.gersteinlab.org

STRESS.molmovdb.org
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github.com/gersteinlab/**Frustration**
S **Kumar**, D Clarke


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Info about this talk

No Conflicts

Unless explicitly listed here. There are no conflicts of interest relevant to the material in this talk

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