

Supplementary material for Toma C, et al. 2015. Common and rare variants of microRNA genes in autism spectrum disorders. World J Biol Psychiatry 2015;16:376–386.

Supplementary Table 1. miRNA genes selected in the present study. The miRNAs were selected on the basis of their target genes, considered good candidates for psychiatric disorders, using Tarbase and MiRecords databases (only validated targets) or because described in neuronal functions.

Selected_miRNA	Target gene-Tarbase	Target gene-MiRecords	Reference	miRNA Gene Studied	Cluster Included in the study
<b>miR-1</b>	SNX6, MET, NRP1, PTBP1, PTBP2, LASP1, LIN7C, PREX1, ZNF264	MET, LASP1, LIN7C, PREX1, ZNF264, FoxP1	1 2, 3, 4	miR-1-1	isolated
				miR-1-2 miR-7-1 miR-7-2	cluster_18.1 (miR-1-2, miR133a-1) isolated cluster_15.1 (miR-7-2, miR-1179)
<b>miR-7</b>				miR-7-3	isolated
				miR-9-1 miR-9-2 miR-9-3	isolated isolated isolated
<b>miR-9</b>		REST, trkC, RCOR1	1, 3, 5	miR-10a miR-15a	cluster_13.1 (miR-15a, miR-16-1)
<b>miR-10a</b>	HOXA1	HOXA1	6, 7	miR-10a	isolated
<b>miR-15a</b>		IGSF4	8	miR-15a	cluster_13.1 (miR-15a, miR-16-1)
<b>miR-16</b>	SNX15, CDK5RAP1, LUZP1, PAXN1	IGSF4	8	miR-16-1 miR-16-2	cluster_13.1 (miR-15a, miR-16-1) cluster_3.2 (miR-16-2, miR-15b)
<b>miR-19a</b>	PTEN	PTEN		miR-19a	cluster_13.2 (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR92a-1)
<b>miR-21</b>	PTEN	PTEN	2, 3, 9	miR-21	isolated
<b>miR-23a</b>			2, 10, 11	miR-23a	cluster_19.1 (miR-23a, miR-27a, miR-24-2)
<b>miR-23b</b>			10, 11	miR-23b	cluster_9.2 (miR-23b, miR-24-1, miR-27b, miR-3074)
<b>miR-24</b>		SLitrk1	12, 13	miR-24-1 miR-24-2	cluster_9.2 (miR-23b, miR-24-1, miR-27b, miR-3074) cluster_19.1 (miR-23a, miR-27a, miR-24-2)
<b>miR-27a</b>	MYT1	Sp4	1, 2, 3	miR-27a	cluster_19.1 (miR-23a, miR-27a, miR-24-2)
<b>miR-30</b>			6, 11, 14, 15, 16	miR-30a miR-30b miR-30c-1 miR-30c-2 miR-30d miR-30e	cluster_6.2 (mir-30a, mir-30c-2) cluster_8.1 (miR-30b, miR-30d) cluster_1.2 (miR-30c-1, miR-30e) cluster_6.2 (mir-30a, mir-30c-2) cluster_8.1 (miR-30b, miR-30d) cluster_1.2 (miR-30c-1, miR-30e)
<b>miR-34b</b>		NOTCH4		miR-34b	cluster_11.1 (miR-34b, miR-34c)
<b>miR-34c</b>		NOTCH4		miR-34c	cluster_11.1 (miR-34b, miR-34c)

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Supplementary Table 1. (Continued)

Selected_miRNA	Target gene-Tarbase	Target gene-MiRecords	Reference	miRNA Gene Studied	Cluster Included in the study
<b>miR-92</b>			3, 9, 10, 13, 17	miR-92a-1	cluster_13.2 (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR92a-1)
				miR-92a-2	cluster_X.3 (hsa-mir-106a, miR-18b, hsa-mir-20b, hsa-mir-19b-2, hsa-mir-92a-2, hsa-mir-363)
<b>miR-93</b>			2, 11	miR-93	isolated
<b>miR-96</b>	<i>HTR1B</i>		18	miR-96	cluster 7.2 (miR-182, miR-96, miR-183)
<b>miR-103</b>			11, 14, 19	miR-103-1	cluster_5.1 (miR-103-1, miR-103-1-as)
				miR-103-1-as	cluster_5.1 (miR-103-1, miR-103-1-as)
				miR-103-2	cluster_20.1 (miR103-2, miR103-2-as)
				miR-103-2-as	cluster_20.1 (miR103-2, miR103-2-as)
<b>miR-106b</b>			2, 11	miR-106b	cluster_7.1 (mir-106b, mir-93, mir-25)
<b>miR-124</b>	<i>EPIM, PTBP1</i>	<i>STX10, SYPL, RHOG, EPIM, PTBP1, JAKMIP1, SYPL, THG-1, TSPAN15</i>	1, 3, 7, 20	miR-124-1	isolated
				miR-124-2	isolated
				miR-124-3	isolated
<b>miR-125b</b>		<i>FAM19A1, ODZ2, PCDHB10</i>	3, 9, 19, 21, 22	miR-125b-1	isolated
<b>miR-128</b>			2, 3, 13, 19	miR-125b-2	isolated
<b>miR-129</b>			2, 7, 23	miR-128-1	isolated
<b>miR-129</b>				miR-128-2	isolated
<b>miR-132</b>	<i>RICS</i>	<i>RICS</i>	3, 5, 9, 10, 11, 18, 24	miR-129-1	isolated
<b>miR-133b</b>	<i>PTBP2, HCN2</i>	<i>PTBP2, PITX3</i>	11, 25	miR-129-2	isolated
<b>miR-134</b>			21, 26	miR-132	cluster_17.1 (miR-132, miR-212)
				miR-133b	cluster_6.1 (miR-133b, miR-206)
				miR-134	cluster_14.1 (mir-379, mir-411, mir-299, mir-380, mir-1197, mir-323, mir-758, mir-329-1, mir-329-2, mir-494, mir-543, mir-495, mir-376c, mir-376a-2, mir-654, mir-376b, mir-376a-1, mir-300, mir-1185-1, mir-1185-2, mir-381, mir-487b, mir-539, mir-889, mir-544, mir-655, mir-487a, mir-382, mir-134, mir-668, mir-485, mir-453, mir-154, mir-496, mir-377, mir-541, mir-409, mir-412, mir-369, mir-410, mir-656)

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Supplementary Table 1. (Continued)

Selected_miRNA	Target gene-Tarbase	Target gene-MiRecords	Reference	miRNA Gene Studied	Cluster Included in the study
<b>miR-137</b>			27, 28	miR-137	isolated
<b>miR-139</b>			3, 11	miR-139	isolated
<b>miR-141</b>	<i>CLOCK</i>			miR-141	cluster_12.1 (miR-141, miR-200c)
<b>miR-146b</b>			2, 10, 29, 30	miR-146b	isolated
<b>miR-148b</b>			2, 11	miR-148b	isolated
<b>miR-153-1</b>			3, 11	miR-153-1	isolated
<b>miR-155</b>	<i>SYPL1, SNAP29, CDK5RAP3, MET, PLXND1, PRAF2, RCOR1</i>			miR-155	isolated
<b>miR-181b</b>	<i>GRIA2</i>	<i>GRIA2, VSNL1</i>	6, 12, 31	miR-181b-1 miR-181b-2	cluster_1.4 (miR-181b, miR-181a) cluster_9.3 (miR-181a-2, miR-181b-2)
<b>miR-181c</b>			6	miR-181c	cluster_19.2 (miR-181c, miR-181d)
<b>miR-182</b>			11, 32	miR-182	cluster 7.2 (miR-182, miR-96, miR-183)
<b>miR-184</b>			33	miR-184	isolated
<b>miR-185</b>			11, 34	miR-185	isolated
<b>miR-190</b>			3, 11	miR-190	isolated
<b>miR-191</b>			11, 14, 19	miR-191	cluster_3.1 (miR-191, miR-425)
<b>miR-193a</b>		<i>PTK2</i>	35	miR-193a	isolated
<b>miR-195</b>			11, 14	miR-195	cluster_17.2 (miR-195, miR-497)
<b>miR-199a</b>	<i>MET</i>		7	miR-199a-1 miR-199a-2	isolated cluster_1.3 (miR-199a-2, miR-214, miR-3120)
<b>miR-199b</b>			6, 11, 30	miR-199b	cluster_9.4(miR-199b, miR-3154)
<b>miR-200</b>		<i>ZEB2</i>	36, 37	miR-200a miR-200b miR-200c	cluster_1.1 (miR200b, miR-200a, miR-429) cluster_1.1 (miR200b, miR-200a, miR-429) cluster_12.1 (miR-141, miR-200c)
<b>miR-205</b>		<i>ZEB2</i>	11	miR-205	isolated
<b>miR-206</b>	<i>UTRN, ESR1</i>	<i>ESR1</i>	38, 39	miR-206	cluster_6.1 (miR-133b, miR-206)
<b>miR-210</b>	<i>EFNA3</i>	<i>EFNA3</i>		miR-210	isolated
<b>miR-212</b>		<i>ZO-1</i>	2, 18, 39	miR-212	cluster_17.1 (miR-132, miR-212)
<b>miR-214</b>	<i>PTEN</i>	<i>PTEN</i>	4, 7, 11	miR-214	cluster_1.3 (miR-199a-2, miR-214, miR-3120)
<b>miR-219</b>			2, 10, 11, 40	miR-219-1 miR-219-2	isolated isolated
<b>miR-325</b>			12	miR-325	isolated
<b>miR-346</b>			11, 41	miR-346	isolated
<b>miR-484</b>			2	miR-484	isolated
<b>miR-486</b>			6	miR-486	isolated
<b>miR-502</b>			6, 42	miR-502	cluster_X.1 (miR-500a, miR-362, miR-501, miR-660, miR-502)
<b>miR-659</b>		<i>GRN</i>	43	miR-659	cluster_22.1 (mir-658, mir-659)
<b>let-7a</b>		<i>ITGB3</i>	1, 44	let-7a-1 let-7a-3	cluster_9.1 (let-7a-1, let-7d, let 7f-1) cluster_22.2 (let-7a-3, 7b)

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Supplementary Table 1. (Continued)

Selected_miRNA	Target gene-Tarbase	Target gene-MiRecords	Reference	miRNA Gene Studied	Cluster Included in the study
<b>let-7b</b>	<i>GPR56, RHOG, SYPL1, SNAP23</i>		1, 44	let-7b	cluster_22.2 (let-7a-3, 7b)
<b>let-7f</b>		<i>KIF1A, NTS</i>	1, 44	let-7f-1	cluster_9.1 (let-7a-1, let-7d, let 7f-1)
				let-7f-2	cluster_X.2 (let-7f-2, miR-98)

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Supplementary Table 2. SNPs genotyped in this study within the region encoding the mature miRNA. Genotyping data are shown in case and control populations.

SNP	miRNA	Alleles	MA (dbSNP137)	MAF	Genotyping Success Rate (%)	Cases		Controls		Allelic Test (P-Value)
						MAF	N MA/total Alleles	MAF	N MA/total Alleles	
rs72563729	miR-200b	A/G	A	0.007	failed	–	–	–	–	
rs72631824	miR-93	C/T	T	0.005	98.53 (monomorphic)	–	0/1272	–	0/1340	
rs72631827	miR-106b	G/T	T	0.003	98.68	0.0008	1/1269	0.0015	2/1344	0.59
rs76481776	miR-182	C/T	T	0.057	96.41	0.12	135/1131	0.09	109/1181	0.056
rs73159662	miR-96	A/G	A	0.007	98.75	0.004	5/1267	0.008	11/1335	0.16
rs72631829	miR-124-2	A/G	G	0.002	98.75 (monomorphic)	–	0/1272	–	0/1346	
rs76662330	miR-7-1	G/T	T	0.014	98.68 (monomorphic)	–	0/1270	–	0/1346	
rs78086449	miR-181b-2	G/T	T	0.083	98.75 (monomorphic)	–	0/1272	–	0/1346	
rs72631835	miR-199b	C/T	T	0.0001	98.53 (monomorphic)	–	0/1266	–	0/1346	
rs76149940	miR-146b	C/T	T	0.013	98.75	–	0/1272	0.0007	1/1345	0.33
rs74878365	miR-148b	A/C	A	–	failed	–	–	–	–	
rs72631826	miR-16-1	C/T	C	0.008	98.75 (monomorphic)	–	0/1272	–	0/1346	
rs72631821	miR-92-a1	C/T	T	0.005	failed	–	–	–	–	
rs41280052	miR-184	G/T	T	0.011	98.24	0.015	19/1253	0.018	24/1308	0.77
rs75737367	miR-7-2	A/C	C	0.14	97.07 (monomorphic)	–	0/1232	–	0/1340	
rs60406007	miR-193-a	G/T	T	–	98.75 (monomorphic)	–	0/1272	–	0/1346	
rs72631828	miR-10a	A/G	A	0.005	98.75 (monomorphic)	–	0/1272	–	0/1346	
rs76199191	miR-7-3	G/T	G	–	98.75 (monomorphic)	–	0/1272	–	0/1346	
rs895819	miR-27a	T/C	C	0.33	failed	–	–	–	–	
rs34059726	miR-124-3	G/T	T	–	failed	–	–	–	–	
rs72631830	miR-325	G/T	T	0.005	98.68 (monomorphic)	–	0/737	–	0/780	

N, Number.

MA, Minor Allele.

MAF, Minor Allele frequency.

Supplementary Table 3. Case-control association study of 350 SNP in 636 ASD patients and 673 controls (discovery study). All miRNA genes included in our case-control association study are listed below. For each miRNA gene (isolated or clustered) data of all SNPs genotyped (tag SNPs from the miRNA region, tag SNPs from the host gene promoter, SNPs under the mature miRNA) are shown. Genotyping success rate, Minor Allele Frequency (MAF), HWE and  $r^2$  among SNPs (only values  $> 0.8$ ) are also indicated. The association study results are shown for the three populations considered in our study and for the overall sample (P-values  $< 0.05$  are in bold).

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping <sup>a</sup>	HWE <sup>b</sup> (P-value)	MAF (All sample)	P-values				
									$r^2 > 0.8$ in controls (SNP)	Spanish	Dutch	German	Overall
<b>miR-200a, miR-200b</b>	cluster_1.1 (miR200b, miR-200a, miR-429)	intergenic	+	rs4970362	miRNA TagSNP	98.24	0.4376	0.328	0.1009	0.9922	0.8044	0.22	
				rs9660710	miRNA TagSNP	96.92	0.5661	0.067	0.207	0.4375	0.6513	0.2134	
				rs72563729	Pre-miRNA SNP	failed	-	-	-	-	-	-	
				rs4970420	miRNA TagSNP	98.53	0.7084	0.184	0.5089	0.09067	0.1276	0.3292	
<b>miR-30c-1, miR-30e</b>	cluster_1.2 (miR-30c-1, miR-30e)	NFYC	+	rs965949	Promoter NFYC	98.31	0.2931	0.392	0.99 (rs928508)	0.5351	0.7856	0.8073	0.6053
				rs552147	TagSNP Promoter NFYC	98.61	0.6415	0.212	0.98 (rs16827532)	0.84148	0.9848	0.7025	0.7766
				rs2744800	Promoter NFYC TagSNP	98.46	0.701	0.111	0.99 (rs7542349)	0.2259	0.4043	0.4992	0.6291
				rs7542349	miRNA TagSNP	87.32	0.3186	0.119	0.99 (rs2744800)	0.5180	genotyped $< 80\%$	0.3029	0.1668
				rs10789206	miRNA TagSNP	98.46	0.3828	0.413	0.4834	0.8234	0.6034	0.6639	
				rs16827532	miRNA TagSNP	98.68	0.558	0.211	0.98 (rs552147)	0.7586	0.9421	0.7025	0.6919
				rs928508	miRNA TagSNP	98.68	0.574	0.394	0.99 (rs965949)	0.5745	0.4520	0.8073	0.4278
				rs11208830	miRNA TagSNP	98.24	0.2454	0.194	0.1228	0.3328	0.3491	0.1763	
<b>miR-137</b>	isolated	MIR137HG	-	rs2802535	miRNA TagSNP	98.61	0.804	0.181	0.5058	0.2012	0.3567	0.1075	
				rs2660303	miRNA TagSNP	98.31	0.2049	0.109	0.2842	0.1643	0.258	0.04214	
<b>miR-92b</b>	isolated	intergenic	+	rs4971100	miRNA TagSNP	98.61	0.8728	0.406	0.7114	0.8506	0.9145	0.7384	
				rs4072037	miRNA TagSNP	98.46	0.9385	0.498	0.1638	0.9571	0.5502	0.2552	
<b>miR-9-1</b>	isolated	C1orf61	-	rs16837375	miRNA TagSNP	98.53	1.00	0.274	0.5673	0.498	0.7507	0.9212	
				rs7548323	miRNA TagSNP	98.68	0.4608	0.153	0.6455	0.3332	0.4993	0.972	

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping <sup>§</sup>	HWE <sup>¶</sup> (P-value)	MAF (All sample)	r <sup>2</sup> >0.8 in controls			Spanish	Dutch	German	Overall	P-values
									HWE <sup>¶</sup> (P-value)	MAF (All sample)	r <sup>2</sup> >0.8 in controls					
<b>miR-214, miR-199a-2</b>	cluster_1. <sup>3</sup> (miR-199a-2, miR-214, miR-3120)	DNM3	-	rs16837386	miRNA	98.68	0.2791	0.13	0.5103	0.08505	0.5238	0.2186	0.2946	0.2946	0.6437	0.2186
					TagSNP	98.24	0.4725	0.087	0.9285	0.8964	0.2946					
<b>miR-181b-1</b>	cluster_1. <sup>4</sup> (miR-181b-1, miR-181a-1)	MIR181AHG	-	rs10494305	Promoter C1orf61	98.31	0.7162	0.201	0.397	0.8343	0.07004	0.8648	0.7511	0.7511	0.7233	0.8648
					TagSNP	98.31	0.7162	0.201	0.397	0.8343	0.07004					
<b>miR-205</b>	isolated	MIR205HG	+	rs10797791	miRNA	98.68	1.00	0.331	0.7842	0.7096	0.03969	0.7653	0.8935	0.8935	0.9043	0.7653
					TagSNP	98.61	0.6891	0.407	0.7654	0.8935	0.7511					
<b>miR-128-1</b>	isolated	R3HDM1	+	rs10194951	miRNA	98.31	0.8364	0.105	0.507	0.5967	0.9892	0.9043	0.4783	0.4783	0.4783	0.4783
					TagSNP	98.31	0.8364	0.105	0.507	0.5967	0.9892					
<b>miR-235</b>	isolated	R3HDM1	+	rs12406238	miRNA	98.53	1.00	0.072	0.07264	0.4553	0.7226	0.5867	0.8981	0.8981	0.998	0.5867
					TagSNP	98.75	0.8228	0.095	0.8412	0.7668	0.8981					
<b>miR-236</b>	isolated	R3HDM1	+	rs10753838	miRNA	94.79	0.931	0.365	0.851	0.7851	0.7779	0.8133	0.5048	0.5048	0.4783	0.8133
					TagSNP	98.24	0.495	0.223	0.1164	0.3832	0.5048					
<b>miR-239</b>	isolated	R3HDM1	+	rs6701884	miRNA	98.31	0.5248	0.06	0.09539	0.857	0.693	0.1448	0.3579	0.3579	0.8133	0.1448
					TagSNP	98.61	0.8027	0.366	0.3478	0.3579	0.71					
<b>miR-243</b>	isolated	R3HDM1	+	rs10795006	miRNA	98.61	0.8027	0.366	0.3478	0.3579	0.71	0.8133	0.5423	0.5423	0.8133	0.8133
					TagSNP	98.61	0.8027	0.366	0.3478	0.3579	0.71					
<b>miR-244</b>	isolated	R3HDM1	+	rs12467569	miRNA	98.61	0.2127	0.117	0.5947	0.2833	0.5423	0.235	0.8433	0.8433	0.1423	0.235
					TagSNP	98.75	0.1497	0.236	0.1073	0.8433	0.1843					
<b>miR-245</b>	isolated	R3HDM1	+	rs1446584	miRNA	97.29	0.1608	0.182	0.6414	0.05928	0.148	0.4108	0.5272	0.5272	0.4108	0.4108
					Promoter R3HDM1	98.75	0.1836	0.126	0.3326	0.08258	0.1409					
<b>miR-246</b>	isolated	R3HDM1	+	rs12467569	miRNA	98.09	0.5978	0.232	0.0687	0.9788	0.3562	0.3307	0.5272	0.5272	0.7402	0.3307
					TagSNP	98.68	0.0188	0.388	0.1272	0.5272	0.7402					

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping <sup>&amp;</sup>	HWE <sup>1</sup> (P-value)	MAF (All sample)	r <sup>2</sup> >0.8 in controls			Dutch	German	Overall
									P-values	Spanish	Dutch			
<b>miR-153-1</b>	isolated	PTPRN	-	rs1374350	miRNA	98.68	0.2996	0.209	0.85 (rs12467569)	0.09907	0.5223	0.2922	0.6634	
					TagSNP	failed	-	-	-	-	-	-	-	
					miRNA	98.53	0.2245	0.123	0.87 (rs2292601), (rs2292607)	0.4841	0.5821	0.6304	0.3725	
					TagSNP	0.87								
					miRNA	98.75	1.00	0.182	0.94 (rs448556)	0.425	0.4227	0.393	0.6341	
					TagSNP	0.94								
					miRNA	98.68	1.00	0.192	0.94 (rs4674373)	0.9076	0.594	0.2618	0.8128	
					TagSNP	0.7022	0.272		0.5037	0.2293		0.2664	0.4619	
					miRNA	98.68	0.7902	0.17	0.99 (rs2271593)	0.3797	0.4723	0.559	0.4376	
					TagSNP	0.96	0.6049	0.12	0.87 (rs1983298), (rs2292601)	0.2625	0.4231	0.8461	0.2195	
<b>miR-128-2</b>	isolated	ARPP21	+	rs9860326	miRNA	98.68	0.7902	0.171	0.99 (rs1188936)	0.4228	0.5267	0.6506	0.4708	
					TagSNP	0.93	0.2903	0.12	0.87 (rs2292607), (rs2292607)	0.3308	0.4237	0.8692	0.2624	
					Promoter	98.17								
					PTPRN									
					TagSNP									
					Promoter	98.31	0.3847	0.325		0.2281	0.907	0.5295	0.333	
					ARPP21									
					TagSNP									
					Promoter	98.61	0.2528	0.291						
					ARPP21									
<b>miR-191</b>	cluster_3-1 (miR-191, miR-425)	DALRD3- NDUFAF3	-	rs7100	TagSNP	98.61	0.2597	0.397		0.5286	0.8753	0.5443	0.9146	
					TagSNP	0.1616	0.446		0.0251	0.79		0.7568	0.09633	
					miRNA	98.46								
					TagSNP	0.1835	0.113		0.5651	0.9449		0.9964	0.7252	
					miRNA	98.68	0.0014	0.303	-	-		-		
					TagSNP	0.2429	0.168		0.05592	0.4811		0.4973	0.04525	
					miRNA	98.75								
					TagSNP	0.7794	0.284		0.5578	0.7076		0.7145	0.4344	
					miRNA	97.65								
					TagSNP	0.9194	0.239		0.2141	0.8455		0.003006	0.0395	

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping*	HWE <sup>i</sup> (P-value)	MAF (All sample)	$r^2 > 0.8$ in controls (SNP)	P-values			
										Spanish	Dutch	German	Overall
miR-16-2	cluster_3_2 (miR-16-2, miR-15b)	SMC4	+	rs11706052	miRNA TagSNP	98.75	0.0413	0.112	0.6348	0.5606	0.6288	0.3939	
				rs4680580	miRNA TagSNP	97.73	0.392	0.498	0.3971	0.6201	0.3758	0.5366	
miR-9-2	isolated	LINC00461	-	rs10936201	miRNA TagSNP	98.39	0.3506	0.238	0.1569	0.4299	0.08831	0.2715	
				rs4679883	miRNA TagSNP	93.48	0.6947	0.186	0.9704	0.01963	0.5342	0.3753	
miR-103-1	cluster_5_1 (miR-103-1, miR-103-1- as)	PANK3	-	rs13174131	miRNA TagSNP	98.61	0.4046	0.141	0.06805	0.3033	0.03797	0.2102	
				rs6882046	miRNA TagSNP	97.65	0.6451	0.305	0.3651	0.0841	0.005273	0.5857	
				rs158896	miRNA TagSNP	98.24	0.5650	0.282	0.92 (rs158895), 0.89 (rs149476)	0.8162	0.9426	0.7919	0.8214
miR-219-1	isolated	intergenic	+	rs13185224	miRNA TagSNP	98.53	0.3438	0.165	0.2714	0.107	0.0297	0.3099	
				rs158895	miRNA TagSNP	98.61	1.00	0.298	0.92 (rs158895), 0.96 (rs149476)	0.8534	0.251	0.877	0.3652
miR-133b, miR-206	cluster_6_1 (miR-133b, miR-206)	intergenic	+	rs110662	miRNA TagSNP*	98.31	0.6190	0.274	0.1545	0.8568	0.6752	0.2116	
				rs383711	miRNA TagSNP*	98.31	0.4163	0.079	0.9423	0.4904	0.8008	0.7963	
				rs107822	miRNA TagSNP*	98.61	0.2692	0.237	0.003908	0.2065	0.7143	0.008931	
				rs2854028	miRNA TagSNP*	97.65	0.0678	0.23	0.1321	0.6093	0.9201	0.1619	
				rs1413918	miRNA TagSNP	failed	-	-	-	-	-	-	
				rs1413917	miRNA TagSNP*	98.75	0.5469	0.141	0.07244	0.6047	0.379	0.1876	

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping*	HWE <sup>1</sup> (P-value)	MAF (All sample)	$r^2 > 0.8$ in controls (SNP)	P-values				
										Spanish	Dutch	German	Overall	
miR-30a, miR-30c-2	cluster_6_2 (mir-30a, mir-30c-2)	C6orf155	-	rs1192037	TagSNP					0.4148	0.8881	0.8266	0.6667	
				rs1192040	miRNA	98.68	0.3273	0.146		0.2999	0.3212	0.7339	0.2126	
				rs1322764	TagSNP	failed	-	-		-	-	-	-	
				rs1192045	miRNA	98.17	0.0175	0.083		0.05614	0.464	0.9304	0.07505	
				rs12208417	TagSNP	miRNA	98.02	0.1594	0.457		0.07401	0.954	0.7119	0.2537
				rs1727650	miRNA	98.68	0.1822	0.316		0.4363	0.3167	0.707	0.8015	
				rs9351811	miRNA	98.68	0.6126	0.077	0.81 (rs7349905)	0.5076	0.2074	0.7198	0.16	
				rs1405848	miRNA	failed	-	-		-	-	-	-	
				rs9283841	miRNA	98.75	0.0749	0.185	0.96 (rs6903167)	0.9886	0.7135	0.7759	0.7557	
				rs7349905	TagSNP	miRNA	98.75	1.00	0.064	0.81 (rs951811)	0.3977	0.435	0.5087	0.1938
				rs852932	miRNA	failed	-	-		-	-	-	-	
				rs1727668	TagSNP	Promoter	98.61	0.3654	0.227	0.9067	0.06904	0.6904	0.2692	C6orf155 TagSNP

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping <sup>&amp;</sup>	HWE <sup>1</sup> (P-value)	MAF (All sample)	r <sup>2</sup> > 0.8 in controls			German	Overall
									P-values	Spanish	Dutch		
<b>miR-93, miR-106b</b>	cluster_7.1 (mir-106b, mir-93, mir-25)	MCM7	-	rs6903167	Promoter C6orf155	98.68	0.0786	0.185	0.96 (rs9283841)	0.9941	0.5422	0.7678	0.6364
				rs4729575	TagSNP miRNA TagSNP*	97.58	0.5805	0.248		0.1435	<b>0.02556</b>	0.3635	<b>0.00648</b>
				rs4928	miRNA TagSNP*	98.75	1.00	0.058		0.1435	0.6464	0.307	0.2571
				rs72631824	Pre-miRNA SNP Pre-miRNA SNP	98.53 (monomorphic)	-	-		-	-	-	-
				rs72631827	Pre-miRNA SNP	98.68	-	<b>0.001</b>		0.9785	0.3375	-	0.5976
				rs13242458	miRNA TagSNP*	98.68	0.5749	0.1117		0.9887	0.6715	0.4489	0.9736
				rs2070215	miRNA TagSNP*	98.75	0.7815	0.28		0.3854	0.07568	0.7396	0.05979
				rs999885	miRNA TagSNP*	98.75	0.589	0.473		0.1969	0.9427	0.6049	0.2941
				rs4729577	miRNA TagSNP*	98.46	0.6335	0.413		0.6652	0.8219	0.8988	0.6117
				rs12538332	miRNA TagSNP	98.68	1.00	0.268		0.4585	0.9933	0.3544	0.3998
<b>miR-129-1</b>	isolated	intergenic	+	rs6956123	miRNA TagSNP	98.61	0.1376	0.117		0.0668	0.1339	0.8686	<b>0.02181</b>
				rs34266279	miRNA TagSNP	98.75	0.4418	0.078	0.93 (rs6467165)	0.4922	0.1779	0.06116	0.3749
				rs6467165	miRNA TagSNP	98.68	0.2102	0.084	0.93 (rs34266279)	0.0793	0.2376	0.083	0.8691
				rs4731416	miRNA TagSNP	98.61	0.8228	0.098		0.3244	0.9211	0.7637	0.458
				rs11772985	miRNA TagSNP	98.68	0.0948	0.377		0.1244	0.4159	0.4091	0.07145
				rs2060736	miRNA TagSNP	98.61	1.00	0.147		0.582	0.9222	0.9966	0.7282
				rs1451006	miRNA TagSNP	78.45	1.00	0.13		0.3612	0.3908	0.1704	0.08907
				rs11981584	miRNA TagSNP	98.53	0.3312	0.201		0.5888	0.9217	0.8125	0.6176
<b>miR-182, miR-96</b>	cluster 7.2 (miR-182, miR-96, miR-183)	intergenic	-	rs2402961	miRNA TagSNP	98.68	0.2563	0.104	<b>0.01769</b>	0.6157	0.4619	0.09999	

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping <sup>&amp;</sup>	HWE <sup>1</sup> (P-value)	MAF (All sample)	r <sup>2</sup> >0.8 in controls			P-values		
									(SNP)	(SNP)	Spanish	Dutch	German	Overall
miR-124-1	isolated			rs2402959	miRNA TagSNP	98.68	1.00	0.269		0.1158	0.3067	0.2173	0.3883	
				rs6467264	miRNA TagSNP	failed	-	-		-	-	-	-	
				rs6965643	miRNA TagSNP	failed	-	-		-	-	-	-	
				rs76481776	Pre-miRNA SNP	96.41	0.4433	0.095		0.311	0.1161	0.57	0.05838	
				rs4626538	miRNA TagSNP	98.24	0.8165	0.479		0.9295	0.9634	0.4879	0.8497	
				rs73159662	Pre-miRNA SNP	98.75	-	<b>0.006</b>		<b>0.02157</b>	0.5853	0.9716	0.1627	
				rs2693727	miRNA TagSNP	98.75	0.2469	0.101		0.2191	0.2954	0.7236	0.1021	
miR-486	isolated			rs531564	miRNA TagSNP	98.39	0.1057	0.127		0.3783	0.2812	<b>0.04504</b>	0.05938	
				rs13252510	miRNA TagSNP	96.19	0.4664	0.089		0.1689	0.4598	0.6073	0.8085	
				rs13252210	miRNA TagSNP	98.61	0.3016	0.232		<b>0.04999</b>	0.5579	0.3473	<b>0.04198</b>	
				rs4317621	miRNA TagSNP	98.02	1.00	0.455		0.2827	0.2225	0.5821	0.8729	
		ANK1		rs492083	miRNA TagSNP	98.61	0.8137	0.214		0.7323	0.2614	0.7077	0.2883	
				rs6981587	miRNA TagSNP	failed	-	-		-	-	-	-	
				rs515071	miRNA TagSNP	98.24	0.8462	0.266		0.1713	0.6693	0.2849	0.3	
				rs474059	miRNA TagSNP	98.53	0.3145	0.474		0.1738	0.7482	0.9567	0.2738	
				rs580901	miRNA TagSNP	98.53	0.5626	0.204		0.4767	0.2808	0.2998	0.4404	
miR-124-2	isolated			rs190938	miRNA TagSNP	96.33	0.904	0.193		0.05834	0.4254	0.3112	0.189	
				rs298210	miRNA TagSNP	98.39	0.5274	0.1	0.84 (rs298216)	0.1616	0.1145	1	0.9059	
				rs298212	miRNA TagSNP	98.53	0.2662	0.196		0.3378	0.07656	0.7774	0.758	
				rs72631829	Pre-miRNA SNP (monomorphic)	98.75	-	-		-	-	-	-	
				rs298216	miRNA TagSNP	98.75	0.7121	0.116	0.84 (rs298210)	0.2178	0.1519	0.7156	0.8337	

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping <sup>&amp;</sup>	HWE <sup>†</sup> (P-value)	MAF (All sample)	r <sup>2</sup> >0.8 in controls			German	Overall
									P-values	Spanish	Dutch		
<b>miR-30b, miR-30d</b>	cluster_8_1 (miR-30b, miR-30d)	intergenic	-	rs4737191	miRNA TagSNP	98.46	1.00	0.071	0.939	0.5291	0.9425	0.7064	
				rs7460121	miRNA TagSNP	98.61	0.5302	0.101	0.7639	0.5108	0.6287	0.6978	
				rs10095483	miRNA TagSNP	98.39	0.8222	0.217	0.3837	0.532	0.702	0.7181	
				rs17709119	miRNA TagSNP	98.53	0.5058	0.139	0.7309	0.5851	0.5226	0.4163	
				rs16905252	miRNA TagSNP	98.75	0.7440	0.131	0.2036	0.2748	0.1909	0.5132	
				rs10103306	miRNA TagSNP	98.68	0.3769	0.27	0.5406	0.1748	0.577	0.8436	
				rs7846345	miRNA TagSNP	98.61	0.2723	0.432	0.6457	0.05681	0.4535	0.5529	
				rs76662330	Pre-miRNA SNP (monomorphic)	-	-	-	-	-	-	-	
				rs296885	miRNA TagSNP	-	-	-	-	-	-	-	
				rs17086750	miRNA TagSNP	98.61	<b>0.0080</b>	0.135	-	-	-	-	
<b>miR-7-1</b>	isolated	HNRNPK	-	rs296889	miRNA TagSNP	97.73	0.3565	0.266	0.6288	0.429	<b>0.0197</b>	0.1003	
				rs296891	miRNA TagSNP	98.68	0.5893	0.478	0.859	0.1569	0.2693	0.1707	
				rs1362820	miRNA TagSNP	98.02	0.1281	0.079	0.3279	0.4688	0.7902	0.2345	
				rs2026618	miRNA TagSNP	98.75	0.1801	0.095	0.5006	0.4717	0.8309	0.9493	
				rs1421135	miRNA TagSNP	97.65	0.1331	0.308	0.06364	0.6174	0.6009	0.1374	
				rs4744321	miRNA TagSNP	98.53	0.0521	0.145	0.88 (rs10821312)	0.0634	0.6173	0.6006	
				rs10821311	miRNA TagSNP	98.53	0.8593	0.302	<b>0.04237</b>	0.08701	0.2048	<b>0.04121</b>	
				rs10821312	miRNA TagSNP	98.75	0.1414	0.165	0.88 (rs4744321)	0.1629	0.2131	0.6345	
												0.1323	

(Continued)

Supplementary Table 3. (Continued)

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping*	HWE <sup>i</sup> (P-value)	MAF (All sample)	$r^2 > 0.8$ in controls (SNP)	P-values			
										Spanish	Dutch	German	Overall
										0.7822	0.4817	<b>0.04583</b>	0.1924
<b>miR-146b</b>	isolated	intergenic	+	rs2814614	Promoter GRID1	98.68	0.8161	0.474					
				rs12220079	TagSNP Promoter GRID1	98.68	0.7498	0.406					
					TagSNP miRNA	98.61	0.5778	0.174					
					TagSNP miRNA	96.99	0.0557	0.346					
					TagSNP miRNA	98.75	0.4290	0.208					
					TagSNP miRNA	98.61	0.1353	0.376					
					TagSNP Pre-miRNA	98.75	1.00	<b>0.0003</b>					
					TagSNP miRNA	95.6	0.3425	0.284					
					TagSNP miRNA	94.65	<b>0.0000</b>	0.221					
					TagSNP miRNA	98.68	0.4594	0.359					
					TagSNP miRNA	98.75	0.6225	0.254					
					TagSNP miRNA	98.68	0.2678	0.227					
					TagSNP failed	-	-	-					
					TagSNP miRNA	98.68	0.5725	0.104					
					TagSNP failed	-	-	-					
					TagSNP miRNA	96.99	0.1957	0.177					
					TagSNP miRNA	95.75	0.7553	0.498					
					TagSNP failed	-	-	-					
					TagSNP miRNA	98.24	0.4676	0.154					
					TagSNP	-	-	-					
<b>miR-210</b>	isolated	MIR210HG	-	rs3740651									
					rs7935908								
					rs12286521								
					rs7936397								
					rs11037479								
					rs1483130								
					rs11606426								
					rs2679051								
					rs11037481								
					rs11235548								
					rs755933								

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping <sup>§</sup>	HWE <sup>¶</sup> (P-value)	MAF (All sample)	r <sup>2</sup> >0.8 in controls			P-values		
									HWE <sup>¶</sup> (P-value)	MAF (All sample)	r <sup>2</sup> >0.8 in controls (SNP)	Spanish	Dutch	German
miR-34b, miR-34c	cluster_11.1 (miR-34b, miR-34c)	intergenic	+	rs4938723	miRNA TagSNP	96.85	0.5160	0.384	0.7093	0.08871	0.7927	0.7927	0.7927	0.2212
miR-125b-1	isolated	MIR100HG	-	rs2081443	miRNA TagSNP	98.61	0.0856	0.174	0.3535	0.08541	0.7105	0.7105	0.7105	0.06377
miR-141, miR-200c	cluster_12.1 (miR-141, miR-200c)	intergenic	+	rs7963446	miRNA TagSNP	98.39	0.2660	0.056	0.9505	0.3016	0.4898	0.4898	0.4898	0.7438
miR-148b	isolated	COPZ1	+	rs2071079	miRNA TagSNP	98.39	0.7091	0.28	0.4728	0.3237	0.1965	0.1965	0.1965	0.1107
				rs2110073	miRNA TagSNP	98.75	0.3104	0.104	0.623	0.8836	0.6562	0.6562	0.6562	0.6869
				rs2159887	miRNA TagSNP	98.68	0.0521	0.162	0.1183	0.9726	0.2666	0.2666	0.2666	0.1318
				rs7964528	miRNA TagSNP	98.68	0.0244	0.138	0.1043	0.03704	0.3394	0.3394	0.3394	0.593
				rs6580981	miRNA TagSNP	98.61	0.7572	0.481	0.3234	0.4536	0.8314	0.8314	0.8314	0.8885

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping <sup>&amp;</sup>	HWE <sup>1</sup> (P-value)	MAF (All sample)	r <sup>2</sup> >0.8 in controls (SNP)			P-values		
									Spanish	Dutch	German	Overall		
<b>miR-16-1, miR-15a</b>	cluster_13.1 (miR-15a, miR-16-1)	DLEU2	rs74878365 rs11170877 rs72631826 rs9535416 rs2177313 rs2066575 rs12100048 MIR17HG rs6492538	Pre-miRNA SNP	failed	-	-	-	-	-	-	-	-	-
				miRNA	98.09	0.4803	0.1116	0.1068	0.4932	0.9727	0.9727	0.9727	0.1123	
				TagSNP SNP	98.75 (monomorphic)	-	-	-	-	-	-	-	-	
				miRNA	97.95	0.0202	0.496	0.7981	0.9843	0.7953	0.7953	0.7923		
				TagSNP*	-	-	-	-	-	-	-	-	-	
				miRNA	98.61	0.5386	0.138	0.81 (rs12100048)	0.634	0.9167	0.0002332	0.131		
				TagSNP	-	-	-	-	-	-	-	-	-	
				Promoter	98.75	0.5722	0.236	0.08652	0.3133	0.1059	0.1059	0.1059	0.02232	
				DLEU2	-	-	-	-	-	-	-	-	-	
				TagSNP*	-	-	-	-	-	-	-	-	-	
<b>miR-19a, miR-92a-1</b>	cluster_13.2 (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR-92a-1)	rs17642969 rs4284505 rs72631821 rs7318578	Pre-miRNA SNP	98.75	0.4813	0.1116	0.81 (rs2177313)	0.6338	0.9166	0.0004	0.1305			
			miRNA	98.61	0.8318	0.213	0.007847	0.572	0.00789	0.00789	0.00789	0.002051		
			TagSNP*	-	-	-	-	-	-	-	-	-		
			miRNA	98.02	0.2569	0.096	0.1695	0.1016	0.8068	0.8068	0.8068	0.8549		
			TagSNP*	-	-	-	-	-	-	-	-	-		
			miRNA	96.92	0.3359	0.401	0.03875	0.6485	0.1064	0.1064	0.1064	0.08381		
			TagSNP*	-	-	-	-	-	-	-	-	-		
			failed	-	-	-	-	-	-	-	-	-		

(Continued)

### Supplementary Table 3. (Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping <sup>&amp;</sup>	HWE <sup>1</sup> (P-value)	MAF (All sample)	r <sup>2</sup> >0.8 in controls			German	Overall
									P-values	Spanish	Dutch		
		rs8018238	miRNA TagSNP	98.46	0.9260	0.3	0.81 (rs8015713)	0.9626	0.3791	0.5833	0.4441		
		rs11160617	miRNA TagSNP	98.24	1.00	0.053		0.05329	0.05194	0.2961	0.5337		
		rs12590815	miRNA TagSNP	98.24	0.3231	0.384		0.2048	0.4337	0.3415	0.4929		
		rs11621499	miRNA TagSNP	98.75	0.3085	0.085		0.6904	0.5449	0.4691	0.8729		
		rs10132916	miRNA TagSNP	98.61	0.4971	0.287		0.02312	0.7414	0.5133	0.1349		
		rs4906032	miRNA failed	-	-	-		-	-	-	-		
		rs6575812	miRNA TagSNP	98.68	0.7031	0.201		0.07705	0.2485	0.9727	0.0605		
		rs4906034	miRNA TagSNP	98.75	0.0920	0.253		0.147	0.3544	0.9049	0.1355		
		rs8015875	miRNA TagSNP	98.61	0.8278	0.239		0.2845	0.4405	0.893	0.2239		
		rs8016185	miRNA TagSNP	98.61	0.7973	0.19		0.1491	0.5757	0.1074	0.4296		
		rs8016966	miRNA TagSNP	98.75	1.00	0.071		0.2123	0.6492	0.6177	0.3648		
		rs4900482	miRNA TagSNP	97.95	0.0030	0.216		-	-	-	-		
		rs2007291	miRNA TagSNP	98.39	0.9303	0.307		0.1578	0.03697	0.5401	0.01347		
		rs941714	miRNA TagSNP	98.61	0.2872	0.329		0.9896	0.1205	0.9978	0.3427		
		rs3742406	miRNA TagSNP	98.68	0.0308	0.353		0.2121	0.3351	0.5318	0.0935		
miR-190	isolated	TLN2	+ Promoter	98.39	0.2186	0.118		0.4048	0.4689	0.682	0.2456		
		rs938979	Promoter TLN2	98.61	0.6292	0.269		0.6352	0.6366	0.4756	0.374		
		rs16945790	miRNA TagSNP	98.68	0.0665	0.127	0.93 (rs16945799)	0.9772	0.1278	0.7068	0.2521		
		rs12594810	miRNA TagSNP	98.53	0.1837	0.335		0.3023	0.7329	0.04179	0.09601		
		rs3816988	miRNA TagSNP	98.68	0.7797	0.156		0.8169	0.08748	0.859	0.2199		

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping <sup>§</sup>	HWE <sup>i</sup> (P-value)	MAF (All sample)	r <sup>2</sup> >0.8 in controls			P-values		
									(SNP)	Spanish	Dutch	German	Overall	
miR-184	isolated	LOC729911	+	rs11856416	TagSNP	failed	-	-	-	-	-	-	0.06754	
				rs1048568	TagSNP	miRNA	98.68	0.4713	0.084	0.6532	0.5422	0.6657	0.3825	
				rs16945799	TagSNP	miRNA	98.68	0.1910	0.131	0.93 (rs16945790)	0.8963	0.1822	0.7698	0.3110
				rs9302287	TagSNP	miRNA	98.68	0.4758	0.477	0.51	0.2264	0.7458	0.2949	
				rs919970	TagSNP	miRNA	96.19	0.8766	0.148	0.5142	0.7474	0.9782	0.7972	
				rs41280052	Pre-miRNA	miRNA	98.24	-	0.017	0.4324	0.893	0.3279	0.534	
				rs1001460	SNP	TagSNP	98.61	0.6994	0.498	0.9599	0.6523	0.7122	0.6957	
				rs4779008	miRNA	TagSNP	97.8	0.2258	0.127	0.42	0.5434	0.1582	0.6295	
				rs16970715	miRNA	TagSNP	97.43	0.2931	0.394	0.2252	0.3664	0.002614	0.7443	
				rs11072835	miRNA	failed	-	-	-	-	-	-	-	
				rs12593742	TagSNP	miRNA	98.53	0.5502	0.063	0.5993	0.0691	0.3186	0.1607	
miR-7-2	cluster_15_1 (miR-7-2, miR-1179)	intergenic	+	rs4100934	miRNA	TagSNP	98.17	0.1308	0.422	0.2534	0.9687	0.1697	0.7019	
				rs1470108	miRNA	TagSNP	98.68	0.5492	0.351	0.4957	0.2244	0.3855	0.3312	
				rs75737367	Pre-miRNA	SNP (monomorphic)	97.07	-	-	-	-	-	-	
				rs11856451	miRNA	TagSNP	98.75	0.6472	0.308	0.5304	0.6134	0.8156	0.4584	
				rs3803528	miRNA	TagSNP	98.75	0.3877	0.422	0.5156	0.4266	0.8651	0.3216	
				NDE1	+	rs9940874	miRNA	97.51	0.7720	0.163	0.2517	0.3705	0.6151	0.6525
				rs4781677	TagSNP	miRNA	98.53	0.3396	0.232	0.225	0.8773	0.7977	0.4037	
				rs11075274	miRNA	TagSNP	98.31	0.6431	0.475	0.0777	0.7643	0.8566	0.309	

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping <sup>&amp;</sup>	HWE <sup>†</sup> (P-value)	MAF (All sample)				Spanish	Dutch	German	Overall
								r <sup>2</sup> >0.8 in controls (SNP)	MAF (All sample)	r <sup>2</sup> >0.8 in controls (SNP)	MAF (All sample)				
<b>miR-132, miR-212</b>	cluster_17.1 (miR-132, miR-212)	intergenic	-	rs877063	miRNA	98.31	0.5203	0.069	0.6543	0.4706	0.4203	0.5241			
				rs11870150	TagSNP	97.8	0.6250	0.39							
<b>miR-195</b>	cluster_17.2 (miR-195, miR-497)	intergenic	-	rs8065878	miRNA	98.61	0.3901	0.297	0.1777	0.1171	0.8778	0.06251			
				rs8065820	miRNA	98.61	1.00	0.083	0.1345	0.3488	0.754	0.1594			
<b>miR-193a</b>	isolated	intergenic	+	rs14309	miRNA	98.24	0.7298	0.135	0.2014	0.7602	0.8941	0.2932			
				rs11078662	miRNA	98.68	0.7578	0.068	0.1667	0.9646	0.4325	0.5774			
<b>miR-10a</b>	isolated	intergenic	+	rs207144	miRNA	97.73	0.8599	0.331	0.82 (rs1551360)	0.2042	0.3989	0.4240	0.5221		
				rs9908294	TagSNP	failed	-	-	-	-	-	-			
<b>miR-10a</b>	isolated	intergenic	-	rs60406007	Pre-miRNA	98.75	-	-	-	-	-	-			
				rs7216082	SNP (monomorphic)	98.39	0.3118	0.153	0.1184	0.5087	0.4042	0.3585			
<b>miR-10a</b>	isolated	intergenic	-	rs1551360	miRNA	98.68	0.4167	0.315	0.82 (rs2074144)	0.2372	0.5037	0.4455	0.5194		
				rs72631828	Pre-miRNA	98.75	-	-	-	-	-	-			
<b>miR-10a</b>	isolated	intergenic	-	rs9907987	SNP (monomorphic)	95.67	0.8083	0.087	0.9852	0.517	0.1007	0.9073			
				rs2288278	miRNA	98.17	0.1821	0.312	0.5485	0.9862	0.4791	0.5122			
<b>miR-21</b>	isolated	intergenic	+	rs2740752	miRNA	98.68	0.3156	0.154	0.4355	0.7957	0.1459	0.3675			
				rs4793944	miRNA	failed	-	-	-	-	-	-			
<b>miR-21</b>	isolated	intergenic	+	rs9299	TagSNP	98.53	0.5585	0.363	0.372	0.5878	0.9044	0.8103			
				rs1529334	miRNA	96.26	0.6899	0.185	0.3536	0.7399	0.06002	0.2883			
<b>miR-21</b>	isolated	intergenic	+	rs1292037	miRNA	98.31	0.2178	0.181	0.1275	0.04785	0.2617	0.05515			
				rs2645479	miRNA	98.75	0.6440	0.478	0.08669	0.4296	0.9405	0.0982			

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping <sup>&amp;</sup>	HWE <sup>1</sup> (P-value)	MAF (All sample)	r <sup>2</sup> >0.8 in controls			Spanish	Dutch	German	Overall	
									P-values							
<b>miR-1-2</b>	cluster_18.1 (miR-1-2, miR133a-1)	MIB1 (-)	-	rs8092100	miRNA TagSNP	98.46	0.6840	0.107	0.5751	0.3033	0.3473	0.9034				
				rs12968949	miRNA TagSNP	98.53	0.7494	0.229	0.8377	0.9995	0.01772	0.3449				
				rs3810042	miRNA TagSNP	98.68	0.9313	0.339	0.5952	0.8695	0.01544	0.6942				
				rs11660303	miRNA TagSNP	98.31	0.4338	0.224	0.3179	0.6844	0.08142	0.8632				
<b>miR-7-3</b>	isolated	MIR7-3HG	+	rs12979279	miRNA TagSNP	98.75	0.1205	0.203	0.82 (rs11668223)	0.7586	0.6522	0.2366	0.9233			
				rs11668223	miRNA TagSNP	98.68	0.1591	0.205	0.82 (rs12979279)	0.8402	0.6004	0.1673	0.7973			
				rs879564	miRNA TagSNP	98.68	0.2591	0.393	0.653	0.4345	0.4136	0.9451				
				rs76199191	Pre-miRNA SNP (monomorphic)	98.75	-	-	-	-	-	-	-			
				rs2885717	miRNA TagSNP	98.46	0.0211	0.384	0.9616	0.6851	0.09343	0.4079				
				rs12462204	miRNA failed	-	-	-	-	-	-	-	-			
				rs12610046	miRNA TagSNP	98.53	0.0367	0.47	0.8216	0.799	0.1316	0.8049				
<b>miR-199a-1</b>	isolated	DNM2 (-)	-	rs3786719	miRNA TagSNP	98.53	0.0823	0.34	0.81 (rs11085748)	0.1512	0.6787	0.0729	0.4982			
				rs11085748	miRNA TagSNP	98.68	0.1935	0.297	0.81 (rs3786719)	0.2408	0.6698	0.05101	0.6555			
<b>miR-27a, miR-23a, miR-24-2</b>	cluster_19.1 (miR-23a, miR-27a, miR-24-2)	intergenic	-	rs12979166	miRNA TagSNP	98.24	0.5328	0.31	0.8521	0.2381	0.8514	0.5526				
				rs895819	Pre-miRNA SNP	failed	-	-	-	-	-	-	-			
				rs1531212	miRNA TagSNP	98.39	0.4969	0.209	0.5267	0.05167	0.4927	0.2641				
<b>miR-181c</b>	cluster_19.2 (miR-181c, miR-181d)	intergenic	+	rs8107465	miRNA TagSNP	98.61	1.00	0.446	0.4065	0.7607	0.9572	0.4516				
				rs11880167	miRNA TagSNP	98.39	0.2024	0.144	0.2441	0.9592	0.3666	0.7025				
				rs10413657	miRNA TagSNP	98.39	0.1907	0.211	0.1241	0.5119	0.6296	0.4409				
<b>miR-103-2</b>	cluster_20.1 (miR103-2, miR103-2-as)	PANK2	+	rs6052147	Promoter PANK2 TagSNP	98.75	0.6495	0.101	0.4987	0.6575	0.2981	0.2582				

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping <sup>&amp;</sup>	HWE <sup>1</sup> (P-value)	MAF (All sample)	r <sup>2</sup> >0.8 in controls			Spanish	Dutch	German	Overall	P-values
									HWE <sup>1</sup> (P-value)	MAF (All sample)	r <sup>2</sup> >0.8 in controls (SNP)					
<b>miR-1-1</b>	isolated	C20orf166	+	rs12480683	Promoter PANK2	98.75	0.5700	0.291				0.8165	0.7126	0.2818	0.4479	
				rs6084506	Promoter PANK2	98.68	0.7393	0.368				0.3673	0.09084	0.6574	0.797	
				rs2282131	TagSNP miRNA	98.61	0.5700	0.279				0.1906	<b>0.03178</b>	0.3901	0.482	
				rs4815627	TagSNP miRNA	98.75	0.8170	0.477				0.4708	0.07411	0.7099	0.4667	
				rs12479469	TagSNP miRNA	98.24	0.5352	0.328				0.2796	0.7588	0.9697	0.3692	
		intergenic	+	rs6062277	TagSNP miRNA	98.39	0.0298	0.452				0.2946	0.296	0.4665	0.1005	
				rs6062275	TagSNP miRNA	98.17	0.2573	0.333				0.8605	0.815	0.9978	0.967	
				rs6062266	TagSNP miRNA	98.53	1.00	0.291				0.7287	0.9204	0.5252	0.9734	
				rs6062830	TagSNP miRNA	98.46	0.5665	0.374				0.6898	0.7402	0.1262	0.5386	
				rs6122389	TagSNP miRNA	98.61	0.1561	0.303				<b>0.0453</b>	0.5952	0.6805	0.0595	
<b>miR-124-3</b>	isolated	LINC00478	+	rs6122390	TagSNP miRNA	98.46	0.7211	0.305				0.2611	0.305	0.1682	0.3242	
				rs34059726	Pre-miRNA failed		-	-				-	-	-	-	
				rs2823592	Promoter1 c21orf34	98.39	0.7361	0.351				0.9457	0.6808	0.7298	0.7071	
				rs2823593	Promoter1 c21orf34	98.46	0.8761	0.443				0.5103	0.9936	0.5501	0.5249	
				rs9984017	Promoter1 c21orf34	98.75	1.00	0.069				<b>0.04074</b>	0.3039	0.7515	0.3502	
<b>miR-125b-2</b>	isolated	LINC00478	+	rs2823635	Promoter2 c21orf34	97.95	0.3037	0.419				0.6798	0.0525	0.3577	0.2315	
				rs17210190	TagSNP miRNA	98.75	0.4726	0.065				0.772	<b>0.03156</b>	0.2461	0.1191	
				rs7279730	TagSNP miRNA	98.24	0.7265	0.131				0.6163	0.06612	0.8676	0.5293	
				rs915860	TagSNP miRNA	98.68	-	0.055				<b>0.4547</b>	0.8788	0.6732	0.7262	

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping <sup>&amp;</sup>	HWE <sup>1</sup> (P-value)	MAF (All sample)	r <sup>2</sup> >0.8 in controls			P-values		
									HWE <sup>1</sup> (P-value)	MAF (All sample)	r <sup>2</sup> >0.8 in controls (SNP)	Spanish	Dutch	German
<b>miR-185</b>	isolated	TANGO2	+	rs928883	miRNA TagSNP	98.31	0.8689	0.134	0.3413	0.7865	0.7213	0.6975		
				rs2829803	miRNA TagSNP	98.46	0.2874	0.277	0.8506	0.7792	0.1951	0.8769		
				rs2531716	miRNA TagSNP	95.75	0.6685	0.253	0.1899	0.2549	0.2505	0.2336		
				rs2518827	miRNA TagSNP	98.68	0.2016	0.068	0.515	0.5382	0.4002	0.6307		
				rs2518829	miRNA TagSNP	98.68	0.5485	0.334	0.9009	0.8164	0.1904	0.4748		
				rs9606211	miRNA TagSNP	98.61	0.5122	0.384	0.415	0.4573	0.06659	0.5872		
<b>miR-659</b>	cluster_22.1 (mir-658, mir-659)	intergenic	-	rs9606213	miRNA TagSNP	98.39	0.1421	0.488	0.7316	0.6922	0.5713	0.8334		
				rs750504	miRNA TagSNP	98.61	0.9372	0.439	0.80 (rs2157472)	0.8355	0.3127	0.05828	0.2312	
				rs4821721	miRNA TagSNP	98.68	0.8449	0.106	0.4216	0.5663	0.879	0.3386		
				rs2157472	miRNA TagSNP	98.53	1.00	0.379	0.80 (rs5750504)	0.3302	0.5201	0.1710	0.8168	
				rs6007640	miRNA TagSNP	failed	-	-	-	-	-	-	-	
				rs12170325	miRNA TagSNP	96.19	0.5143	0.191	0.9726	0.1637	0.6214	0.2832		
<b>let-7a-3, let-7b</b>	cluster_22.2 (let-7a-3, let-7b)	MIRLET7BHG	+	rs11090910	miRNA TagSNP	98.46	0.2576	0.256	0.8376	0.2222	0.7724	0.4331		
				rs11090911	miRNA TagSNP	98.75	1.00	0.06	0.5235	0.8139	0.165	0.9695		
				rs4823529	miRNA TagSNP	98.68	1.00	0.08	0.5239	0.0357	0.4502	0.5164		
				rs5768746	miRNA TagSNP	98.02	<b>0.005</b>	0.053	-	-	-	-		
				rs151259	Promoter CLCN5 TagSNP	97.58	0.8731	0.259	0.4628	0.6527	0.6012	0.9574		

(Continued)

Supplementary Table 3. (Continued)

Selected miRNAs	Clustering	Host Gene	Strand	SNP	SNP_type	Genotyping <sup>&amp;</sup>	HWE <sup>†</sup> (P-value)		MAF (All sample) (SNP)	$r^2 > 0.8$ in controls	P-values		
							HWE <sup>†</sup> (P-value)	MAF (All sample) (SNP)			Spanish	Dutch	German
				rs5906695	Promoter CLCN5	98.31	0.0949	0.205	0.6343	0.8638	0.9604	0.654	
				rs10521460	TagSNP miRNA failed	-	-	-	-	-	-	-	
				rs179824	miRNA TagSNP	98.61	0.5834	0.49	0.4609	0.9704	0.7855	0.5755	
				rs179830	miRNA TagSNP	98.46	0.444	0.185	0.1166	0.8616	0.7073	0.4179	
				rs12387959	miRNA TagSNP	98.68	0.4875	0.238	0.7965	0.817	0.4322	0.7958	
<b>let-7f-2</b>	cluster_X_2 (let-7f-2, miR-98)	HUWE1	-	rs5978136	miRNA TagSNP	98.39	0.9076	0.461	0.97 (rs6638417)	0.3512	0.0573	0.3724	0.3724
				rs6638417	Promoter HUWE1	98.53	1.00	0.454	0.97 (rs5978136)	0.2921	0.0366	0.4605	0.3809
				rs12853099	Promoter HUWE1	98.68	1.00	0.134	0.8607	0.0437	0.4879	0.128	
<b>miR-325</b>	isolated	intergenic	-	rs7049980	miRNA TagSNP	98.53	0.529	0.147	0.7412	0.2684	0.4378	0.2235	
				rs72631830	Pre-miRNA SNP (monomorphic)	98.68 98.61	-	-	-	-	-	-	
<b>miR-92a-2</b>	cluster_X_3 (hsa-mir- 106a, miR-18b, hsa-mir-20b, hsa-mir- 19b-2, hsa-mir- 92a-2, hsa-mir-363)	intergenic	-	rs6638179	miRNA TagSNP	0.1505	0.086	0.91 (rs5977965)	0.5844	0.9836	0.5326	0.5495	
				rs5977965	miRNA TagSNP	98.68	0.1487	0.086	0.91 (rs6638179)	0.3219	0.7357	0.5326	0.2836

<sup>†</sup>HWE test performed in the control sample. P-values < 0.01 are in bold.

(-), the miRNA is transcribed from the opposite strand of the host gene.

\*, TagSNP included in the replication study.

&amp;, Genotyping column shows success Rate (%), Failed SNPs or Monomorphic SNPs.

Supplementary Table 4. Assessment of population stratification using 44 unlinked SNPs in our European sample of 636 cases and 673 controls with the STRUCTURE v2.3 software.

Number of subpopulations (K)	LnP(D) <sup>a</sup>	SD [Ln(P)] <sup>b</sup>	Posterior probability of K <sup>c</sup>
1	-59615.7	0.10	1
2	-59655.8	31.1	3.72e-18
3	-60766.5	685.2	<1.0e-306
4	-60279.8	458.1	3.9e-289

<sup>a</sup>, Ln of the probability of the data, calculated as an average of five independent iterations, with burning period and number of MCMC repeats set to 10,000. An admixture ancestry model with correlated allele frequencies ( $\lambda = 1$ ) was assumed.

<sup>b</sup>, Standard Deviation of the five LnP(D) iterations.

<sup>c</sup>, Calculated using Bayes' rule.

Supplementary Table 5. Primers and conditions used for PCR amplification in the mutational screening of miRNA genes associated with ASD in our case-control association study.

Amplified miRNA gene	Primers	T1	T2
<i>miR-133b</i>	F: ACATTCTGGACAAGGCAAGC R: TGTGTTGAGCATTAAAATCTTGCT	64°C	57°C
<i>miR-206</i>	F: GAATAAGCCAGGGAAACGTG F: CTCAAGAGGGGGAGATAGGG	64°C	57°C
<i>miR-17, miR-18<sup>o</sup>, miR-19<sup>o</sup>,</i> <i>miR-20<sup>o</sup>, miR-19b-1, miR92a-1</i>	F: CCCCATTAGGGATTATGCTG R: GCAACCCCCAAAGTGAAATG	64°C	57°C

All PCR amplifications were performed under the following conditions:

15μl final volume.

30 ng of genomic DNA.

0.25μM of each primer.

0.45U of GoTaq® DNA polymerase (Promega, Madison, WI, USA).

2 mM MgCl<sub>2</sub> Solution (Promega).

3 μM 5X GoTaq® Flexi Buffer (Promega).

Cycles were performed with a touch-down protocol (14 cycles of 1' at 95°C, 30" at T1-0.5°C/cycle, 30" at 72°C, followed by 30 cycles of 1' at 95°C, 30" at T2, 30" at 72°C).

Supplementary Table 6. Statistics for the ‘callability’ of each sample under study in %. ‘Callability’ is defined as the percentage of the exome covered by at least 10 reads with a mapping quality score greater than 30, and with a base quality phred-score greater than 20. The first column lists the family ID (Fam\_ID) and the second the family type; the following columns list every single individual.

Fam_ID	Family Type	Father (.1)	Mother (.2)	Sib1 (.3)	Sib2 (.4)	Sib3 (.5)
MT_28	M	87.02	86.59	86.45	88.09	
SJD_49	M	83.91	79.14	81.44	82.80	
MT_151	M	88.30	88.00	88.60	89.10	
SJD_10	M	87.81	86.96	89.31	89.25	
MT_69	M	80.80	75.89	75.25	80.01	
MT_109	M	87.78	88.42	85.91	83.80	
SJD_50	M	85.90	86.28	85.80	84.17	85.13
SJD_34	M	77.70	73.64	75.76	75.70	
MT_160	M	78.03	78.25	79.22	79.34	
MT_76	M	87.59	84.56	89.93	78.82	
MT_107	S	84.42	81.96	84.26		
MT_110	S	83.35	49.90	83.28		
MT_120	S	85.80	87.11	86.02		
MT_121	S	83.93	81.90	84.22		
MT_128	S	70.26	78.94	82.74		
MT_168	S	83.47	87.83	87.67		
MT_42	S	83.67	78.32	80.98		
MT_46	S	83.91	84.82	81.01		
MT_67	S	83.49	84.11	85.84		
MT_85	S	83.04	85.50	83.60		
SJD_15	S	78.14	78.11	78.75		
SJD_18	S	82.22	82.70	82.42		
SJD_22	S	83.33	79.96	82.78		
SJD_23	S	81.80	81.98	81.25		
SJD_33	S	78.71	78.44	82.95		
SJD_3	S	78.40	78.75	80.28		
SJD_45	S	84.00	84.63	84.45		
SJD_58	S	85.41	83.99	85.08		
SJD_59	S	84.64	84.74	82.92		
SJD_61	S	83.27	84.06	84.57		

M, Multiplex family.

S, Singleton family.

Supplementary Table 7. Results of the case-control association study in the replication sample. Nominal P-values < 0.05 are indicated in bold.

miRNA gene	SNP	Alleles	MA	Genotyping Success Rate (%)	HWE <sup>1</sup> (P-value)	MAF Cases	MAF Controls	P-values			
								German	Spanish	Italian	Overall
miR-219-1	rs110662	C/T	C	99.31	1	0.22	0.24	0.595	0.171	0.239	0.154
	rs383711*			-	-	-	-	-	-	-	-
	rs107822	A/G	A	99.88	0.41	0.24	0.24	0.525	0.804	0.916	0.645
	rs2854028	A/G	A	99.07	0.23	0.28	0.24	0.667	0.853	<b>0.046</b>	0.059
cluster_6.1 (miR-133b, miR-206)	rs1413917	A/G	G	99.88	0.27	0.15	0.13	0.898	0.881	0.238	0.216
	rs9370102	A/G	A	99.77	0.38	0.29	0.34	0.953	0.072	0.082	<b>0.029</b>
	rs17640030	G/T	T	99.77	0.6	0.13	0.11	0.83	0.639	0.305	0.236
	rs1892275	C/T	C	100	1	0.07	0.09	0.21	0.85	0.824	0.437
	rs16882131	C/T	T	99.65	0.91	0.29	0.31	0.155	0.503	0.877	0.51
	rs1537670	C/T	C	100	0.65	0.05	0.06	<b>0.031</b>	0.42	0.849	0.391
	rs17578851	C/T	T	99.19	0.37	0.19	0.21	0.309	0.91	0.595	0.453
	rs10484882	C/T	T	100	1	0.1	0.1	0.355	0.61	1	0.561
	rs3789779	C/T	T	99.65	0.14	0.22	0.24	0.452	<b>0.043</b>	0.836	0.457
	rs12153884	A/C	C	99.77	0.67	0.37	0.37	0.856	0.16	0.292	0.977
cluster_7.1 (mir-106b, mir-93, mir-25)	rs4729575	G/T	T	99.07	0.4	0.29	0.29	0.086	0.528	0.54	0.908
	rs4928	C/G	G	99.88	0.55	0.05	0.04	0.915	0.312	0.932	0.611
	rs13242458	A/G	A	99.88	1	0.1	0.15	0.241	0.171	0.102	<b>0.011</b>
	rs2070215	A/G	G	99.77	0.21	0.26	0.26	0.958	0.065	0.155	0.773
	rs999885	C/T	C	99.88	0.92	0.39	0.45	0.253	<b>0.042</b>	0.75	0.879
miR-129-2	rs4729577	C/T	T	99.88	0.68	0.39	0.41	0.509	<b>0.006</b>	0.779	0.468
	rs11037479	C/T	C	100	0.39	0.23	0.22	0.65	0.527	0.186	0.53
	rs11606426	A/G	G	99.88	0.4	0.1	0.1	0.509	0.708	0.423	0.992
cluster_13.1 (miR-15a, miR-16-1)	rs11037481	A/G	G	99.88	0.38	0.19	0.17	1	0.689	0.158	0.182
	rs9535416	A/G	A	99.88	1	0.48	0.49	0.208	0.533	0.963	0.303
cluster_13.2 (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR92a-1)	rs2177313*			-	-	-	-	-	-	-	-
	rs2066575	A/T	A	100	0.49	0.23	0.23	0.619	0.917	<b>0.515</b>	0.989
	rs6492538	A/C	A	100	0.43	0.16	0.19	0.82	0.749	0.06	0.186
	rs17642969	C/T	C	99.88	0.41	0.11	0.1	0.292	0.707	0.511	0.729
	rs4284505	A/G	A	100	0.31	0.37	0.4	0.58	0.516	0.194	0.16
	rs7318578	A/C	C	99.77	1	0.26	0.29	0.712	0.415	0.11	0.176

MA, Minor Allele.

MAF, Minor Allele frequency.

\*, Out of the genotyping design.

<sup>1</sup>, HWE test performed in the whole control sample.

Supplementary Table 8. Results of the case-control association study in each European population and in the pooled sample from the discovery and replication phases. Nominal P-values < 0.05 are in bold.

miRNA genes	SNP	Spanish			Dutch			German			Italian			Overall			
		MAF Ca	MAF Co	P-values	MAF Ca	MAF Co	P-values	MAF Ca	MAF Co	P-values	MAF Ca	MAF Co	P-values	MAF Ca	MAF Co	P-values	Perm-P
miR-219-1	rs1106622	0.27	0.26	0.4958	0.28	0.27	0.85568	0.29	0.27	0.521	0.18	0.21	0.239	0.26	0.26	0.9567	1
	rs107822	0.20	0.25	<b>0.0208</b>	0.24	0.28	0.2065	0.25	0.23	0.4548	0.23	0.23	0.916	0.23	0.25	0.08892	0.8767
cluster_6.1 (miR-133b, miR-206)	rs2854028	0.26	0.23	0.164	0.22	0.20	0.6093	0.24	0.23	0.6825	0.30	0.23	<b>0.046</b>	0.26	0.23	<b>0.0203</b>	0.3869
	rs1413917	0.13	0.15	0.1471	0.14	0.15	0.6047	0.13	0.12	0.4711	0.17	0.14	0.238	0.14	0.14	0.8135	1
cluster_7.1 (mir-106b, mir-93, mir-25)	rs9370102	0.32	0.32	0.7766	0.28	0.29	0.8881	0.29	0.30	0.8597	0.29	0.34	0.082	0.30	0.31	0.2961	0.9995
	rs17640030	0.10	0.14	<b>0.0048</b>	0.11	0.12	0.8468	0.12	0.09	0.2417	0.14	0.11	0.305	0.11	0.12	0.3963	1
	rs1892275	0.08	0.09	0.3437	0.08	0.09	0.4337	0.07	0.10	0.08101	0.08	0.07	0.824	0.07	0.09	0.08876	0.8761
	rs16882131	0.27	0.33	<b>0.0039</b>	0.28	0.29	0.6615	0.26	0.34	<b>0.0193</b>	0.28	0.29	0.877	0.27	0.32	<b>0.0016</b>	<b>0.0373</b>
	rs1537670	0.06	0.06	0.6033	0.07	0.08	0.7391	0.04	0.11	<b>0.0099</b>	0.04	0.04	0.849	0.05	0.07	<b>0.0244</b>	0.4458
	rs17578831	0.17	0.23	<b>0.0023</b>	0.15	0.16	0.6054	0.16	0.17	0.716	0.21	0.22	0.595	0.17	0.20	<b>0.0152</b>	0.3039
	rs10484882	0.10	0.10	0.8615	0.12	0.13	0.772	0.10	0.16	<b>0.0059</b>	0.08	0.08	1.000	0.10	0.12	0.06867	0.8042
	rs3789779	0.25	0.24	0.6639	0.24	0.24	0.9003	0.25	0.22	0.4474	0.22	0.23	0.836	0.24	0.23	0.6039	1
	rs12153884	0.37	0.36	0.6804	0.40	0.41	0.8449	0.38	0.43	0.2202	0.37	0.34	0.292	0.38	0.38	0.9305	1
	rs4729575	0.30	0.27	0.1126	0.25	0.19	0.02556	0.21	0.23	0.4699	0.33	0.31	0.540	0.28	0.25	<b>0.0236</b>	0.436
cluster_7.1 (mir-106b, mir-93, mir-25)	rs4928	0.06	0.07	0.39	0.05	0.05	0.6464	0.04	0.05	0.6165	0.05	0.05	0.932	0.05	0.06	0.5217	1
	rs13242458	0.12	0.13	0.4582	0.10	0.09	0.6715	0.11	0.15	0.1588	0.10	0.14	0.102	0.11	0.13	0.09851	0.9002
	rs2070215	0.26	0.26	0.9042	0.27	0.33	0.07568	0.28	0.29	0.7889	0.23	0.27	0.155	0.26	0.28	0.08836	0.8751
	rs999885	0.43	0.48	<b>0.0352</b>	0.48	0.48	0.9427	0.49	0.47	0.564	0.44	0.43	0.750	0.46	0.47	0.3315	0.9999
	rs4729577	0.37	0.41	0.09558	0.43	0.44	0.8219	0.44	0.42	0.6517	0.39	0.38	0.779	0.40	0.41	0.3633	1
miR-129-2	rs11037479	0.22	0.23	0.8308	0.22	0.21	0.7151	0.22	0.22	0.787	0.27	0.22	0.186	0.23	0.22	0.5232	1
	rs11606426	0.08	0.12	<b>0.0084</b>	0.10	0.10	0.9703	0.08	0.10	0.4545	0.11	0.09	0.423	0.09	0.11	0.1102	0.9235
	rs11037481	0.14	0.17	0.07701	0.21	0.19	0.3321	0.19	0.19	0.981	0.22	0.18	0.158	0.18	0.18	0.8629	1
	rs9355416	0.49	0.47	0.5904	0.49	0.49	0.9843	0.47	0.50	0.2494	0.49	0.49	0.963	0.51	0.49	0.3773	1
cluster_13.1 (miR-15a, miR-16-1)	rs2066575	0.21	0.18	0.11162	0.31	0.28	0.3133	0.28	0.23	0.151	0.22	0.24	0.515	0.25	0.22	0.07456	0.8294
cluster_13.2 (miR-17, miR-18a, miR-19a, miR-20a, miR-19a-1, miR-92a-1)	rs6492538	0.16	0.20	<b>0.0122</b>	0.24	0.26	0.572	0.19	0.23	0.1543	0.14	0.19	0.060	0.18	0.22	<b>0.0008</b>	<b>0.019</b>

MAF Ca, Minor Allele frequency in cases.

MAF Co, Minor Allele frequency in controls.

Supplementary Table 9. The genes regulated by the clusters miR-133b/miR-206 and miR-17/miR-18a/miR-19a/miR-20a/miR-19b-1/miR92a-1 were pooled together to analyse the biological categories enriched in Gene Ontology. The ten most significant categories for ‘molecular function’, ‘cellular component’ and ‘biological process’ were considered in this analysis.

Molecular function	GO number	Genes	P-value	Adjusted P-value
growth factor binding	0019838	BMPR2, CTGF, HOXA5, NR4A2, RUNX1, TGFBR2, THBS1	0.000002865	0.000002819
protein kinase binding	0019901	CCND1, HOXA5, MAP3K12, NR4A2, TGFBR2, VIM	0.0003614	0.00007427
glycosaminoglycan binding	0005539	CTGF, FSTL1, HOXA5, TGFBR2, THBS1, VEGFA	0.0003081	0.00007427
ligand-dependent nuclear receptor activity	0004879	E2F1, ESR1, HOXA5, MEF2D, NR4A2, PITX3, RUNX1	0.0003774	0.00007427
sequence-specific DNA binding	0043565	E2F1, ERG, ESR1, HOXA5, MECP2, MEF2D, NR4A2, PITX3, RUNX1, SRF	0.0002651	0.00007427
polysaccharide binding	0030247	CTGF, FSTL1, HOXA5, TGFBR2, THBS1, VEGFA	0.0006328	0.0001038
kinase binding	0019900	CCND1, HOXA5, MAP3K12, NR4A2, TGFBR2, VIM	0.000001053	0.000148
protein kinase regulator activity	0019887	CCND1, CDKN1A, HCN2, HCN4, HOXA5	0.000001961	0.0002144
protein complex binding	0032403	CCND1, CDKN1A, CTGF, HOXA5, ITGA5, THBS1	0.000001833	0.0002144
enzyme binding	0019899	BCL2, CCND1, HOXA5, MAP3K12, MECP2, NR4A2, TGFBR2, VIM	0.000003972	0.0003006
Cellular Component	GO number	Genes	P-value	Adjusted P-value
external side of plasma membrane	0009897	HOXA5, ITGA5, NR4A2, RUNX1, S1PR1, TGFBR2, THBS1, TNF	0.0000002214	0.00005113
cell surface	0009986	BMPR2, HOXA5, ITGA5, NR4A2, RUNX1, S1PR1, TGFBR2, THBS1, TNF, VEGFA	0.0000005694	0.00006576
axon	0030424	BACE1, ESR1, HCN4, HOXA5, MAP3K12, TAC1, VIM	0.00002439	0.000001878
cell projection	0042995	BACE1, ESR1, HCN4, HOXA5, ITGA5, MAP3K12, MET, NR4A2, TAC1, UTRN, VIM	0.0001103	0.000006368
neuron projection membrane raft	0043005	BACE1, ESR1, HCN4, HOXA5, MAP3K12, TAC1, UTRN, VIM	0.0003369	0.00001556
axon part	0045121	BMPR2, ERBB4, GJA1, KRAS, TGFBR2, TNF	0.0004726	0.0000182
extracellular space	0033267	ESR1, HCN4, HOXA5, MAP3K12	0.000005237	0.0001728
cAMP-dependent protein kinase complex	0005615	FSTL1, HOXA5, IL8, NR4A2, RUNX1, TAC1, THBS1, TNF, VEGFA	0.00000707	0.0002041
membrane fraction	0005952	HCN2, HCN4, HOXA5	0.0000122	0.000313
membrane fraction	0005624	BACE1, BCL2, HOXA5, ITGA5, KRAS, MAP3K12, MET, NR4A2, UTRN	0.00002007	0.0004593
Biological Process	GO number	Genes	P-value	Adjusted P-value
organ morphogenesis	0009887	BCL2, BDNF, BMPR2, CCND1, CDKN1A, CTGF, E2F1, ERBB4, HOXA5, IL8, MEF2D, NR4A2, PITX3, PTEN, RUNX1, S1PR1, SRF, TGFBR2, THBS1, TNF, VEGFA	7.49E-20	1.64E-16
cell migration	0016477	BCL2, CTGF, E2F1, ERBB4, HOXA5, IL8, ITGA5, MET, NR4A2, PTEN, S1PR1, SRF, TAC1, THBS1, TNF, VEGFA	7.97E-18	8.73E-12
cellular component movement	0006928	BCL2, BDNF, CTGF, E2F1, ERBB4, HOXA5, IL8, ITGA5, MET, NR4A2, PTEN, S1PR1, SRF, TAC1, THBS1, TNF, VEGFA, VIM	4.34E-14	3.17E-11
regulation of cell proliferation	0042127	BCL2, BDNF, BMPR2, CCND1, CDKN1A, E2F1, ERBB4, GJA1, HOXA5, IL8, KRAS, NR4A2, PTEN, S1PR1, TAC1, TGFBR2, THBS1, TNF, VEGFA	9.27E-14	5.08E-11
cell motility	0048870	BCL2, CTGF, E2F1, ERBB4, HOXA5, IL8, ITGA5, MET, NR4A2, PTEN, S1PR1, SRF, TAC1, THBS1, TNF, VEGFA	1.43E-13	6.30E-11
response to hormone stimulus	0009725	BCL2, CCND1, CDKN1A, ERBB4, ESR1, HOXA5, KRAS, NR4A2, PTEN, SRF, TAC1, TGFBR2, THBS1, TNF	4.28E-12	1.56E-09
behavior	0007610	BCL2, CCND1, CDKN1A, ERBB4, ESR1, HOXA5, KRAS, NR4A2, PTEN, SRF, TAC1, TGFBR2, THBS1, TNF	3.18E-11	9.94E-09
regulation of locomotion	0040012	BCL2, E2F1, ERBB4, HOXA5, IL8, NR4A2, PTEN, S1PR1, TAC1, THBS1, VEGFA	4.06E-11	1.11E-08
regulation of developmental process	0050793	BCL2, BDNF, BMPR2, CCND1, CDKN1A, E2F1, ERBB4, ESR1, HOXA5, KRAS, NR4A2, PTEN, RUNX1, SRF, TGFBR2, THBS1, TNF, VEGFA	5.55E-14	1.35E-08
response to steroid hormone stimulus	0048545	BCL2, CCND1, CDKN1A, ERBB4, ESR1, KRAS, NR4A2, PTEN, TGFBR2, THBS1, TNF	8.50E-11	1.86E-08

Supplementary Table 10. Rare variants identified by whole-exome sequencing (WES) in miRNA genes not transmitted to affected siblings by parents. Thirty families (20 singletons and 10 multiplex) were included in this study.

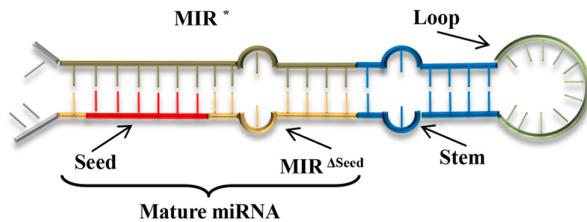
Chr	Genomic position (GRCh37/hg19)	Pre-miRNA						Conservation
		Expected	Found	gene	Fam_Type	Origin		
4	38869742	A	G	MIR574	S	Mother	Not conserved	
5	159912376	CTTT	CTT	MIR146A	S	Father	Conserved	
8	141742707	T	C	MIR151	S	Father	Conserved	
9	96938681	C	G	MIRLET7F1	S	Father	Not conserved	
11	111383694	A	T	MIR34B	S	Father	Conserved	
14	101377518	C	T	MIR370	S	Mother	Not conserved	
15	55665200	T	C	MIR628	S	Mother	Not conserved	
17	79099712	G	C	MIR338	S	Mother	Not conserved	
19	54210774	T	G	MIR520C	M	Father	Not conserved	
19	54206067	G	A	MIR518B	S	Father	Not conserved	
20	33578253	C	A	MIR499	S	Father	Conserved	
22	23165356	C	T	MIR650	M	Father	Conserved	

M, Multiplex family.

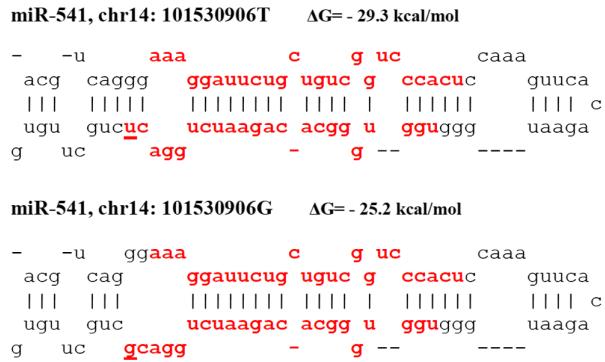
S, Singleton family.

Supplementary Table 11. Comparison of all enriched categories between the two pools of miRNAs which rare variants were either transmitted or not transmitted by parents to affected sibs. The range of P-values for each category as calculated with Ingenuity Pathway Analysis are shown.

Enriched Category	Pool	P-value Max	P-value Min
Hereditary Disorder	Transmitted	5.63E-07	1.49E-02
Hereditary Disorder	Not transmitted	9.58E-05	2.15E-02
Skeletal and Muscular Disorders	Transmitted	5.63E-07	4.03E-02
Skeletal and Muscular Disorders	Not transmitted	9.58E-05	2.77E-02
Developmental Disorder	Transmitted	6.01E-07	1.49E-02
Developmental Disorder	Not transmitted	9.58E-05	2.15E-02
Connective Tissue Disorders	Transmitted	1.12E-05	2.77E-02
Connective Tissue Disorders	Not transmitted	1.02E-04	2.77E-02
Inflammatory Disease	Transmitted	1.12E-05	2.77E-02
Inflammatory Disease	Not transmitted	3.93E-05	4.59E-02
Inflammatory Response	Transmitted	1.12E-05	1.12E-05
Inflammatory Response	Not transmitted	9.44E-04	4.59E-02
Organismal Injury and Abnormalities	Transmitted	1.12E-05	1.12E-05
Organismal Injury and Abnormalities	Not transmitted	9.44E-04	9.44E-04
Respiratory Disease	Transmitted	1.12E-05	1.12E-05
Respiratory Disease	Not transmitted	2.51E-04	5.30E-03
Neurological Disease	Transmitted	1.16E-04	5.78E-03
Neurological Disease	Not transmitted	4.83E-04	5.78E-03
Psychological Disorders	Transmitted	1.16E-04	1.16E-04
Psychological Disorders	Not transmitted	3.25E-03	3.25E-03
Dermatological Diseases and Conditions	Transmitted	1.30E-04	2.77E-02
Dermatological Diseases and Conditions	Not transmitted	1.30E-04	2.77E-02
Cancer	Transmitted	4.83E-04	2.67E-02
Cancer	Not transmitted	2.20E-06	5.00E-02
Cell Death and Survival	Transmitted	4.83E-04	1.82E-02
Cell Death and Survival	Not transmitted	2.41E-03	4.96E-02
Hematological Disease	Transmitted	4.83E-04	4.83E-04
Hematological Disease	Not transmitted	1.75E-03	2.72E-02
Immunological Disease	Transmitted	4.83E-04	4.83E-04
Immunological Disease	Not transmitted	3.86E-03	2.72E-02
Cellular Development	Transmitted	9.66E-04	3.75E-02
Cellular Development	Not transmitted	2.41E-03	3.10E-02
Cellular Growth and Proliferation	Transmitted	9.66E-04	3.75E-02
Cellular Growth and Proliferation	Not transmitted	2.41E-03	2.34E-02
Organ Morphology	Transmitted	1.45E-03	1.45E-03
Organ Morphology	Not transmitted	1.93E-03	4.17E-02
Cell Cycle	Transmitted	1.93E-03	4.27E-02
Cell Cycle	Not transmitted	1.58E-02	2.03E-02
Cellular Function and Maintenance	Transmitted	2.41E-03	2.41E-03
Cellular Function and Maintenance	Not transmitted	8.67E-03	2.25E-02
Tumor Morphology	Transmitted	2.41E-03	1.82E-02
Tumor Morphology	Not transmitted	2.41E-03	4.82E-03
Cardiovascular Disease	Transmitted	4.82E-03	4.03E-02
Cardiovascular Disease	Not transmitted	9.66E-04	2.77E-02
Cell-To-Cell Signaling and Interaction	Transmitted	5.30E-03	5.30E-03
Cell-To-Cell Signaling and Interaction	Not transmitted	1.45E-03	3.85E-02
Endocrine System Disorders	Transmitted	5.78E-03	2.67E-02
Endocrine System Disorders	Not transmitted	5.78E-03	4.50E-02
Reproductive System Disease	Transmitted	5.78E-03	7.71E-03
Reproductive System Disease	Not transmitted	2.20E-06	4.78E-02
Cellular Movement	Transmitted	7.71E-03	3.75E-02
Cellular Movement	Not transmitted	1.45E-03	4.16E-02
Metabolic Disease	Transmitted	7.71E-03	7.71E-03
Metabolic Disease	Not transmitted	7.71E-03	1.58E-02
Gastrointestinal Disease	Transmitted	8.47E-03	2.67E-02
Gastrointestinal Disease	Not transmitted	7.93E-06	1.96E-02
Connective Tissue Development and Function	Transmitted	1.58E-02	1.58E-02
Connective Tissue Development and Function	Not transmitted	1.58E-02	2.30E-02
Hepatic System Disease	Transmitted	2.44E-02	2.44E-02
Hepatic System Disease	Not transmitted	7.93E-06	6.67E-05
Cellular Assembly and Organization	Transmitted	3.00E-02	3.00E-02
Cellular Assembly and Organization	Not transmitted	6.27E-03	3.00E-02



Supplementary Figure 1. Typical miRNA secondary structure. The hairpin includes a loop, the mature miRNA (~20 nt) and a complementary region of the mature miRNA (MIR\*). The mature miRNA bears the active region (seed) involved in the binding with the target mRNA.



Supplementary Figure 2. Rare T/G variant found in the mature miR-541 gene in one autistic proband. The upper and lower figures show the secondary structure of the wild-type and mutated miR-541, respectively, as predicted by UNAFold. The mature miRNA is coloured in red and the identified change is underlined. Free energy depending on the allele present at position chr14:101530906 is calculated for both RNA structures. The allelic variant determines the enlargement of one hairpin bulge as shown in the predicted structure for the mutated variant.