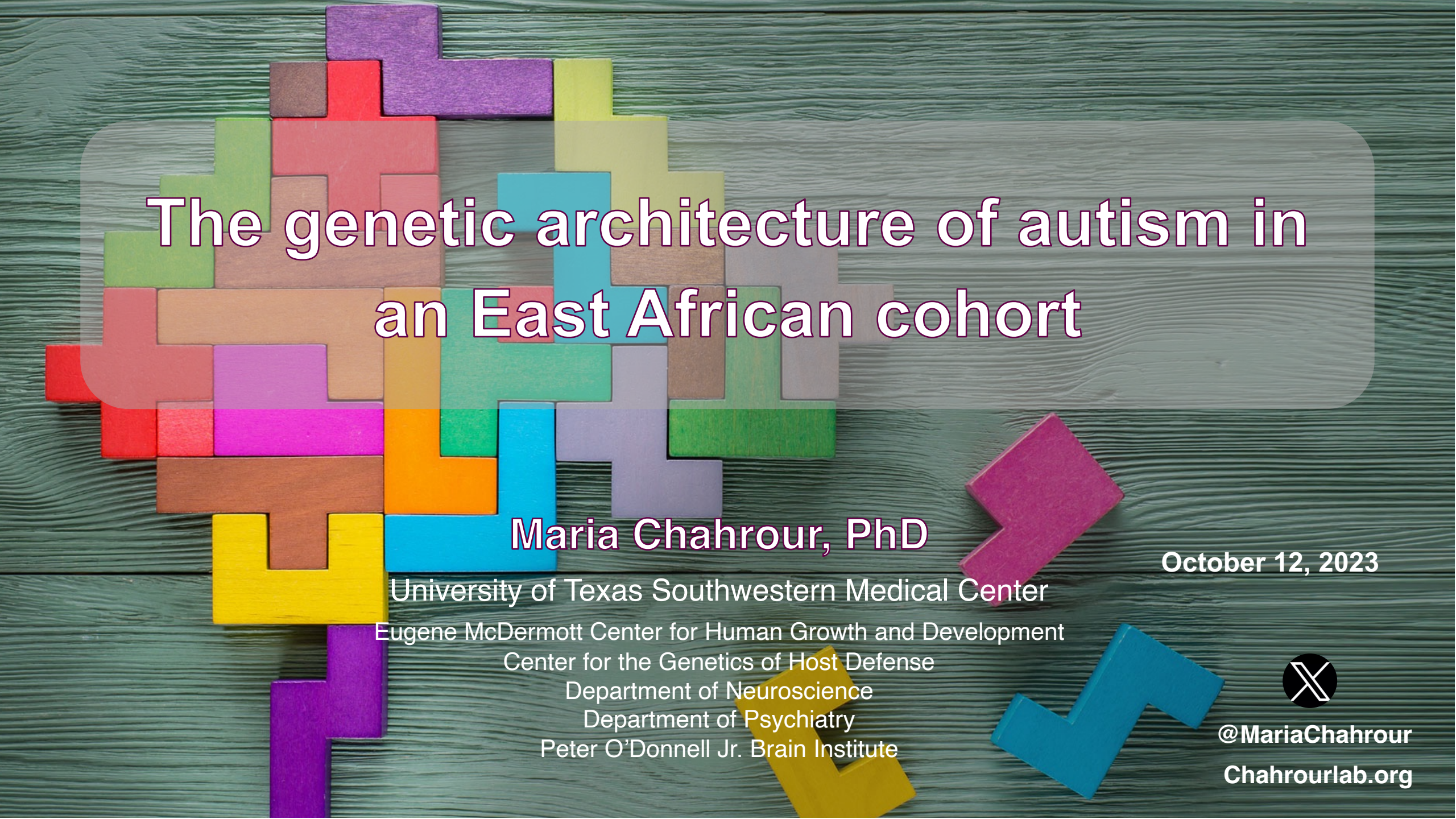

The genetic architecture of autism in an East African cohort

Maria Chahrour, PhD

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October 12, 2023

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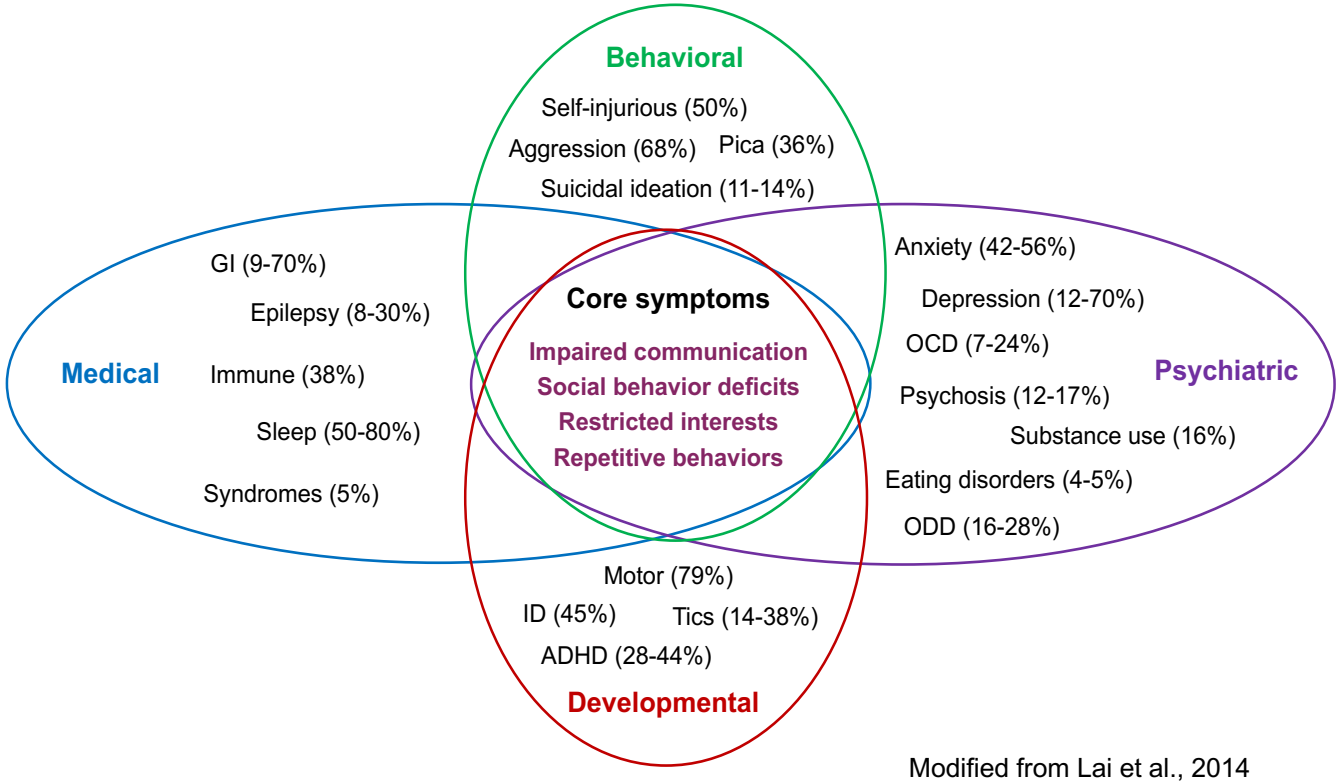
Autism spectrum disorder

- A spectrum of neurodevelopmental disorders
- Affects ~ 2.8% of children in the USA (~ 1:36)
- More males affected than females (~ 3 X more)
- Prevalence rate increasing ~7% annually for the past 20 years
- Huge societal and economic burdens

ASD comorbidities



Modified from Lai et al., 2014

Data from the CDC Autism and Developmental Disabilities Monitoring (ADDM) Network

Causes of ASD

Heritability ~83-90%

Genetics

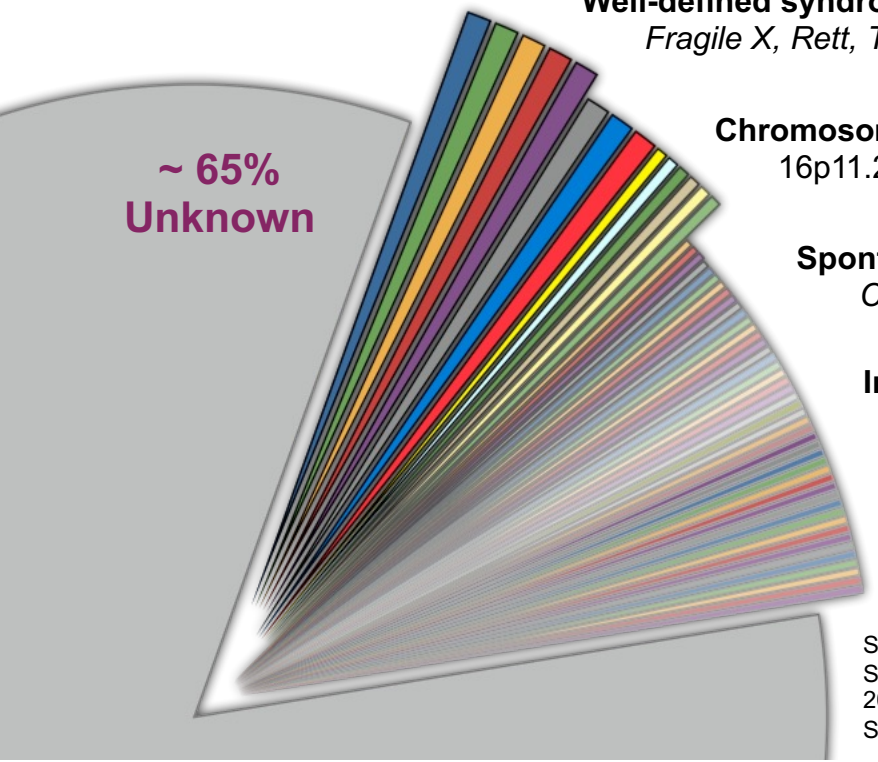
Environment

Autism is very complex

Tick et al. 2016, Sandin et al. 2017

ASD genetics is heterogeneous and complex

- High heritability ~83-90%
- Hundreds of genes contribute to ASD
- Each gene contributes to a small proportion of patients



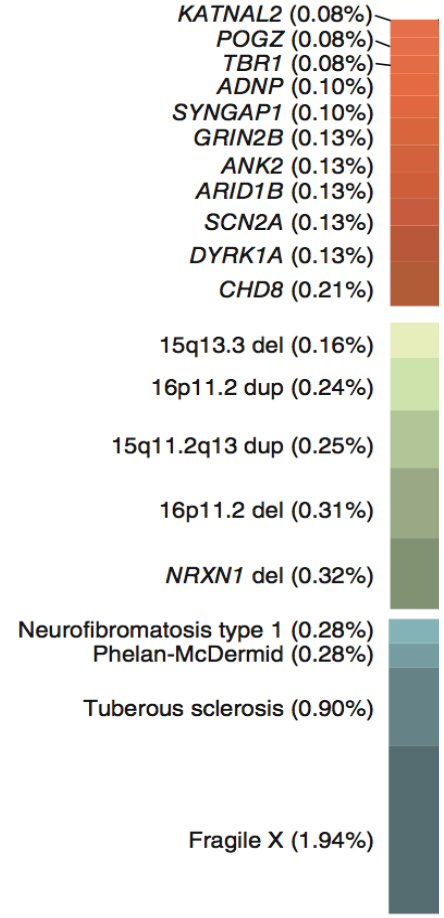
Well-defined syndromes
Fragile X, Rett, Tuberous Sclerosis, Angelman…

Chromosomal abnormalities or copy number variants
16p11.2, 15q11-q13, 22q11, 7q11.23, *NRXN1*, *SHANK3*, *NLGNs*…

Spontaneous (*de novo*) mutations
CHD8, SYNGAP1, SCN2A, *ADNP*, *ARID1B, FOXP1*…

Inherited mutations
SLC9A9, CC2D1A, BCKDK, AMT, KDM5A, UBE3B…

Somatic (in the brain) mutations



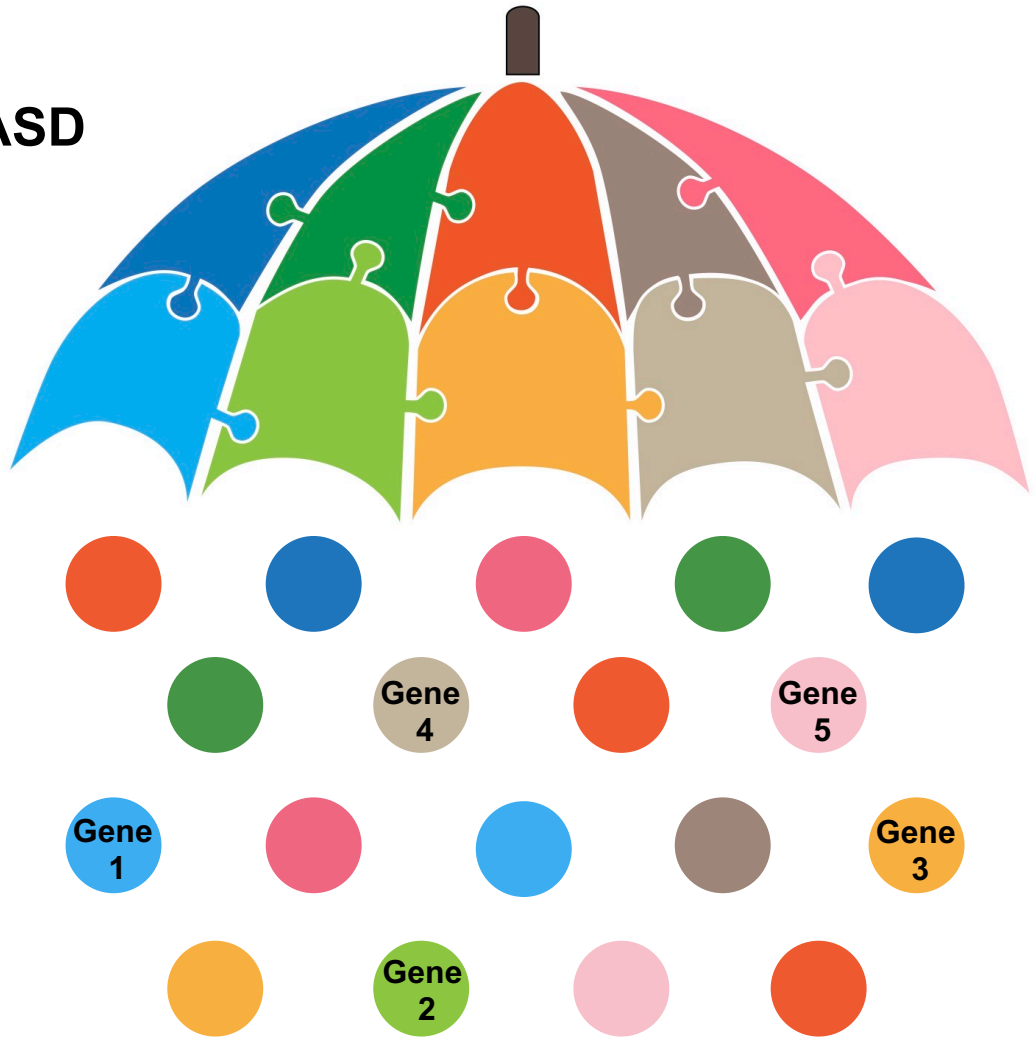
Modified from de la Torre-Ubieta et al., 2016

Sebat et al. 2007, Morrow et al. 2008, Weiss et al. 2008, Miller et al. 2010, Pinto et al. 2010, Betancur 2011, Sanders et al. 2011, O' Roak et al. 2011, Sanders et al. 2012, Neale et al. 2012, O' Roak et al. 2012, Iossifov et al. 2012, Chahrour et al. 2012, Yu & Chahrour et al. 2013, Lim et al. 2013, De Rubeis et al. 2014, Doan et al. 2019, Satterstrom et al. 2020, Fu et al. 2022, Tuncay et al. 2022, Zhou et al. 2022, Tuncay et al. 2023

ASD as a collection of individually rare disorders

Hundreds of genes contribute to ASD

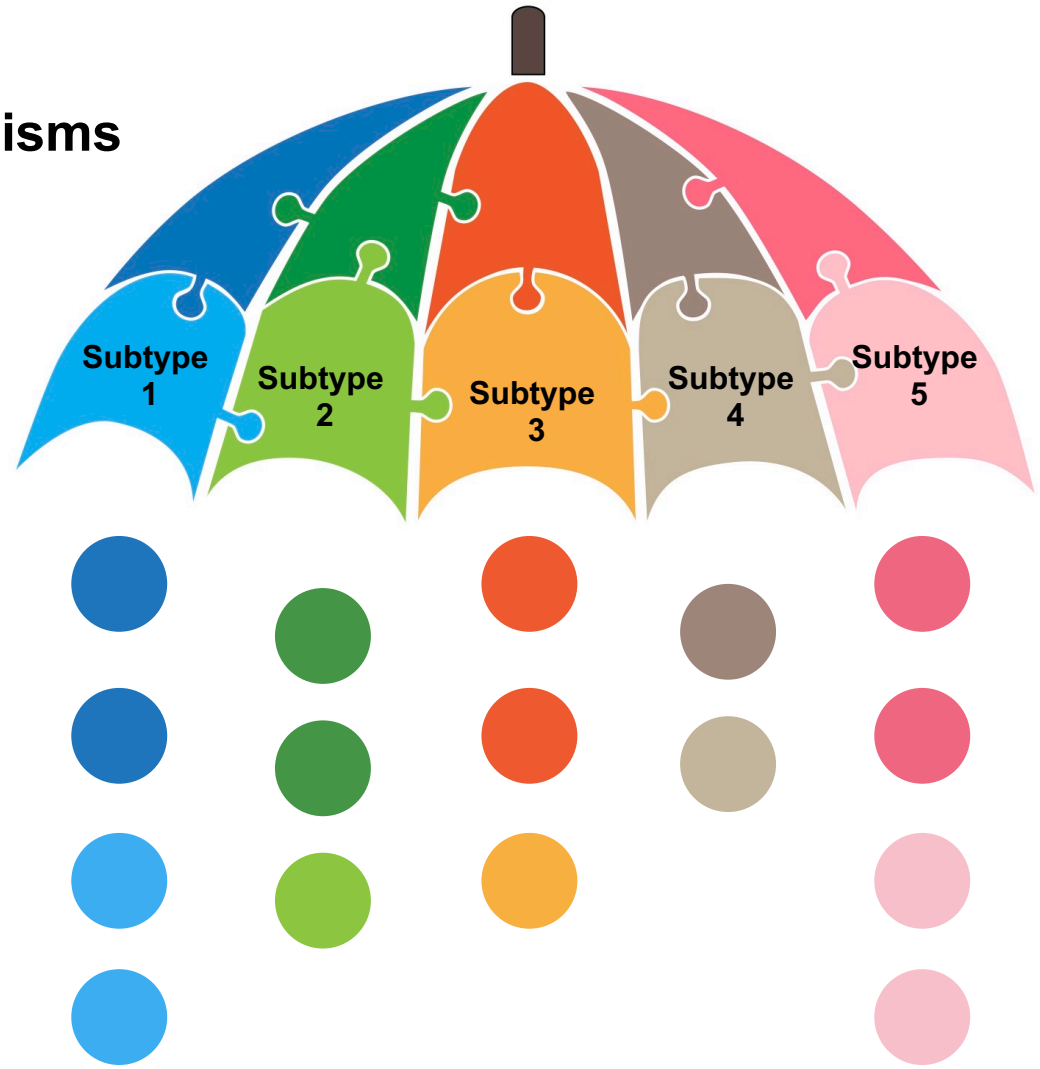
Each gene contributes to a small proportion of patients (< 2% of cases)



ASD as a collection of individually rare disorders

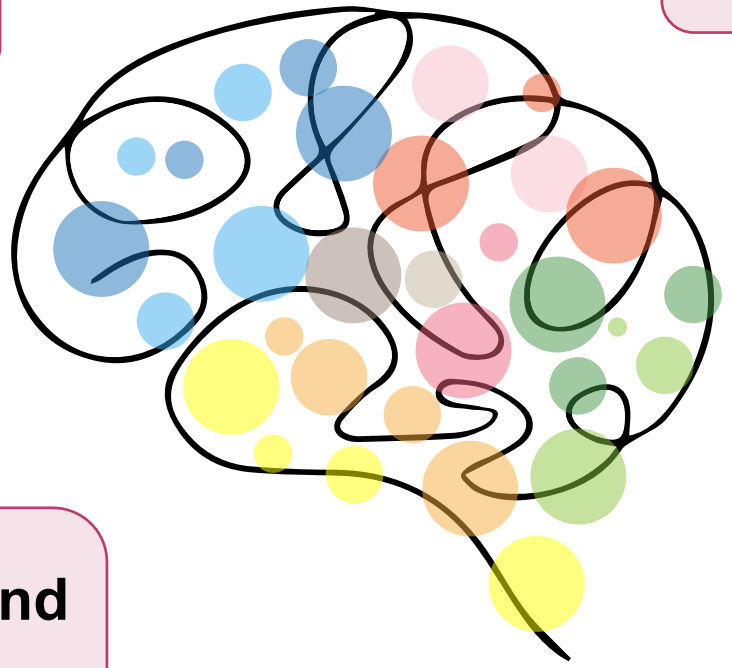
Understanding molecular mechanisms underlying each genetic subtype

Grouping genes based on molecular pathways



Genomics in familial cohorts
Forward genetics

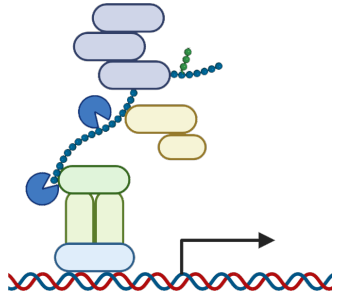
Gene discovery in ASD



Impact of patient mutations
Neurobehavioral phenotyping of mouse models

Functional characterization

Molecular mechanisms



Function-dependent questions:
ex. ubiquitin proteasome pathway
ex. single-cell transcriptional programs

Diagnosis and targeted therapies

Actionable pathways

Genomics in familial cohorts
Forward genetics

Gene discovery in ASD

Impact of patient mutations
Neurobehavioral phenotyping of mouse models

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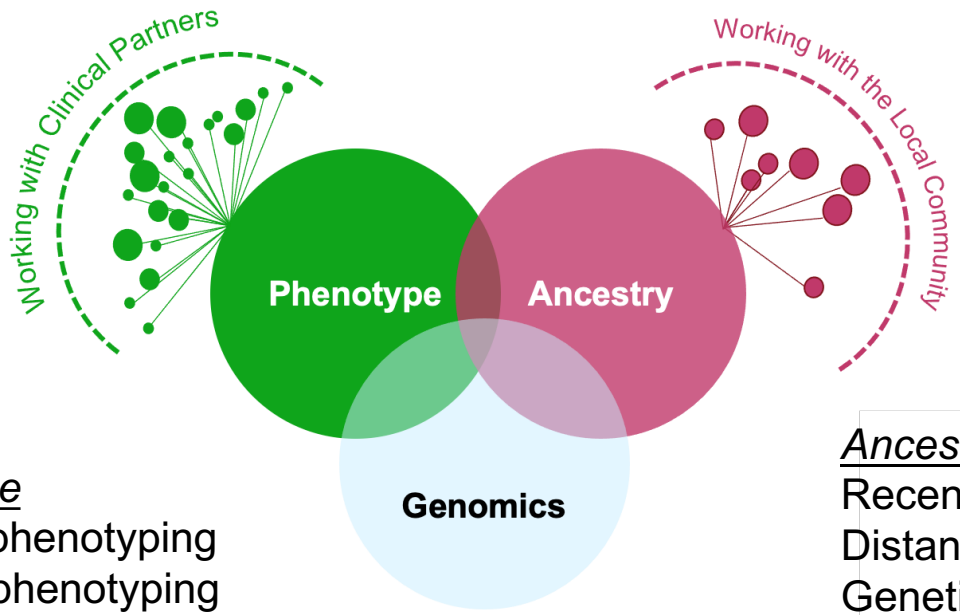


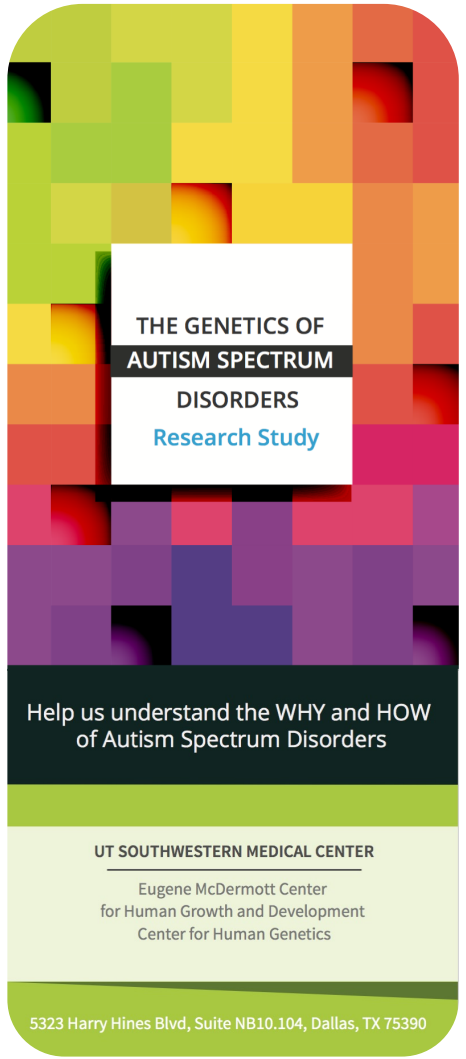
Phenotype
Detailed phenotyping
Reverse phenotyping

Ancestry
Recent shared ancestry
Distant shared ancestry
Genetically diverse populations

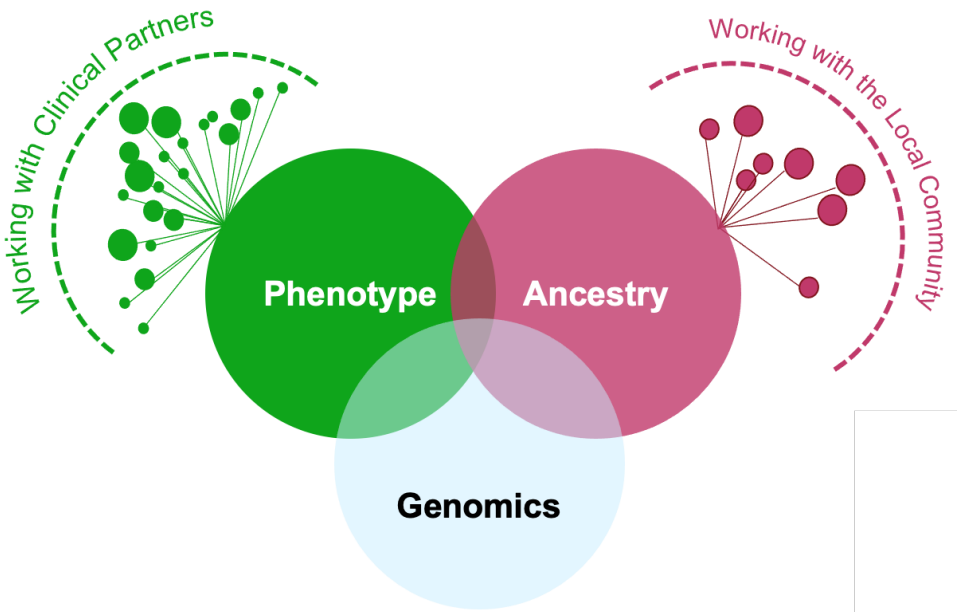
ASD genes

Diagnosis & Therapeutics

Brain development, Social behavior, Language



Genomics in familial cohorts

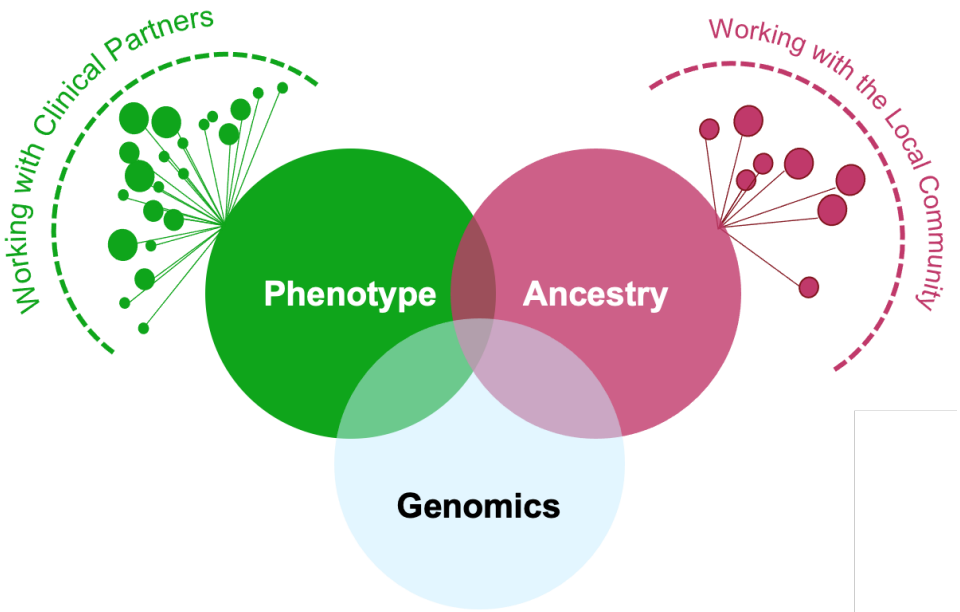


Families	859
Individuals	3,269

DFW cohort | **Shared ancestry cohorts** | **African cohort**

ASD variants in known genes and new candidates

Genomics in familial cohorts



Families with ASD from the East African community in Dallas

- Higher prevalence of ASD (~5%)
- Genetic diversity in Africa
- Underrepresented in genomics studies

Tuncay et al., 2023 *Cell Genomics*

DFW cohort | Shared ancestry cohorts | **African cohort**

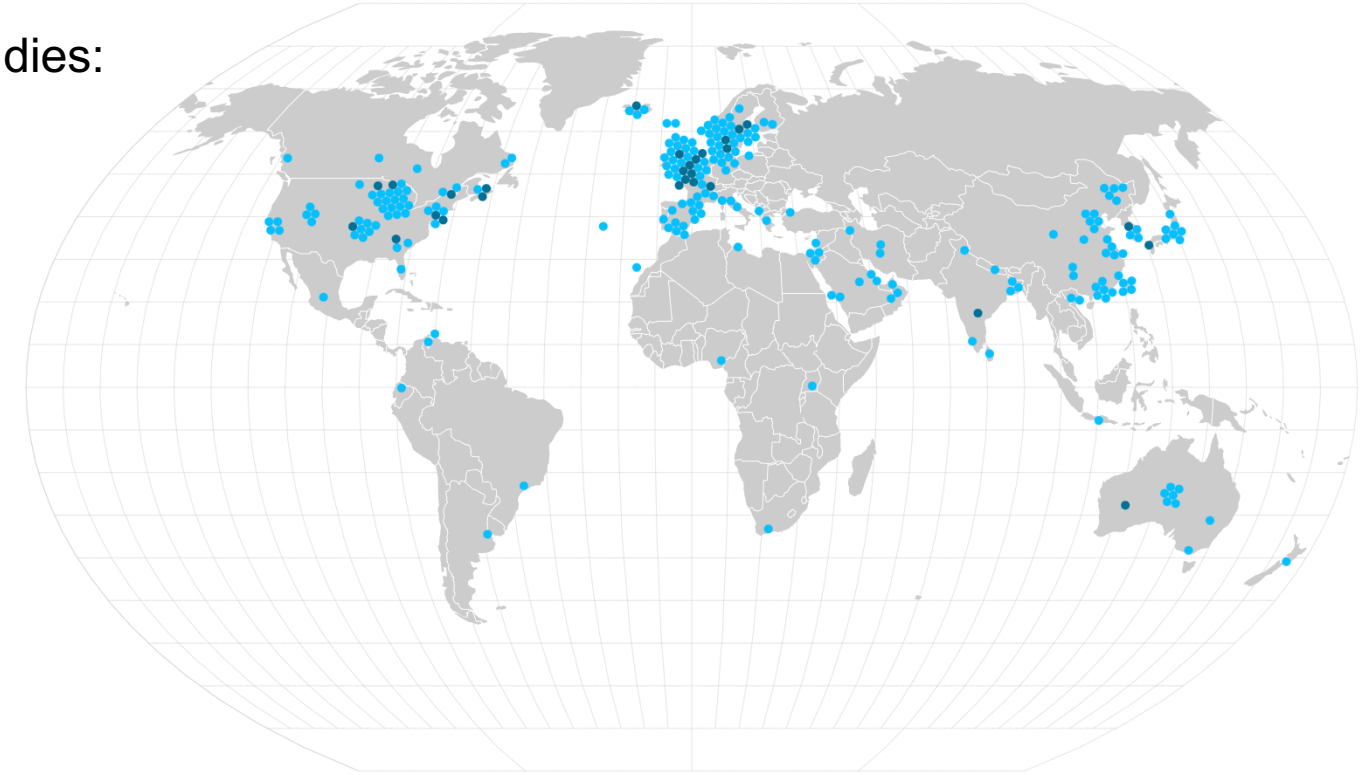
ASD variants in known genes and new candidates

Global prevalence of ASD

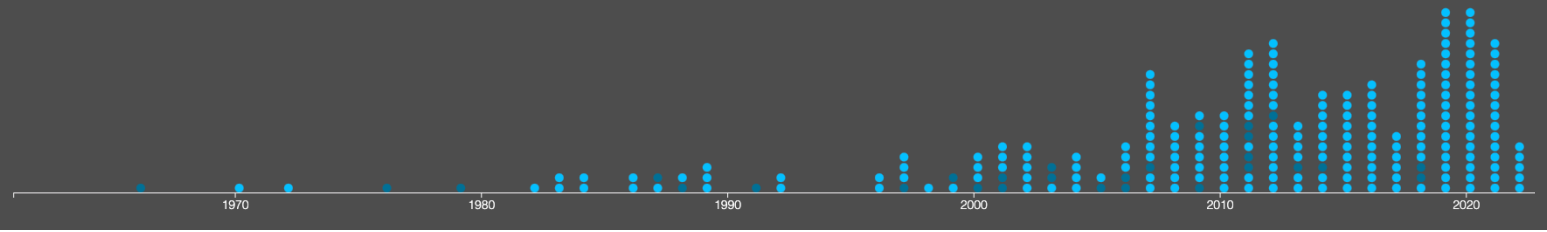
- ASD affects 1% of children worldwide; the prevalence in many low- and middle-income countries is unknown

Global prevalence of ASD

- ASD affects 1% of children worldwide; the prevalence in many low- and middle-income countries is unknown
- Prevalence studies:



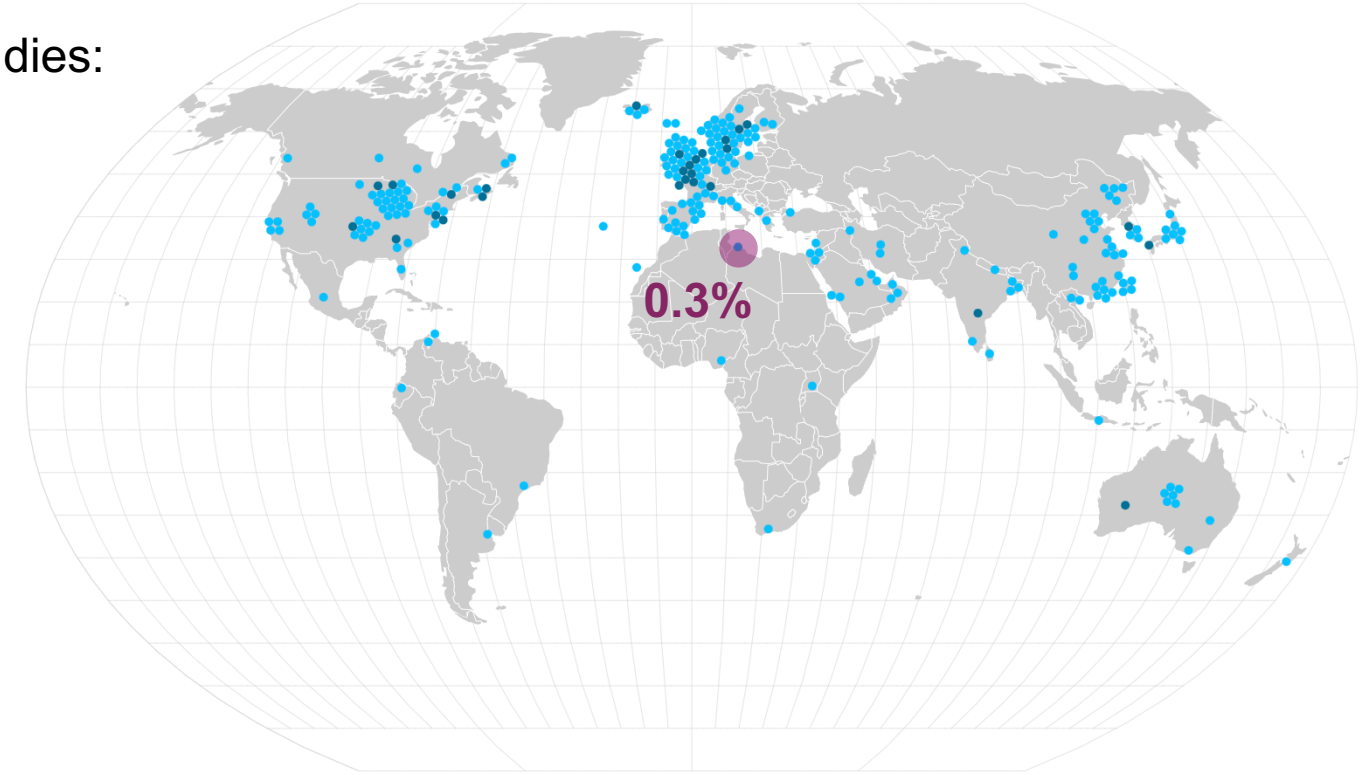
Global map of autism prevalence by Spectrum
Prevalence.spectrumnews.org



Global prevalence of ASD

- ASD affects 1% of children worldwide; the prevalence in many low- and middle-income countries is unknown
- Prevalence studies:

Libya



Zeglam A.M. and Maound A.J. 2012

Country
Libya

Area
Tripoli

Sample size
30,508

Age (years)
0-16

Diagnostic criteria
DSM-IV

Diagnostic tools
Unavailable

Percent w/ average IQ
31

Sex ratio (M:F)
4

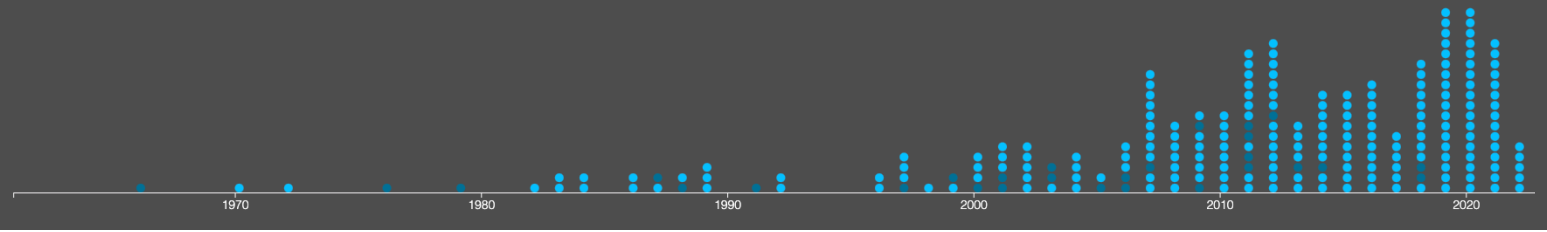
Prevalence (per 10,000)
33

95% Confidence interval
27.5-39

Year(s) studied
2005-2009

Category
ASD

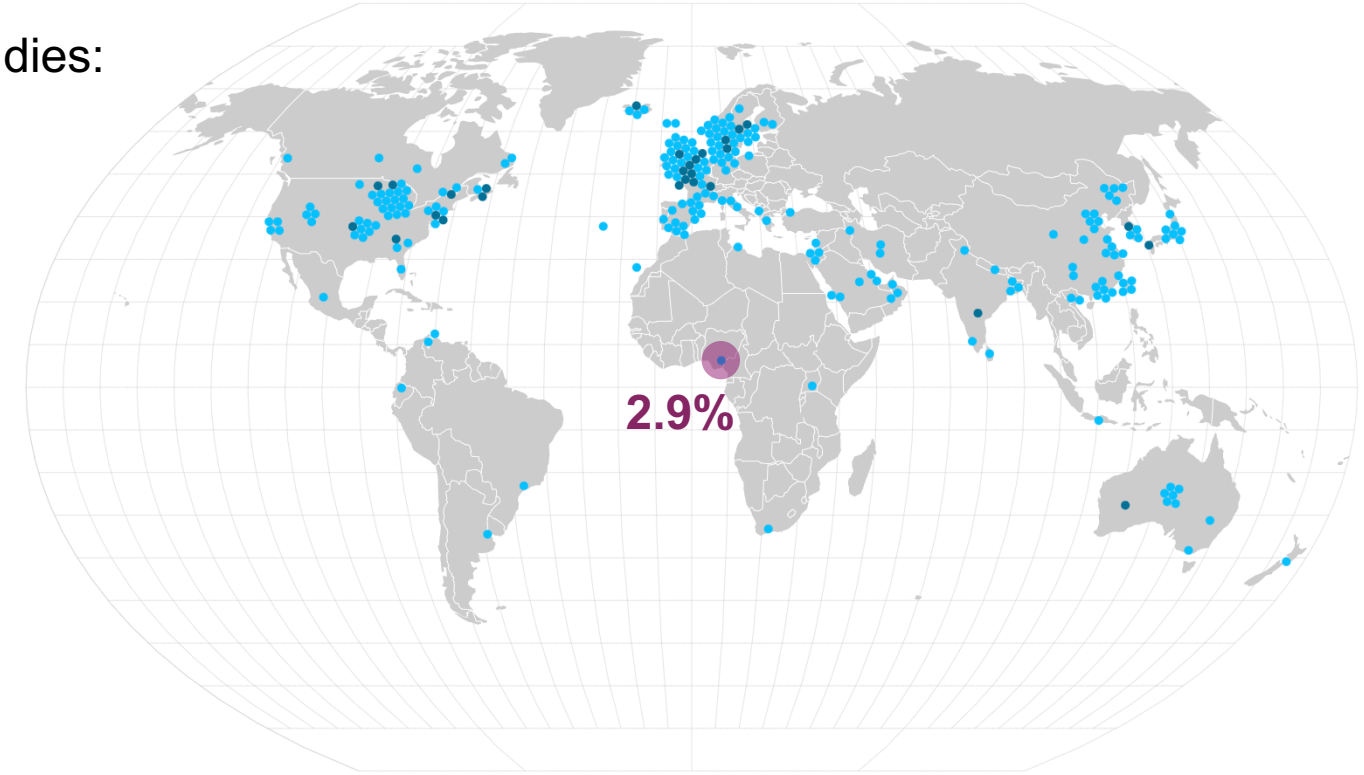
Global map of autism prevalence by Spectrum
Prevalence.spectrumnews.org



Global prevalence of ASD

- ASD affects 1% of children worldwide; the prevalence in many low- and middle-income countries is unknown
- Prevalence studies:

Nigeria



Chinawa J.M. *et al.* 2016

Country
Nigeria

Area
Enugu and Ebonyi states

Sample size
721

Age (years)
3-18

Diagnostic criteria
DSM-IV-TR

Diagnostic tools
Parent report, Teacher report

Percent w/ average IQ
Unavailable

Sex ratio (M:F)
0.9

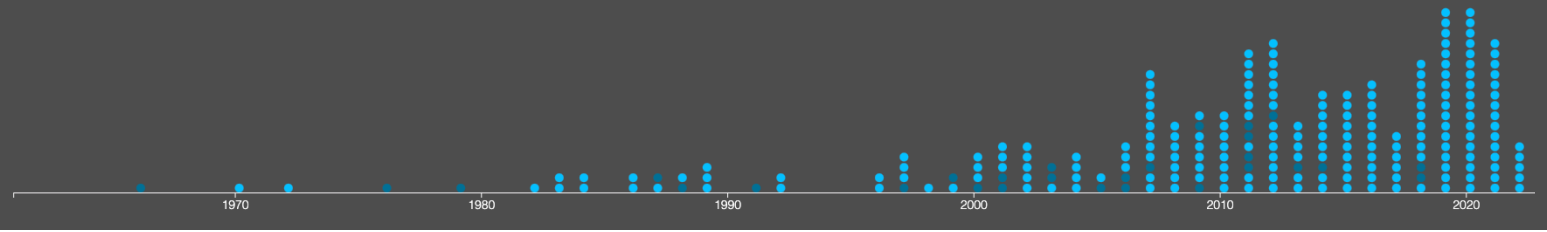
Prevalence (per 10,000)
290

95% Confidence interval
169-414

Year(s) studied
2014

Category
ASD

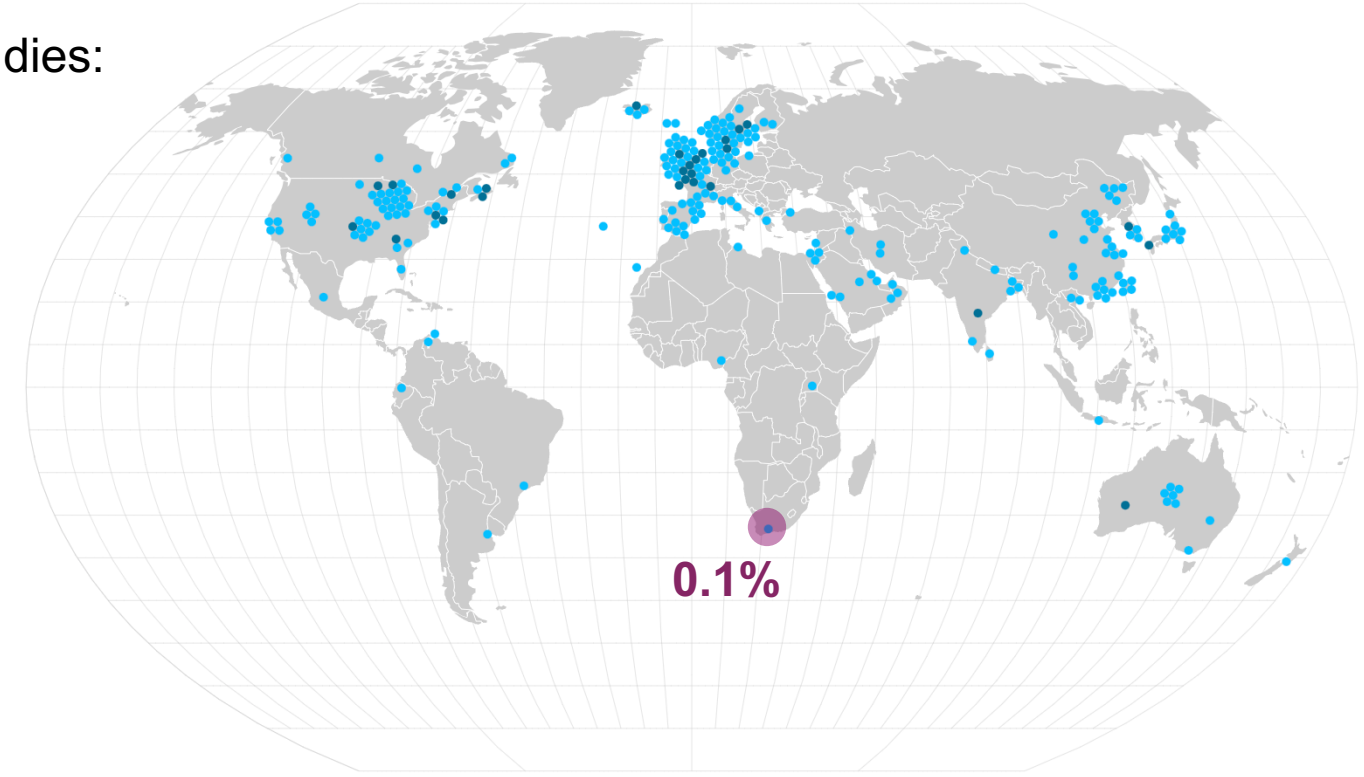
Global map of autism prevalence by Spectrum
Prevalence.spectrumnews.org



Global prevalence of ASD

- ASD affects 1% of children worldwide; the prevalence in many low- and middle-income countries is unknown
- Prevalence studies:

South Africa



Pillay S. *et al.* 2020

Country
South Africa

Area
Western Cape

Sample size
1,154,353

Age (years)
3-23

Diagnostic criteria
Unavailable

Diagnostic tools
Unavailable

Percent w/ average IQ
77.8

Sex ratio (M:F)
5.5

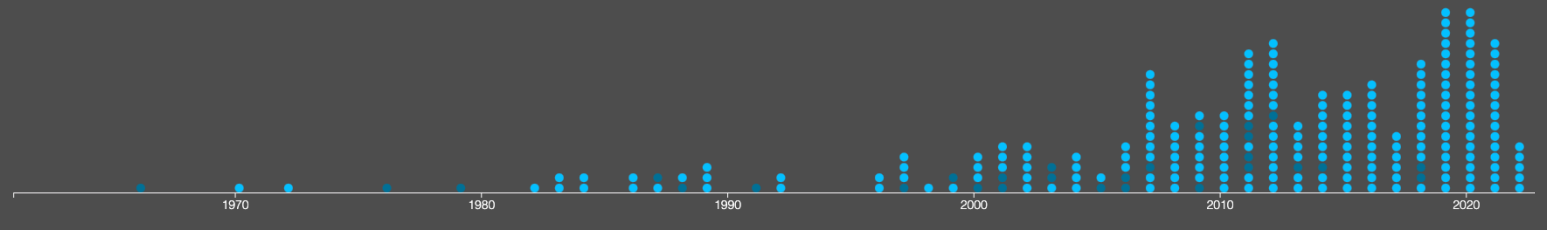
Prevalence (per 10,000)
8.1

95% Confidence interval
7.6-8.7

Year(s) studied
2016

Category
ASD

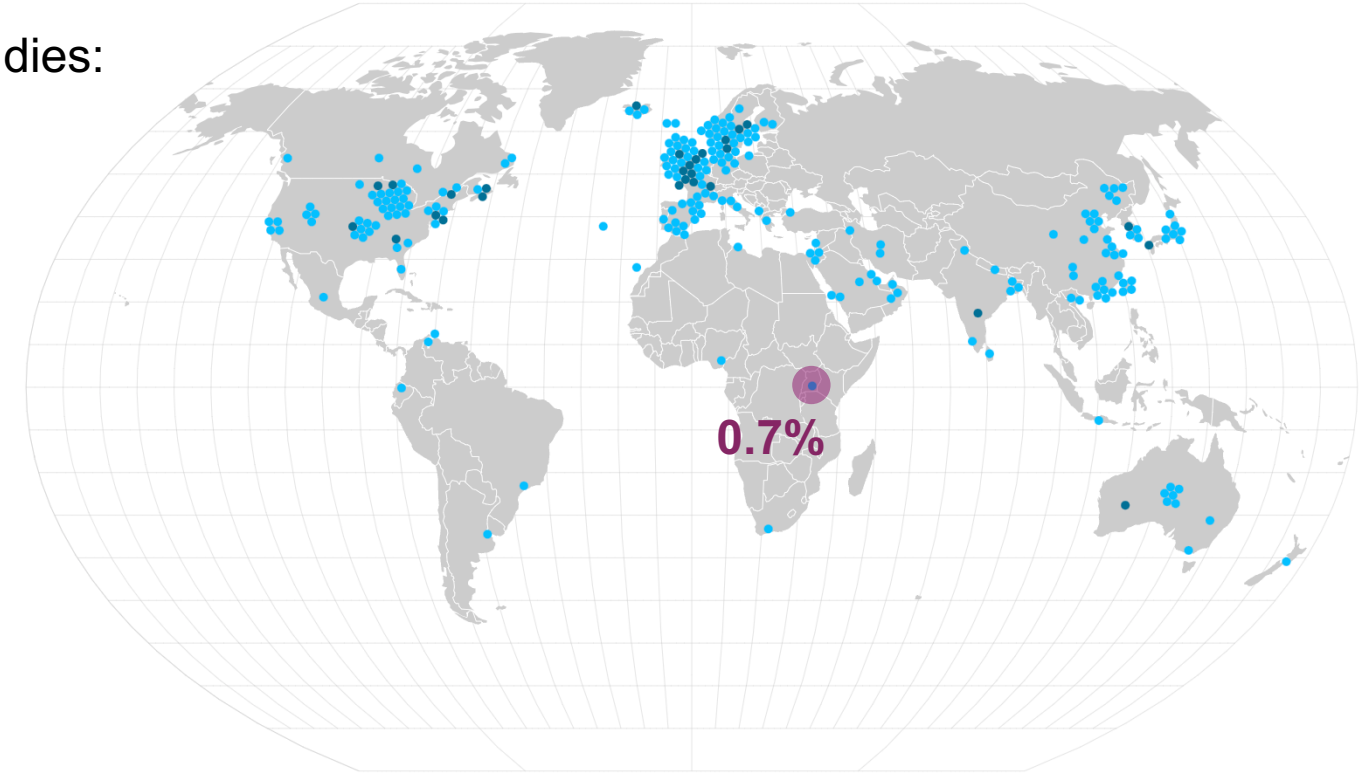
Global map of autism prevalence by Spectrum
Prevalence.spectrumnews.org



Global prevalence of ASD

- ASD affects 1% of children worldwide; the prevalence in many low- and middle-income countries is unknown
- Prevalence studies:

Uganda



Kakooza-Mwesige A. *et al.* 2014

Country
Uganda

Area
Kampala and Wakiso Districts

Sample size
1,169

Age (years)
2-9

Diagnostic criteria
DSM-IV-TR

Diagnostic tools
23Q

Percent w/ average IQ
Unavailable

Sex ratio (M:F)
Unavailable

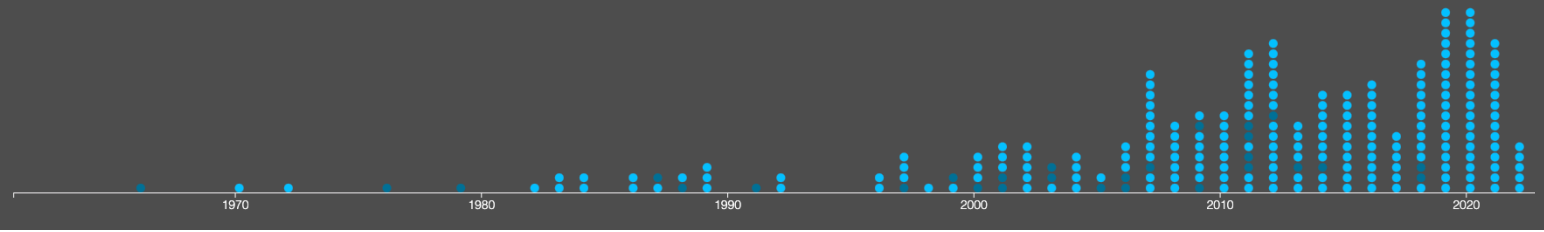
Prevalence (per 10,000)
68

95% Confidence interval
35-134

Year(s) studied
2010-2011

Category
PDD

Global map of autism prevalence by Spectrum
Prevalence.spectrumnews.org



The Prevalence of Autism Spectrum Disorder in the East African Community

Leah Seyoum-Tesfa, RN, MEd

Mother, Advocate, and Founder

Reaching Families Advocacy and Support Group

Dallas, Texas

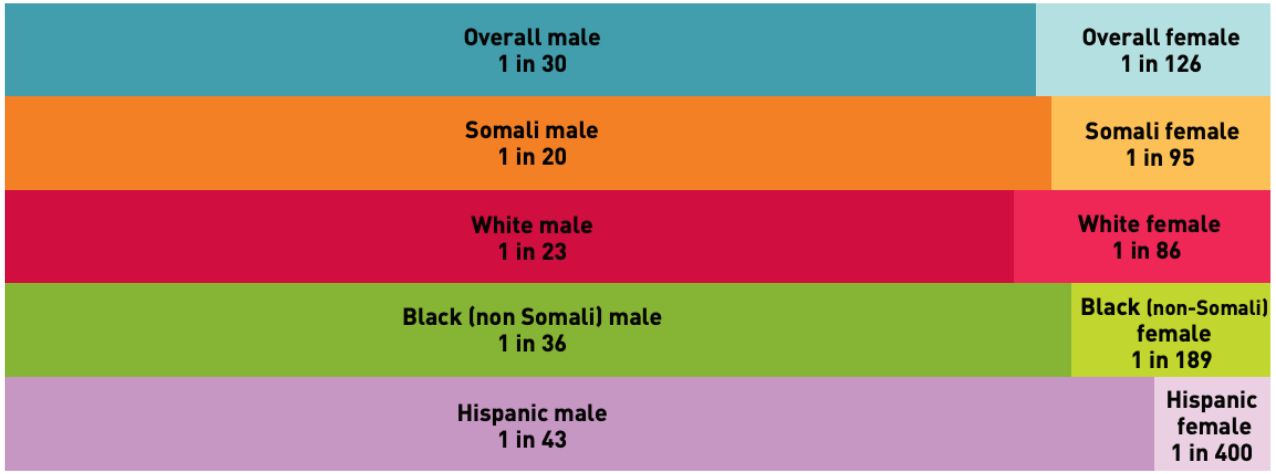
Reaching Families Advocacy and Support Group

- Non-profit organization
- Supports Ethiopian / Eritrean families who have children with special needs
- 25 support groups in major US cities and Europe
- Education, empowerment
- Advocacy, mentorship
- Community outreach to promote early identification and early intervention and break the stigma
- Individual and family counseling
- Grant and scholarship for therapies, swimming, and other immediate needs

Minneapolis Somali Autism Spectrum Disorder Prevalence Project (2013)

Community Report

By gender



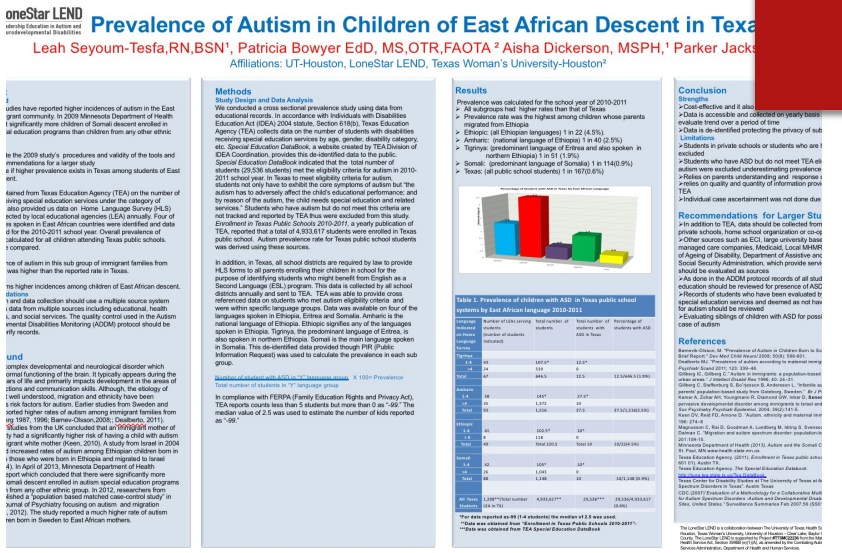
Children with ASD who were identified as having ID

	Percentage of children with ID	Percentage of children missing IQ scores
Overall	33%	28%
Somali	100%	35%
White	20%	26%
Black (non-Somali)	30%	19%
Hispanic	22%	40%

The Prevalence of Autism Spectrum Disorder in Children of East African Descent in Texas (2013)

Lonestar Lend Fellowship Training Program

- Prevalence rate was the highest among children whose parents migrated from Ethiopia.
- All subgroups had higher rates than that of other peers in Texas.
- Ethiopic: 1:22 (4.5%)
- Amharic: 1:40 (2.5%)
- Tigrinya: 1:51 (1.9%)
- Texas (all public-school students): 1:167



oneStar LEND

Prevalence of Autism in Children of East African Descent in Texa

Leah Seyoum-Tesfa,RN,BSN[1], Patricia Bowyer EdD, MS,OTR,FAOTA [2] Aisha Dickerson, MSPH,[1] Parker Jacks

Affiliations: UT-Houston, LoneStar LEND, Texas Woman's University-Houston[2]

Methods

Study Design and Data Analysis

Results

Conclusion

Strengths

Limitations

Recommendations for Larger Stu

References

References

- Fairthorne (2017) Australia: immigrant mothers from East Africa are 3.5 times more likely to have a child with ASD and ID
- Bacerra (2014) Los Angels County, USA: higher incidence of ASD with ID in children of foreign-born black mothers
- Bolton (2014) Ireland: higher prevalence of ASD and more affected children in immigrants from Africa
- Magnusson (2012) Sweden: higher incidence of ASD born to immigrant mothers and more children with ID
- Dealberto (2011) Canada: immigration and black ethnicity associated with increased risk of having a child with ASD
- Kamer (2004) Israel: Higher incidence of ASD in Ethiopian Israeli children born in Israel than those who were born in Ethiopia
- Gillberg (1987) Sweden: autism more common form "Exotic" countries

Prevalence of ASD in African populations

- ASD affects an average of 1% of children worldwide (WHO) and 2.8% of children in the USA (CDC)

- Higher prevalence of ASD in children born to East African parents:
  - Prevalence is ~3-4 X higher in children of Somali parents in Sweden
  - Higher rate of autism in children born to East African (Somali and Ethiopian) parents in Sweden
  - Prevalence of ~3% in the Somali population in Minnesota
  - Prevalence of ~5% in the Ethiopian population in Texas

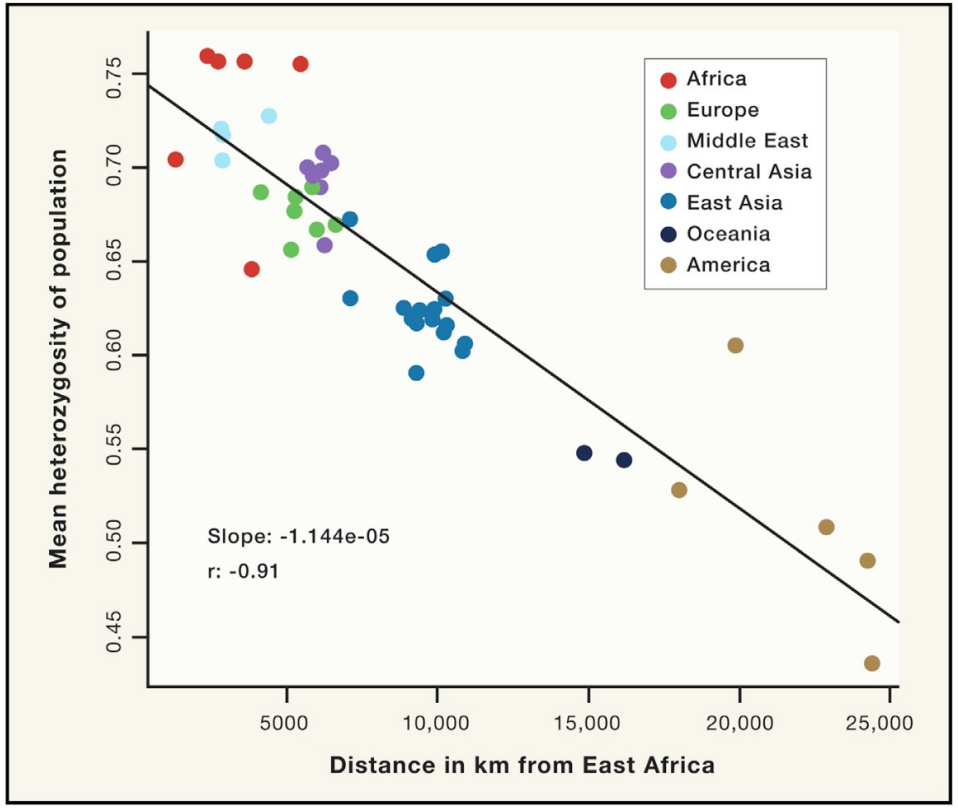
- The higher incidence of ASD in East African populations suggests possible shared genetic susceptibility factor(s) that predisposes to autism

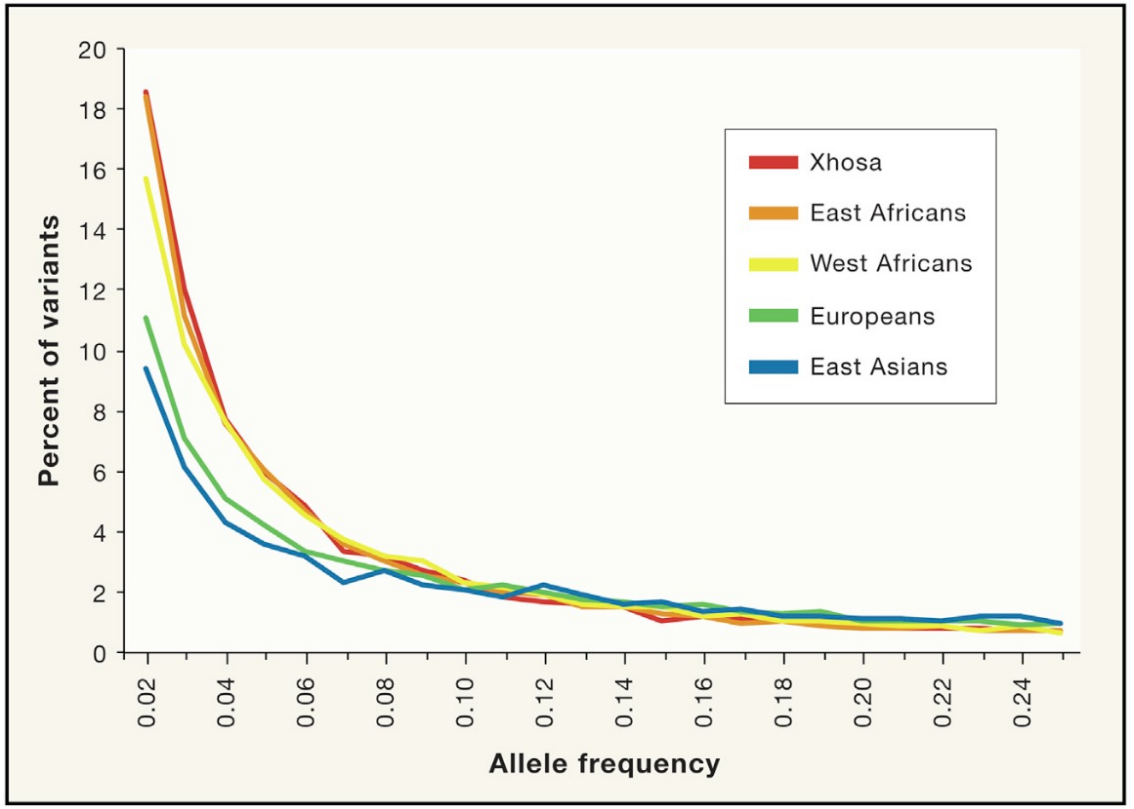
What is the genetic contribution to the increased ASD prevalence in children from East African origin?

Barnevik-Olsson et al., 2008; Magnusson et al., 2012; Seyoum-Tesfa et al. 2015
The Minnesota-Autism and Developmental Disabilities Monitoring Network 2018

Genetic diversity in Africa

- Populations in Africa are the most genetically diverse in the world, carrying up to 3 times as many rare variants as populations of European or East Asian origin

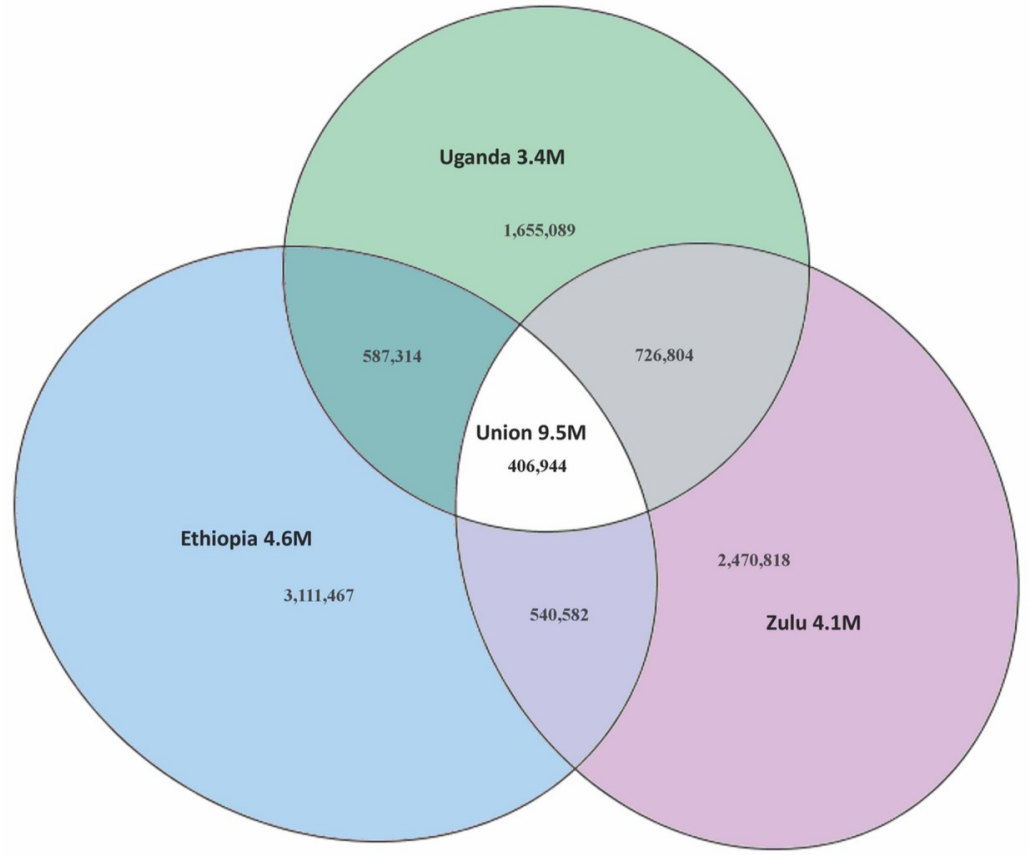


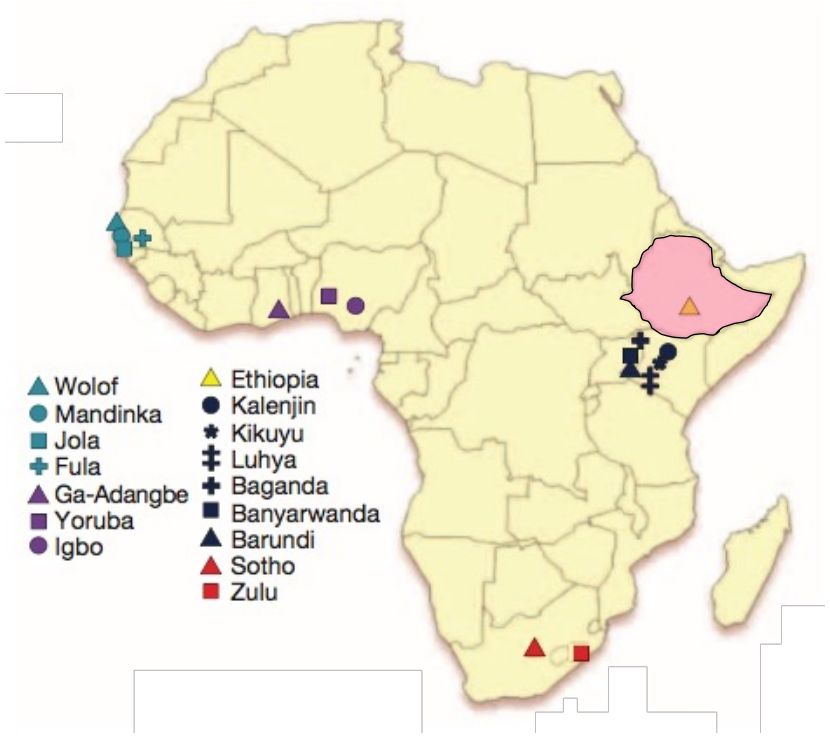


Li et al., 2008; 1000G, Abecasis et al. 2012; McClellan, Lehner, King 2017

Genetic diversity in Africa

- The Ethiopian population has the greatest proportion of all the novel and private genomic variation found in Africa (~24% of genomic variants)



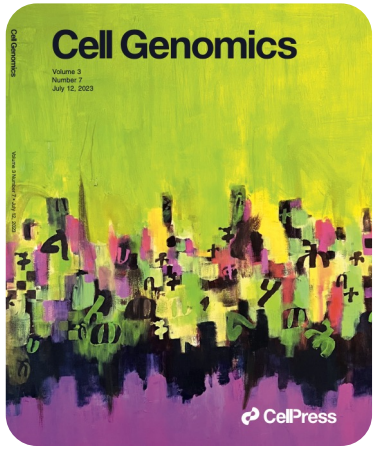


Gurdasani et al., 2015 (AGV Project)

The genetics of ASD in an East African familial cohort

Leverage ancestral genomic information to identify ASD genes through whole genome sequencing and admixture analysis in a familial cohort from a population with an unusually high rate of ASD

One of the first studies to investigate the genetic underpinnings of ASD in an African population

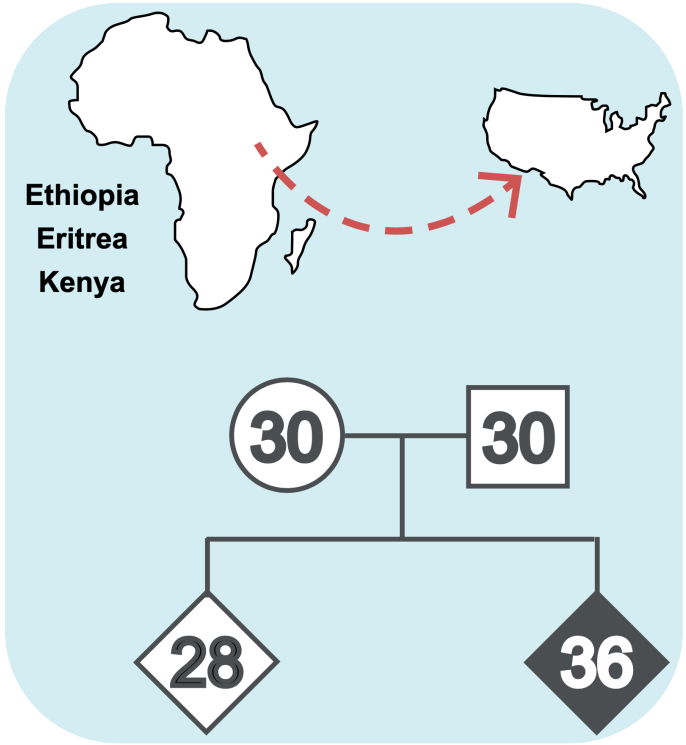


Tuncay et al., 2023 *Cell Genomics*

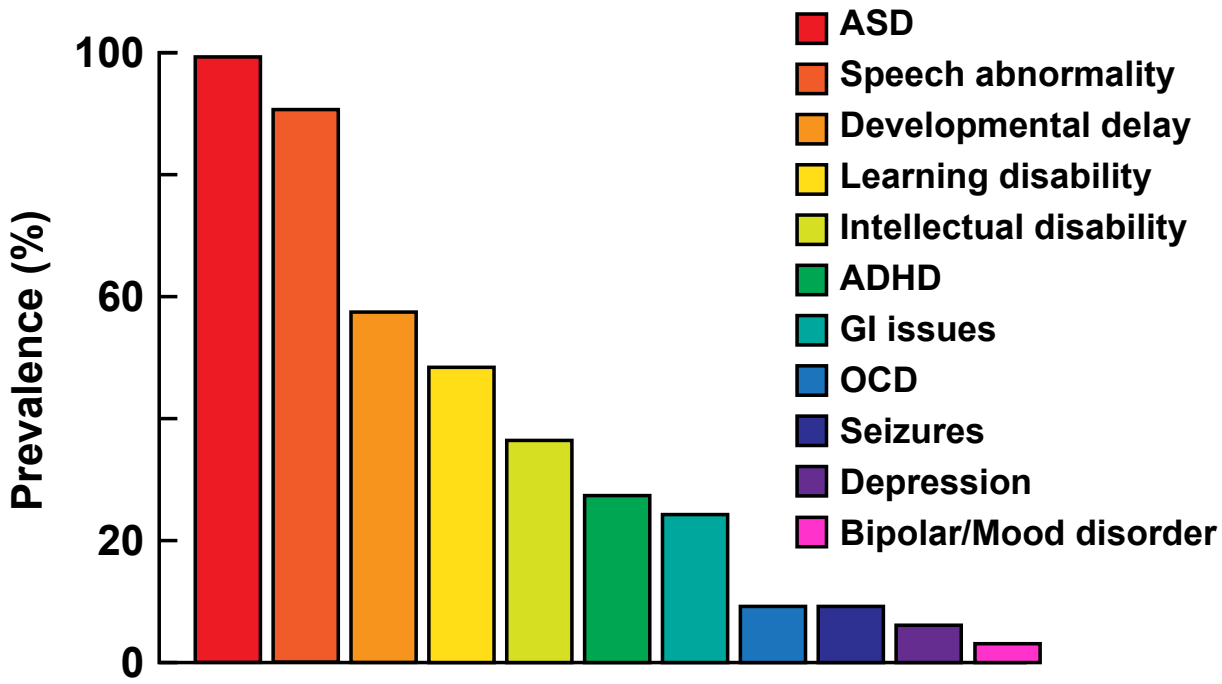
RFASG

Ongoing enrollment through collaboration with our community partner

The genetics of ASD in an East African familial cohort



33 families (129 individuals)



Tuncay et al., 2023 *Cell Genomics*

The genetics of ASD in an East African familial cohort

The human genome has **3 billion** “letters”

~ 3 to 4 million “changes” in the genome

~ 1 to 2 “changes” in the genome that cause autism

5,016,279	TOTAL VARIANTS PER GENOME
223,867	RARE VARIANTS PER GENOME
132,314	NOVEL VARIANTS PER GENOME
2,130,150	PRIVATE VARIANTS IN COHORT

Tuncay et al., 2023 *Cell Genomics*

The genetics of ASD in an East African familial cohort

ASD VARIANTS

VARIANTS IN KNOWN GENES

CODING
CACNA1C
CHD7
TCF7L2

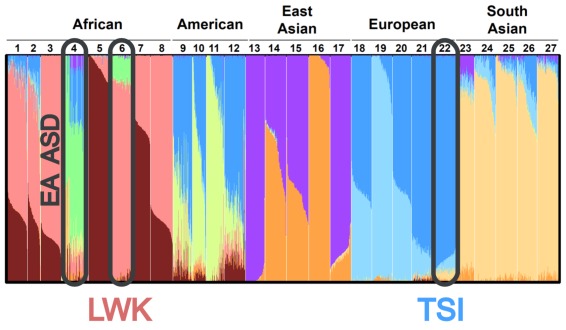
NONCODING
CTCF
MED13L
PTPN11

VARIANTS IN NEW GENES

CODING
GLUD2
IDH3G

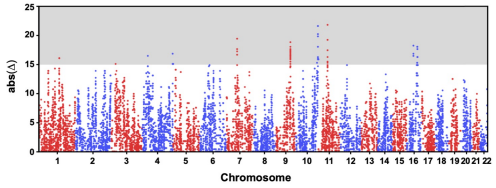
NONCODING
BDNF
NPAS4

POPULATION ADMIXTURE



Luhya in Webuye, Kenya (LWK) and the Toscani in Italy (TSI) are the most closely related to the ancestral admixed populations in the East African ASD cohort (EA ASD)

POPULATION SPECIFIC ASD VARIANTS



Population specific variants are preferentially transmitted to affected offspring

Transmission disequilibrium test identified 10 loci that confer ASD risk on the African haplotypes

Known ASD genes in these loci: *ASDL*, *CREBBP*, *EHMT1*, *GRIN1*

Tuncay et al., 2023 *Cell Genomics*

Summary and ongoing work

- Established an African ASD familial cohort for genetics research through community partnership
- Leveraged ancestral genomic information and genetic diversity in an African cohort with increased prevalence to identify ASD variants and risk loci
  - Discovered 2.13 million novel private variants
  - Rare variants in known and in new candidate ASD genes
  - Admixture mapping identified several ASD risk loci on the African haplotypes

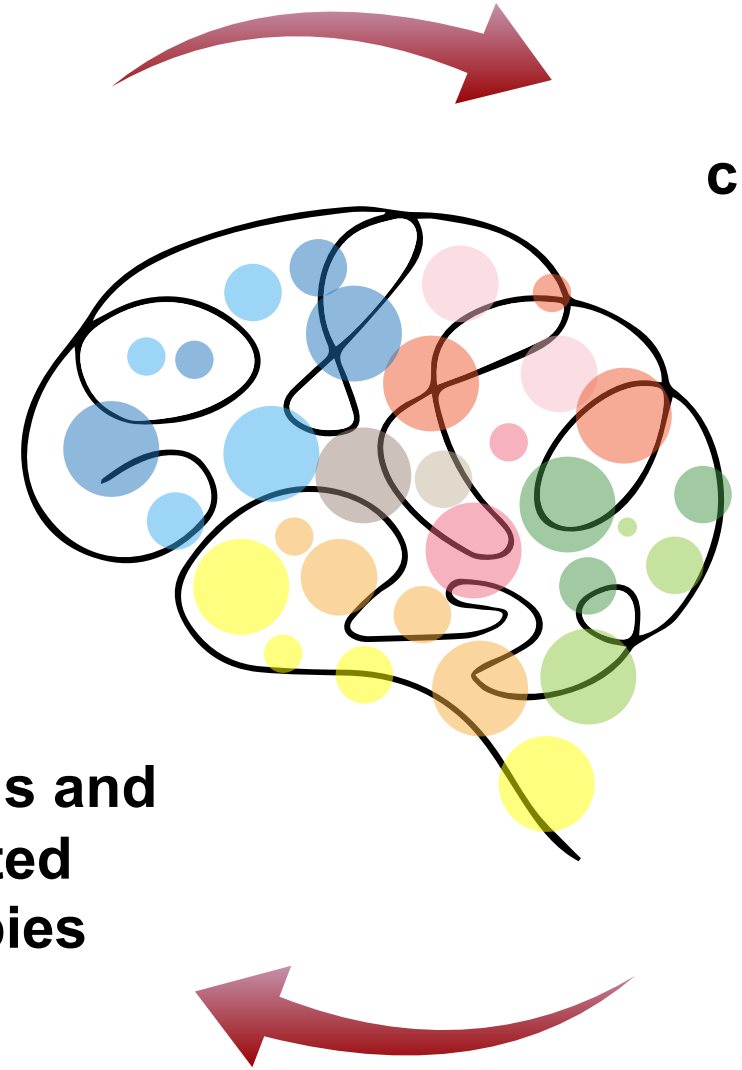
Tuncay et al., 2023 *Cell Genomics*

- Actively enrolling to expand the ASD cohort
- Prioritizing genes for follow up functional studies
- Investigate the underlying mechanisms

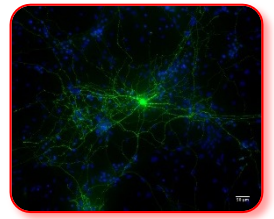
Conclusions

- Community partnerships to drive research
- Equity in healthcare depends on inclusion of all human populations
- The power of African genetic diversity to inform complex disorders, even for the highly heterogeneous ASD
    - Ultra rare (private) variants
    - Population allele frequencies
    - Ancestral information
- Concerted efforts; the Human Heredity and Health in Africa (H3Africa) consortium

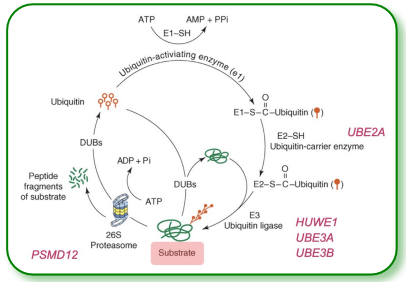
Gene discovery in ASD



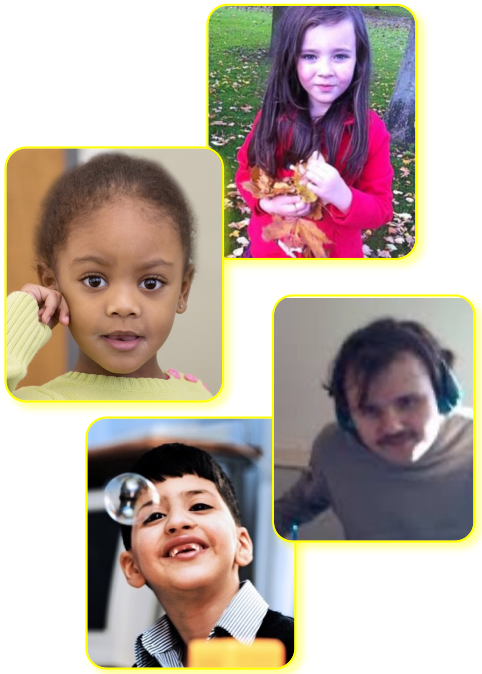
Functional characterization



Molecular mechanisms



Diagnosis and targeted therapies



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