Prevalence and correlates of attention-deficit/hyperactivity disorder among youth with 16p11.2 copy number variation

Amandeep Jutla, MD
Whitaker Scholar in Developmental Neuropsychiatry
Division of Child & Adolescent Psychiatry
Columbia University / New York State Psychiatric Institute

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Background: Constraining heterogeneity

Neurodevelopmental disorders are heterogeneous in part because of their complex genetic underpinnings[1]

A deliberate focus on specific, rare genetic variants known to be associated with neurodevelopmental disorders can constrain this heterogeneity

1: Insel TR, Cuthbert BN. Endophenotypes: bridging genomic complexity and disorder heterogeneity. *Biol Psychiatry*. 2009;66(11):988-989.

Background: 16p11.2 CNV

Simons Variation in Individuals Project (VIP): focus on 16p11.2 copy number variation (CNV)[2]

16p11.2 duplication (dup) and deletion (del) are known to be associated with[3,4] ASD, ADHD, intellectual disability and language disorders

2: Simons VIP Consortium. Simons Variation in Individuals Project (Simons VIP): a genetics-first approach to studying autism spectrum and related neurodevelopmental disorders. *Neuron*. 2012;73(6):1063-1067.
3: Hanson E, Bernier R, Porche K, et al. The cognitive and behavioral phenotype of the 16p11.2 deletion in a clinically ascertained population. *Biol Psychiatry*. 2015;77(9):785-793.
4: Snyder LG, D'Angelo D, Chen Q, et al. Autism spectrum disorder, developmental and psychiatric features in 16p11.2 duplication. *J Autism Dev Disord*. 2016;46(8):2734-2748.

Background: ADHD in 16p11.2 CNV

ADHD as it presents in the 16p11.2 CNV population has not previously been characterized.

Broad hypothesis: ADHD's predictors and correlates would differ among 16p11.2dup, 16p11.2del, and noncarriers.

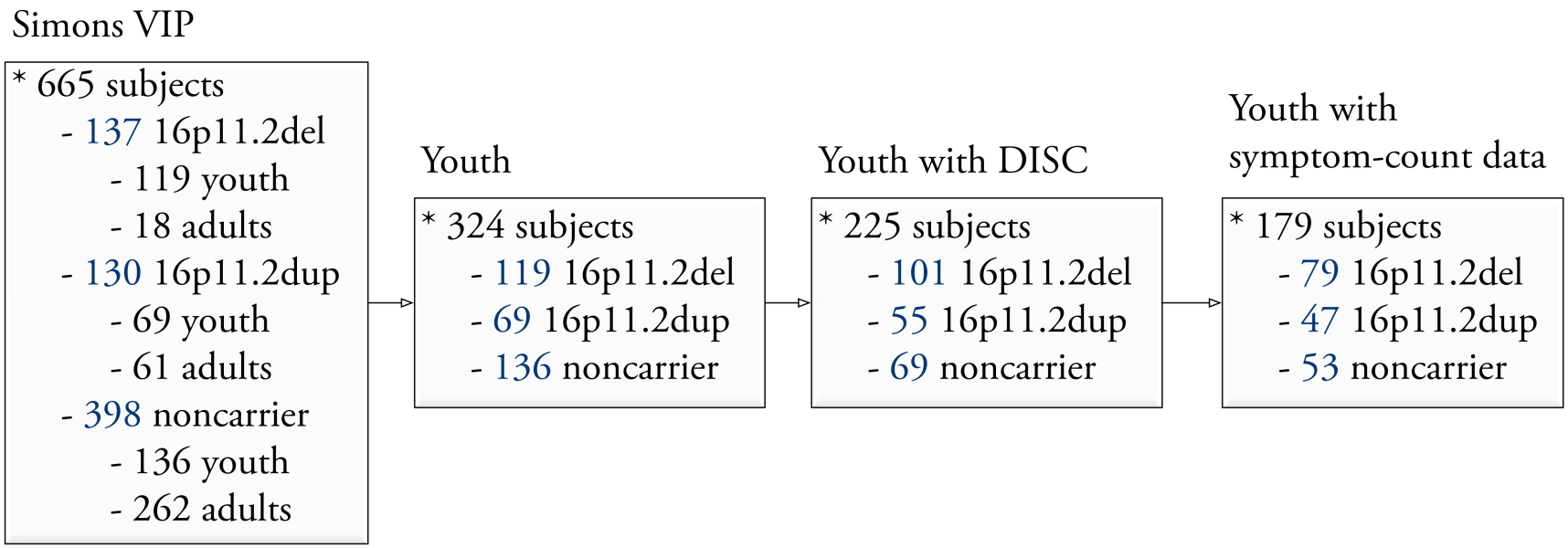
Background: Predictors and correlates

Predictors and correlates to examine were selected *a priori* based on the literature:

- Age[5],
- Gender[6],
- Intelligence[7]
- ASD diagnosis[8,9]

5: Rucklidge JJ, Tannock R. Age of onset of ADHD symptoms. *J Am Acad Child Adol Psychiatry*. 2002;41(5):496-497.
6: Bauermeister JJ, Shrout PE, Chávez L, et al. ADHD and gender: are risks and sequela of ADHD the same for boys and girls? *J Child Psychol Psychiatry*. 2007;48(8):831-839.
7: Frazier TW, Demaree HA, Youngstrom EA. Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. *Neuropsychology*. 2004;18(3):543-555.
8: LaBianca S, Pagsberg AK, Jakobsen KD, et al. Brief report: clusters and trajectories across the autism and/or ADHD spectrum. *J Autism Dev Disord*. 2018;48(10):3629-3636. doi:10.1007/s10803-018-3618-6
9: Baribeau DA, Doyle-Thomas KAR, Dupuis A, et al. Examining and comparing social perception abilities across childhood-onset neurodevelopmental disorders. *J Am Acad Child Adol Psychiatry*. 2015;54(6):479-486.

Method: Sample selection



Probands with 16p11.2dup or 16p11.2del were initially recruited; their biological relatives (primarily parents and siblings) received cascade genetic testing to identify additional carriers

Method: Statistical procedure

Group comparisons: ANOVA with post-hoc Tukey procedure or χ^2 with post-hoc Bonferroni-corrected χ^2

Primary analyses: logistic regression vs. categorical ADHD diagnosis (conducted in entire sample and in subgroups)

Exploratory analysis: linear regression vs. number of ADHD symptoms endorsed

GEEs used to control for intra-family correlation

Results: Group characteristics

Characteristic	Total (n = 179)		16p11.2dup (n = 47)		16p11.2del (n = 79)		Noncarrier (n = 53)		Main effect	Post-hoc comparisons	
	M	SD	M	SD	M	SD	M	SD	ANOVA *p*	Tukey's HSD	
										Comparison	*p*
Age	7.83	4.20	6.65	4.15	7.45	3.92	9.45	4.25	**0.002**	dup-del **dup-noncarrier** **del-noncarrier**	0.54 **0.002** **0.02**
IQ	87.87	19.98	77.87	20.47	82.33	14.99	104.98	14.95	**< 0.001**	dup-del **dup-noncarrier** **del-noncarrier**	0.31 **< 0.001** **< 0.001**
ADHD Sx	6.78	6.26	8.79	6.62	7.48	5.85	3.94	5.59	**< 0.001**	dup-del **dup-noncarrier** **del-noncarrier**	0.46 **< 0.001** **0.003**
	#	%	#	%	#	%	#	%	χ^2 *p*	Pairwise χ^2	
										Comparison	*p* (corrected)
Female gender	80	45	25	53	36	46	19	36	0.22	dup-del dup-noncarrier del-noncarrier	1.00 0.37 1,00
ASD Dx	25	14	9	19	14	18	2	4	**0.04**	dup-del dup-noncarrier del-noncarrier	1.00 0.10 0.10
ADHD Dx	78	44	24	52	42	53	12	23	**0.001**	dup-del **dup-noncarrier** **del-noncarrier**	1.00 **0.003** **0.02**

Results: Predictors of categorical ADHD diagnosis in entire sample

Predictor	β	SE	OR (95% CI)	p
16p11.2del	0.910	0.482	2.49 (0.966 – 6.390)	0.059
16p11.2dup	0.727	0.532	2.07 (0.729 – 5.874)	0.172
Age	0.006	0.003	1.01 (0.999 – 1.012)	0.099
IQ	**-0.025**	**0.010**	**0.97 (0.956 – 0.995)**	**0.016**
Female gender	0.517	0.324	1.68 (0.888 – 3.166)	0.111
ASD diagnosis	0.300	0.509	1.35 (0.498 – 3.662)	0.555

Results: Predictors of categorical ADHD diagnosis among 16p11.2dup carriers only

Predictor	β	SE	OR (95% CI)	p
Age	0.014	0.008	1.01 (0.997 – 1.030)	0.098
IQ	-0.018	0.015	0.98 (0.952 – 1.010)	0.231
Female gender	0.634	0.697	1.89 (0.481 – 7.390)	0.363
ASD diagnosis	-0.371	0.898	0.69 (0.119 – 4.010)	0.680

Results: Predictors of categorical ADHD diagnosis among 16p11.2del carriers only

Predictor	β	SE	OR (95% CI)	p
Age	0.007	0.005	1.00 (0.997 – 1.020)	0.150
IQ	-0.022	0.017	0.98 (0.946 – 1.010)	0.190
Female gender	0.369	0.473	1.50 (0.673 – 3.650)	0.430
ASD diagnosis	0.574	0.601	1.80 (0.547 5.760)	0.340

Results: Predictors of categorical ADHD diagnosis among noncarriers only

Predictor	β	SE	OR (95% CI)	p
Age	-0.013	0.007	0.99 (0.973 – 1.000)	0.073
IQ	**-0.110**	**0.040**	**0.90 (0.829 – 0.968)**	**0.006**
Female gender	0.976	0.860	2.65 (0.492 – 14.300)	0.256
ASD diagnosis	-0.712	1.088	0.49 (0.058 – 4.110)	0.508

Results: Predictors of ADHD symptoms among entire sample

Predictor	B	**SE**	**β (95% CI)**	***p***
16p11.2del	2.148	1.335	0.11 (-0.057 – 0.272)	0.201
16p11.2dup	11.057	2.608	0.15 (-0.033 – 0.336)	0.108
Age	-0.004	0.007	-0.04 (-0.153 – 0.081)	0.545
IQ	**-0.069**	**0.0229**	**-0.22 (-0.365 – -0.078)**	**0.003**
Female gender	1.606	0.915	0.13 (-0.015 – 0.271)	0.079
ASD diagnosis	**2.523**	**1.178**	**0.14 (0.012 – 0.269)**	**0.032**

Conclusions: ADHD, IQ, and 16p11.2 CNV

ADHD is more prevalent, and IQ is on average lower, in 16p11.2dup or 16p11.2del carriers, but low IQ does not predict ADHD among either group

Lower IQ may be a better predictor of ADHD among neurotypical youth than among youth who may already have some level of cognitive compromise – this may generalize beyond the 16p11.2 CNV

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