Data Supplement for St Pourcain et al., Association Between a High-Risk Autism Locus on 5p14 and Social Communication Spectrum Phenotypes in the General population, American Journal of Psychiatry (doi: 10.1176/appi.ajp.2010.09121789)

Part 1

Wang and colleagues (1) used for their study subjects of the Autism Genetic Resource Exchange (AGRE) who were diagnosed with Autism Spectrum Disorder (ASD) using both the Autism Diagnostic Interview-Revised (ADI-R) (2) and the Autism Diagnostic Observation Schedule (ADOS) (3) diagnostic tools that represent gold-standard for the diagnosis of ASD.

Part 2

The repetitive interests, behaviours, and activities (RIBA) spectrum was excluded from the analysis for several reasons: First, we specifically focussed on standardised instruments rather than ALSPAC-specific measures, and ALSPAC did not employ standardised measures of RIBAs. Second, we aimed for a high-density coverage of multiple facets of the broader autism phenotype that are captured as continuous traits. Our RIBA-equivalent measurements however rely on ALSPAC-specific questions on 'rocking behaviour', 'abnormal behaviour' and 'tics', where parent-reports were coded on a three-point Likert scale that is unlikely to reflect the entire breadth and subtlety of a continuous RIBAs spectrum, although it may adequately capture more extreme cases. Finally, some studies have suggested that the genetic influences underlying social-communication-spectrum traits are likely to be distinct from the genetic determinants of RIBAs (e.g. Ronald et al., 2006). There is growing evidence that social and communication impairments may share common genetic susceptibilities, which are distinct from those affecting RIBAs (Mandy and Skuse, 2008).

Part 3

A special educational needs (SEN) code of practice, introduced in Wales and England, recommends that children with SEN receive graduated assistance that supports more efficient learning (6-9). 'School Action' points to the level of help that is generally available at school. In consultation with the parents, an individual education plan (IEP) will be established that sets short-term targets for the child, and specifies teaching schemes, provision and monitoring details. The IEP will include strategies like the use of different learning materials, special equipment, extra individual or group support, staff training and access to local authority support services for advice. If the learning progress of the child is not sufficient under the 'School Action' educational setting, 'School Action Plus' support will be provided. This includes specialist support from educational psychologists, specialist teachers or other health professionals such as speech and language therapists that will aid the tailoring of an improved IEP. For a small number of children with severe, complex and long-term needs, it is necessary that the local authority will determine the level of support that is needed for the child to achieve sufficient learning progress. Based on the reports from parents, schools/preschools, educational psychologists and other health or social care professionals, a 'Statutory assessment and statement of Special Educational Needs' will be carried out that defines long-term objectives for the child, specifies the support needed, and establishes short-term targets that will be regularly reviewed.

Part 4

Repeated measures of total behavioural difficulties (SDQ), friendship scores (SDQ) and social communication (SCDC) showed at some measurement time points nominal evidence for association with rs4307059 in cross-sectional analysis. We therefore investigated for these phenotypes the evidence for time-invariant SNP effects and changes in SNP effect over time, and compared mixed model analyses (R lme4 library) (10) with cross-sectional analysis (see supplement Table S2). Mixed models were fitted with random intercepts, and fixed effects for rs4307059, continuous age at measurement, sex and maternal education. Changes in SNP effect over time were captured as fixed effect age - rs4307059 interaction. Trajectories of total behavioural difficulties and friendship scores over time were modelled with linear mixed models, whereas trajectories of social communication were modelled with Quasi-Poisson mixed models. Cross-sectional analyses were described in the Methods section. To note, multilevel model were not incorporated within the empirical approach within our study, as the often complex model fit cannot be monitored during the permutation procedure.

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Table S1: Non-parametric rank correlation among all investigated spectrum phenotypes

	1	2	3	4	5	6	7	8	9	10
1	1.00(5948)									
2	-0.13(4810)	1.00(5319)								
3	0.21(4700)	-0.08(4614)	1.00(5181)							
4	0.16(4691)	-0.14(4601)	0.3(5153)	1.00(5161)						
5	0.05(4690)	-0.23(4605)	0.01(5156)	0.16(5157)	1.00(5164)					
6	0.26(4694)	-0.29(4607)	0.33(5160)	0.35(5158)	0.23(5161)	1.00(5169)				
7	0.07(4676)	-0.27(4595)	0.06(5142)	0.19(5139)	0.45(5146)	0.29(5149)	1.00(5149)			
8	0.18(4634)	-0.32(4556)	0.18(5085)	0.26(5075)	0.38(5082)	0.38(5084)	0.44(5082)	1.00(5093)		
9	0.19(4635)	-0.27(4557)	0.25(5087)	0.21(5075)	0.04(5081)	0.39(5085)	0.15(5081)	0.33(5083)	1.00(5094)	
10	0.19(4613)	-0.39(4541)	0.20(5065)	0.31(5064)	0.67(5071)	0.59(5071)	0.74(5071)	0.74(5071)	0.48(5071)	1.00(5071)
11	-0.10(4478)	0.57(4417)	-0.08(4538)	-0.13(4527)	-0.25(4530)	-0.29(4531)	-0.29(4518)	-0.32(4483)	-0.26(4483)	-0.40(4465)
12	0.22(4390)	-0.10(4269)	0.19(4295)	0.17(4285)	0.12(4285)	0.21(4285)	0.12(4277)	0.25(4233)	0.12(4235)	0.23(4218)
13	0.09(5925)	0.03(4927)	0.10(4797)	0.06(4784)	-0.06(4786)	0.07(4788)	-0.01(4773)	0.06(4729)	0.13(4730)	0.04(4708)
14	-0.13(5275)	0.20(4782)	-0.11(4637)	-0.11(4622)	-0.14(4625)	-0.17(4628)	-0.17(4614)	-0.21(4575)	-0.23(4578)	-0.27(4556)
15	0.05(5408)	0.03(4969)	0.09(4823)	0.06(4805)	-0.07(4807)	0.07(4814)	0.01(4797)	0.07(4757)	0.14(4760)	0.04(4737)
16	0.05(5097)	0.02(4833)	0.08(4692)	0.05(4679)	-0.08(4679)	0.07(4684)	<0.00(4668)	0.03(4626)	0.13(4629)	0.02(4609)
17	-0.10(5004)	0.25(4806)	-0.07(4657)	-0.13(4643)	-0.17(4643)	-0.19(4648)	-0.2(4636)	-0.25(4596)	-0.20(4596)	-0.30(4576)
18	-0.11(4601)	0.27(4601)	-0.08(4532)	-0.15(4520)	-0.22(4523)	-0.22(4526)	-0.24(4515)	-0.27(4476)	-0.22(4479)	-0.34(4460)
19	-0.08(4257)	0.09(4129)	-0.03(4161)	-0.04(4151)	-0.04(4151)	-0.11(4151)	-0.05(4144)	-0.07(4100)	-0.10(4102)	-0.10(4086)
20	-0.13(4664)	0.25(4590)	-0.11(5115)	-0.14(5097)	-0.21(5100)	-0.24(5107)	-0.23(5091)	-0.26(5044)	-0.25(5048)	-0.34(5025)
21	-0.09(4305)	0.05(4159)	-0.05(4267)	-0.05(4257)	-0.02(4257)	-0.09(4259)	-0.02(4246)	-0.05(4203)	-0.08(4205)	-0.07(4189)
22	-0.11(4313)	0.24(4266)	-0.08(4354)	-0.14(4343)	-0.22(4342)	-0.21(4346)	-0.21(4334)	-0.25(4297)	-0.20(4300)	-0.32(4283)
23	-0.16(5517)	0.39(4887)	-0.10(4755)	-0.12(4737)	-0.22(4739)	-0.26(4745)	-0.27(4727)	-0.24(4685)	-0.19(4686)	-0.34(4664)
24	-0.17(5173)	0.40(4700)	-0.12(4555)	-0.15(4541)	-0.24(4544)	-0.29(4546)	-0.28(4534)	-0.30(4495)	-0.25(4496)	-0.39(4476)
25	-0.17(4996)	0.51(4799)	-0.13(4649)	-0.20(4636)	-0.29(4636)	-0.34(4641)	-0.33(4629)	-0.35(4589)	-0.29(4589)	-0.46(4569)
26	-0.16(4597)	0.51(4596)	-0.13(4528)	-0.18(4516)	-0.3(4519)	-0.35(4522)	-0.34(4511)	-0.35(4472)	-0.30(4475)	-0.48(4456)
27	-0.16(4652)	0.49(4580)	-0.15(5102)	-0.21(5086)	-0.33(5090)	-0.40(5095)	-0.36(5082)	-0.40(5034)	-0.35(5038)	-0.53(5015)
28	-0.14(4314)	0.46(4267)	-0.14(4355)	-0.19(4345)	-0.30(4345)	-0.34(4348)	-0.32(4337)	-0.34(4300)	-0.27(4303)	-0.46(4286)
29	-0.14(4923)	0.17(4402)	-0.20(4327)	-0.22(4307)	-0.12(4310)	-0.22(4315)	-0.11(4295)	-0.21(4243)	-0.16(4244)	-0.21(4222)

Table S1(cont'd-1): Non-parametric rank correlation among all investigated spectrum phenotypes

	11	12	13	14	15	16	17	18	19	20
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11	1.00(4920)									
12	-0.09(4104)	1.00(4925)								
13	0.03(4572)	0.04(4475)	1.00(6099)							
14	0.16(4423)	-0.07(4316)	-0.22(5413)	1.00(5754)						
15	0.04(4581)	0.04(4463)	0.5(5541)	-0.2(5362)	1.00(5932)					
16	0.04(4464)	0.03(4316)	0.44(5225)	-0.18(5053)	0.57(5297)	1.00(5562)				
17	0.22(4418)	-0.08(4291)	-0.12(5120)	0.37(4948)	-0.16(5179)	-0.17(5060)	1.00(5442)			
18	0.25(4306)	-0.07(4180)	-0.1(4702)	0.38(4558)	-0.15(4720)	-0.15(4612)	0.53(4578)	1.00(5028)		
19	0.09(3977)	-0.07(4714)	-0.02(4338)	0.09(4176)	-0.06(4327)	-0.05(4180)	0.12(4154)	0.14(4050)	1.00(4770)	
20	0.27(4515)	-0.06(4260)	-0.1(4764)	0.32(4606)	-0.14(4797)	-0.14(4662)	0.45(4629)	0.53(4514)	0.15(4127)	1.00(5138)
21	0.04(4171)	-0.08(4308)	-0.05(4391)	0.09(4224)	-0.06(4367)	-0.06(4225)	0.10(4186)	0.14(4047)	0.22(4170)	0.14(4236)
22	0.25(4294)	-0.07(3983)	-0.08(4406)	0.27(4273)	-0.11(4428)	-0.13(4317)	0.39(4289)	0.44(4167)	0.13(3865)	0.52(4333)
23	0.33(4523)	-0.09(4427)	0.02(5656)	0.27(5382)	0.03(5514)	0.03(5182)	0.25(5073)	0.24(4644)	0.07(4287)	0.25(4719)
24	0.35(4347)	-0.16(4241)	-0.02(5310)	0.56(5642)	<0.00(5258)	0.01(4965)	0.30(4864)	0.31(4480)	0.07(4104)	0.29(4525)
25	0.46(4412)	-0.19(4286)	0.01(5111)	0.31(4941)	0.01(5171)	0.01(5052)	0.55(5429)	0.42(4573)	0.13(4150)	0.38(4621)
26	0.46(4301)	-0.16(4176)	<0.00(4698)	0.31(4555)	0.01(4715)	0.01(4608)	0.39(4573)	0.59(5023)	0.13(4046)	0.41(4510)
27	0.50(4502)	-0.18(4253)	<0.00(4753)	0.27(4594)	-0.01(4783)	<0.00(4652)	0.35(4622)	0.41(4503)	0.13(4120)	0.59(5118)
28	0.49(4295)	-0.18(3984)	<0.00(4408)	0.25(4274)	<0.00(4427)	-0.01(4317)	0.33(4288)	0.38(4169)	0.13(3866)	0.41(4335)
29	0.16(4106)	-0.25(4138)	-0.05(5051)	0.11(4771)	-0.05(4926)	-0.03(4616)	0.13(4509)	0.15(4165)	0.05(4019)	0.16(4288)

Table S1(cont'd-2): Non-parametric rank correlation among all investigated spectrum phenotypes

	21	22	23	24	25	26	27	28	29
1									
2									
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9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
19									
20									
21	1.00(4821)								
22	0.15(4024)	1.00(4726)							
23	0.05(4334)	0.22(4365)	1.00(6007)						
24	0.06(4150)	0.24(4204)	0.57(5281)	1.00(5642)					
25	0.09(4179)	0.34(4282)	0.5(5063)	0.57(4857)	1.00(5432)				
26	0.09(4043)	0.38(4163)	0.48(4639)	0.57(4477)	0.71(4568)	1.00(5023)			
27	0.10(4226)	0.40(4324)	0.46(4710)	0.52(4514)	0.67(4614)	0.70(4499)	1.00(5124)		
28	0.10(4027)	0.59(4720)	0.40(4365)	0.45(4205)	0.62(4281)	0.66(4165)	0.69(4326)	1.00(4725)	
29	0.07(4098)	0.16(3935)	0.10(4982)	0.16(4674)	0.21(4500)	0.20(4161)	0.23(4275)	0.22(3934)	1.00(6057)

For simplicity, it was assumed the SEN (29) is an ordinal trait; All correlation coefficients are based Spearman's rank correlation coefficient using pairwise-complete observations as the number of samples with complete observation is small (1915)
1 (Language CDI, 3y3m), 2 (Social communication SCDC, 7y8m), 3 (Intelligibility and fluency CCC, 9y8m), 4 (Syntax CCC, 9y8m), 5 (Inappropriate initiation CCC, 9y8m), 6 (Coherence CCC, 9y8m), 7 (Stereotyped conversation CCC, 9y8m), 8 (Use of conversational context CCC, 9y8m), 9 (Conversational rapport CCC, 9y8m), 10 (Pragmatic aspects of communication CCC, 9y8m), 11 (Social communication SCDC, 10y9m), 12 (Verbal IQ WISC-III, 8y7m), 13 (Sociability EAS, 3y3m), 14 (Peer problems SDQ, 4y0m), 15 (Sociability EAS, 4y9m), 16 (Sociability EAS, 5y10m), 17 (Peer problems SDQ, 6y9m), 18 (Peer problems SDQ, 8y2m), 19 (Friendships score HMP-FQ, 8y7m), 20 (Peer problems SDQ, 9y8m), 21 (Friendships score HMP-FQ, 10y8m), 22 (Peer problems SDQ, 11y9m), 23 (Total difficulties R-RPS-PC, 3y6m), 24 (Total difficulties SDQ, 4y0m), 25 (Total difficulties SDQ, 6y9m), 26 (Total difficulties SDQ, 8y2m), 27 (Total difficulties SDQ, 9y8m), 28 (Total difficulties SDQ, 11y9m), 29 (SEN , 11y10m), y – years, m – months, Measurement abbreviations are given in the Methods section

Table S2: Association between repeatedly measured spectrum phenotypes and rs4307059 using cross-sectional and longitudinal analysis

Analysis	Age	N	β	SE	Nominal P[a]	Adjusted P[a]
Total behavioural difficulties (SDQ)						
Cross-sectional[b]	4y0m	5642	0.091	0.087	0.15	0.92
	6y9m	5432	0.12	0.092	0.11	0.84
	8y2m	5023	0.13	0.10	0.10	0.83
	9y8m	5124	0.21	0.098	0.014	0.26
	11y9m	4725	0.24	0.10	0.010	0.20
Multilevel[c]		6525[f]	0.14[g]	0.074[h]	0.090	-
Friendship scores (HMP-FQ)						
Cross-sectional[b]	8y7m	4770	0.093	0.052	0.036	0.50
	10y8m	4821	0.008	0.045	0.43	1.00
Multilevel[c]		5421[f]	0.052[g]	0.037[i]	0.10	-
Social communication scores (SCDC)						
Cross-sectional[d]	7y8m	5319	0.018	0.026	0.25	0.98
	10y9m	4920	0.076	0.031	0.0070	0.15
Multilevel[e]		5822[f]	0.044[g]	0.027[k]	0.088	-

a – One-sided p-values; b – Ordinary-Least-Squared regression; c – Linear mixed model; d – Quasi-Poisson regression; e – Quasi-Poisson mixed model; f – Number of individuals with at least one measurement, g – Effect is given for age centred at 10-years; h – (age - rs4307059 interaction: p=0.19); i – (age - rs4307059 interaction: p=0.21); k – (age - rs4307059 interaction: p=0.20); SE – Standard error