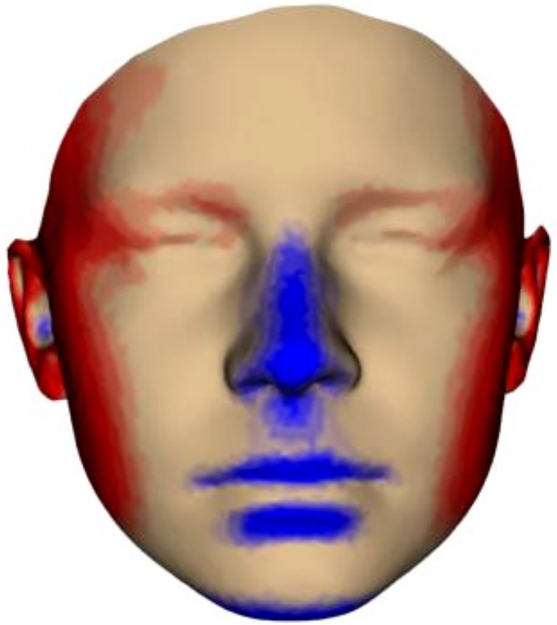
Facial Imaging and Genetic Disease



Benedikt Hallgrímsson, Dept. of Cell Biology & Anatomy,
Alberta Children's Hospital Research Institute

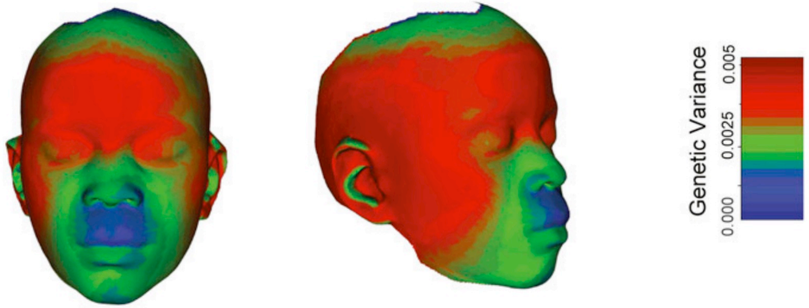
UNIVERSITY OF CALGARY

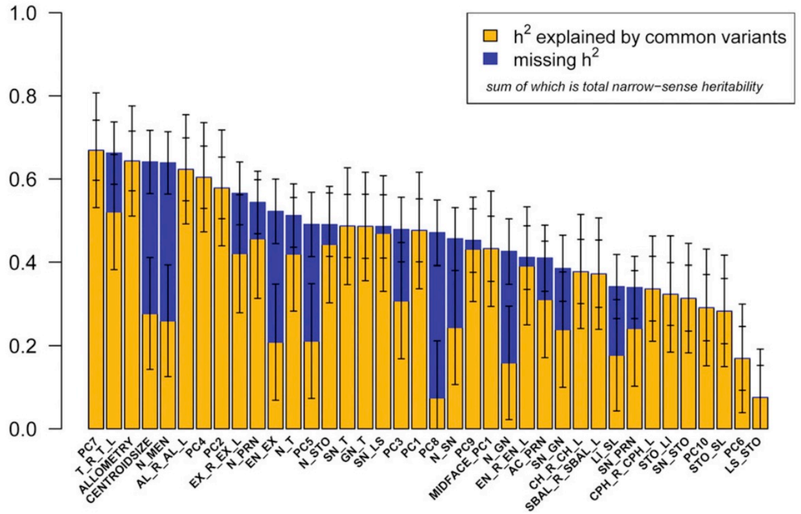

0:10 / 2:29
Global
NEWS

Why would facial shape variation be useful for syndrome diagnosis?

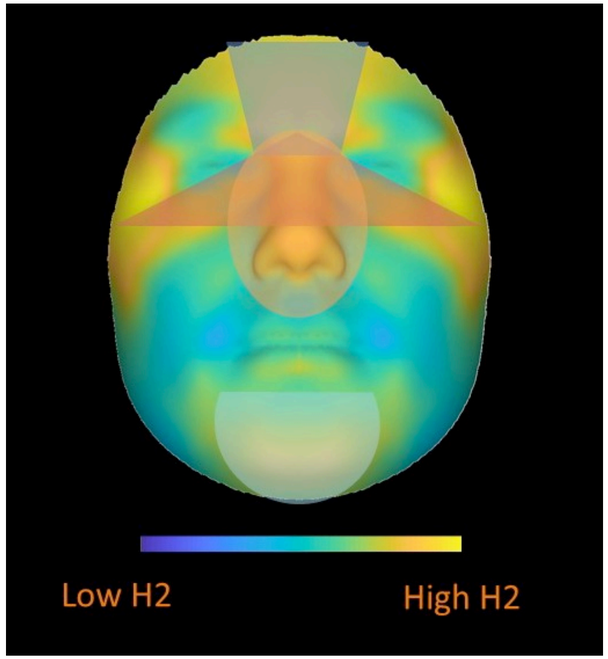
1. Facial shape is heritable and also highly polygenic

Cole *et al.*. 2017 *Genetics*

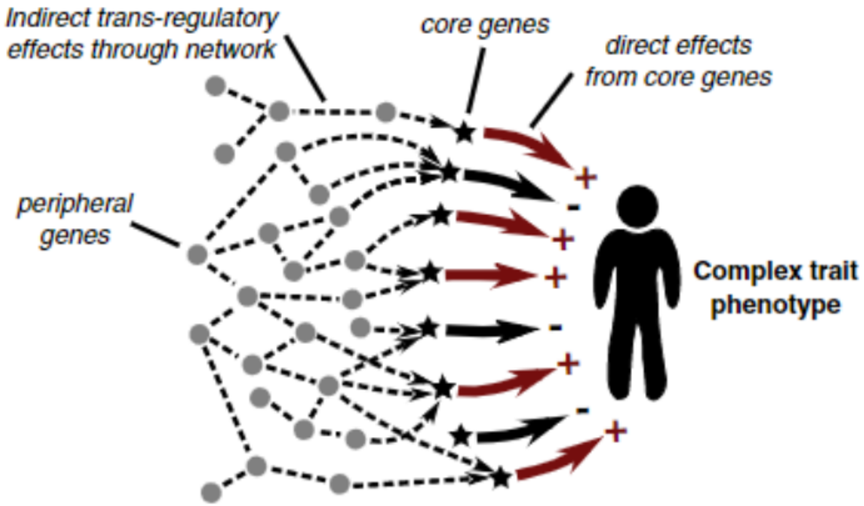




Hoskens *et al.*. 2018 *Frontiers in Genetics*



Liu. Yang and Pritchard. 2019 *Cell*

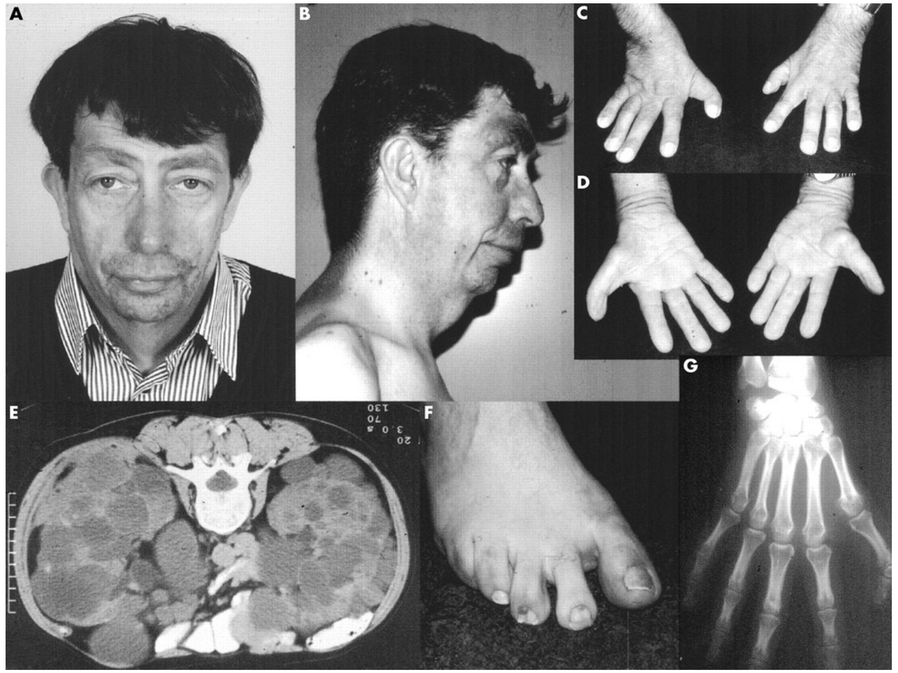


Facial shape is *at least* as polygenic as stature. Perhaps more so (figure depicts the “omnigenic” model for complex traits).

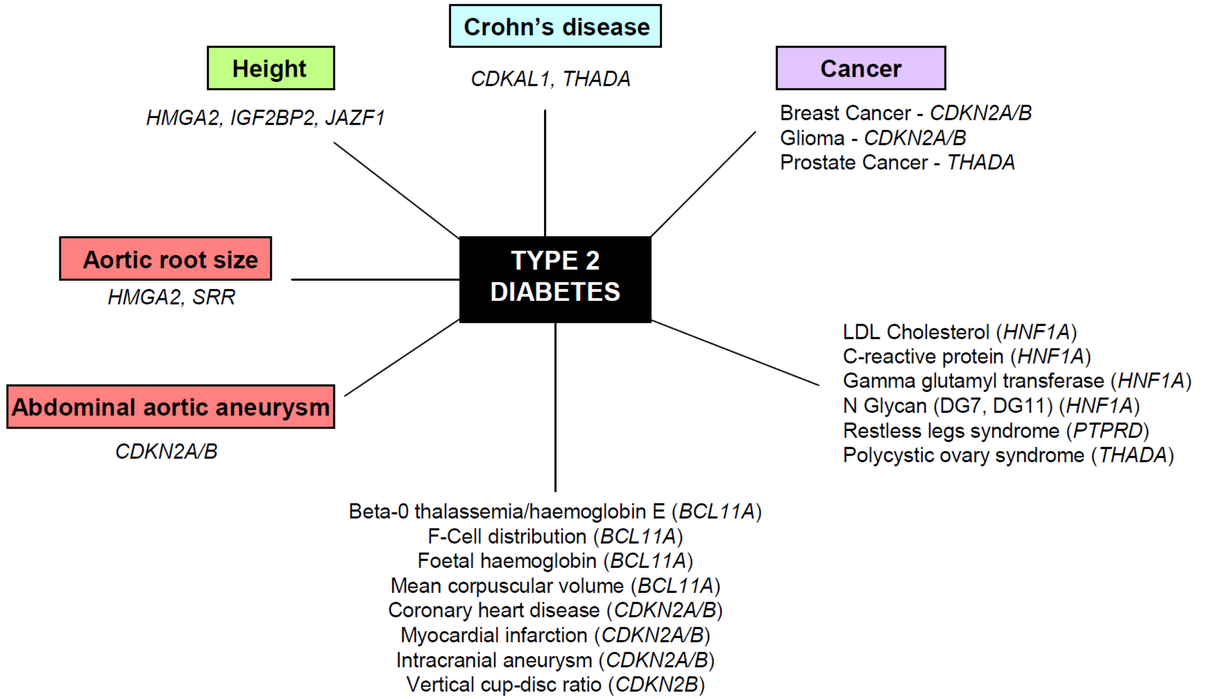
High polygenicity means that many genes/genetic disorders can impact facial shape

2. Pleiotropy is very common. This means that many mutations that cause disease may also affect facial shape.

Example: Patient with acrofacial dysostosis.
tuberous sclerosis. and polycystic kidney disease.



J G Dauwerse et al. J Med Genet 2002;39:136-141

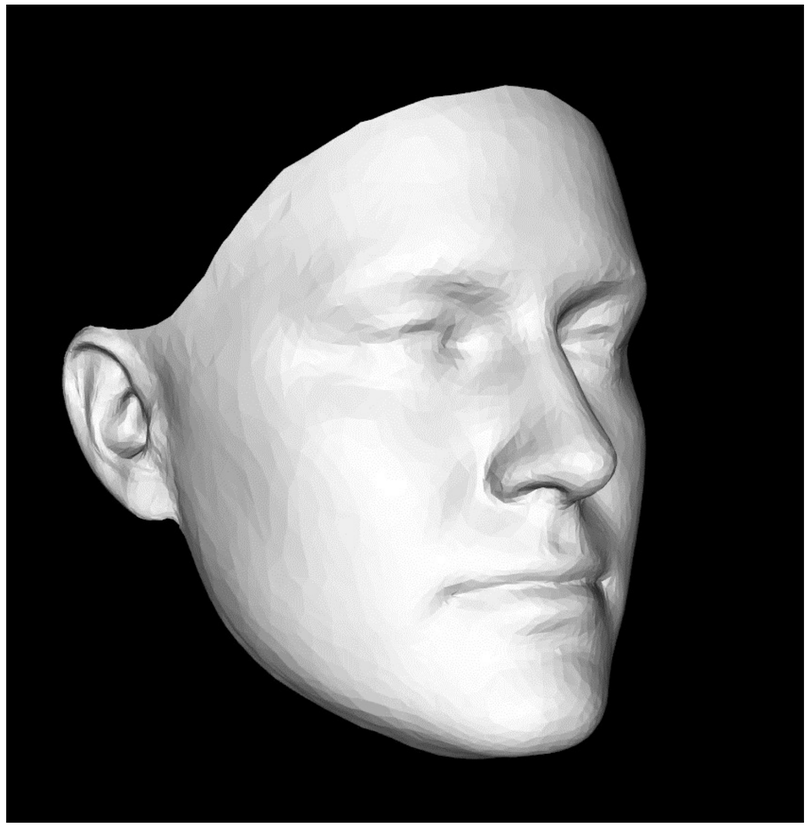


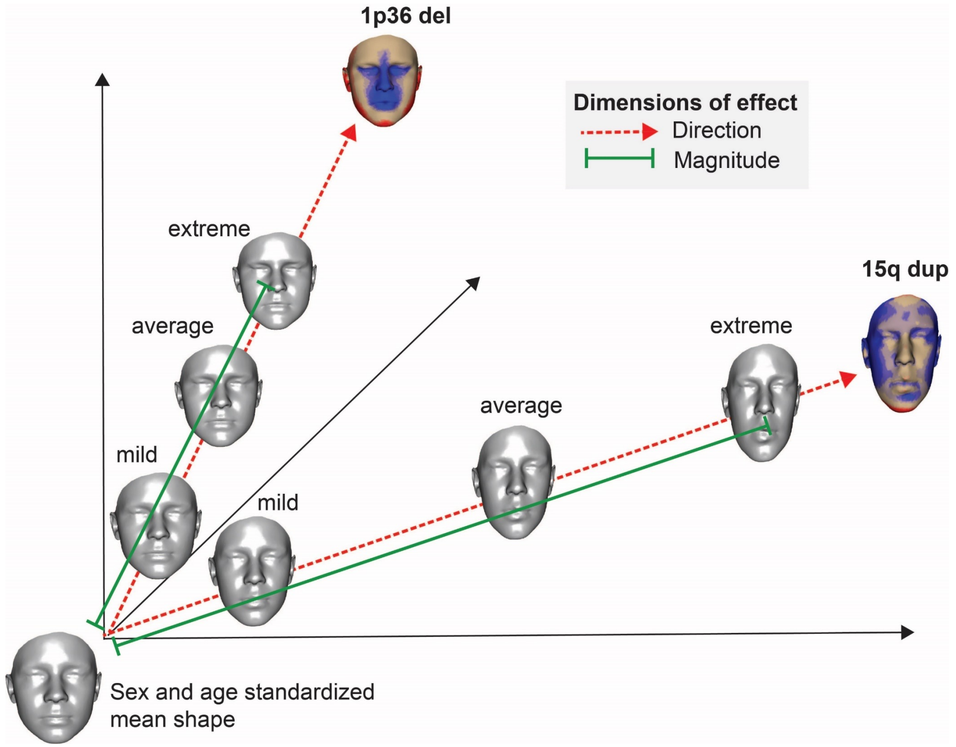
Sivakumaran et al. 2011. Am. J. Hum Gen.

3. Facial shape is a high dimensional trait – thus. genetic variants can have specific and highly distinctive effects

Facial shape can vary in many ways. This creates many. potentially distinctive. directions of genetic effects.

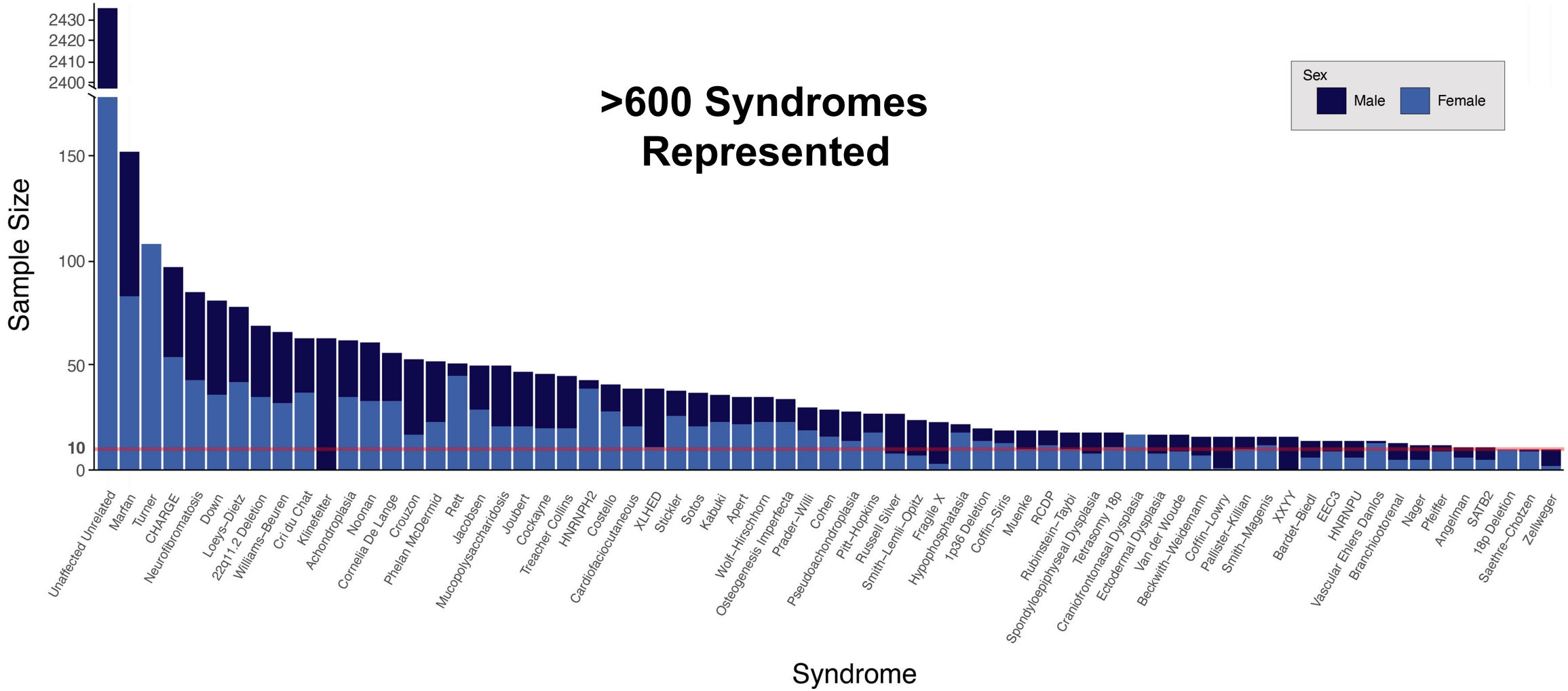
This contrasts with a trait like stature that varies only along a single dimension. While also heritable. polygenic and subject to pleiotropy. this makes stature less useful for disease diagnosis.





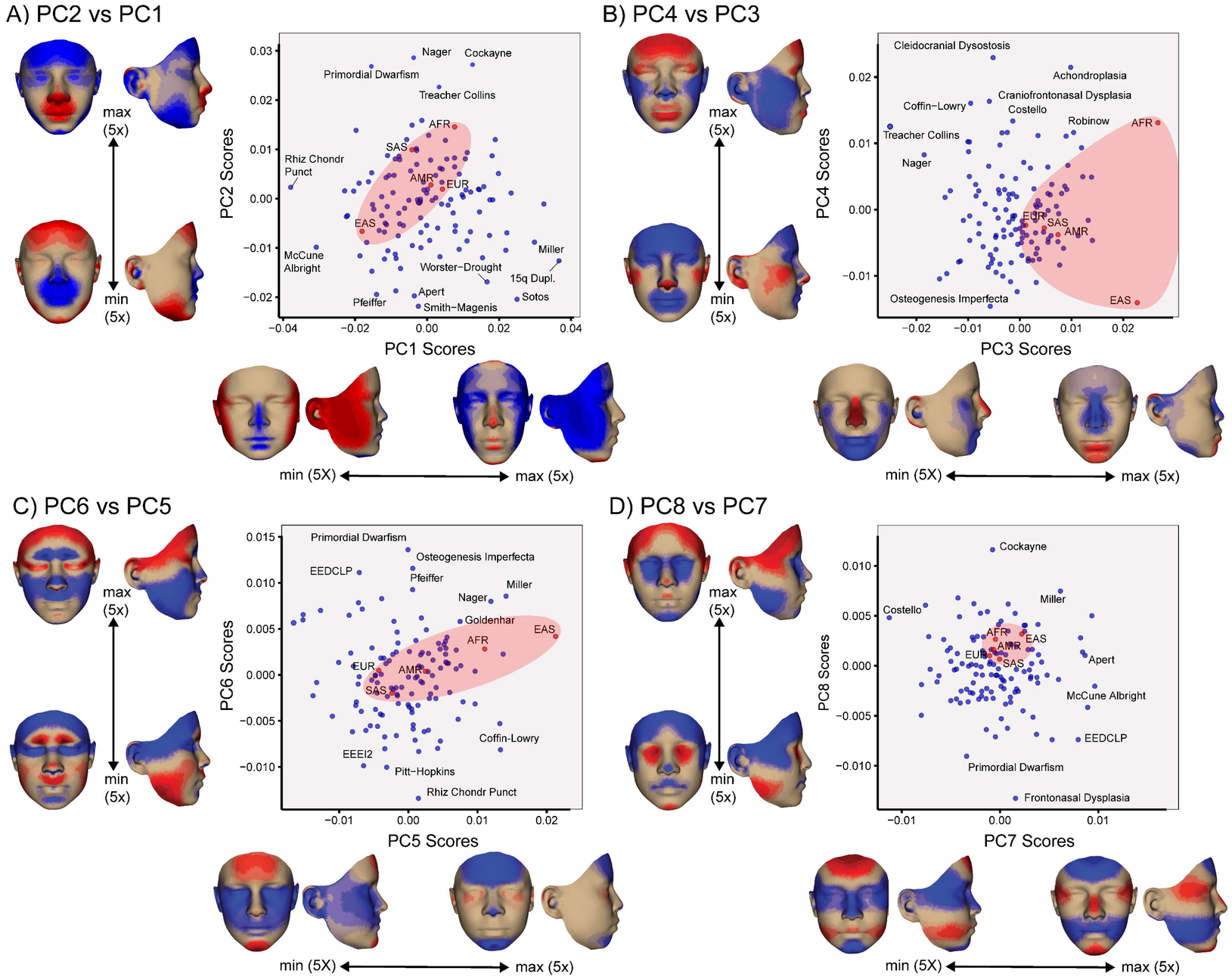
Facebase 2 (2014-Present): *Developing 3D Craniofacial Morphometry Data and Tools to Transform Dysmorphology*

Library of 3D Facial Scans



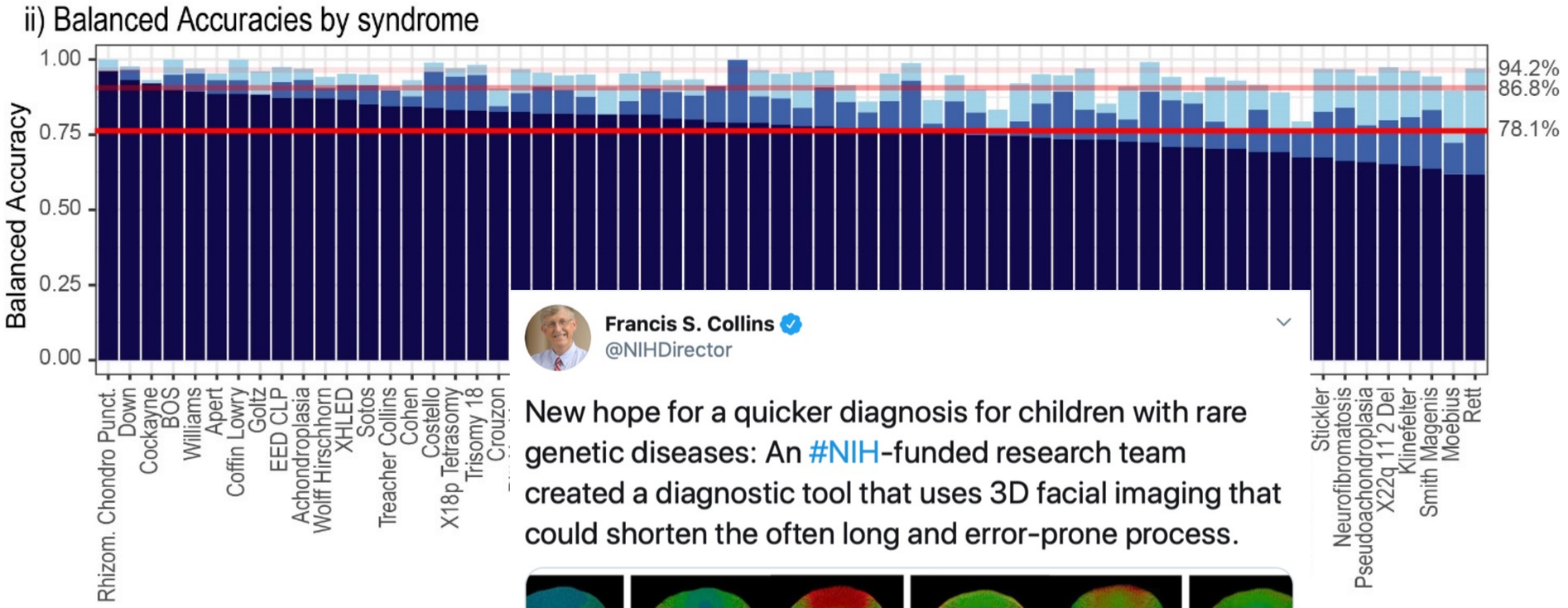
Facial shape is altered in many genetic syndromes

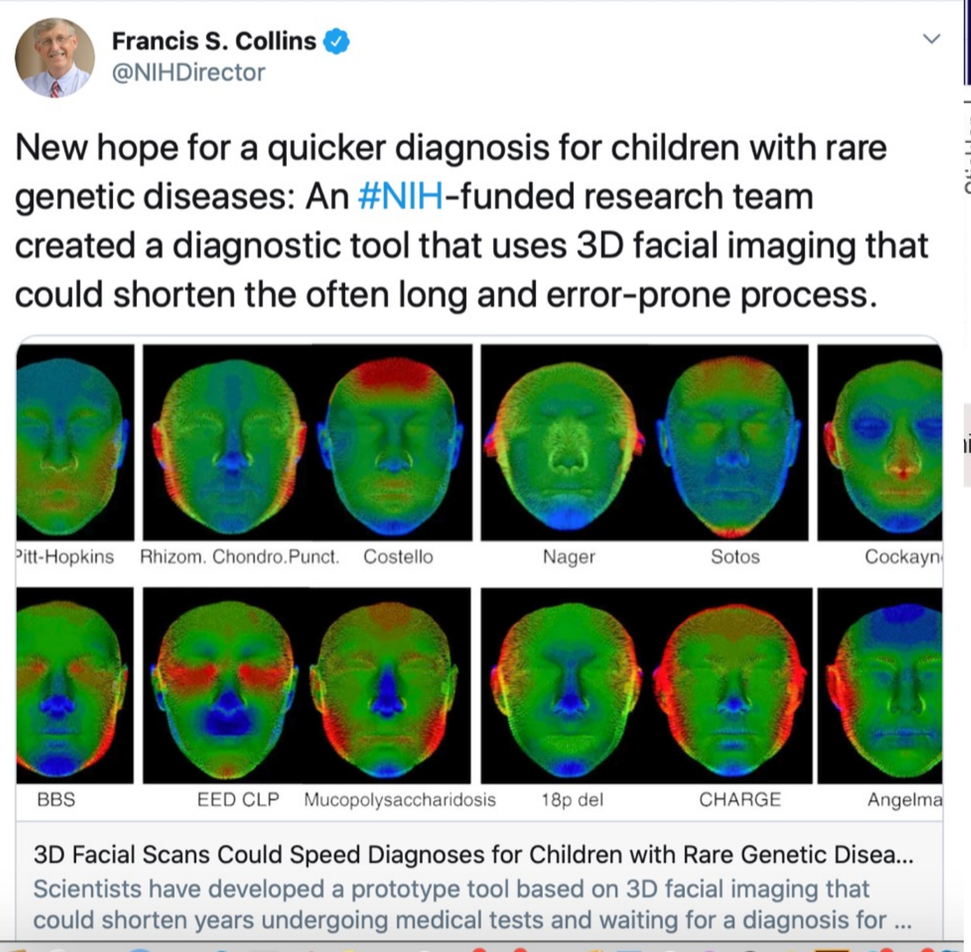
>7000 human syndromes; 30-40% involve facial dysmorphology



Collaboration with Francois Bernier, Ophir Klein, Rich Spritz, and Peter Claes.

Machine-Learning Based Classification





ARTICLE Genetics inMedicine

Open

Automated syndrome diagnosis by three-dimensional facial imaging

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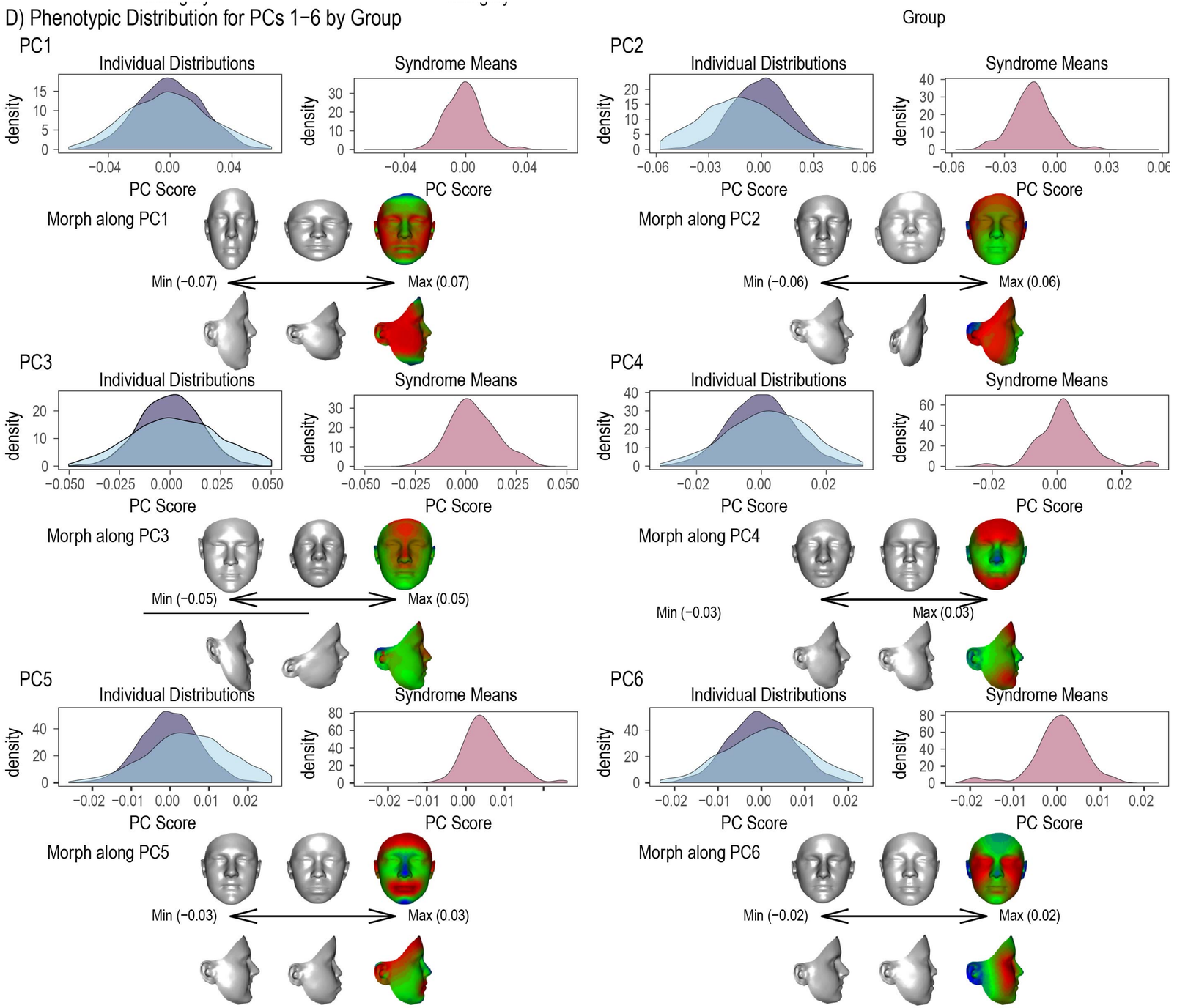
Syndromic influences on craniofacial shape follow the same covariance structure as the background variation

The covariance structure for syndromic faces is virtually identical (random skewers and Mantel's tests r>0.88) to the control sample.

The covariance structure for syndromic means is also very similar.

Syndromic faces vary along the same axes as normal variation but do a greater extent.



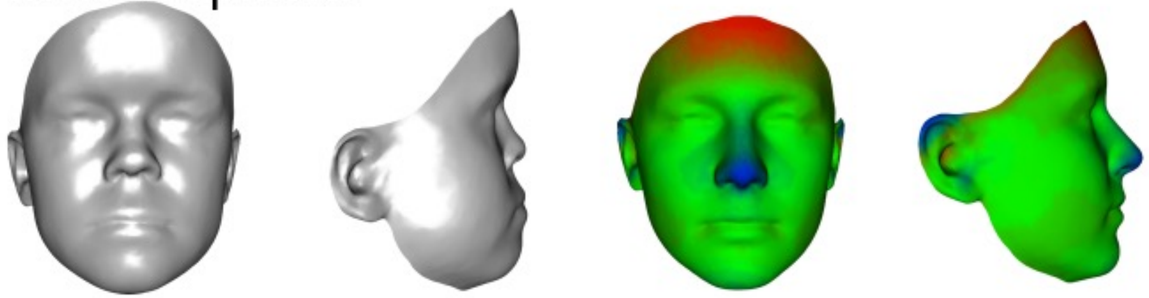
- **David Aponte. PDF**
- **David Katz. PDF**
- **Jordan Bannister. Ph.D Student**

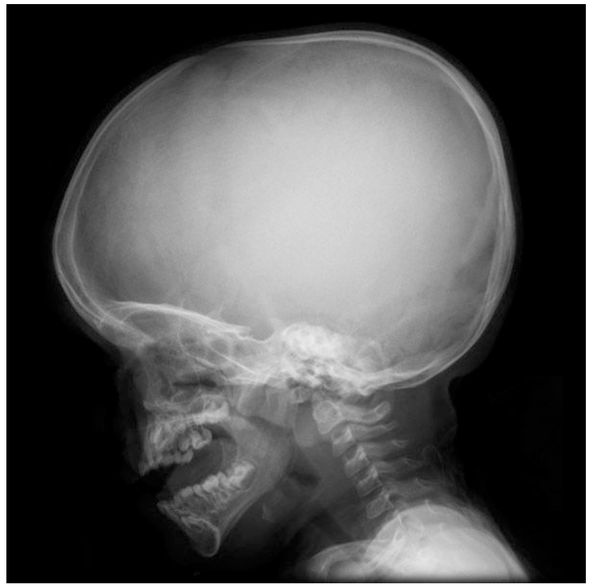
Collaboration with Francois Bernier, Ophir Klein, Rich Spritz, and Peter Claes.

Morphological Integration

Integration refers to the *tendency* for traits to covary.

Achondroplasia





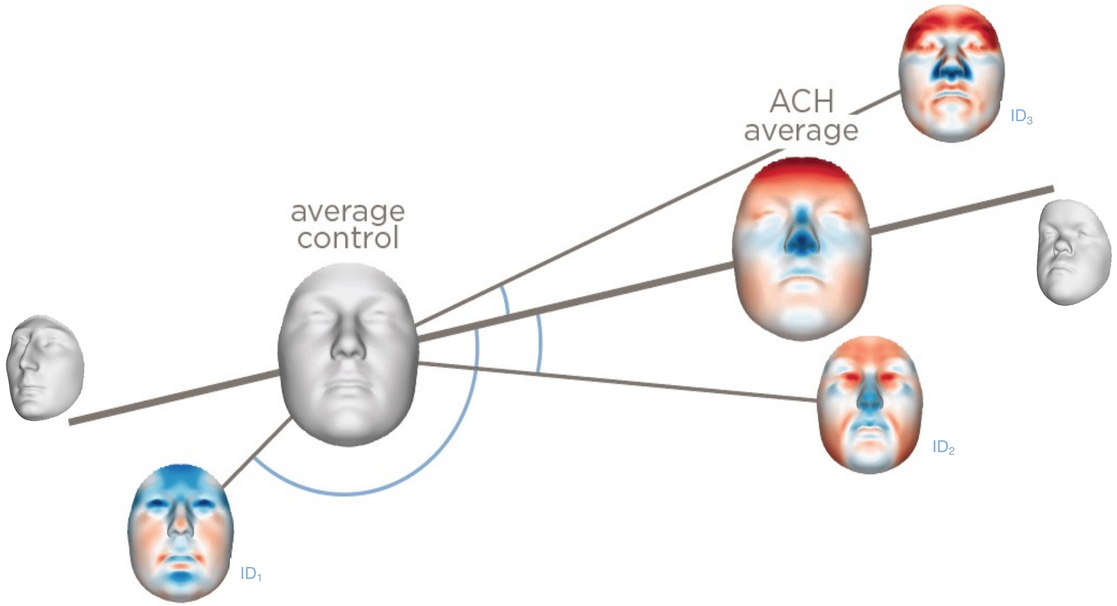
Peter Dinklage

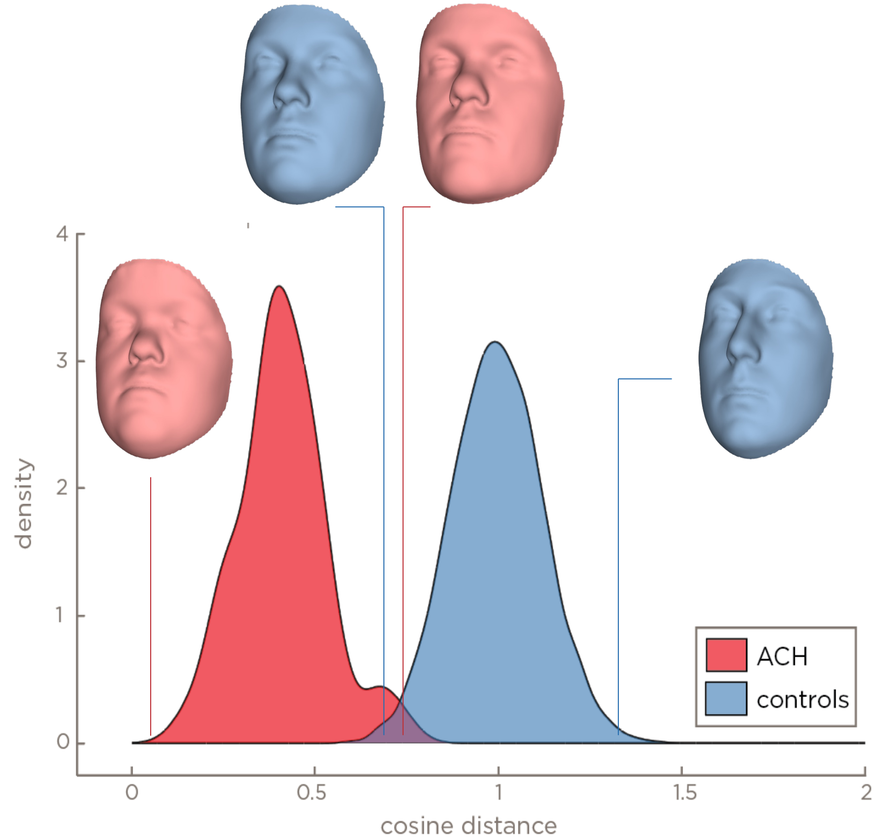
Many syndromes. such as achondroplasia. produce a correlated suite of phenotypic effects because of **integration.** Often, such traits covary along an axis of penetrance for a disease-related mutation or severity for an environmental effect.

Syndromic phenotypes as traits. E.g. Achondroplasia

Hanne Hoskens. Postdoc
Michiel Vanneste. Resident (Leuven)

Collaboration with Hilde Peeters and Peter Claes





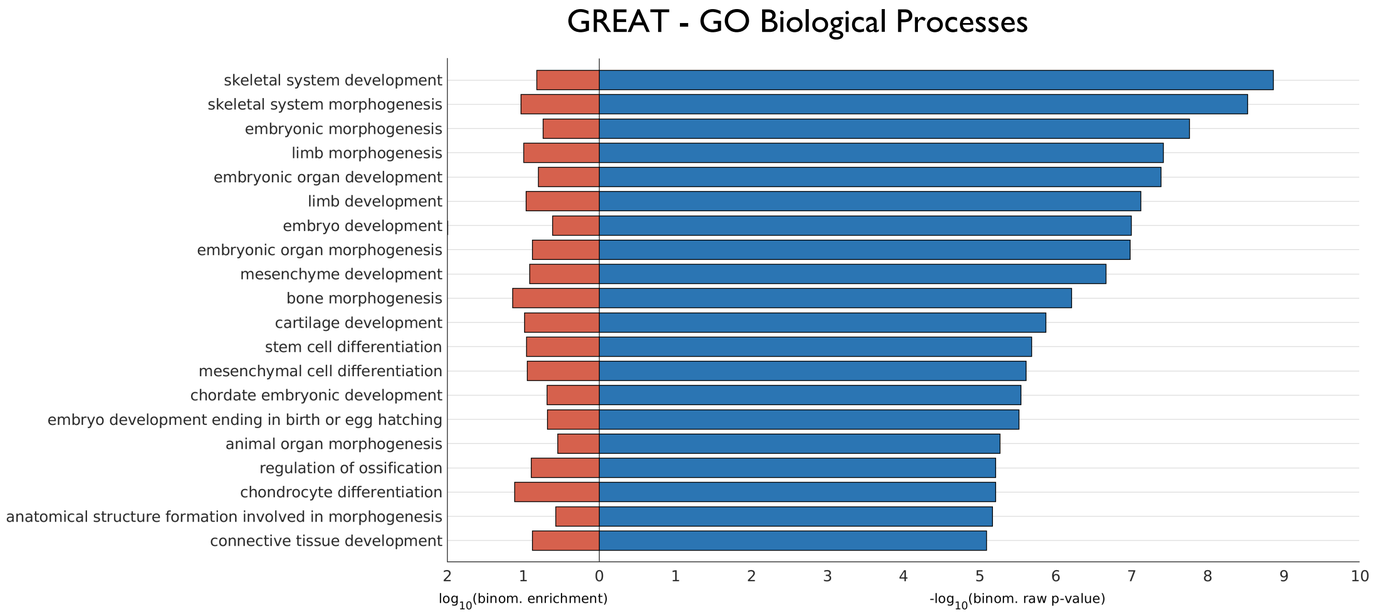
Achondroplasia GWAS Result

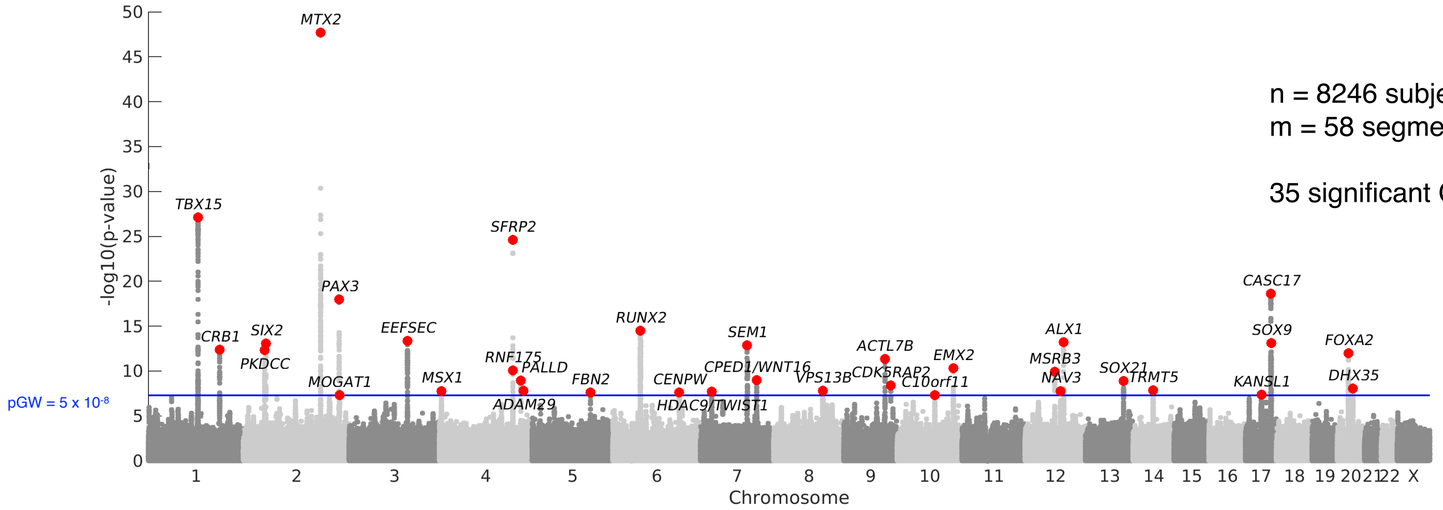
Hanne Hoskens. Postdoc
Michiel Vanneste. Resident (Leuven)

Collaboration with Hilde Peeters and Peter Claes

- We performed a GWAS for the achondroplasia axis in individuals who do not have achondroplasia.

Overlap with achondroplasia-related genes





n = 8246 subjects
m = 58 segments

35 significant GWAS hits

nature communications

Article

https://doi.org/10.1038/s41467-024-54839-1

Syndrome-informed phenotyping identifies a polygenic background for achondroplasia-like facial variation in the general population

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Check for updates

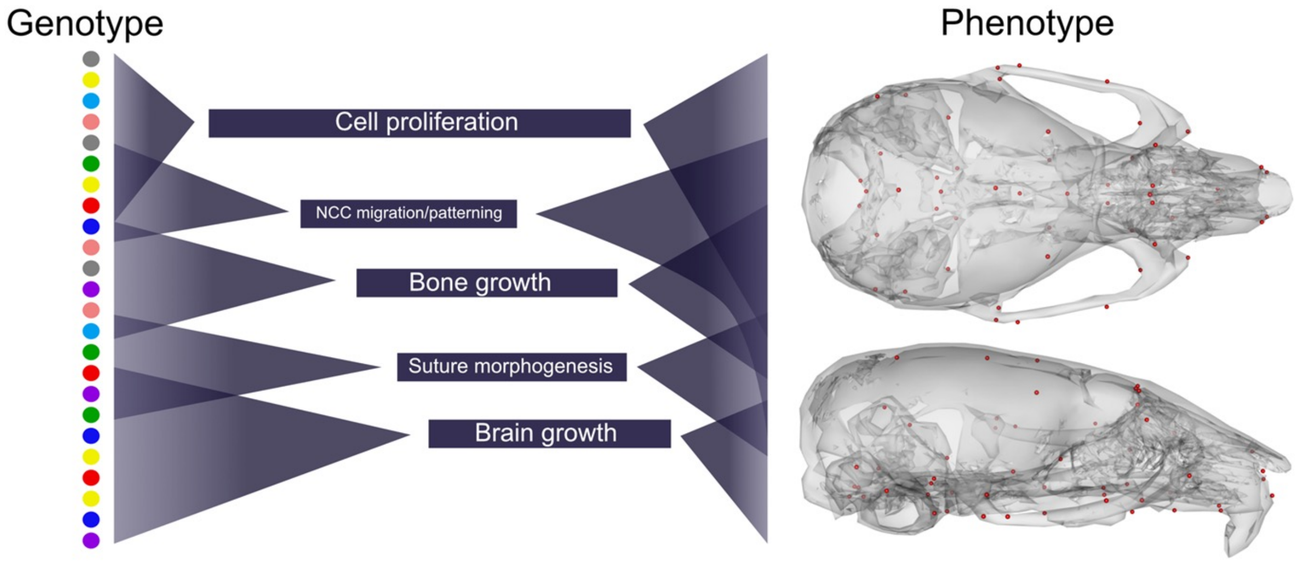
Michiel Vanneste[1,15], Hanne Hoskens[2,3,4,15], Seppe Goovaerts[1,5], Harold Matthews[1,5], Jay Devine[5,6], Jose D. Aponte[2,3,4], Joanne Cole[7], Mark Shriver[8], Mary L. Marazita[9,10], Seth M. Weinberg[9,10], Susan Walsh[11], Stephen Richmond[12], Ophir D. Klein[13], Richard A. Spritz[14], Hilde Peeters[1] ✉, Benedikt Hallgrímsson[2,3,4] ✉ & Peter Claes[1,5,6] ✉

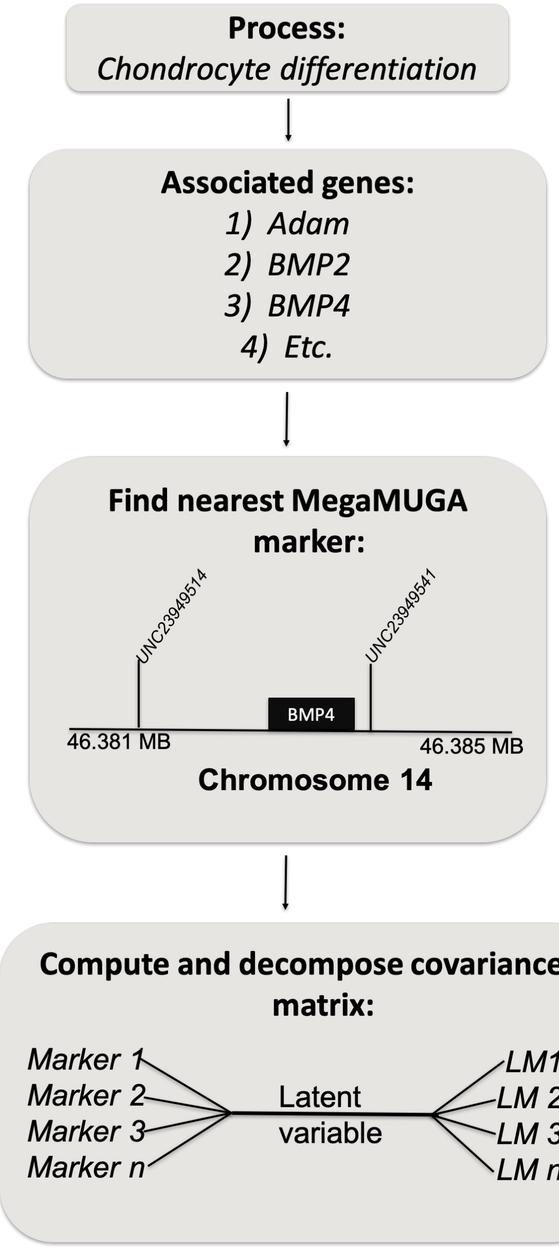
Hanne Hoskens. Postdoc
Michiel Vanneste. Resident (Leuven)

Collaboration with Hilde Peeters and Peter Claes

Multivariate Genotype-Phenotype Mapping

David Aponte PhD student





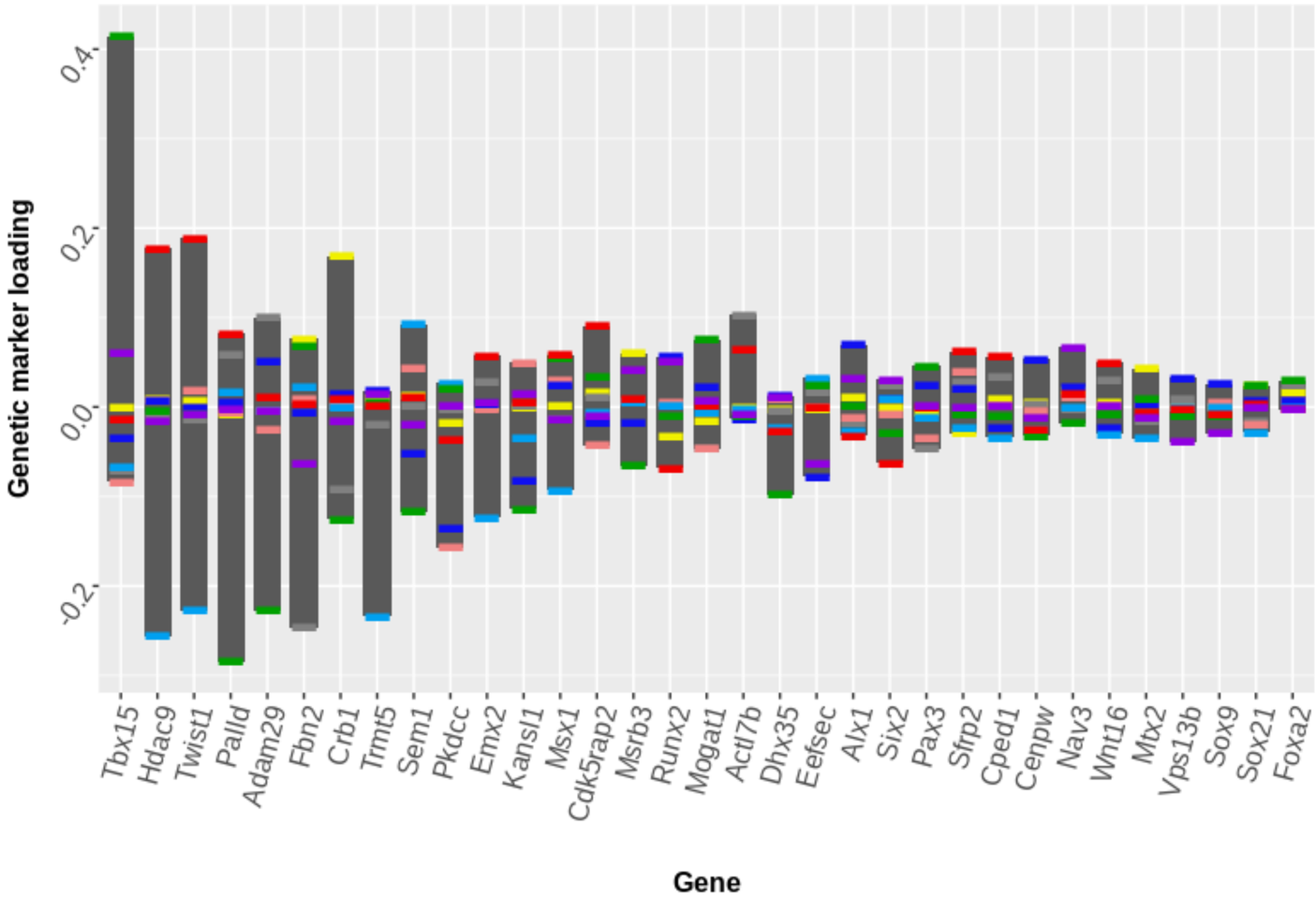
- We used the Mitteroecker *et al.* method (MGP)
- The method relates latent variables from the genetic and phenotypic variance-covariance matrices to perform a multi-variate to multivariate mapping of genotype to phenotype.

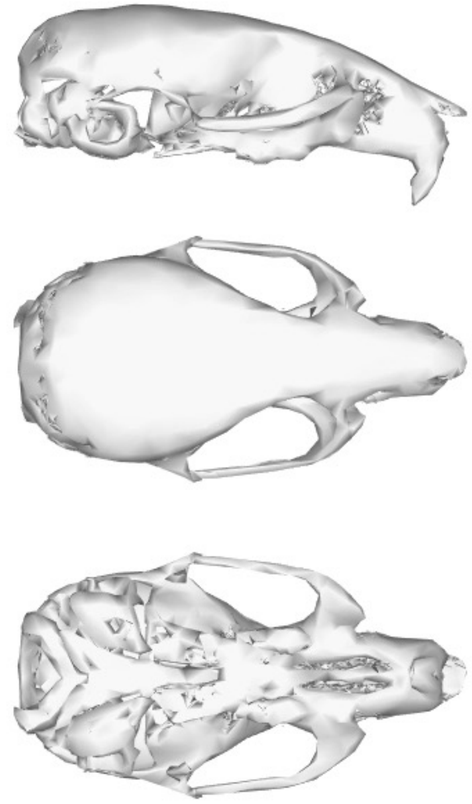
Collaboration with Ralph Marcucio, Daniel Graf, Steve Murray, Jim Cheverud

Aponte *et al.. 2021 eLife*

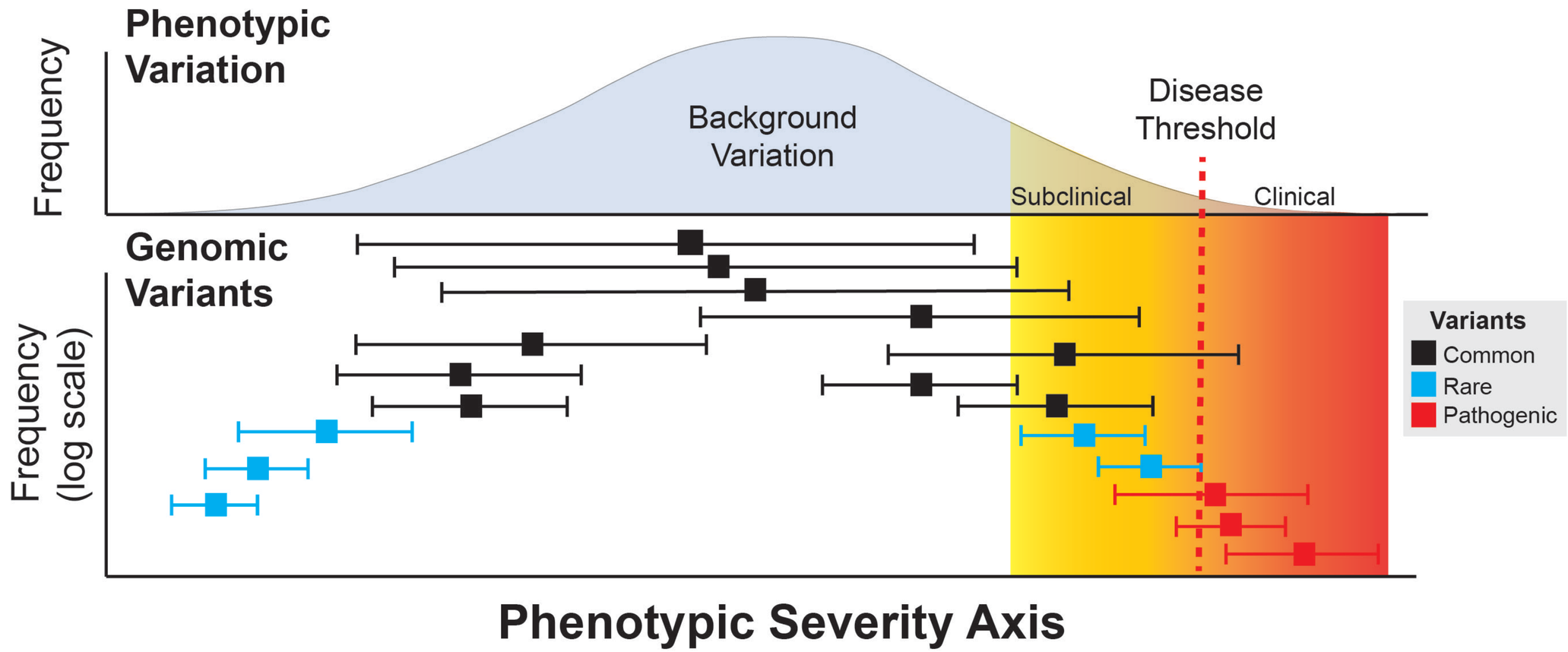
Multivariate Geno-Pheno (MGP) method

We then ran the 35 hits from the human GWAS on Diversity-Outbred mice using MGP





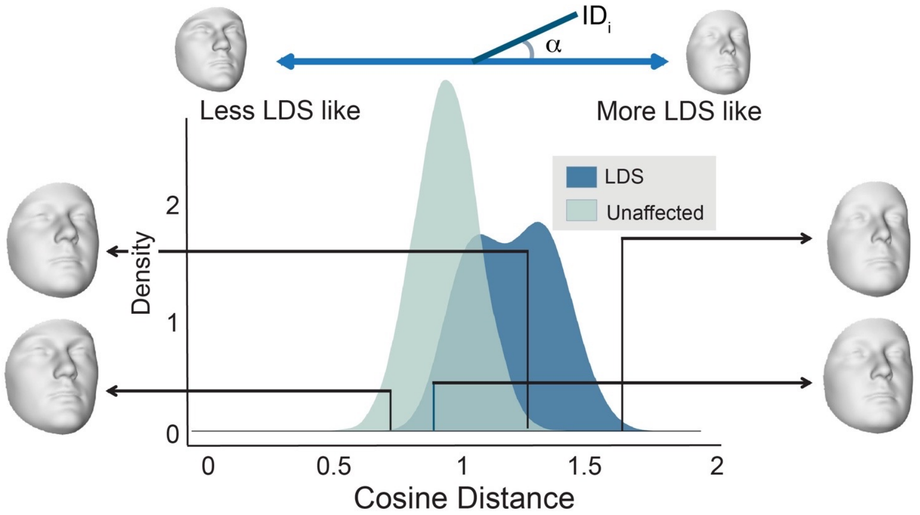
Integration and the genetics of Mendelian disorders



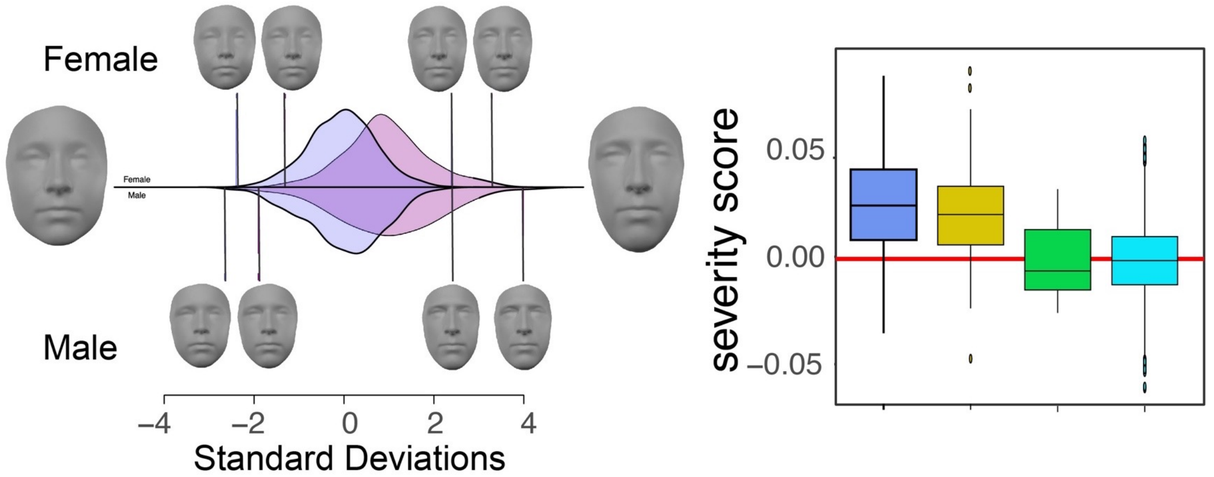
If the genes that drive variation along facial shape severity axes have similar patterns of pleiotropy to the disease-associated variants, then such axes have predictive value in clinical context.

Axes of Facial Shape Severity for HTADs

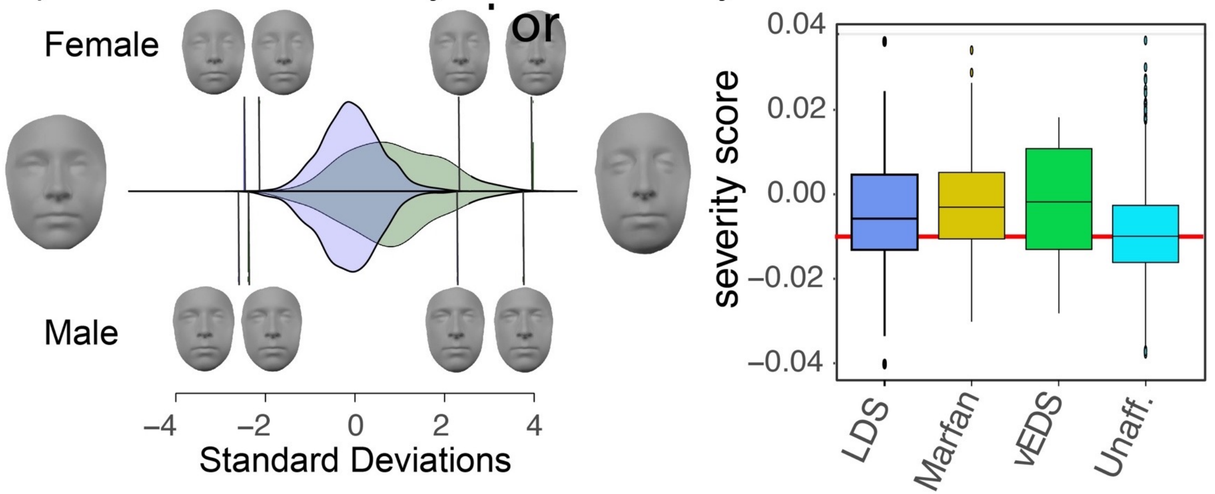
A) Calculation of Facial Shape Severity Score



B) Distributions for Marfan Severity Score



C) Distributions for Loeys-Dietz Severity Score

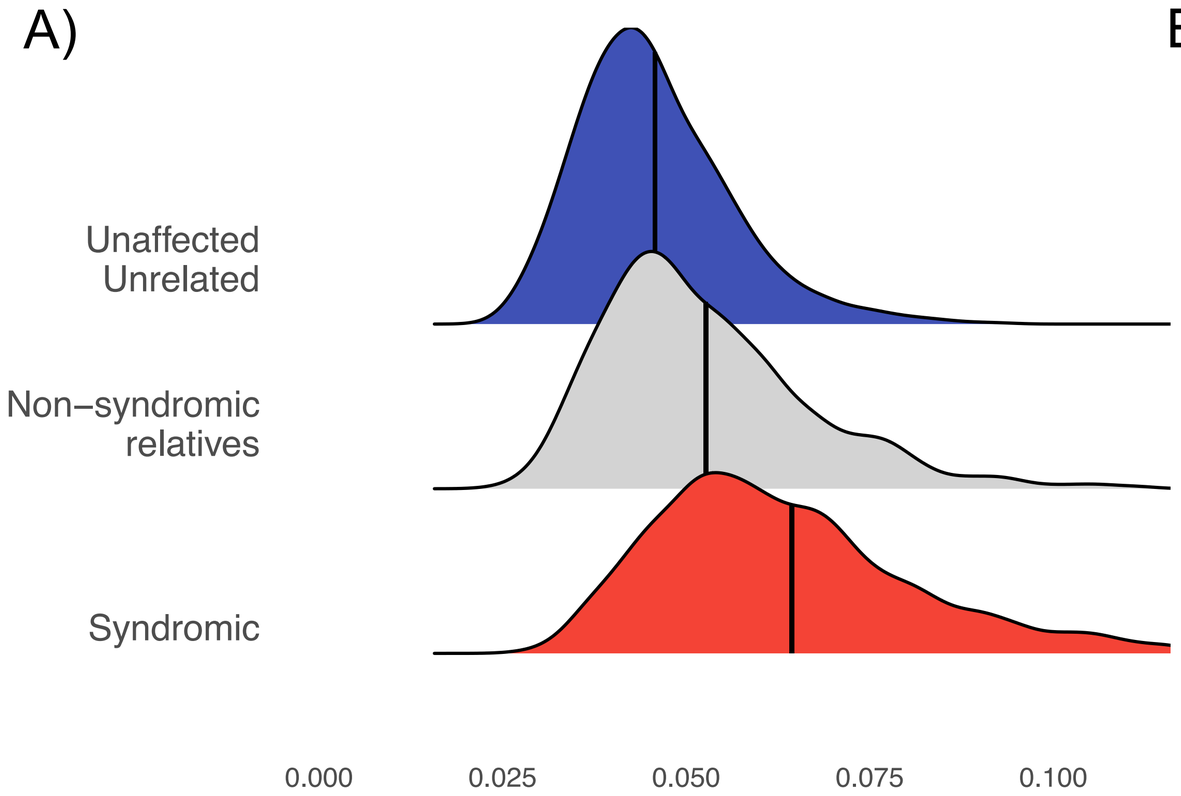


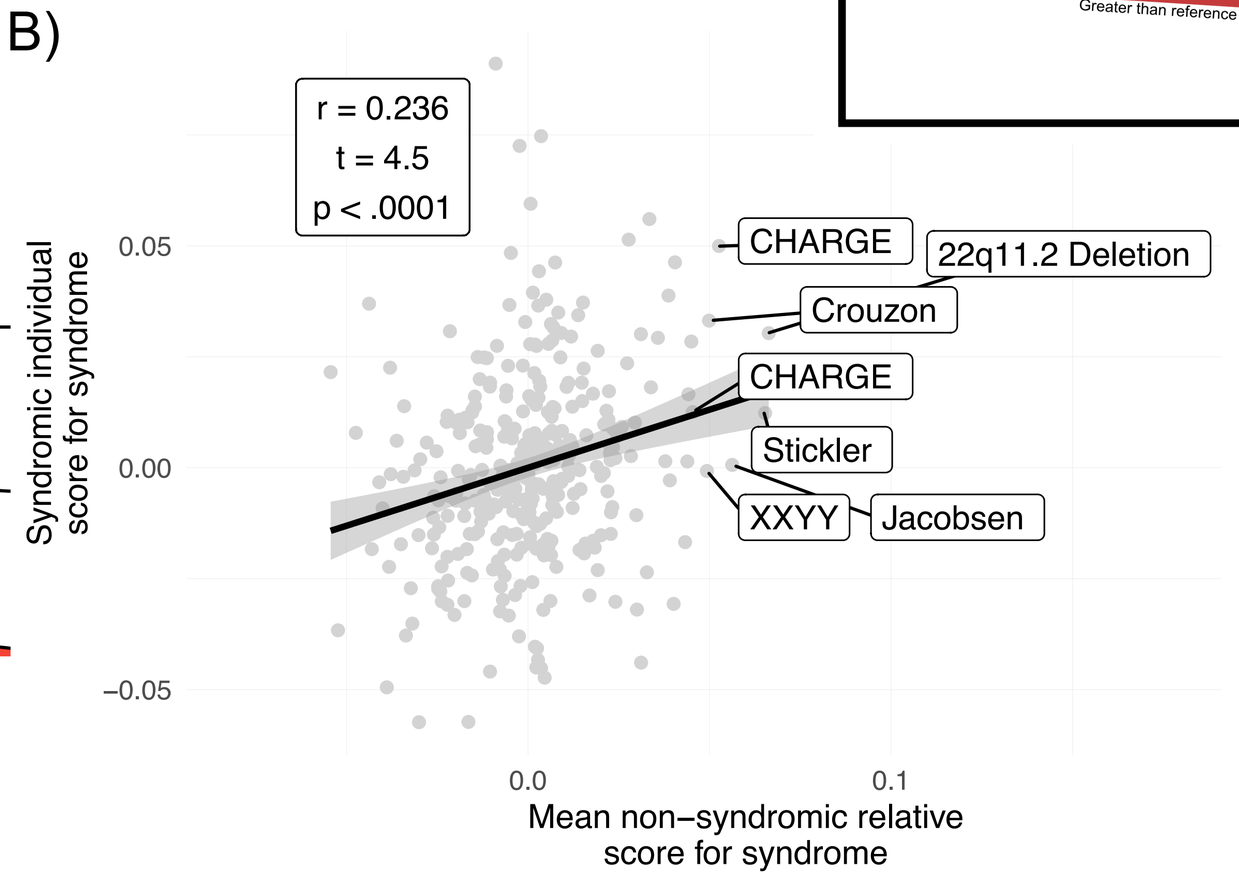
Connective tissue syndromes also fall along axes of severity that have a polygenic basis. These syndromes are associated with dramatically increased risk of sudden death due to aortic dissection

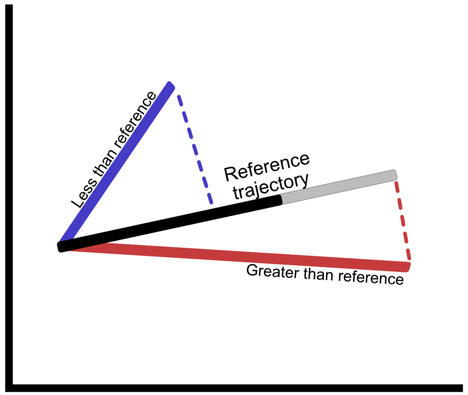
Jay Devine, PDF

CAN-ACT Consortium and Peter Claes, collaborator

Non-syndromic relatives harbor signs of syndromic morphology

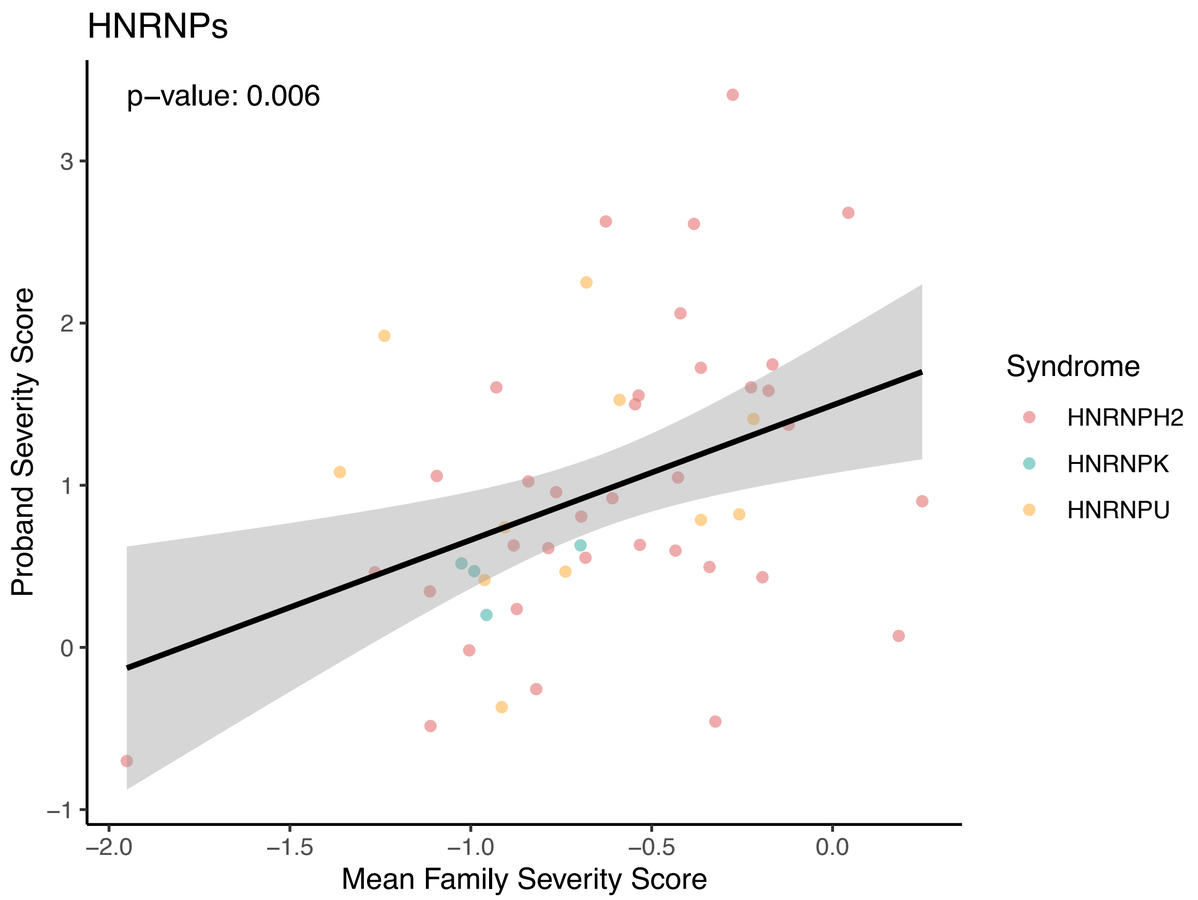


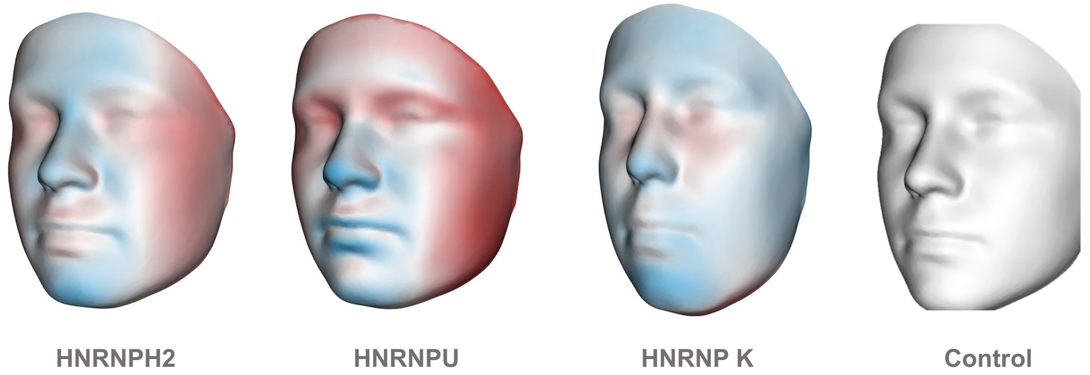




- **David Aponte. PDF**

Does familial resemblance to a syndrome predict severity?





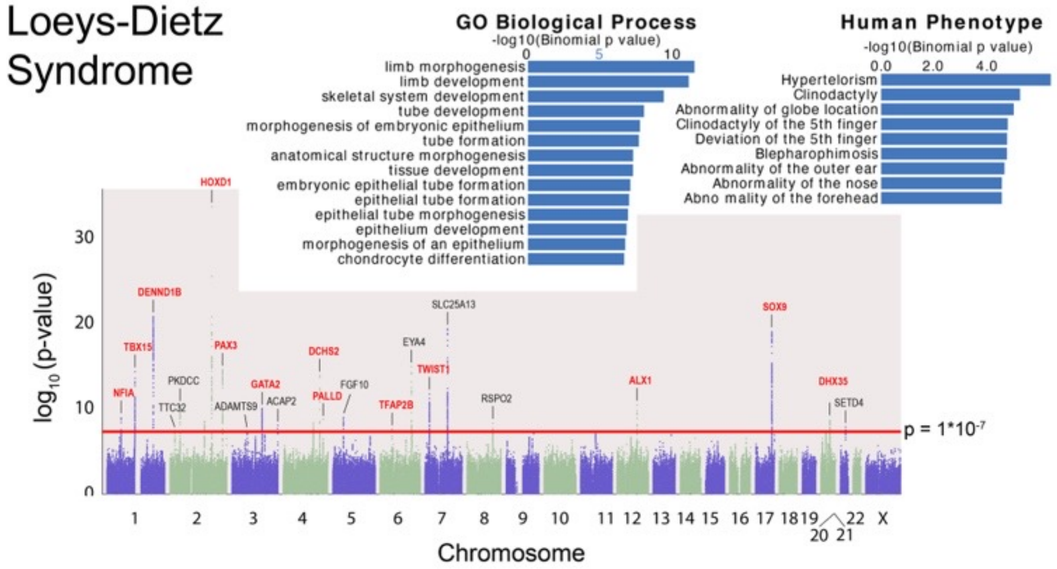
Familial facial shape severity predicts proband facial shape severity for Au-Klein Syndrome.

Cassidy DaSilva, PhD student

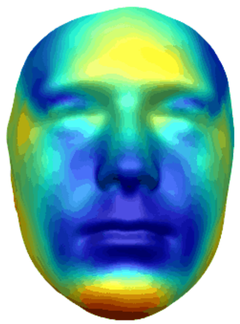
Billie Au, Collaborator

Is variation in facial shape severity meaningful?

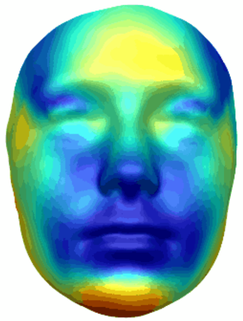
Syndrome-Informed GWAS for Loeys-Dietz



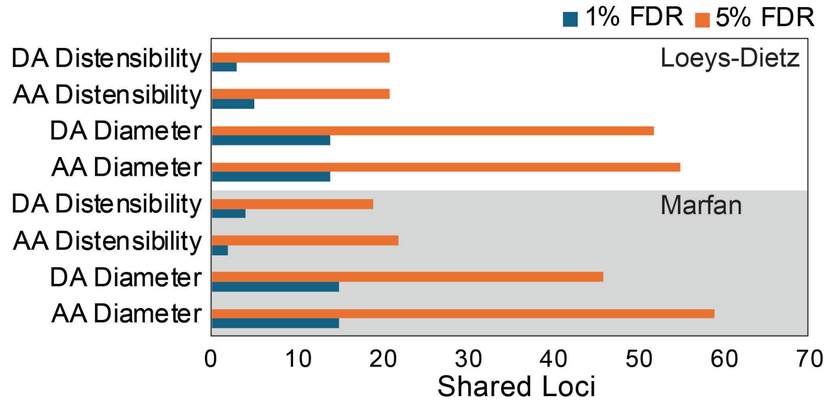
Male



Female

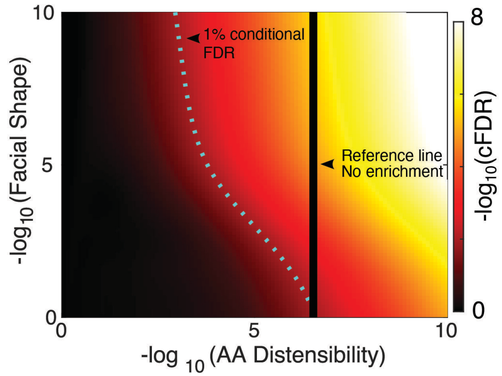


A) Shared loci between TAD and Syndrome-Informed GWAS

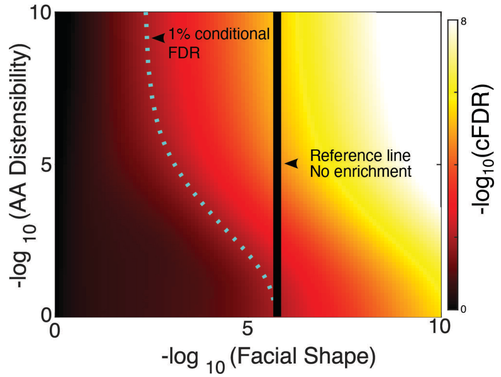


B) Conditional False Discovery Rate Heatmaps

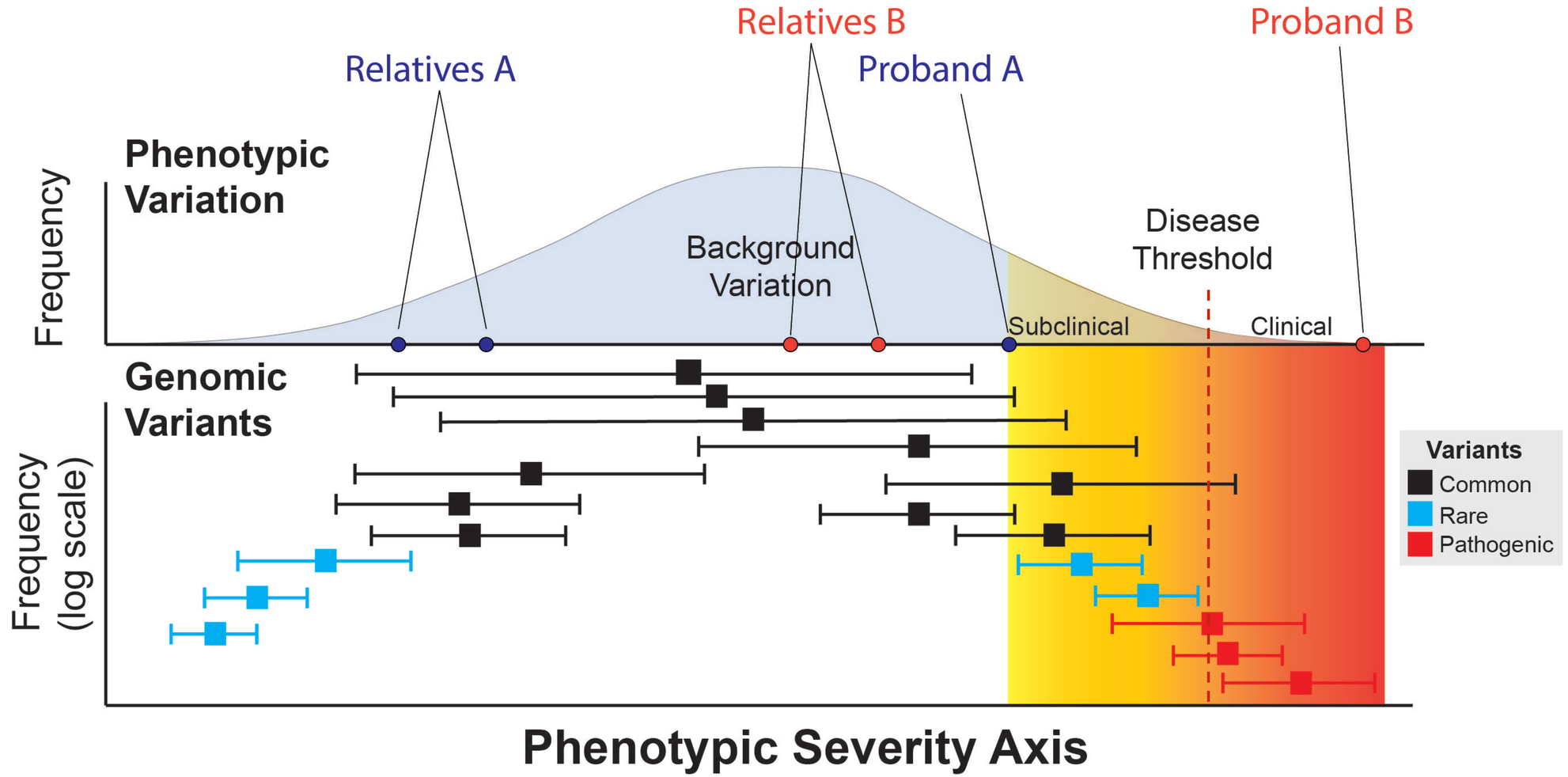
i) Aortic Distensibility GWAS on Marfan



i) Marfan GWAS on Aortic Disensibility



For heritable aortophathies, preliminary analyses reveal significant overlap between the genetics of facial shape severity for these syndromic axes and the genetics of Thoracic Aortic Dissection.



Relatives of probands who have been diagnosed with a disease are more likely to have a genetic background that elevates disease-related severity even when they don't have the pathogenic variant.

Conclusions

- Many pathogenic mutations influence the face due to pleiotropy and the massive polygenicity of facial shape variation.

- Variation in facial shape is high dimensional but also highly structured or *integrated*. This means that many pathogenic variants alter facial shape along directions of variation that are present in the background population.

- This feature can be used to construct axes of phenotypic severity or penetrance. Such axes can have a polygenic basis in the background population. It is not known whether axes of facial shape severity predict underlying disease severity for specific diseases, but this is an issue of current concern.

Acknowledgements

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- ***Lab Alumni***: Nathan Young, Campbell Rolian, Heather Jamniczky, Trish Parsons, Mange Manyama, Paula Gonzales, Eric Schmidt, Kathy Willmore, Jevon Brown, Dave Cooper, Julia Boughner, Lynnette Hornung, Jared Spitzmacher, Jacinda Larson, Hayley Britz, Whitney Poay Lim, Chris Percival, Denise Liberton, Francis Smith, Brenda McKinnes, Danika Lipman, Steve Wat, Marta Marchini, David Katz, Malcolm Eaton, Jordan Bannister, Michelle Leong, Sienna Guo, David Aponte, Rebecca Green and Jay Devine.

- ***Collaborators:*** Francois Bernier, Ralph Marcucio, Ophir Klein, Nathan Young, Peter Claes, Jim Cheverud, Rebecca Green, Rich Spritz, Kim McBride, Myriam Hemberger, Mihaela Pavlicev, Gunter Wagner, Wendy Dean, Nils Folkert, Jim Cheverud, Chris Pervical, Ian Dworkin, Arnar Pálsson, Skúli Skúlason, Kalina Kaprilova, Quentin Horta-Lacueva, Julien Claude, Anne Calof, Arthur Lander, Amy Merril, Allan Pack, Richard Schwab and others.

one child every child

Canada First Research Excellence Fund

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NSERC CRSNG

Alberta Children's Hospital Research Institute for Child and Maternal Health

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Fondation du syndrome Loeys-Dietz Syndrome Foundation Canada

syndrome-atlas.ca

- Model-driven visualizations of age/sex/severity
- Simulated skin texture
- Directly compare syndromes