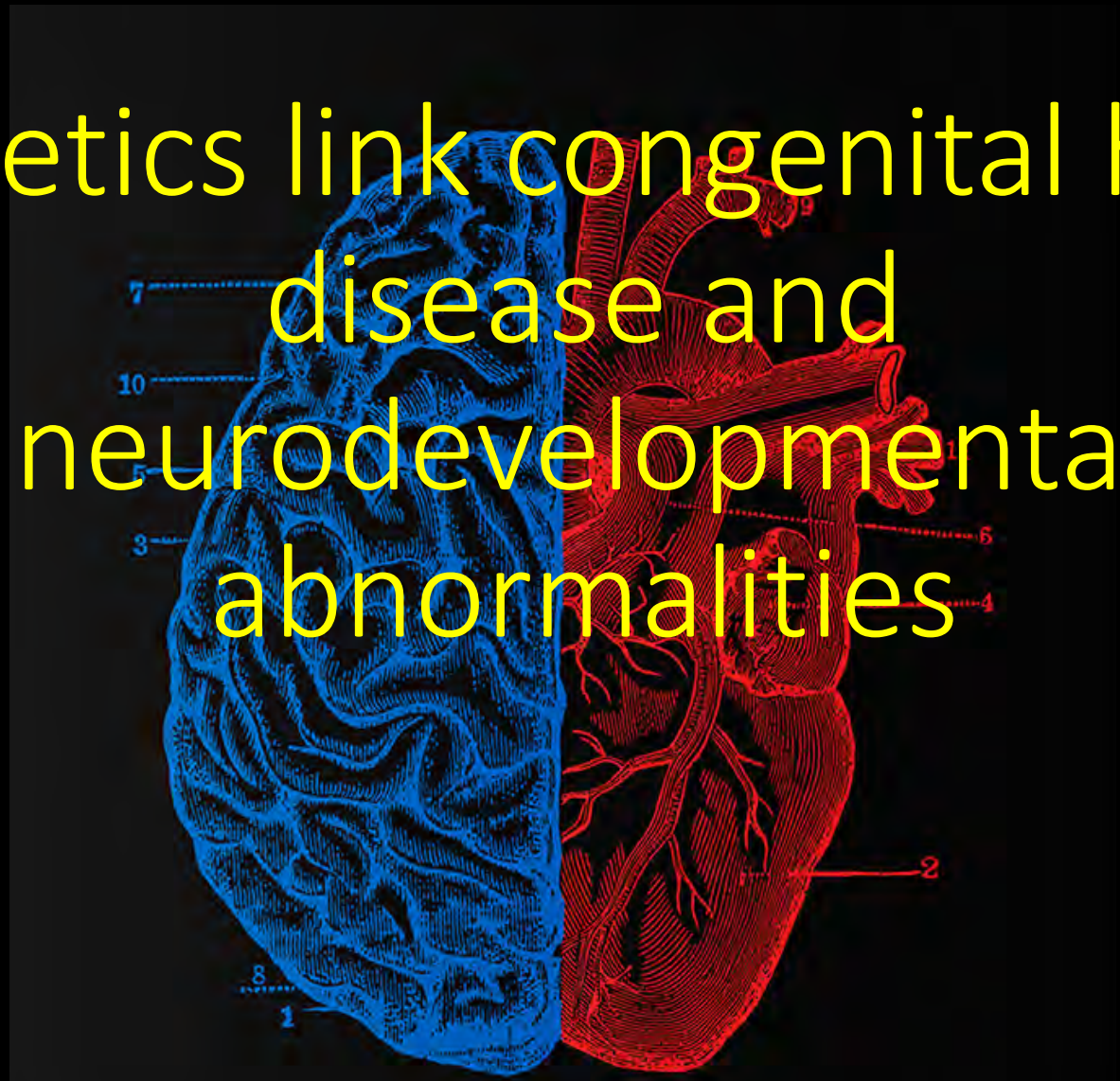
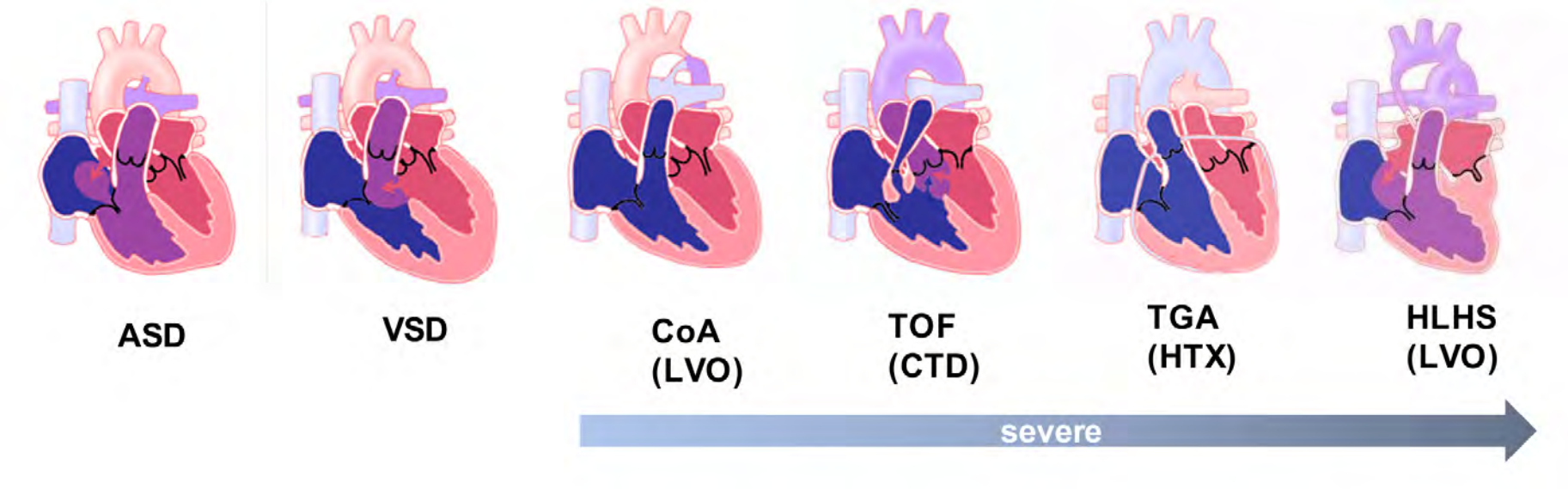
Genetics link congenital heart disease and neurodevelopmental abnormalities



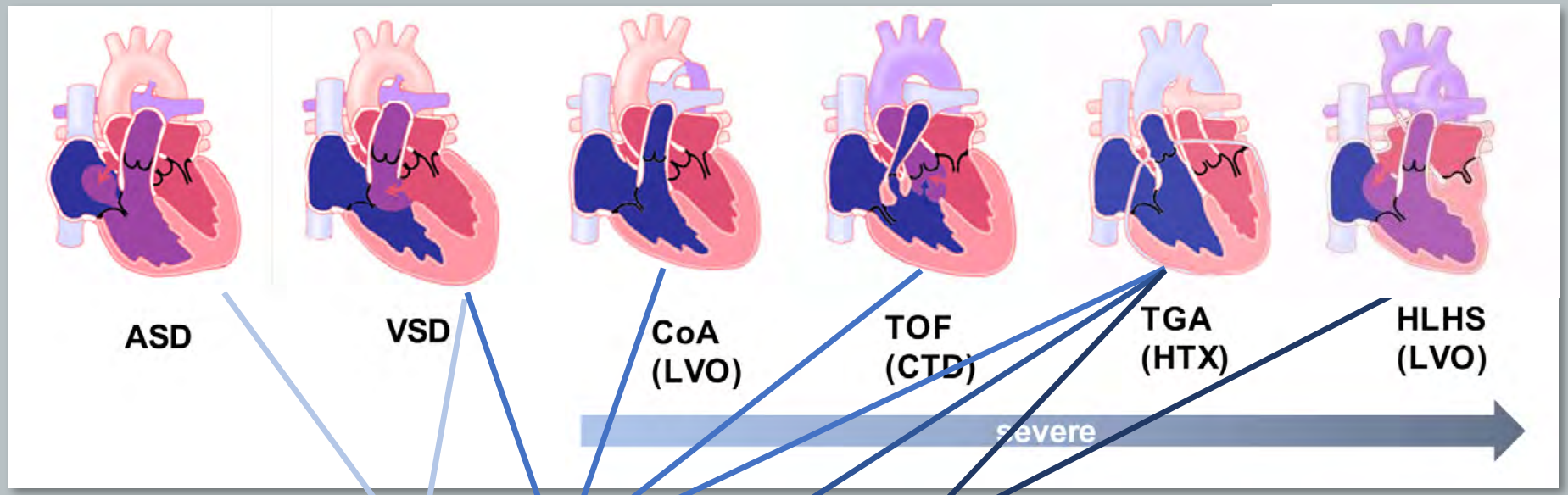
Martina Brueckner

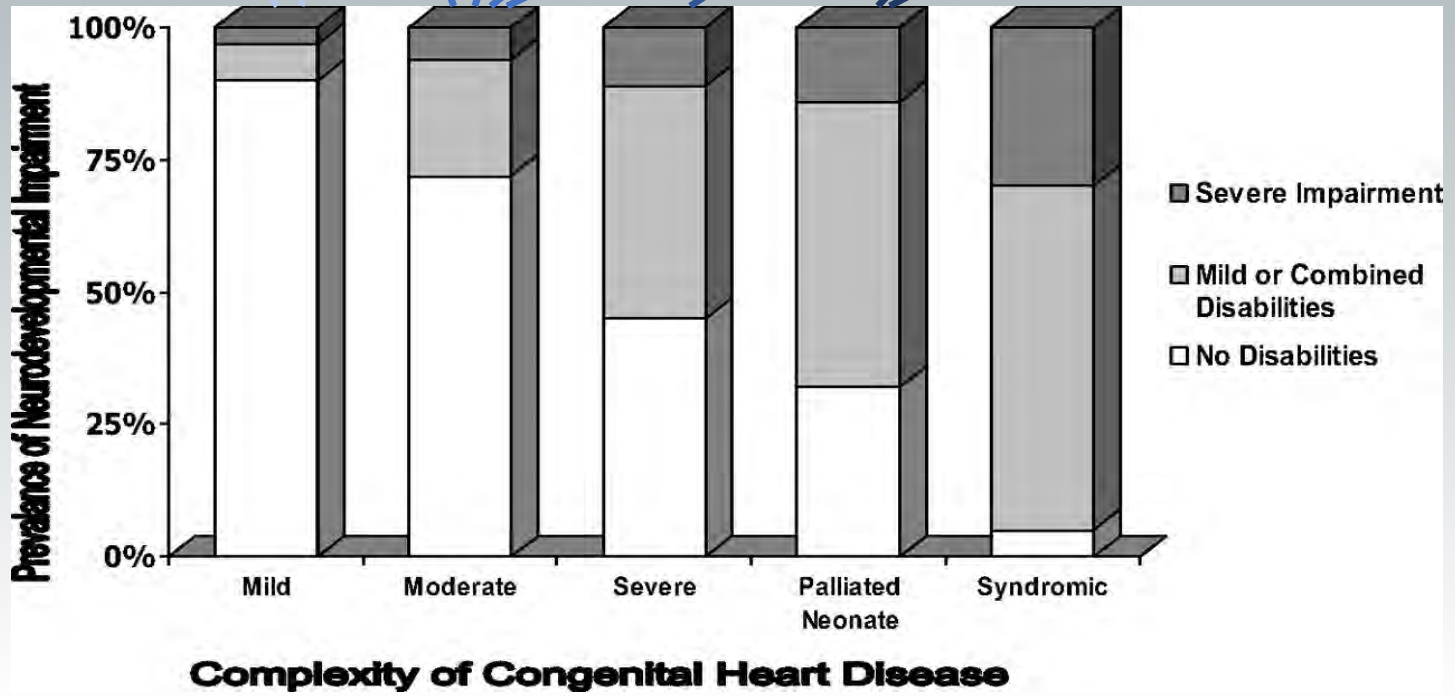
Congenital heart disease:



- Affects 1% of liveborn infants, most common cause of mortality from congenital defects
- 90% of patients survive to adulthood, but many suffer co-morbidities including neurodevelopmental abnormality and respiratory disease
- Genetic contribution likely in 90%
- Chromosomal aneuploidy and copy-number variation contributes to at least 23%
- High genetic heterogeneity makes identification of specific genes underlying CHD difficult

10-20% of all CHD patients have some neurodevelopmental impairment

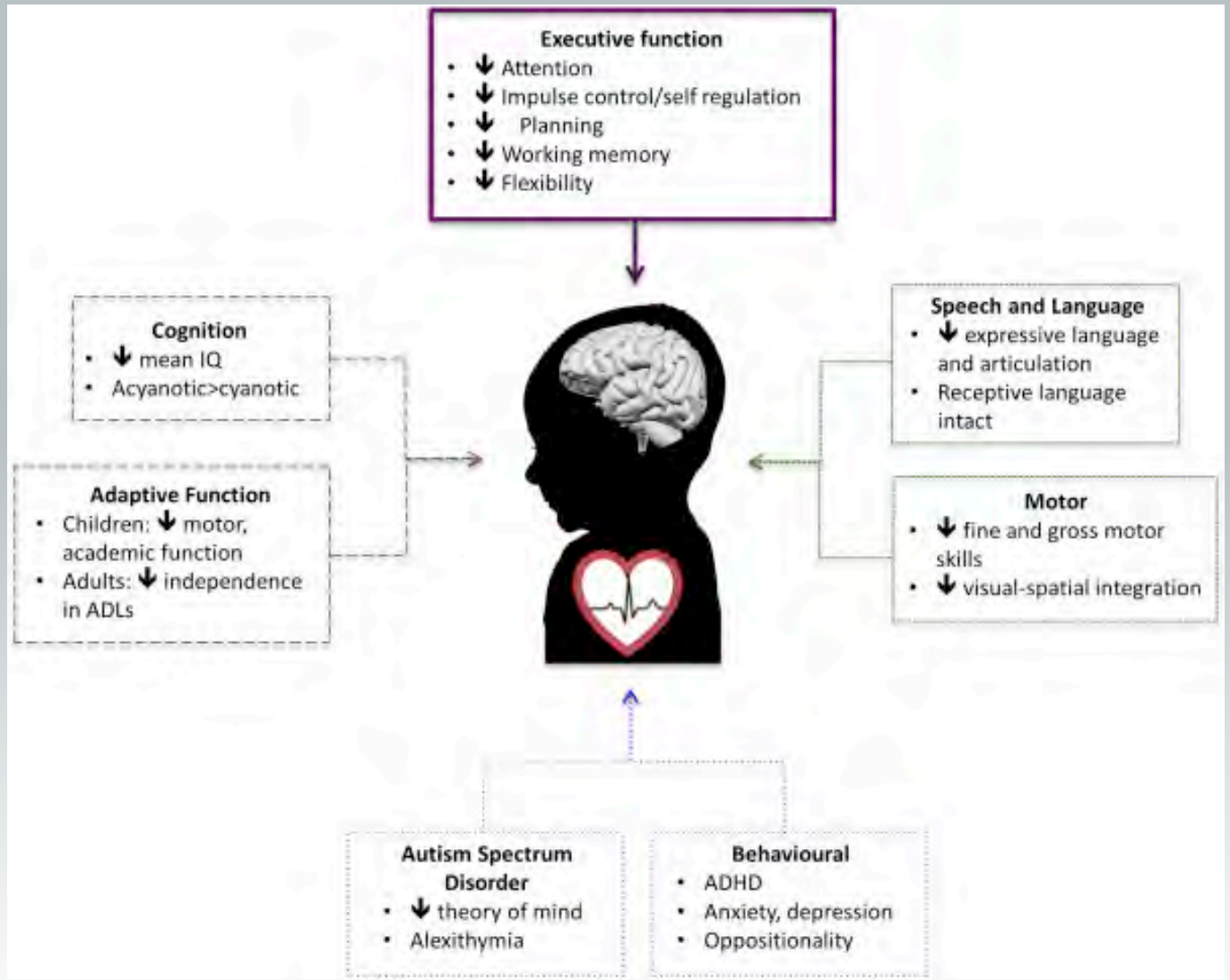




Marino et al, *Circulation*, 2012

Broad range of neurodevelopmental abnormalities in CHD:

- Cognitive impairment
- Learning disability
- Executive functioning
- School functioning
- Deficits in fine and gross motor skills
- Behavioral difficulty
- Autism-Spectrum disorder



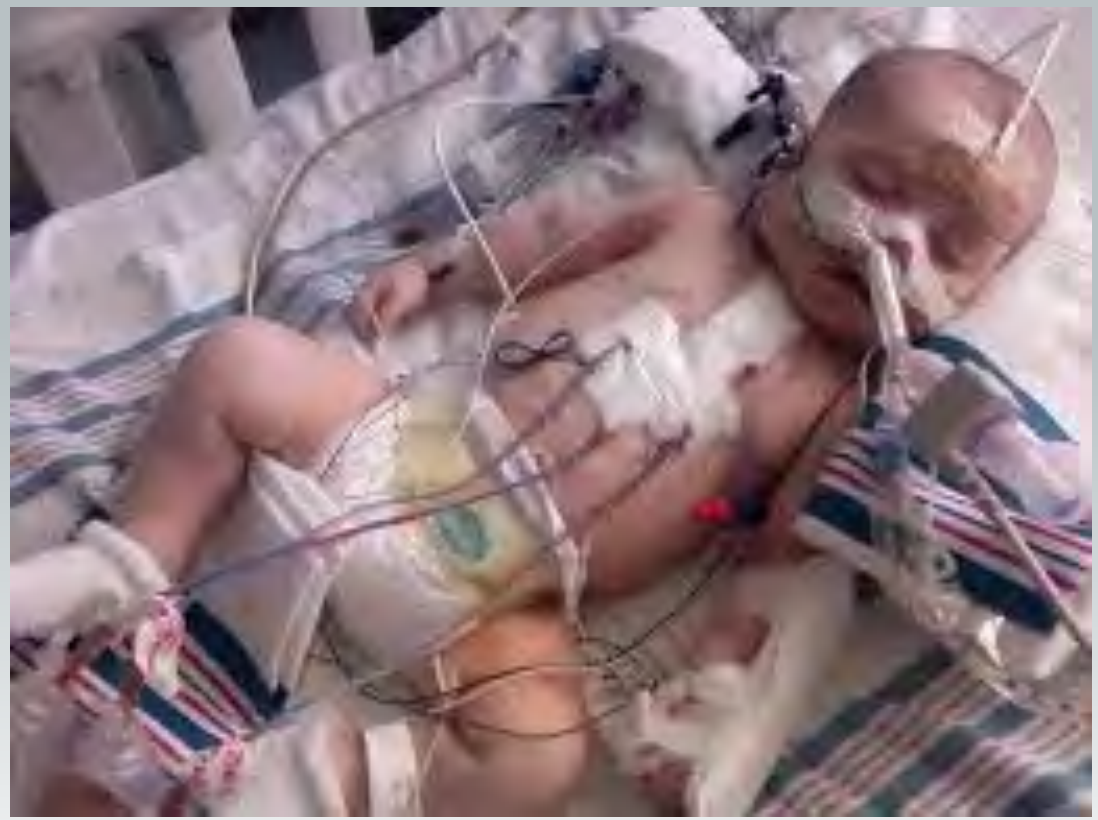
Nattel et al, *Canadian Journal of Cardiology*, 2017

Neurodevelopment in Congenital Heart Disease: possible mechanisms

- Circulatory abnormalities impacting brain development pre- and postnatally
- Complications of surgical and medical management
- Psychosocial stresses associated with disease and management
- Developmental pathways shared between brain and heart development

Complications of surgery:

- Cyanosis
- Impaired cerebral perfusion during cardio-pulmonary bypass
- Perioperative acidosis
- Microemboli
- ICU interventions

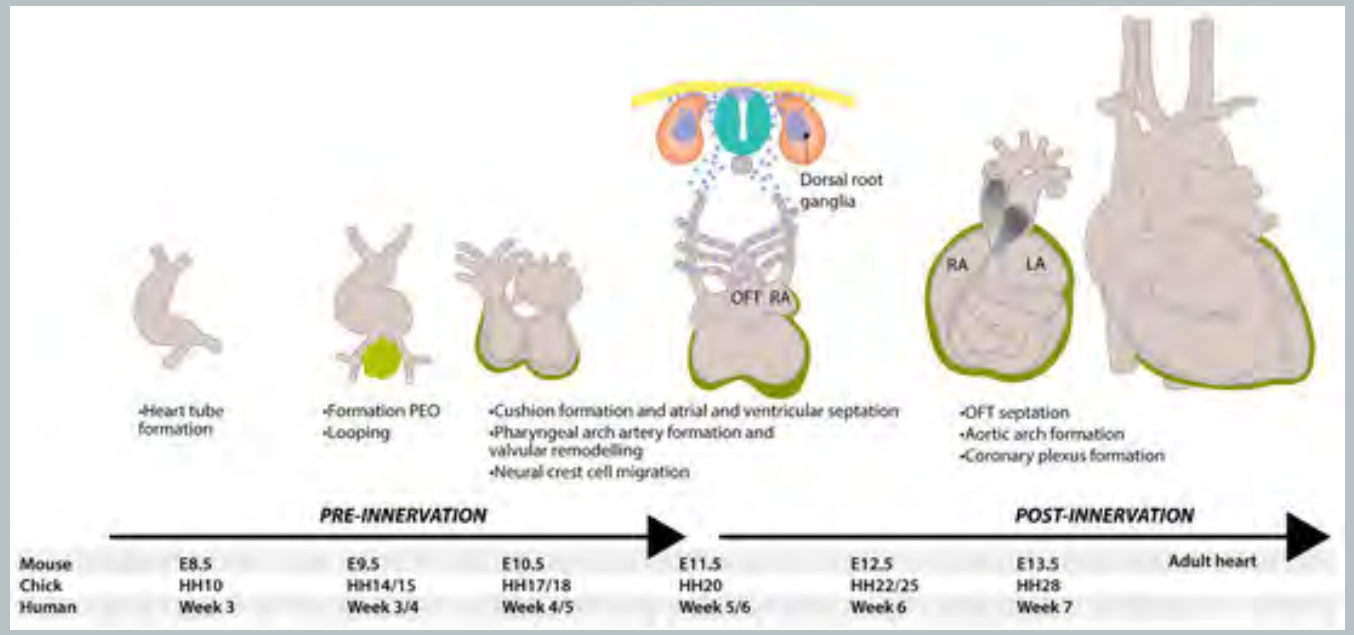


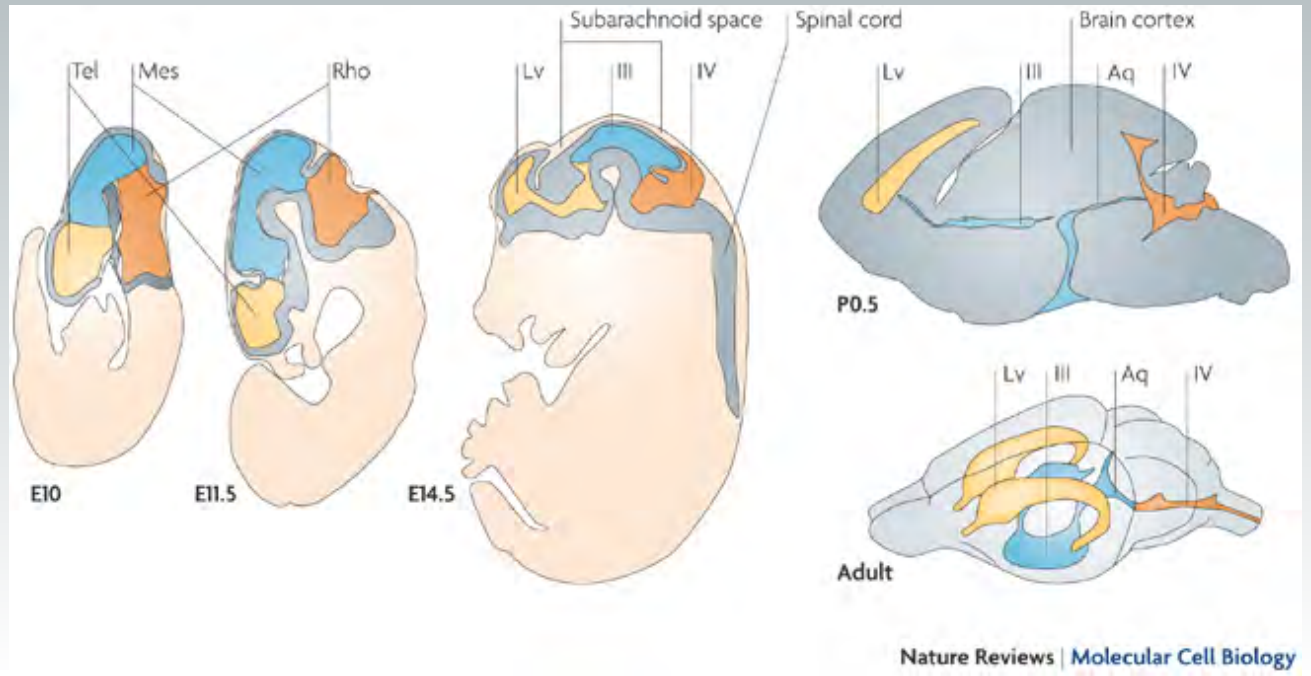
But: Cardiac surgery had no significant impact on ND outcome in school-age children with Down Syndrome

	DS+CHD (n = 7)	**DS−CHD (n = 31)**	***P* value**
Preschoolers age (year)	5.7 + 1.3	5.2 + 1.5	.403
PLS-5 expressive	46.25 ± 14.8 (n = 7)	52.71 ± 15.8 (n = 31)	.428
PLS-5 auditory	40.67 ± 18.21 (n = 7)	51.9 ± 13.39 (n = 31)	.2
PB VISUAL MOTOR	90.75 ± 9.91 (n = 4)	100 ± 19.9 (n = 15)	.55
PB GRASPING	41.5 (40.25−44.25) (n = 4)	42 (42−44) (n = 15)	.35
PB fine motor	7.5 (5.25−11.25) (n = 4)	7 (5.5−10.5) (n = 13)	.549

Alsaid et al, *Congenital Heart Disease*, 2016

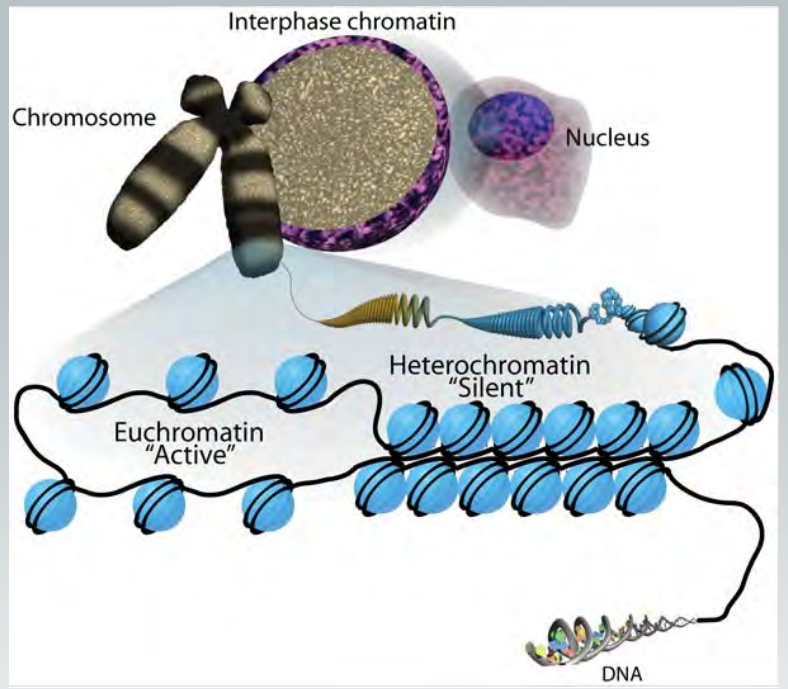
Early brain and heart development temporally overlap



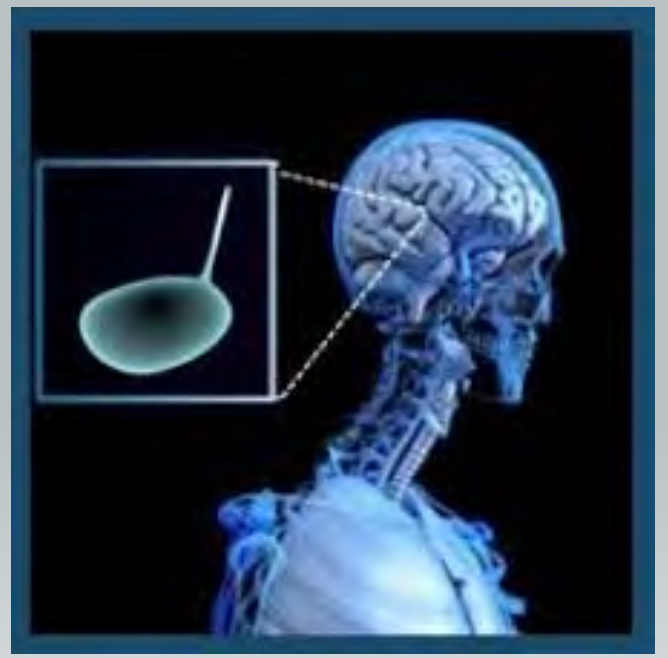


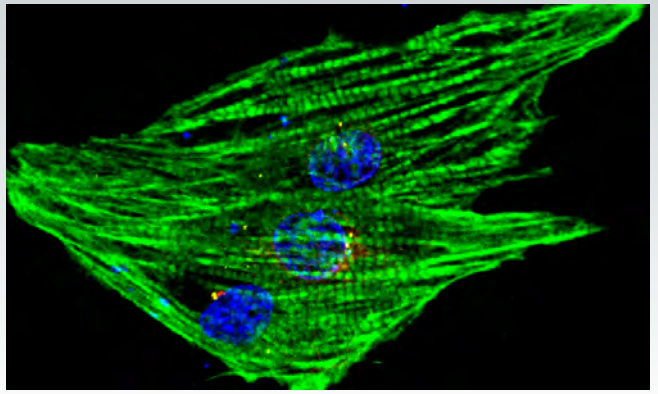
Many molecular and cellular building blocks are shared between heart and brain development

Regulation of transcription/
Chromatin remodeling

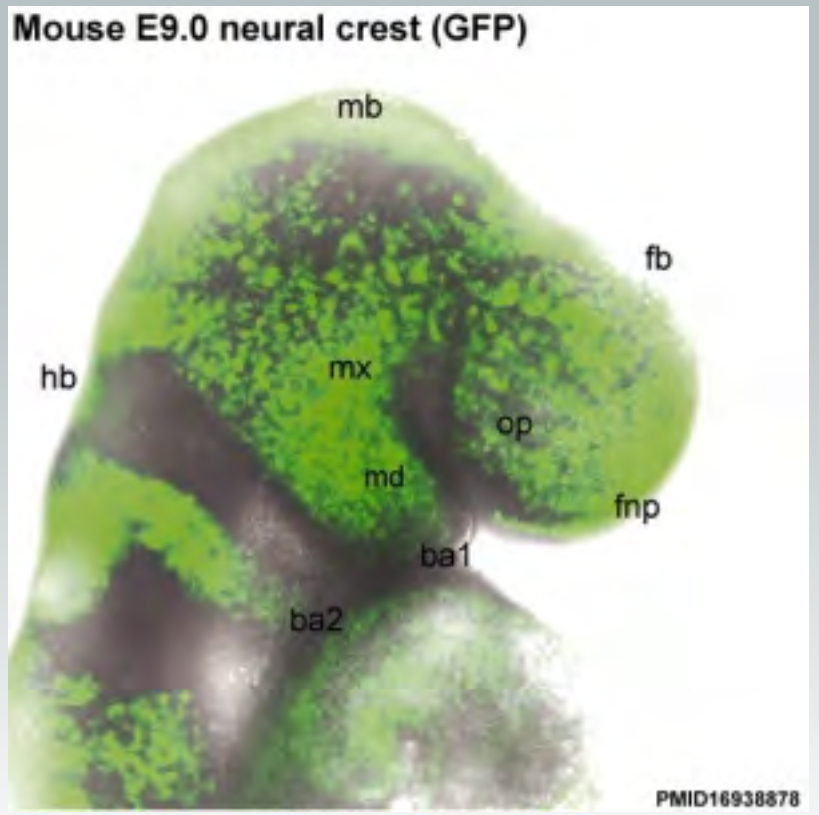


Cilia

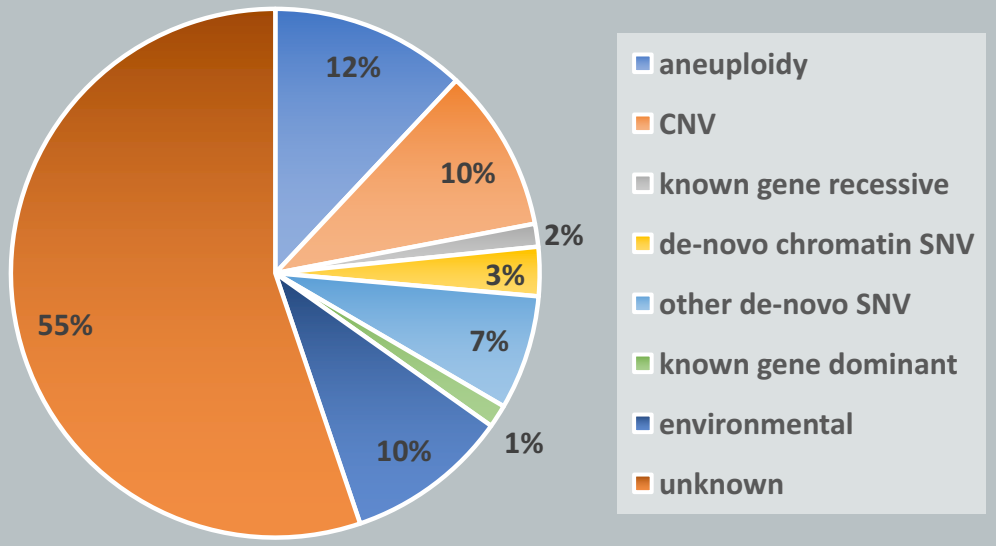




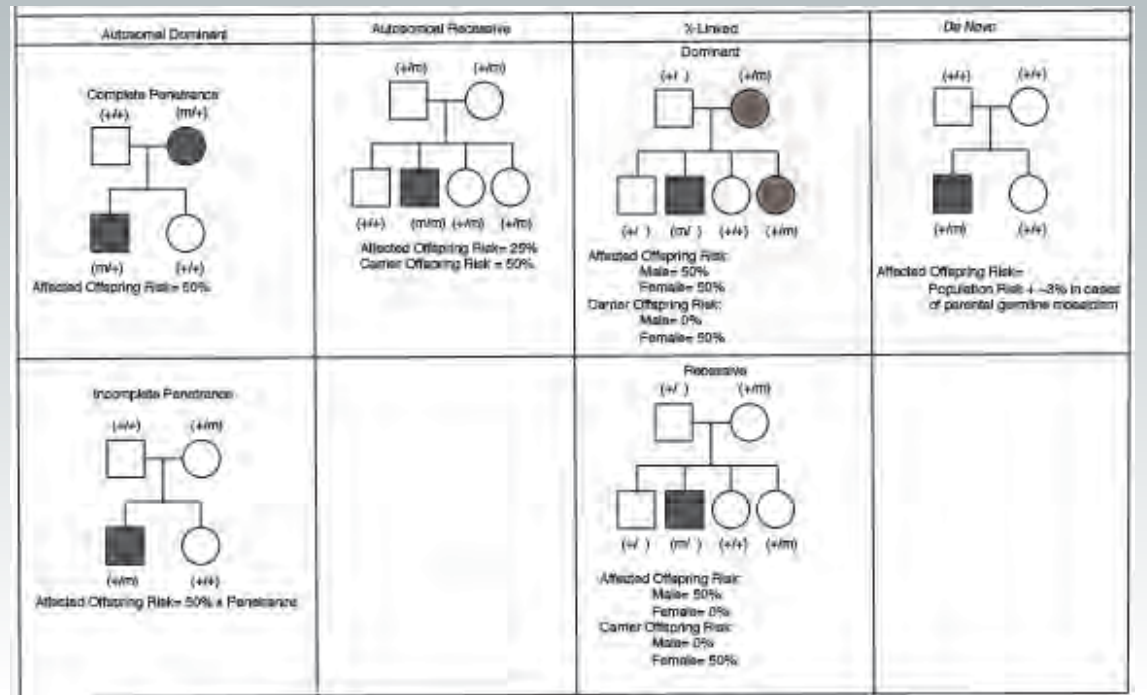
Neural crest cells



Causes of CHD:



Inheritance patterns of CHD:



There are many ways to get a broken heart: Human genetics predicts 300-500 genes associated with CHD

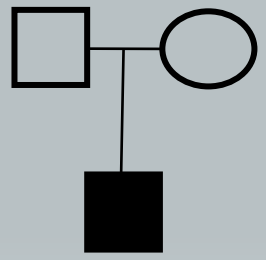
- Effort by NHLBI B2B (Bench-to-Bassinet) program
- Multi-center collaboration **>12,000** patients
- Whole-exome sequencing ~3,500 patient-parent trios
- Highly heterogeneous: 300-500 genes
- Genetic cause may be predictive of outcome, and may influence management of CHD
- Identified novel developmental mechanisms for heart development

Samir Zaidi, Peter (Shen Chih) Jin

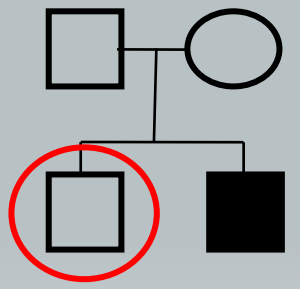
B♥B Bench to Bassinet Funded by NHLBI

The low-hanging fruit: *de-novo* mutations in CHD

PCGC (n=2,645)



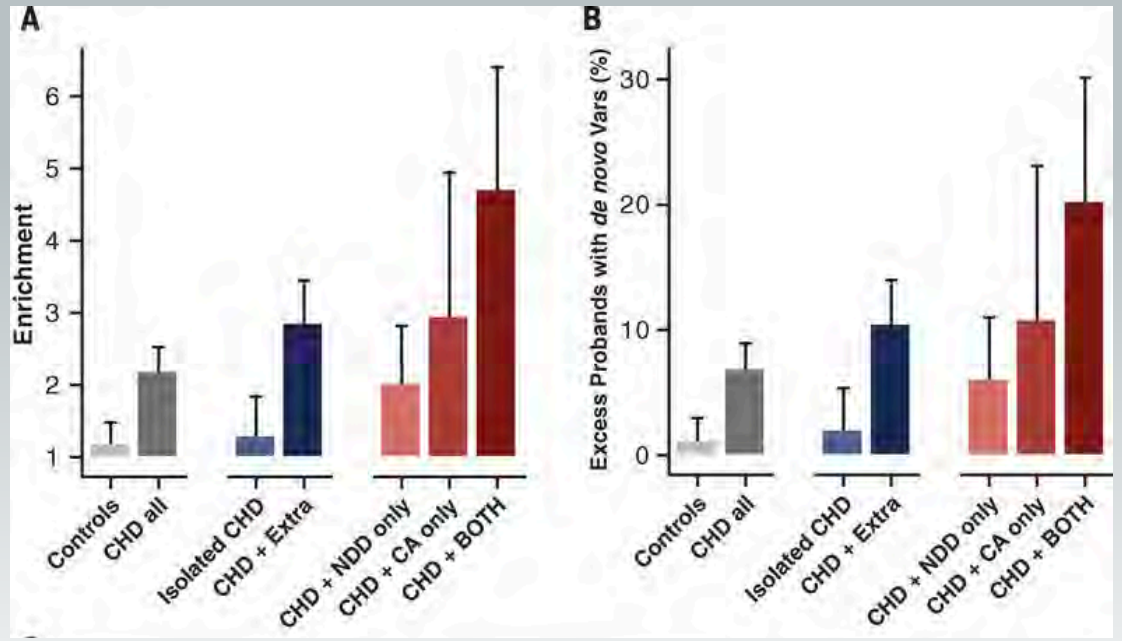
Simons Simplex Autism (n=1,789)



- *De-novo* mutations account for 8% of CHD
- 3% of isolated CHD
- 28% of CHD + extracardiac abnormalities and NDD
- Approximately 440 genes contribute to CHD by a *de-novo* dominant mechanism

S. Zaidi et al, *Na*t 2013, Homsy et al *Science* 2015, Jin et al, *Nat Gen* 2017

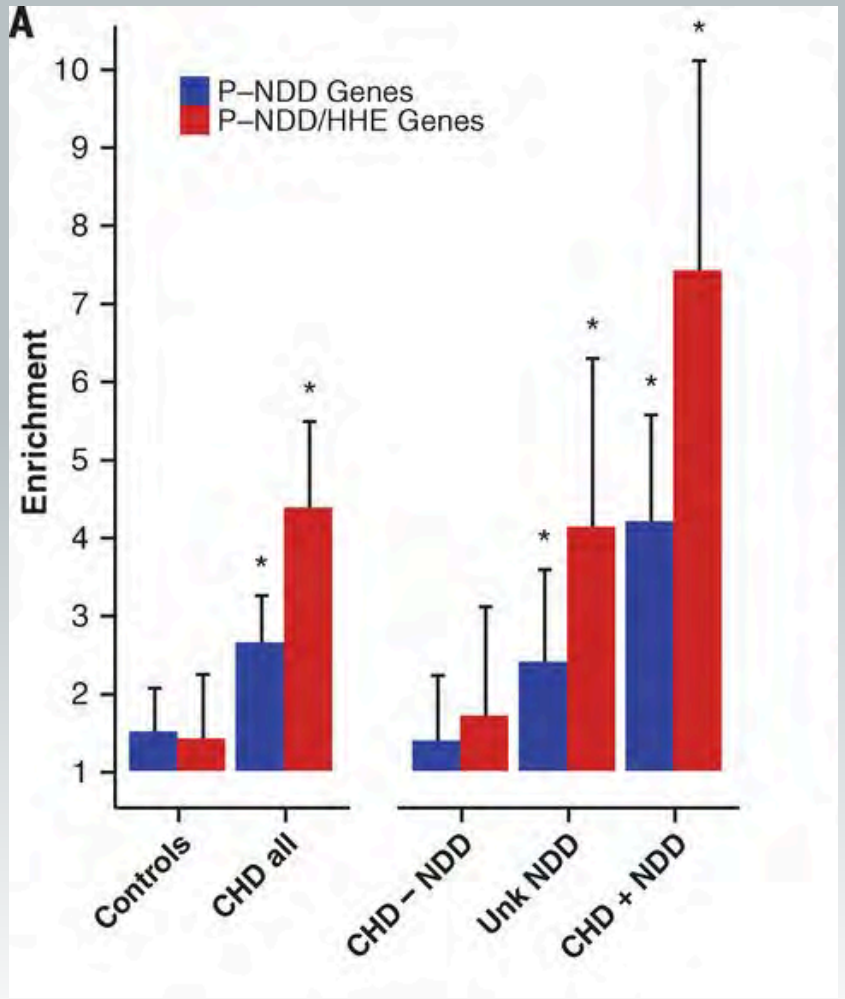
De-novo mutations are enriched in patients with CHD and neurodevelopmental abnormality

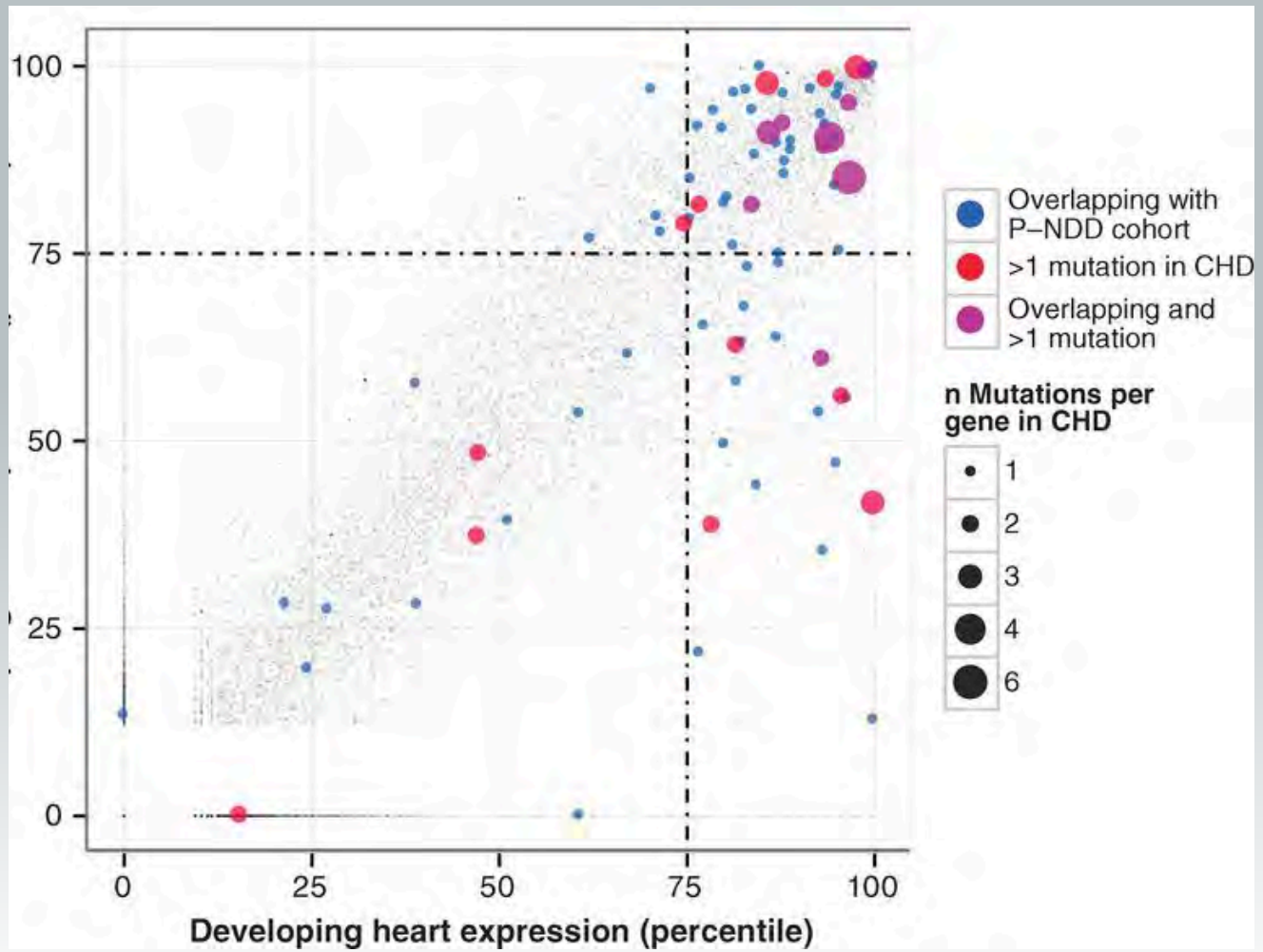


	Observed		Expected		Enrichment	p
	n	Rate	n	Rate		
Isolated CHD (356)						
Synonymous	17	0.05	30	0.09	0.6	1
Missense	83	0.23	69	0.19	1.2	0.052
D-Mis	17	0.05	12	0.03	1.4	0.097
LoF	11	0.03	10	0.03	1.1	0.43
Damaging	28	0.08	22	0.06	1.3	0.12
CHD + Extra (559)						
Synonymous	38	0.07	48	0.09	0.8	0.94
Missense	130	0.23	108	0.19	1.2	0.022
D-Mis	49	0.09	19	0.03	**2.6**	**$4.3x10^{-09}$**
LoF	49	0.09	16	0.03	**3.1**	**$2.2x10^{-11}$**
Damaging	98	0.18	35	0.06	**2.8**	**$1.1x10^{-18}$**
CHD + NDD only (252)						
Synonymous	22	0.09	22	0.09	1.0	0.49
Missense	46	0.18	49	0.19	0.9	0.67
D-Mis	15	0.06	8	0.03	1.8	0.026
LoF	16	0.06	7	0.03	**2.2**	**0.003**
Damaging	31	0.12	16	0.06	2.0	**0.00038**
CHD + CA only (72)						
Synonymous	4	0.06	6	0.08	0.7	0.86
Missense	19	0.26	14	0.19	1.4	0.11
D-Mis	9	0.12	2	0.03	**3.7**	**0.00089**
LoF	4	0.06	2	0.03	2.0	0.15
Damaging	13	0.18	4	0.06	**2.9**	**0.00074**
CHD + Both (138)						
Synonymous	6	0.04	12	0.09	0.5	0.98
Missense	43	0.31	27	0.19	1.6	**0.0022**
D-Mis	17	0.12	5	0.03	**3.7**	**$7.4x10^{-06}$**
LoF	23	0.17	4	0.03	**5.9**	**$4.1x10^{-11}$**
Damaging	40	0.29	8	0.06	**4.7**	**$5.6x10^{-15}$**

Homsy et al, *Science*, 2015

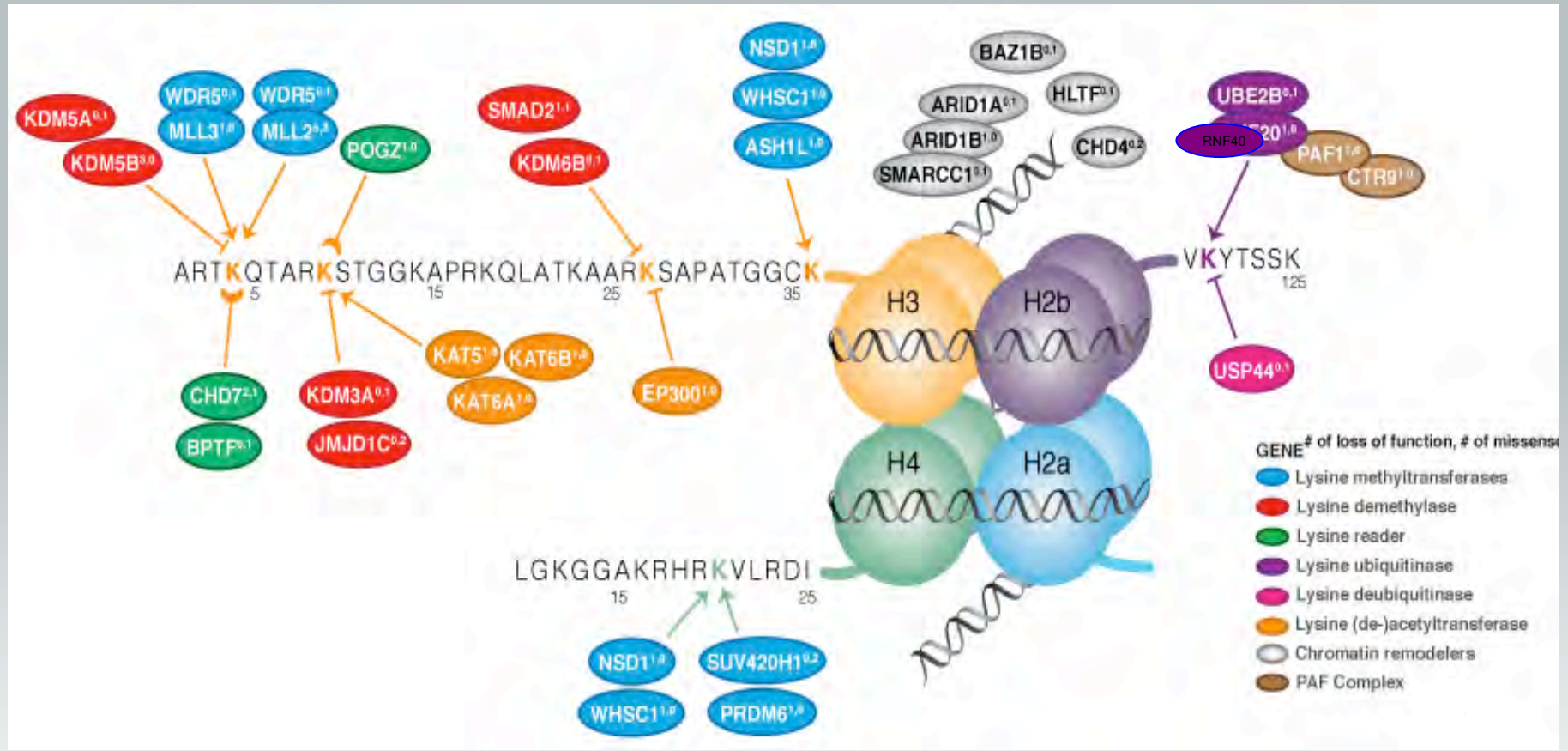
Mutations in genes that are co-expressed in the developing heart and brain are associated with neurodevelopmental abnormalities and CHD



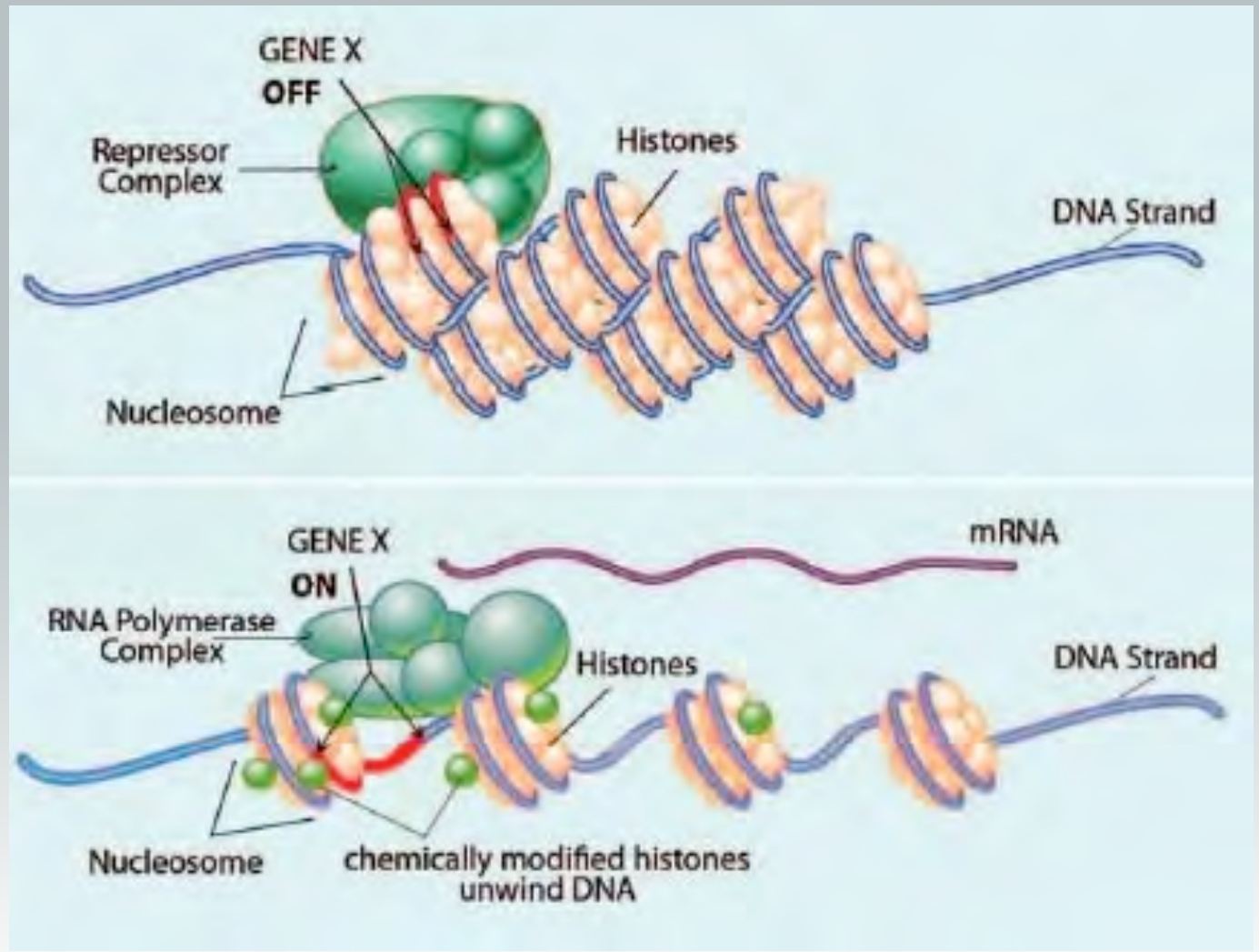


Homsy et al, *Science*, 2015

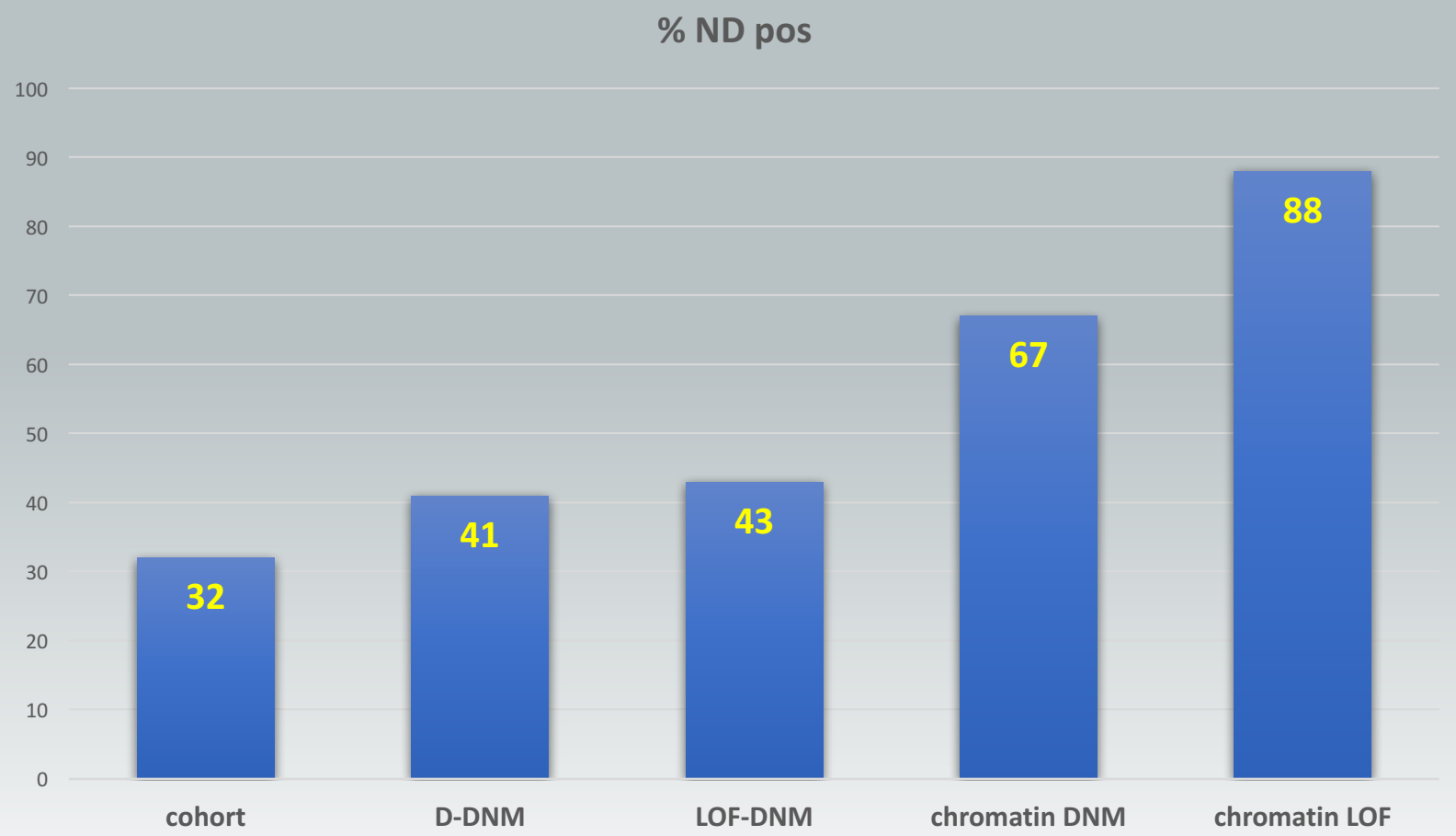
De-novo mutations affecting chromatin remodeling genes contribute to 2.3% of CHD



Chromatin remodeling globally regulates transcription



Mutations affecting chromatin remodeling predict a high risk of neurodevelopmental abnormalities



ND pos: answered “yes” to ? Developmental delay, MR, learning disability, autism

Genetic overlap between autism susceptibility and congenital heart disease genes

ARTICLE

doi:10.1038/nature13908

The contribution of *de novo* coding mutations to autism spectrum disorder

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ARTICLE

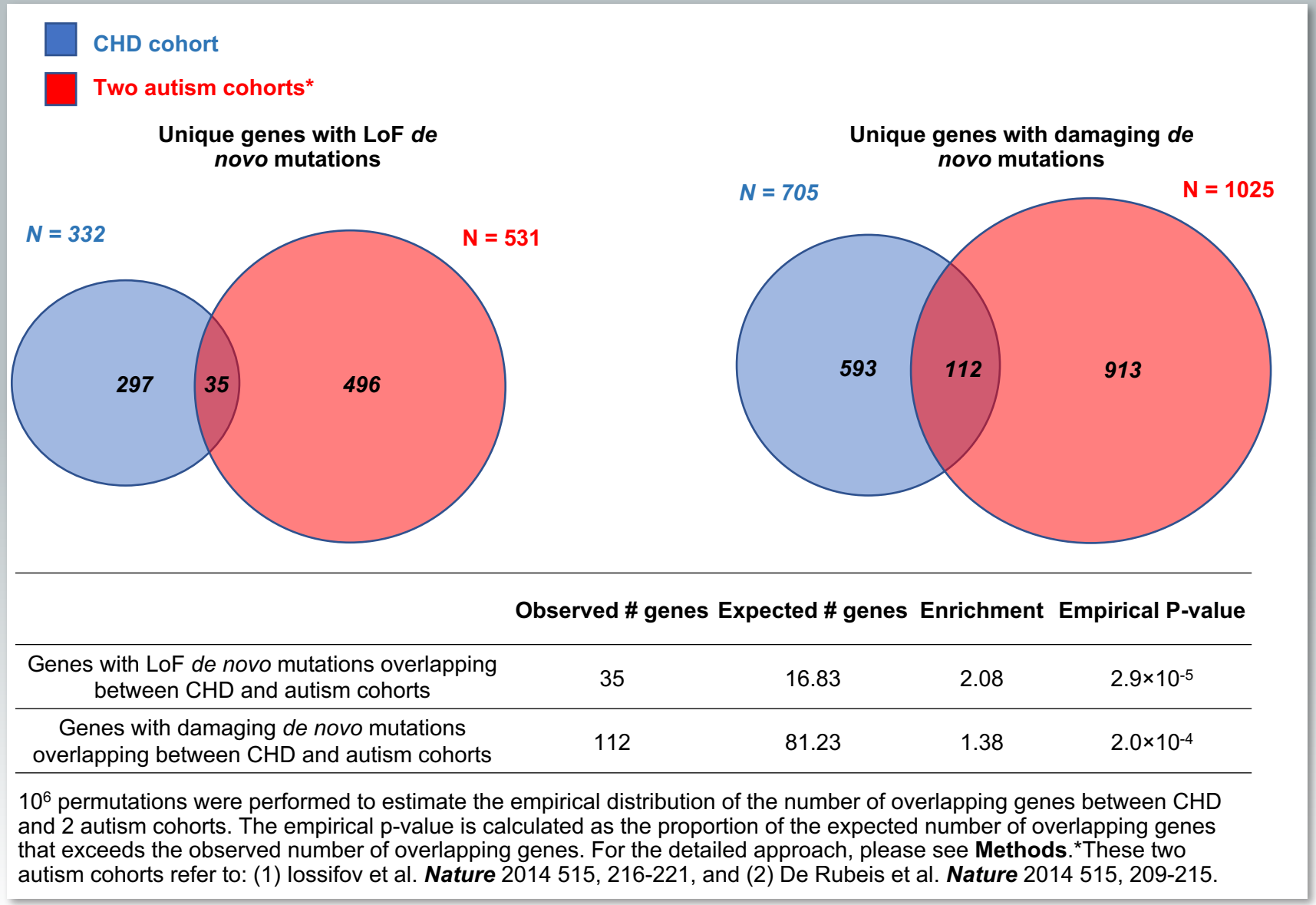
doi:10.1038/nature13772

Synaptic, transcriptional and chromatin genes disrupted in autism

A list of authors and their affiliations appears at the end of the paper

The genetic architecture of autism spectrum disorder involves the interplay of common and rare variants and their impact on hundreds of genes. Using exome sequencing, here we show that analysis of rare coding variation in 3,871 autism cases and 9,937 ancestry-matched or parental controls implicates 22 autosomal genes at a false discovery rate (FDR) < 0.05, plus a set of 107 autosomal genes strongly enriched for those likely to affect risk (FDR < 0.30). These 107 genes, which show unusual evolutionary constraint against mutations, incur *de novo* loss-of-function mutations in over 5% of autistic subjects. Many of the genes implicated encode proteins for synaptic formation, transcriptional regulation and chromatin-remodelling pathways. These include voltage-gated ion channels regulating the propagation of action potentials, pacemaking and excitability-transcription coupling, as well as histone-modifying enzymes and chromatin remodellers—most prominently those that mediate post-translational lysine methylation/demethylation modifications of histones.

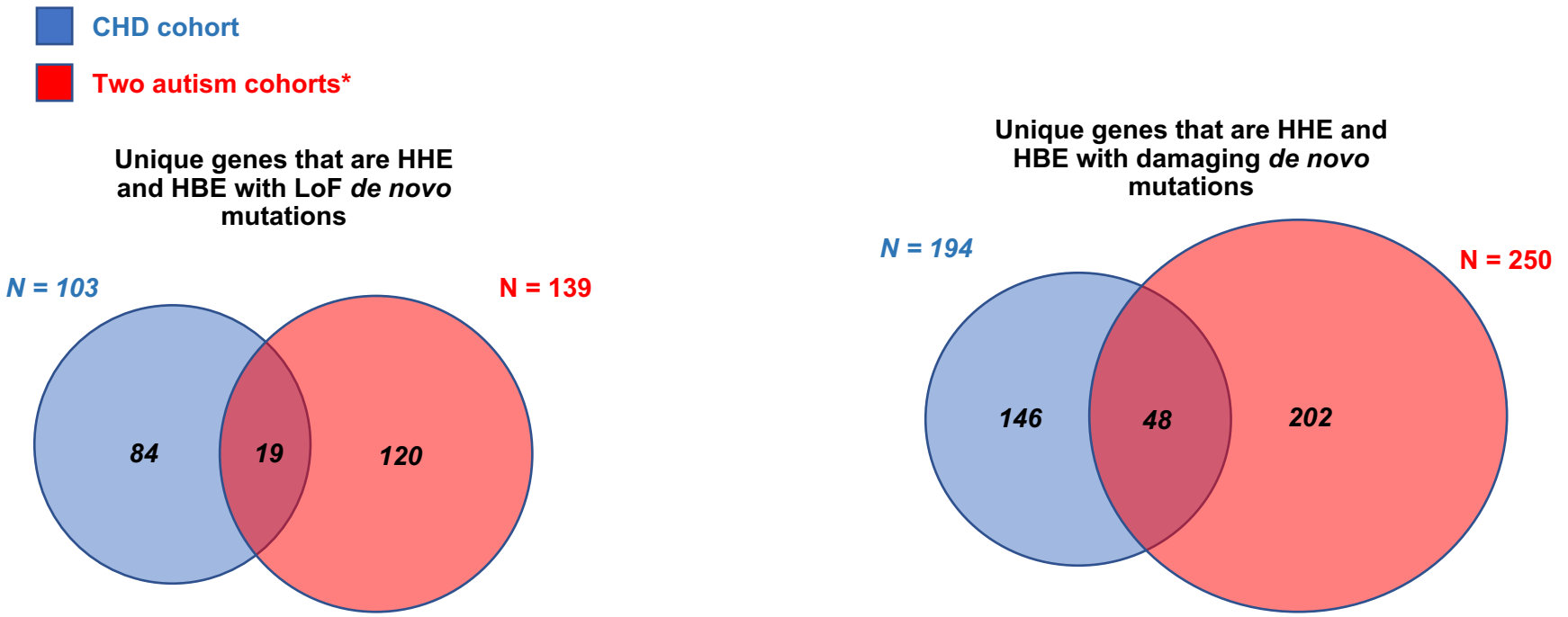
Enrichment of overlapping genes with LoF or damaging *de novo* mutations between CHD and autism cohorts



	Observed # genes	Expected # genes	Enrichment	Empirical P-value
Genes with LoF *de novo* mutations overlapping between CHD and autism cohorts	35	16.83	2.08	2.9×10^{-5}
Genes with damaging *de novo* mutations overlapping between CHD and autism cohorts	112	81.23	1.38	2.0×10^{-4}

10^6 permutations were performed to estimate the empirical distribution of the number of overlapping genes between CHD and 2 autism cohorts. The empirical p-value is calculated as the proportion of the expected number of overlapping genes that exceeds the observed number of overlapping genes. For the detailed approach, please see **Methods**.*These two autism cohorts refer to: (1) Iossifov et al. ***Nature*** 2014 515, 216-221, and (2) De Rubeis et al. ***Nature*** 2014 515, 209-215.

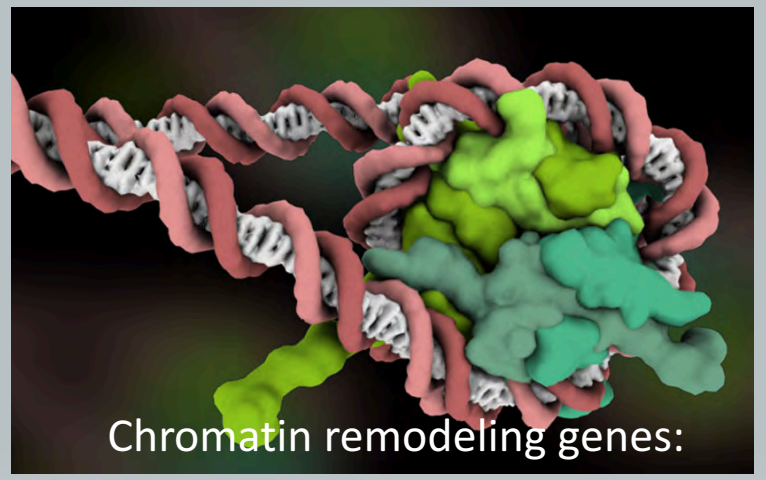
Enrichment of overlapping high heart expressed and high brain expressed genes with damaging *de novo* mutations between CHD and autism cohorts



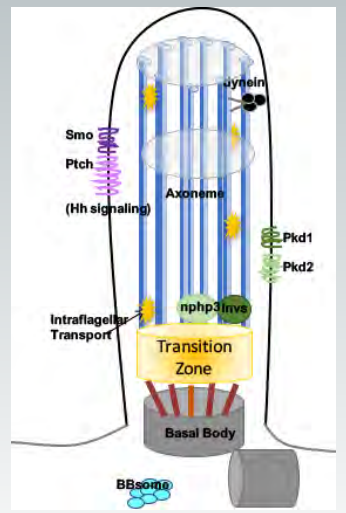
	Observed # genes	Expected # genes	Enrichment	Empirical P-value
HHE + HBE Genes with LoF *de novo* mutations overlapping between CHD and autism cohorts	19	3.68	5.16	$<10^{-6}$
HHE + HBE Genes with damaging *de novo* mutations overlapping between CHD and autism cohorts	48	17.35	2.77	$<10^{-6}$

10^6 permutations were performed to estimate the empirical distribution of the number of overlapping high heart expressed (HHE) + high brain expressed (HBE) genes between CHD and 2 autism cohorts. The empirical p-value is calculated as the proportion of the expected number of overlapping genes that exceeds the observed number of overlapping genes. For the detailed approach, please see **Methods.** *These two autism cohorts refer to: (1) Iossifov et al. ***Nature*** 2014 515, 216-221, and (2) De Rubeis et al. ***Nature*** 2014 515, 209-215.

Gene ontologies may predict clinical risks better than specific gene defects



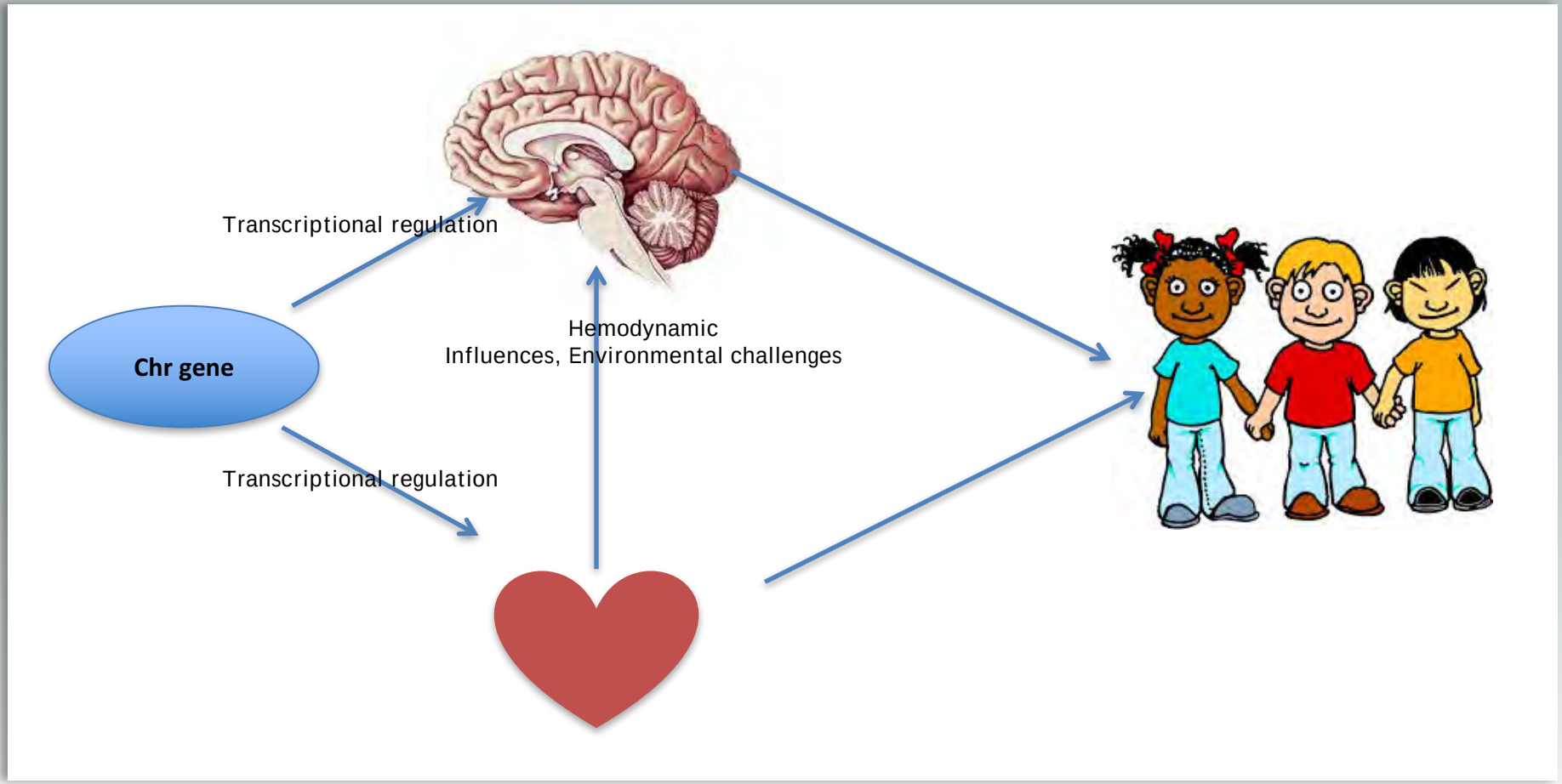
CHD, LVOT abnormalities
Neurodevelopmental abnormalities



Cilia genes

CHD, laterality defects,
respiratory complications

Genetic defects affecting heart and brain development are likely to underlie some neurodevelopmental abnormalities in CHD patients



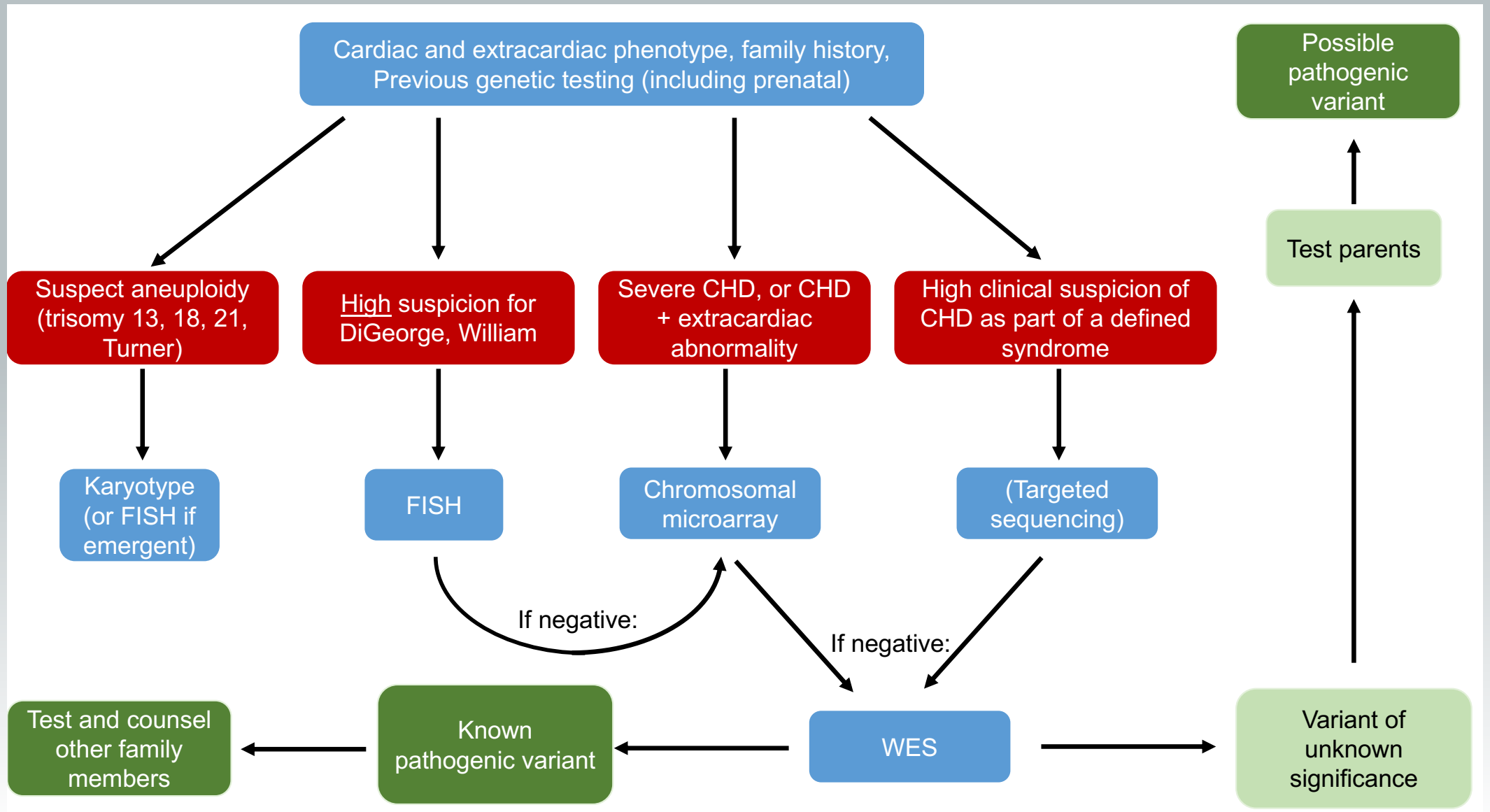
Clinical approach: clinical risk stratification

Categories of Pediatric CHD Patients at High Risk for Developmental Disorders or Disabilities

1. Neonates or infants requiring open heart surgery (cyanotic and acyanotic types), for example, HLHS, IAA, PA/IVS, TA, TAPVC, TGA, TOF, tricuspid atresia.
2. Children with other cyanotic heart lesions not requiring open heart surgery during the neonatal or infant period, for example, TOF with PA and MAPCA(s), TOF with shunt without use of CPB, Ebstein anomaly.
3. Any combination of CHD and the following comorbidities:
3.1. Prematurity (<37 wk)
3.2. Developmental delay recognized in infancy
3.3. Suspected genetic abnormality or syndrome associated with DD
3.4. History of mechanical support (ECMO or VAD use)
3.5. Heart transplantation
3.6. Cardiopulmonary resuscitation at any point
3.7. Prolonged hospitalization (postoperative LOS >2-wk in the hospital)
3.8. Perioperative seizures related to CHD surgery
3.9. Significant abnormalities on neuroimaging or microcephaly*
4. Other conditions determined at the discretion of the medical home providers

Marino et al, *Circulation*, 2012

Clinical approach: genetic risk stratification



Neurodevelopmental evaluation in CHD patients, AHA recommendations

Domains and Suggested Instruments for Developmental Evaluation of Children and Adolescents With CHD

Age	Evaluation component
Infant (0-1 year)	Developmental History
	Growth
	Feeding history
	Neuromotor evaluation
	Audiologic evaluation
Toddler (1-3.5 yr)	Standardized developmental measure
	Behavior parent report
Preschooler (3.5-5yr)	Standardized developmental measure
	Speech-language evaluation
	Behavior parent report
Child and adolescent (6-18 yr)	Intelligence
	Academic achievement
	Language
	Visual construction and perception
	Attention
	Processing speed
	Memory
	Executive function
	Fine motor skills
	Gross motor skills
	ADHD
	Behavioral functioning
	Adaptive functioning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Zhaoxia Sun
Lu Zhao
WES project:
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YCGA:
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Shrikant Mane
Patients and families
B2B
Bench to Bassinet
Funding: NHLBI, Hartwell foundation