# Individual common variants exert weak effects on risk for Autism Spectrum Disorders

Richard Anney<sup>1†</sup>, Lambertus Klei<sup>2</sup>, Dalila Pinto<sup>3,71†</sup>, Joana Almeida<sup>4</sup>, Elena Bacchelli<sup>5</sup>, Gillian Baird<sup>6</sup>, Nadia Bolshakova<sup>1</sup>, Sven Bölte<sup>7</sup>, Patrick F. Bolton<sup>8</sup>, Thomas Bourgeron<sup>9</sup>, Sean Brennan<sup>1</sup>, Jessica Brian<sup>10</sup>, Jillian Casey<sup>11</sup>, Judith Conroy<sup>11</sup>, Catarina Correia<sup>12,13</sup>, Christina Corsello<sup>14</sup>, Emily L. Crawford<sup>15</sup>, Maretha de Jonge<sup>16</sup>, Richard Delorme<sup>17</sup>, Eftichia Duketis<sup>7</sup>, Frederico Duque<sup>4</sup>, Annette Estes<sup>18</sup>, Penny Farrar<sup>19</sup>, Bridget A. Fernandez<sup>20</sup>, Susan E. Folstein<sup>21</sup>, Eric Fombonne<sup>22</sup>, John Gilbert<sup>23</sup>, Christopher Gillberg<sup>24</sup>, Joseph T. Glessner<sup>25</sup>, Andrew Green<sup>11</sup>, Jonathan Green<sup>26</sup>, Stephen J. Guter<sup>27</sup>, Elizabeth A. Heron<sup>1</sup>, Richard Holt<sup>19</sup>, Jennifer L. Howe<sup>3</sup>, Gillian Hughes<sup>1</sup>, Vanessa Hus<sup>14</sup>, Roberta Igliozzi<sup>13</sup>, Suma Jacob<sup>27</sup>, Graham P Kenny<sup>1</sup>, Cecilia Kim<sup>25</sup>, Alexander Kolevzon<sup>28</sup>, Vlad Kustanovich<sup>29</sup>, Clara M. Lajonchere<sup>29</sup>, Janine A. Lamb<sup>30</sup>, Miriam Law-Smith<sup>1</sup>, Marion Leboyer<sup>31</sup>, Ann Le Couteur<sup>32</sup>, Bennett L. Leventhal<sup>33,34</sup>, Xiao-Qing Liu<sup>35</sup>, Frances Lombard<sup>1</sup>, Catherine Lord<sup>36</sup>, Linda Lotspeich<sup>37</sup>, Sabata C. Lund<sup>15</sup>, Tiago R. Magalhaes<sup>12,13</sup>, Carine Mantoulan<sup>38</sup>, Christopher J. McDougle<sup>39</sup>, Nadine M. Melhem<sup>2</sup>, Alison Merikangas<sup>1</sup>, Nancy J. Minshew<sup>2,40</sup>, Ghazala K. Mirza<sup>19</sup>, Jeff Munson<sup>41</sup>, Carolyn Noakes<sup>10</sup>, Katerina Papanikolaou<sup>42</sup>, Alistair T. Pagnamenta<sup>19</sup>, Barbara Parrini<sup>43</sup>, Tara Paton<sup>3</sup>, Andrew Pickles<sup>8,44</sup>, David J Posey<sup>39</sup>, Fritz Poustka<sup>7</sup>, Jiannis Ragoussis<sup>19</sup>, Regina Regan<sup>11</sup>, Katy Renshaw<sup>33</sup>, Wendy Roberts<sup>10</sup>, Kathryn Roeder<sup>45</sup>, Bernadette Roge<sup>38</sup>, Michael L. Rutter<sup>46</sup>, Sabine Schlitt<sup>7</sup>, Naisha Shah<sup>11</sup>, Val C. Sheffield<sup>47</sup>, Latha Soorya<sup>28</sup>, Inês Sousa<sup>19</sup>, Vera Stoppioni<sup>48</sup>, Nuala Sykes<sup>19</sup>, Raffaella Tancredi<sup>43</sup>, Ann P. Thompson<sup>49</sup>, Susanne Thomson<sup>15</sup>, Ana Tryfon<sup>28</sup>, John Tsiantis<sup>44</sup>, Herman Van Engeland<sup>16</sup>, John B. Vincent<sup>50</sup>, Fred Volkmar<sup>51</sup>, JAS Vorstman<sup>52</sup>, Simon Wallace<sup>33</sup>, Kirsty Wing<sup>19</sup>, Kerstin Wittemeyer<sup>46</sup>, Shawn Wood<sup>2</sup>, Danielle Zurawiecki<sup>28</sup>, Lonnie Zwaigenbaum<sup>53</sup>, Anthony J. Bailey<sup>54§</sup>, Agatino Battaglia<sup>43§</sup>, Rita M. Cantor<sup>55§</sup>, Hilary Coon<sup>56§</sup>, Michael L. Cuccaro<sup>23</sup>, Geraldine Dawson<sup>57,58§</sup>, Sean Ennis<sup>11§</sup>, Christine M. Freitag<sup>7§</sup>, Daniel H. Geschwind<sup>59§</sup>, Jonathan L. Haines<sup>60§</sup>, Sabine M. Klauck<sup>61§</sup>, William M. McMahon<sup>56§</sup>, Elena Maestrini<sup>5§</sup>, Judith Miller<sup>56</sup>, Anthony P. Monaco<sup>19,62§</sup>, Stanley F. Nelson<sup>55§</sup>, John I. Nurnberger Jr.<sup>39§</sup>, Guiomar Oliveira<sup>4§</sup>, Jeremy R. Parr<sup>63§</sup>, Margaret A. Pericak-Vance<sup>23§</sup>, Joseph Piven<sup>64§</sup>, Gerard D. Schellenberg<sup>65§</sup>, Stephen W. Scherer<sup>3§</sup>, Astrid M. Vicente<sup>12,13§</sup>, Thomas H. Wassink<sup>66§</sup>, Ellen M. Wijsman<sup>67§</sup>, Catalina Betancur<sup>68§†</sup>, Joseph D. Buxbaum<sup>28§†</sup>, Edwin H. Cook<sup>27§†</sup>, Louise Gallagher<sup>1§†</sup>, Michael Gill<sup>1§†</sup>, Joachim Hallmayer<sup>37§†</sup>, Andrew D. Paterson<sup>3§†</sup>, James S. Sutcliffe<sup>15§†</sup>, Peter Szatmari<sup>49§†</sup>, Veronica J. Vieland<sup>69§†</sup>, Hakon Hakonarson<sup>25,70§‡</sup>, Bernie Devlin<sup>2§†\*</sup>

<sup>1</sup>Autism Genetics Group, Department of Psychiatry, School of Medicine, Trinity College Dublin 8, Ireland. <sup>2</sup>Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, 15232, USA.<sup>3</sup>The Centre for Applied Genomics and Program in Genetics and Genomic Biology, The Hospital for Sick Children and Department of Molecular Genetics, University of Toronto, Ontario, M5G 1L7, Canada.<sup>4</sup>Hospital Pediátrico de Coimbra, 3000 – 076 Coimbra, Portugal.<sup>5</sup>Department of Biology, University of Bologna, 40126 Bologna, Italy.<sup>6</sup>Newcomen Centre, Guy's Hospital, London, SE1 9RT, UK.<sup>7</sup>Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, J.W. Goethe University Frankfurt, 60528 Frankfurt, Germany.<sup>8</sup>Department of Child and Adolescent Psychiatry, Institute of Psychiatry, London, SE5 8AF, UK.<sup>9</sup>Human Genetics and Cognitive Functions, Institut Pasteur; University Paris Diderot-Paris 7, CNRS URA 2182, Fondation FondaMental, 75015 Paris, France.<sup>10</sup>Autism Research Unit, The Hospital for Sick Children and Bloorview Kids Rehabilitation, University of Toronto, Toronto, Ontario, M5G 1Z8, Canada.<sup>11</sup>School of Medicine and Medical Science University College, Dublin 4, Ireland.<sup>12</sup>Instituto Nacional de Saude Dr Ricardo Jorge and Instituto Gulbenkian de Cîencia, 1649-016 Lisbon, Portugal. <sup>13</sup>BioFIG - Center for Biodiversity, Functional & Integrative Genomics, Campus da FCUL, C2.2.12, Campo Grande, 1749-016 Lisboa, Portugal.<sup>14</sup>Autism and Communicative Disorders Centre, University of Michigan, Ann Arbor, Michigan, 48109, USA.<sup>15</sup>Department of Molecular Physiology and Biophysics, Vanderbilt Kennedy Center, and Centers for Human Genetics Research and Molecular Neuroscience, Vanderbilt University, Nashville, Tennessee 37232, USA.<sup>16</sup>Department of Child Psychiatry, University Medical Center, Utrecht, 3508 GA, The Netherlands.<sup>17</sup>APHP, Hôpital Robert Debré, Child and Adolescent Psychiatry, 75019 Paris, France.<sup>18</sup>Department of Speech and Hearing Sciences, University of Washington, Seattle, Washington 98195, USA.<sup>19</sup>Wellcome Trust Centre for Human Genetics, University of Oxford, OX3 7BN, UK.<sup>20</sup>Disciplines of Genetics and Medicine, Memorial University of Newfoundland, St. John's Newfoundland, A1B 3V6, Canada.<sup>21</sup>Department of Psychiatry, University of Miami School of Medicine, Miami, FL 33136, USA. <sup>22</sup>Division of Psychiatry, McGill University, Montreal, Quebec, H3A 1A1, Canada. <sup>23</sup>The John P. Hussman Institute for Human Genomics, University of Miami, Miami, Florida 33101, USA.<sup>24</sup>Gillberg Neuropsychiatry Centre, Sahlgrenska Academy, University of Gothenburg, Sweden.<sup>25</sup>The Center for Applied Genomics, Division of Human Genetics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania 19104, USA. <sup>26</sup>Academic Department of Child Psychiatry, Booth Hall of Children's Hospital, Blackley, Manchester, M9 7AA, UK.<sup>27</sup>Institute for Juvenile Research, Department of Psychiatry, University of Illinois at Chicago, Chicago, Illinois, 60608, USA.<sup>28</sup>The Seaver Autism Center for Research and Treatment, Department of Psychiatryand The Friedman Brain Institute, Mount Sinai School of Medicine, New York 10029, USA.<sup>29</sup>Autism Genetic Resource Exchange, Autism Speaks, Los Angeles, California90036-4234, USA.<sup>30</sup>Centre for Integrated Genomic Medical Research, University of Manchester, Manchester, M13 9PT, UK. <sup>31</sup>INSERM U995, Department of Psychiatry, Groupe hospitalier Henri Mondor-Albert Chenevier, AP-HP; University Paris 12, Fondation FondaMental, Créteil, 94000, France. <sup>32</sup>Child and Adolescent Mental Health, University of Newcastle, Sir James Spence Institute, Newcastle upon Tyne, NE1 4LP, UK. <sup>33</sup>Nathan Kline Institute for Psychiatric Research (NKI), 140 Old Orangeburg Road, Orangeburg, New York, New York 10962, USA. <sup>34</sup>Department of Child and Adolescent Psychiatry, New York University and NYU Child Study Center, New York, New York 10016, USA.<sup>35</sup>Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Manitoba, Winnipeg, Manitoba, Canada.<sup>36</sup>Institute for Brain Development, Weill Cornell Medical College, White Plains, New York. <sup>37</sup>Department of Psychiatry, Division of Child and Adolescent Psychiatry and Child Development, Stanford University School of Medicine, Stanford,

California 94304, USA. <sup>38</sup>Centre d'Eudes et de Recherches en Psychopathologie, University de Toulouse Le Mirail, Toulouse 31200, France.<sup>39</sup>Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana 46202, USA.<sup>40</sup>Departments of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213. <sup>41</sup>Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington 98195, USA.<sup>42</sup>University Department of Child Psychiatry, Athens University, Medical School, Agia Sophia Children's Hospital, 115 27 Athens, Greece.<sup>43</sup>Stella Maris Institute for Child and Adolescent Neuropsychiatry, 56128 Calambrone (Pisa), Italy<sup>44</sup>Department of Medicine, School of Epidemiology and Health Science, University of Manchester, Manchester, M13 9PT, UK.<sup>45</sup>Department of Statistics, Carnegie Mellon University, Pittsburgh, Pennsylvania, USA. <sup>46</sup>Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, London, SE5 8AF, UK.<sup>47</sup>Department of Pediatrics and Howard Hughes Medical Institute Carver College of Medicine, University of Iowa, Iowa City, Iowa 52242, USA.<sup>48</sup>Neuropsichiatria Infantile, Ospedale Santa Croce, 61032 Fano, Italy.<sup>49</sup>Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, L8N 3Z5, Canada.<sup>50</sup>Centre for Addiction and Mental Health, Clarke Institute and Department of Psychiatry, University of Toronto, Toronto, Ontario M5G 1X8, Canada. <sup>51</sup>Child Study Centre, Yale University, New Haven, Connecticut 06520, USA.<sup>52</sup>Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Utrecht 3584 CX, Netherlands.<sup>53</sup>Department of Pediatrics, University of Alberta, Edmonton, Alberta T6G 2J3, Canada.<sup>54</sup>BC Mental Health and Addictions Research Unit, University of British Columbia, Vancouver, British Columbia, Canada V5Z4H4. <sup>55</sup>Department of Human Genetics, University of California - Los Angeles School of Medicine, Los Angeles, California 90095, USA.<sup>56</sup>Psychiatry Department, University of Utah Medical School, Salt Lake City, Utah 84108, USA.<sup>57</sup>Autism Speaks, New York, New York, USA. <sup>58</sup>Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.<sup>59</sup>Department of Neurology, University of California - Los Angeles School of Medicine, Los Angeles, California 90095, USA.<sup>60</sup>Center for Human Genetics Research, Vanderbilt University Medical Centre, Nashville, Tennessee 37232, USA.<sup>61</sup>Division of Molecular Genome Analysis, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.<sup>62</sup>Office of the President, Tufts University, Boston, Massachusetts, USA.<sup>63</sup>Institutes of Neuroscience and Health and Society, Newcastle University, Newcastle Upon Tyne, NE1 7RU, UK.<sup>64</sup>Carolina Institute for Developmental Disabilities, University of North Carolina at Chapel Hill, North Carolina 27599-3366, USA.<sup>65</sup>Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.<sup>66</sup>Department of Psychiatry, Carver College of Medicine, Iowa City, Iowa 52242, USA.<sup>67</sup>Departments of Biostatistics and Medicine, University of Washington, Seattle, Washington 98195, USA.<sup>68</sup>INSERM U952 and CNRS UMR 7224 and UPMC Univ Paris 06, Paris 75005, France.<sup>69</sup>Battelle Center for Mathematical Medicine, The Research Institute at Nationwide Children's Hospital and The Ohio State University, Columbus, Ohio 43205, USA.<sup>70</sup>Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.<sup>71</sup>Current address: 28.

<sup>§</sup>Lead AGP investigators; <sup>†</sup>Writing Committee; <sup>‡</sup>Genotype production.

\*Correspondence should be addressed to Bernie Devlin, Department of Psychiatry, University of Pittsburgh School of Medicine, 3811 O'Hara St., Pittsburgh, PA 15213.

e-mail: devlinbj@upmc.edu; phone: 412-246-6642; fax 412-246-6640.

Chr	Position	SNP	Allele	Gene	Diagnosis	Ancestry	Inheritance	Р	OR
1	94924400	rs841361	G	None	Lower-IQ	All	Paternal Transmissions	9.361e-07	0.37 (0.24-0.56)
1	116327194	rs12726299	G	SLC22A15	Verbal	European	Paternal Transmissions	1.496e-07	1.51 (1.29-1.76)
1	204764871	rs11118968	А	RASSF5	Spectrum	All	Maternal Transmissions	2.452e-07	0.44 (0.32-0.61)
2	31000000	rs10205350	А	GALNT14	Non-verbal	All	Maternal Transmissions	3.942e-07	0.50 (0.38-0.66)
2	230226476	rs6752370	G	DNER	Strict	All	Maternal Transmissions	8.526e-07	1.62 (1.33-1.96)
3	185006350	rs263035	G	YEATS2	Spectrum	All	Paternal Transmissions	2.258e-07	1.39 (1.22-1.57)
4	147068744	rs12331851	А	ZNF827	Verbal	European	Paternal Transmissions	6.081e-07	0.38 (0.26-0.57)
5	2162900	rs6879627	А	None	Higher-IQ	European	Maternal Transmissions	3.992e-07	0.52 (0.40-0.67)
5	11424304	rs6891903	G	CTNND2	Lower-IQ	European	Maternal Transmissions	7.801e-07	0.08 (0.02-0.32)
5	65575602	rs29456	А	None	Strict	All	Maternal Transmissions	1.226e-07	1.65 (1.37-1.99)
7	145753720	rs1718101	А	CNTNAP2	Higher-IQ	European	Additive	7.783e-09	2.13 (1.63-2.80)
10	55971935	rs1930165	А	PCDH15	Higher-IQ	All	Maternal Transmissions	9.861e-08	0.60 (0.50-0.73)
10	119652081	rs1936295	А	None	Spectrum	European	Maternal Transmissions	6.636e-07	1.69 (1.37-2.09)
11	106363884	rs11211996	G	GUCY1A2	Non-verbal	European	Paternal Transmissions	4.287e-07	2.11 (1.56-2.85)
11	113578084	rs3782000	А	ZBTB16	Higher-IQ	All	Additive	1.842e-07	1.41 (1.24-1.61)
12	76273679	rs4761371	А	None	Strict	European	Paternal Transmissions	3.914e-07	0.46 (0.34-0.63)
16	4941380	rs9635542	G	None	Non-verbal	All	Paternal Transmissions	3.268e-07	0.44 (0.32-0.61)
16	61230112	rs288604	G	None	Spectrum	All	Maternal Transmissions	2.975e-07	1.58 (1.32-1.88)
17	68575820	rs9302952	С	SLC39A11	Verbal	All	Maternal Transmissions	4.039e-07	1.64 (1.35-1.99)
18	7024945	rs600695	G	LAMA1	Higher-IQ	All	Paternal Transmissions	3.578e-07	1.61 (1.34-1.94)
18	34259508	rs932026	А	None	Higher-IQ	European	Maternal Transmissions	1.473e-07	0.44 (0.32-0.60)
20	4921455	rs6053022	G	SLC23A2	Phrase	All	Additive	4.970e-07	N/A
20	14810971	rs6110458	А	MACROD2	Spectrum	All	Maternal Transmissions	1.806e-07	1.46 (1.27-1.69)
20	14813155	rs14135	G	MACROD2 NCRNA00186	Spectrum	European	Maternal Transmissions	1.778e-07	1.49 (1.28-1.74)
20	14815421	rs1475531	С	NCRNA00186 MACROD2	Strict	All	Maternal Transmissions	2.011e-07	1.53 (1.30-1.79)
21	38787019	rs2836439	Α	ERG	Lower-IQ	European	Paternal Transmissions	6.638e-07	0.42 (0.30-0.60)

# Supplementary Table 1. Top findings (<1x10<sup>-6</sup>) from exploratory (secondary analyses) of the combined sample.

Chr	Position	SNP	Allele	Gene	Diagnosis	Ancestry	Inheritance	Р	OR
1	12758454	rs1812242	А	PRAMEF12	Spectrum	European	Additive	4.286e-07	1.44 (1.25-1.66)
2	151714270	rs289932	А	None	Strict	European	Additive	5.424e-07	0.67 (0.57-0.79)
2	212147556	rs1879532	А	ERBB4	Strict	European	Additive	1.656e-07	1.72 (1.39-2.11)
12	124650315	rs16919315	А	TMEM132B	Spectrum	All	Additive	5.120e-08	0.53 (0.42-0.67)
22	25529236	rs9608521	А	None	Strict	All	Additive	7.619e-07	1.46 (1.25-1.69)
1	94924400	rs841361	G	None	Lower-IQ	All	Paternal Transmissions	9.361e-07	0.37 (0.24-0.56)
2	151714270	rs289932	А	None	Strict	European	Paternal Transmissions	5.039e-08	0.49 (0.38-0.64)
2	151760571	rs289858	А	None	Strict	European	Paternal Transmissions	2.810e-07	0.52 (0.40-0.67)
2	206402425	rs10185592	С	None	Verbal	All	Maternal Transmissions	3.148e-07	0.42 (0.30-0.59)
2	212147556	rs1879532	А	ERBB4	Spectrum	European	Maternal Transmissions	1.548e-08	2.02 (1.57-2.59)
3	185007814	rs263030	G	YEATS2	Verbal	All	Additive	2.756e-07	1.37 (1.21-1.54)
3	185010311	rs263025	G	YEATS2	Verbal	All	Paternal Transmissions	1.576e-07	1.71 (1.39-2.09)
4	85060273	rs17007739	С	None	Lower-IQ	All	Maternal Transmissions	4.770e-07	2.96 (1.88-4.66)
5	77011794	rs351871	G	None	Verbal	European	Additive	3.819e-07	1.40 (1.23-1.59)
6	20839502	rs7741604	С	CDKAL1	Lower-IQ	All	Maternal Transmissions	8.814e-07	0.21 (0.10-0.43)
6	23898093	rs1408744	А	None	Spectrum	All	Paternal Transmissions	8.056e-07	0.65 (0.54-0.77)
6	160754504	rs12194182	G	SLC22A3	Non-verbal	All	Maternal Transmissions	8.858e-07	2.63 (1.75-3.94)
7	6400611	rs836474	А	RAC1	Lower-IQ	European	Additive	5.862e-07	0.04 (0.01-0.32)
7	16746533	rs7800565	G	None	Verbal	All	Maternal Transmissions	7.951e-07	0.54 (0.42-0.69)
7	41089976	rs12701862	G	None	Verbal	All	Additive	8.762e-07	1.38 (1.21-1.57)
10	5414464	rs10904487	G	None	Spectrum	All	Paternal Transmissions	4.292e-07	0.63 (0.52-0.75)
10	108357717	rs7910584	С	SORCS1	Higher-IQ	All	Paternal Transmissions	7.135e-07	0.47 (0.34-0.64)
11	66419306	rs7122539	А	PC	Spectrum	European	Paternal Transmissions	9.641e-07	0.60 (0.49-0.74)
11	106488937	rs1895729	А	None	Non-verbal	All	Paternal Transmissions	1.315e-07	2.53 (1.76-3.64)
11	106505744	rs10749886	А	None	Non-verbal	European	Paternal Transmissions	4.049e-07	2.74 (1.81-4.15)
12	76273679	rs4761371	А	None	Strict	European	Paternal Transmissions	3.914e-07	0.46 (0.34-0.63)
13	87962320	rs519700	А	None	Lower-IQ	All	Additive	9.060e-07	2.97 (1.85-4.78)
14	63401175	rs2150291	А	SYNE2	Spectrum	All	Paternal Transmissions	2.828e-07	1.72 (1.40-2.13)
17	125891	rs7207517	А	RPH3AL	Spectrum	European	Paternal Transmissions	3.047e-07	1.97 (1.51-2.57)
18	45347861	rs2000813	А	LIPG	Lower-IQ	European	Additive	2.622e-07	0.47 (0.35-0.64)

Supplementary Table 2. Top findings (<1x10<sup>-6</sup>) from association analyses (primary and secondary analyses) of the Stage-2 only sample.

Supplementary Figure 1. Plot highlighting population ancestry. Groups A through C delineate 1285, 771, and 486 families of European ancestry as determined by representation of European recruitment sites. All other families were assigned to be non-European for purposes of association analysis.



Supplementary Figure 2. Analytic Strategy: graphic to highlight the primary and secondary analyses performed as part of the Autism Genome Project GWA strategy. Arrows indicate groups that are subsets of the originating group. Sample sizes for Stage 2 and the combined Stage1 and Stage analyses are given in Table 1.





# Supplementary Figure 3A.QQ-plot and Manhattan-plot: All ancestries, spectrum diagnostic classification.



Supplementary Figure 3B. QQ-plot and Manhattan-plot: All ancestries, strict diagnostic classification.



Supplementary Figure 3C. QQ-plot and Manhattan-plot: European ancestries, spectrum diagnostic classification.



Supplementary Figure 3D. QQ-plot and Manhattan-plot: European ancestries, strict diagnostic classification.

Supplementary Figure 4. Regional association plots for SNPs highlighted in the primary analyses of the combined sample. Linkage disequilibrium based on HapMap r3 CEU+TSI. Index SNP shown in blue diamond. Markers in linkage disequilibrium with the index SNP are shown in large circles; red  $r^2 \ge 0.8$ , orange  $r^2 \ge 0.6$ , yellow  $r^2 \ge 0.4$ , green  $r^2 \ge 0.2$ , white  $r^2 < 0.2$ . Recombination rates plotted in gold.



#### rs4675502 (Strict Diagnosis, All Ancestries)



## rs7711337 (Spectrum Diagnosis, All Ancestries)

## rs7834018 (Strict Diagnosis, European Ancestries)





### rs4150167 (Spectrum Diagnosis, All Ancestries)

Supplementary Figure 5. Overview of additional associations observed for SNPs highlighted in the primary analyses of the combined sample. Red=index association; Orange=index association for Stage 1, Stage 2 and parent of origin (combined samples); Blue=Other primary analyses (combined sample); Green=Other secondary analyses (combined sample).









Supplementary Figure 6A. Additive Genetic Variance at Marker (Vm) explained by Stage1-derived allele-score in Stage 2 probands and pseudo-controls for strict autism and European ancestry. Note the stratification by quintile of minor allele frequency (header). Significant association of allele-score denoted by (\*p<.05, \*\*p<.01, \*\*\*p<.001).



Graphs by freq\_threshold

Supplementary Figure 6B. Additive Genetic Variance at Marker (VM) explained by Stage1-derived allele-score in Stage 2 probands and pseudo-controls for spectrum diagnosis and European ancestry. Note the stratification by quintile of minor allele frequency (header). Significant association of allele-score denoted by (\*p<.05, \*\*p<.01, \*\*\*p<.001).



Graphs by freq\_threshold

Supplementary Figure 6C. Additive Genetic Variance at Marker (VM) explained by Stage1-derived allele-score in Stage 2 probands and pseudo-controls for strict autism of any ancestry. Note the stratification by quintile of minor allele frequency (header). Significant association of allele-score denoted by (\*p<.05, \*\*p<.01, \*\*\*p<.001).



Graphs by freq\_threshold

Supplementary Figure 6D. Additive Genetic Variance at Marker (VM) explained by Stage1-derived allele-score in Stage 2 probands and pseudo-controls for strict autism and European ancestry. Note the stratification by quintile of minor allele frequency (header). Significant association of allele-score denoted by (\*p<.05, \*\*p<.01, \*\*\*p<.001).



Graphs by freq\_threshold

Supplementary Figure 7. Genotype clustering for associated SNPs not in substantial linkage disequilibrium with surrounding SNPs.





Supplementary Figure 8. Distribution within the combined AGP sample for age at first word.

Supplementary Figure 9. Distribution within the combined AGP sample for age at first phrase.

