3q29 Deletion Syndrome

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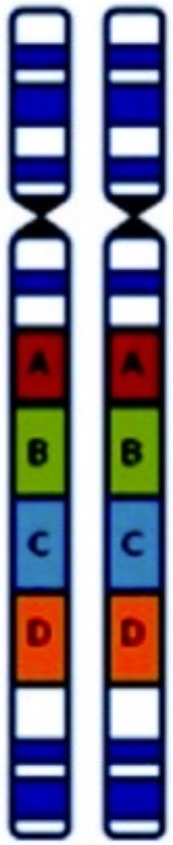
Thank you.

Reporting our results

- First paper with overall description of phenotypes: *Submitted*
- *In development:*
- Feeding behaviors (registry questionnaire)
- Detailed descriptions of neurodevelopmental phenotypes
- Unique social ability profile
- Psychosis and subthreshold psychosis
- Neuroimaging results
- …and many more

What is a Copy Number Variant?



3q29 deletion = 3q29 microdeletion

First description of the 3q29 deletion:

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3q29 Microdeletion Syndrome: Clinical and Molecular Characterization of a New Syndrome

- Willatt et al, AJHG 2005 describes six patients
- Facial dysmorphology subtle, “not striking”
- All have mild to moderate ID and language delay
- Level of developmental delay not apparent until after the first year of life
- “Autism was a feature of the behavior of two of the patients”; a 3rd pt had features of ASD but no diagnosis

Expanding the clinical phenotype of the 3q29 microdeletion syndrome and characterization of the reciprocal microduplication

- Ballif et al 2008, Mol Cytogenetics: 14 patients out of 14,698 with idiopathic ID referred for aCHG
- Mild to moderate ID the only feature common to all patients
- Syndrome includes:
  - Speech Delay (53%)
  - Autism/autistic features (27%)
  - Recurrent ear infections, heart defects, widely spaced teeth (13%)

Microdeletions of 3q29 Confer High Risk for Schizophrenia

Jennifer Gladys Mulle,[1,*] Anne F. Dodd,[1] John A. McGrath,[2] Paula S. Wolyniec,[2] Adele A. Mitchell,[3] Amol C. Shetty,[1] Nara L. Sobreira,[4] David Valle,[4] M. Katharine Rudd,[1] Glen Satten,[1,5] David J. Cutler,[1] Ann E. Pulver,[2,6] and Stephen T. Warren[1,7,*]

The 3q29 Project

New Research

Full Access

Copy Number Variants in Schizophrenia: Confirmation of Five Previous Findings and New Evidence for 3q29 Microdeletions and VIPR2 Duplications

Douglas F. Levinson, M.D., Jubao Duan, Ph.D., Sang Oh, M.Sc., Kai Wang, Ph.D., Alan R. Sanders, M.D., Jianxin Shi, Ph.D., Nancy Zhang, Ph.D., Bryan J. Mowry, M.D., F.R.A.N.Z.C.P., Ann Olincy, M.D., Farooq Amin, M.D., C. Robert Cloninger, M.D., Jeremy M. Silverman, M.D., **... Show all Authors**

Mol Psychiatry. 2014 Jul;19(7):762-73. doi: 10.1038/mp.2014.40. Epub 2014 Apr 29.

Copy number variation in schizophrenia in Sweden.

Szatkiewicz JP[1], O'Dushlaine C[2], Chen G[1], Chambert K[2], Moran JL[2], Neale BM[2], Fromer M[3], Ruderfer D[3], Akterin S[4], Bergen SE[5], Kähler A[4], Magnusson PK[4], Kim Y[1], Crowley JJ[1], Rees E[6], Kirov G[6], O'Donovan MC[6], Owen MJ[6], Walters J[6], Scolnick E[2], Sklar P[3], Purcell S[7], Hultman CM[4], McCarroll SA[8], Sullivan PF[9].

The 3q29 deletion confers >40-fold increase in risk for schizophrenia

J G Mulle

Molecular Psychiatry **20**, 1028–1029 (2015) | Download Citation

Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects

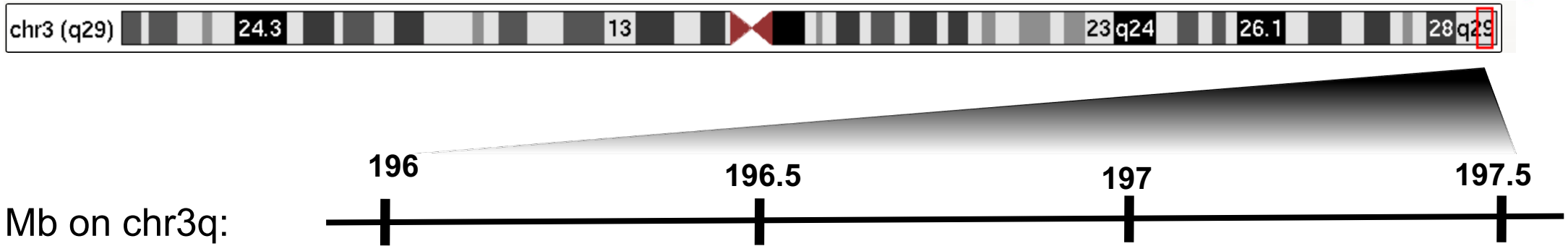
Christian R Marshall, Daniel P Howrigan […] CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium

Nature Genetics **49**, 27–35 (2017) | Download Citation

"Genome-wide significant evidence was obtained for eight loci, including 1q21.1, 2p16.3 (*NRXN1*), **3q29**, 7q11.2, 15q13.3, distal 16p11.2, proximal 16p11.2 and 22q11.2."

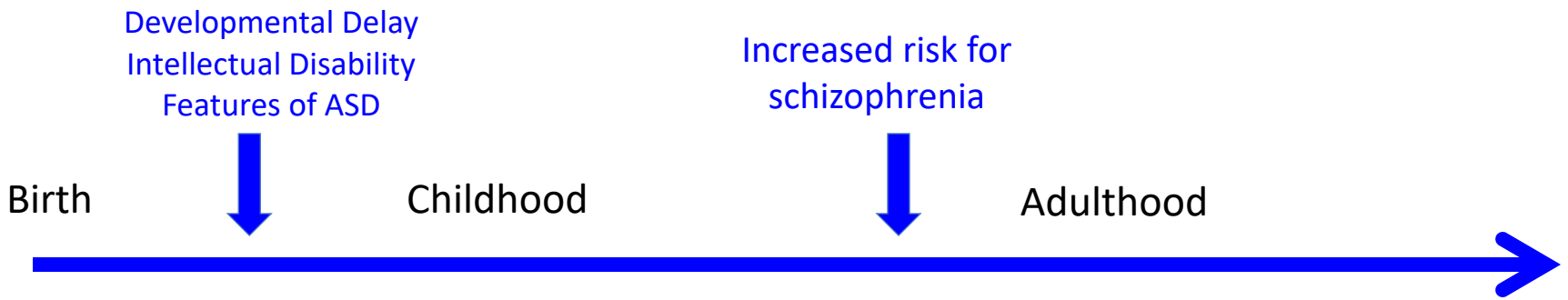
What is the 3q29 deletion?

The 3q29 Project



Rare Syndrome: 1 in 30,000 in the general population

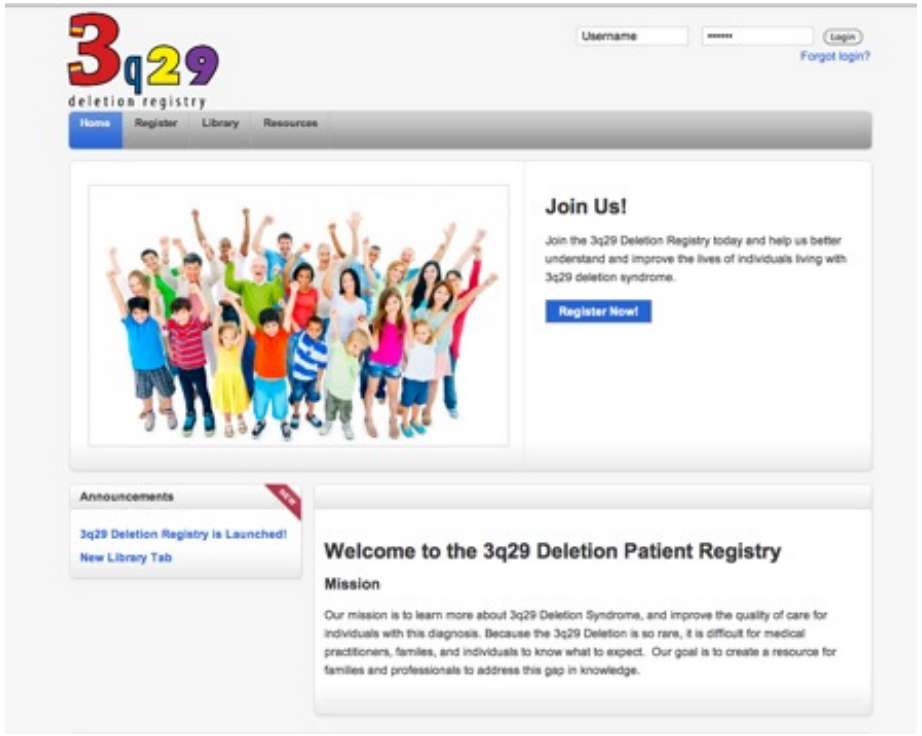
3q29 deletion syndrome: 2010



What tools do we need to learn more?

- Animal Model?
  - Emory Investigators create the first 3q29 deletion mouse model
- Human Cohort?
  - YES! But challenging when the deletion is rare (1 in 30,000) in the general population

The Registry: 3q29deletion.org



Web-based:
- Recruitment
- Consent
- Data collection
- Confirmation of genetic dx

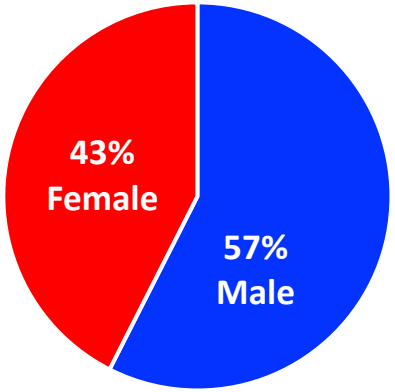
Community Development
Education
Outreach

Our registry collects self-report data from families and, in some cases, the deletion carriers themselves

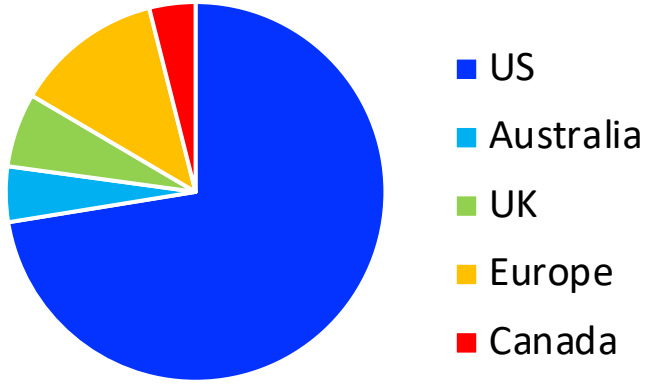
Current Recruitment

N = 213 individuals with 3q29 deletion:

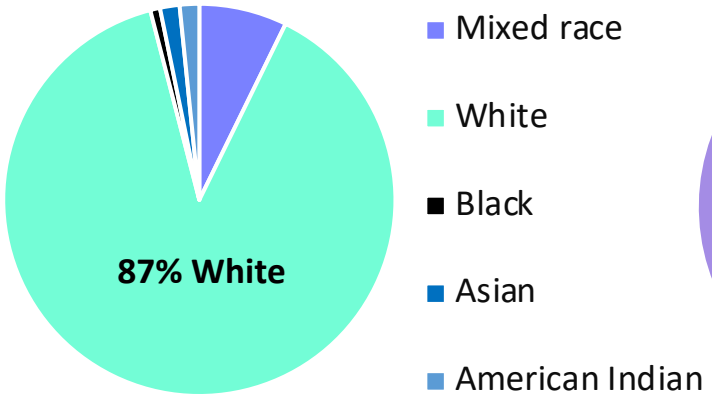
Sex



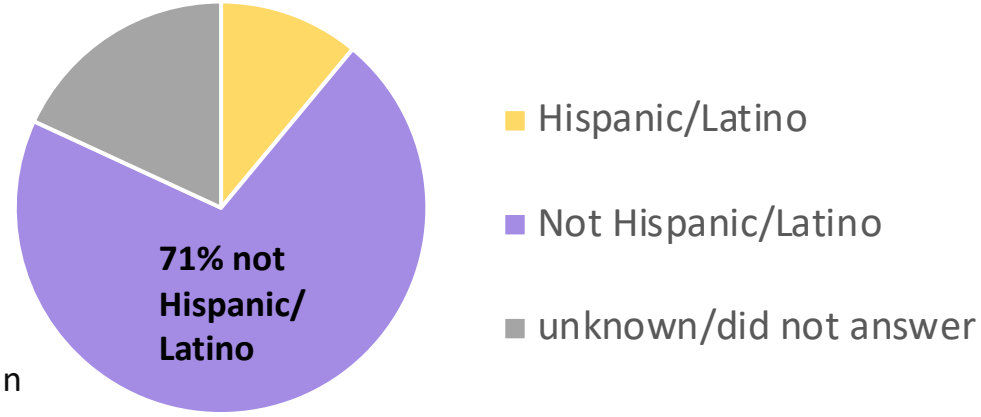
Country



Race



Ethnicity

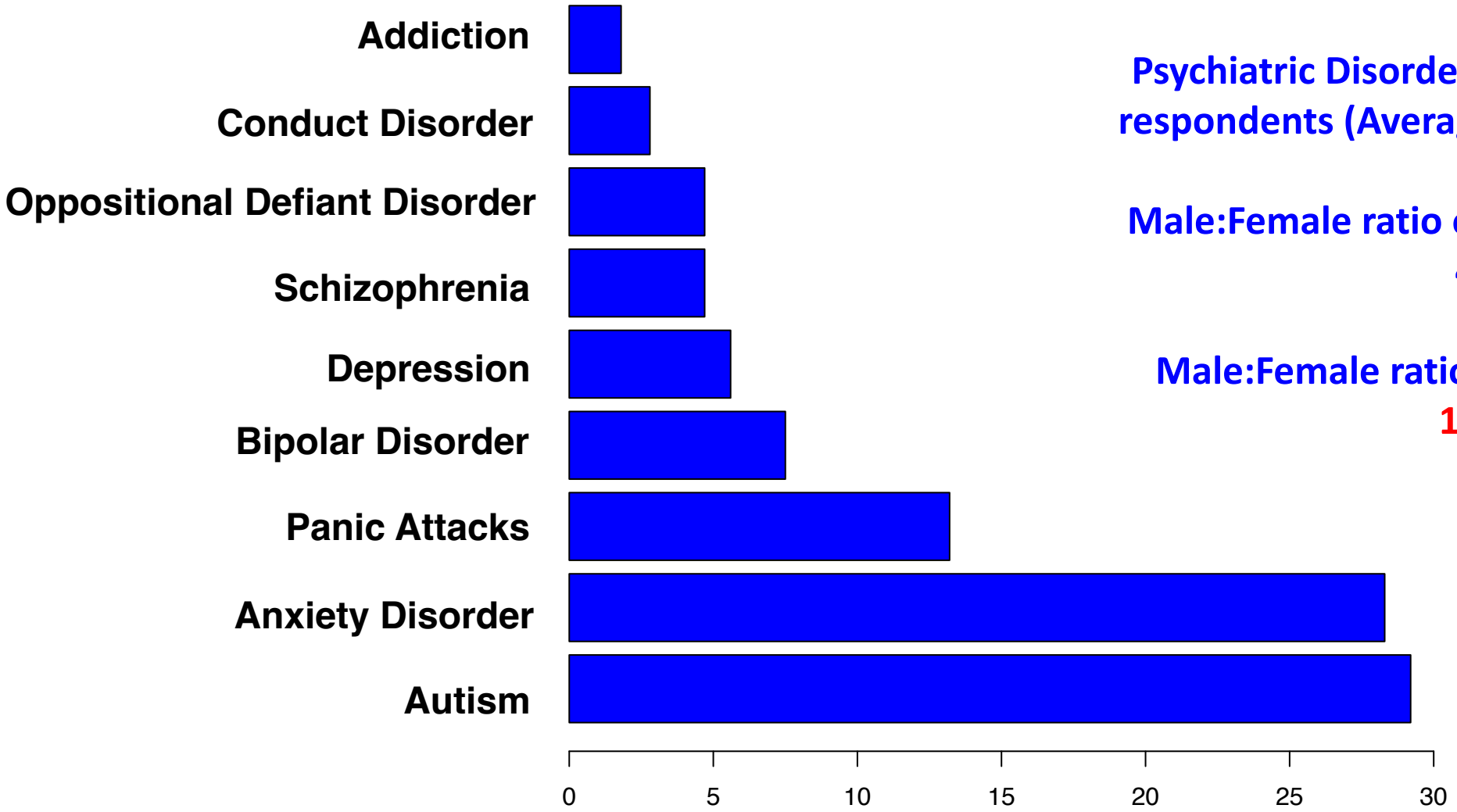


Mean Age 12.5 years (Median 10; Range 1.8– 45.1)

The 3q29 Registry: Data Collection Instruments

Scale	Number/type of questions	Dimensions assessed	Sample question
Medical and demographic questionnaire	20; combination of dropdown menus, matrices with dropdown menus, and checkboxes	Birth history, development, ear/nose/throat, GI, renal, oral/dental, and seizure	"At what age were the following gross motor milestones met?"
Social Responsiveness Scale (SRS)	65; 4-point scale	Social reciprocity and ASD symptoms	"Seems to react to people as if they are objects."
Social Communication Questionnaire (SCQ)	40; yes/no	Social communication and history of ASD symptomology	"Has she/he ever gotten his/her pronouns mixed up?"
Autism Spectrum Screening Questionnaire (ASSQ)	27; 3-point scale	ASD symptoms in high-functioning individuals	"Accumulates facts on certain subjects but does not really understand the meaning."
Child Behavior Checklist (CBCL) and Adult Behavior Checklist (ABCL)	100 (preschool), 119 (school age), or 126 (adult); 3-point scale	General developmental and behavioral problems	"Feels he/she has to be perfect."

Self-Report of Neuropsychiatric Disorders



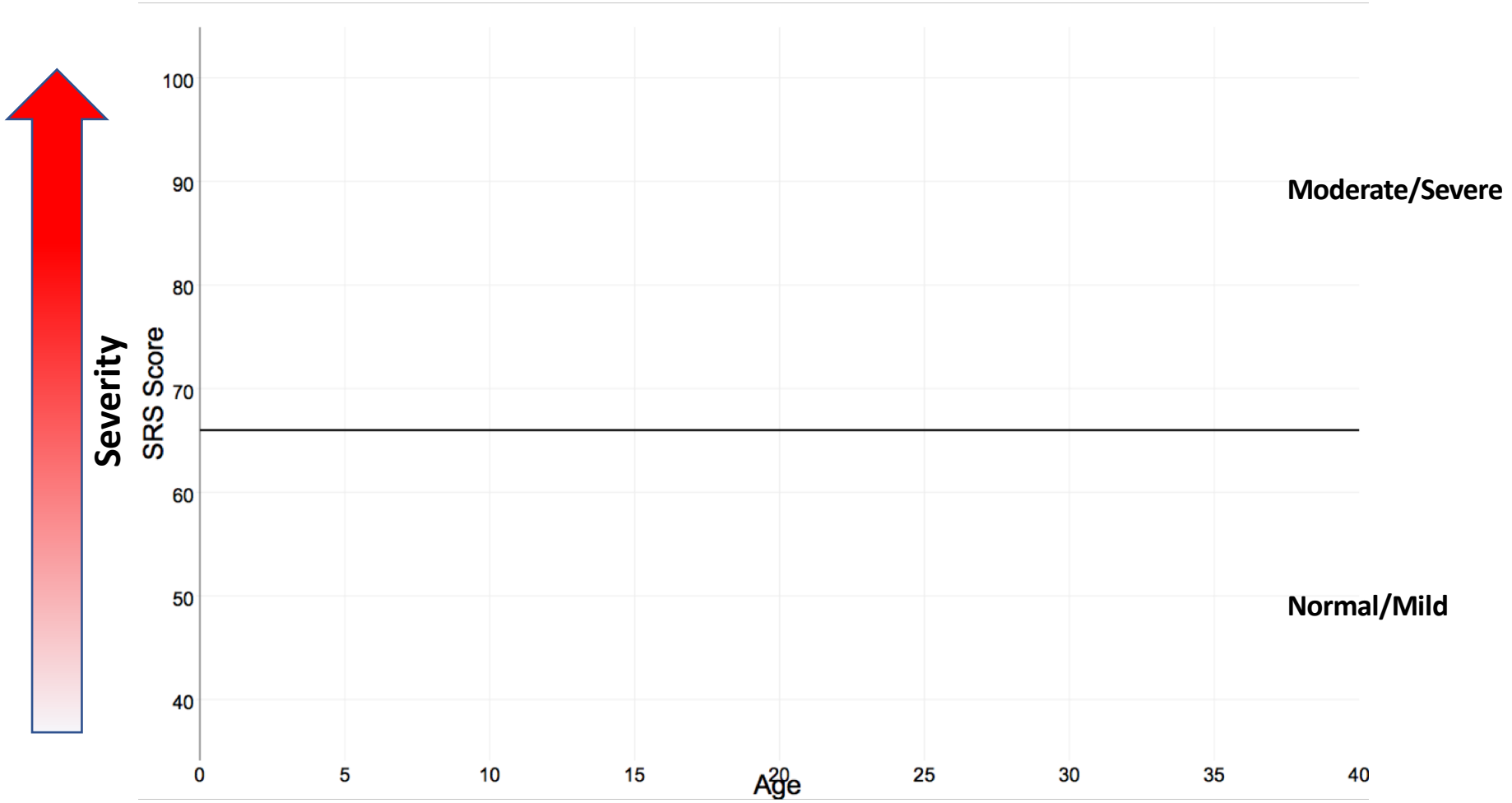
Psychiatric Disorders present in 35.8% of respondents (Average Age: 12.5 years old)

Male:Female ratio of ASD in general pop: 4:1

Male:Female ratio of ASD in 3q29 del: 1.8:1

Glassford et al, *AJMG*, 2016

Social Responsiveness Scale



Pollak RM et al,
Mol Autism, 2019

Social Responsiveness Scale: 3q29 Deletion Syndrome

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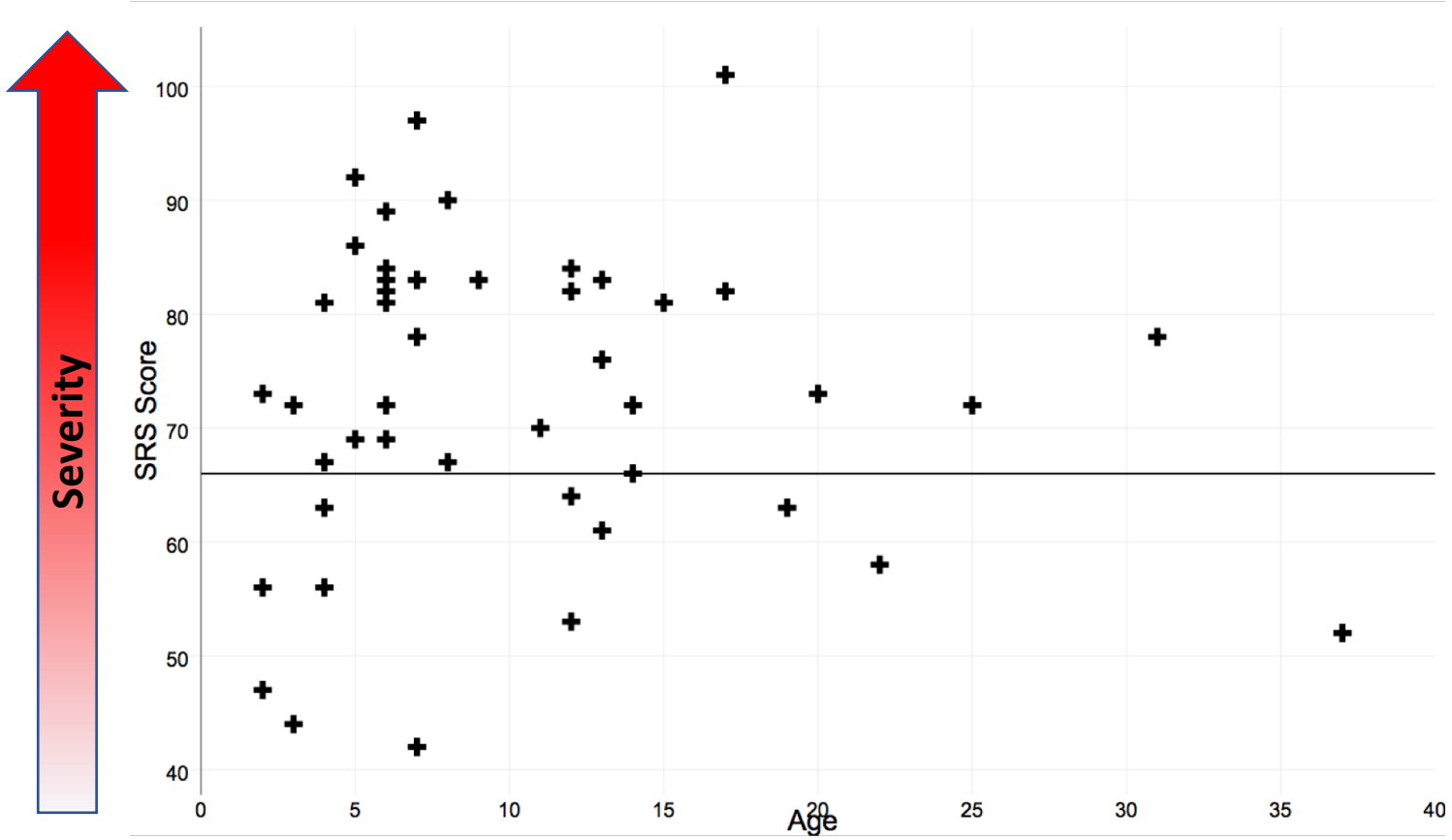
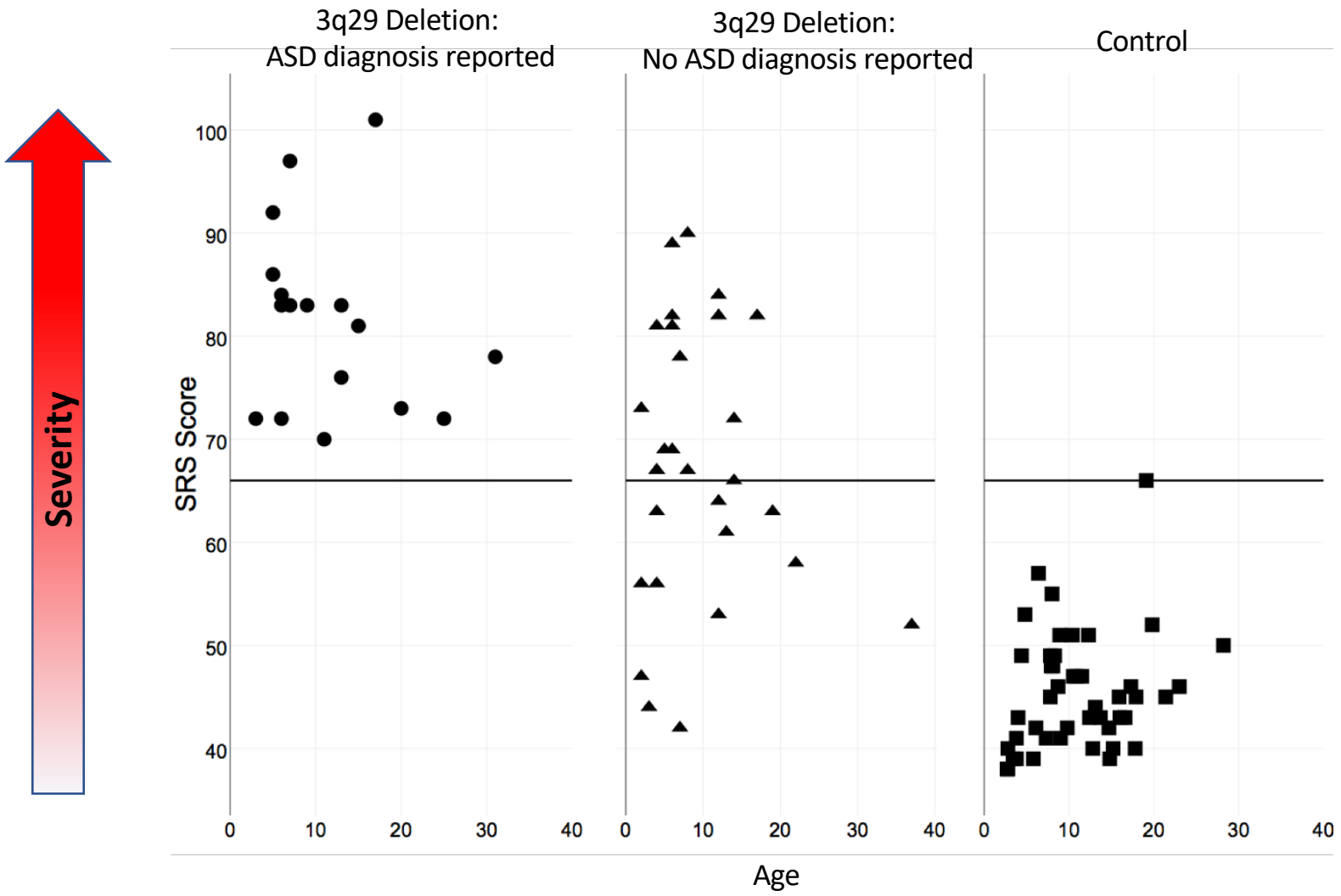


Moderate/Severe

Normal/Mild

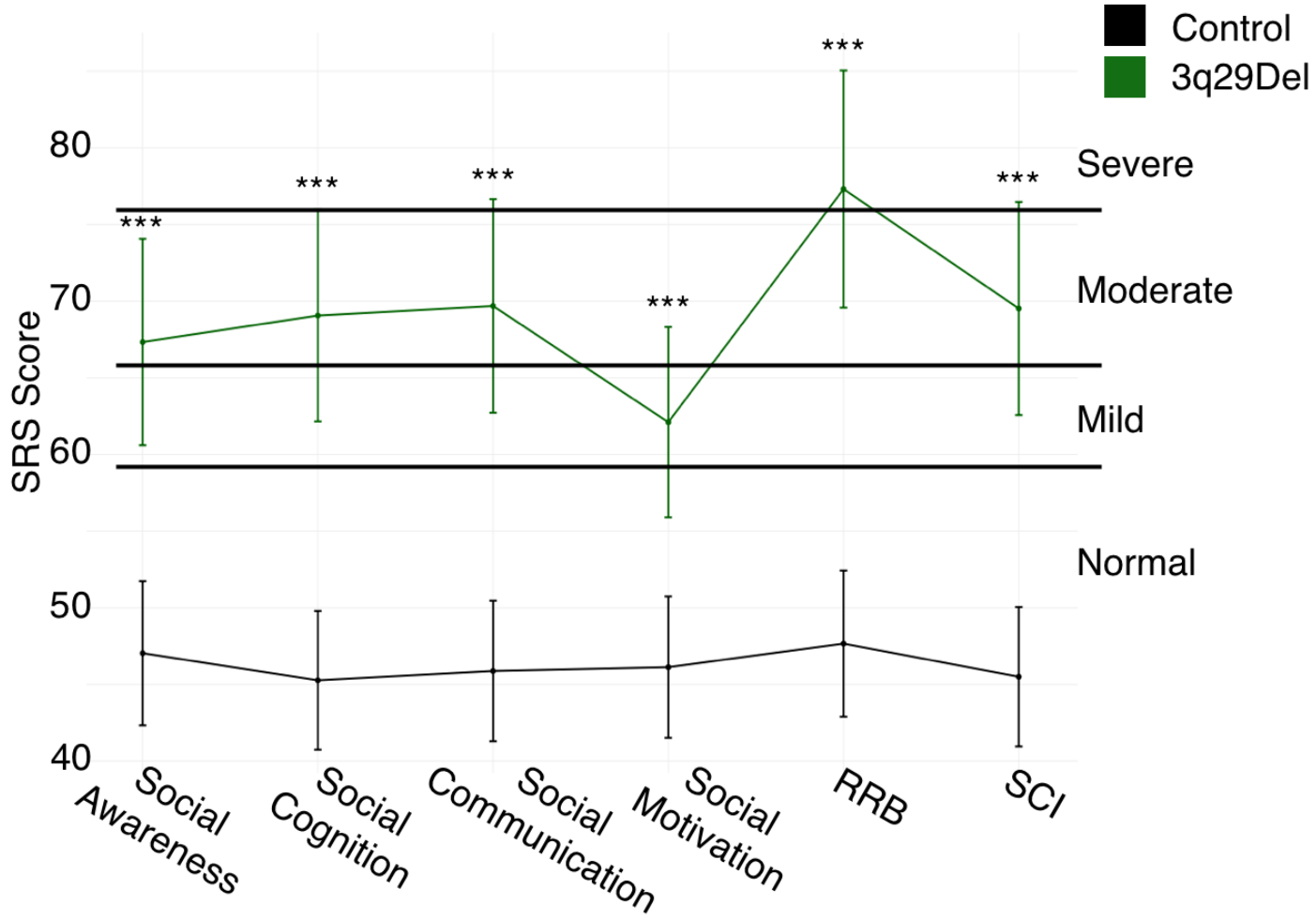
Pollak RM et al, *Mol Autism*, 2019

Social Responsiveness Scale



Pollak RM et al,
Mol Autism, 2019

A Unique Autism Profile



These data will be validated by direct clinical assessment

Pollak RM, et al, "Neuropsychiatric phenotypes and novel features of ASD in 3q29 Deletion Syndrome: Results from the 3q29 Registry," Mol Autism, *In Press, 2019*

Motivating Questions

- What is the cognitive profile of individuals with 3q29 deletion syndrome?
- What is the nature of anxiety in 3q29 deletion syndrome?
- Are there other neuropsychiatric phenotypes in this population?

Answering these questions requires *direct evaluation*

Modeling the Human Neuronal Phenotype of the Schizophrenia-Associated 3q29 Deletion

The 3q29 Project

- AIMS:
  - **To determine and quantify the behavioral and clinical phenotype of 3q29 deletion syndrome in children and adults along four dimensions: anxiety, cognitive ability, autism spectrum, and psychosis and prodromal symptoms.**
  - To create a publicly available resource of biomaterials from 3q29 deletion carriers at the Rutgers University Cell and DNA Repository (RUCDR).
  - To ascertain the functional consequences of 3q29 deletion in iPSC-derived neuronal cell lines.

Gary Bassell

Funded by NIMH 3/2017: R01 MH110701
$3.1 M

Phenotypic Measures

Phenotypes measured and instruments used in this study
Retrospective medical history: Review of major systems Custom intake questionnaire
Physical Exam Custom REDCap form
Craniofacial: 2D and 3D photos
Neurology exam Custom REDCap form
Cerebellar cognitive affective/Schmahmann syndrome scale CCASS
Cognitive ability (GCA and subtest scores) DAS-II, WASI-II
Visual-Motor Integration Beery-Buktenica Developmental test of visual-motor integration, 6th ed
Autism + Social disability ADOS-2, ADI-R, SRS, SCQ
Anxiety ADIS-P, ADIS-C, SCID-5-RV
Prodrome/Psychosis SIPS
Adaptive Behavior Vineland-3
Executive Function BRIEF-2
General Psychopathology KSADS, SCID-5-RV

The 3q29 Project

Study protocol for The Emory 3q29 Project: evaluation of neurodevelopmental, psychiatric, and medical symptoms in 3q29 deletion syndrome

Melissa Murphy
***BMC Psych*, 2018**

Phenotypic Measures

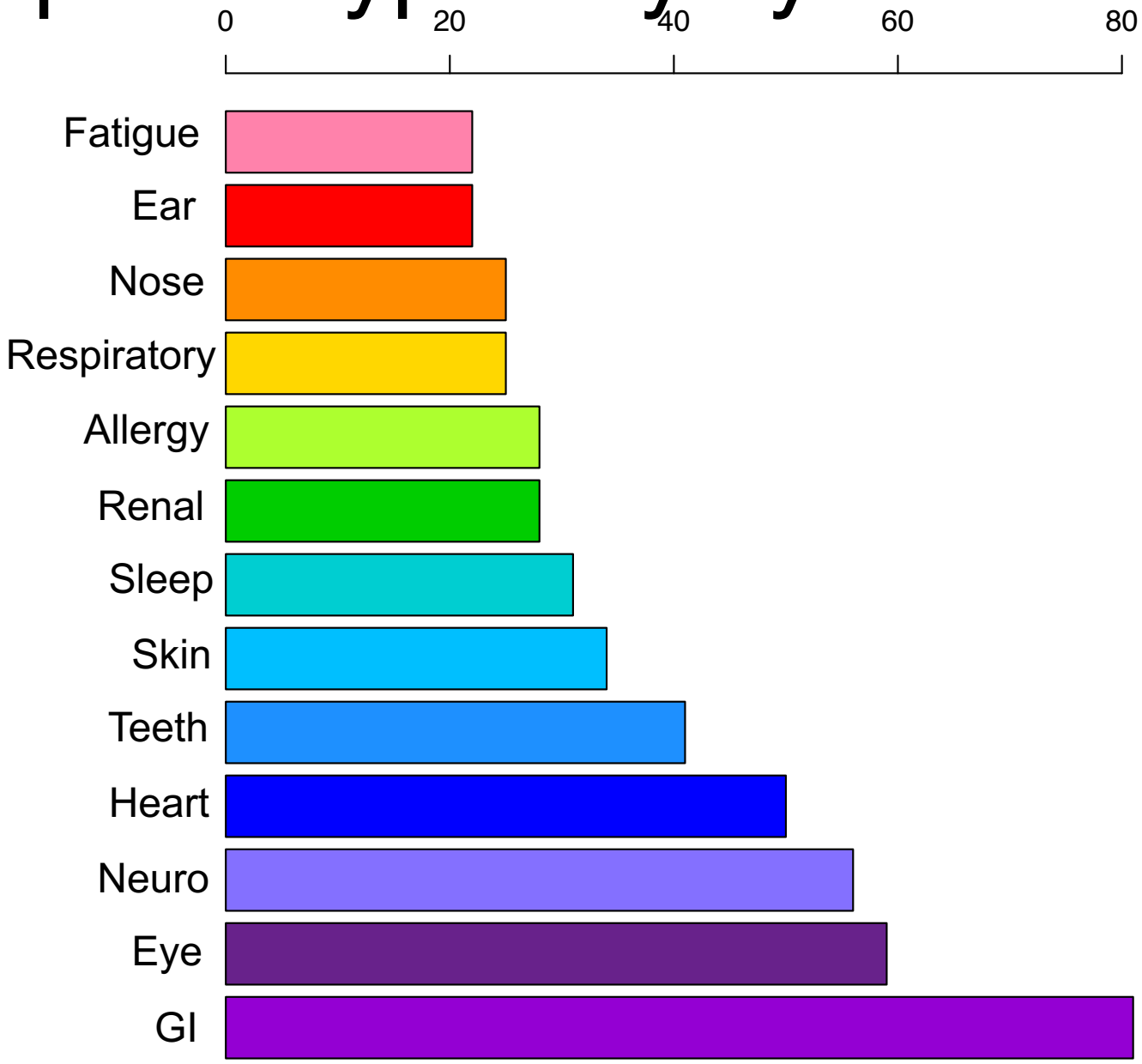
Schedule - 8 thr 17 years (ADOS Mod 3 - verbally fluent)					
	Pre-visit & Arrival Day	Testing Day 1: Mon		Testing Day 2: Tues	
		Parent	Child	Parent	Child
8:00 AM		8 - Pick up at Marcus		8:00 - Pick up at Marcus	
8:15 AM					
8:30 AM		8:30 - 9:30 Consent & Assent (1h) [Melissa]		8:30 - 10:30 KSADS Parent (3h) [Elaine Trainee]	8:30 - 10:30 ADIS (30m-2h) [Lindsey]
8:45 AM					
9:00 AM	Pre-visit: Phone screening & Surveys				
9:15 AM					
9:30 AM		9:30 - 12:30 ADI (1.5 - 3 hr) [Celine]	9:30 - 11:30 SIPS (1.5-2h) [Elaine Trainee]		
9:45 AM					
10:00 AM					
10:15 AM					
10:30 AM					10:30-10:45 Snack
10:45 AM				10:45-11:30 ADIS (45m) [Lindsey]	10:45-11:30 Cognitive Testing (1h); VMI (15m) [Celine]
11:00 AM					
11:15 AM					
11:30 AM			11:30-11:45 Snack	11:30 - 12: 15 Lunch (45m) [All]	
11:45 AM			11:45 - 12:45 KSADS (1h) [Elaine Trainee]		
12:00 PM					
12:15 PM				12:15 - 2:15 ADIS (30m - 2h) [Lindsey]	12:15-1:45 ADOS (1-1.5h) [Celine]
12:30 PM					
12:45 PM		12:45 - 1:30 Lunch (45m) [All]			
1:00 PM					
1:15 PM			1:15-2:15 Finish KSADS (1h) [Elaine Trainee]		
1:30 PM					
1:45 PM					1:45 - 2:15 Snack (30m)
2:00 PM					
2:15 PM		2:15 - 2:45 Blood Draw (0.5h) [Jeceah]			
2:30 PM				2:30 - 3:00 Travel to Wesley Woods (30m)	
2:45 PM		2:45 - 3:45 Medical Exam (1h) [Michael/Rossana] ** optional: Joe Cubells eval while parent in Med Hist Review			
3:00 PM				3:00 - 5:00 Feedback Mtg at Wesley Woods [Celine, Joe, Lindsey, Melissa/Jen]	3:00-5:00 Imaging (2h) [Sarah]
3:15 PM					
3:30 PM					
3:45 PM		3:45 - 4:00 Snack (15m)			
4:00 PM	4p Check in at Emory Conference Center	4:00 - 4:30 Travel to Wesley Woods (30m)			
4:15 PM					
4:30 PM			4:30-5:30 Practice Imaging (1h) [Sarah]		
4:45 PM					
5:00 PM				5:00 Return Family to Hotel	
5:15 PM					
5:30 PM		5:30 Return Family to Hotel			

With incredible participation from the 3q29 deletion community, we have now evaluated 32 individuals

Demographic info

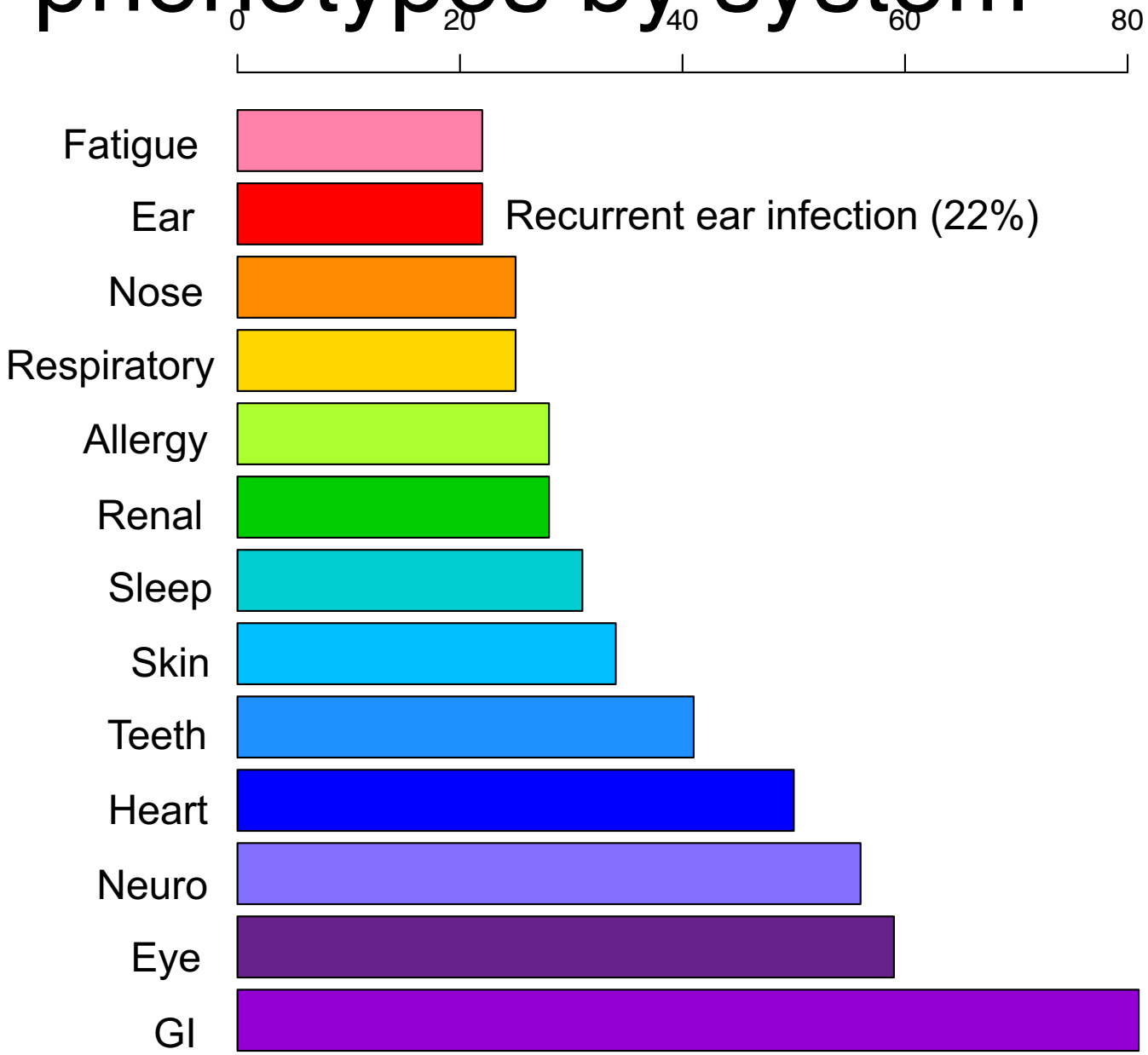
	Typical Deletion	
Number of individuals evaluated	32	
Age Range, years (mean)	4.8 – 39 years (14.5)	
Male:female	20:12	
Inheritance status	2 inherited; remaining *de novo* or unknown	
Geography	NE	9
	NW	0
	SE	11
	SW	5
	Outside US	2 UK (5 subjects); 2 Canada

Medical phenotypes by system



The 3q29 Project

Medical phenotypes by system



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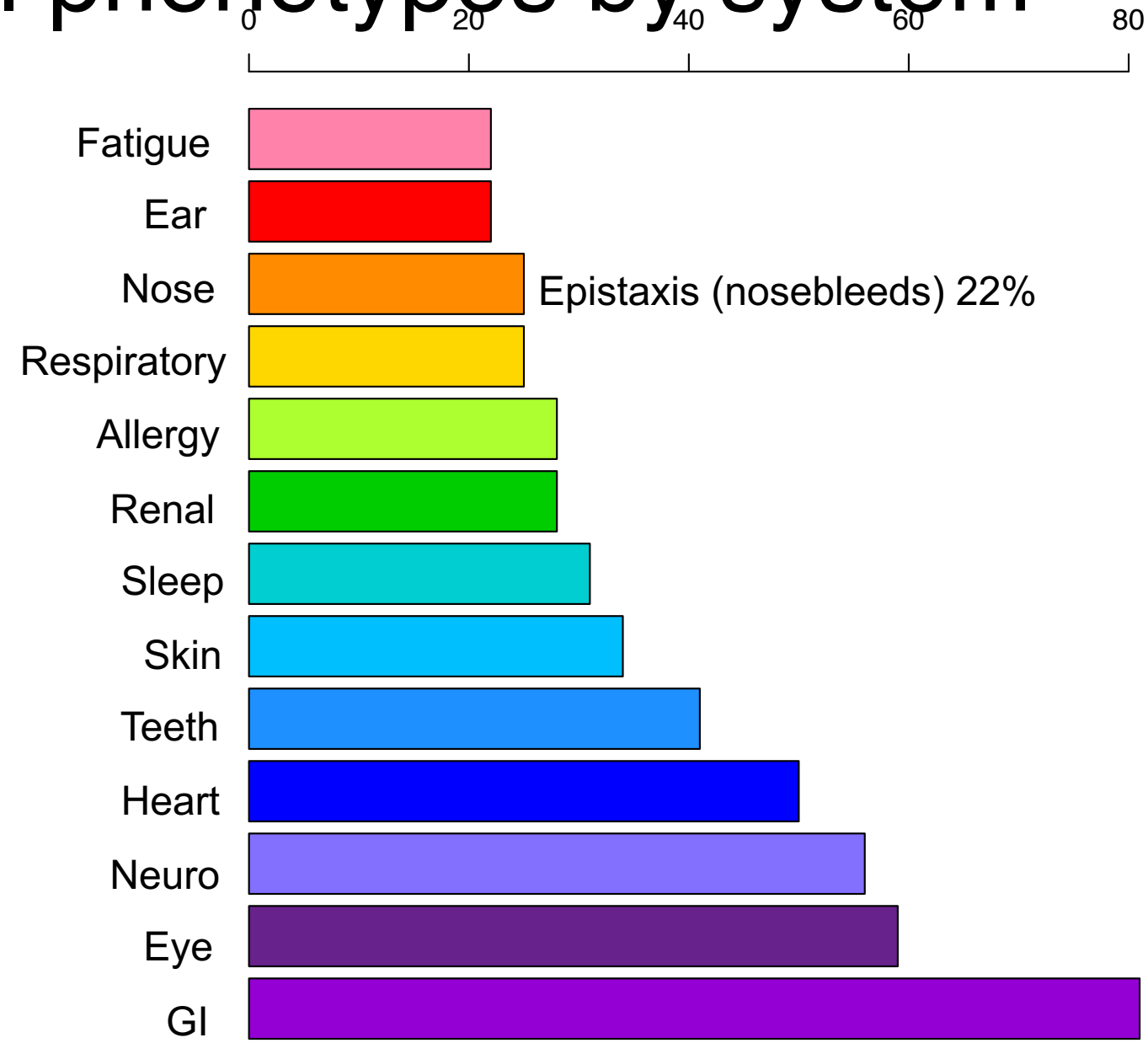
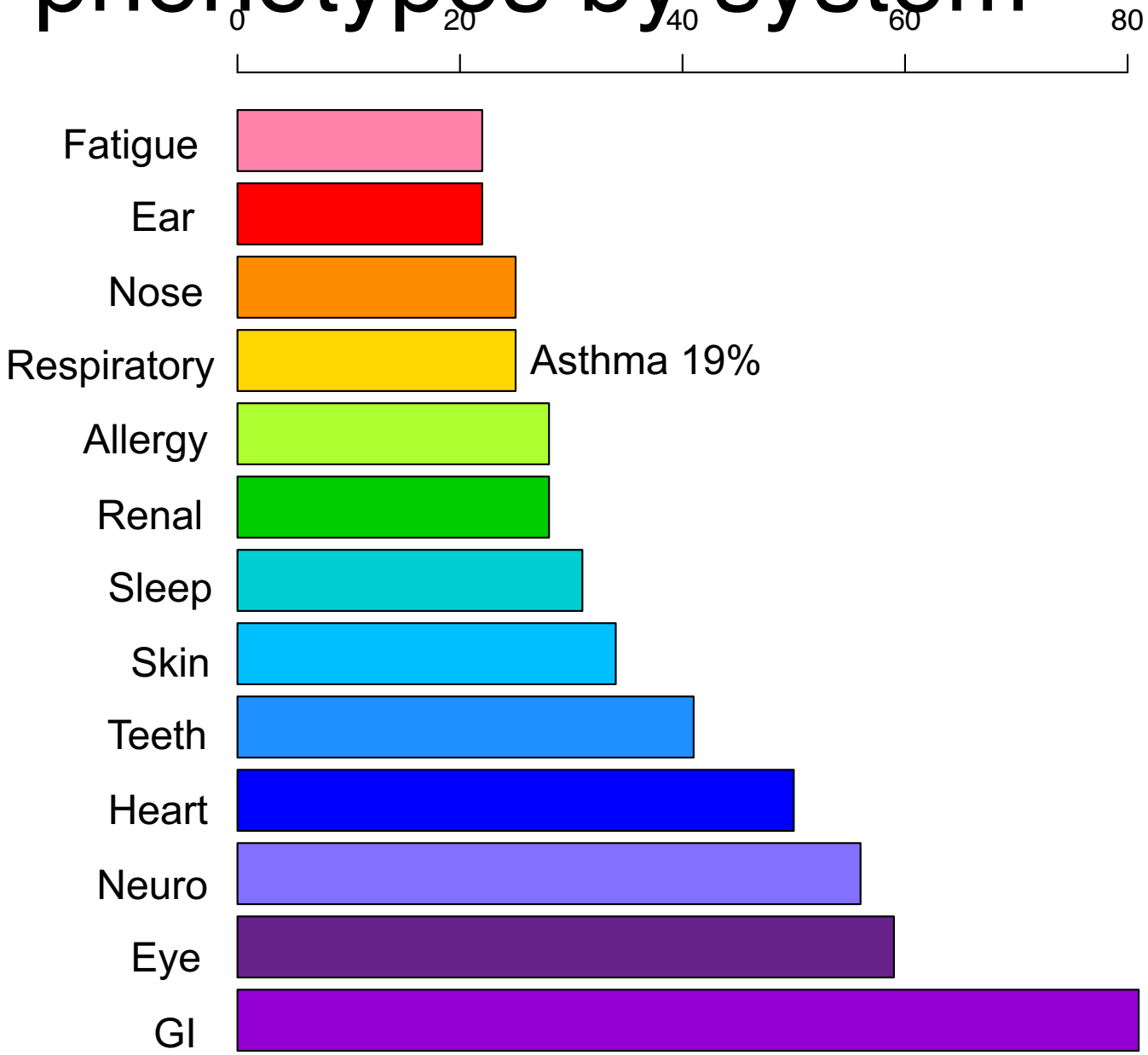
Medical phenotypes by system



Medical phenotypes by system



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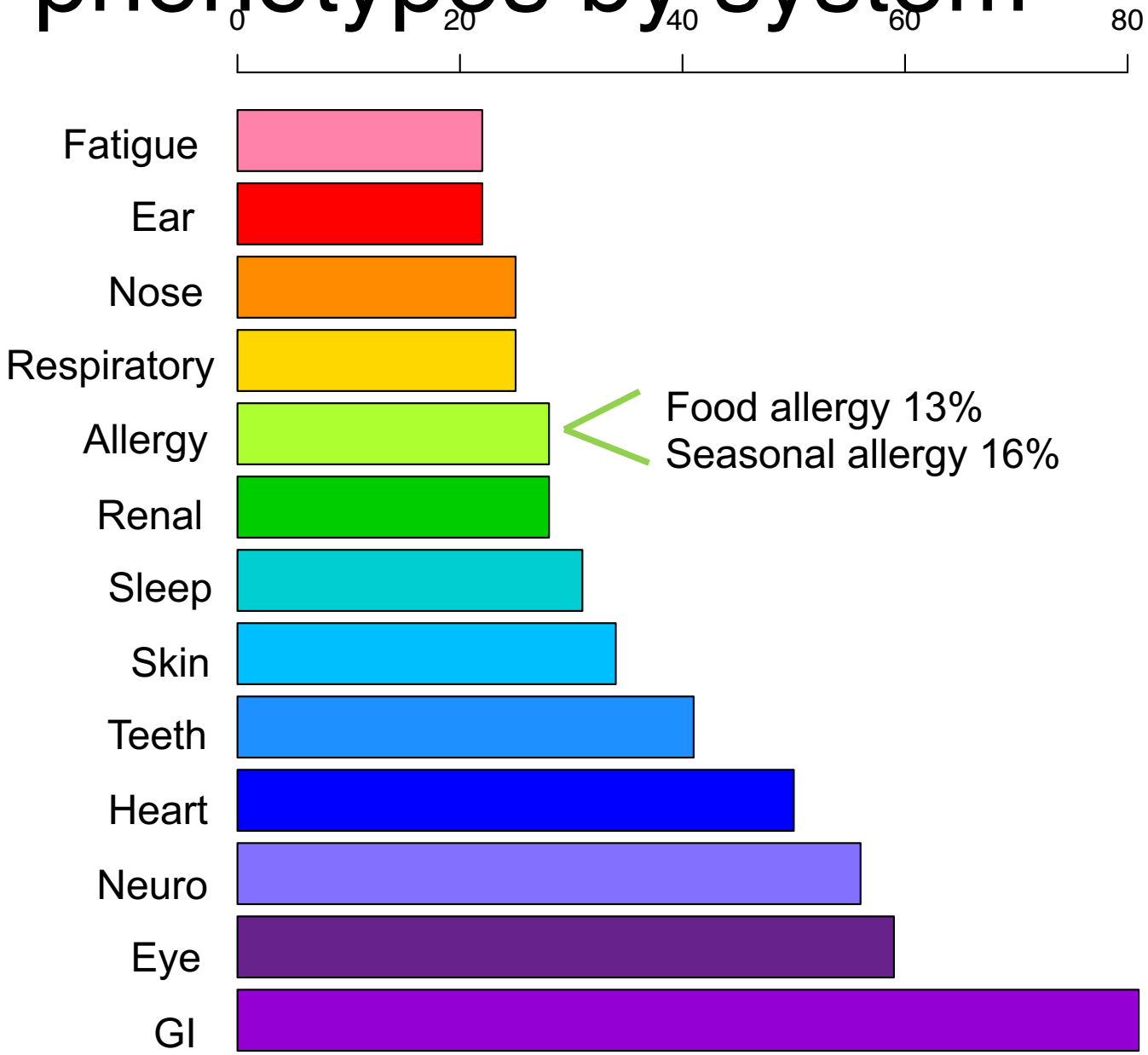
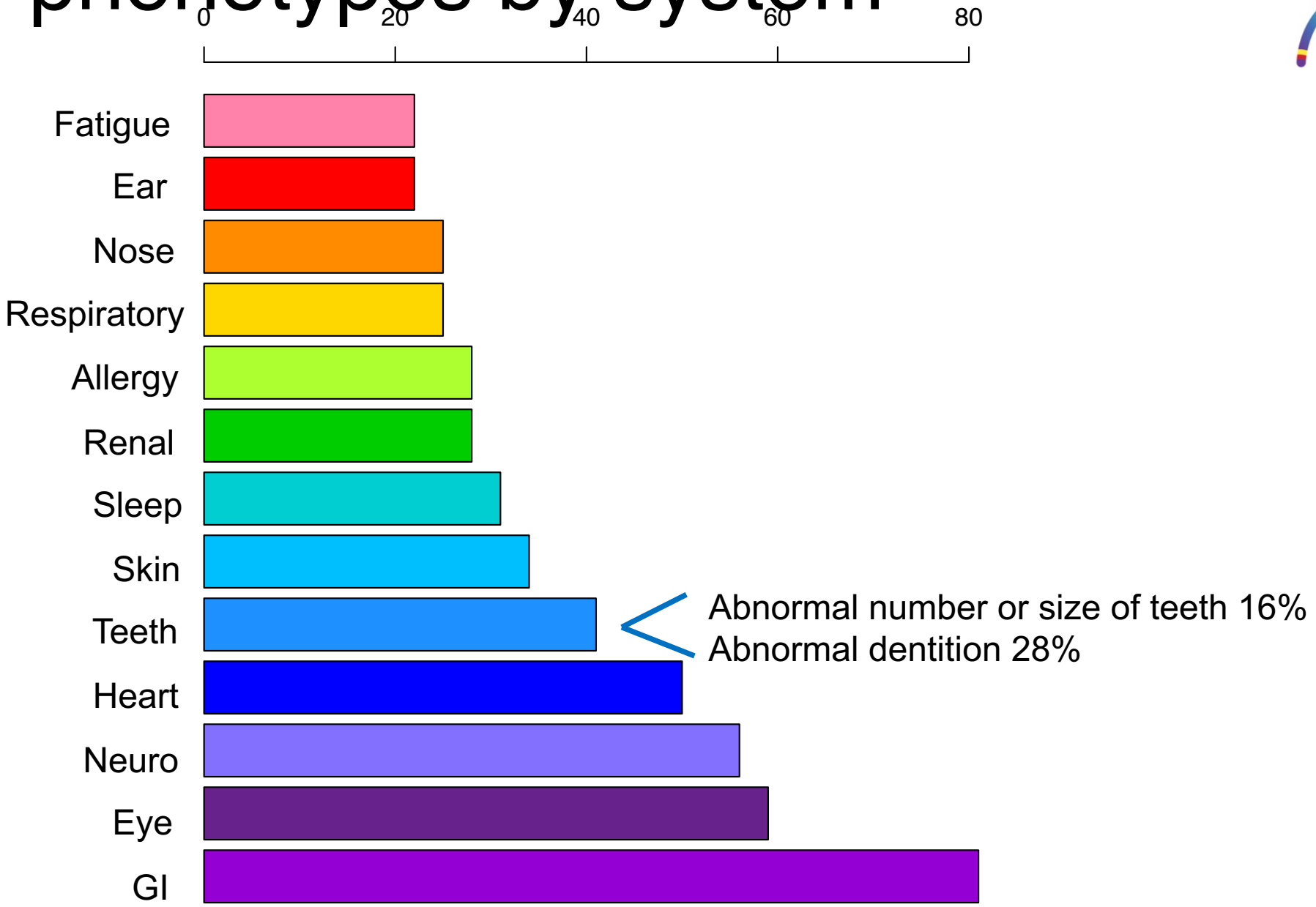
Medical phenotypes by system

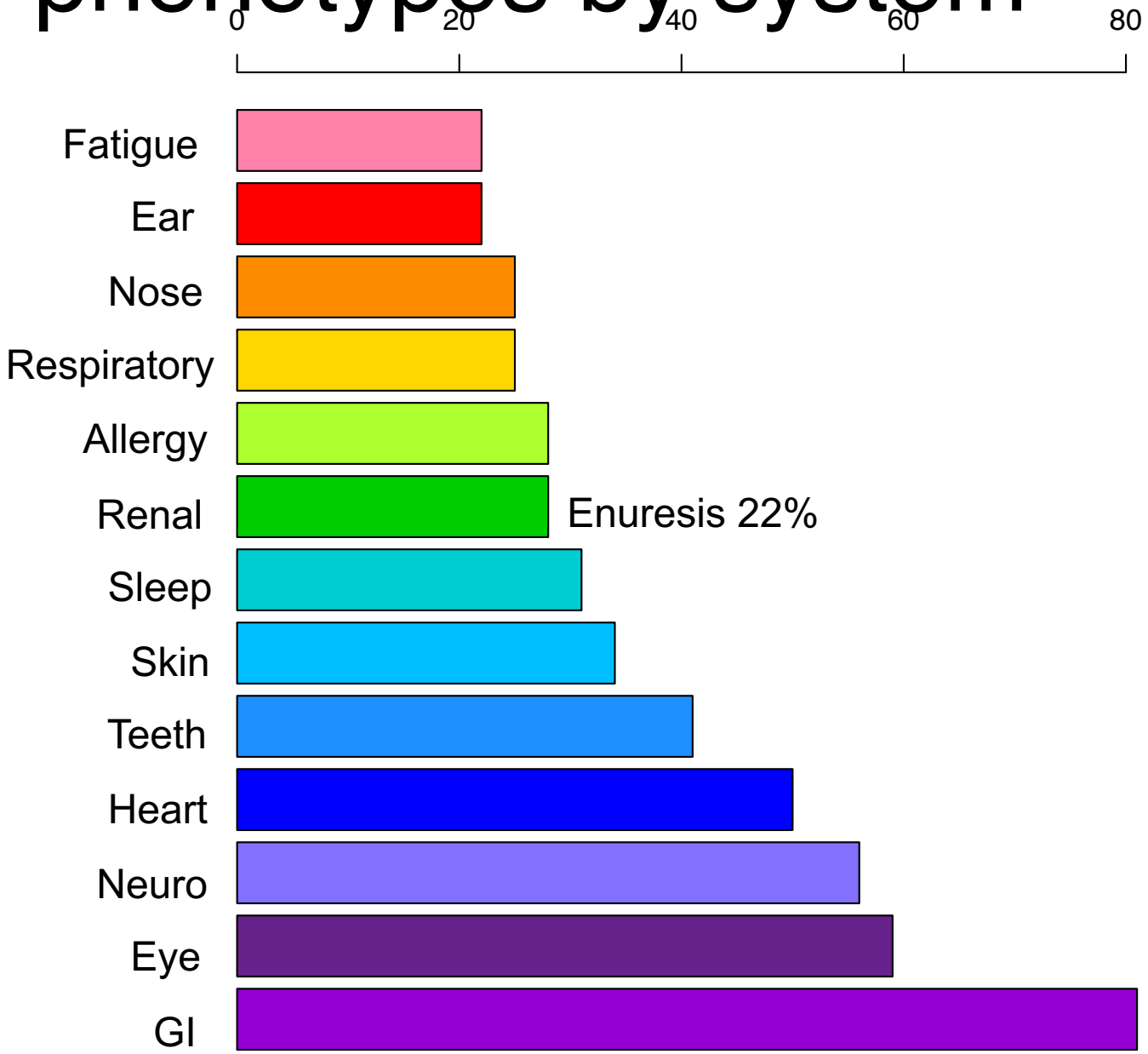


The 3q29 Project

Medical phenotypes by system



Medical phenotypes by system



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