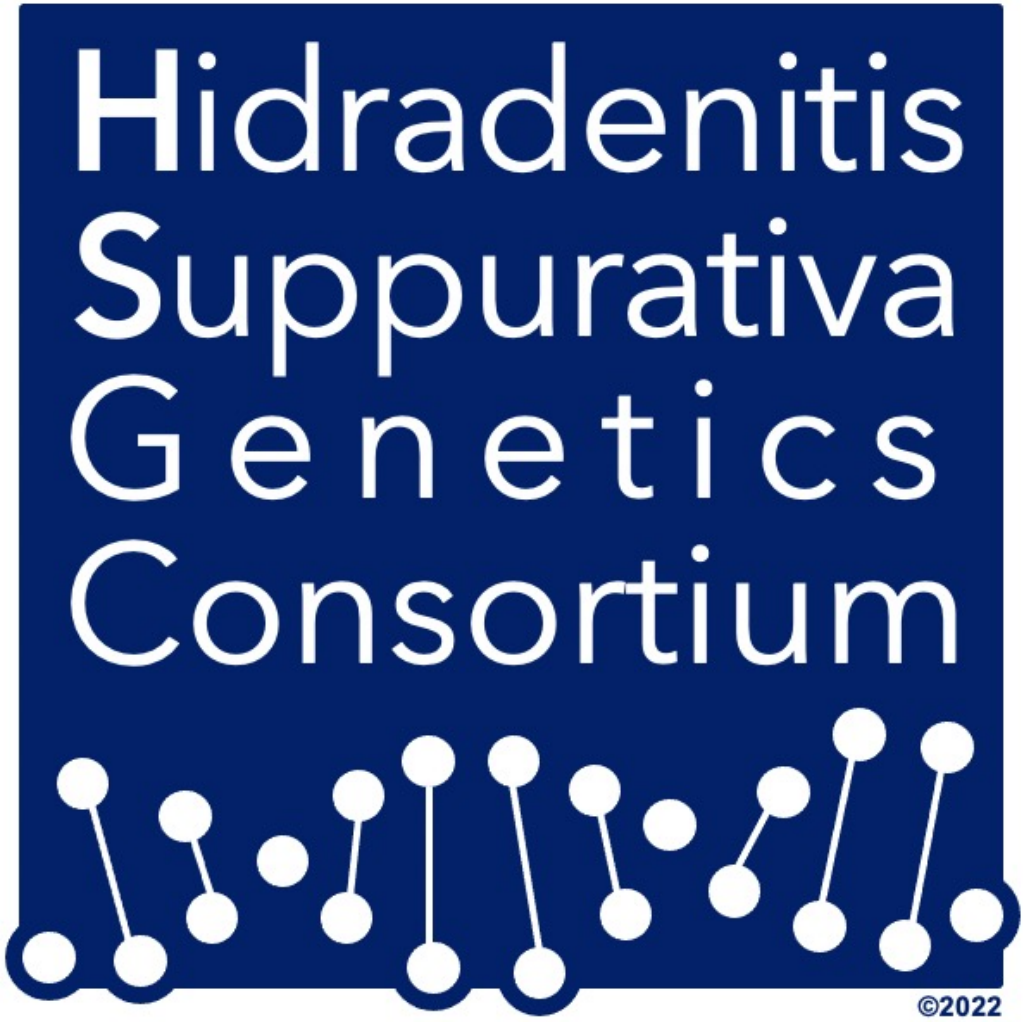

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Sister Society Scientific Meeting on HS
World Congress of Dermatology

Suntec Singapore Convention & Exhibition Centre

Monday, July 3, 2023

HS Genetics Consortium Mission

We use ***human genetic studies*** of mutations and polymorphisms *as a starting point* to:

- discover HS ***disease mechanisms***
- identify and prioritize ***drug targets***
- improve the accuracy and utility of an ***HS diagnosis***

Our goal is to use human genetic studies to ***improve the clinical management of HS***.

This objective requires ***global collaboration***.

Jabbour et al., BJD, 2021

Hidradenitis Suppurativa Genetics Consortium

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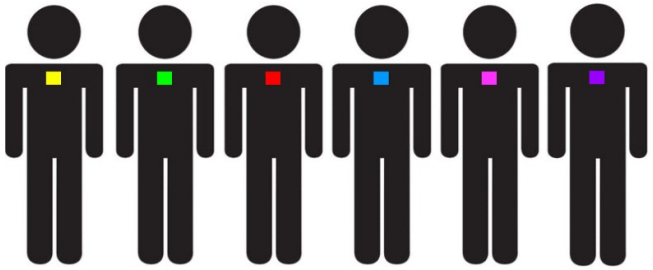
Jabbour et al., BJD, 2021

Hidradenitis Suppurativa Genetics Consortium

HS Genetics Consortium Mission

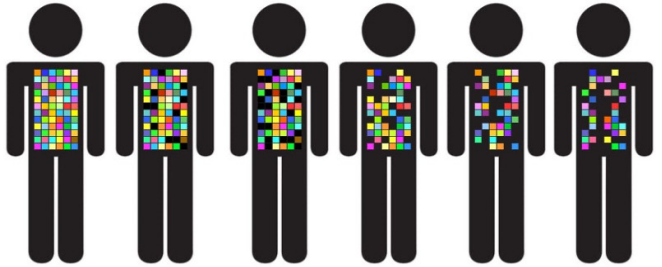
mutations



rare genetic variants

strong correlations with disease

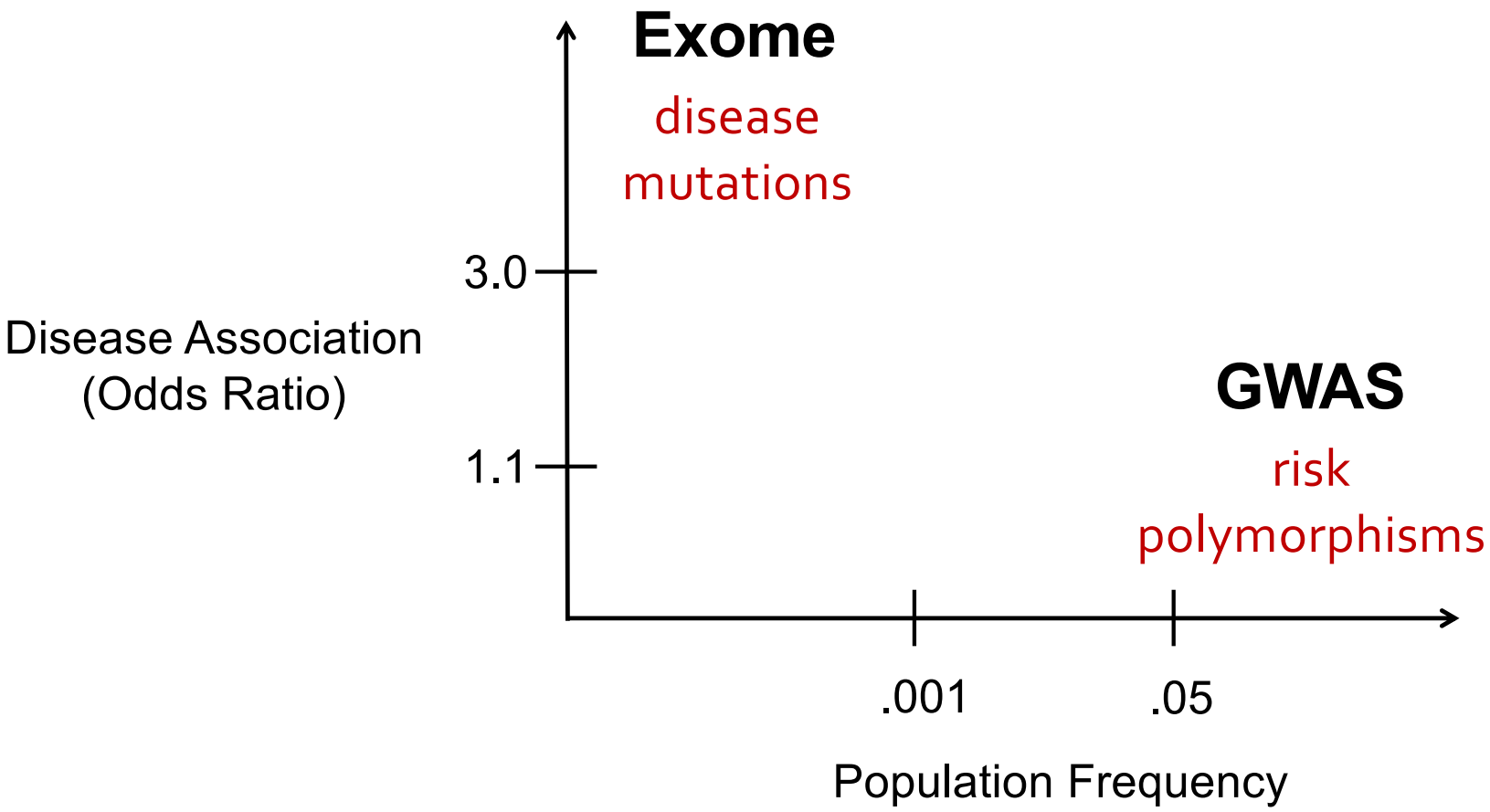
polymorphisms



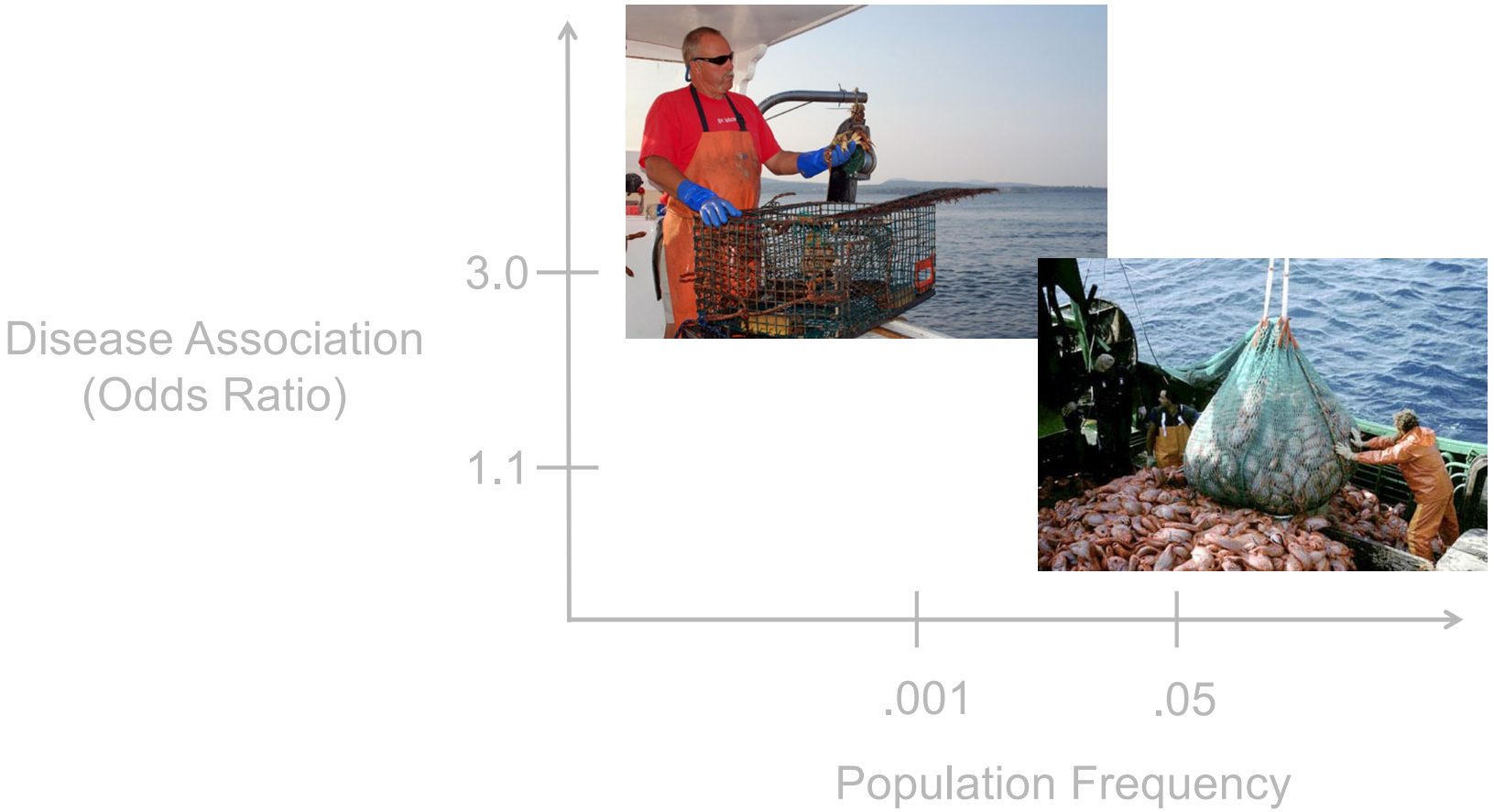
common genetic variants

weak correlations with disease

Hidradenitis Suppurativa Genetics Consortium

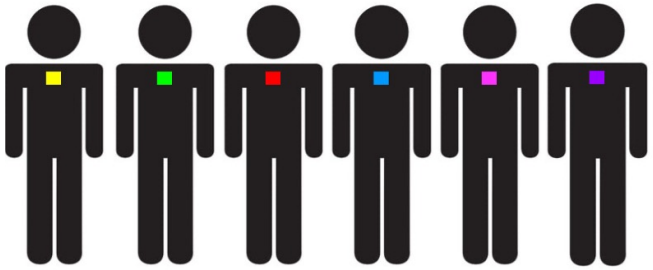

Exome
disease
mutations
3.0
Disease Association
(Odds Ratio)
1.1
GWAS
risk
polymorphisms
.001
.05
Population Frequency

Genetic Architecture and Method



HS Genetics Consortium Mission

mutations



rare genetic variants

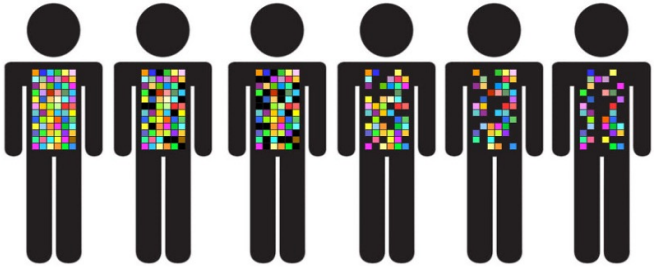
strong correlations with disease

exome sequencing studies

single-gene causes of disease

principle parameter: **phenotype**

polymorphisms



common genetic variants

weak correlations with disease

genome-wide association studies

polygenic risk

principle parameter: **sample size**

Hidradenitis Suppurativa Genetics Consortium

HS Genetics Consortium GWAS

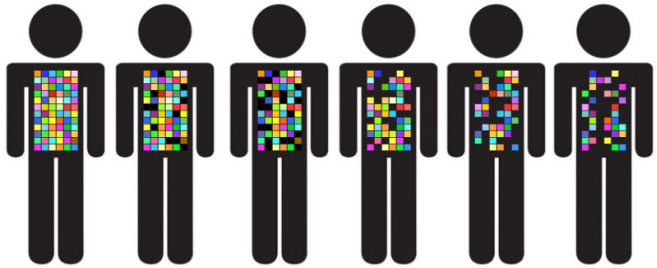
Collaborations are fast, easy, flexible.

Standardized protocols

Accept data or samples for inclusion:

- GWAS summary statistics
- genotype data
- samples

polymorphisms



common genetic variants

weak correlations with disease

genome-wide association studies

polygenic risk

principle parameter: **sample size**

e.g., height GWAS:
5.4 Million people, 12,000 variants

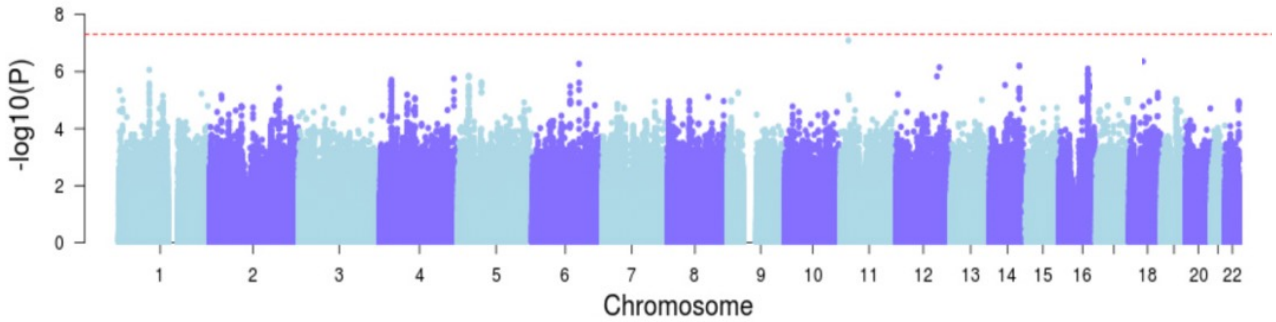
Hidradenitis Suppurativa Genetics Consortium

EHSF 2020
5-7 February 2020

Genome-wide association study of hidradenitis suppurativa in a multiethnic cohort

Atlas Khan, M. Geoffrey Hayes, John Connolly, Frank Mentch, Patrick Sleiman, Hakon Hakonarson, Joshua Denny, Chunhua Wang, George Hripcsak, Krzysztof Kiryluk, **Lynn Petukhova** (USA)

Cohorts	Cases	**Controls**	**Loci**
1	593	86,084	0



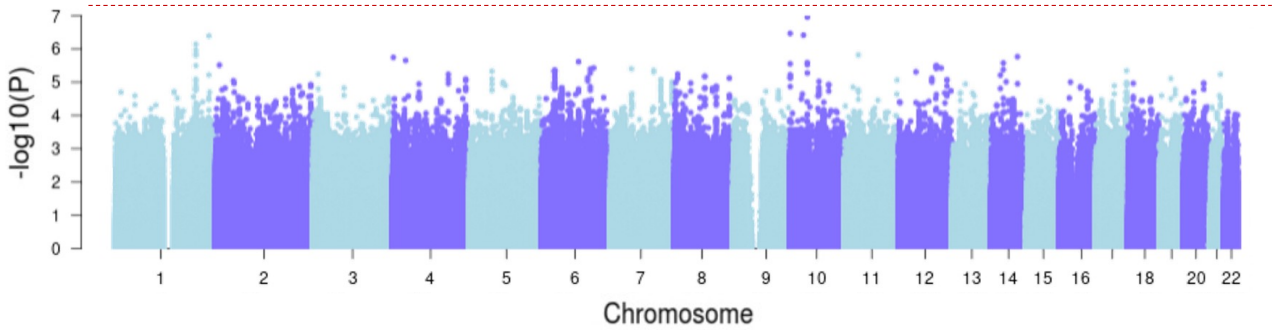
HS Genetics Consortium GWAS results

12th EHSF Conference | Florence | February 8-10 2023

The Polygenic Architecture of HS revealed by a first meta-analysis GWAS

Atlas Khan, Errol P. Prens, Lam Tsoi, Johann E. Gudjonsson, Theodore G. Drivas, Marylyn D. Ritchie, Amir Hossein Sadian, Hákon Hákonarson, Nick Dand, Jonathan Barker, Michael Simpson, Jake Saklatvala, Brian Kirby, The Hidradenitis Suppurativa Genetics Consortium, Kelsey R. van Straalen*, Lynn Petukhova*

Cohorts	Cases	**Controls**	**Loci**
5	1,626	210,675	0

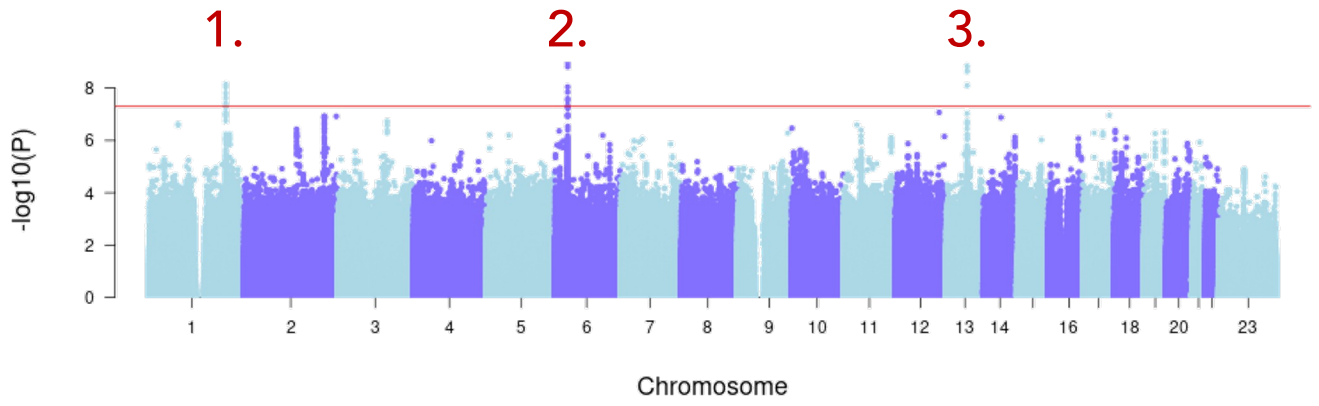


unpublished

The Polygenic Architecture of HS

Atlas Khan, Errol P. Prens, Lee Wheless, Adriana M. Hung, Maris Teder-Laving, Carole Ober, Lam Tsoi, Johann E. Gudjonsson, Theodore G. Drivas, Marylyn D. Ritchie, Amir Hossein Sadian, Hákon Hákonarson, Nick Dand, Jonathan Barker, Michael Simpson, Jake Saklatvala, Brian Kirby, The Hidradenitis Suppurativa Genetics Consortium, Kelsey R. van Straalen, Lynn Petukhova

Cohorts	Cases	Controls	Loci
7	4,308	987,206	3



HS Genetics Consortium GWAS Future Directions

More cohorts, more samples, more collaborators.

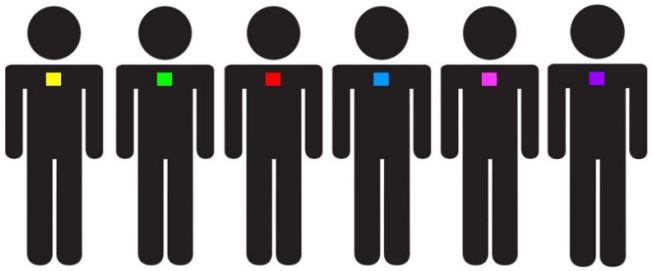
Cohorts	Cases	**Controls**	**Loci**
10	6,000	1,200,000	?

Columbia University | Erasmus University | Vanderbilt University | University of Michigan | University of Pennsylvania | Children's Hospital of Philadelphia | Montefiore Hospital | NYU Langone | University of Chicago | Cardiff University | King's College London | University College Dublin | University Medical Center Groningen | Bonn University | Charité – Berlin University of Medicine

Hidradenitis Suppurativa Genetics Consortium

HS Genetics Consortium Mission

mutations



rare genetic variants

strong correlations with disease

exome sequencing studies

single-gene causes of disease

principle parameter: **phenotype**

Collaborations are more involved

We work with deidentified data or samples

Validations are iterative

- Experimental validations
- Clinical validations

Analytic Strategies

- Diagnostic Analysis unpublished

  Resolving Etiological Heterogeneity

- Exome-wide Burden Testing

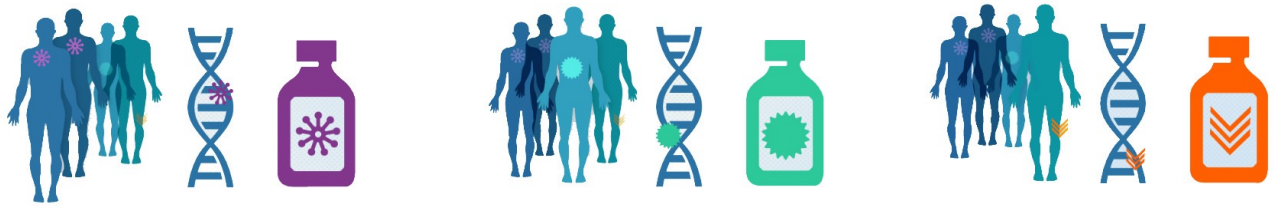
Etiological Heterogeneity Attenuates Power In Clinical Trials

People who share a diagnosis can have different biological causes of disease.

Figure adapted from NCI Precision Medicine Tutorial

Etiological Heterogeneity Creates Inefficiency in Healthcare

Disease subtypes can have clinical implications for patients and family members.



PARP inhibitors

Figure adapted from NCI Precision Medicine Tutorial

Analytic Strategies

- Diagnostic Analysis unpublished
  Resolving Etiological Heterogeneity
- Exome-wide Burden Testing

Analytic Strategies

- Diagnostic Analysis unpublished

  Resolving Etiological Heterogeneity

HS Genetics Consortium Exome Studies

Cases

Hidradenitis Suppurativa Center

Montefiore | EINSTEIN
Albert Einstein College of Medicine

Dr. Steven Cohen

- +1,000 patients, ~700 receive on-going care and +500 have been consented for research.
- We sequenced 200 participants.
- Race:
  - 26.9% Black/African-American
  - 8.2% White
  - 1.7% Asian
  - 31.0% Other
  - 28.6% Declined/Unavailable
- Ethnicity:
  - 24.5% Spanish/Hispanic/Latino
  - 39.8% Not Spanish/Hispanic/Latino
  - 35.7% Declined/unavailable

Controls

COLUMBIA | IGM Institute for Genomic Medicine

Dr. David Goldstein

Over 40,000 exome sequences available as controls:

5,000 African Americans
5,100 Hispanics

Data generated with the same experimental and analytic pipelines as HS cases.

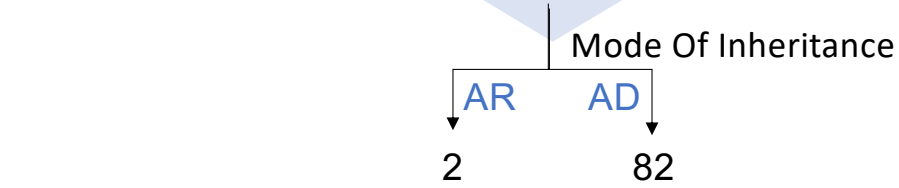
Used in +200 exome studies:

Groopman et al., NEJM, 2019
Zoghbi et al. PNAS, 2021
Erjavec et al., Nat. Comm., 2022
Kosmicki et al., AJHG, 2021
Marcogliese et al., AJHG, 2018
Halvorsen, et al., Nat. Neuro., 2021
Dobbs et al., NEJM, 2015
Cirulli et al., Science, 2015

Additional publications:
https://www.igm.columbia.edu/gene-list

Results of Diagnostic Analysis and Burden Testing among Inborn Errors of Immunity

Variant is:	Variant Count	Gene Count
in Mendelian gene with f_{max}<.001	977	302
and not benign in ClinVar	955	301
and matches known MOI	296	84



Can we use knowledge about the ***molecular functions*** of these 84 genes to understand ***clinically relevant relationships***?

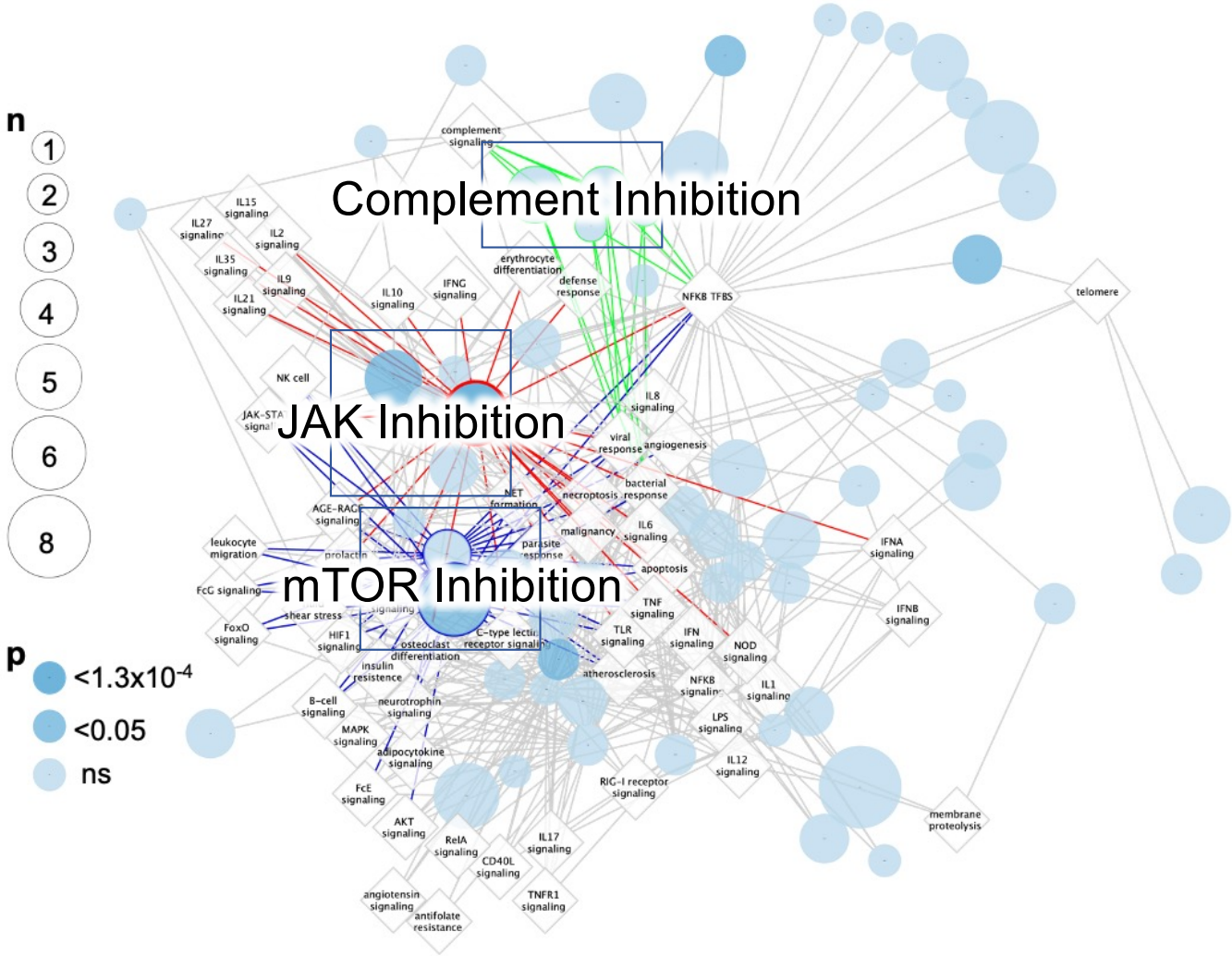
Diagnostic Analysis reveals heterogeneity

unpublished

a set of participants with a mutation in the same **gene**

immune response **pathway**

pathway membership



Analytic Strategies

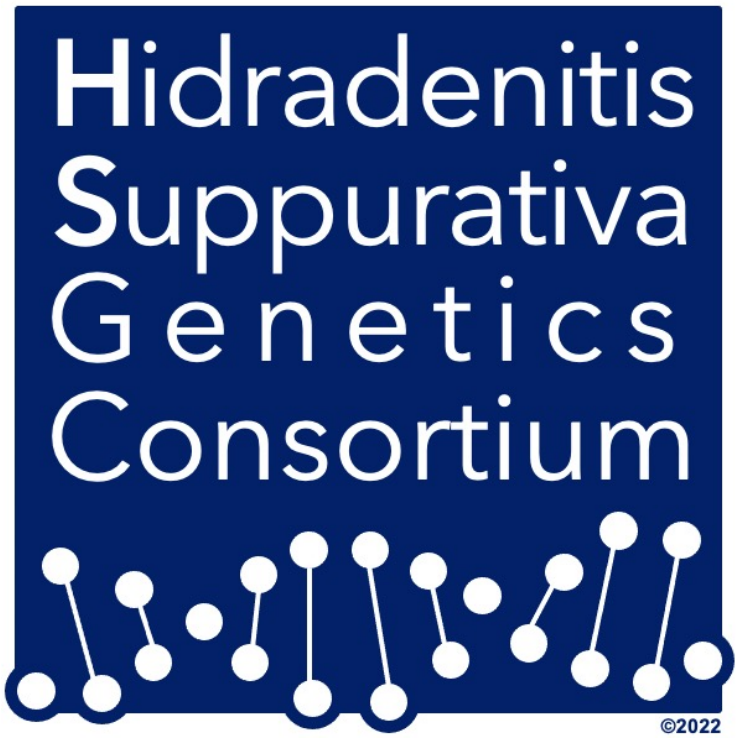
- Diagnostic Analysis unpublished

  Resolving Etiological Heterogeneity

- Exome-wide Burden Testing unpublished

  Animal model development is underway

Improving the clinical management of HS with human genetic studies.



R01AR080796 (PI: Petukhova)

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Kelsey van Straalen k.vanstraalen@erasmusmc.nl

www.hs-genetics.com

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Petukhova Lab
Annelise Colvin
Ghislaine Jumonville
Julia Wright

Columbia Collaborators
Atlas Khan
David Goldstein
Joshua Milner

Montefiore
Steven Cohen

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases NIAMS K01AR075111
Columbia | Precision Medicine emerge network Electronic Medical Records & Genomics NHGRI U01HG008680
Columbia | Vagelos College of Physicians and Surgeons
NIAMS R13AR SHSA Symposium on Hidradenitis Suppurativa Advances
NIH National Center for Advancing Translational Sciences NCATS KL2 TR001874
CTSA Clinical & Translational Science Awards Program NCATS UL1 TR001873
epiCURE NIAMS P30 AR069632
Columbia University Data Science Institute
DF Dermatology Foundation