

Supplementary Information

Table S1. Comparison of observed miRNA genotype frequencies with expected frequencies according to Hardy-Weinberg equilibrium.

		Healthy Controls							MS Patients								
	Gene SNP ID	Genotype	Observed	Observed	Expected	Expected	χ^2	<i>p</i> -Value		Gene SNP ID	Genotype	Observed	Observed	Expected	Expected	χ^2	<i>p</i> -Value
			No. of Patients	Genotype Frequencies	Genotype Frequencies	No. of Patients						No. of Patients	Genotype Frequencies	Genotype Frequencies	No. of Patients		
Entire group	<i>MIR146A</i> rs2910164	C/C	20	0.045	0.048	21	0.097	0.760		<i>MIR146A</i> rs2910164	C/C	30	0.053	0.043	24	2.402	0.12
		C/G	153	0.347	0.342	151					C/G	172	0.307	0.328	184		
		G/G	268	0.608	0.611	269					G/G	359	0.64	0.630	353		
	<i>MIR196A2</i> rs11614913	C/C	172	0.390	0.400	176	0.854	0.360		<i>MIR196A2</i> rs11614913	C/C	220	0.392	0.391	219	0.0051	0.94
		C/T	214	0.485	0.465	205					C/T	262	0.467	0.468	263		
		T/T	55	0.125	0.135	60					T/T	79	0.141	0.140	79		
	<i>MIR499A</i> rs3746444	C/C	13	0.029	0.034	15	0.503	0.480		<i>MIR499A</i> rs3746444	C/C	21	0.037	0.038	21	0.0029	0.96
		C/T	138	0.313	0.302	133					C/T	176	0.314	0.313	175		
		T/T	290	0.658	0.663	293					T/T	364	0.649	0.650	364		
Women	<i>MIR146A</i> rs2910164	C/C	12	0.042	0.054	15	1.196	0.270		<i>MIR146A</i> rs2910164	C/C	15	0.038	0.036	14	0.034	0.85
		C/G	108	0.379	0.356	101					C/G	121	0.306	0.309	122		
		G/G	165	0.579	0.591	168					G/G	259	0.656	0.654	259		
	<i>MIR196A2</i> rs11614913	C/C	113	0.396	0.396	113	0.00044	0.99		<i>MIR196A2</i> rs11614913	C/C	158	0.400	0.398	157	0.050	0.82
		C/T	133	0.467	0.466	133					C/T	182	0.461	0.466	184		
		T/T	39	0.137	0.137	39					T/T	55	0.139	0.137	54		
	<i>MIR499A</i> rs3746444	C/C	4	0.014	0.028	8	2.982	0.084		<i>MIR499A</i> rs3746444	C/C	13	0.033	0.036	14	0.165	0.68
		C/T	88	0.309	0.280	80					C/T	124	0.314	0.308	122		
		T/T	193	0.677	0.691	197					T/T	258	0.653	0.656	259		
	<i>MIR223</i> rs1044165	C/C	220	0.772	0.763	217	1.729	0.190		<i>MIR223</i> rs1044165	C/C	273	0.691	0.691	273	0.0051	0.94
		C/T	58	0.203	0.221	63					C/T	111	0.281	0.280	111		
		T/T	7	0.025	0.016	5					T/T	11	0.028	0.028	11		

Table S1. Cont.

Healthy Controls									MS Patients								
-	Gene SNP ID	Genotype	Observed	Observed	Expected	Expected	χ^2	<i>p</i> -Value	-	Gene SNP ID	Genotype	Observed	Observed	Expected	Expected No. of Patients	χ^2	<i>p</i> -Value
			No. of Patients	Genotype Frequencies	Genotype Frequencies	No. of Patients						No. of Patients	Genotype Frequencies	Genotype Frequencies			
Men	<i>MIR146A</i> rs2910164	C/C	8	0.054	0.039	6	1.241	0.270	Men	<i>MIR146A</i> rs2910164	C/C	15	0.090	0.059	10	4.653	0.031
		C/G	43	0.288	0.318	47					C/G	51	0.307	0.368	61		
		G/G	98	0.658	0.643	96					G/G	100	0.603	0.572	95		
	<i>MIR196A2</i> rs11614913	C/C	56	0.376	0.411	61	3.440	0.064		<i>MIR196A2</i> rs11614913	C/C	62	0.373	0.377	63	0.049	0.83
		C/T	79	0.530	0.460	69					C/T	80	0.482	0.474	79		
		T/T	14	0.094	0.129	19					T/T	24	0.145	0.149	25		
	<i>MIR499A</i> rs3746444	C/C	8	0.054	0.049	7	0.108	0.740		<i>MIR499A</i> rs3746444	C/C	8	0.048	0.042	7	0.245	0.62
		C/T	50	0.336	0.345	51					C/T	52	0.313	0.325	54		
		T/T	91	0.610	0.605	90					T/T	106	0.639	0.633	105		

Significant *p*-values are in bold.

Table S2. Case-control comparison of genetic variants in miRNA genes with MS risk.

Gene SNP ID	Carriage of Genotypes and Alleles	Carriers (%)		<i>p</i> -Value	OR (95% CI)	Carriers (%)		<i>p</i> -Value	OR (95% CI)	Carriers (%)		<i>p</i> -Value	OR (95% CI)
		MS Cases <i>n</i> = 561	Controls <i>n</i> = 441			MS Cases <i>n</i> = 395	Controls <i>n</i> = 285			MS Cases <i>n</i> = 166	Controls <i>n</i> = 149		
		Without gender stratification				Women				Men			
<i>MIR146A</i> rs2910164	C/C	30 (5.3)	20 (4.5)	0.33	1.19 (0.67–2.12)	15 (3.8)	12 (4.2)	0.47	0.90 (0.41–1.95)	15 (9.0)	8 (5.4)	0.15	1.75 (0.72–4.26)
	C/G	172 (30.7)	153 (34.7)	0.10	0.83 (0.64–1.09)	121 (30.6)	108 (37.9)	0.030	0.72 (0.53–1.00)	51 (30.7)	43 (28.8)	0.41	1.09 (0.67–1.77)
	G/G	359 (64.0)	268 (60.8)	0.16	1.15 (0.89–1.48)	259 (65.6)	165 (57.9)	0.025	1.39 (1.01–1.90)	100 (60.3)	98 (65.8)	0.19	0.79 (0.50–1.25)
	C	202 (36.0)	173 (39.2)	0.16	0.87 (0.67–1.13)	136 (34.4)	120 (42.1)	0.025	0.72 (0.53–0.99)	66 (39.8)	51 (34.2)	0.19	1.27 (0.80–2.01)
	G	531 (94.7)	421 (95.5)	0.33	0.84 (0.47–1.50)	380 (96.2)	273 (95.8)	0.47	1.11 (0.51–2.42)	151 (91.0)	141 (94.6)	0.15	0.57 (0.23–1.39)
<i>MIR196A2</i> rs11614913	C/C	220 (39.2)	172 (39.0)	0.50	1.01 (0.78–1.30)	158 (40.0)	113 (39.6)	0.50	1.01 (0.74–1.39)	62 (37.3)	56 (37.6)	0.53	0.99 (0.63–1.56)
	C/T	262 (46.7)	214 (48.5)	0.31	0.93 (0.72–1.19)	182 (46.1)	133 (46.7)	0.47	0.98 (0.72–1.33)	80 (48.2)	79 (53.0)	0.23	0.82 (0.53–1.28)
	T/T	79 (14.1)	55 (12.5)	0.26	1.15 (0.80–1.66)	55 (13.9)	39 (13.7)	0.51	1.02 (0.66–1.59)	24 (14.5)	14 (9.4)	0.11	1.63 (0.81–3.28)
	C	482 (86.0)	386 (87.5)	0.26	0.87 (0.60–1.26)	340 (86.1)	246 (86.3)	0.51	0.98 (0.63–1.52)	142 (85.5)	135 (90.6)	0.11	0.61 (0.30–1.24)
	T	341 (60.8)	269 (61.0)	0.50	0.99 (0.77–1.28)	237 (60.0)	172 (60.4)	0.50	0.99 (0.72–1.35)	104 (62.7)	93 (62.4)	0.53	1.01 (0.64–1.60)

Table S2. Cont.

Gene SNP ID	Carriage of Genotypes and Alleles	Carriers (%)			OR (95% CI)	Carriers (%)			OR (95% CI)	Carriers (%)			OR (95% CI)
		MS Cases <i>n</i> = 561	Controls <i>n</i> = 441	<i>p</i> -Value		MS Cases <i>n</i> = 395	Controls <i>n</i> = 285	<i>p</i> -Value		MS Cases <i>n</i> = 166	Controls <i>n</i> = 149	<i>p</i> -Value	
		Without gender stratification				Women				Men			
<i>MIR499A</i> rs3746444	C/C	21 (3.7)	13 (2.9)	0.24	1.38 (0.67–2.84)	13 (3.3)	4 (1.4)	0.095	2.38 (0.77–7.38)	8 (4.8)	8 (5.4)	0.51	0.89 (0.32–2.42)
	C/T	176 (31.4)	138 (31.3)	0.52	1.00 (0.76–1.30)	124 (31.4)	88 (30.9)	0.49	1.02 (0.73–1.42)	52 (31.3)	50 (33.6)	0.41	0.92 (0.57–1.48)
	T/T	364 (64.9)	290 (65.8)	0.40	0.96 (0.74–1.25)	258 (65.3)	193 (67.7)	0.30	0.90 (0.65–1.25)	106 (63.9)	91 (61.0)	0.38	1.11 (0.70–1.75)
	C	197 (35.1)	151 (34.2)	0.40	1.04 (0.80–1.36)	137 (34.7)	92 (32.3)	0.30	1.11 (0.80–1.53)	60 (36.1)	58 (38.9)	0.38	0.90 (0.57–1.43)
	T	540 (96.3)	428 (97.1)	0.24	0.72 (0.35–1.49)	382 (96.7)	281 (98.6)	0.095	0.42 (0.14–1.30)	158 (95.2)	141 (94.6)	0.51	1.13 (0.41–3.09)
<i>MIR223</i> rs1044165	C/C	-	-	-	-	273 (69.1)	220 (77.2)	0.012	0.66 (0.47–0.94)	-	-	-	-
	C/T	-	-	-	-	111 (28.1)	58 (20.3)	0.013	1.53 (1.06–2.20)	-	-	-	-
	T/T	-	-	-	-	11 (2.8)	7 (2.5)	0.50	1.14 (0.44–2.97)	-	-	-	-
	C	517 (92.2)	413 (93.7)	0.22	0.80 (0.49–1.30)	384 (97.2)	278 (97.5)	0.50	0.88 (0.34–2.30)	133 (80.1)	128 (85.9)	0.11	0.66 (0.36–1.20)
	T	155 (27.6)	86 (19.5)	0.0017	1.58 (1.17–2.13)	122 (30.9)	65 (22.8)	0.012	1.51 (1.07–2.15)	33 (19.9)	21 (14.1)	0.11	1.51 (0.83–2.75)

Significant *p*-values are in bold.

Table S3. Case-control comparison of genetic variants in miRNA genes with MSSS.

Gene SNP ID	Carriage of Genotypes and Alleles	Carriers (%)			OR (95% CI)	Carriers (%)			OR (95% CI)	Carriers (%)			OR (95% CI)
		MSSS > 3.5 <i>n</i> = 304	MSSS ≤ 3.5 <i>n</i> = 242	<i>p</i> -Value		MSSS > 3.5 <i>n</i> = 207	MSSS ≤ 3.5 <i>n</i> = 181	<i>p</i> -Value		MSSS > 3.5 <i>n</i> = 97	MSSS ≤ 3.5 <i>n</i> = 61	<i>p</i> -Value	
Without gender stratification					Women				Men				
<i>MIR146A</i> rs2910164	C/C	15 (4.9)	13 (5.4)	0.48	0.91 (0.43–1.96)	8 (3.9)	7 (3.9)	0.60	1.00 (0.36–2.81)	7 (7.2)	6 (9.8)	0.38	0.71 (0.23–2.23)
	C/G	91 (30.0)	75 (31.0)	0.43	0.95 (0.66–1.37)	61 (29.4)	57 (31.5)	0.37	0.91 (0.59–1.40)	30 (30.9)	18 (29.5)	0.50	1.07 (0.53–2.15)
	G/G	198 (65.1)	154 (63.6)	0.39	1.07 (0.75–1.52)	138 (66.7)	117 (64.6)	0.38	1.09 (0.72–1.67)	60 (61.9)	37 (60.7)	0.51	1.05 (0.55–2.03)
	C	106 (34.9)	88 (36.4)	0.39	0.94 (0.66–1.33)	69 (33.3)	64 (35.4)	0.38	0.91 (0.60–1.39)	37 (38.1)	24 (39.3)	0.51	0.95 (0.49–1.83)
	G	289 (95.1)	229 (94.6)	0.48	1.09 (0.51–2.35)	199 (96.1)	174 (96.1)	0.60	1.00 (0.36–2.82)	90 (92.8)	55 (90.2)	0.38	1.40 (0.45–4.39)
<i>MIR196A2</i> rs11614913	C/C	110 (36.2)	101 (41.7)	0.11	0.79 (0.56–1.12)	77 (37.2)	78 (43.1)	0.14	0.78 (0.52–1.18)	33 (34.0)	23 (37.7)	0.38	0.85 (0.44–1.66)
	C/T	153 (50.3)	103 (42.6)	0.043	1.37 (0.97–1.92)	103 (49.8)	76 (42.0)	0.076	1.37 (0.92–2.04)	50 (51.6)	27 (44.3)	0.23	1.34 (0.70–2.55)
	T/T	41 (13.5)	38 (15.7)	0.27	0.84 (0.52–1.35)	27 (13.0)	27 (14.9)	0.35	0.86 (0.48–1.52)	14 (14.4)	11 (18.0)	0.35	0.77 (0.32–1.82)
	C	263 (86.5)	204 (84.3)	0.27	1.19 (0.74–1.93)	180 (87.0)	154 (85.1)	0.35	1.17 (0.66–2.08)	83 (85.6)	50 (82.0)	0.35	1.30 (0.55–3.10)
	T	194 (63.8)	141 (58.2)	0.11	1.26 (0.89–1.79)	130 (62.8)	103 (56.9)	0.14	1.28 (0.85–1.92)	64 (66.0)	38 (62.3)	0.38	1.17 (0.60–2.29)

Table S3. Cont.

Gene SNP ID	Carriage of Genotypes and Alleles	Carriers (%)			OR (95% CI)	Carriers (%)			OR (95% CI)	Carriers (%)			OR (95% CI)
		MSSS > 3.5 <i>n</i> = 304	MSSS ≤ 3.5 <i>n</i> = 242	<i>p</i> -Value		MSSS > 3.5 <i>n</i> = 207	MSSS ≤ 3.5 <i>n</i> = 181	<i>p</i> -Value		MSSS > 3.5 <i>n</i> = 97	MSSS ≤ 3.5 <i>n</i> = 61	<i>p</i> -Value	
Without gender stratification					Women				Men				
<i>MIR499A</i> rs3746444	C/C	7 (2.3)	11 (4.5)	0.11	0.49 (0.19–1.30)	3 (1.4)	9 (5.0)	0.043	0.28 (0.075–1.05)	4 (4.1)	2 (3.3)	0.57	1.27 (0.23–7.15)
	C/T	112 (36.8)	58 (24.0)	0.00081	1.85 (1.27–2.70)	86 (41.6)	37 (20.4)	0.0000056	2.77 (1.76–4.36)	26 (26.8)	21 (34.4)	0.20	0.70 (0.35–1.40)
	T/T	185 (60.9)	173 (71.5)	0.0059	0.62 (0.43–0.89)	118 (57.0)	135 (74.6)	0.00020	0.45 (0.29–0.70)	67 (69.1)	38 (62.3)	0.24	1.35 (0.69–2.65)
	C	119 (39.1)	69 (28.5)	0.0059	1.61 (1.12–2.32)	89 (43.0)	46 (25.4)	0.00020	2.21 (1.44–3.41)	30 (30.9)	23 (37.8)	0.24	0.74 (0.38–1.45)
	T	297 (91.8)	231 (95.5)	0.11	2.02 (0.77–5.29)	204 (98.6)	172 (95.0)	0.043	3.56 (0.95–13.35)	93 (95.9)	59 (96.7)	0.57	0.79 (0.14–4.44)
<i>MIR223</i> rs1044165	C/C	-	-	-	-	140 (67.6)	129 (71.3)	0.25	0.84 (0.55–1.30)	-	-	-	-
	C/T	-	-	-	-	62 (30.0)	46 (25.4)	0.19	1.25 (0.80–1.96)	-	-	-	-
	T/T	-	-	-	-	5 (2.4)	6 (3.3)	0.41	0.72 (0.22–2.41)	-	-	-	-
	C	283 (93.1)	220 (91.0)	0.22	1.35 (0.72–2.51)	202 (97.6)	175 (96.7)	0.41	1.39 (0.42–4.62)	81 (83.5)	45 (73.8)	0.10	1.80 (0.82–3.94)
	T	83 (27.3)	68 (28.1)	0.46	0.96 (0.66–1.40)	67 (32.4)	52 (28.7)	0.25	1.19 (0.77–1.83)	16 (16.5)	16 (26.2)	0.10	0.56 (0.25–1.22)

Significant *p*-values are in bold.