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_____ *Jingqi Chen* _____

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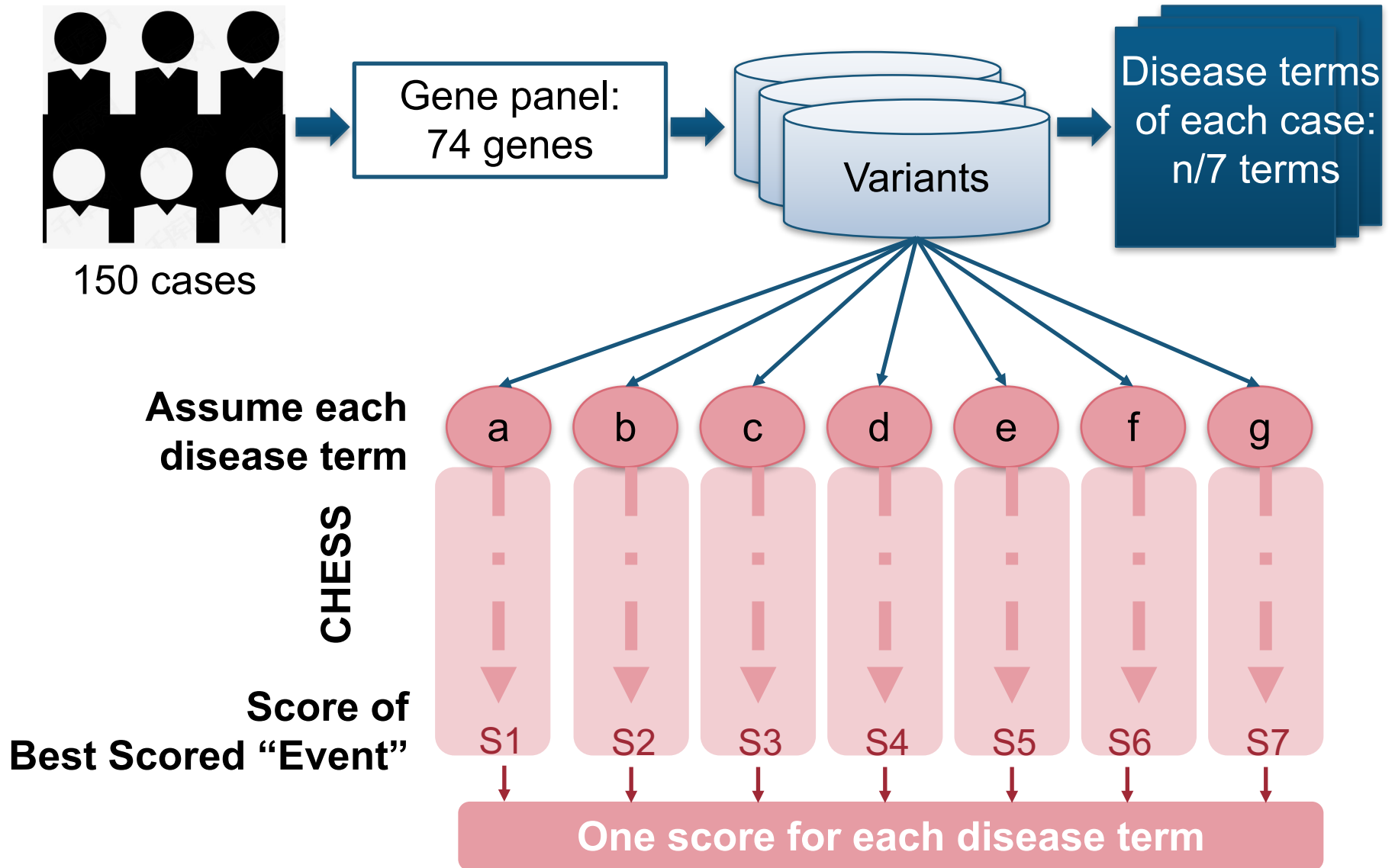


CAGI 5: IDP Challenge

Context and inHeritance Event based Systematic Scoring (CHESS) *for candidate variants in patients with genetic diseases*

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July 7th, 2018

Overview: Solution to the IDP challenge



Overview of CHESS

Input

Disease/
Phenotype
terms

All variants

1. **Variant quality**

2. **Predicted
Deleteriousness:**
a. Impact on transcripts
b. Pathogenic score

3. **Phenotype match**

4. **Modifiers:**
a. ClinVar annotation
b. MAF

Variant scoring

X

Inheritance Event

1. Homozygous

2. Hemizygous (for males)

3. Compound-heterozygous

4. Dominant heterozygous

Output



Continuous scores for

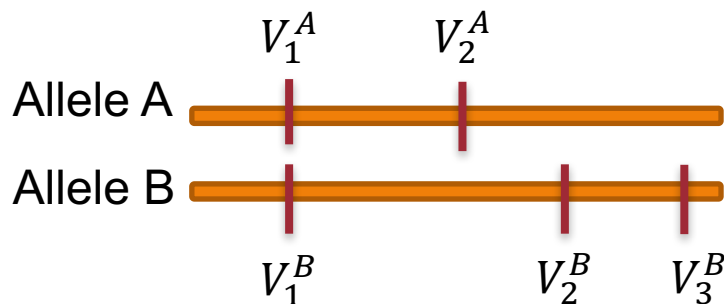
All
possible
inheritance
events

CHES: 1. variant scoring system

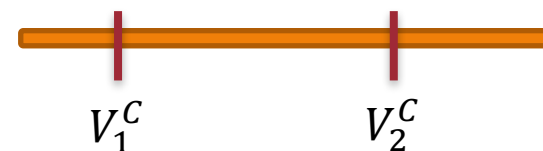
REDACTED

CHESS: 2. inheritance events

Autosomal, or female chrX



Male chrX



Homozygote

**Compound
Heterozygote**

**Dominant
Heterozygote
(especially de-novo)**

Hemizygote

V_1^A & V_1^B

$V_2^A + V_2^B$
 $V_2^A + V_3^B$

V_2^A
 V_2^B
 V_3^B

V_1^C
 V_2^C

Figure courtesy of Dr Yaqiong Wang

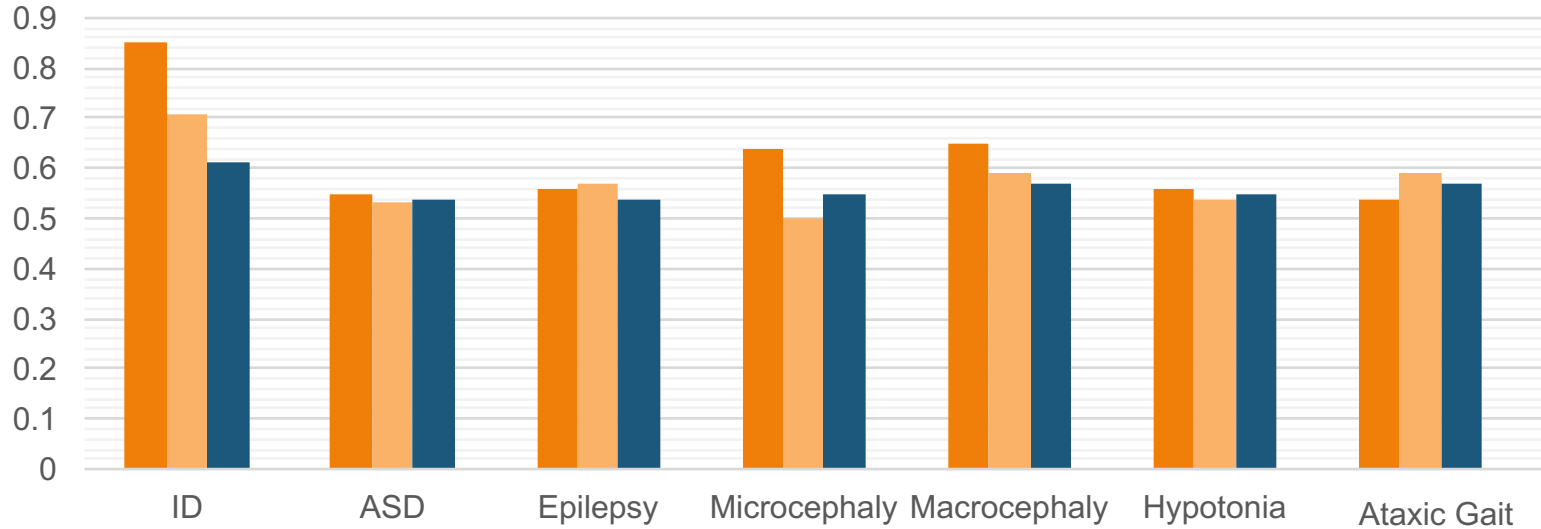
Special adjustments for *IDP challenge*

- IDP challenge data: gene-panel, singleton, not phased, gender unknown
- CHESSE adjustments

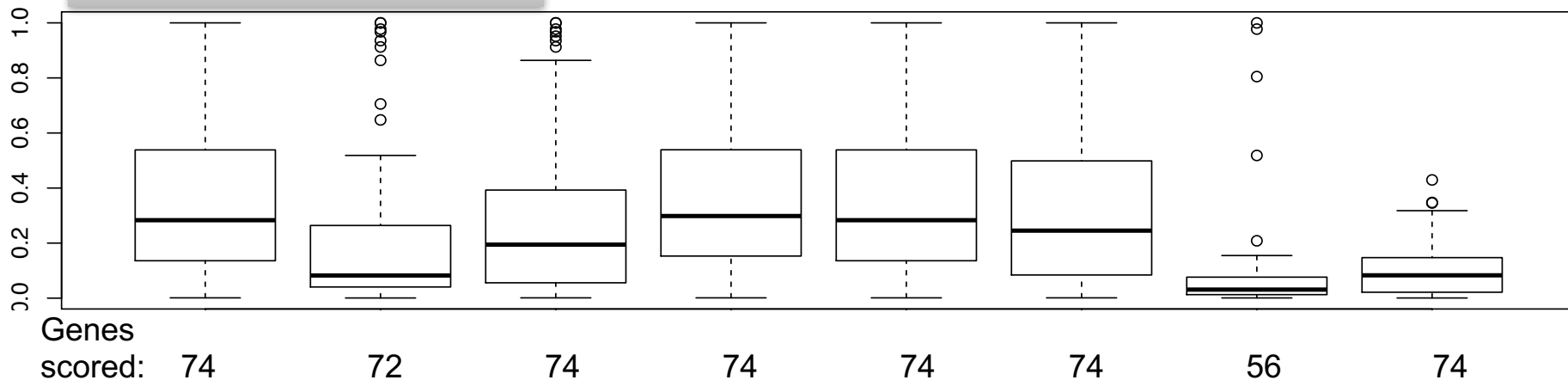
	Stringent	Medium stringent	Less stringent 
“Dominant heterozygote”	Low weight	Low weight	Low weight
“Compound heterozygote”	Low weight	Low weight	Normal weight
Excluded variants	called in >30% samples	called in >30% samples	called in >50% samples
Score of each disease	Top event score; exclude score<0.5	Top event score	Mean of top 2 event scores

AUC_{ROC}, for each disease term

best_submission scaled score random



Gene phenotype scores



How to improve the performance

- Input
 - More precise, detailed phenotype information
 - Gender/Family data
 - Gene panel -> exome?
- Scoring scheme
 - Single-gene → multi-gene, to account for “modifier” mutations
 - Noncoding variants as “modifiers”
- Logic: disease not independence of each other

Acknowledgements



Brenner Lab

Steven Brenner

Yaqiong Wang

Zhiqiang Hu

Andrew Sharo (*for naming
CHESS*)



Berkeley
UNIVERSITY OF CALIFORNIA



California Initiative to Advance
Precision Medicine



Jeffrey Modell
Foundation

CAGI organizers and participants