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

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Introduction

- Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental syndrome affecting about 5% of children worldwide[1]. Like many behavioral disorders, ADHD is a phenotypically heterogeneous construct. The type and severity of symptoms present[2, 3] can vary across cases, as can age of onset[4]. Gender[5], intelligence[6], and co-occurring autism spectrum disorder (ASD)[7] may also influence the disorder's presentation. These factors all tend to complicate diagnosis and treatment.
- One way to constrain heterogeneity is by focusing on subgroups of individuals with ADHD associated with specific genetic risk factors. 16p11.2 copy number variation (CNV) is one such factor. 16p11.2 deletion (16p11.2del) and 16p11.2 duplication (16p11.2dup) are each associated with a neurodevelopmental syndrome that includes ADHD[8].
- The present study analyzed data from the Simons Variations in Individuals Project (VIP) cohort to compare the prevalence and correlates of ADHD among youth carrying 16p11.2del or 16p11.2dup and their noncarrier biological siblings.with 16p11.2 duplications (16p11.2dup), youth with 16p11.2 deletions (16p11.2del), and their noncarrier biological siblings.

Methods

- As shown in Figure 1, the Simons VIP cohort was progressively narrowed down to youth only; to youth who underwent structured assessment for ADHD using the NIMH Diagnostic Interview Schedule for Children (DISC-Youth) or Diagnostic Interview Schedule for Young Children (DISC-YC); and finally to youth with symptom-count-level data available from those measures.
- For each member of the sample, DISC data were used to calculate variables representing presence of ADHD diagnosis and number of ADHD symptoms endorsed in the past year.
- 16p11.2dup carriers, 16p11.2del carriers, and noncarriers were compared in terms of age, IQ, number of ADHD symptoms, ADHD diagnosis, female gender, and ASD diagnosis. Pairwise post-hoc comparisons were carried out using Tukey's procedure (for continuous variables) or Bonferroni-corrected chi-square (for categorical variables).
- For the primary analysis, ADHD diagnosis was used as the outcome variable in a logistic regression model that included 16p11.2del carrier status, 16p11.2dup carrier status, age, full-scale IQ, gender, and co-occurring ASD diagnosis as predictors.
- Subsequent regressions were conducted among 16p11.2del carrier, 16p11.2dup carrier, and noncarrier family member subgroups.
- An exploratory linear regression analysis was also conducted using number of ADHD symptoms (rather than categorical diagnosis) as the outcome. Generalized estimating equations (GEEs) were used to estimate parameters in all regressions to control for correlations between family members.

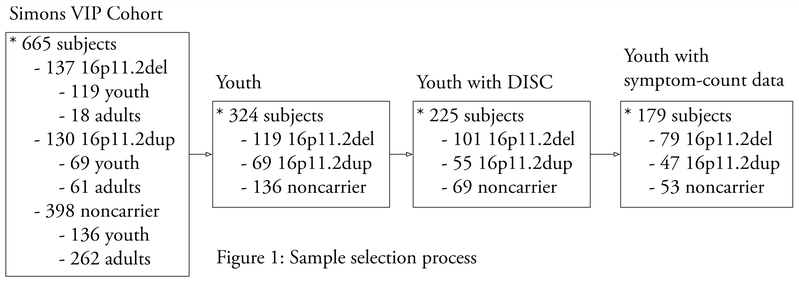

Figure 1: Sample selection process

Table 1: Characteristics of 16p11.2 CNV carriers and their non-carrier siblings.

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**

Table 2: Predictors of ADHD diagnosis among 16p11.2 CNV carriers and their non-carrier siblings.

Predictor	β	SE	OR (95% CI)	p
16p11.2del carrier	0.910	0.482	2.49 (0.966 — 6.390)	0.059
16p11.2dup carrier	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 Dx	0.300	0.509	1,35 (0.498 — 3.662)	0.555

Table 3: Predictors of ADHD diagnosis among duplication 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 Dx	-0.371	0.898	0.69 (0.119 — 4.010)	0.680

Table 4: Predictors of ADHD diagnosis among deletion carriers only.

Predictor	β	SE	OR (95% CI)	p
Age	0.007	0.005	1.0 (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	1.5 (0.673 — 3.650)	0.430
ASD Dx	0.574	0.601	1.8 (0.547 — 5.760)	0.340

Table 5: Predictors of ADHD diagnosis among non-carrier siblings only.

Predictor	β	SE	OR (95% CI)	p
Age	-0.013	0.007	0.99 (0.973 — 1.00)	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 Dx	-0.712	1.088	0.49 (0.058 — 4.110)	0.508

Table 6: Predictors of ADHD symptoms among 16p11.2 CNV carriers and their non-carrier siblings.

Predictor	B	SE	β (95% CI)	p
16p11.2dup carrier	11.057	2.608	0.15 (-0.033 — 0.336)	0.108
16p11.2del carrier	2.148	1.335	0.11 (-0.057 — 0.272)	0.201
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 Dx	**2.523**	**1.178**	**0.14 (0.012 — 0.269)**	**0.032**

Results

- Relative to noncarriers, 16p11.2dup and 16p11.2del carriers were younger, had lower IQs, and had more ADHD symptoms. They were also more likely to have a diagnosis of ADHD or ASD (Table 1). Among the entire sample, ADHD diagnosis was weakly negatively predicted by IQ (OR 0.97 for every point decrease, 95% CI 0.956 - 0.995, p = 0.016) (Table 2). This relationship was not identified in regressions conducted among duplication carriers only (Table 3) or deletion carriers only (Table 4), but remained in a regression carried out among noncarriers only (OR 0.90 for every point decrease, 95% CI 0.829 - 0.968, p = 0.006) (Table 5).
- In the exploratory regression against number of ADHD symptoms endorsed in the past year, IQ negatively predicted ADHD symptoms, with 0.07 fewer symptoms for every point decrease (standardized effect -0.22, 95% CI -0.365 - -0.078, p - 0.003). ASD was a positive predictor: subjects with ASD had 2.5 more ADHD symptoms than those without (standardized effect 0.14, 95% CI 0.012 - 0.269, p = 0.032).

Conclusions

- The finding that IQ negatively predicts ADHD diagnosis in our entire analysis sample and among noncarriers is consistent with evidence that children with ADHD tend to have lower IQ than their unaffected peers[9]. The lack of an association between IQ and ADHD within 16p11.2dup or 16p11.2del carriers is interesting given that ADHD is more prevalent, and IQ is on average lower, in those groups. It may be that IQ differences are a better predictor of ADHD among neurotypical youth than those who may already have some level of cognitive compromise. The finding that ASD diagnosis predicts number of ADHD symptoms but not ADHD diagnosis per se is consistent with emerging evidence that phenotypic traits of ASD and ADHD can tend to overlap[10], which may be particularly true in those affected by the 16p11.2 CNV. In the future, with the recruitment of more 16p11.2 CNV carriers, it may be possible to characterize their overlapping symptoms in more detail.

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