

Supplementary Material

***LAG3/CD4* Genes Variants and the Risk for Restless Legs Syndrome**

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Supplementary Table S1. Genotypes and allelic variants of female patients with RLS and healthy controls. The values in each cell represent the number (percentage; 95% confidence intervals) P: crude probability; Pc: probability after multiple comparisons; NPV: negative predictive value.

GENOTYPES	<i>RLS WOMEN (N=217)</i>	<i>CONTROL WOMEN (N=270)</i>	<i>INTERGROUP COMPARISON OR (95%CI), P; PC ; NPV (95%CI)</i>
rs1922452 A/A	39 (18.0; 12.9-23.1)	46 (17.0; 12.6-21.5)	1.07 (0.67-1.71); 0.787; 0.852; 0.56 (0.54-0.58)
rs1922452 A/G	106 (48.8; 42.2-55.5)	126 (46.7; 40.7-52.6)	1.09 (0.76-1.56); 0.632; 0.852; 0.57 (0.52-0.61)
rs1922452 G/G	72 (33.2; 26.9-39.4)	98 (36.3; 30.6-42.0)	0.88 (0.60-1.27); 0.474; 0.852; 0.54 (0.51-0.58)
rs951818 A/A	71 (32.7; 26.5-39.0)	96 (35.6; 29.8-41.3)	0.88 (0.60-1.29); 0.513; 0.852; 0.54 (0.51-0.58)
rs951818 A/C	114 (52.5; 45.9-59.2)	131 (48.5; 42.6-54.5)	1.17 (0.82-1.68); 0.379; 0.852; 0.57 (0.53-0.62)
rs951818 C/C	32 (14.7; 10.0-19.5)	43 (15.9; 11.6-20.3)	0.91 (0.56-1.50); 0.720; 0.852; 0.55 (0.53-0.57)
rs870849 C/C	87 (40.1; 33.6-46.6)	106 (39.3; 33.4-45.1)	1.04 (0.72-1.49); 0.852; 0.852; 0.56 (0.52-0.60)
rs870849 C/T	102 (47.0; 40.4-53.6)	132 (48.9; 42.9-54.9)	0.93 (0.65-1.33); 0.679; 0.852; 0.55 (0.50-0.59)
rs870849 T/T	28 (12.9; 8.4-17.4)	32 (11.9; 8.0-15.7)	1.10 (0.64-1.89); 0.726; 0.852; 0.56 (0.54-0.58)
ALLELES	<i>RLS WOMEN (N= 434 ALLELES)</i>	<i>CONTROL WOMEN (N= 540 ALLELES)</i>	<i>INTERGROUP COMPARISON OR (95%CI), P; PC ; NPV (95%CI)</i>
rs1922452 A	184 (42.4; 37.7-47.0)	218 (40.4; 36.2-44.5)	1.09 (0.84-1.41); 0.523; 0.972; 0.56 (0.54-0.59)
rs1922452 G	250 (57.6; 53.0-62.3)	322 (59.6; 55.5-63.8)	0.92 (0.71-1.19); 0.523; 0.972; 0.54 (0.50-0.58)
rs951818 A	256 (59.0; 54.4-63.6)	323 (59.8; 55.7-64.0)	0.97 (0.75-1.25); 0.794; 0.972; 0.55 (0.51-0.59)
rs951818 C	178 (41.0; 36.4-45.6)	217 (40.2; 36.0-44.3)	1.04 (0.80-1.34); 0.794; 0.972; 0.56 (0.53-0.59)
rs870849 C	276 (63.6; 59.1-68.1)	344 (63.7; 59.6-67.8)	1.00 (0.77-1.29); 0.972; 0.972; 0.55 (0.51-0.60)
rs870849 T	158 (36.4; 31.9-40.9)	196 (36.3; 32.2-40.4)	1.00 (0.77-1.29); 0.972; 0.972; 0.55 (0.51-0.60)

Supplementary Table S2. Genotypes and allelic variants of male patients with RLS and healthy controls. The values in each cell represent the number (percentage; 95% confidence intervals) P: crude probability; Pc: probability after multiple comparisons; NPV: negative predictive value.

GENOTYPES	<i>RLS MEN</i> (N=68)	<i>CONTROL MEN</i> (N=80)	<i>INTERGROUP COMPARISON</i> <i>OR (95%CI) P; PC ; NPV (95%CI)</i>
rs1922452 A/A	13 (19.1; 9.8-28.5)	13 (16.3; 8.2-24.3)	1.22 (0.52-2.84); 0.649; 0.861; 0.55 (0.51-0.59)
rs1922452 A/G	29 (42.6; 30.9-54.4)	39 (48.8; 37.8-59.7)	0.78 (0.41-1.50); 0.459; 0.861; 0.51 (0.44-0.59)
rs1922452 G/G	26 (38.2; 26.7-49.8)	28 (35.0; 24.5-45.5)	1.15 (0.59-2.25); 0.685; 0.861; 0.55 (0.49-0.62)
rs951818 A/A	28 (41.2; 29.5-52.9)	31 (38.8; 28.1-49.4)	1.11 (0.57-2.14); 0.765; 0.861; 0.55 (0.48-0.62)
rs951818 A/C	30 (44.1; 32.3-55.9)	38 (47.5; 36.6-58.4)	0.87 (0.46-1.67); 0.682; 0.861; 0.53 (0.45-0.61)
rs951818 C/C	10 (14.7; 6.3-23.1)	11 (13.8; 6.2-21.3)	1.08 (0.43-2.73); 0.869; 0.869; 0.54 (0.51-0.58)
rs870849 C/C	33 (48.5; 36.7-60.4)	32 (40.0; 29.3-50.7)	1.41 (0.74-2.72); 0.299; 0.861; 0.58 (0.50-0.65)
rs870849 C/T	26 (38.2; 26.7-49.8)	36 (45.0; 34.1-55.9)	0.76 (0.39-1.46); 0.407; 0.861; 0.51 (0.44-0.59)
rs870849 T/T	9 (13.2; 5.2-21.3)	12 (15.0; 7.2-22.8)	0.86 (0.34-1.20); 0.760; 0.861; 0.54 (0.50-0.57)
ALLELES	<i>RLS MEN</i> (N= 136 ALLELES)	<i>CONTROL MEN</i> (N= 160 ALLELES)	<i>INTERGROUP COMPARISON</i> <i>OR (95%CI) P; PC ; NPV (95%CI)</i>
rs1922452 A	55 (40.4; 32.2-48.7)	65 (40.6; 33.0-48.2)	0.99 (0.62-1.58); 0.974; 0.974; 0.54 (0.49-0.59)
rs1922452 G	81 (59.6; 51.3-67.8)	95 (59.4; 51.8-67.0)	1.01 (0.63-1.61); 0.974; 0.974; 0.54 (0.47-0.61)
rs951818 A	86 (63.2; 55.1-71.3)	100 (62.5; 55.0-70.0)	1.03 (0.64-1.66); 0.896; 0.974; 0.55 (0.47-0.62)
rs951818 C	50 (36.8; 28.7-44.9)	60 (37.5; 30.0-45.0)	0.97 (0.60-1.56); 0.896; 0.974; 0.54 (0.49-0.58)
rs870849 C	92 (67.6; 59.8-75.5)	100 (62.5; 55.0-70.0)	1.26 (0.78-2.03); 0.356; 0.974; 0.58 (0.50-0.66)
rs870849 T	44 (32.4; 24.5-40.2)	60 (37.5; 30.0-45.0)	0.78 (0.49-1.29); 0.356; 0.974; 0.52 (0.48-0.57)

Supplementary Table S3. Genotypes and allelic variants of patients with RLS distributed by response to dopamine agonists. The values in each cell represent the number (percentage; 95% confidence intervals).

GENOTYPES	POSITIVE RESPONSE TO DOPAMINE AGONISTS (N=222)	NEGATIVE RESPONSE TO DOPAMINE AGONISTS (N=18)	INTERGROUP COMPARISON VALUES <i>OR (95%CI) P; PC; NPV OR (95%CI)</i>
rs1922452 A/A	37 (16.7; 11.8-21.6)	4 (22.2; 3.0-41.4)	0.70 (0.22-2.25); 0.548; 0.789; 0.07 (0.05-0.08)
rs1922452 A/G	105 (47.3; 40.7-53.9)	7 (38.9; 16.4-61.4)	1.41 (0.53-3.77); 0.493; 0.789; 0.09 (0.05-0.12)
rs1922452 G/G	80 (36.0; 29.7-42.4)	7 (38.9; 16.4-61.4)	0.89 (0.33-2.37); 0.809; 0.910; 0.07 (0.04-0.10)
rs951818 A/A	85 (38.3; 31.9-44.7)	4 (22.2; 3.0-41.4)	2.17 (0.69-6.19); 0.176; 0.789; 0.09 (0.06-0.11)
rs951818 A/C	109 (49.1; 42.5-55.7)	10 (55.6; 32.6-78.5)	0.77 (0.29-2.03); 0.599; 0.789; 0.07 (0.03-0.10)
rs951818 C/C	28 (12.6; 8.2-17.0)	4 (22.2; 3.0-41.4)	0.51 (0.16-1.64); 0.250; 0.789; 0.07 (0.05-0.08)
rs870849 C/C	100 (45.0; 38.5-51.6)	7 (38.9; 16.4-61.4)	1.29 (0.48-3.45); 0.614; 0.789; 0.08 (0.05-0.11)
rs870849 C/T	97 (43.7; 37.2-50.2)	8 (44.4; 21.5-67.4)	0.97 (0.37-2.55); 0.951; 0.951; 0.07 (0.04-0.10)
rs870849 T/T	25 (11.3; 7.1-15.4)	3 (16.7; -0.6-33.9)	0.64 (0.17-2.35); 0.493; 0.789; 0.07 (0.05-0.08)
ALLELES	POSITIVE RESPONSE TO DOPAMINE AGONISTS (N=444 ALLELES)	NEGATIVE RESPONSE TO DOPAMINE AGONISTS (N=36 ALLELES)	INTERGROUP COMPARISON VALUES <i>OR (95%CI) P; PC; NPV OR (95%CI)</i>
rs1922452 A	179 (40.3; 35.8-44.9)	15 (41.7; 25.6-57.8)	0.95 (0.48-1.88); 0.874; 0.874; 0.07 (0.05-0.09)
rs1922452 G	265 (59.7; 55.1-64.2)	21 (58.3; 42.2-74.4)	1.06 (0.53-2.11); 0.874; 0.874; 0.08 (0.05-0.11)
rs951818 A	279 (62.8; 58.3-67.3)	18 (50.0; 33.7-66.3)	1.69 (0.86-3.34); 0.128; 0.384; 0.10 (0.07-0.13)
rs951818 C	165 (37.2; 32.7-41.7)	18 (50.0; 33.7-66.3)	0.59 (0.30-1.17); 0.128; 0.384; 0.06 (0.04-0.08)
rs870849 C	297 (66.9; 62.5-71.3)	22 (61.1; 45.2-77.0)	1.29 (0.64-2.59); 0.480; 0.720; 0.09 (0.05-0.13)
rs870849 T	147 (33.1; 28.7-37.5)	14 (38.9; 23.0-54.8)	0.78 (0.39-1.56); 0.480; 0.720; 0.07 (0.05-0.09)

Supplementary Table S4. Genotypes and allelic variants of patients with RLS distributed by response to clonazepam (CNZ). The values in each cell represent the number (percentage; 95% confidence intervals).

GENOTYPES	POSITIVE RESPONSE TO CNZ (N=92)	NEGATIVE RESPONSE TO CNZ (N=16)	INTERGROUP COMPARISON VALUES <i>OR (95%CI) P; PC; NPV OR (95%CI)</i>
rs1922452 A/A	22 (23.9; 15.2-32.6)	1 (6.3; -5.6-18.1)	4.71 (0.59-37.74); 0.113; 0.337; 0.18 (0.13-0.19)
rs1922452 A/G	39 (42.4; 32.3-52.5)	6 (37.5; 13.8-61.2)	1.23 (0.41-3.66); 0.715; 0.715; 0.16 (0.10-0.21)
rs1922452 G/G	31 (33.7; 24.0-43.4)	9 (56.3; 31.9-80.6)	0.40 (0.13-1.16); 0.086; 0.337; 0.10 (0.05-0.16)
rs951818 A/A	30 (32.6; 23.0-42.2)	8 (50.0; 25.5-74.5)	0.48 (0.17-1.41); 0.181; 0.337; 0.11 (0.06-0.17)
rs951818 A/C	49 (53.3; 43.1-63.5)	7 (43.8; 19.4-68.1)	1.47 (0.50-4.27); 0.484; 0.622; 0.17 (0.10-0.24)
rs951818 C/C	13 (14.1; 7.0-21.2)	1 (6.3; -5.6-18.1)	2.47 (0.30-20.31); 0.389; 0.584; 0.16 (0.12-0.17)
rs870849 C/C	40 (43.5; 33.3-53.6)	6 (37.5; 13.8-61.2)	1.28 (0.43-3.82); 0.657; 0.715; 0.16 (0.10-0.22)
rs870849 C/T	41 (44.6; 34.4-54.7)	10 (62.5; 38.8-86.2)	0.48 (0.16-1.44); 0.187; 0.337; 0.11 (0.05-0.18)
rs870849 T/T	11 (12.0; 5.3-18.6)	0 (0.0; 0.0-0.0)	1.20 (0.82-1.20) ¹ ; 0.146; 0.337; 0.17 (0.13-0.17)
ALLELES	POSITIVE RESPONSE TO CNZ (N=184 ALLELES)	NEGATIVE RESPONSE TO CNZ (N=32 ALLELES)	INTERGROUP COMPARISON VALUES <i>OR (95%CI) P; PC; NPV OR (95%CI)</i>
rs1922452 A	83 (45.1; 37.9-52.3)	8 (25.0; 10.0-40.0)	2.47 (1.06-5.78); 0.034; 0.102; 0.19 (0.15-0.22)
rs1922452 G	101 (54.9; 47.7-62.1)	24 (75.0; 60.0-90.0)	0.41 (0.17-0.95); 0.034; 0.102; 0.09 (0.04-0.15)
rs951818 A	109 (59.2; 52.1-66.3)	23 (71.9; 56.3-87.5)	0.57 (0.25-1.30); 0.177; 0.266; 0.11 (0.06-0.17)
rs951818 C	75 (40.8; 33.7-47.9)	9 (28.1; 12.5-43.7)	1.76 (0.77-4.01); 0.177; 0.266; 0.17 (0.13-0.21)
rs870849 C	121 (65.8; 58.9-72.6)	22 (68.8; 52.7-84.8)	0.87 (0.39-1.96); 0.742; 0.742; 0.14 (0.08-0.213)
rs870849 T	63 (34.2; 27.4-41.1)	10 (31.3; 15.2-47.3)	1.15 (0.51-2.57); 0.742; 0.742; 0.15 (0.12-0.19)

Armitage's test for trend with the number of variant rs1922452 alleles = Z- squared = 3.95, P = 0.047. ¹ The RR value is shown instead of the OR because at least one of the values in the comparison is equal to 0.

Supplementary Table S5. Genotypes and allelic variants of patients with RLS distributed by response to GABAergic drugs. The values in each cell represent the number (percentage; 95% confidence intervals).

GENOTYPES	POSITIVE RESPONSE TO GABAERGIC DRUGS (N=51)	NEGATIVE RESPONSE TO GABAERGIC DRUGS (N=12)	INTERGROUP COMPARISON VALUES <i>OR (95%CI), P; PC; NPV OR (95%CI)</i>
rs1922452 A/A	12 (23.5; 11.9-35.2)	2 (16.7; -4.4-37.8)	1.54 (0.30-8.01); 0.610; 0.620; 0.20 (0.14-0.24)
rs1922452 A/G	17 (33.3; 20.4-46.3)	6 (50.0; 21.7-78.3)	0.50 (0.14-1.79); 0.284; 0.535; 0.15 (0.07-0.23)
rs1922452 G/G	22 (43.1; 29.5-56.7)	4 (33.3; 6.7-60.0)	1.52 (0.41-5.69); 0.538; 0.620; 0.22 (0.12-0.29)
rs951818 A/A	18 (35.3; 22.2-48.4)	1 (8.3; -7.3-24.0)	6.00 (0.72-50.30); 0.069; 0.273; 0.25 (0.17-0.27)
rs951818 A/C	22 (43.1; 29.5-56.7)	10 (83.3; 62.2-104.4)	0.15 (0.03-0.76); 0.013; 0.117; 0.07 (0.01-0.18)
rs951818 C/C	11 (21.6; 10.3-32.9)	1 (8.3; -7.3-24.0)	3.03 (0.35-26.05); 0.297; 0.535; 0.22 (0.15-0.23)
rs870849 C/C	21 (41.2; 27.7-54.7)	4 (33.3; 6.7-60.0)	1.40 (0.37-5.26); 0.620; 0.620; 0.21 (0.12-0.28)
rs870849 C/T	26 (51.0; 37.3-64.7)	5 (41.7; 13.8-69.6)	1.46 (0.41-1.20); 0.565; 0.620; 0.22 (0.11-0.31)
rs870849 T/T	4 (7.8; 0.5-15.2)	3 (25.0; 0.5-49.5)	0.26 (0.05-1.34); 0.091; 0.273; 0.16 (0.12-0.20)
ALLELES	POSITIVE RESPONSE TO GABAERGIC DRUGS (N=110 ALLELES)	NEGATIVE RESPONSE TO GABAERGIC DRUGS (N=24 ALLELES)	INTERGROUP COMPARISON VALUES <i>OR (95%CI), P; PC; NPV OR (95%CI)</i>
rs1922452 A	41 (40.2; 30.7-49.7)	10 (41.7; 21.9-61.4)	0.94 (0.38-2.32); 0.895; 0.895; 0.19 (0.12-0.24)
rs1922452 G	61 (59.8; 50.3-69.3)	14 (58.3; 38.6-78.1)	1.06 (0.43-2.62); 0.895; 0.895; 0.20 (0.11-0.29)
rs951818 A	58 (56.9; 47.3-66.5)	12 (50.0; 30.0-70.0)	1.32 (0.54-3.21); 0.544; 0.816; 0.21 (0.13-0.30)
rs951818 C	44 (43.1; 33.5-52.7)	12 (50.0; 30.0-70.0)	0.76 (0.31-1.85); 0.544; 0.816; 0.17 (0.11-0.24)
rs870849 C	68 (66.7; 57.5-75.8)	13 (54.2; 34.2-74.1)	1.69 (0.69-4.17); 0.252; 0.756; 0.24 (0.15-0.35)
rs870849 T	34 (33.3; 24.2-42.5)	11 (45.8; 25.9-65.8)	0.59 (0.24-1.46); 0.252; 0.756; 0.16 (0.10-0.22)