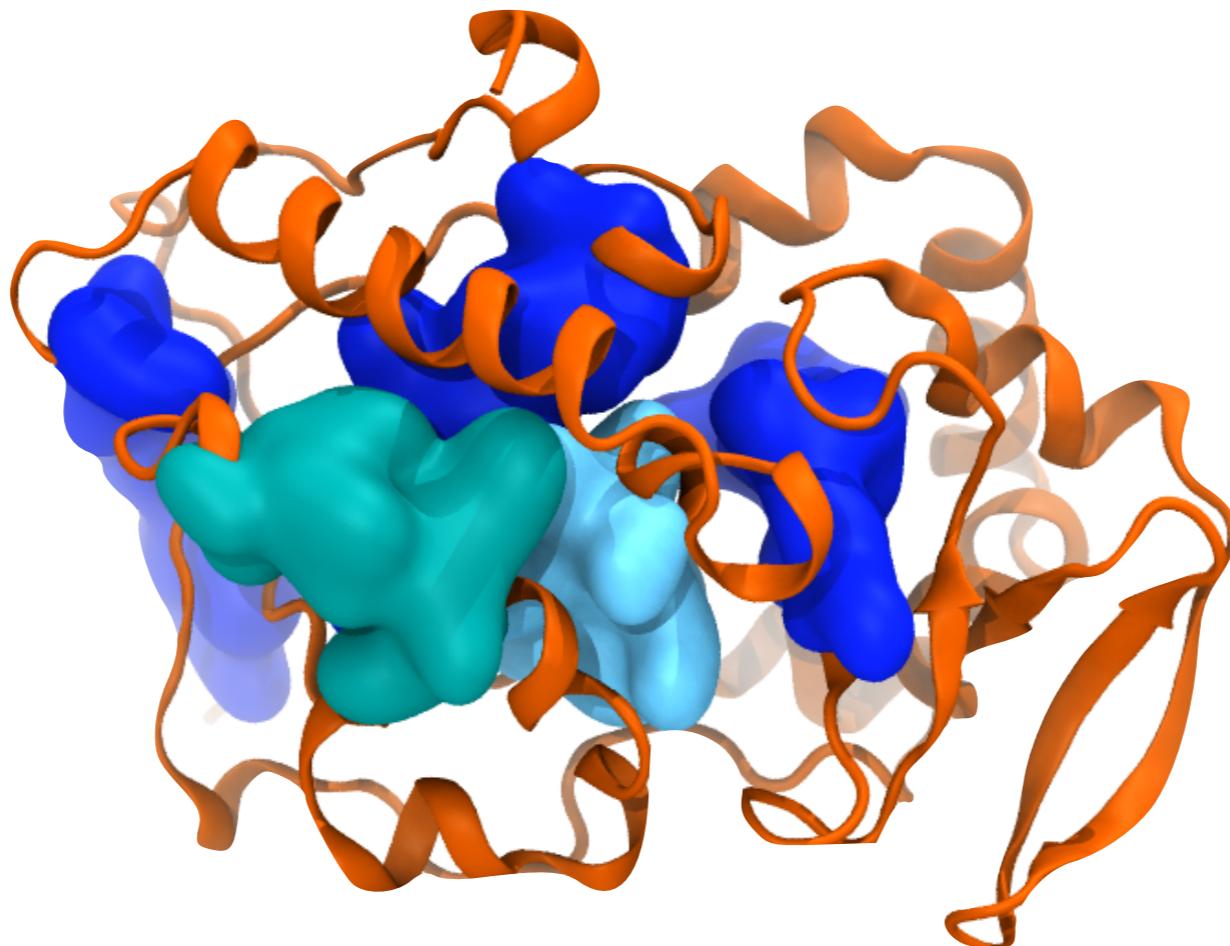


Contiguously-hydrophobic sequences are functionally significant throughout the human exome

Grace Brannigan
Department of Physics
Center for Computational and
Integrative Biology
Rutgers University-Camden



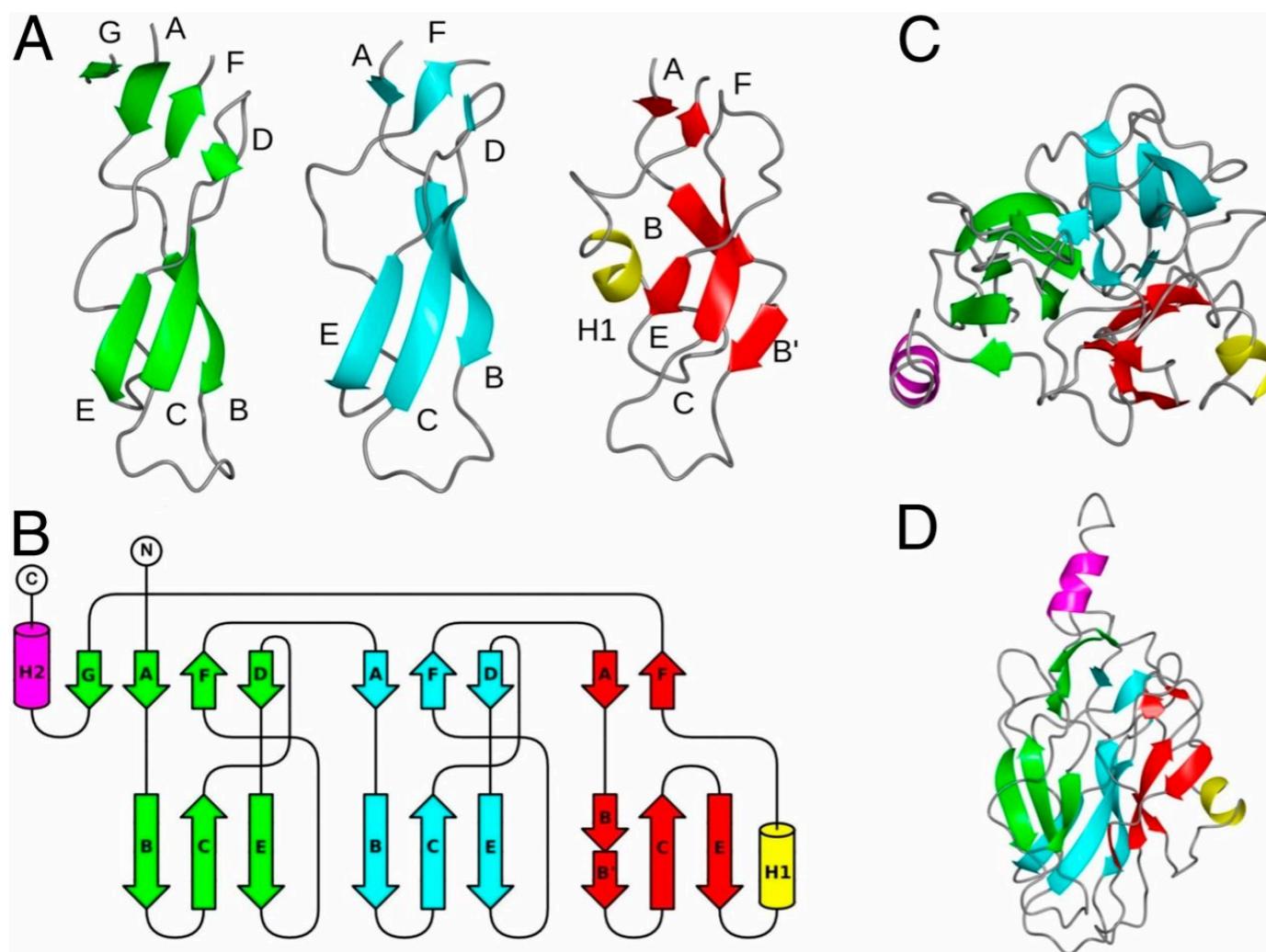
Questions

- **How can we detect the underlying organization of a protein sequence?**
 - From that organization, can we extract any information about function?
 - Could this information be useful for detecting causal mutations?

Protein topology and organization

Protein topology is a critical **conceptual** tool

usually: sequence of secondary structure elements



Does secondary
structure provide
the most
meaningful
topology?

What about
proteins without
intrinsic structure?

Brief Communication

The Brain-Derived Neurotrophic Factor val66met Polymorphism and Variation in Human Cortical Morphology

Lukas Pezawas, Beth A. Verchinski, Venkata S. Mattay, Joseph H. Callicott, Bhaskar S. Kolachana, Richard E. Straub, Michael F. Egan, Andreas Meyer-Lindenberg, and Daniel R. Weinberger
Genes, Cognition, and Psychosis Program, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland 20892-1379

Brain-Derived Neurotrophic Factor Val66Met and Psychiatric Disorders: Meta-Analysis of Case-Control Studies Confirm Association to Substance-Related Disorders, Eating Disorders, and Schizophrenia

Mònica Gratacòs, Juan R. González, Josep M. Mercader, Rafael de Cid, Mikel Urretavizcaya, and Xavier Estivill

Cell

CellPress

Volume 112, Issue 2, 24 January 2003, Pages 257-269

Article

The BDNF val66met Polymorphism Affects Activity-Dependent Secretion of BDNF and Human Memory and Hippocampal Function

Michael F. Egan¹, Masami Kojima^{7, 4, 5, 6}, Joseph H. Callicott^{7, 1}, Terry E. Goldberg^{7, 1}, Bhaskar S. Kolachana¹, Alessandro Bertolino¹, Eugene Zaitsev⁴, Bert Gold³, David Goldman², Michael Dean³, Bai Lu^{*, 4}, Daniel R. Weinberger^{*, 1}✉

Molecular Psychiatry (2010) 15, 260–271

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www.nature.com/mp

ORIGINAL ARTICLE

Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity

M Verhagen¹, A van der Meij¹, PAM van Deurzen^{1, 2}, JGE Janzing¹, A Arias-Vásquez^{1, 3, 4}, JK Buitelaar^{1, 2} and B Franke^{1, 3}

A Genetic Variant BDNF Polymorphism Alters Extinction Learning in Both Mouse and Human

Fatima Soliman,^{1, 2*} Charles E. Glatt,² Kevin G. Bath,² Liat Levita,^{1, 2} Rebecca M. Jones,^{1, 2} Siobhan S. Pattwell,² Deqiang Jing,² Nim Tottenham,^{1, 2} Dima Amso,^{1, 2} Leah H. Somerville,^{1, 2} Henning U. Voss,³ Gary Glover,⁴ Douglas J. Ballon,³ Conor Liston,^{1, 2} Theresa Teslovich,^{1, 2} Tracey Van Kempen,^{1, 2} Francis S. Lee,^{2*} B. J. Casey^{1, 2*}

REPORTS

Genetic Variant BDNF (Val66Met) Polymorphism Alters Anxiety-Related Behavior

Zhe-Yu Chen,^{1, 4†} Deqiang Jing,^{1*} Kevin G. Bath,^{1*} Alessandro Ieraci,¹ Tanvir Khan,¹ Chia-Jen Siao,² Daniel G. Herrera,¹ Miklos Toth,³ Chingwen Yang,⁵ Bruce S. McEwen,⁶ Barbara L. Hempstead,² Francis S. Lee^{1, 3†}

Molecular Psychiatry (2005) 10, 631–636
© 2005 Nature Publishing Group All rights reserved 1359-4184/05 \$30.00
www.nature.com/mp

ORIGINAL RESEARCH ARTICLE

Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation

PR Szeszko^{1, 2}, R Lipsky³, C Mentschel⁴, D Robinson^{1, 2}, H Gunduz-Bruce⁵, S Sevy^{1, 2}, M Ashtari⁶, B Napolitano¹, RM Bilder⁷, JM Kane^{1, 2}, D Goldman³ and AK Malhotra^{1, 2}

Results: 2,258

(from Web of Science Core Collection)

You searched for: TOPIC: (Val66Met)
...More

generalizing the central dogma

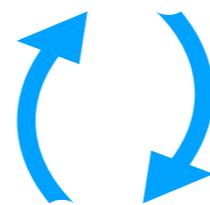
status quo:

sequence → structure → function

cluster residues by **backbone** interactions (secondary structure)

shift in this talk:

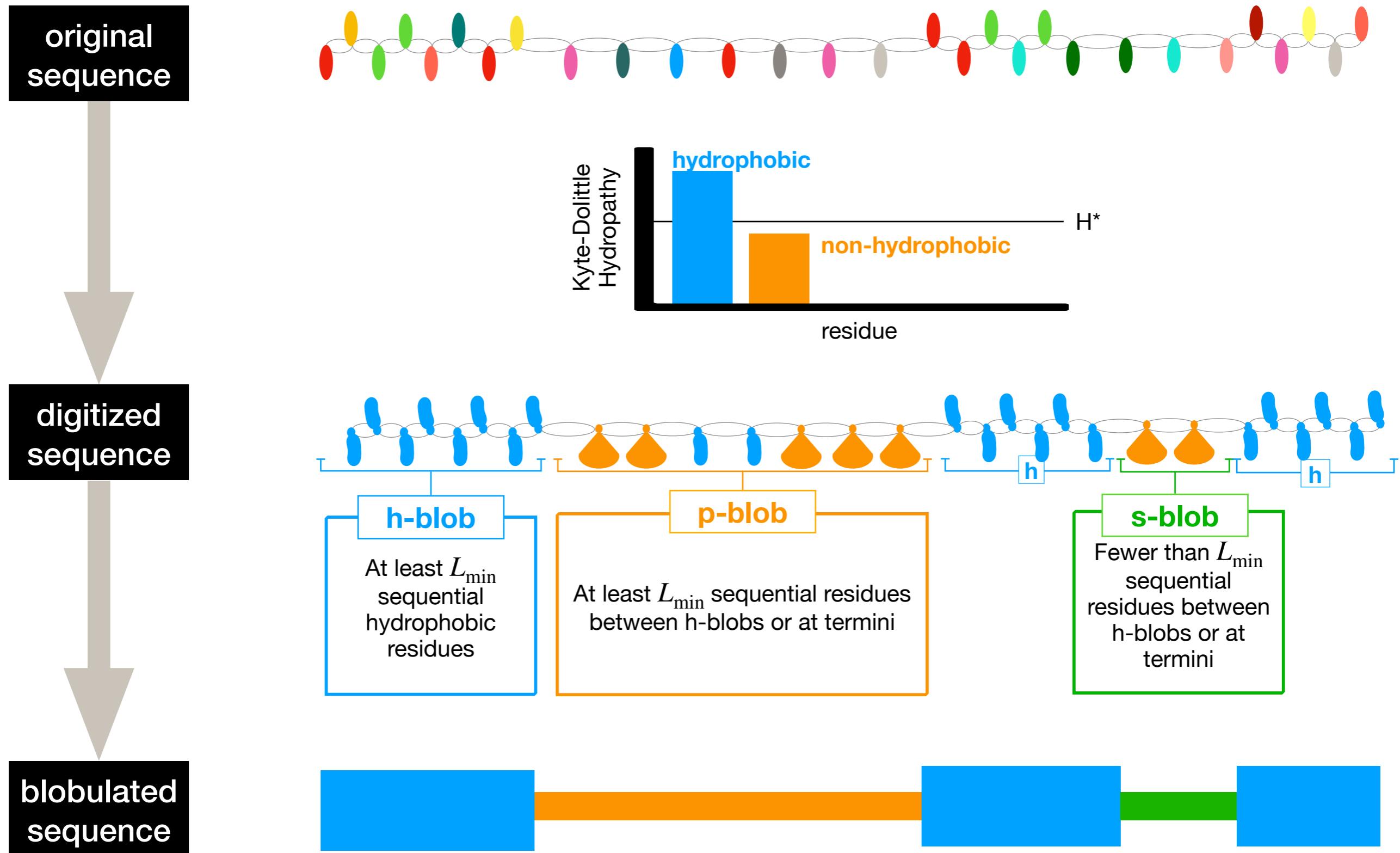
sequence → interactions → function



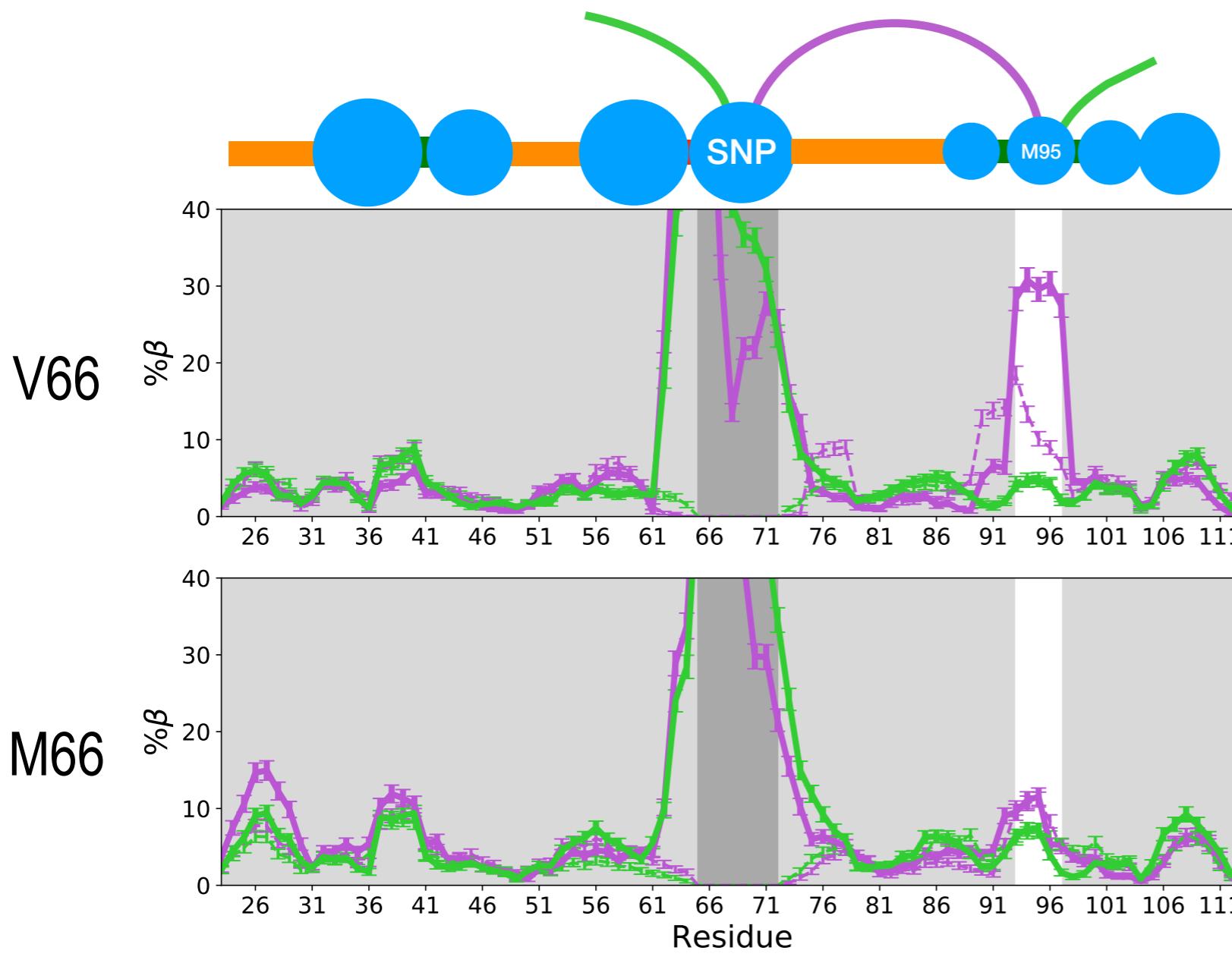
structure

cluster residues by **side-chain hydrophobicity**

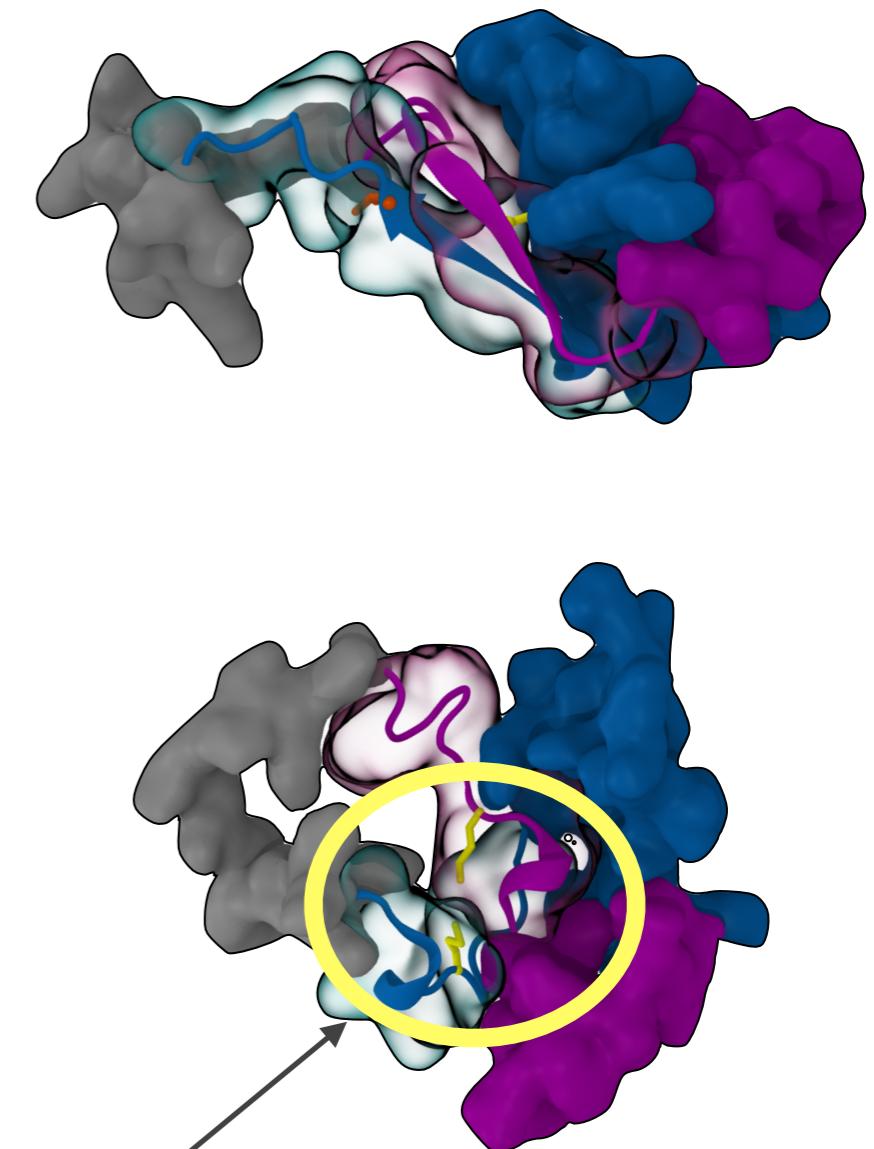
introducing...blobulation



Blobulation: Essential for revealing the Val66Met mechanism



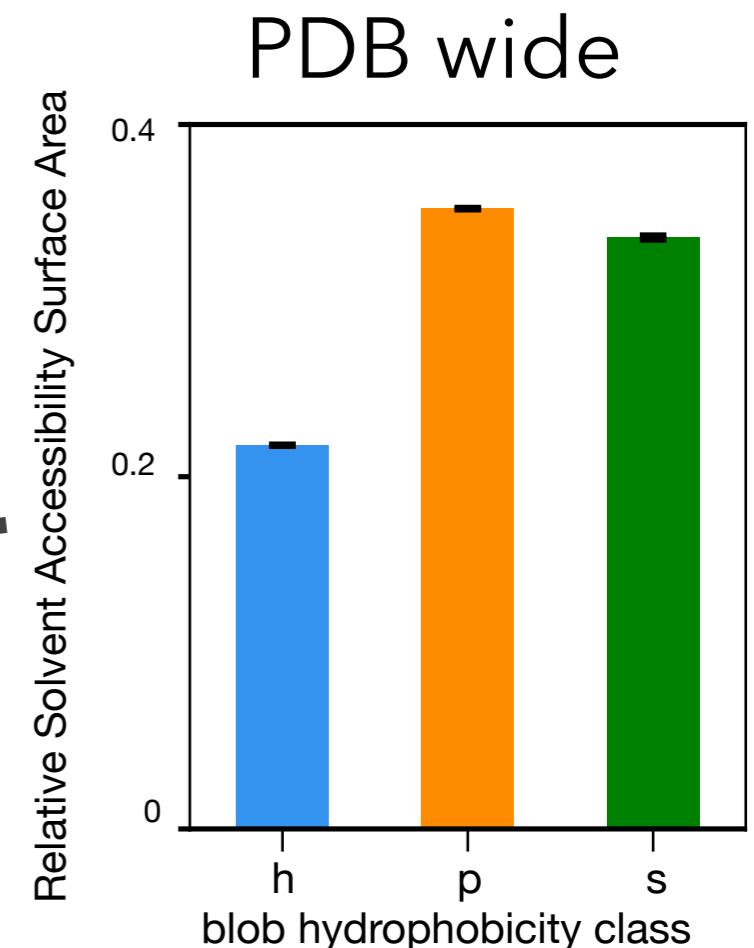
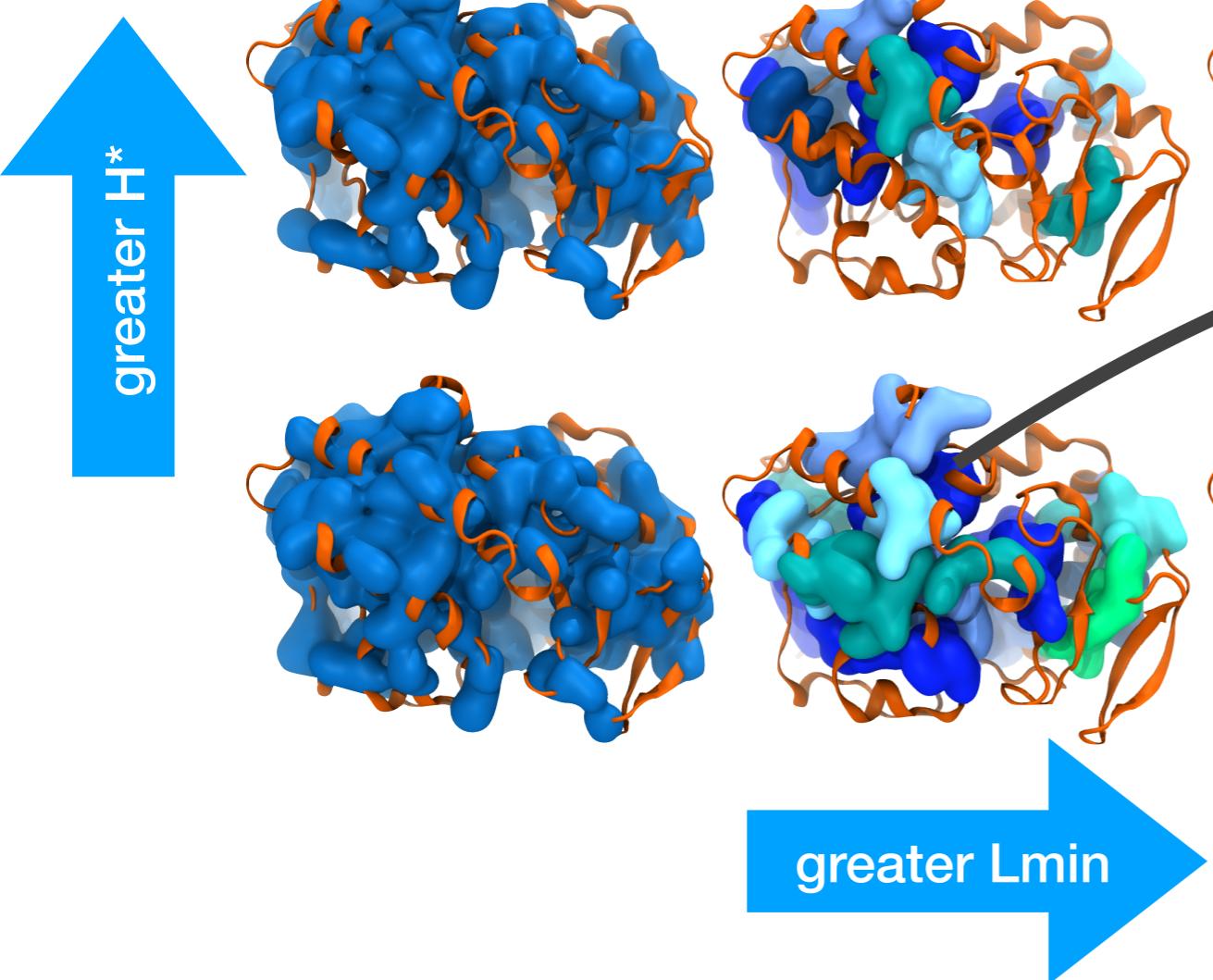
Lohia, Salari, Brannigan, PLOS Comp Bio, 2019



Backbone-Backbone switches to
Sidechain-Sidechain (Met-Met)

How well can blobulation predict buried regions?

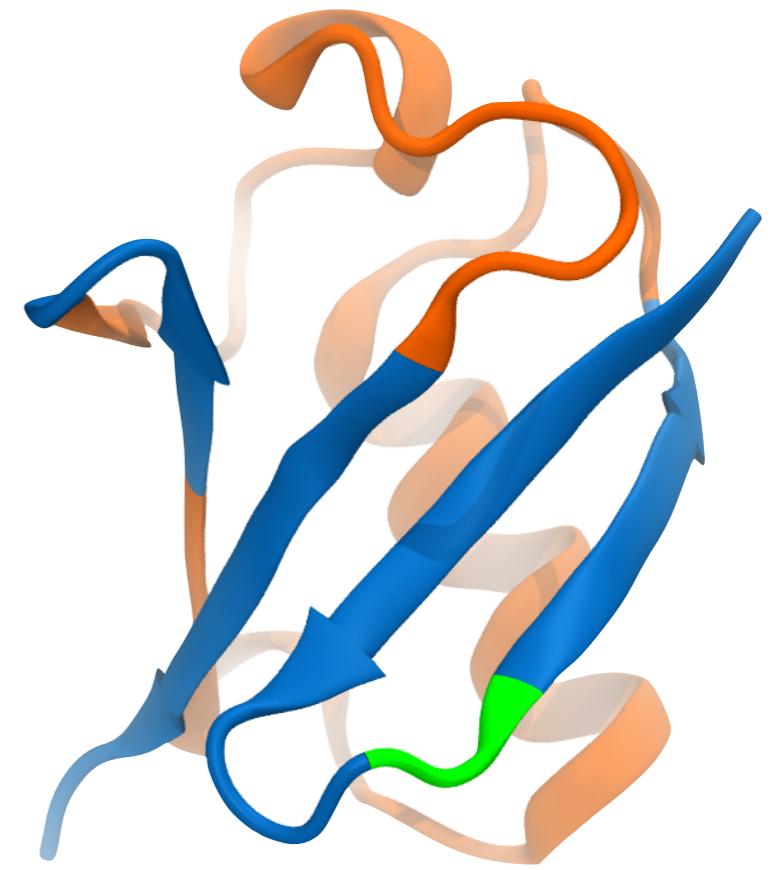
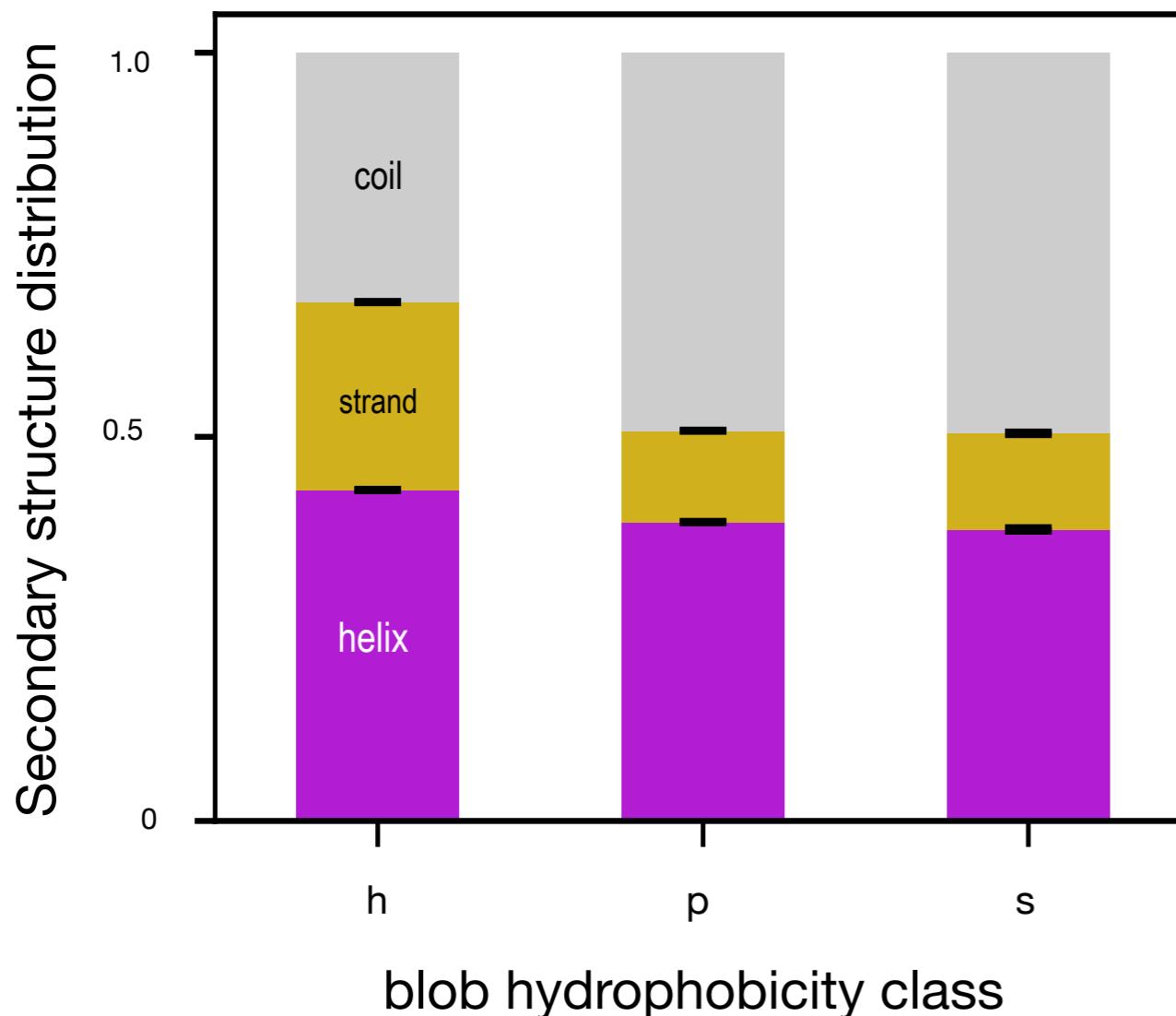
example: cytochrome C peroxidase



Pretty well!!

Blobs vs Secondary structure elements

across the pdb databank



example: ubiquitin

h-blobs have twice as many beta strands

How to blobulate your own sequences

blobulator.branniganlab.org

(or go to my website and click on “Resources”)

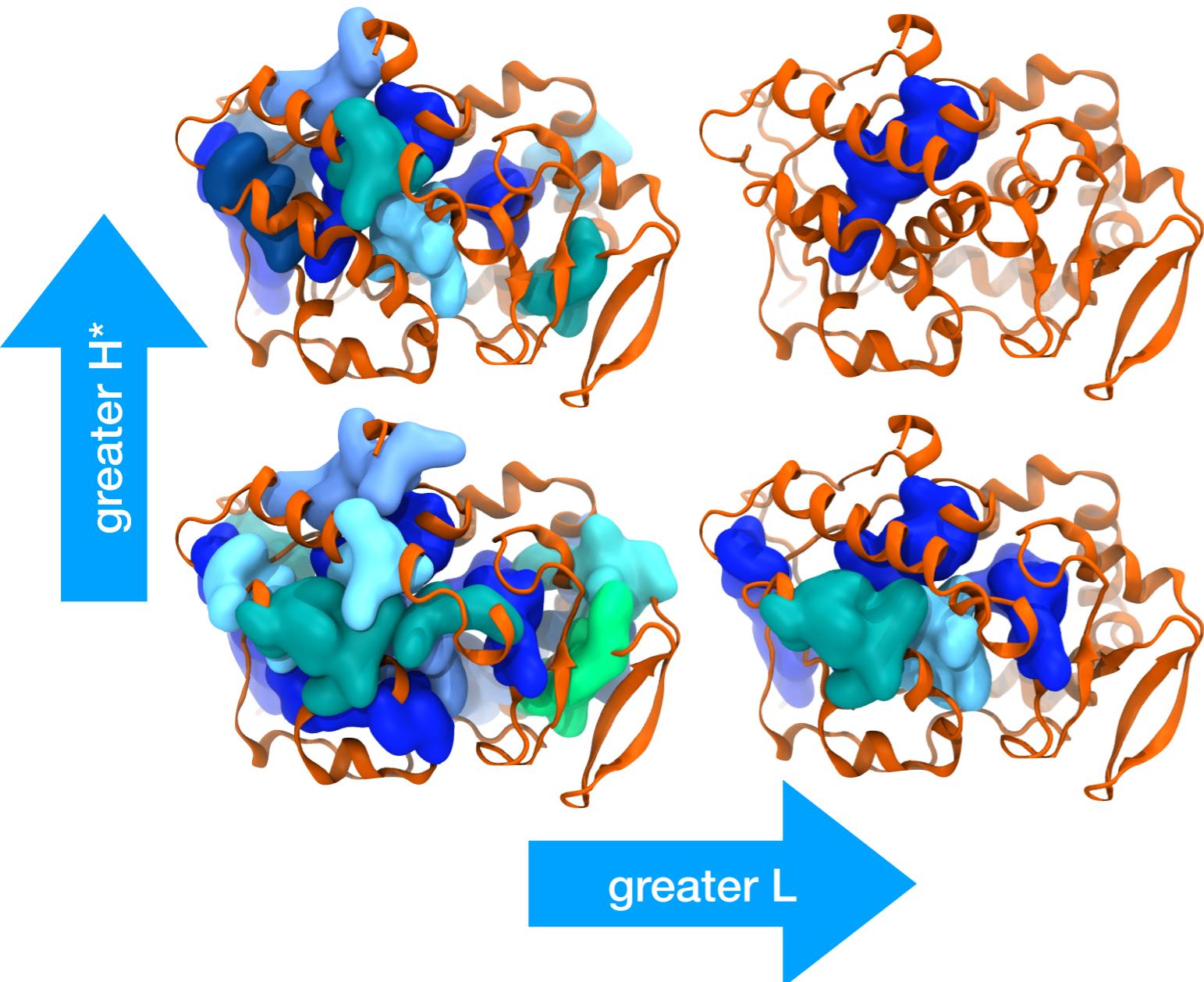


blobulator™
edge detection for protein sequences
Brannigan Lab • Rutgers University – Camden

Questions

- How can we detect the underlying organization of a protein sequence?
 - **From that organization, can we extract any information about function?**
 - Could this information be useful for detecting causal mutations?

Hypothesis: h-blobs will be more mutation sensitive...

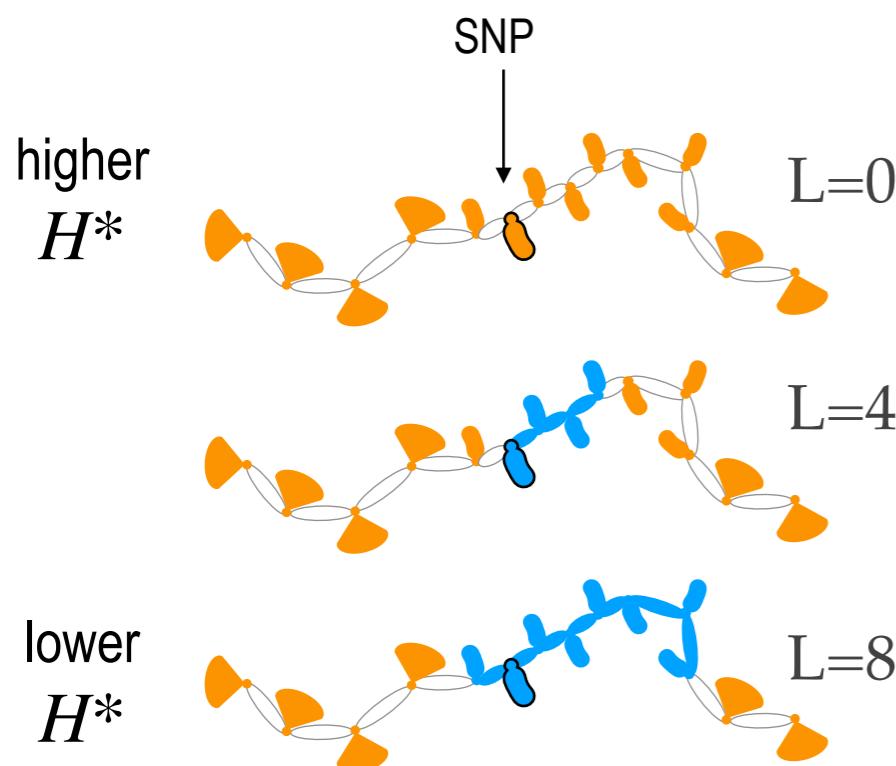


...and the more hydrophobic the blob, the more sensitive it will be

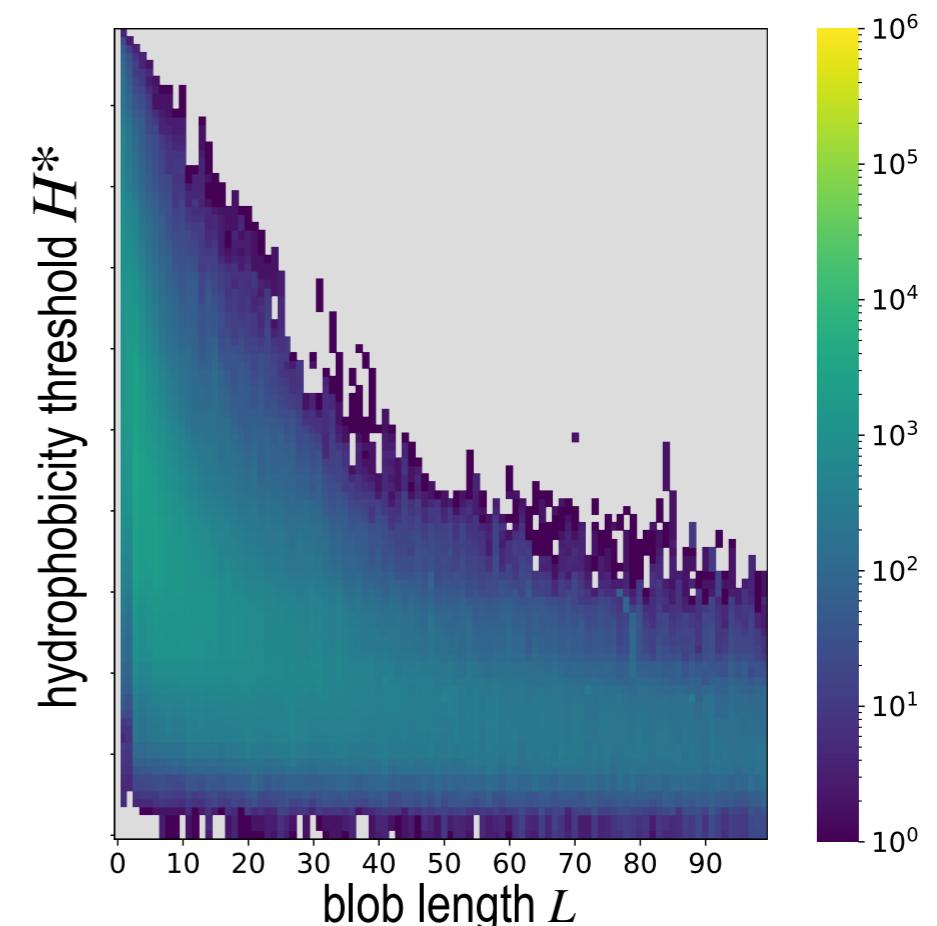
Approach: test for h-blob enrichment of human disease-associated SNPs

SNP-focused blobulation

Variation: "Fixed-threshold" blobulation



number of non disease associated SNPs

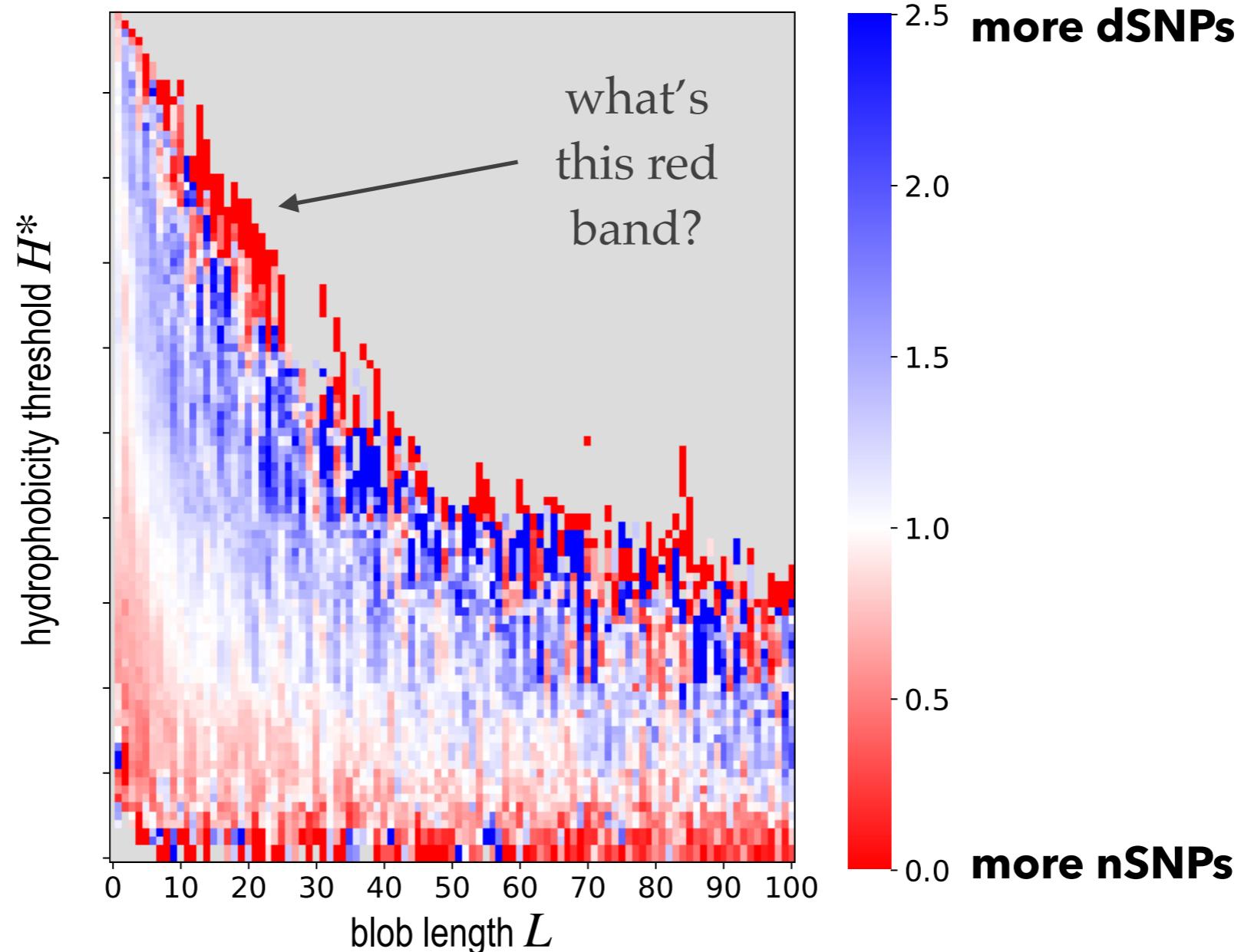


For any threshold H^* , how many SNPs are in h-blobs of length L ?

Calculated L for ~70K missense variants (UniProtKB)

- 57% "likely benign or benign" (nSNPs)
- 43% "likely pathogenic or pathogenic" (dSNPs)

enrichment of disease-associated SNPs (dSNPs)



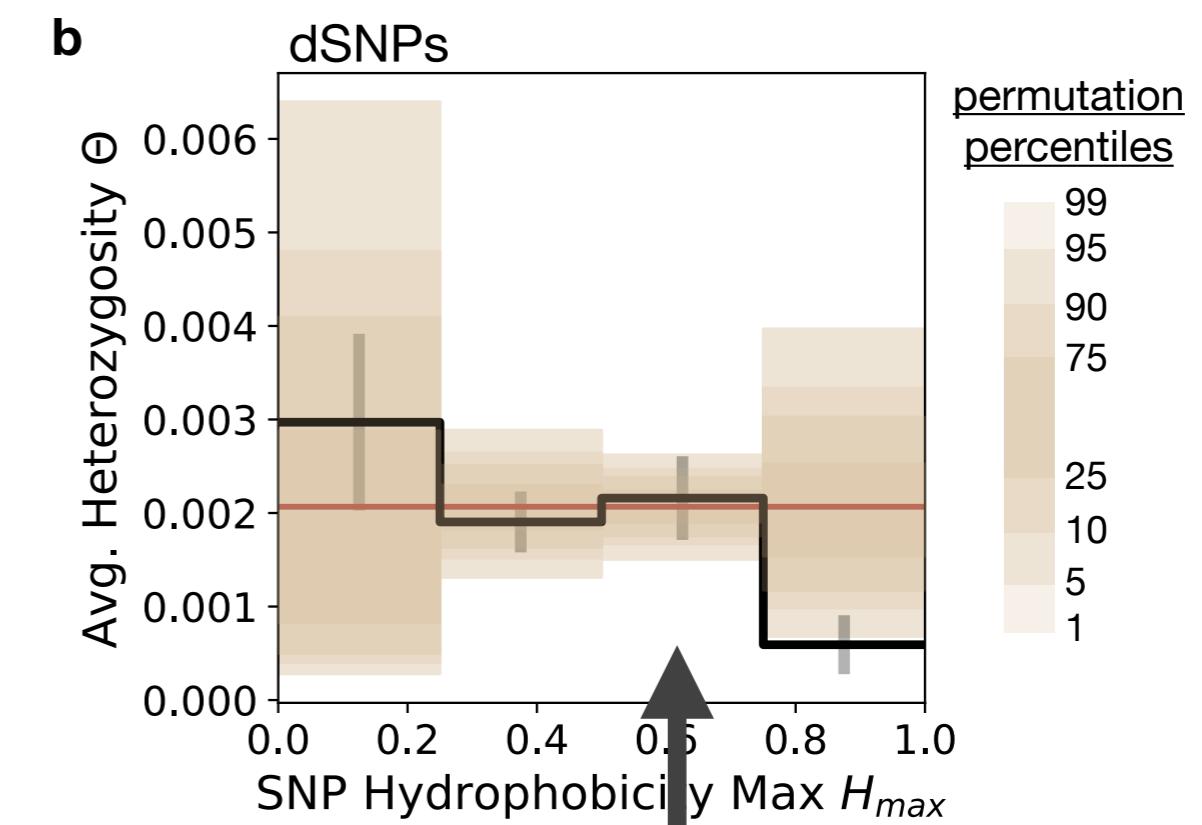
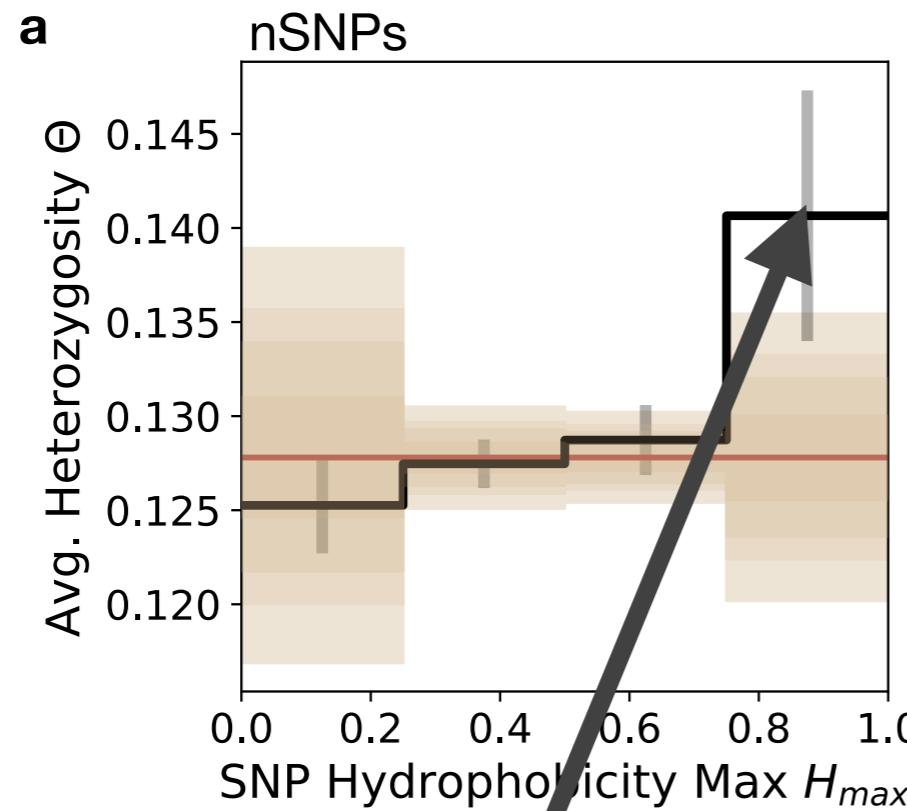
trend supports the hypothesis, except...

Why the exception to the trend?

dSNPs/nSNPs plunges for most extreme blobs:

- ✓ Possibility 1: more nSNPs (SNPs are functional, but not deleterious)
- ✓ Possibility 2: fewer dSNPs (so deleterious, they are not observed)

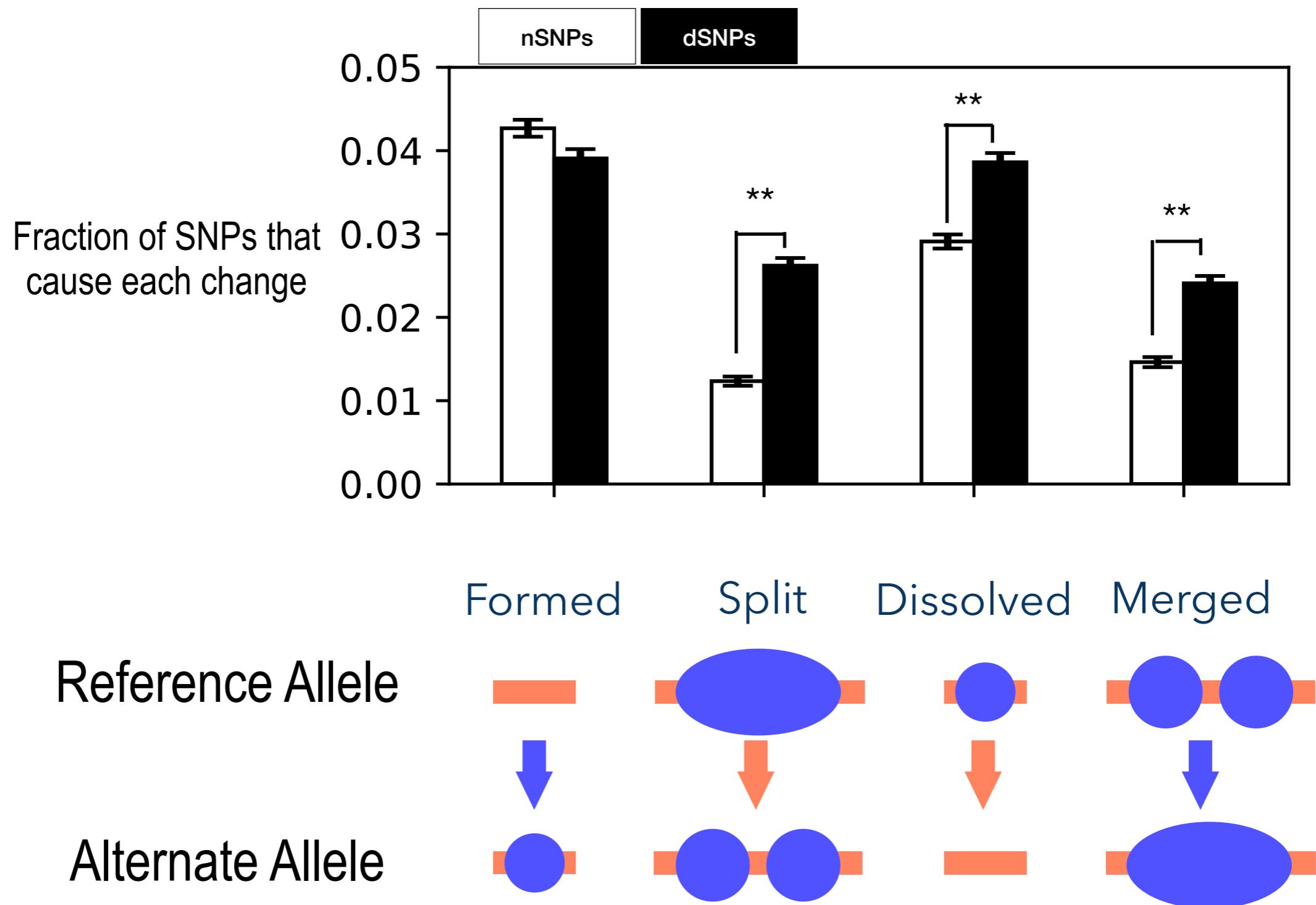
gnomAD : non-Finnish Europeans



ex: olfactory receptors

ex: transporters

dSNPs change blob topology



Questions

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blobulator.branniganlab.org

Summary

- blobulation yields interesting and useful **trends across the human exome** (not just in one protein)
- results are consistent with h-blobs as **physical interaction nodes**
- resulting odds ratios **could be used as priors** in prediction of causal SNPs
- **evidence for selection** on SNPs in most extreme h-blobs
- SNPs that **split h-blobs** are 3 times as likely to be **disease-associated**
- you too can blobulate! at **blobulator.branniganlab.org**

Acknowledgments

Functional Effects

Dr. Ruchi Lohia, Cold Spring Harbor Laboratory

Dr. Matthew Hansen, University of Pennsylvania

Current Blobulator Development Team

Dr. Ruchi Lohia, Cold Spring Harbor Laboratory

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Connor Pitman and Ezry St. Iago-McRae, CCIB

Kaitlin Bassi and Lindsey Riggs, Contributors, CCIB



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edge detection for protein sequences

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