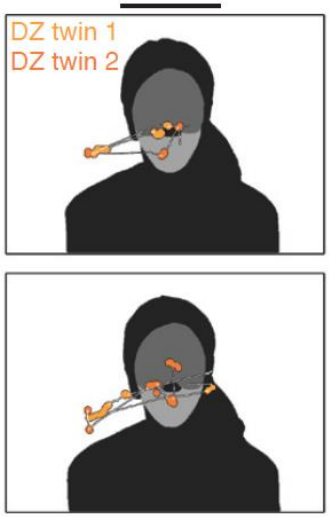
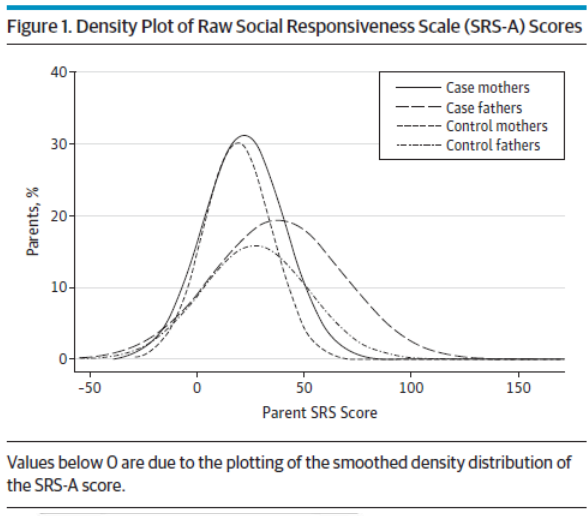
Surprising New Insights on the Early Origins of Autism: Implications for Support from Birth through Adulthood

John N. Constantino, M.D.
Washington University in St. Louis





Washington University in St. Louis
School of Medicine

IDDRC
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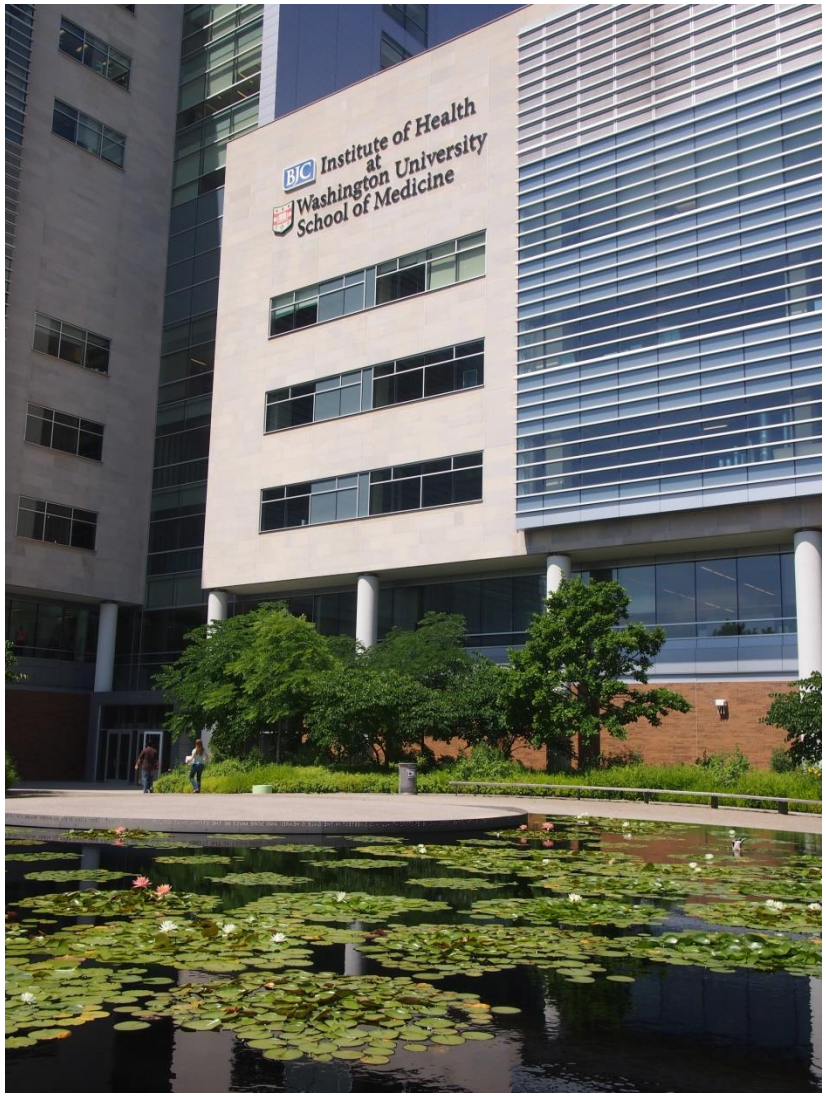
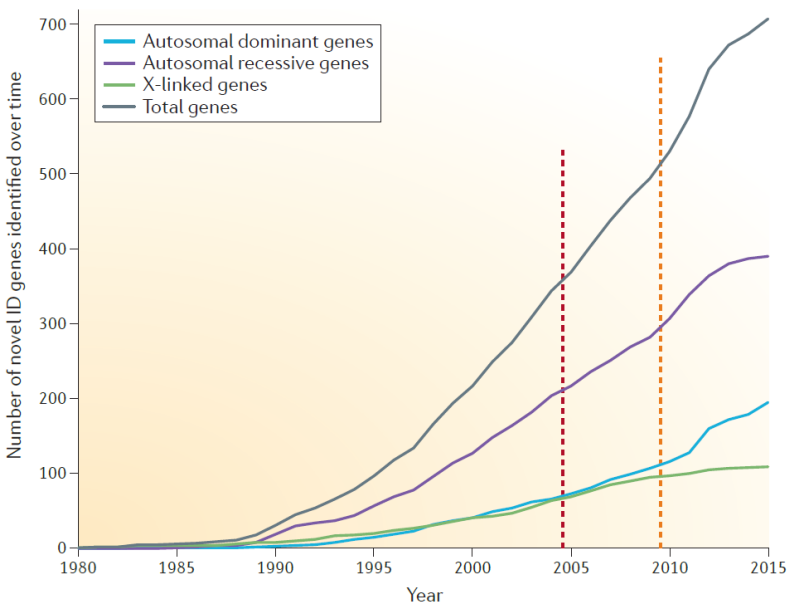
Disclosure of Interests



- Industry Consulting: *Cognoa*
- Stock Equity: None
- Royalties: Western Psychological Services
  The Social Responsiveness Scale (SRS-2)
- Research Support:
  - *NICHD*
  - *NIMH*
  - *U.S. Centers for Disease Control*

Rare Germline Mutations



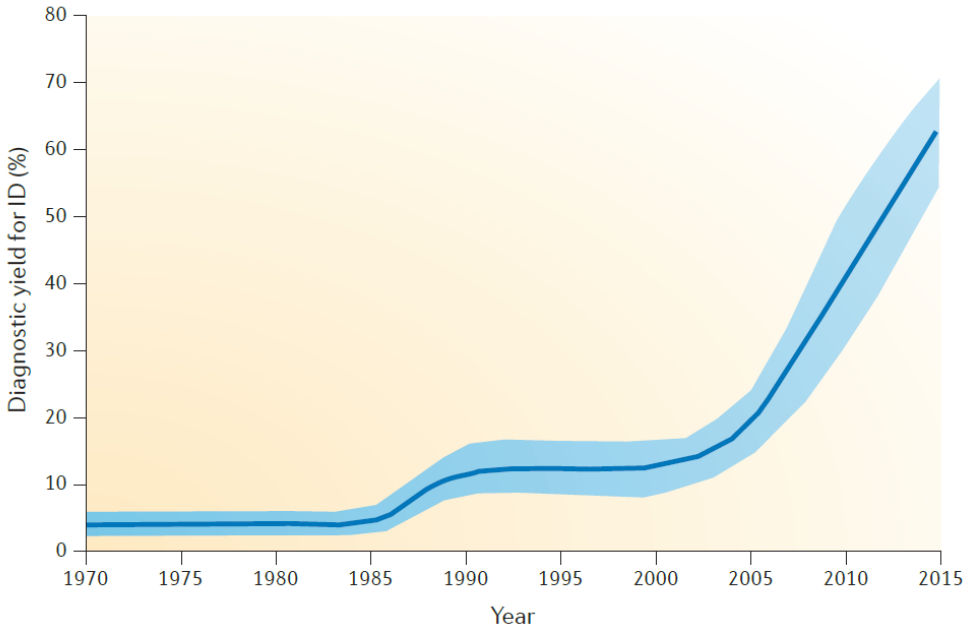


Figure 2 | **Diagnostic yield for ID over time.** Graphical overview of the diagnostic yield for moderate to severe intellectual disability (ID) (excluding Down syndrome, which represents 6–8% of all ID) over time. Solid line indicates the mean of published studies, and the shaded background indicates the lower and upper boundaries of reported diagnostic yields. In the 1970s, conventional karyotyping became a routine diagnostic test and provided a conclusive diagnosis in 3–6.5% of ID cases. The

Insufficient Evidence for "Autism-Specific" Genes

Scott M. Myers,[1,*] Thomas D. Challman,[1] Raphael Bernier,[2] Thomas Bourgeron,[3] Wendy K. Chung,[4,5] John N. Constantino,[6,7] Evan E. Eichler,[8] Sebastien Jacquemont,[9] David T. Miller,[10] Kevin J. Mitchell,[11,12] Huda Y. Zoghbi,[13,14,15,16,17] Christa Lese Martin,[1] and David H. Ledbetter[1,*]

Despite evidence that deleterious variants in the same genes are implicated across multiple neurodevelopmental and neuropsychiatric disorders, there has been considerable interest in identifying genes that, when mutated, confer risk that is largely specific for autism spectrum disorder (ASD). Here, we review the findings and limitations of recent efforts to identify relatively "autism-specific" genes, efforts which focus on rare variants of large effect size that are thought to account for the observed phenotypes. We present a divergent interpretation of published evidence; discuss practical and theoretical issues related to studying the relationships between rare, large-effect deleterious variants and neurodevelopmental phenotypes; and describe potential future directions of this research. We argue that there is currently insufficient evidence to establish meaningful ASD specificity of any genes based on large-effect rare-variant data.

--association with intellectual disability
--timing of effect
--absence of sex differences

Recurrence Rates and Inherited Transmission in Autism

MZ concordance:	90%
DZ concordance:	20%
Non-twin sib recurrence:	18%
Half-sib recurrence	6%
General population risk	1%

Table. Autism Spectrum Disorder Heritability Model Comparisons and Parameter Estimates

	Model Comparison Measures				Estimated Variance (95% CI)[a]				
Models[b]	No. of Model Parameters	−2LL	Diff − 2LL	*P* Value[c]	Additive Genetic (Narrow-Sense Heritability)	Nonadditive Genetic	Environment		Total Genetic (Broad-Sense Heritability)
							Shared	Nonshared	
ACDE	14	146 836	NA	NA	0.69 (0.40-0.86)	0.10 (0.00-0.38)	0.04 (0.00-0.14)	0.16 (0.05-0.30)	0.80 (0.59-0.95)
ACE	13	146 836	0.4	.52	0.77 (0.58-0.87)	NA	0.03 (0.00-0.13)	0.20 (0.13-0.30)	0.77 (0.58-0.87)
ADE	13	146 836	0.8	.38	0.80 (0.68-0.87)	0.05 (0.00-0.26)	NA	0.15 (0.05-0.21)	0.85 (0.79-0.95)
CDE	13	146 856	20.9	<.001	NA	0.64 (0.48-0.75)	0.25 (0.21-0.29)	0.11 (0.03-0.24)	0.64 (0.48-0.75)
AE	12	146 836	0.9	.64	0.83 (0.79-0.87)	NA	NA	0.17 (0.13-0.21)	0.83 (0.79-0.87)
DE	12	147 100	264	<.001	NA	0.99 (0.97-1.00)	NA	0.01 (0.00-0.03)	0.99 (0.97-1.00)
CE	12	146 897	61	<.001	NA	NA	0.39 (0.37-0.41)	0.61 (0.59-0.63)	NA
E	11	147 996	1160	<.001	NA	NA	NA	1.00 (1.00-1.00)	NA

Abbreviations: 2LL, 2 × logarithm of the likelihood; Diff − 2LL, 2 × difference in log-likelihood between the model and the full model; NA, not applicable.

[a] The 95% CIs are 2-sided CIs. Variances are based on the tetrachoric correlations. The unadjusted tetrachoric correlation (SD) was estimated to 0.87 (0.08) and 0.40 (0.10) for monozygotic and dizygotic twins; 0.41 (0.01) for full siblings; 0.22 (0.03) and 0.17 (0.04) for maternal and paternal half siblings.

[b] All models adjusted for sex and birth cohort. The genetic terms for each model are shown in each row, which include additive genetic effect (A; inherited additive effects of different alleles), shared environmental factors (C; nongenetic influences contributing to similarity within sibling pairs), nonadditive (dominant) genetic factors (D; interaction effects between alleles at the same locus), and nonshared environmental factors (E; making siblings dissimilar).

[c] *P* value for testing the hypothesis: the parameters not in the model but in the full model are all equal to 0.

Quantitative autistic traits

Tracing phenotypic manifestations of inherited variant liability in families

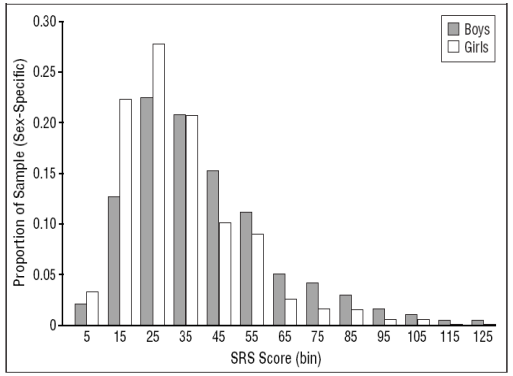
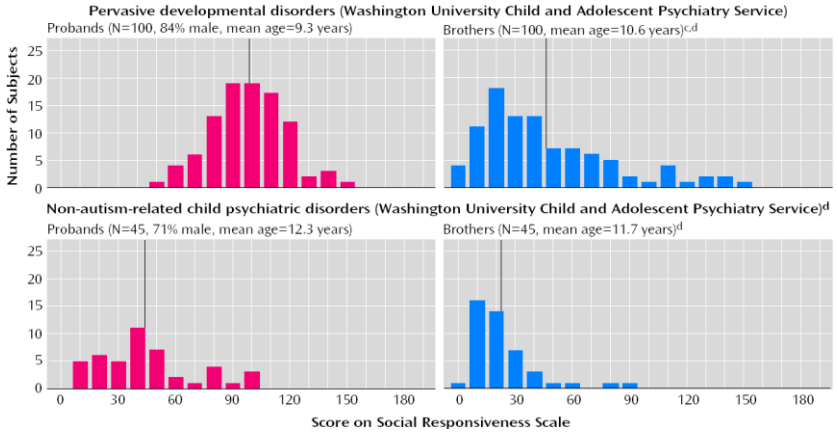


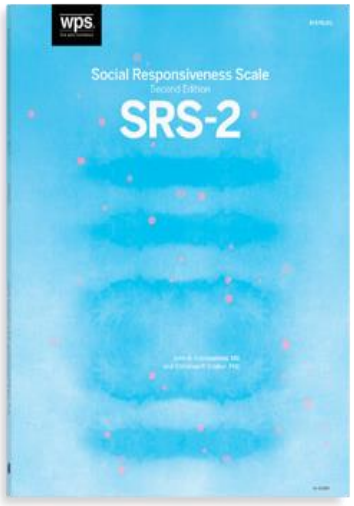
Figure 2. Distribution of Social Responsiveness Scale (SRS) scores as a function of sex (n=1576).

General Population Twins

$h^2 = 0.85$



Male First Degree Relatives:
Shifted Unimodal Distribution



www.thelancet.com/neurology 2015

CHILD DEVELOPMENT

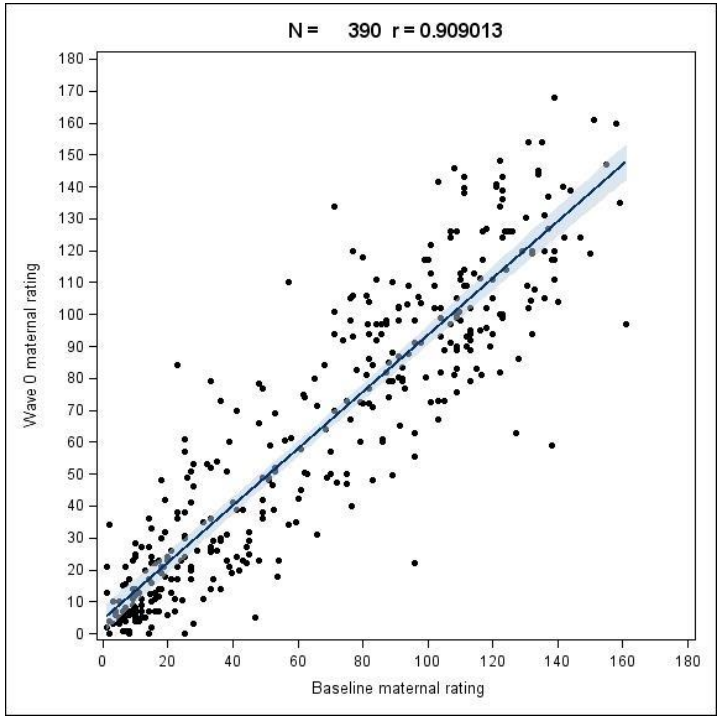
Child Development, xxxx 2018, Volume 00, Number 0, Pages 1–11

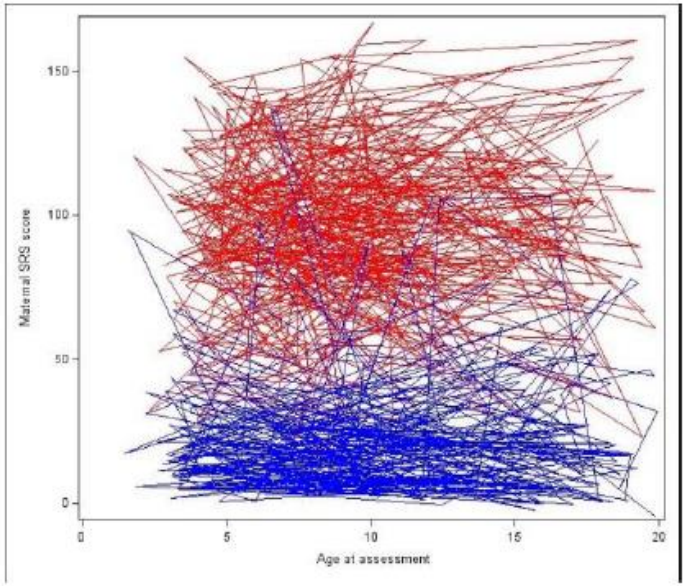
Autism-Related Variation in Reciprocal Social Behavior: A Longitudinal Study

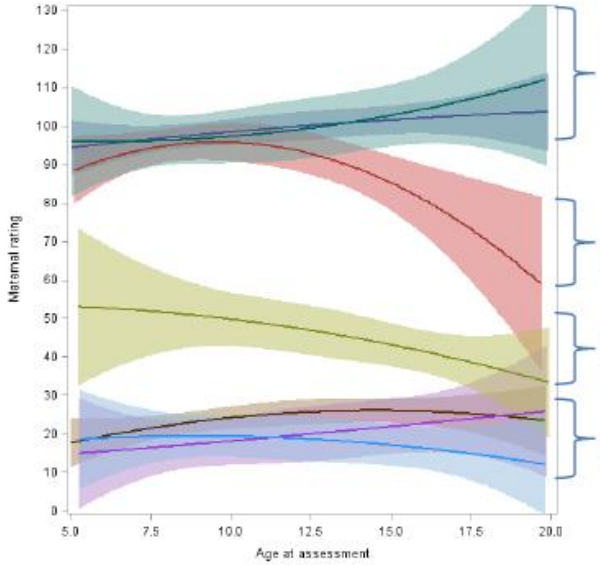
Rachael E. Wagner, Yi Zhang, Teddi Gray, and Anna Abbacchi
Washington University in Saint Louis School of Medicine

Deporres Cormier
St. Louis University

Alexandre Todorov and John N. Constantino
Washington University in Saint Louis School of Medicine







Male multiplex ASD, simplex ASD

Female multiplex ASD

Child psychiatric contrast group

Unaffected sib controls

Wagner et al., 2019, *Child Dev*

THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY

ACAMH

Journal of Child Psychology and Psychiatry *:* (2012), pp **–** doi:10.1111/j.1469-7610.2012.02589.x

Vanessa Hus,[1] Somer Bishop,[2] Katherine Gotham,[1] Marisela Huerta,[3] and Catherine Lord[3]

[1]Department of Psychology, University of Michigan; [2]Cincinnati Children's Hospital Medical Center; [3]Department of Psychiatry, Weill-Cornell Medical School

Parent SRS reports in the Simons Simplex Collection

	Probands		Siblings	
	Males (n = 2,056)	Females (n = 312)	Males (n = 890)	Females (n = 1,023)
Age (years)	8.74 (3.32)	8.90 (3.60)	9.49 (3.71623)	9.46 (3.65)
SRS-Raw	97.56 (26.82)	99.32 (27.24)	**20.53 (15.44)**	**17.22 (13.02)**
SRS T-score	**80.56 (12.83)**	**89.63 (15.05)**	43.70 (7.39)	44.26 (7.19)
VSOC	71.54 (12.57)	70.15 (12.71)	*101.77 (11.93)*	*103.19 (11.29)*
CBCL-E	*56.39 (10.7)*	*57.79 (10.2)*	46.84 (9.81)	46.19 (9.42)
CBCL-I	60.35 (9.47)	59.96 (9.98)	*48.29 (10.19)*	*47.32 (9.96)*
VEC	*10.23 (3.06)*	*9.71 (3.03)*	**16.02 (2.37)**	**16.39 (2.34)**
ADI-Current	17.04 (7.30)	17.59 (7.80)		
ADOS-CSS	7.43 (1.68)	7.43 (1.73)		
NVIQ	**85.81 (25.70)**	**78.12 (25.18)**		

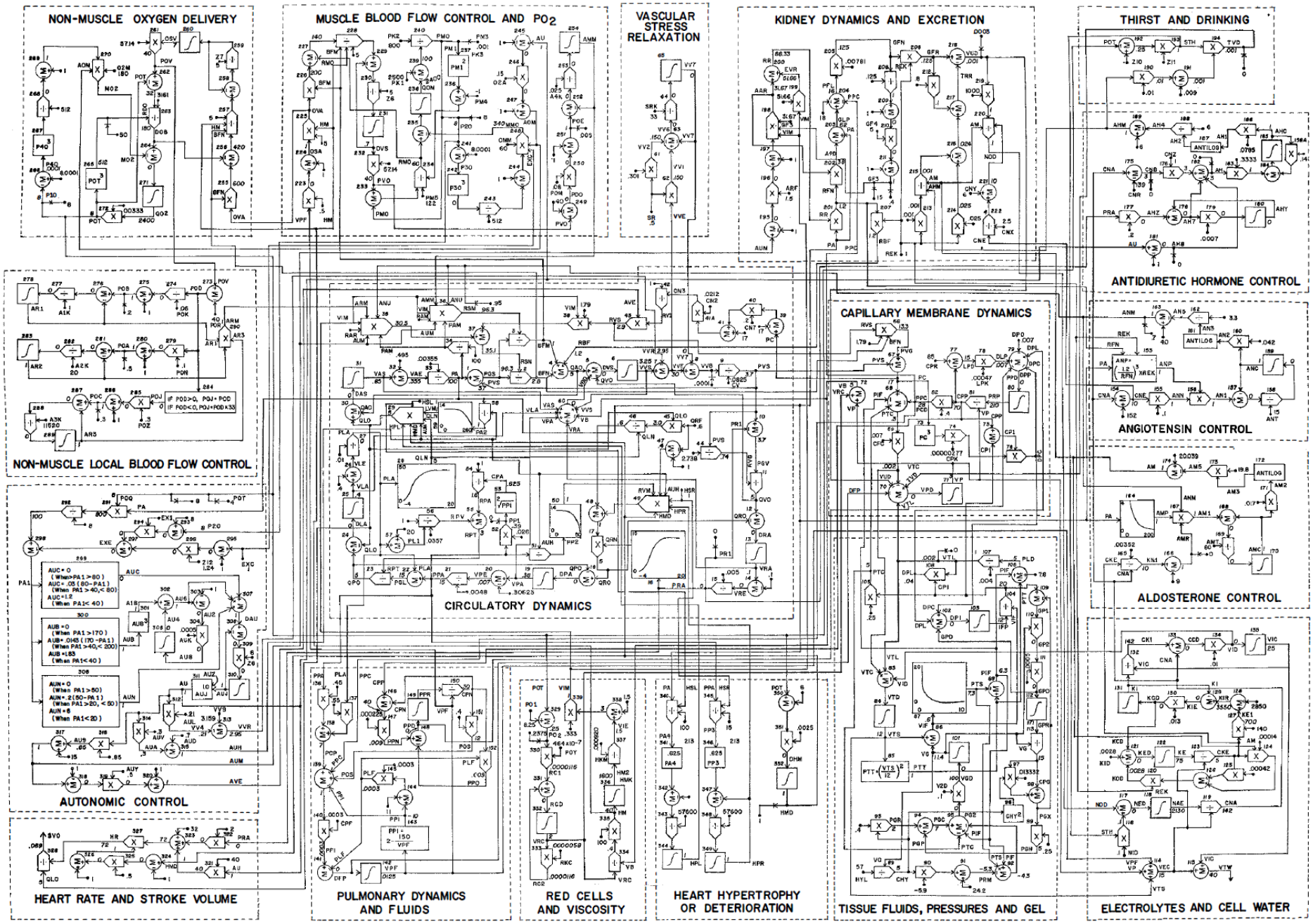
3 S.D. difference between children with ASD (probands) and their unaffected sibs

Trait correlation with Attention Problems on the order of r=0.50

Annu. Rev. Clin. Psychol. 2021. 17:X–X
https://doi.org/10.1146/annurev-clinpsy-081219-110503

1. A developmental sub structure for autism

"Grand Unified Theory" ☺ Inheritance exerts effects via independent components of additive genetic liability, MOST NOT SPECIFIC TO AUTISM, each with its own link to early developmental endophenotypes which jointly give rise to the autistic syndrome



[Circulation: Overall Regulation](#) A C Guyton, et al. *Annual Review of Physiology* 1972 34:1, 13-44

What exactly is heritable in the causation of autism?

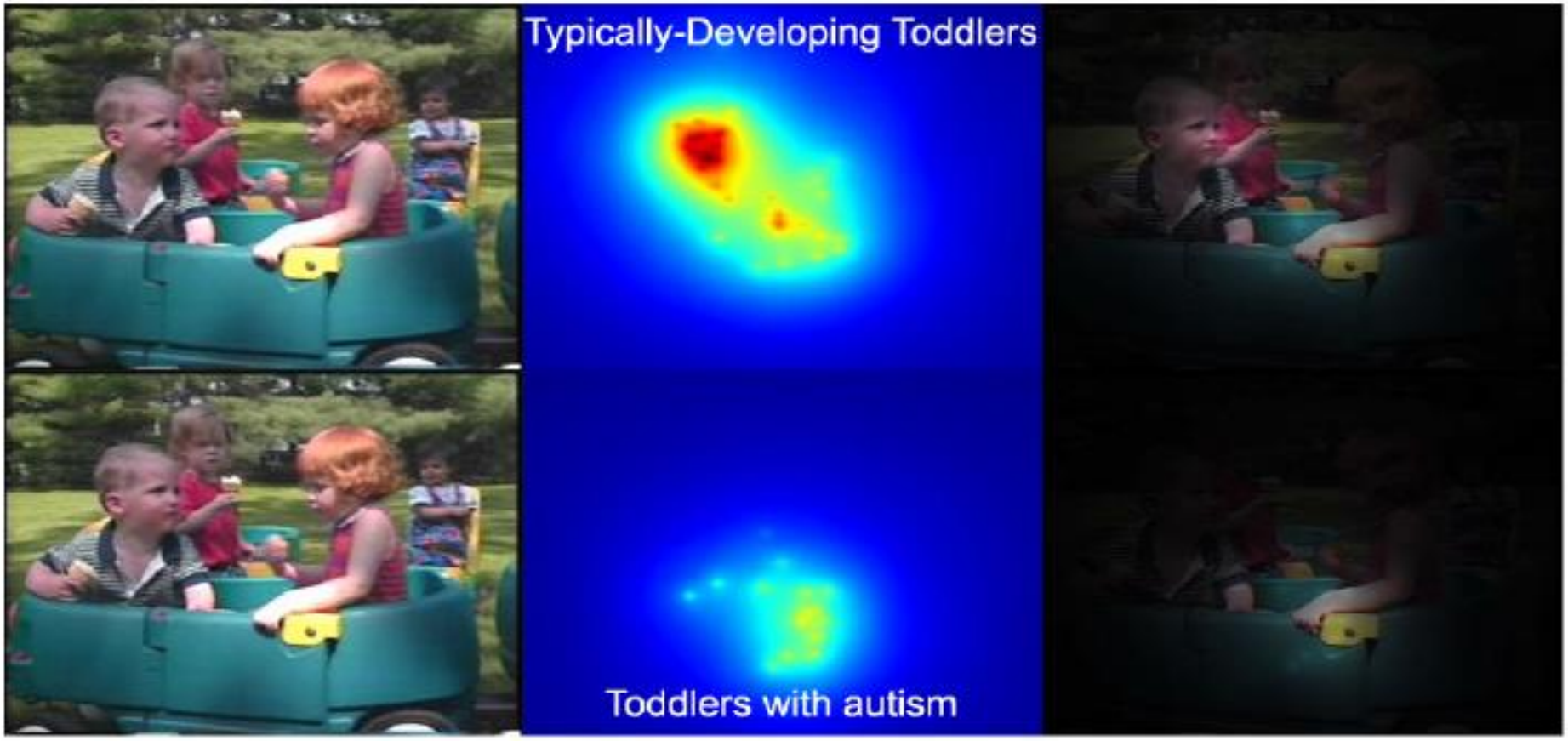
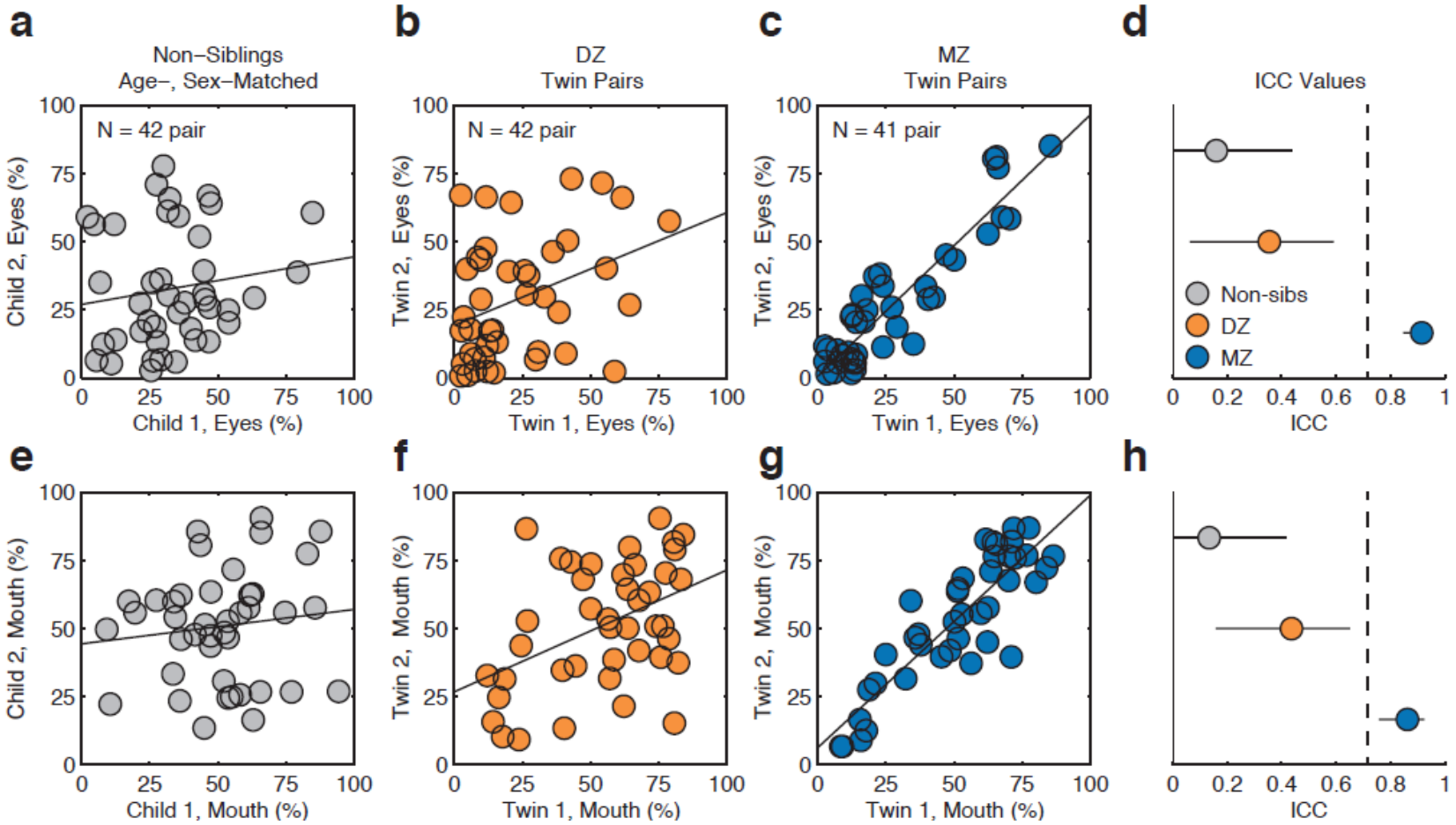


Figure 3. Salience maps for typically-developing 2-year-olds (top) and for 2-year-olds with au tism (bottom). Images at right show color data scaled from black to transparent and overlaid on the still image from the video scene.

Courtesy, Ami Klin and Warren Jones, Emory University

Social visual engagement in infants is under stringent genetic control



Constantino et al., *Nature (2017)*

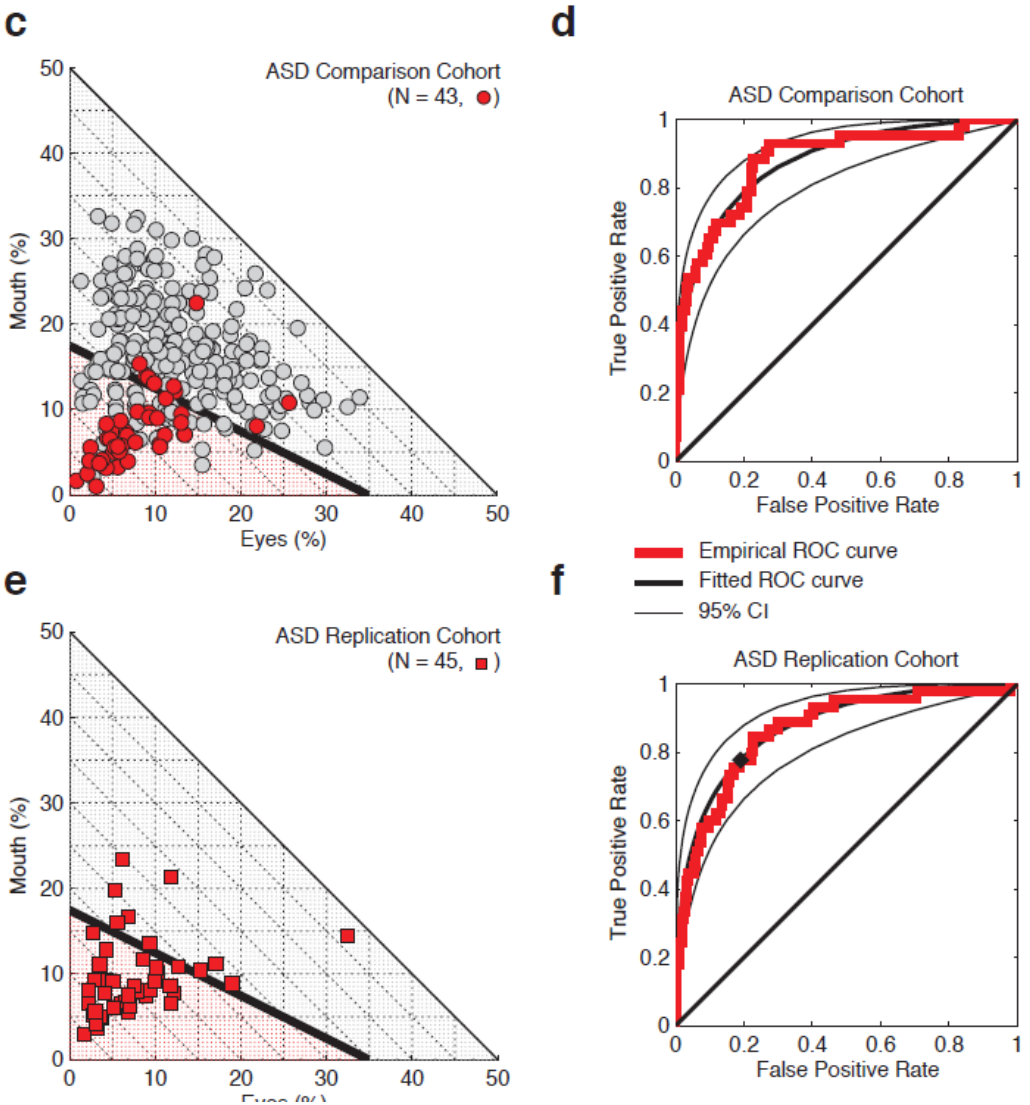

MZ males
Constantino & Colleagues


DZ males
Constantino & Colleagues

Constantino et al., *Nature* 2017

Discovery

Replication



1. Most children with ASD are in the lower range of eye and mouth looking
2. Some children in the lower range of eye and mouth looking are typically-developing

Early eye gaze abnormalities as "necessary but not sufficient" to cause ASD

Psychological Medicine

cambridge.org/psm

Attention-deficit/hyperactivity disorder and risk for psychiatric and neurodevelopmental disorders in siblings

Original Article

Elina Jokiranta-Olkoniemi[1], Keely Cheslack-Postava[2], Petteri Joelsson[1], Auli Suominen[1], Alan S. Brown[2,3] and Andre Sourander[1,2]

Methods. Every child born in Finland in 1991–2005 and diagnosed with ADHD in 1995–2011 were identified from national registers. Each case was matched with four controls on sex, place, and date of birth. The full siblings of the cases and controls were born in 1981–2007 and diagnosed in 1981–2013. In total, 7369 cases with 12 565 siblings and 23 181 controls with 42 753 siblings were included in the analyses conducted using generalized estimating equations.

Table 2. Associations between ADHD and psychiatric and neurodevelopmental disorders among the siblings of cases and matched controls

	ADHD[a]		Adjusted[b] (model I)		Adjusted[c] (model II)		Adjusted[d] (model III)	
	Case *n* = 7369 (%)	Control *n* = 23 181 (%)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
ADHD	1134 (15.4)	598 (2.6)	7.1	(6.4–7.8)***	6.5	(5.9–7.2)***	5.7	(5.1–6.3)***
Conduct and oppositional disorders	705 (9.6)	461 (2.0)	5.6	(5.0–6.3)***	5.0	(4.5–5.7)***	4.0	(3.5–4.5)***
ASD	322 (4.4)	264 (1.1)	4.6	(3.9–5.4)***	4.4	(3.7–5.2)***	3.9	(3.3–4.6)***

Mous *et al. Journal of Neurodevelopmental Disorders* (2017) 9:32
DOI 10.1186/s11689-017-9212-y

Journal of Neurodevelopmental Disorders

Candidate #4 ADHD

RESEARCH Open Access

Attention and motor deficits index non-specific background liabilities that predict autism recurrence in siblings

Sabine E. Mous[1,2], Allan Jiang[2], Arpana Agrawal[2] and John N. Constantino[2*]

S. Mous
Erasmus University
The Netherlands

Table 4. Linear regression analyses predicting parent-reported autistic trait severity in siblings

	Model 1		Model 2		Model 3		Model 4		Model 5	
	β	p	β	p	β	p	β	p	β	p
Proband SRS-2 score (teacher-report)	0.30	0.086	0.26	0.098	0.19	0.109	0.19	0.111		
Sibling TRF ADHP score (teacher-report)			0.45	0.005	0.24	0.066	0.25	0.074	0.24	0.063
Sibling DCDQ score (parent-report)					-0.60	<0.001	-0.60	<0.001	-0.62	<0.001
TRF ADHP x DCDQ interaction							0.03	0.793		
Adjusted R^2	0.059		0.247		0.554		0.540		0.530	

Pohl et al. *Translational Psychiatry* (2019)9:202
https://doi.org/10.1038/s41398-019-0545-z

Translational Psychiatry

ARTICLE Open Access

Behavioral predictors of autism recurrence are genetically independent and influence social reciprocity: evidence that polygenic ASD risk is mediated by separable elements of developmental liability

Alexa Pohl[1], Warren R. Jones[2], Natasha Marrus[3], Yi Zhang[3], Ami Klin[2] and John N. Constantino[4]

Table 3 Results of linear regression analysis examining the joint contribution of three behavioral predictors of autism recurrence (measured at 36-48 months) to variation in autism-related variation in early childhood reciprocal social behavior

Outcome modeled	Adj R^2	BPAR	*B*	*t*	Sig	Δ Adj R^2
SRS at 36 months	0.35	Biparental QAT	0.255	5.568	<0.001	0.06
		Variation in attentional impairment	0.355	3.996	<0.001	0.12
		Variation in motor coordination	−0.242	−3.830	<0.001	0.05
		Site	.079	1.252	0.212	0.00

Adjusted R square is reported for the full regression model, along with changes in adjusted R square that occur when a given individual behavioral trait is excluded from the model, and the result compared with that for the full model. A companion table for SRS outcome at 48 months (for which there were fewer twin pairs with complete data) yielded highly comparable results and is provided in Supplementary Table 2
SRS social responsiveness scale

NEUROSCIENCE

REVIEW

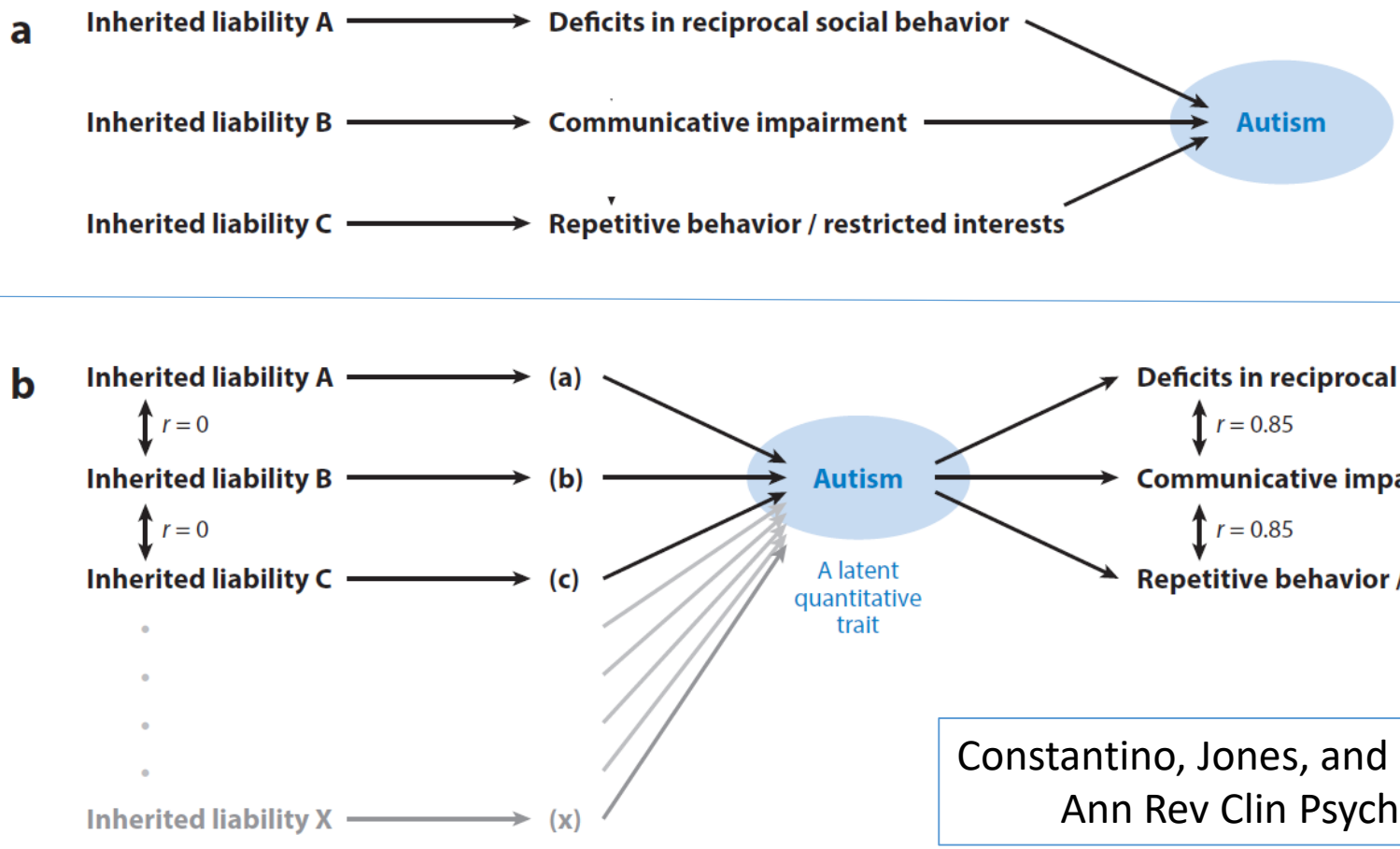
L. L. Orefice / Neuroscience 445 (2020) 120–129

Peripheral Somatosensory Neuron Dysfunction: Emerging Roles in Autism Spectrum Disorders

Lauren L. Orefice

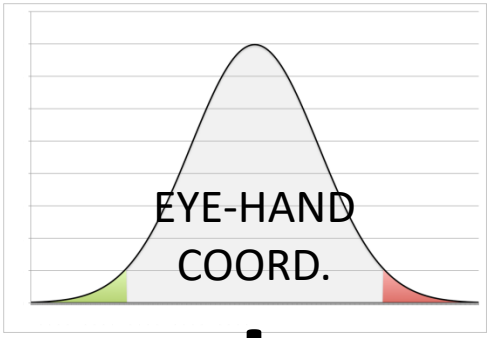
Department of Molecular Biology, Massachusetts General Hospital and Department of Genetics, Harvard Medical School, 185 Cambridge Street, Boston, MA 02114, USA

Tactile sensitivity → acquired deviation in brain / behavioral development



Constantino, Jones, and Charman
Ann Rev Clin Psychol *in press*

An Analogy…


EYE-HAND
COORD.

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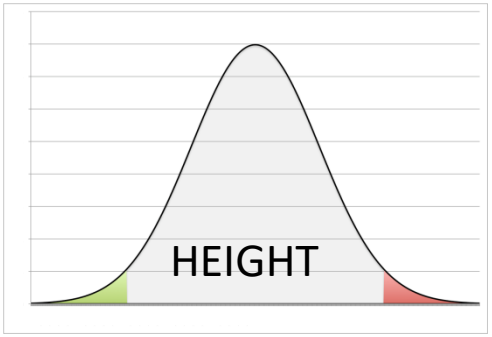
HEIGHT

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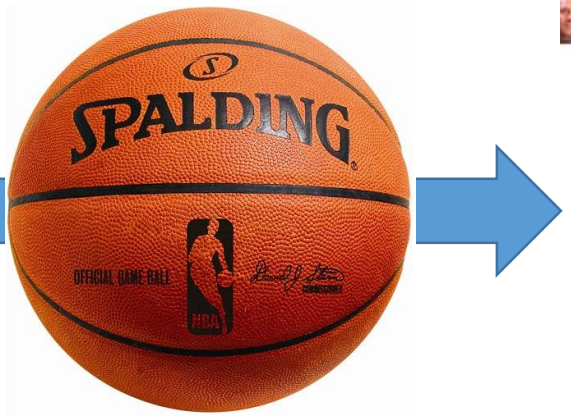
SPALDING
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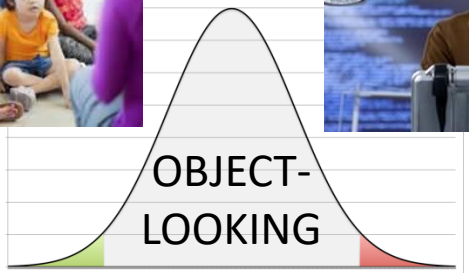
ORONTO 2016
NBA ALL



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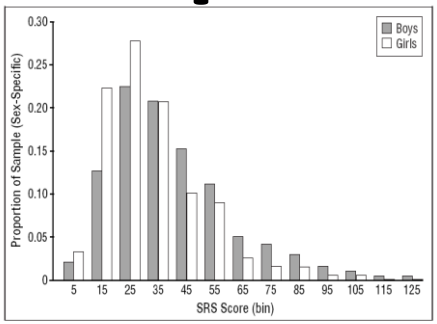

Figure 2. Distribution of Social Responsiveness Scale (SRS) scores as a function of sex (n = 1576).

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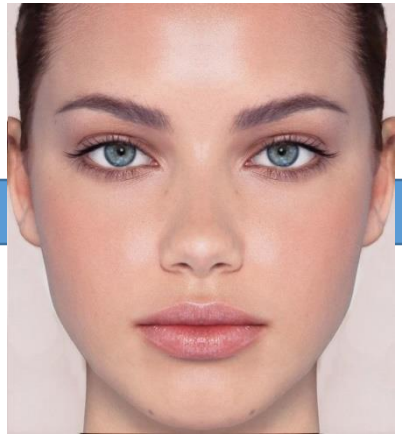


Autism Spectrum Disorder

INTERNATIONAL REVIEW OF PSYCHIATRY, 2018
https://doi.org/10.1080/09540261.2018.1433133

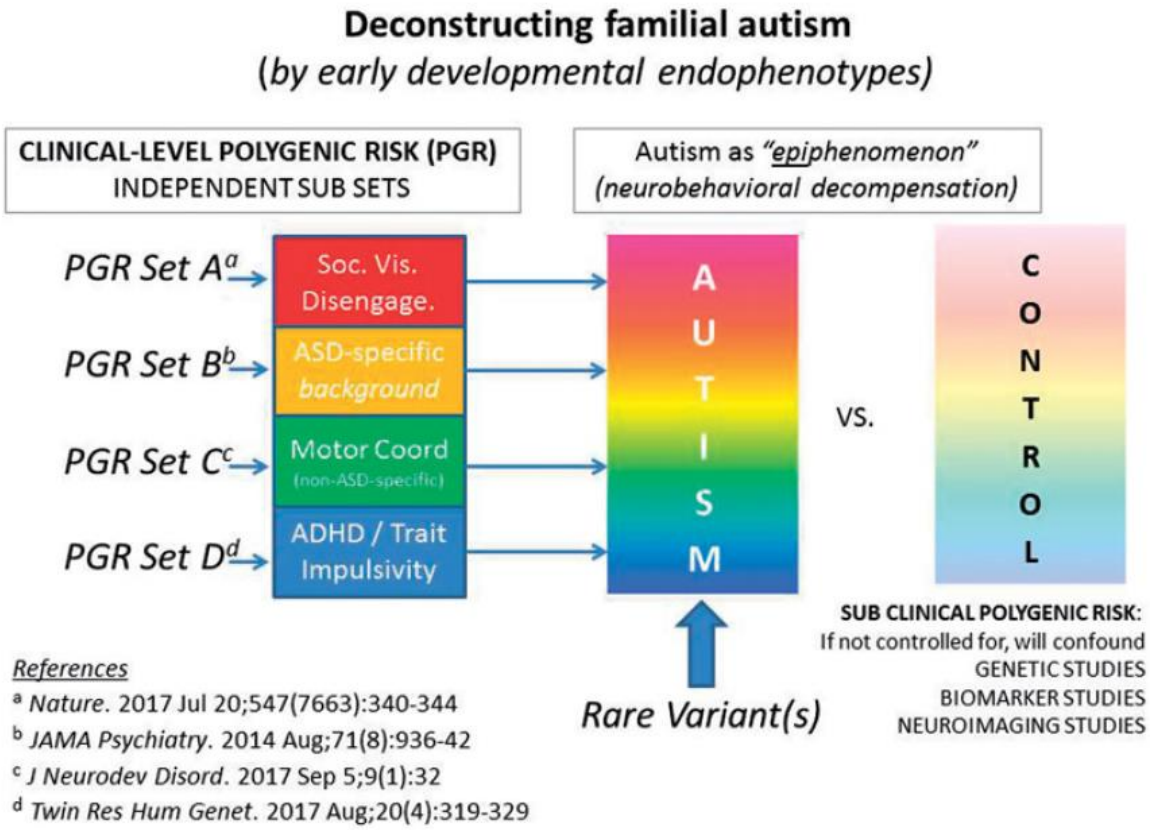
Taylor & Francis
Taylor & Francis Group

ARTICLE

Deconstructing autism: from unitary syndrome to contributory developmental endophenotypes

John N. Constantino

Departments of Psychiatry and Pediatrics, Washington University School of Medicine, St Louis, MO, USA



Constantino *Molecular Autism* _####################_
https://doi.org/10.1186/s13229-021-00434-w

Molecular Autism

COMMENTARY Open Access

New guidance to seekers of autism biomarkers: an update from studies of identical twins

John N. Constantino*

Abstract

Background: The autism spectrum disorders (ASD) are common neuropsychiatric conditions of childhood for which the vast proportion of population risk is attributable to inheritance, and for which there exist few if any replicated biomarkers.

Main body: This commentary summarizes a set of recent studies involving identical (monozygotic, MZ) twins which, taken together, have significant implications for the search for biomarkers of inherited susceptibility to autism. A first is that variation-in-severity of the condition (above the threshold for clinical diagnosis) appears more strongly influenced by stochastic/non-shared environmental influences than by heredity. Second is that there exist disparate early behavioral predictors of the familial recurrence of autism, which are themselves strongly genetically influenced but largely independent from one another. The nature of these postnatal predictors is that they are trait-like, continuously distributed in the general population, and largely independent from variation in general cognition, thereby reflecting a developmental substructure for familial autism. A corollary of these findings is that autism may arise as a developmental *consequence* of an allostatic load of earlier-occurring liabilities, indexed by early behavioral endophenotypes, in varying permutations and combinations. The clinical threshold can be viewed as a "tipping point" at which stochastic influences and/or other non-shared environmental influences assert much stronger influence on variation-in-severity (a) than do the genetic factors which contributed to the condition in the first place, and (b) than is observed in typical development.

Conclusion: Biomarkers identified on the basis of association with clinical symptom severity in ASD may reflect *effects* rather than *causes* of autism. The search for biomarkers of pathogenesis may benefit from a greater focus on traits that predict autism recurrence, among both clinical and general populations. In case–control studies, salient developmental liabilities should be systematically measured in both cases and controls, to avoid the erosion in statistical power (i.e., to detect differences) that can occur if control subjects carry sub-clinical aggregations of the same unmeasured traits that exert causal influences on the development of autism.

2. Stochastic Influences on Severity

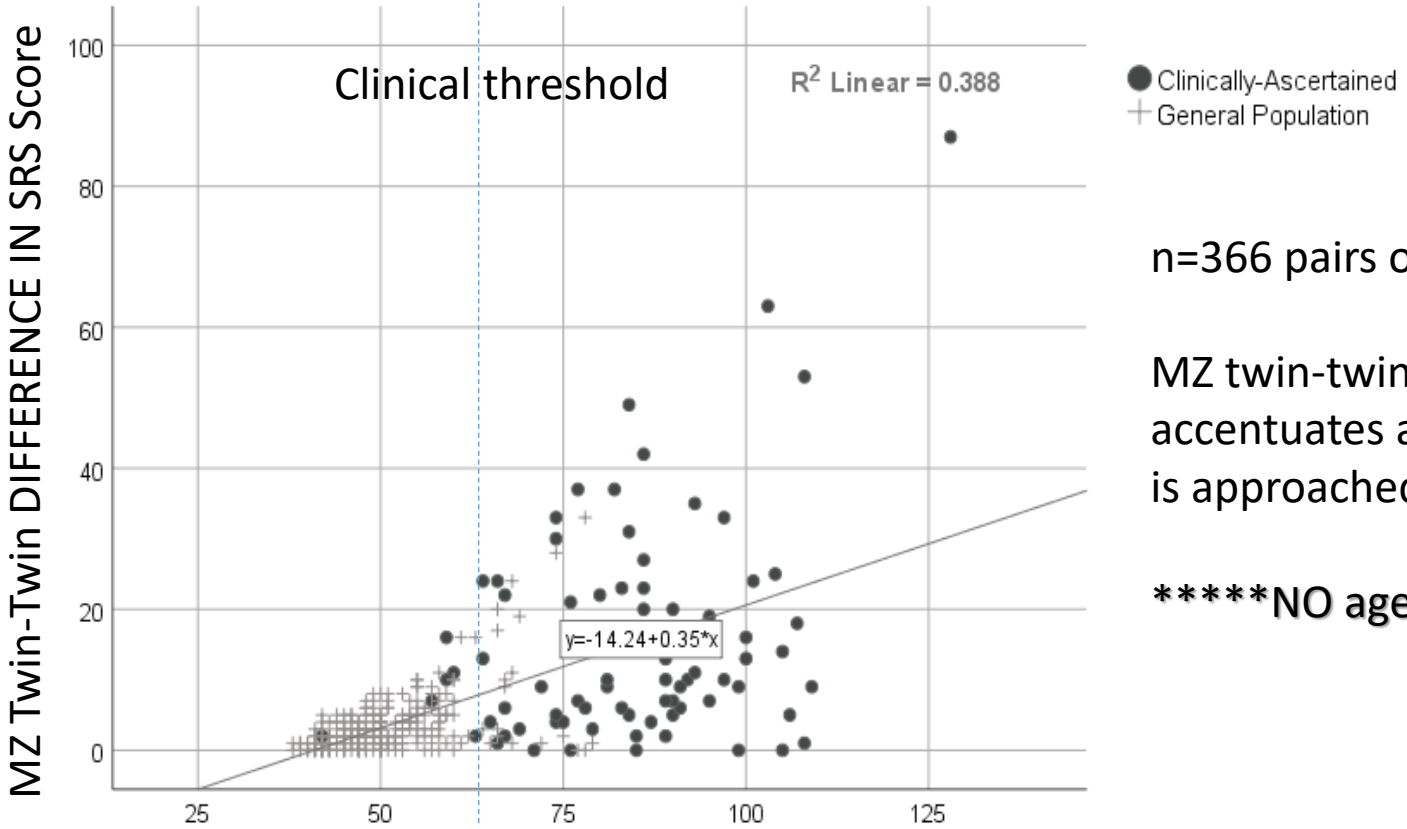
Differential Heritability Below versus Above the Clinical Threshold for Severity

Behavior Genetics
https://doi.org/10.1007/s10519-019-09987-2

ORIGINAL RESEARCH

On the Nature of Monozygotic Twin Concordance and Discordance for Autistic Trait Severity: A Quantitative Analysis

Lauren Castelbaum[1] · Chad M. Sylvester[1] · Yi Zhang[1] · Qiongru Yu[1] · John N. Constantino[1,2]



n=366 pairs of MZ twins

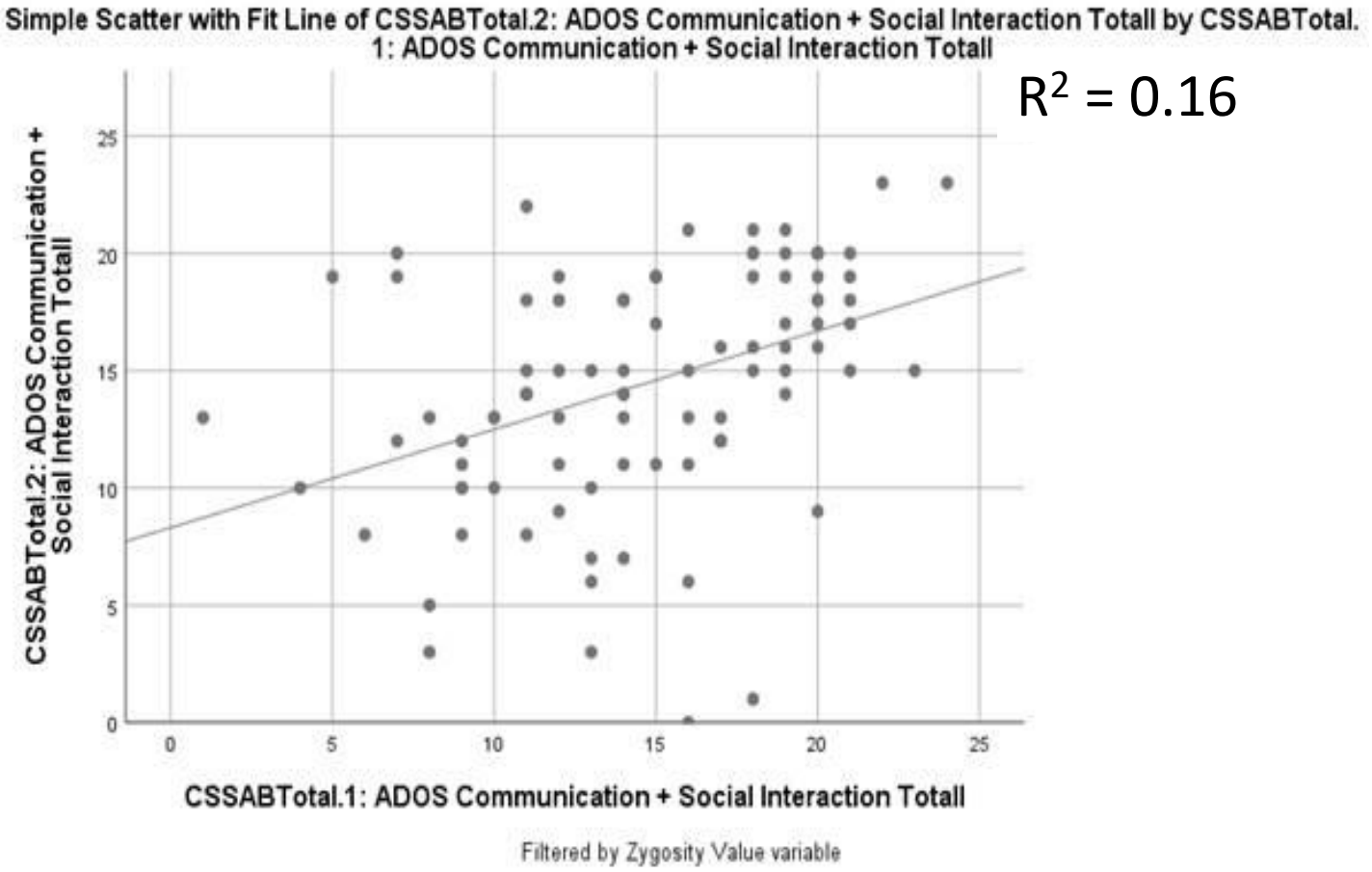
MZ twin-twin difference accentuates as clinical threshold is approached and exceeded

*****NO age effects observed

Castelbaum et al., *Behav Genet* 2019

ADOS SCORES OF IDENTICAL CO-TWINS IN AGRE

MZ Co-TWIN



MZ TWIN 1

N. B. Acutal MZ twin discordance (4%) is much rarer than presumed by families / community

Published in final edited form as:
Res Autism Spectr Disord. 2008 April 1; 2(2): 320–331. doi:10.1016/j.rasd.2007.08.002.

Genetic and Environmental Influences on Symptom Domains in Twins and Siblings with Autism

Carla A. Mazefsky, Ph.D, **Robin P. Goin-Kochel, P.hD**, **Brien P. Riley, P.hD**, **Hermine H. Maes, Ph.D**, and **The Autism Genetic Resource Exchange Consortium***

N=1,294 twins and siblings with ASD, AGRE ADI-R Data

Unstandardized Estimates of Additive Genetic (A), Dominant Genetic (D), and Unique Environmental (E) Influences for ADI Nonverbal Communication and Social Dysfunction Total Scores, With 95% Confidence Intervals in Parentheses

	Nonverbal Communication		Social Dysfunction		Common influences on Both Phenotypes	
Estimates from the full ADE model, with males and females free						
	Males	Females	Males	Females	Males	Females
A	.00 (.00 – .29)	.08 (.00 – .53)	.20 (.09 – .35)	.08 (.00 – .53)	.00 (.00 – .15)	.06 (.00 – .39)
D	.44 (.25 – .58)	.58 (.07 – 1.02)	.16 (.00 – .34)	.38 (.03 – .96)	.26 (.04 – .43)	.46 (.05 – .75)
E	.48 (.35 – .71)	.48 (.32 – .71)	.57 (.39 – .77)	.76 (.35 – .98)	.36 (.20 – .51)	.46 (.25 – .80)
Estimates from the best fitting model, with males and females equal for all parameters						
A	.01 (.00 – .19)		.16 (.00 – .35)		−.02 (−.06 – .15)	
D	.46 (.13 – .64)		.24 (.01 – .56)		.33 (.04 – .50)	
E	.51 (.35 – .71)		.59 (.40 – .80)		.39 (.24 – .57)	

3. The Nature of Sex Effects…

…may not be what we have thought they are; two implications of the Female Protective Effect (FPE):

a.) ~~The Carter Effect~~

b.) Risk of ASD among the Children of Sisters of ASD Probands…

Archival Report

Biological Psychiatry

Inherited Risk for Autism Through Maternal and Paternal Lineage

Dan Bai, Natasha Marrus, Benjamin Hon Kei Yip, Abraham Reichenberg, John N. Constantino, and Sven Sandin

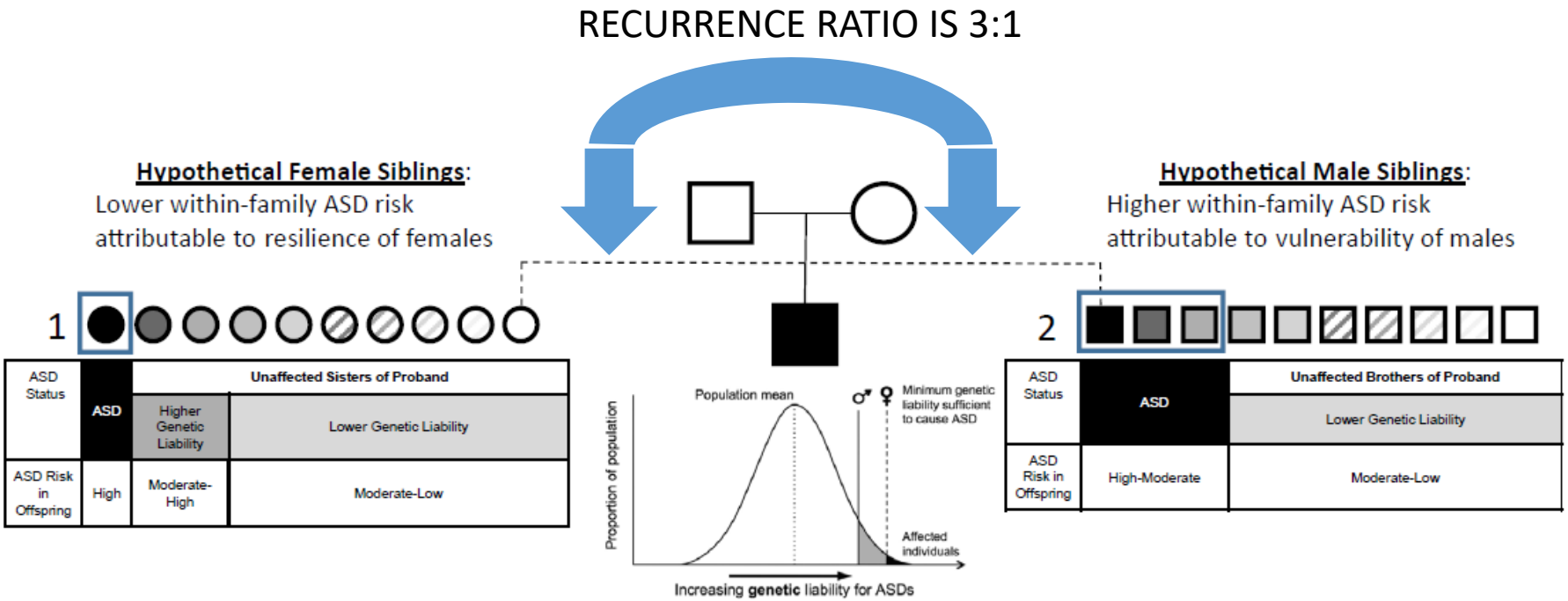


Figure 1. The expected autism spectrum disorder (ASD) liability under the female protective effect. Example: an individual has ASD and, hypothetically, he has 10 sisters (left panel, circles) and 10 brothers (right panel, squares). Under a female protective effect, 1) only the sisters with very high genetic liability will be diagnosed with ASD; and 2) for the brothers, there will be more diagnosed cases of ASD: in this example, a 3:1 male-to-female ratio. In the next generation (not shown in the pedigree), because it is more likely that undiagnosed sisters carry a moderate-to-high genetic liability, the relative risk of ASD among offspring to the undiagnosed siblings is expected to be higher among those to the sisters than among those to the brothers.

Biological Psychiatry

Table 2. Relative Risks for ASD Among Participants With ASD-Affected Uncle(s)/Aunt(s) Compared With Participants With Uncle(s)/Aunt(s) Free From ASD Diagnosis

	Person-Years of Follow-up		Rates of ASD per 100,000 Person-Years		Relative Risk (95% CI)[a]		
Exposure	Exposed	Unexposed	Exposed	Unexposed	Crude	Adjusted 1[b]	Adjusted 2[c]
Maternal Lineage							
Uncle(s) affected by ASD	19,662	6,675,534	401.79	151.07	3.22 (2.54–3.91)	2.75 (2.15–3.36)	1.92 (1.49–2.37)
Aunt(s) affected by ASD	9984	6,337,615	340.54	152.71	2.73 (1.88–3.73)	2.36 (1.62–3.21)	1.73 (1.19–2.35)
Uncle(s)/aunt(s) affected by ASD	29,646	13,013,149	381.16	151.87	3.05 (2.52–3.64)	2.62 (2.17–3.14)	1.88 (1.54–2.26)
Paternal Lineage							
Uncle(s) affected by ASD	13,274	6,723,265	301.35	153.23	2.39 (1.72–3.13)	2.09 (1.50–2.74)	1.63 (1.16–2.16)
Aunt(s) affected by ASD	7342	6,292,408	190.68	151.99	1.52 (0.79–2.30)	1.33 (0.69–2.01)	1.07 (0.56–1.63)
Uncle(s)/aunt(s) affected by ASD	20,616	13,015,674	261.94	152.63	2.08 (1.53–2.67)	1.82 (1.32–2.34)	1.44 (1.05–1.86)

"Affected by ASD" refers to an individual with a clinical diagnosis of ASD.
ASD, autism spectrum disorder; CI, confidence interval.
[a]Bootstrapped 95% CI: 2.5%–97.5% percentiles of estimates from 1000 bootstrapped samples.
[b]Adjusted for the birth year of the participant, the mother, and the uncle/aunt.
[c]Adjusted for covariates in Adjusted 1 and any mental illness (yes/no) of the mother and the uncle/aunt.

First epidemiologic estimate of risk to second generation offspring:

For sisters of an ASD-affected individual, risk of autism = 2-3 x population risk (2-5%)
And not significantly elevated over that for the offspring of brothers of an ASD proband

4. Shift Happens

Background genetic variation within the normal range shifts the “starting point” for the deleterious effects of some (not all) mutations

VARIABLE PENETRANCE

Research

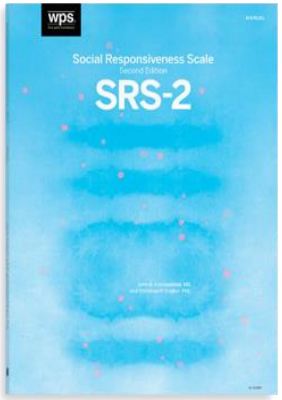
Original Investigation

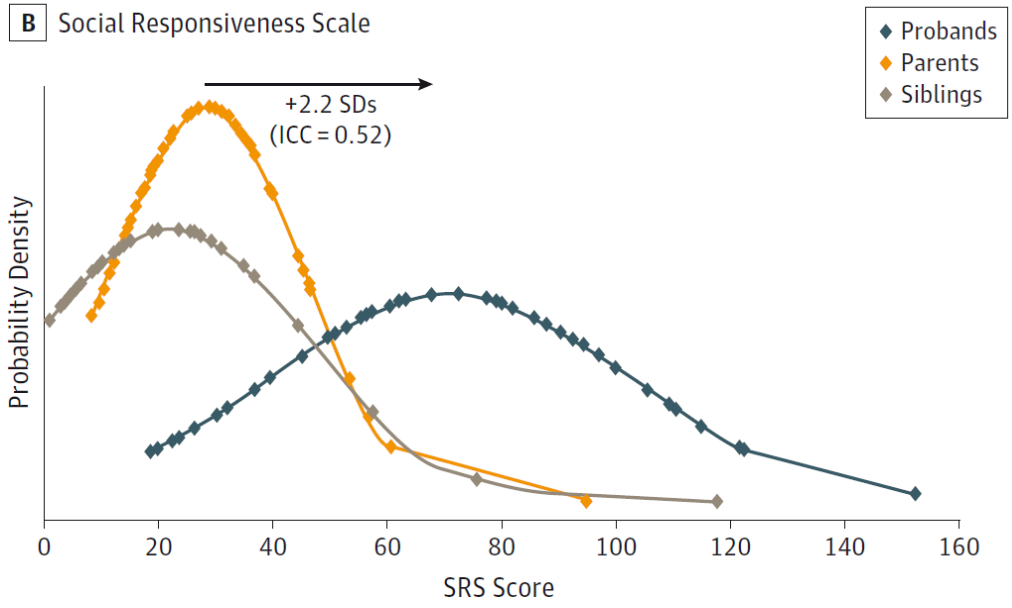
The Role of Parental Cognitive, Behavioral, and Motor Profiles in Clinical Variability in Individuals With Chromosome 16p11.2 Deletions

Andres Moreno-De-Luca, MD; David W. Evans, PhD; K. B. Boomer, PhD; Ellen Hanson, PhD; Raphael Bernier, PhD; Robin P. Goin-Kochel, PhD; Scott M. Myers, MD; Thomas D. Challman, MD; Daniel Moreno-De-Luca, M Mylissa M. Slane, MS; Abby E. Hare, PhD; Wendy K. Chung, MD; John E. Spiro, PhD; W. Andrew Faucet Christa L. Martin, PhD; David H. Ledbetter, PhD

Shift happens: family background influences clinical variability in genetic neurodevelopmental disorders

Brenda Finucane, MS, LGC[1], Thomas D. Challman, MD, FAAP[1], Christa Lese Martin, PhD, FACMG[1] and David H. Ledbetter, PhD, FACMG[1]





Conclusions

- The strong family genetic liability to ***autism*** operates via multiple independent liabilities, permutations and combinations of which give rise to autism; in this sense autism is “fractionable” before it develops BUT NOT AFTER
- Autism ***severity*** is strongly influenced by stochastic influences / non-shared environmental effects—this is true above, but not below, the clinical threshold
- If the components of the developmental sub structure for autism are not measured among CONTROL subjects (or as indexed by parental background traits in “shift” studies), expect erosion in ***statistical power*** to identify a genotype-phenotype association (or any biomarker association related to cause of ASD
- Framing the ASD sex bias as a function of ***male sensitivity*** rather than female protection has major implications for the design of future studies (including cell, organoid, rodent) of the effects of sex on ASD
- New approach to ***early behavioral intervention***?: “nudging” endophenotypic liabilities into the safe/normative range before autism develops
    - Social visual disengagement
    - Inattention
    - Motor coordination deficits (cerebellar learning)
    - ? Tactile sensitivity

Human Genetics (2018) 137:665–678
https://doi.org/10.1007/s00439-018-1916-x

REVIEW

Multiplexed assays of variant ef genotype–phenotype atlas

Jochen Weile[1,2,3,4] · Frederick P. Roth[1,2,3,4]

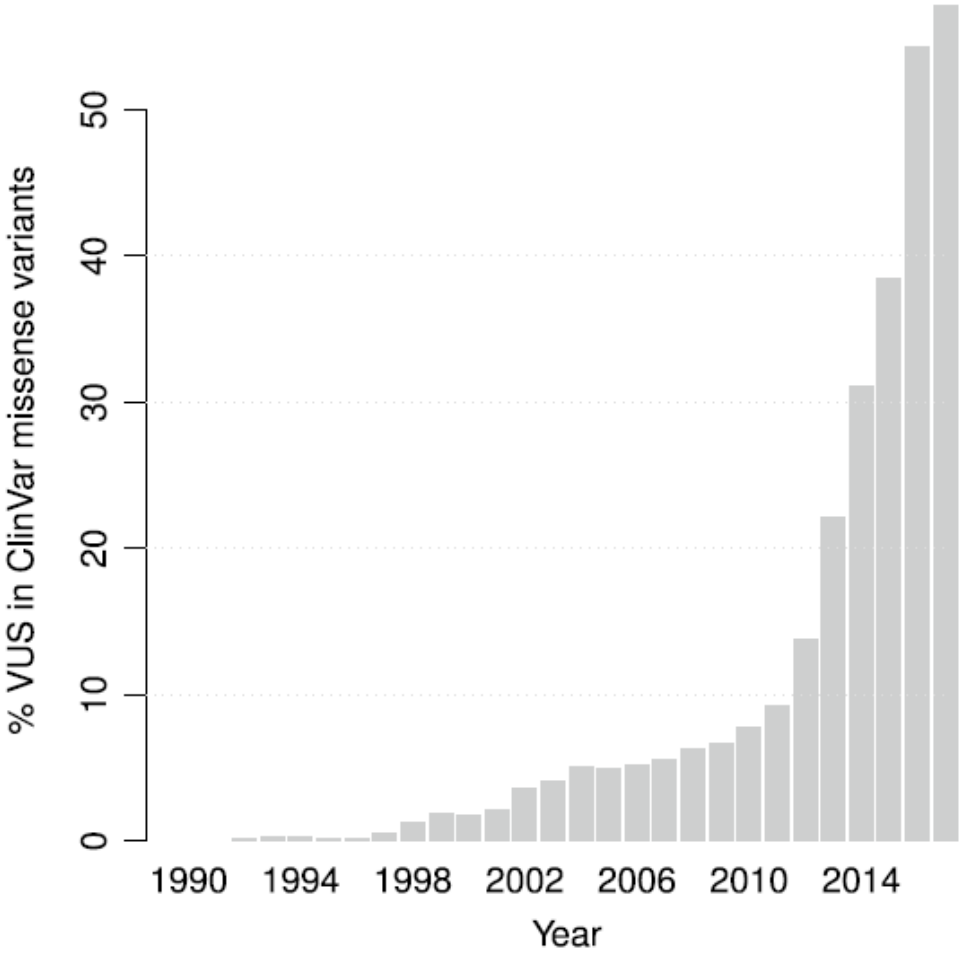
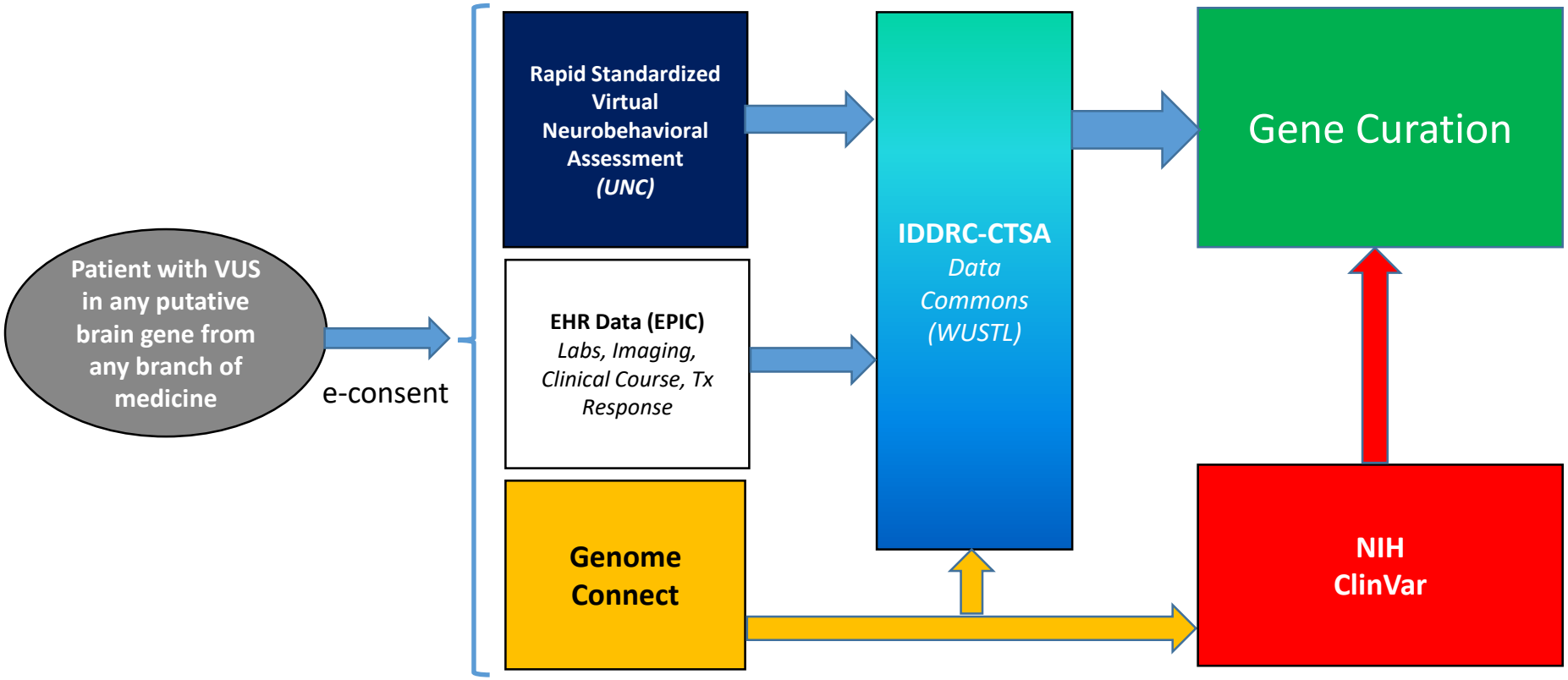


Fig. 1 Percentage of variants of uncertain significance (VUS) among missense allele Clinvar records over time from 1990 until 2017



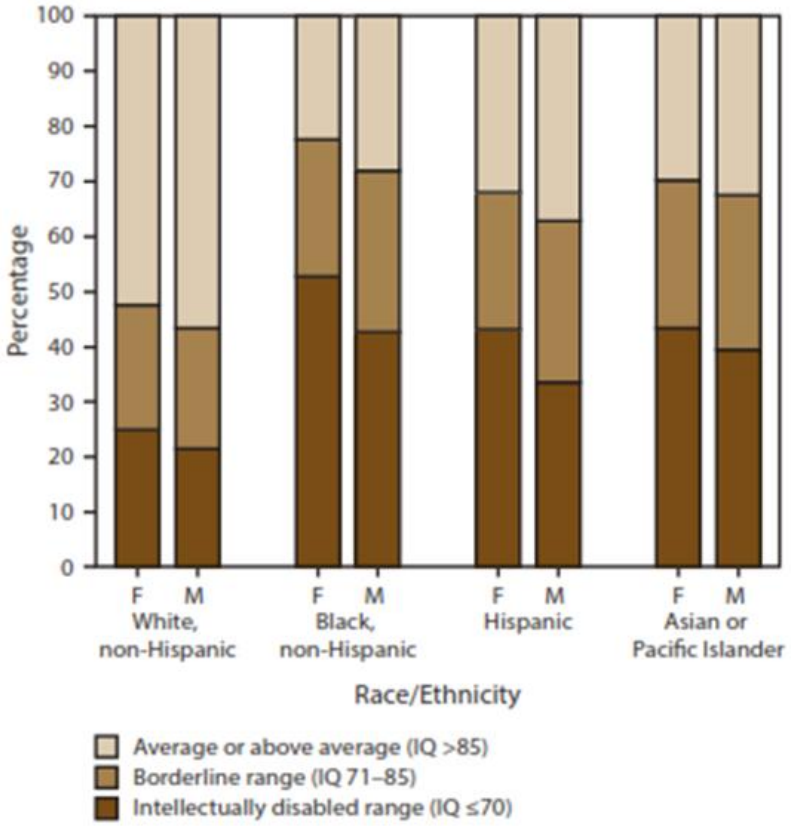
NATIONAL BRAIN-GENE REGISTRY

NIH National Center for Advancing Translational Sciences

Co-registration of
A) clinically-identified variants of unknown significance (VUS)
B) Rapid Standardized (Virtual) Neurobehavioral Phenotyping Data
C) Electronic Health Record Data

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Surveillance Summaries / Vol. 67 / No. 6
2018
April 27, 2018

FIGURE 2. Most recent intelligence quotient score as of age 8 years among children with autism spectrum disorder for whom test data were available, by sex and race/ethnicity — Autism and Developmental Disabilities Monitoring Network, nine sites,* United States, 2014



Abbreviations: ASD = autism spectrum disorder; F = female; IQ = intelligence quotient; M = male.

* Includes nine sites (Arizona, Arkansas, Colorado, Georgia, Maryland, Minnesota, New Jersey, North Carolina, and Tennessee) that had intellectual ability data available for ≥70 of children who met the ASD case definition (n = 3,714).

Maenner et al. MMWR 2020

Prevalence estimates were approximately identical for non-Hispanic white and non-Hispanic black children (18.5 and 18.3, per thousand, respectively)

Among children with ASD for whom data on intellectual or cognitive functioning were available, 33% were classified as having intellectual disability (intelligence quotient [IQ] ≤70); this percentage was higher among black and Hispanic than white children (47%, 36%, and 27%, respectively).

Black children with ASD were less likely to have a first evaluation by age 36 months than were white children with ASD (40% versus 45%).

Black children with IQ ≤70 had a later median age at ASD diagnosis than white children with IQ ≤70 (48 months versus 42 months).

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Structural Racism and Autism

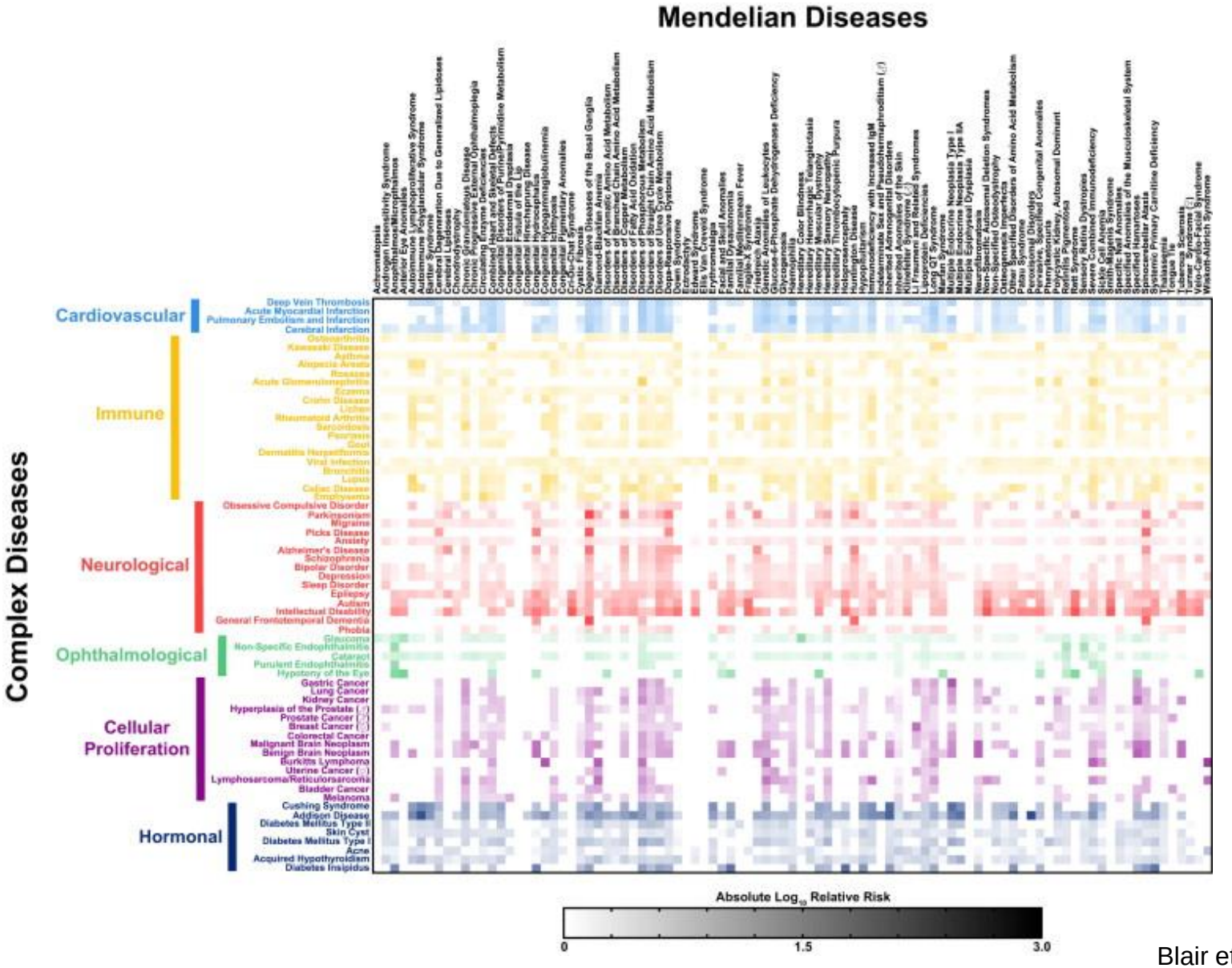
Sarabeth Broder-Fingert, MD, MPH,[a] Camilla Mateo, MD, MPH,[b] Katherine E. Zuckerman, MD, MPH[c]

- **We believe these data shed light on structural racism as a driver of inequity for children with ASD.**
- **31.3% of parents cited availability of professionals as a barrier to diagnosis.**
  - Workforce capacity has long been a major challenge in the field of ASD.
  - This issue may be compounded for AA families who may be more likely than white families to live in areas with few ASD diagnostic specialists and also be more likely to rely on Medicaid.
  - Medicaid may aggravate inequities because low rates of Medicaid reimbursement for diagnostic services can create challenges to supporting and maintaining a workforce.
- **Thus, AA families may be suffering from a lack of available workforce related to <u>where they live</u> (as a result of structural racism in housing policy), whereas clinics serving these communities may be <u>unable to expand capacity</u> (because of structural racism in Medicaid reimbursement rates).**
- **These issues are likely exacerbated by additional issues on the provider level including a lack of cultural humility and workforce diversity. Notably, a recent workforce survey showed that only 2% of developmental-behavioral or neurodevelopmental pediatricians are AA.**

constantino@WUSTL.edu

Washington University in St. Louis
School of Medicine

Genetic relationships between Mendelian and Complex Diseases



Blair et al. *Cell* 2013

Behavior Genetics
https://doi.org/10.1007/s10519-019-09987-2

ORIGINAL RESEARCH

On the Nature of Monozygotic Twin Concordance and Discordan for Autistic Trait Severity: A Quantitative Analysis

Lauren Castelbaum[1] · Chad M. Sylvester[1] · Yi Zhang[1] · Qiongru Yu[1] · John N. Constantino[1,2]

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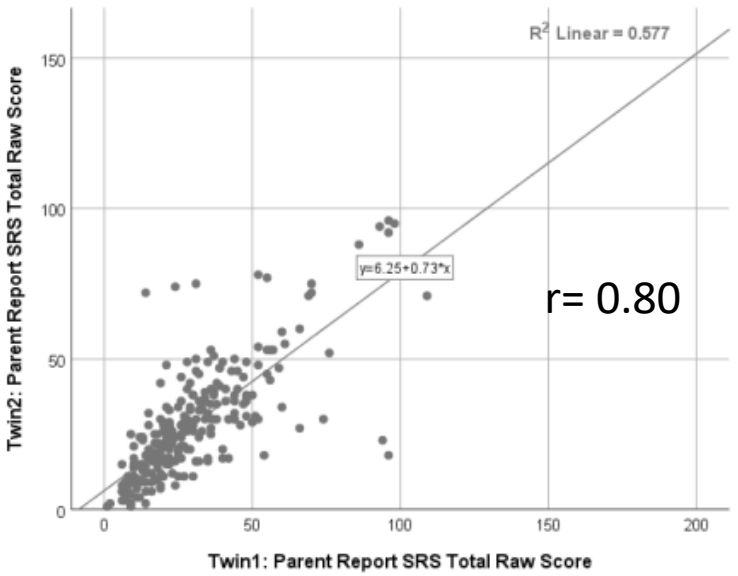
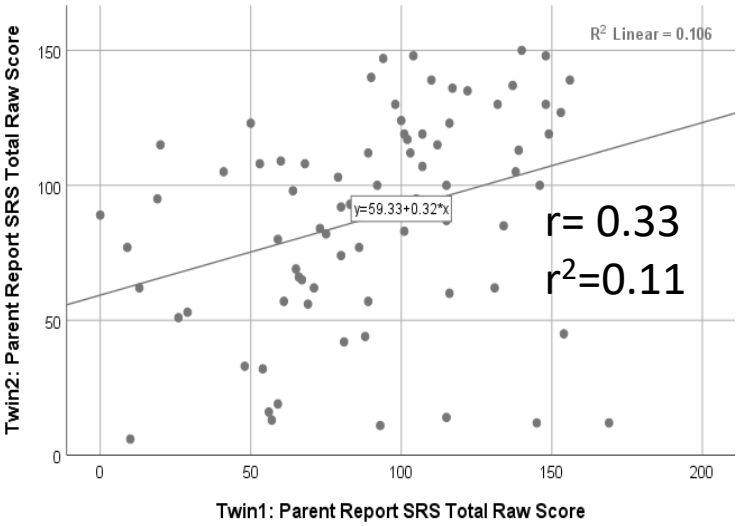
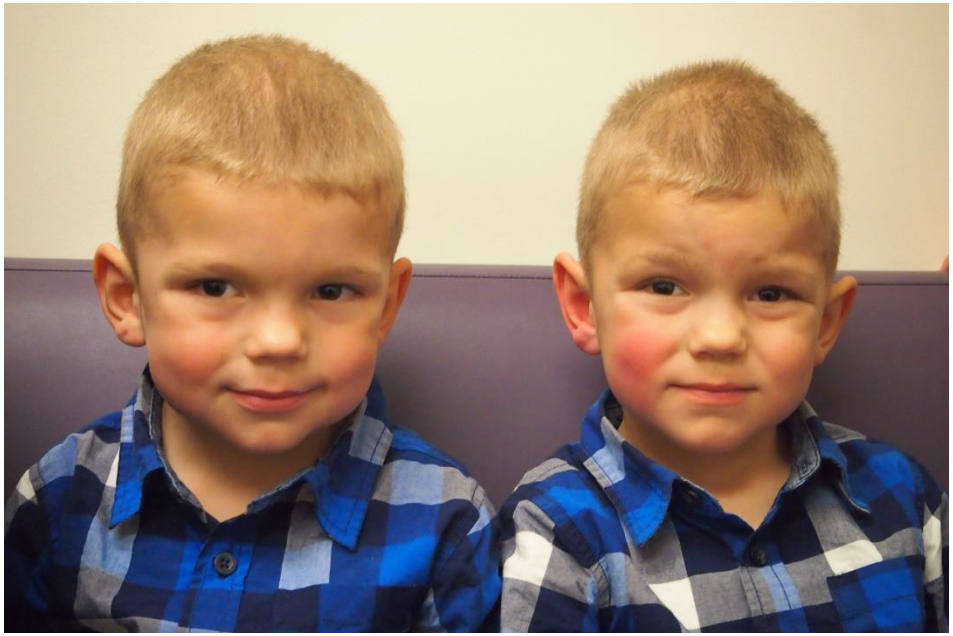
General Population MZ Twins, n=268 pairs



Clinically-ascertained MZ twins, n= 79 pairs





LETTER

doi:10.1038/nature22999

Infant viewing of social scenes is under genetic control and is atypical in autism

John N. Constantino[1,2,3], Stefanie Kennon-McGill[1], Claire Weichselbaum[1], Natasha Marrus[1,3], Alyzeh Haider[1], Anne L. Glowinski[1], Scott Gillespie[4], Cheryl Klaiman[5,6], Ami Klin[5,6,7] & Warren Jones[5,6,7]

Table 1 Falconer's heritability and twin-twin correlations for two behavioral predictors of ASD recurrence (Attention Problems and variation in Motor Coordination) and autism-related variation in reciprocal social behavior in the fourth year of life

	Attention problem (CBCL)	Motor coordination (Little DCDQ)	Reciprocal social behavior (SRS-2)
MZM twin-twin correlation	.527	.937	.784
DZM twin-twin correlation	−.013	.734	.327
MZF twin-twin correlation	.583	.898	.913
DZF twin-twin correlation	−.081	.625	.352
Heritability (males)	.53*	.41	.91
Heritability (females)	.58*	.55	.91*

The analysis excluded opposite sex twin pairs and pairs with uncertain zygosity; they are derived from 66 MZ pairs (34 male-male and 32 female-female) and 58 DZ pairs (30 male-male, 28 female-female) with complete data for these three variables
*For heritability estimate >1, MZ concordance rate is used by convention
MZM monozygotic male
DZM dizygotic male
MZF monozygotic female
DZF dizygotic female
CBCL child behavior checklist
Little DCDQ developmental coordination disorder questionnaire
SRS-2 social responsiveness scale, 36 months

Table 2 Matrix depicting within-individual correlations (Pearson's *r*) between autism recurrence predictors in 174 general population twins (one twin selected at random from each pair)

	Attentional impairment	QAT-p	Motor coord	SRS 36 months	SRS 48 months
Attentional impairment	1				
QAT-p	.20	1			
Motor coordination	−.20	−.16	1		
SRS-2 (36 months)	.46	.38	−.36	1	
SRS-2 (48 months., $n = 160$)	.48	.28	−.35	.71	1

All correlations above 0.29 were statistically significant at $p < .01$; none of the bivariate associations between BPARs reached this threshold. Bivariate cross-twin cross-trait correlations encompassing attentional impairment, QAT-p, and motor coordination were uniformly non-statistically significant
QAT-p Quantitative Autistic Traits of Parents, as measured by the Social Responsiveness Scale, Adult Version

Points of bifurcation in Waddington's epigenetic landscape