ADDENDUM

Population Analysis of Large Copy Number Variants and Hotspots of Human Genetic Disease

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Because data from one large study of autism[1] provided genomic coordinates for an exceptionally small fraction of CNVs (31 CNVs in 1562 samples) found in affected individuals, we have repeated the analysis summarized in Table 2 from our recent paper excluding data from that particular study. The new analysis includes CNVs from a total of 10,972 individuals: 5,674 controls as before, but only 5,298 affected individuals as compared to 6,860 in our previous analysis. The ranking among the top-scoring loci has changed slightly (see Alternate Table 2 below), and p values have uniformly decreased (suggesting stronger associations) with two exceptions: duplications at the VCFS locus went from $p = 0.330$ to 0.454 and duplications overlapping the Terminal 22 del syndrome region went from $p = 0.160$ to 0.167. The qualitative conclusions we made on the basis of the previous analysis and other evidence (that 3q29, 16p12, and 15q25 merit further investigation) have not changed. We believe the new analysis more accurately reflects CNV frequencies in individuals with neurologic disease.

Alternate Table 2. Loci Enriched for CNVs in Autism, Mental Retardation, and Schizophrenia Identified by Disease Meta-analysis

Chr	Start	Stop	Length	Note	NAHR[a]	Total CNVs	Type	Disease CNVs	Control CNVs	Diseases[d]	Studies	CNV p Value	Locus p Value
chr15	27,015,263	30,650,000	3,634,737	Prader-Willi/ 15q13	yes	19	loss	19	0	S	affected individuals[2]	9.67E-07	
chr15	18,376,200	30,756,771	12,380,571			55	gain	42	13	A, MR, S, C	controls and affected individuals[2,3,4,5,6,7,c]	1.90E-05	1.13E-09
chr22	17,014,900	19,993,127	2,978,227	VCFS	yes	30	loss	30	0	A, MR, S	affected individuals[2,3,6,7,8]	3.14E-10	
chr22	17,200,000	21,546,762	4,346,762			11	gain	6	5	A, S, C	controls and affected individuals[2,3,5,6,c]	0.454	1.25E-07
chr1	142,540,000	146,059,433	3,519,433	1q21	yes	26	loss	23	3	S, C	controls and affected individuals[2]	2.12E-05	
chr1	142,800,580	146,009,436	3,208,856			13	gain	10	3	A, MR, S, C	controls and affected individuals[2,3,7]	0.035	2.64E-06
chr22	45,144,027	49,509,153	4,365,126	Terminal 22	no	4	loss	4	0	A	[3,4,6]	0.054	
chr22	47,572,875	48,323,417	750,542	del syndrome		5	gain	4	1	A, S, C	controls and affected individuals[2,5,6]	0.167	0.015
chr17	14,000,000	15,421,835	1,421,835	CMT1A/HNPP	yes	6	loss	5	1	A, S, C	controls and affected individuals[2,5]	0.094	
chr17	12,650,000	15,540,000	2,890,000			5	gain	4	1	A, MR, S, C	controls and affected individuals[2,3,7]	0.167	0.025
chr16	60,141,700	61,581,600	1,439,900	16q21, *CDH8*	no	4	loss	4	0	A	[3]	0.054	
chr16	60,552,237	61,294,685	742,448			1	gain	1	0	S	affected individuals[2]	0.483	0.026
chr16	29,470,951	30,252,473	781,522	16p11.2	yes	10	loss	7	3	A,C	controls[2,4–6]	0.145	
chr16	29,474,810	30,235,818	761,008			6	gain	5	1	A, S, C	affected individuals[2,6,9,c]	0.094	0.028
chr11	78,120,000	85,610,000	7,490,000	11q14.1	no	3	loss	3	0	MR, S	affected individuals[2,7]	0.113	
chr11	84,304,683	85,042,205	737,522			1	gain	1	0	S	affected individuals[2]	0.483	0.054

Alternate Table 2. ***Continued***

Chr	Start	Stop	Length	Note	NAHR[a]	Total CNVs	Type	Disease CNVs	Control CNVs	Diseases[d]	Studies	CNV p Value	Locus p Value
chr2	185,118,087	185,909,729	791,642	2q32.1	no	1	loss	1	0	S	affected individuals[2]	0.483	
chr2	184,270,000	186,892,000	2,622,000			3	gain	3	0	A	[3]	0.113	0.054
chr15	82,573,421	83,631,697	1,058,276	15q25	yes	4	loss	4	0	A, S	affected individuals[2,5,6]	0.054	
chr15	na	na	na			0	gain	0	0	none	none	1	0.054
chr9	140575	1175526	1,034,951	9p24	no	1	loss	1	0	S	affected individuals[2]	0.483	
chr9	206456	1599250	1,392,794			3	gain	3	0	A, S	affected individuals[2,3]	0.113	0.054
chr16	21,693,739	22,611,363	917,624	16p12	yes	5[b]	loss	5[b]	0	A, S	affected individuals[2,6]	0.026	
chr16	21,441,805	22,688,093	1,246,288			5	gain	2	3	A, S, C	controls and affected individuals[2,6]	1	0.145
chr3	197,179,156	198,842,299	1,663,143	3q29	yes	3	loss	3	0	S	affected individuals[2,9]	0.113	
chr3	198,325,925	199,384,429	1,058,504			2	gain	1	1	S, C	controls and affected individuals[2]	1	0.167
chr16	80,722,684	82,227,917	1,505,233	16q23.3,	no	2	loss	0	2	C	controls[2,c]	1	
chr16	80,737,839	82,208,451	1,470,612	*CDH13*		4	gain	4	0	A, S	affected individuals[2,5,9]	0.054	0.312

[a] Indicates whether there are large segmental duplications near breakpoints in hg17.
[b] A deletion of ~480 kb in size in a schizophrenic sample is included in this count.
[c] Controls from this study
[d] A, autism; MR, mental retardation; S, schizophrenia; C, controls.

References

1. Weiss, L.A., Shen, Y., Korn, J.M., Arking, D.E., Miller, D.T., Fossdal, R., Saemundsen, E., Stefansson, H., Ferreira, M.A., Green, T., et al. (2008). Association between microdeletion and microduplication at 16p11.2 and autism. N. Engl. J. Med. *358*, 667–675.
2. International Schizophrenia Consortium. (2008). Rare chromosomal deletions and duplications increase risk of schizophrenia. Nature *455*, 237–241.
3. Autism Genome Project Consortium, Szatmari, P., Paterson, A.D., Zwaigenbaum, L., Roberts, W., Brian, J., Liu, X.Q., Vincent, J.B., Skaug, J.L., Thompson, A.P., Senman, L. et al. (2007). Mapping autism risk loci using genetic linkage and chromosomal rearrangements. Nat. Genet. *39*, 319–328.
4. Sebat, J., Lakshmi, B., Malhotra, D., Troge, J., Lese-Martin, C., Walsh, T., Yamrom, B., Yoon, S., Krasnitz, A., Kendall, J., et al. (2007). Strong association of de novo copy number mutations with autism. Science *316*, 445–449.
5. Christian, S.L., Brune, C.W., Sudi, J., Kumar, R.A., Liu, S., Karamohamed, S., Badner, J.A., Matsui, S., Conroy, J., McQuaid, D., et al. (2008). Novel submicroscopic chromosomal abnormalities detected in autism spectrum disorder. Biol. Psychiatry *63*, 1111–1117.
6. Marshall, C.R., Noor, A., Vincent, J.B., Lionel, A.C., Feuk, L., Skaug, J., Shago, M., Moessner, R., Pinto, D., Ren, Y., et al. (2008). Structural variation of chromosomes in autism spectrum disorder. Am. J. Hum. Genet. *82*, 477–488.
7. de Vries, B.B., Pfundt, R., Leisink, M., Koolen, D.A., Vissers, L.E., Janssen, I.M., Reijmersdal, S., Nillesen, W.M., Huys, E.H., Leeuw, N., et al. (2005). Diagnostic genome profiling in mental retardation. Am. J. Hum. Genet. *77*, 606–616.
8. Xu, B., Roos, J.L., Levy, S., van Rensburg, E.J., Gogos, J.A., and Karayiorgou, M. (2008). Strong association of de novo copy number mutations with sporadic schizophrenia. Nat. Genet. *40*, 880–885.
9. Walsh, T., McClellan, J.M., McCarthy, S.E., Addington, A.M., Pierce, S.B., Cooper, G.M., Nord, A.S., Kusenda, M., Malhotra, D., Bhandari, A., et al. (2008). Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science *320*, 539–543.

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