Unraveling Complex Connections between Genomic Variation and Disease Trait Manifestation

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ASHG Annual Meeting

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Functional & disease annotation of human genome

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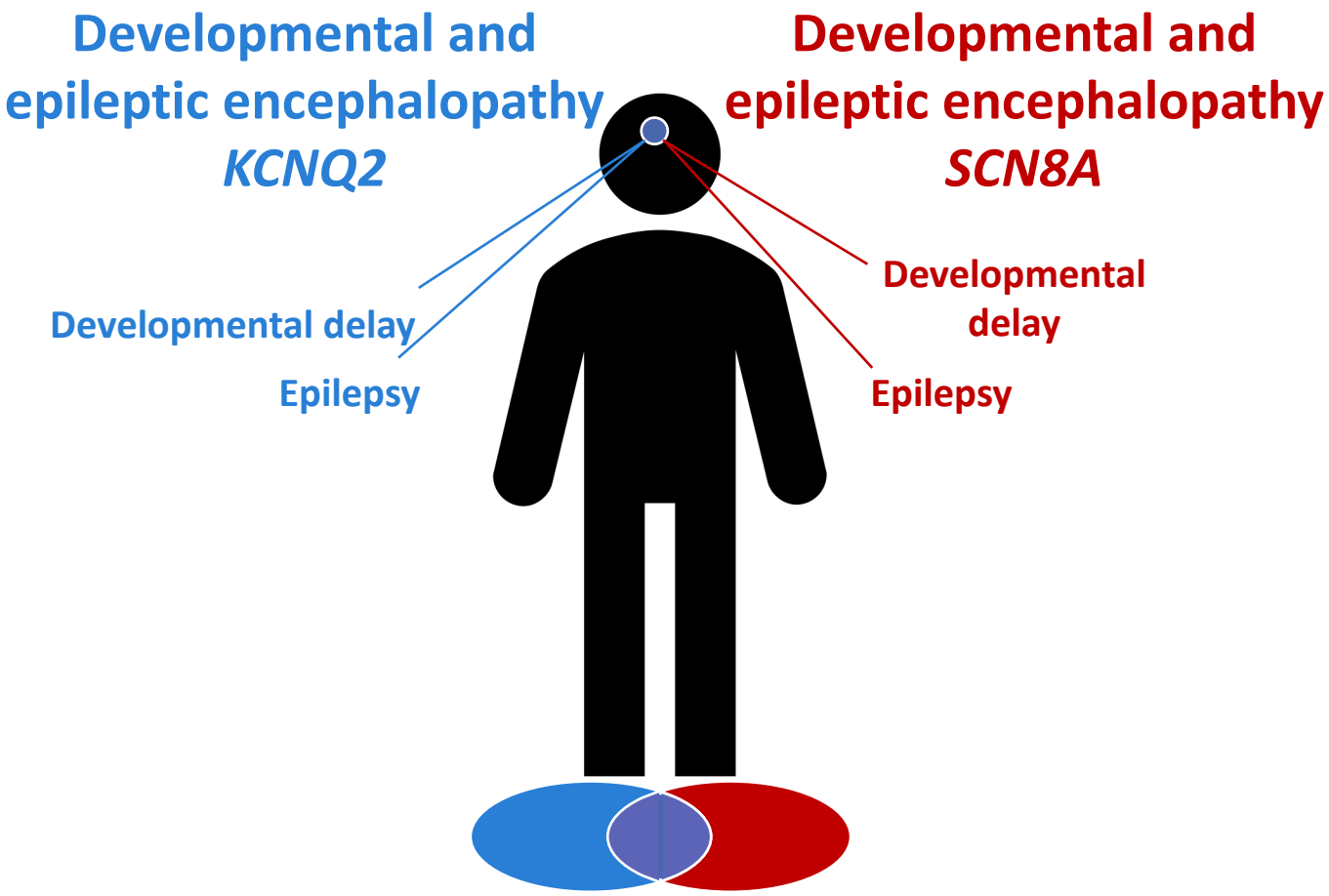
Genomics Research to Elucidate the Genetics of Rare disease

More work is needed to be done to understand:

- The biological functions – and disease relationships – of all 20,000 protein coding human genes
- The influence of different variant types on gene and protein function, and their ultimate impact on health
- The impact of combinations of pathogenic variants in more than one gene/locus

Dual molecular diagnoses

Two genes
Two disease traits



Blended phenotype, overlapping disease traits

Independent molecular diagnoses

- Variants in Gene A + Gene B
- Resulting in blended phenotypes

Accurate diagnosis is critical

- Informs surveillance and management
- Informs recurrence risk estimates for family
- Diagnostic odyssey may not end with first molecular diagnosis

Frequency of multiple molecular diagnoses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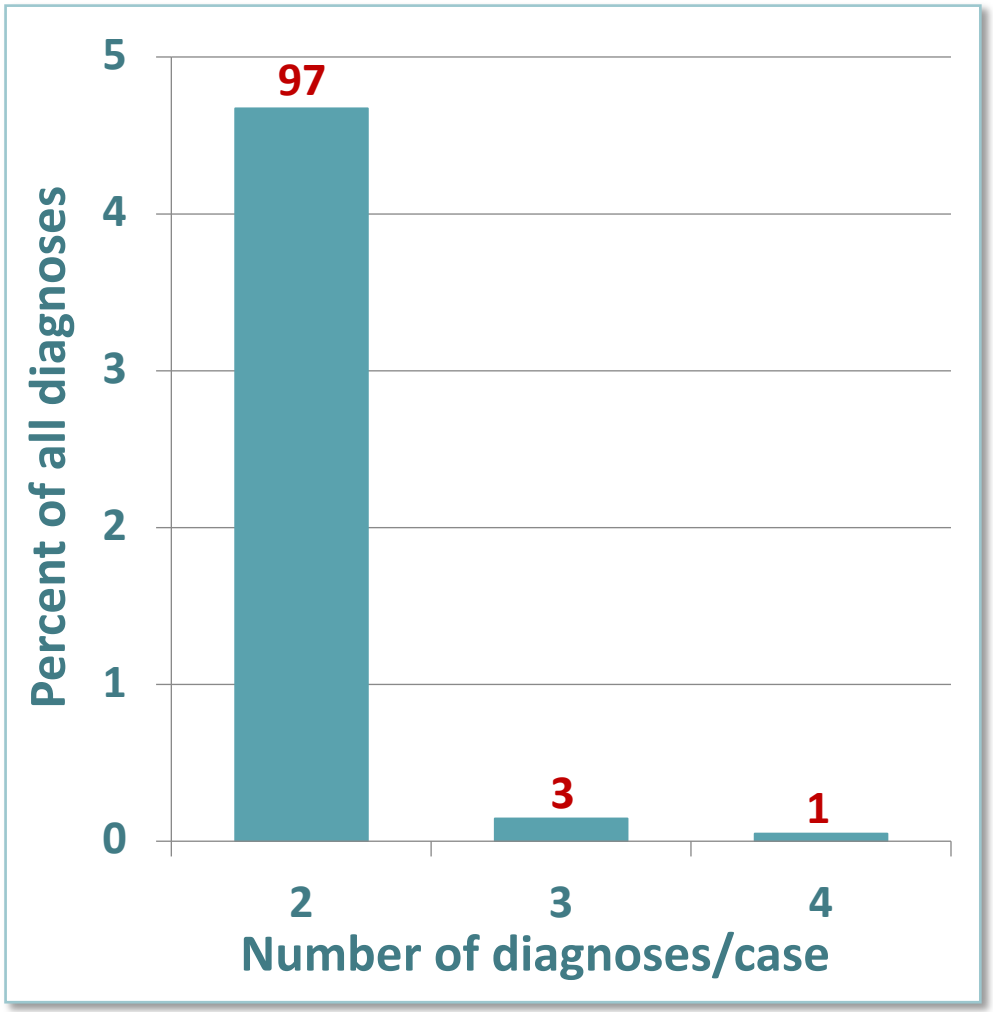
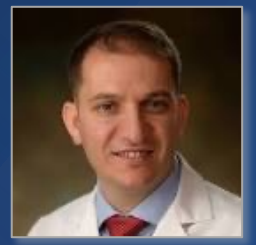
- Analysis of 7374 sequential diagnostic laboratory referrals for ES
- Molecular diagnosis in **28.2%** (2076/7374)
- Two or more diagnoses **related to phenotype** in **4.9%** (101/2076) of diagnosed cases



Posey JE, Harel T, *et al. N Engl J Med* (2017) *376:*21-31.

AOH-mediated recessive disease burden



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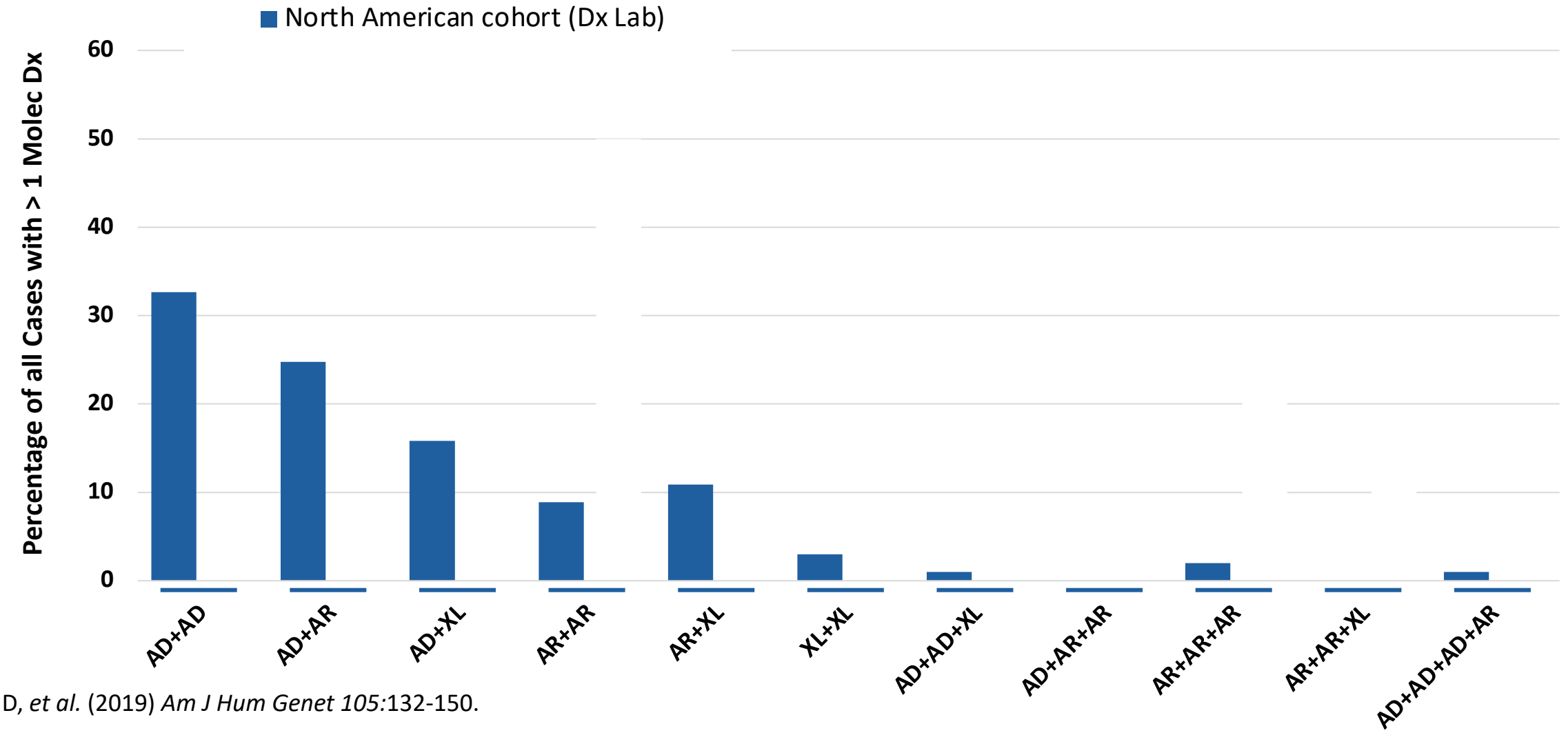

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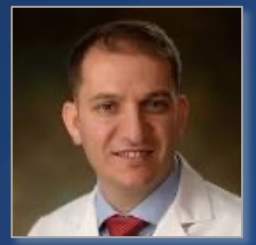

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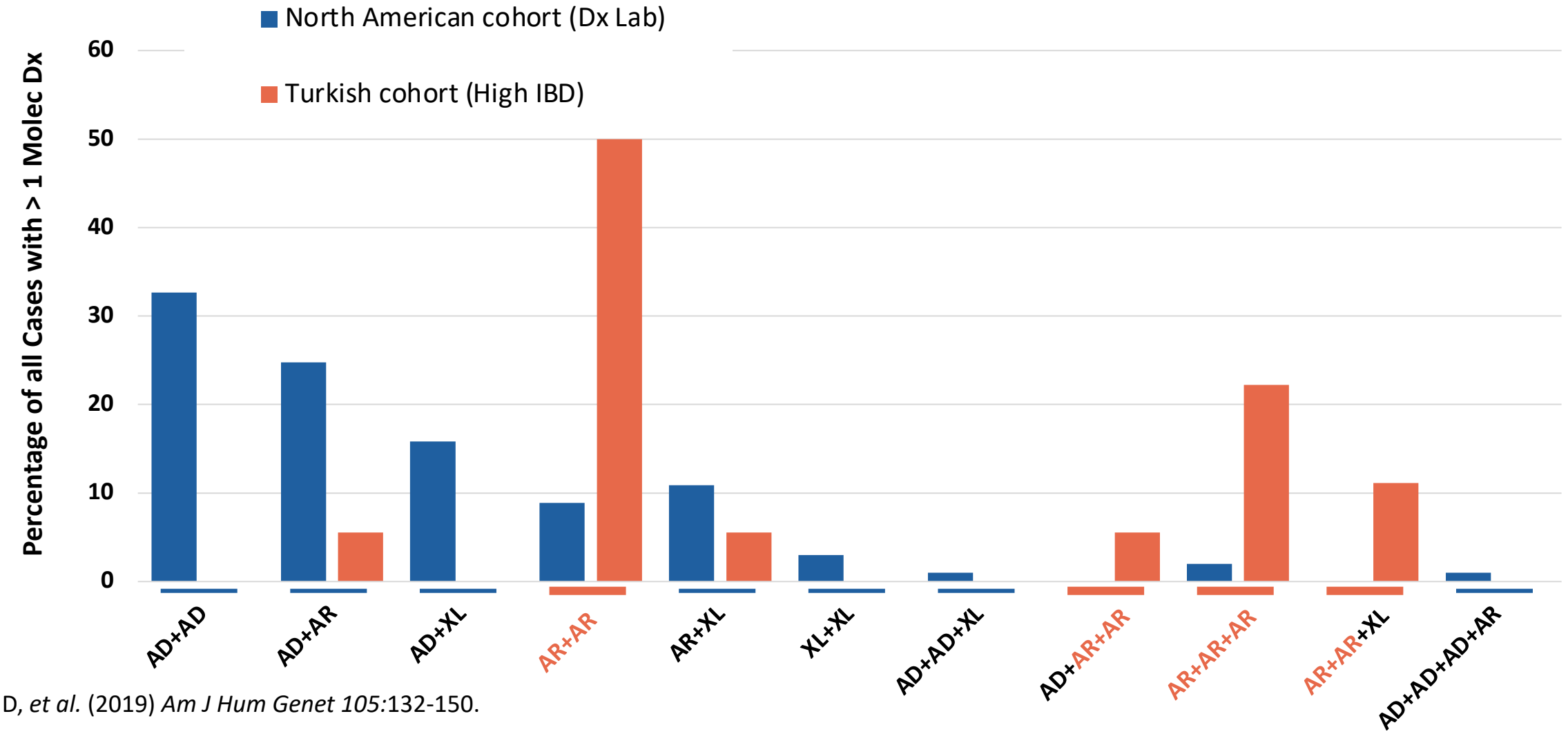

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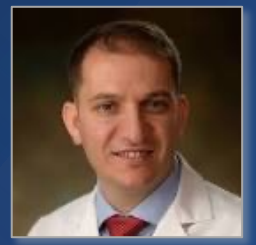

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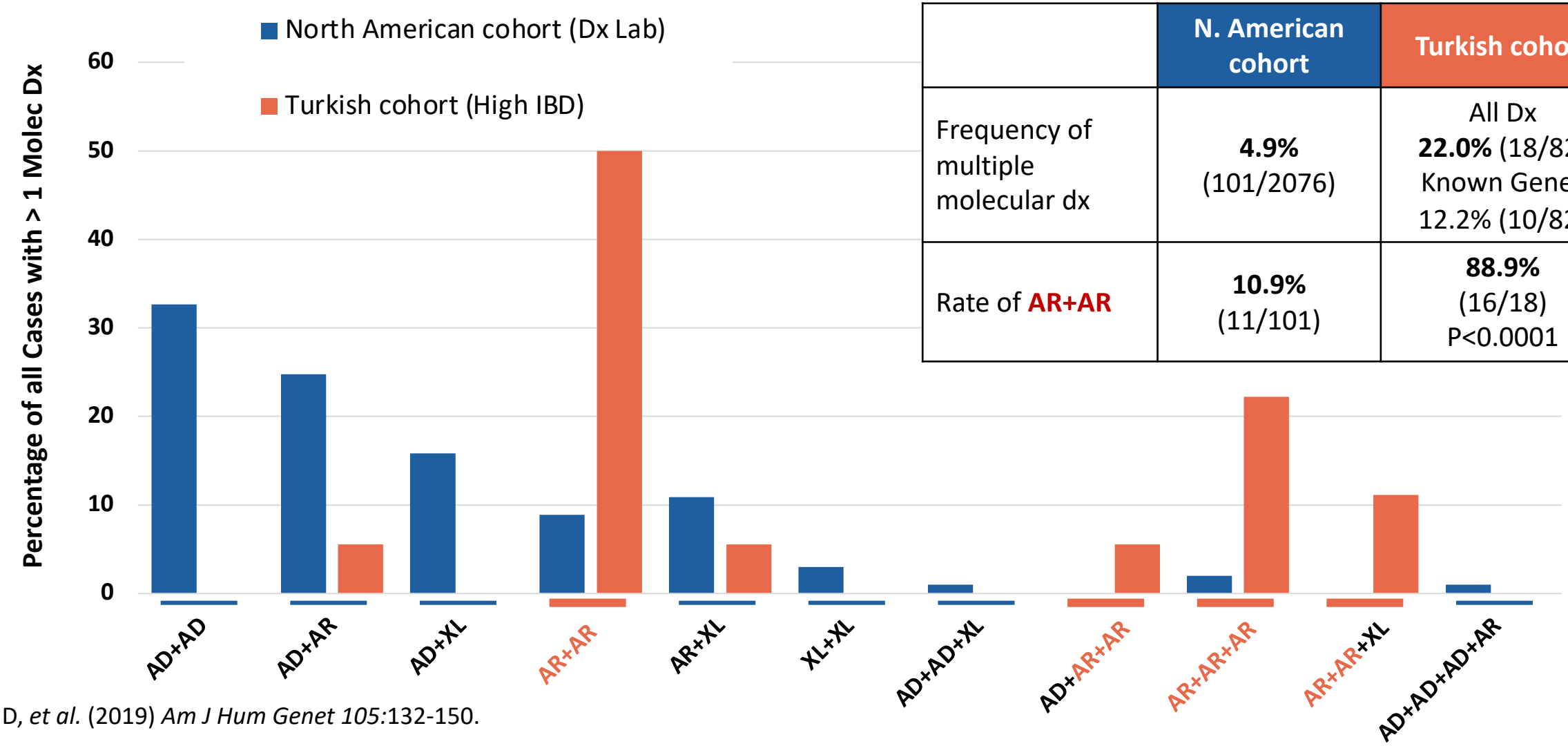

	N. American cohort	Turkish cohort
Frequency of multiple molecular dx	**4.9%** (101/2076)	All Dx **22.0%** (18/82) Known Genes 12.2% (10/82)
Rate of **AR+AR**	**10.9%** (11/101)	**88.9%** (16/18) P<0.0001

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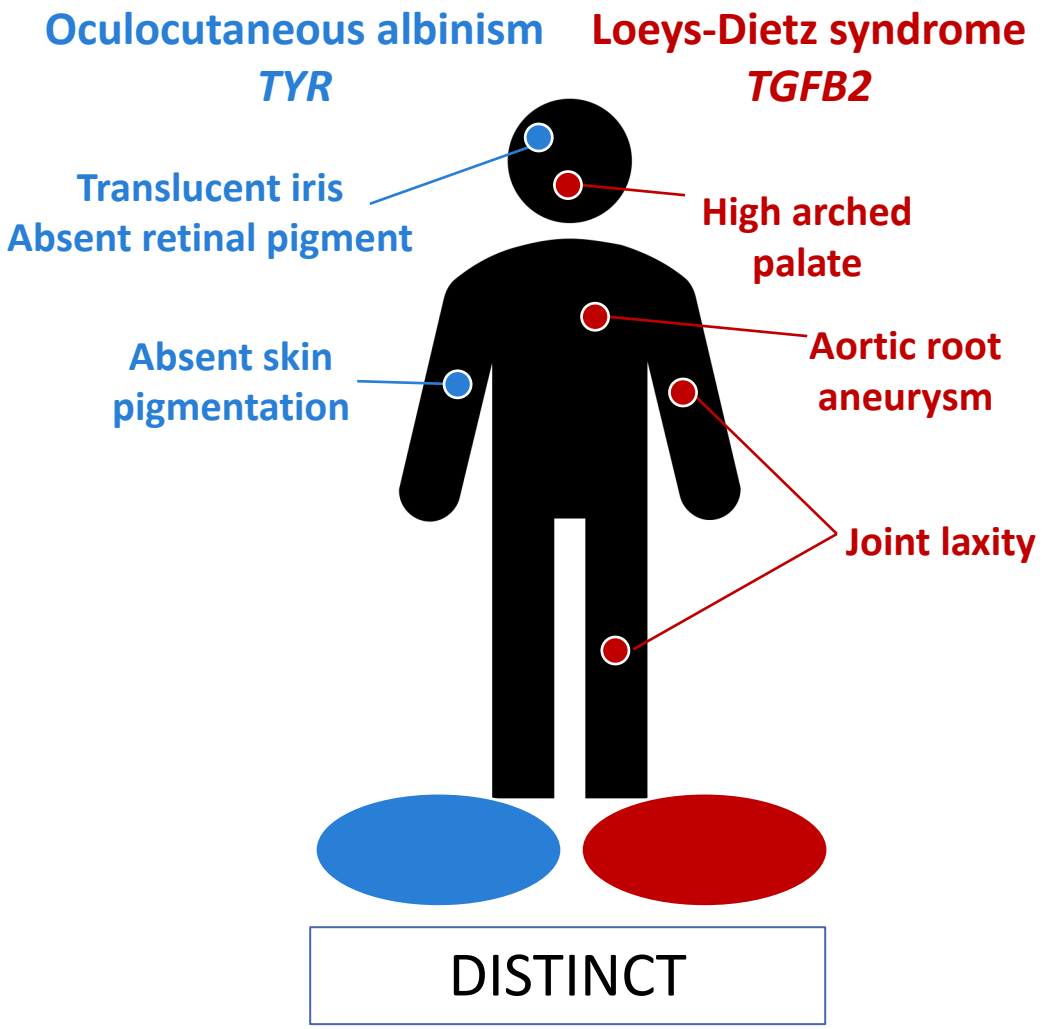
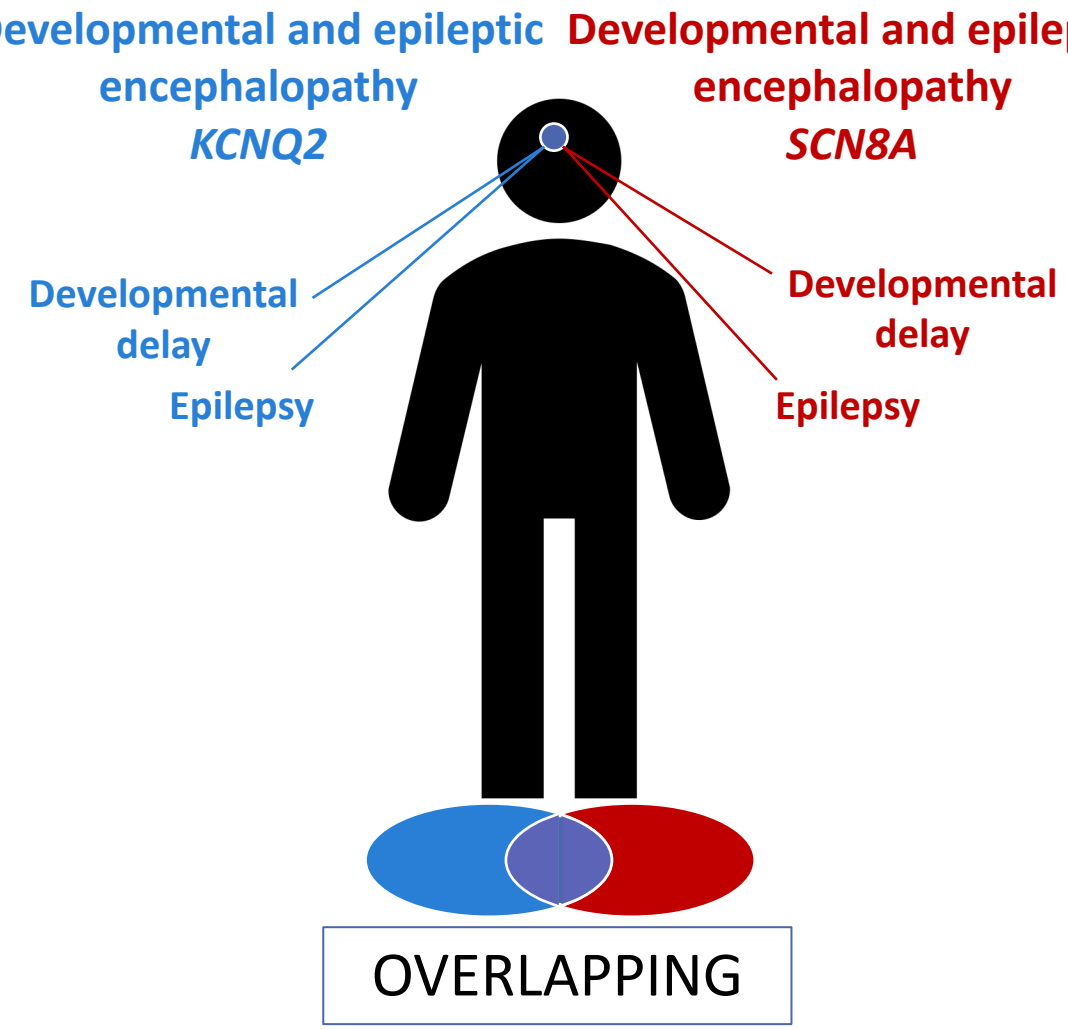
Dual molecular diagnoses

Distinct
Overlapping





Computational dissection of blended phenotypes

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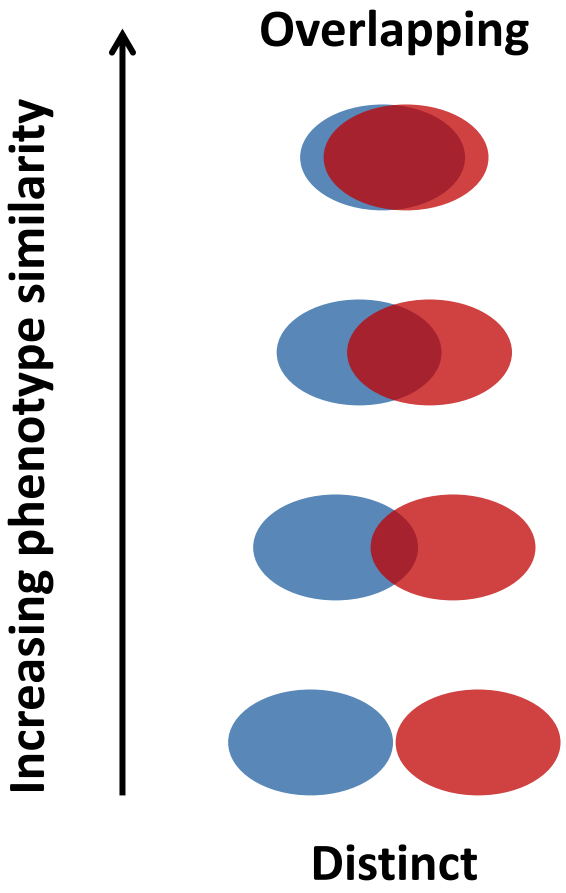
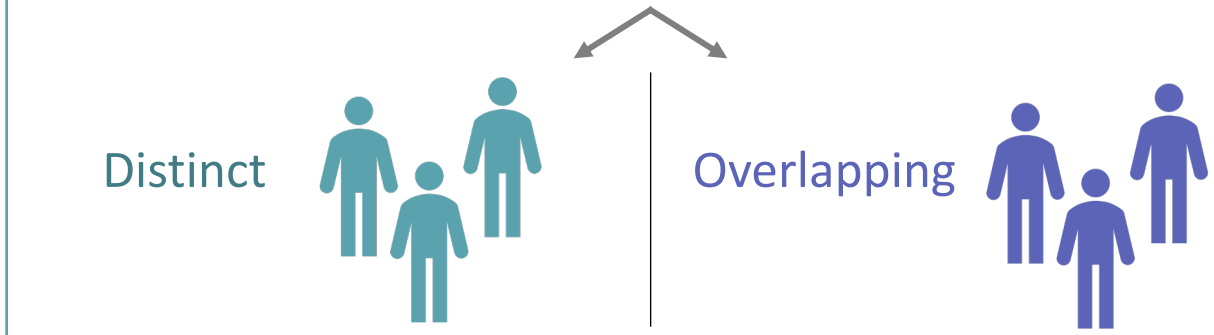


Independent assignment of blended phenotypes into 2 categories performed by 2 physician-scientists.



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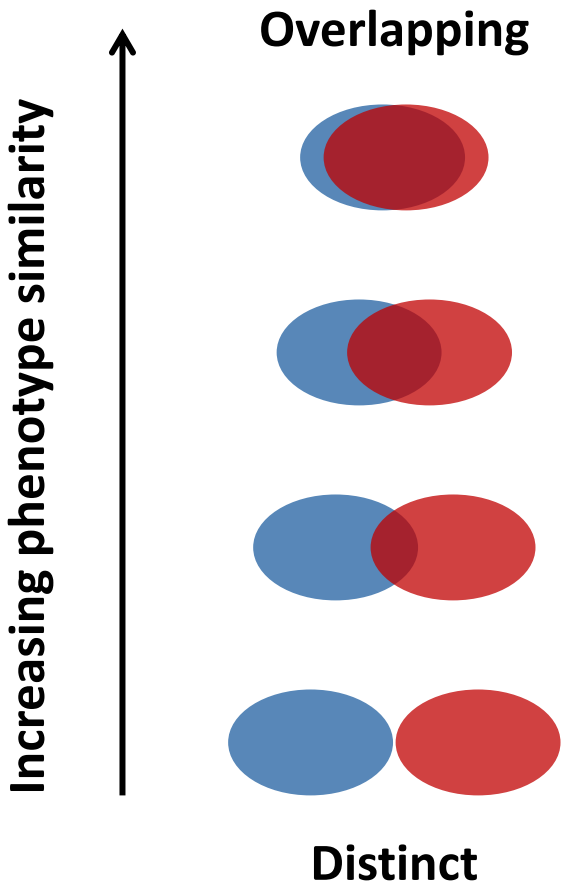

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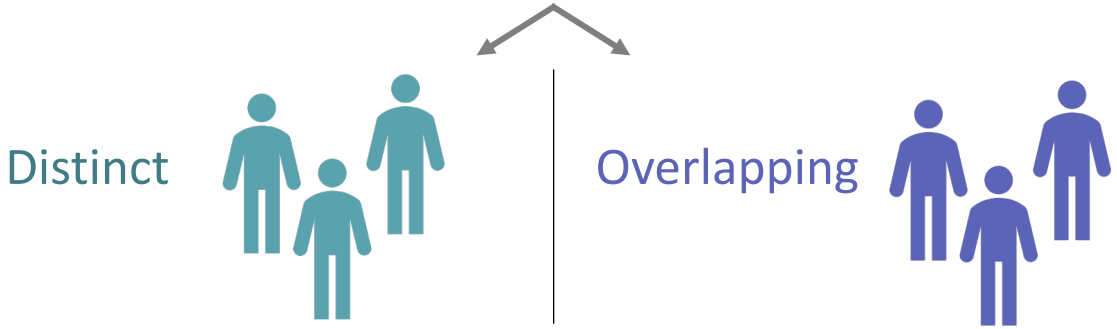
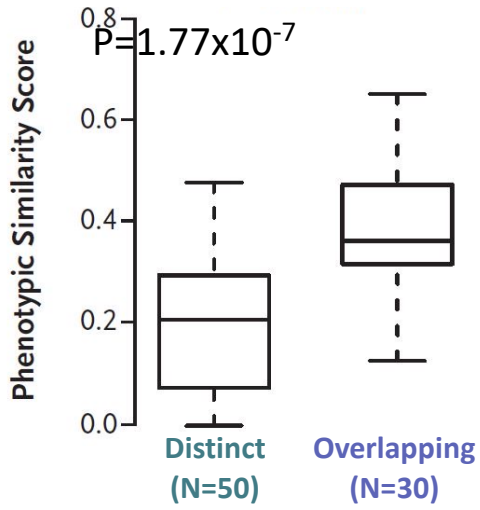


Computational modeling of 2 extreme classifications of blended phenotypes

- Human phenotype ontology (HPO) terms
- Phenotype similarity score



Computational clustering of patient phenotypes within a single disease trait

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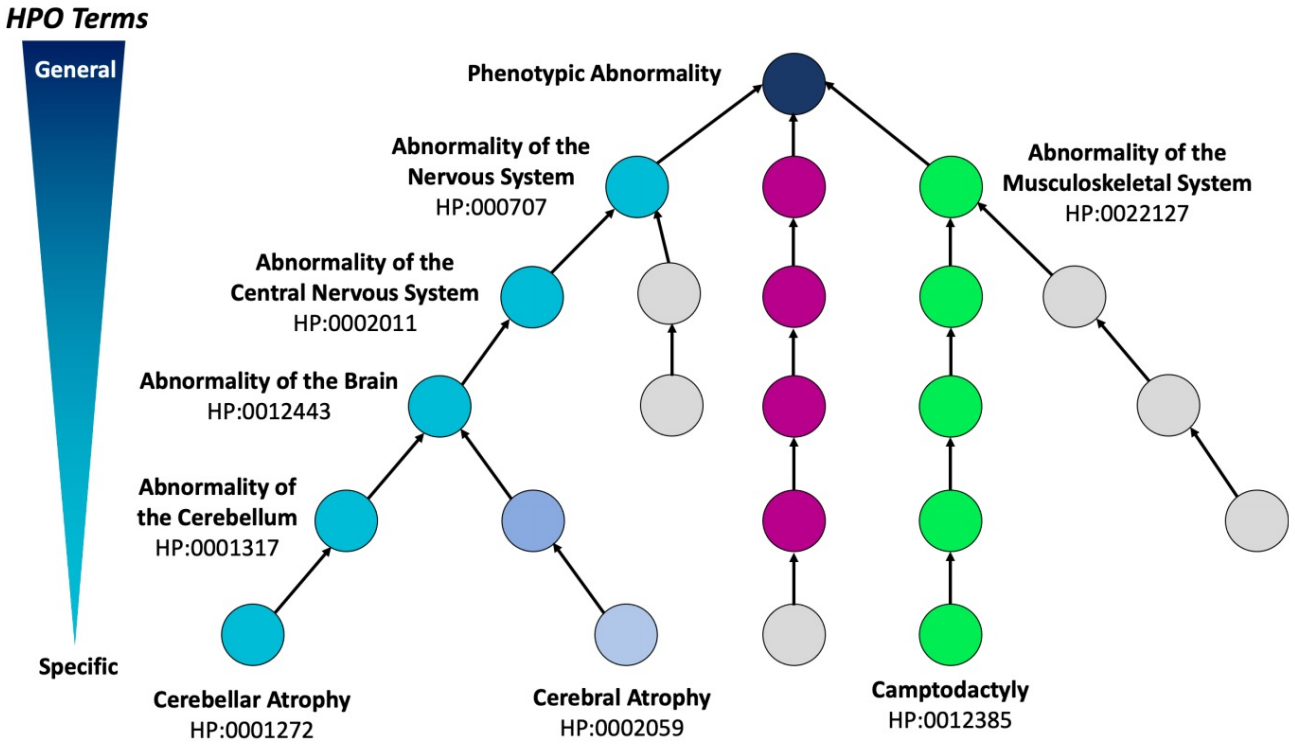
Can we take advantage of ontological structure of HPO to perform pairwise comparisons of patient phenotypes?



What can we learn if we apply this approach to a single, genetically heterogeneous condition?

Patient 1

Condition A

Patient 2

Condition A

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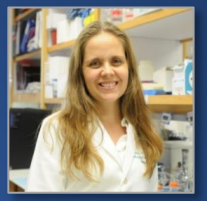
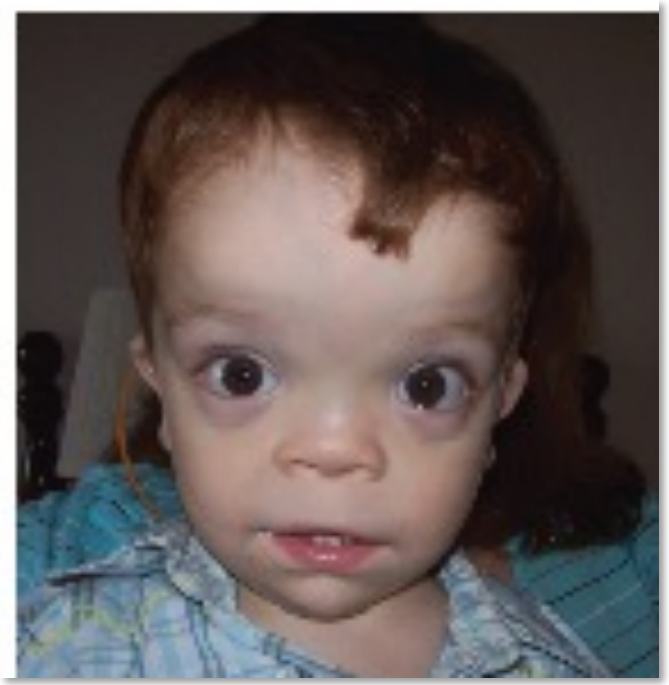
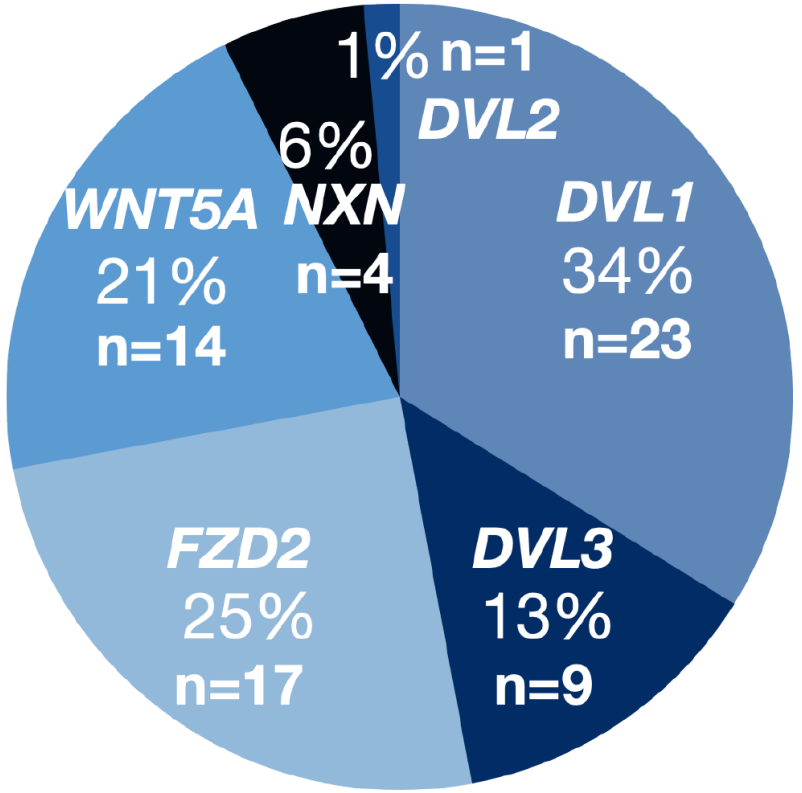


Robinow syndrome

Skeletal dysplasia with characteristic clinical findings



Genetic heterogeneity

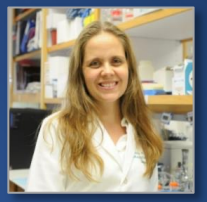


All subjects (n=68)

Zhang C, Jolly A, *et al. HGG Advances* (2021) *3:*100074

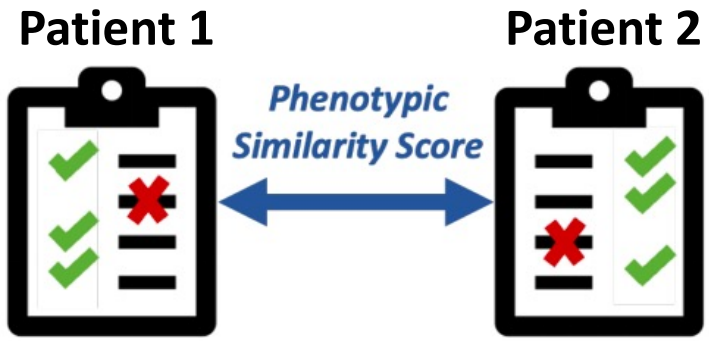
Computational clustering of patient phenotypes within a single disease trait

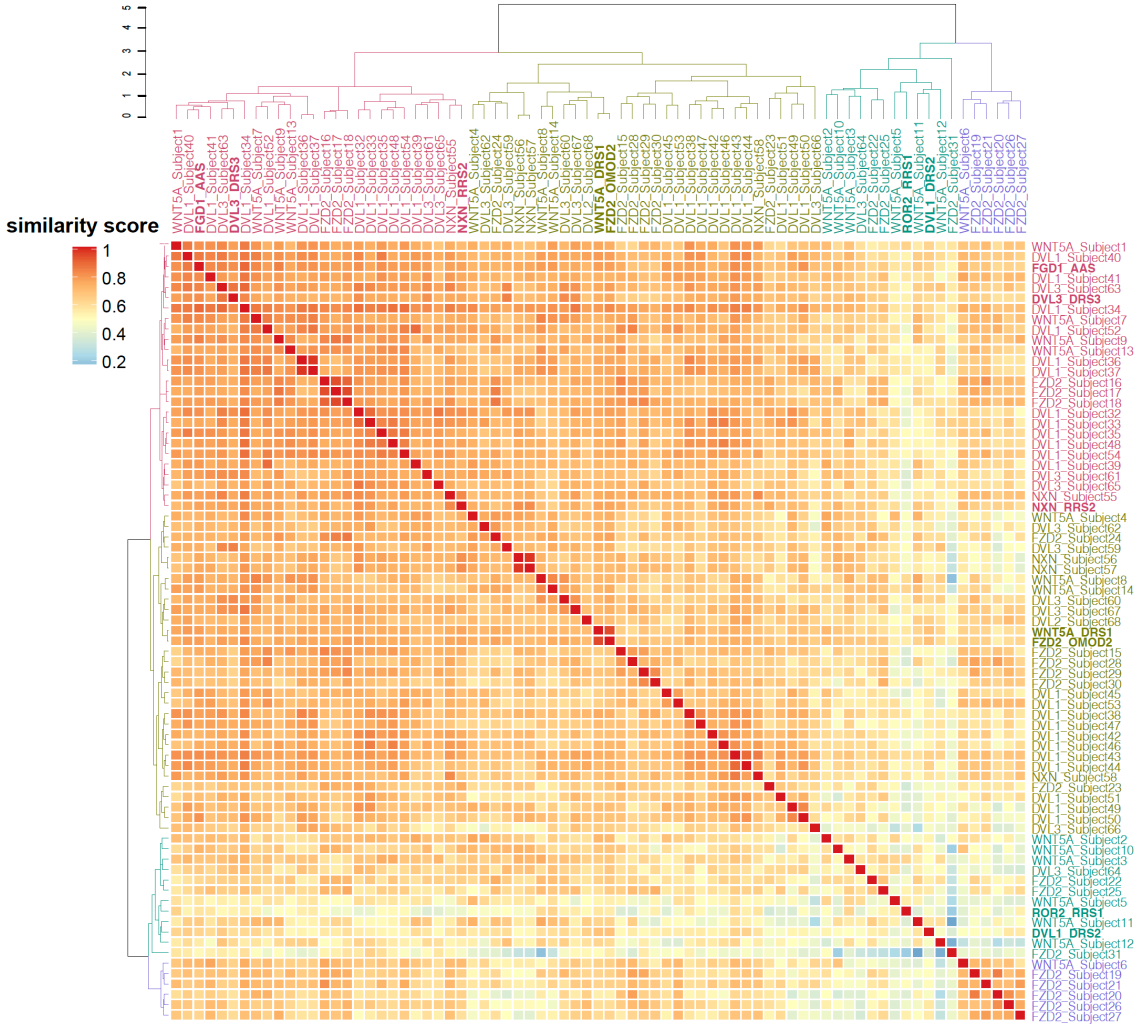




Robinow syndrome

- 68 subjects
- Pairwise comparison of phenotypes
- Despite genetic heterogeneity, cluster analysis by phenotype yielded gene-specific clusters





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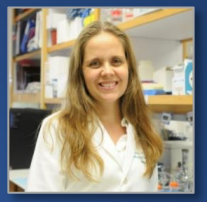

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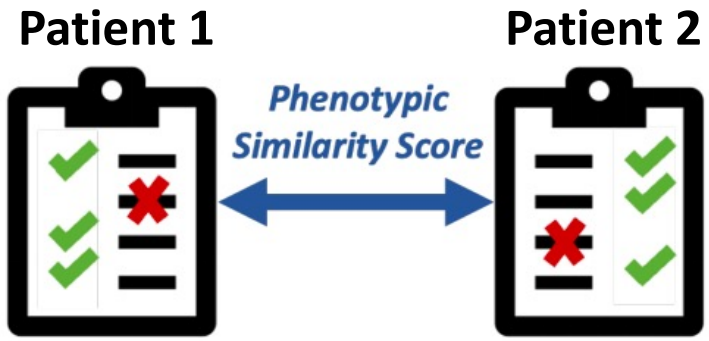

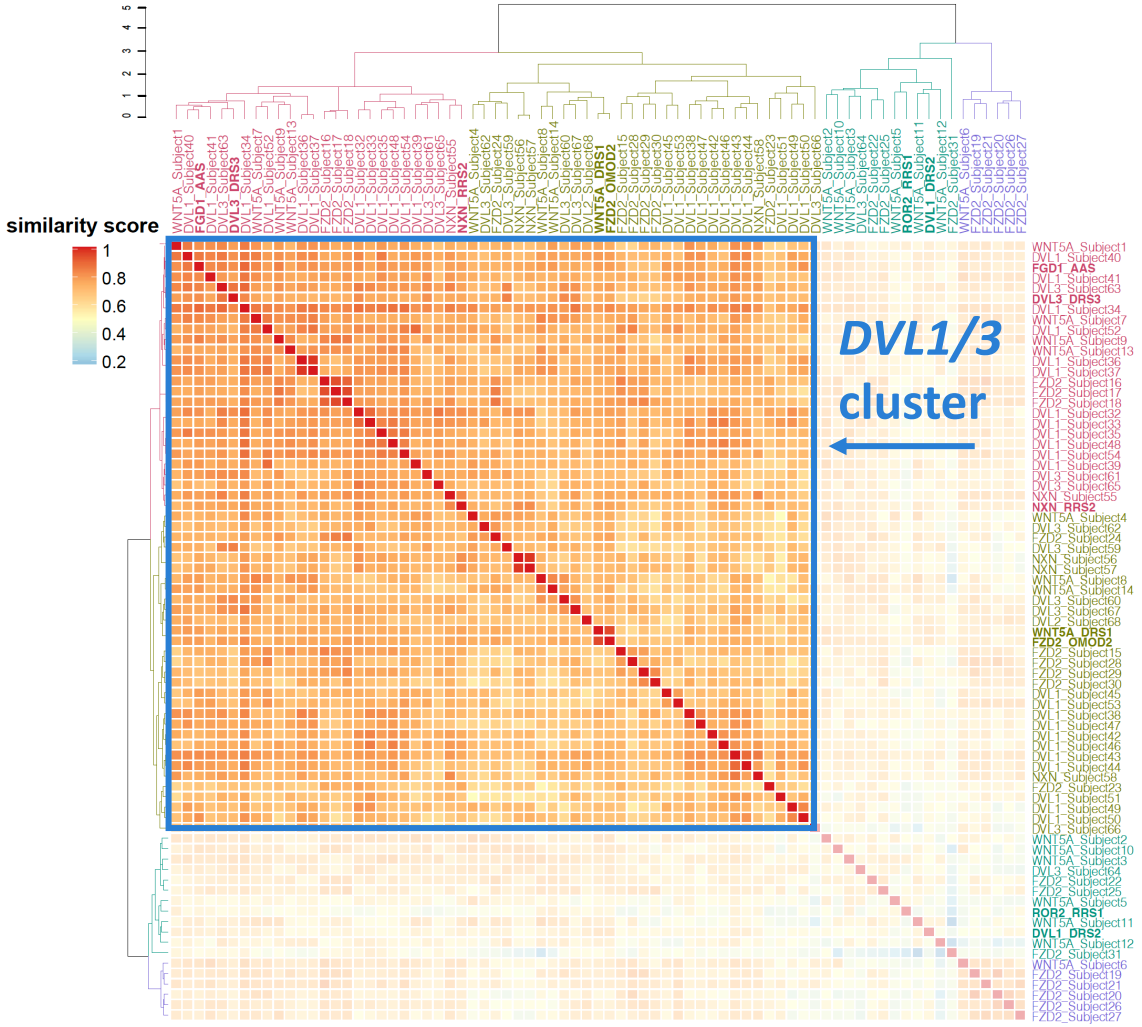

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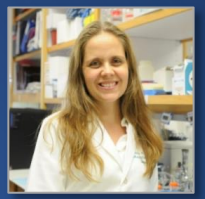

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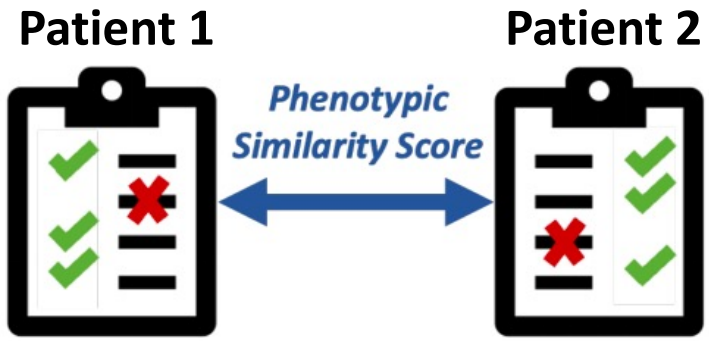

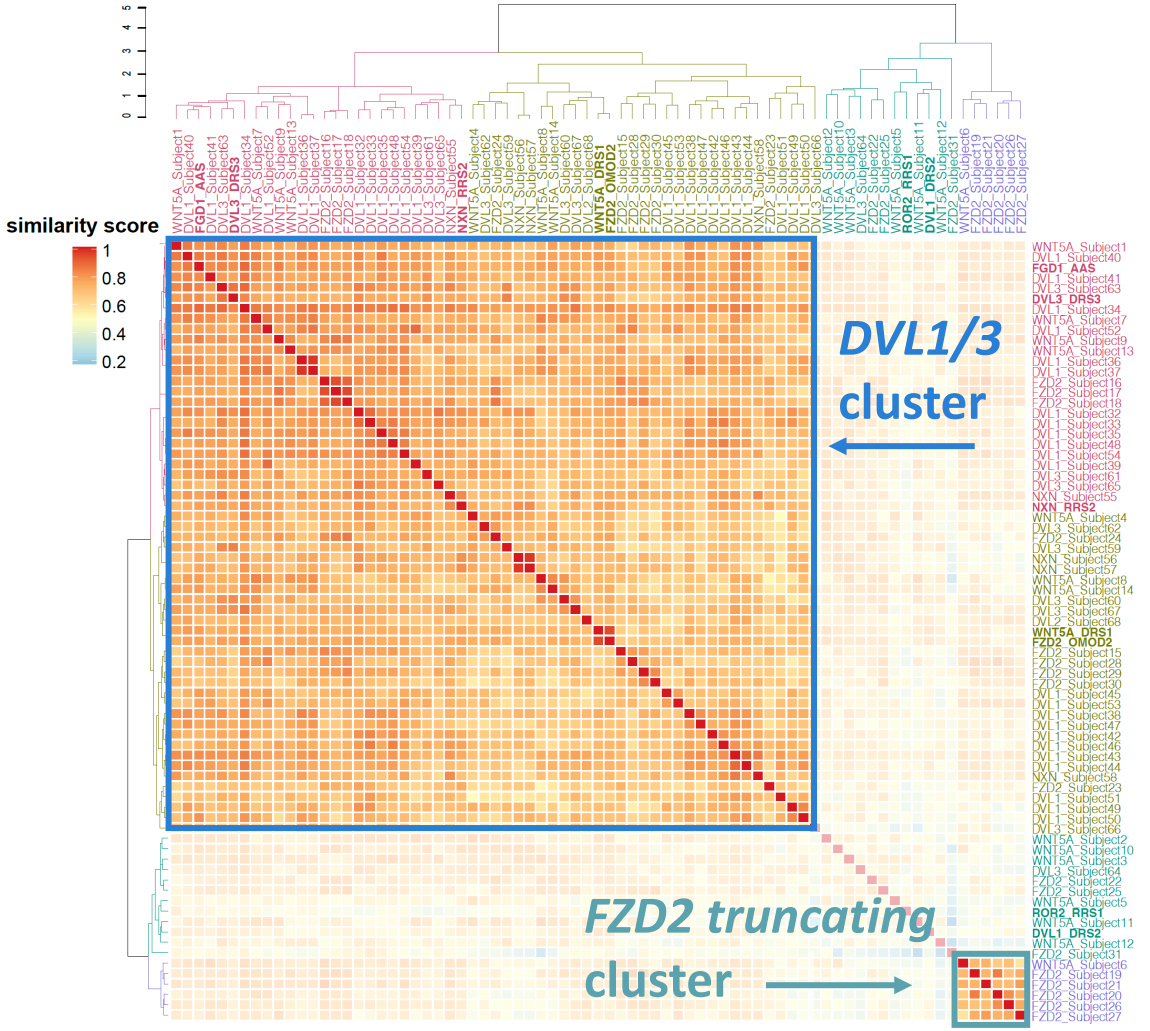

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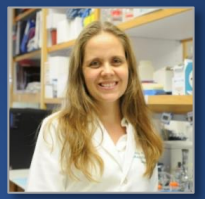

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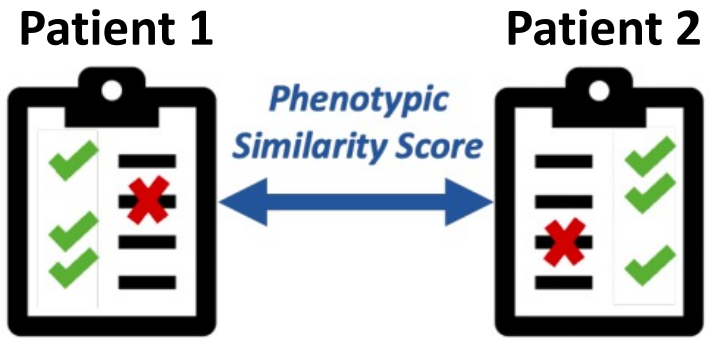

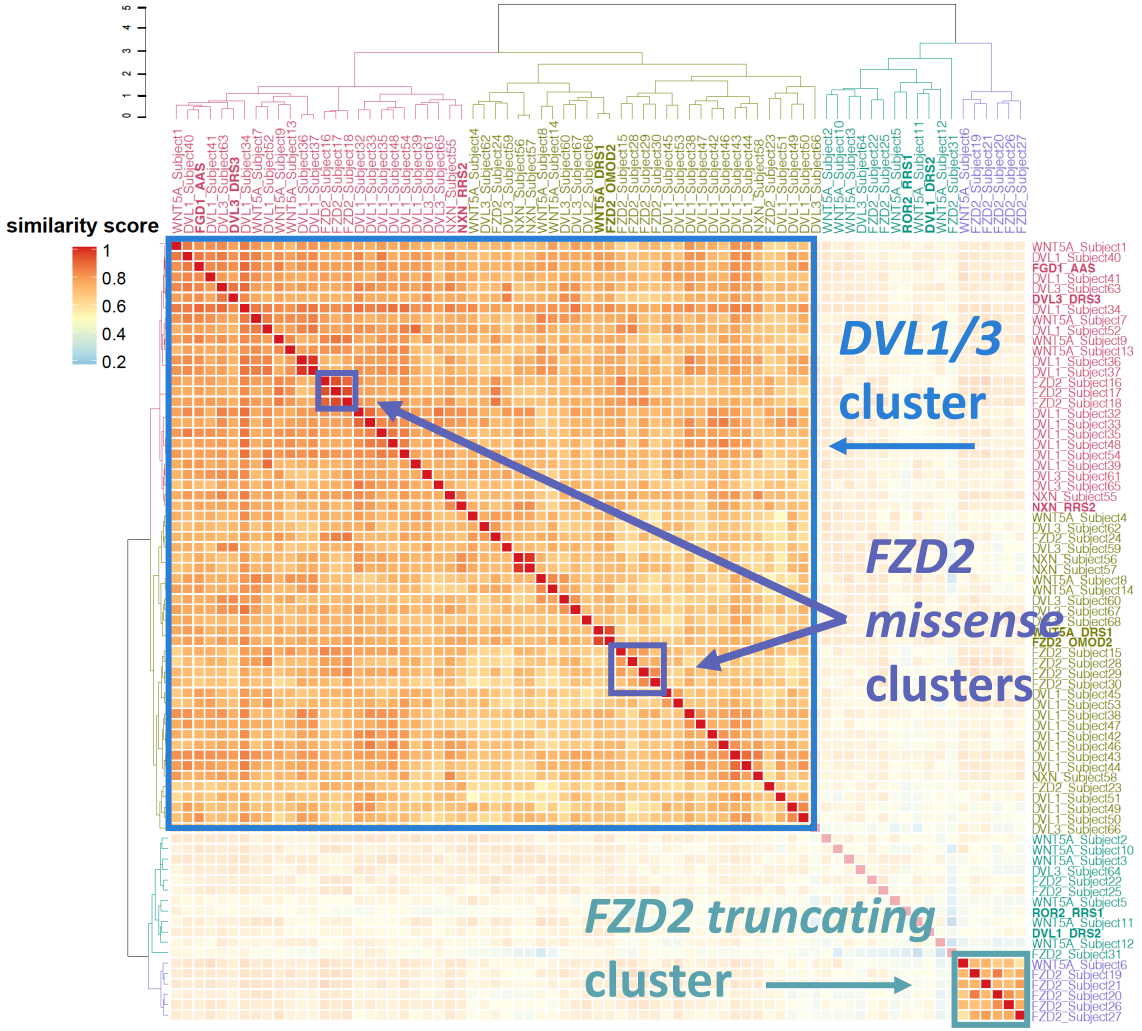

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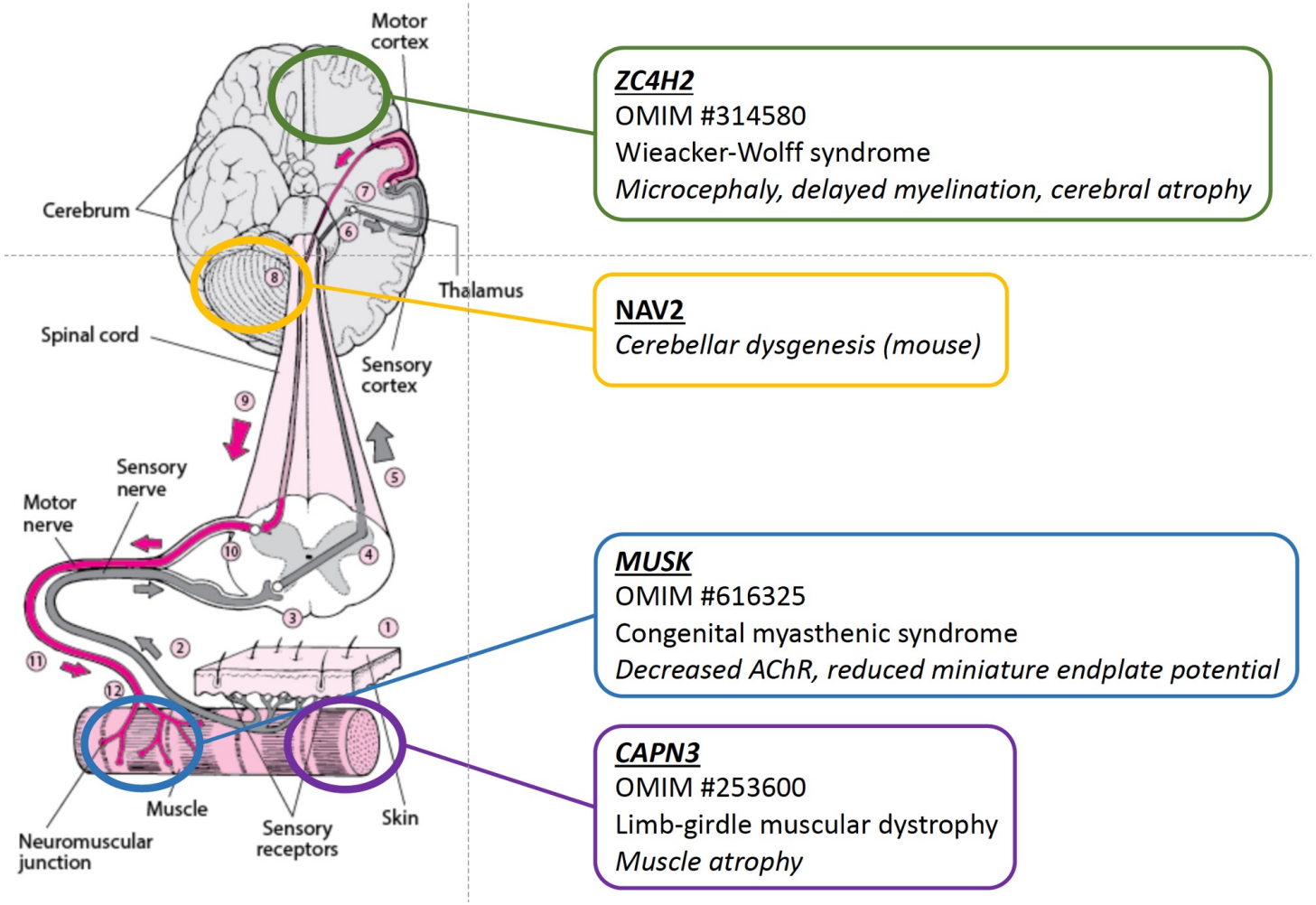
Using HPO to dissect multilocus pathogenic variation

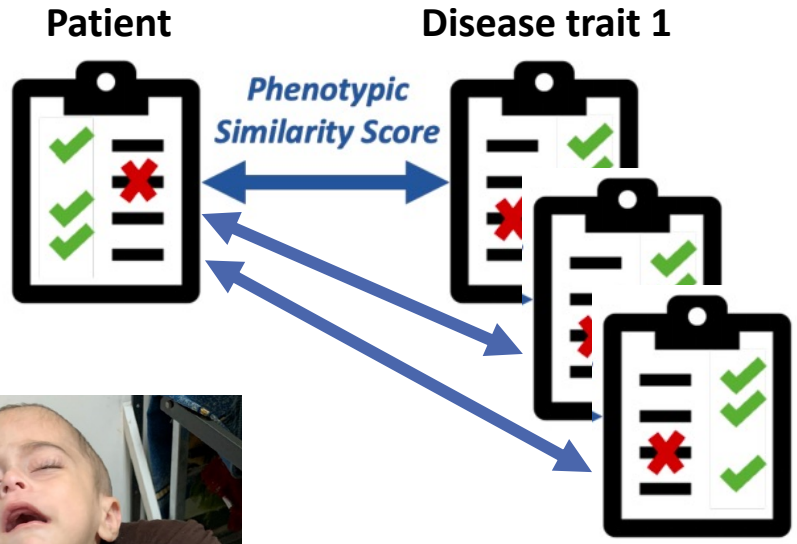


ZC4H2
OMIM #314580
Wieacker-Wolff syndrome
Microcephaly, delayed myelination, cerebral atrophy

NAV2
Cerebellar dysgenesis (mouse)

MUSK
OMIM #616325
Congenital myasthenic syndrome
Decreased AChR, reduced miniature endplate potential

CAPN3
OMIM #253600
Limb-girdle muscular dystrophy
Muscle atrophy



Herman I, Jolly A, *et al. Am J Med Genet A* (2022) *188*:735-750.

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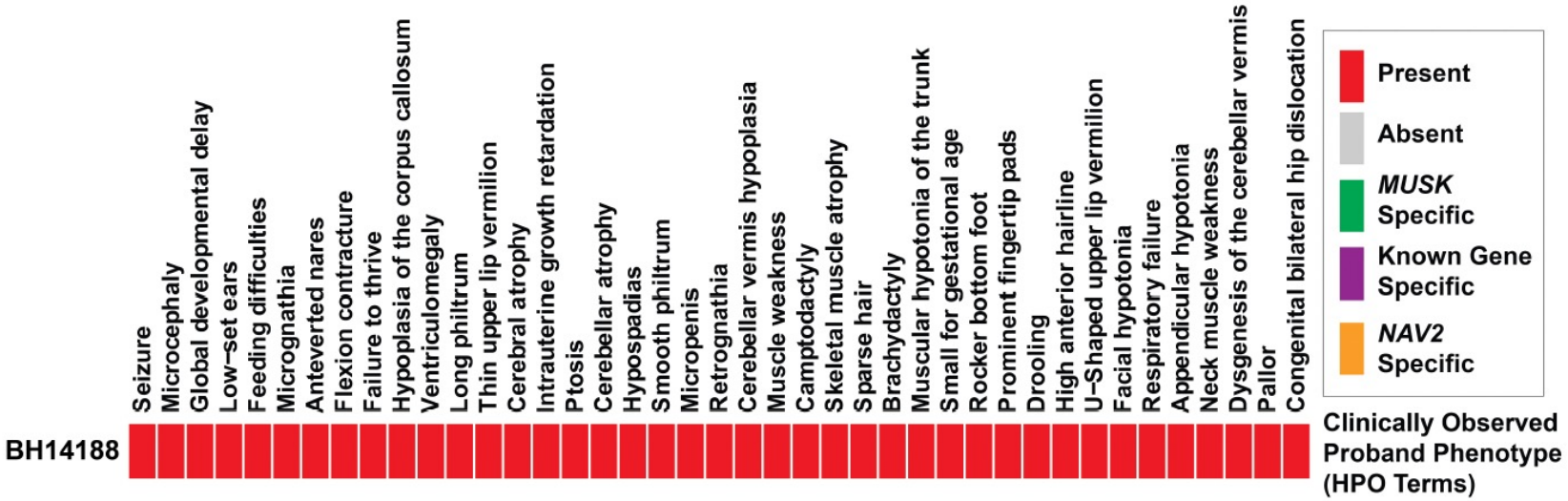

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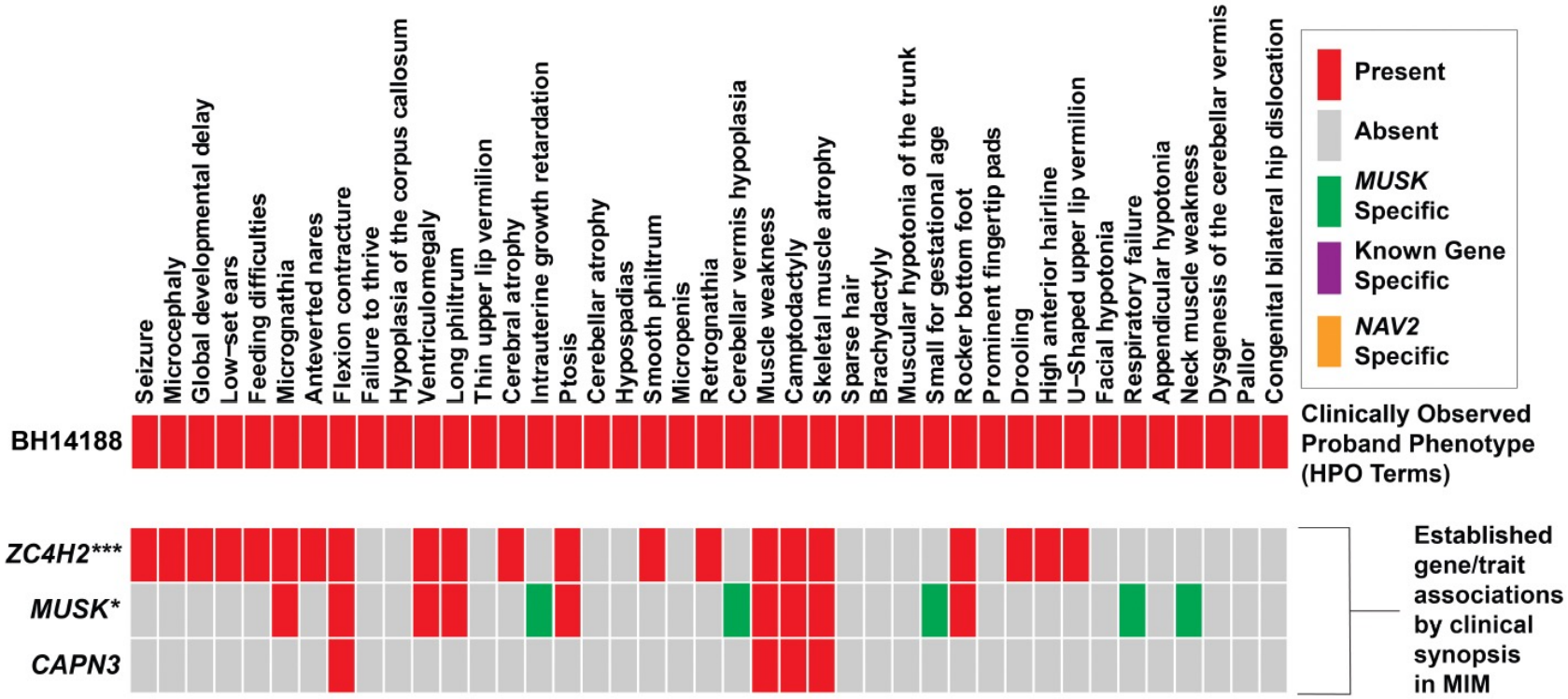

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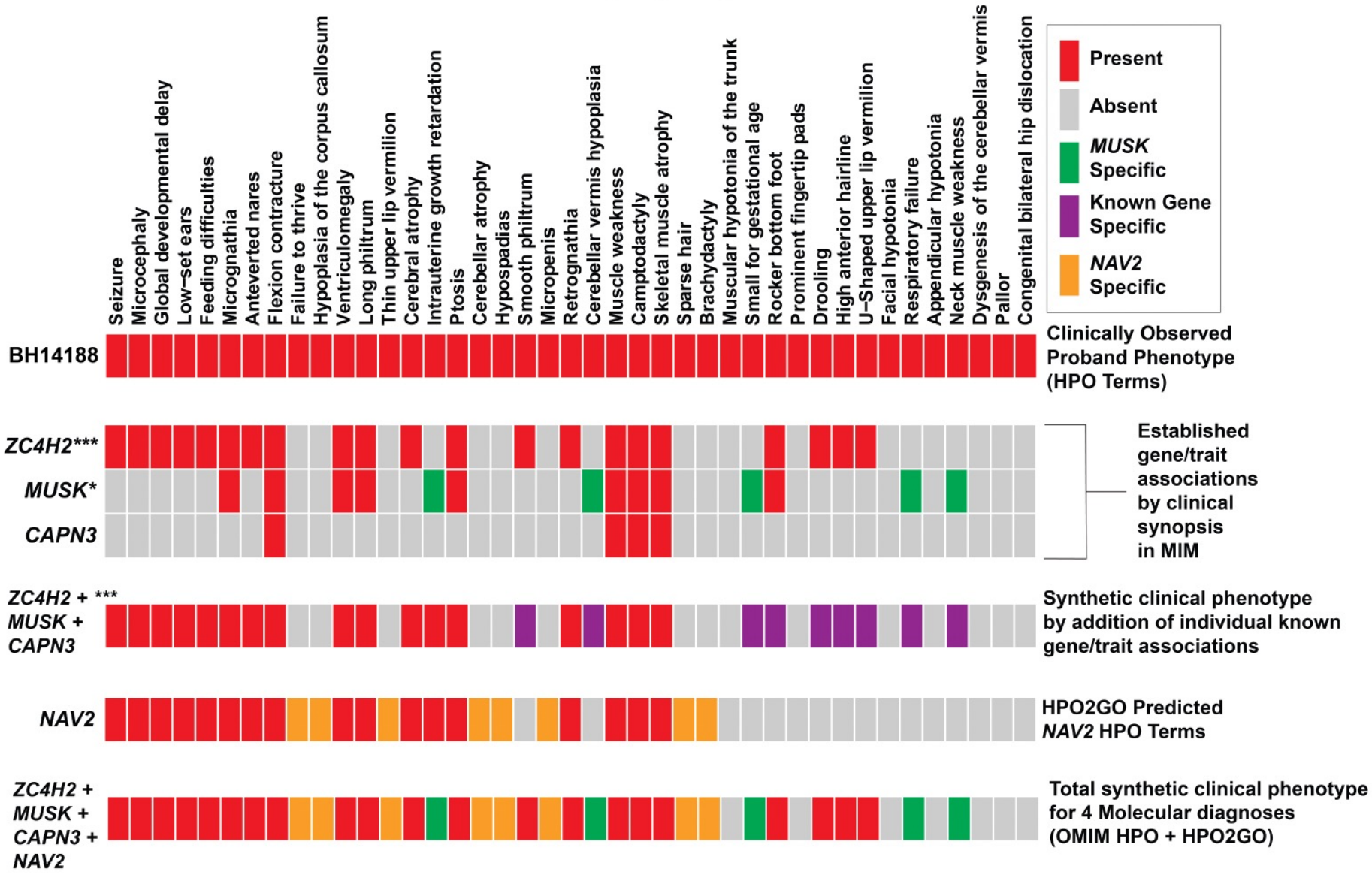

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Mayer-Rokitansky-Küster-Houser syndrome (MRKHS)

Congenital reproductive disorder in women

- Absent – or underdeveloped – uterus and vagina
- Ascertainment often in teens due to amenorrhea
- Type I: isolated
- Type II: syndromic

American/European cohort:

- 148 affected individuals
- ~ 55% type MRKH type I

Han Chinese cohort:

- 442 affected individuals
- ~ 75% MRKH type II

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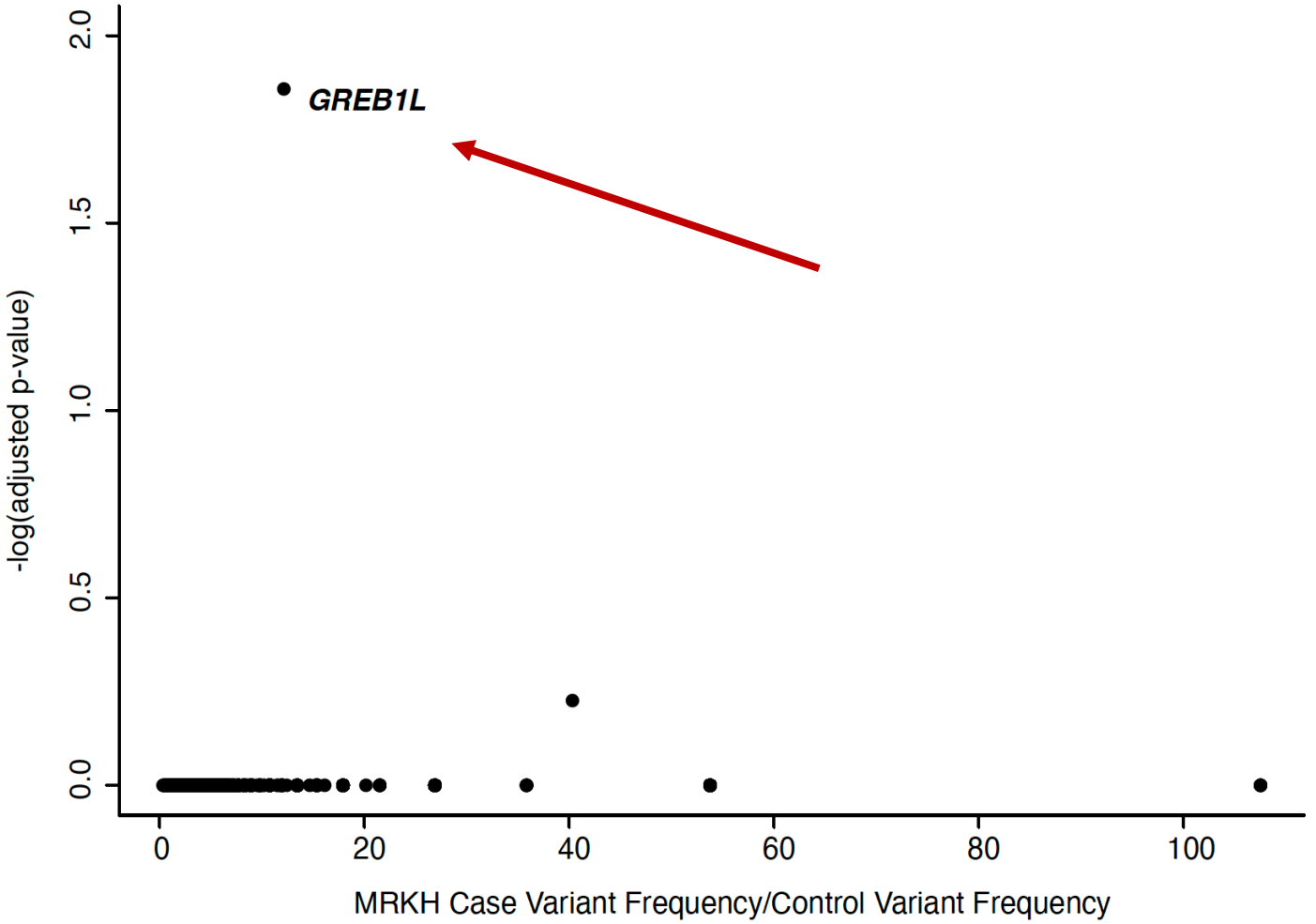

GREB1L: established renal hypodysplasia/aplasia disease gene

Exome-wide Association Study Identifies *GREB1L* Mutations in Congenital Kidney Malformations

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REPORT

Mutations in *GREB1L* Cause Bilateral Kidney Agenesis in Humans and Mice

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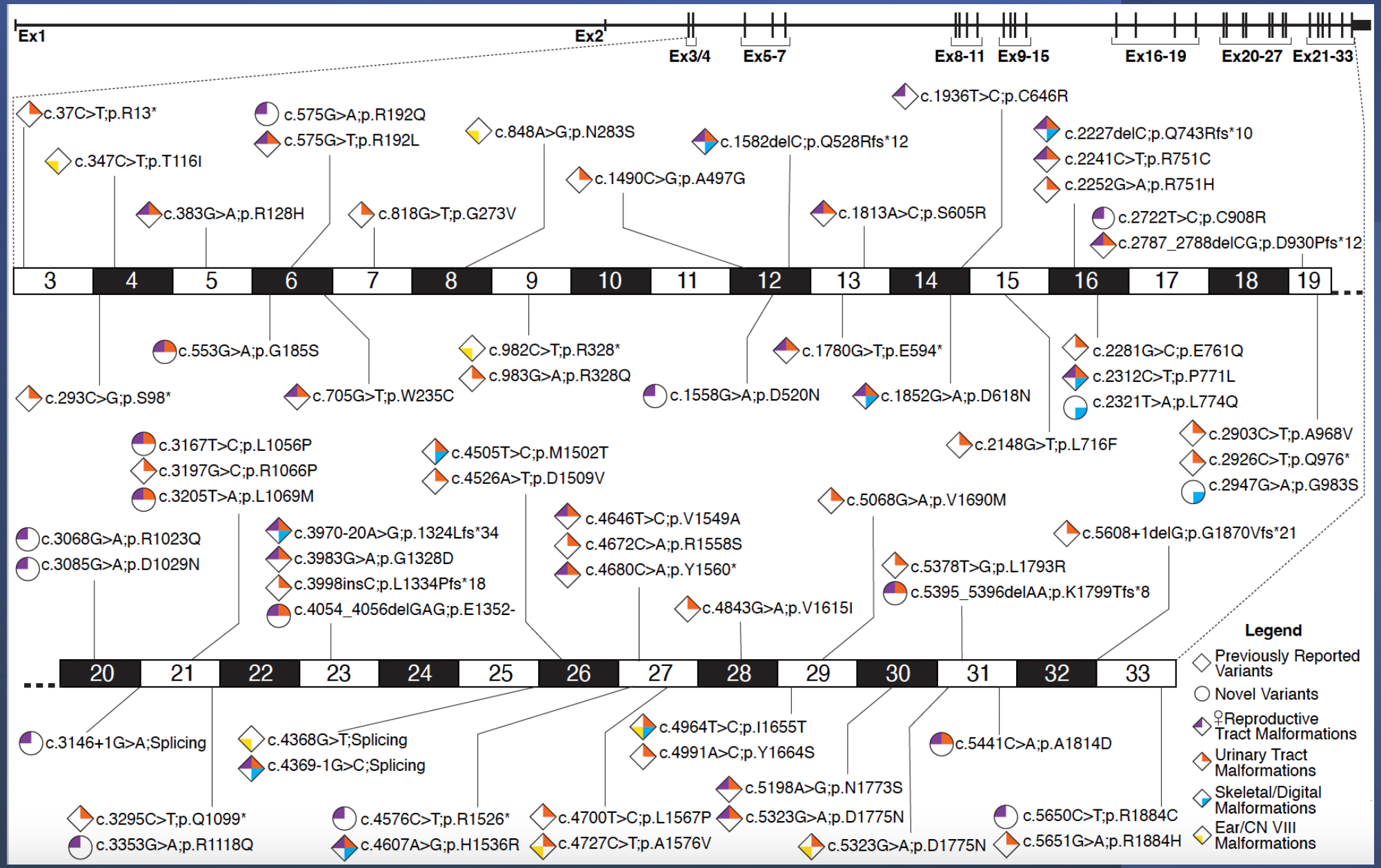
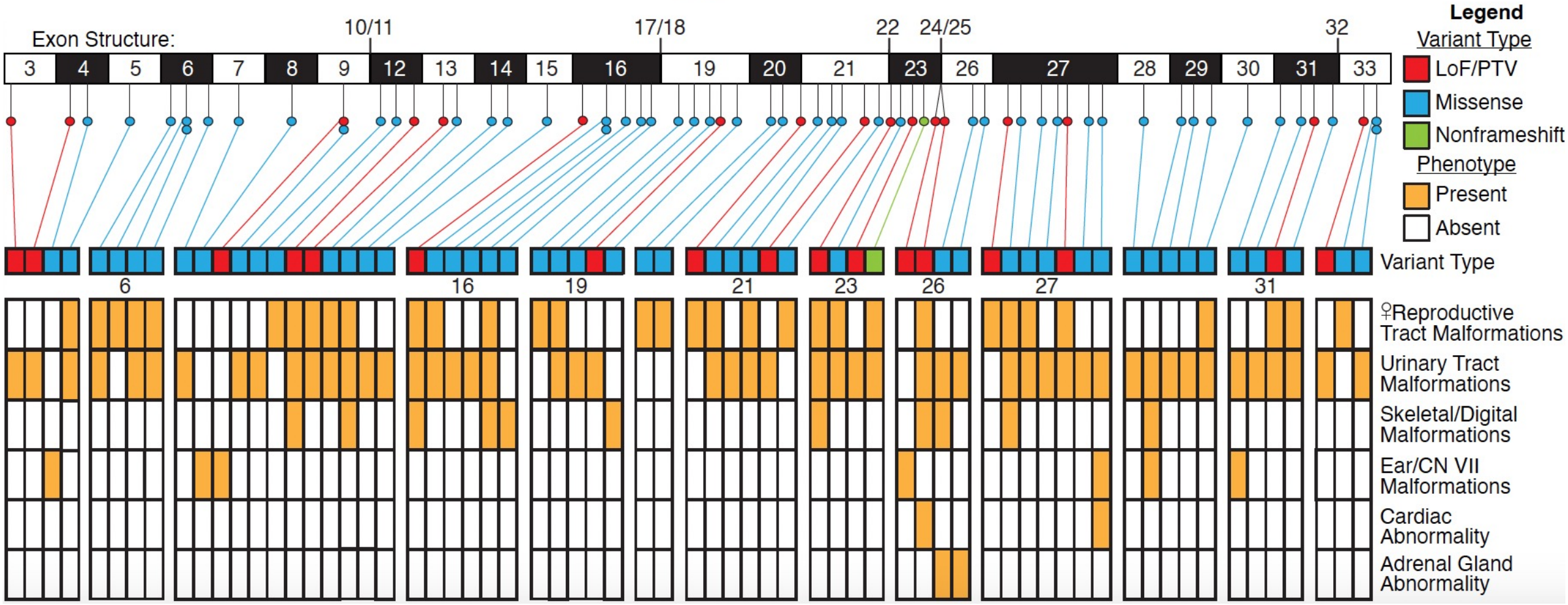
A Gene Implicated in Activation of Retinoic Acid Receptor Targets Is a Novel Renal Agenesis Gene in Humans

Patrick D. Brophy,*[,1] Maria Rasmussen,[†,1] Mrutyunjaya Parida,[‡,1] Greg Bonde,[§] Benjamin W. Darbro,* Xiaojing Hong,[‡] Jason C. Clarke,* Kevin A. Peterson,** James Denegre,** Michael Schneider,[††] Caroline R. Sussman,[‡‡] Lone Sunde,[†] Dorte L. Lildballe,[†] Jens Michael Hertz,[§§] Robert A. Cornell,[§] Stephen A. Murray,** and J. Robert Manak*[,‡,2]

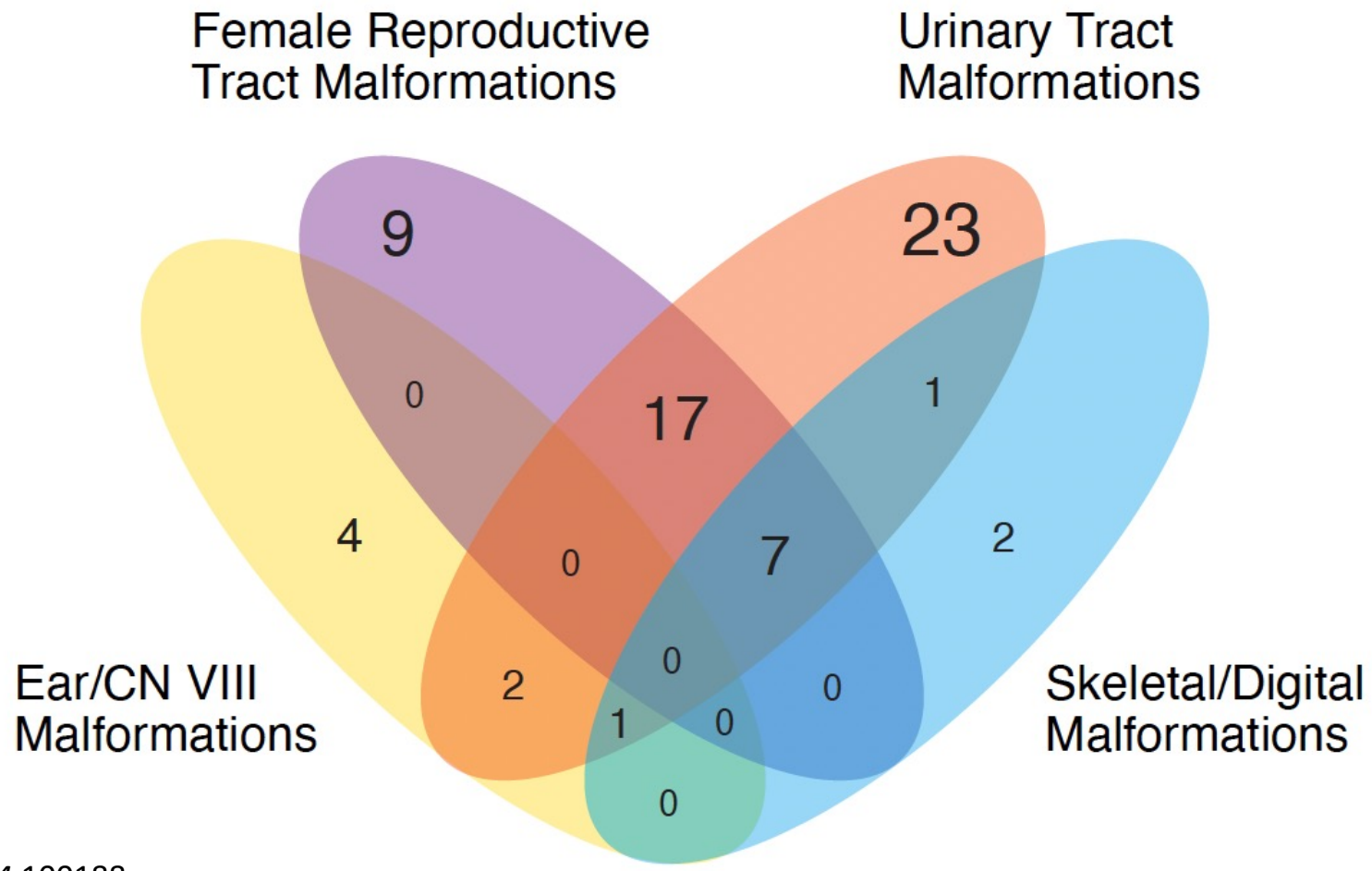

Ex1
Ex2
Ex3/4
Ex5-7
Ex8-11
Ex9-15
Ex16-19
Ex20-27
Ex21-33
c.37C>T;p.R13*
c.347C>T;p.T116I
c.383G>A;p.R128H
c.575G>A;p.R192Q
c.575G>T;p.R192L
c.818G>T;p.G273V
c.848A>G;p.N283S
c.1490C>G;p.A497G
c.1582delC;p.Q528Rfs*12
c.1813A>C;p.S605R
c.1936T>C;p.C646R
c.2227delC;p.Q743Rfs*10
c.2241C>T;p.R751C
c.2252G>A;p.R751H
c.2722T>C;p.C908R
c.2787_2788delCG;p.D930Pfs*12
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
c.293C>G;p.S98*
c.553G>A;p.G185S
c.705G>T;p.W235C
c.982C>T;p.R328*
c.983G>A;p.R328Q
c.1558G>A;p.D520N
c.1780G>T;p.E594*
c.1852G>A;p.D618N
c.2148G>T;p.L716F
c.2281G>C;p.E761Q
c.2312C>T;p.P771L
c.2321T>A;p.L774Q
c.2903C>T;p.A968V
c.2926C>T;p.Q976*
c.2947G>A;p.G983S
c.3068G>A;p.R1023Q
c.3085G>A;p.D1029N
c.3167T>C;p.L1056P
c.3197G>C;p.R1066P
c.3205T>A;p.L1069M
c.3970-20A>G;p.1324Lfs*34
c.3983G>A;p.G1328D
c.3998insC;p.L1334Pfs*18
c.4054_4056delGAG;p.E1352-
c.4505T>C;p.M1502T
c.4526A>T;p.D1509V
c.4646T>C;p.V1549A
c.4672C>A;p.R1558S
c.4680C>A;p.Y1560*
c.4843G>A;p.V1615I
c.5068G>A;p.V1690M
c.5378T>G;p.L1793R
c.5395_5396delAA;p.K1799Tfs*8
c.5608+1delG;p.G1870Vfs*21
20
21
22
23
24
25
26
27
28
29
30
31
32
33
c.3146+1G>A;Splicing
c.4368G>T;Splicing
c.4369-1G>C;Splicing
c.3295C>T;p.Q1099*
c.3353G>A;p.R1118Q
c.4576C>T;p.R1526*
c.4607A>G;p.H1536R
c.4700T>C;p.L1567P
c.4727C>T;p.A1576V
c.4964T>C;p.I1655T
c.4991A>C;p.Y1664S
c.5198A>G;p.N1773S
c.5323G>A;p.D1775N
c.5323G>A;p.D1775N
c.5441C>A;p.A1814D
c.5650C>T;p.R1884C
c.5651G>A;p.R1884H
Legend
Previously Reported Variants
Novel Variants
♀Reproductive Tract Malformations
Urinary Tract Malformations
Skeletal/Digital Malformations
Ear/CN VIII Malformations

GREB1L genotype-phenotype analysis



Jolly A, *et al. HGG Adv* (2023) *4*:100188.

GREB1L associated with isolated & syndromic MRKHs (phenotypic expansion)



Jolly A, *et al. HGG Adv* (2023) *4*:100188.

Overall Conclusions

Deep phenotyping, and quantitative phenotypic analysis, can uncover novel gene- and variant-disease relationships

Structured phenotyping can inform individual gene/variant contributions to blended phenotypes resulting from multi-locus pathogenic variation

Careful phenotypic assessment can uncover previously unrecognized phenotypic expansion at a locus

THANK YOU

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