

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Stefansson H, Rye DB, Hicks A, et al. A genetic risk factor for periodic limb movements and restless legs syndrome. *N Engl J Med* 2007;357. DOI: 10.1056/NEJMoa072743.

**A Major Genetic Risk Factor of  
Periodic Limb Movements and  
Restless Legs Syndrome**

## Supplementary Material

**Supplementary Table 1.** Demographics, age and phenotype breakdown

<b>Phenotype</b>	<b>Count</b>	<b>Male count (mean age±sd)</b>	<b>Female count (mean age±sd)</b>	<b>Description of phenotype</b>
RLS+PLMs	429	142 (60.6±14.5)	287 (56.0 ± 13.6)	RLS and PLMs
RLS-PLMs	229	73 (50.6±14.8)	156 (49.8±14.1)	RLS but not PLMs
PLMs-RLS	105	45 (57.3±15.4)	60 (56.5±15.1)	PLMs but no RLS

Fraction of RLS in PLMs =  $429 / (429 + 105) = 0.80$ , 80% of those with PLMs have RLS. Fraction of PLMs in RLS =  $429 / (429 + 229) = 0.65$ , 65% of those with RLS have PLMs.

Of the 943 genotyped samples with PLM measurements 763 are accounted for in the table above. (Supplementary Figure 3 for more detailed phenotype breakdown).

**Supplementary Table 2.** The 70 SNPs in a 600kb region around rs3923809 that satisfied quality criteria in the discovery genome-wide scan. All P values have been corrected by genomic controls.

SNP	Position	Control frequency	OR (95% CI)	P value for SNP	P value for SNP corrected for rs3923809	P value for rs3923809 corrected for SNP	Genotype counts					
							Cases			Controls		
							aa	aA	AA	aa	aA	AA
rs3800358	38249982	0.53	1.0 (0.8, 1.2)	0.96	0.88	2x10 <sup>-9</sup>	70	149	87	3554	7659	4385
rs2235711	38256748	0.76	1.1 (0.9, 1.4)	0.23	0.34	3x10 <sup>-9</sup>	13	107	186	936	5625	9102
rs10807192	38267796	0.48	1.0 (0.8, 1.2)	0.96	0.73	2x10 <sup>-9</sup>	83	149	74	4227	7699	3736
rs742538	38268605	0.66	1.0 (0.8, 1.2)	0.96	0.79	2x10 <sup>-9</sup>	40	126	140	1852	6869	6936
rs13206817	38281343	0.48	1.0 (0.9, 1.2)	0.62	0.65	2x10 <sup>-9</sup>	76	162	68	4277	7848	3536
rs1931765	38282799	0.8	1.2 (1.0, 1.5)	0.12	0.48	6x10 <sup>-9</sup>	7	95	204	692	5036	9935
rs4299828	38285645	0.8	1.2 (1.0, 1.5)	0.1	0.42	6x10 <sup>-9</sup>	7	94	205	692	5034	9934
rs926564	38307237	0.72	1.2 (1.0, 1.5)	0.04	0.73	2x10 <sup>-8</sup>	16	113	177	1220	6183	8193
rs909997	38310342	0.07	1.1 (0.8, 1.6)	0.43	0.66	3x10 <sup>-9</sup>	262	42	2	13663	1914	85
rs12202202	38312281	0.12	1.2 (0.9, 1.5)	0.23	0.55	4x10 <sup>-9</sup>	227	70	8	12024	3375	246
rs9296239	38315614	0.92	1.3 (0.9, 1.9)	0.12	0.97	7x10 <sup>-9</sup>	2	32	272	104	2170	13389
rs9366950	38324672	0.87	1.2 (0.9, 1.6)	0.16	0.89	6x10 <sup>-9</sup>	2	66	238	298	3614	11750
rs726160	38329617	0.65	1.1 (0.9, 1.4)	0.18	0.51	4x10 <sup>-9</sup>	30	138	137	1937	7138	6578
rs13194038	38338207	0.92	1.5 (1.1, 2.2)	0.02	0.45	3x10 <sup>-8</sup>	0	34	272	104	2372	13187
rs9462426	38354751	0.37	1.2 (1.0, 1.4)	0.04	0.61	2x10 <sup>-8</sup>	107	142	56	6167	7289	2208
rs6905637	38385888	0.67	1.4 (1.2, 1.7)	0.0002	0.23	1x10 <sup>-6</sup>	17	121	168	1671	6911	7082
rs228181	38408118	0.67	1.5 (1.2, 1.8)	8x10 <sup>-5</sup>	0.30	4x10 <sup>-6</sup>	16	123	167	1704	6978	6975
rs12660215	38413748	0.18	1.1 (0.9, 1.4)	0.25	0.99	4x10 <sup>-9</sup>	193	103	10	10505	4632	526
rs228188	38426351	0.47	1.2 (1.1, 1.5)	0.01	0.67	6x10 <sup>-8</sup>	66	161	79	4470	7783	3409
rs4573069	38431723	0.33	1.2 (1.0, 1.4)	0.05	0.36	1x10 <sup>-8</sup>	124	135	47	6955	6980	1729
rs13200372	38436415	0.88	1.2 (0.9, 1.6)	0.12	0.50	6x10 <sup>-9</sup>	2	56	248	217	3293	12153
rs6907434	38444627	0.79	1.1 (0.9, 1.4)	0.37	0.30	2x10 <sup>-9</sup>	14	92	200	706	5225	9731
rs1883610	38448077	0.64	1.1 (0.9, 1.3)	0.18	0.09	1x10 <sup>-9</sup>	29	140	124	2082	7181	6289
rs4711542	38450140	0.43	1.2 (1.0, 1.4)	0.03	0.62	2x10 <sup>-8</sup>	86	151	69	5123	7732	2809
rs9357271	38473851	0.76	1.8 (1.4, 2.3)	2x10 <sup>-7</sup>	0.28	0.001	5	80	221	896	5632	9135
rs4711546	38474164	0.76	1.7 (1.4, 2.1)	2x10 <sup>-6</sup>	0.65	0.0003	7	82	217	931	5696	9036
rs4565302	38508117	0.12	1.6 (1.2, 2.0)	0.0002	0.03	2x10 <sup>-7</sup>	211	85	10	12214	3229	216

rs9470878	38514714	0.89	1.2 (0.9, 1.6)	0.22	0.96	5x10 <sup>-9</sup>	3	54	249	202	3189	12272
rs12208647	38516201	0.12	1.6 (1.2, 2.0)	0.0002	0.02	2x10 <sup>-7</sup>	210	85	11	12157	3278	227
rs6904723	38544295	0.53	1.5 (1.3, 1.8)	7x10 <sup>-7</sup>	0.45	0.0006	37	151	118	3517	7716	4346
rs3923809	38548948	0.66	1.8 (1.5, 2.2)	2x10 <sup>-9</sup>	-	-	12	114	180	1816	7120	6698
rs4236058	38550426	0.33	1.2 (1.0, 1.5)	0.02	0.53	3x10 <sup>-8</sup>	118	144	43	7013	6987	1661
rs9470887	38558410	0.89	1.1 (0.9, 1.5)	0.33	0.40	2x10 <sup>-9</sup>	3	54	249	187	3103	12374
rs9380755	38580104	0.83	1.1 (0.8, 1.3)	0.65	0.94	2x10 <sup>-9</sup>	10	77	219	408	4376	10880
rs6923737	38591542	0.65	1.7 (1.4, 2.0)	1x10 <sup>-7</sup>	0.16	0.002	16	116	174	1885	7096	6679
rs10498741	38594688	0.14	1.4 (1.1, 1.7)	0.008	0.29	5x10 <sup>-8</sup>	206	86	14	11424	3926	293
rs2748156	38621152	0.32	1.2 (1.0, 1.4)	0.06	1.00	1x10 <sup>-8</sup>	120	150	36	7129	6890	1644
rs6931131	38623973	0.45	1.1 (1.0, 1.4)	0.12	0.93	7x10 <sup>-9</sup>	82	153	71	4706	7840	3105
rs2748173	38638120	0.32	1.2 (1.0, 1.4)	0.07	0.99	1x10 <sup>-8</sup>	120	151	35	7151	6881	1631
rs1321056	38643554	0.6	1.5 (1.2, 1.7)	4x10 <sup>-5</sup>	0.12	4x10 <sup>-6</sup>	27	137	142	2394	7641	5597
rs2814891	38644949	0.07	1.3 (1.0, 1.8)	0.06	0.05	2x10 <sup>-9</sup>	256	47	3	13673	1909	73
rs17543178	38651355	0.14	1.5 (1.2, 1.9)	0.0003	0.03	2x10 <sup>-7</sup>	198	98	10	11655	3731	275
rs2814894	38652475	0.6	1.5 (1.2, 1.7)	3x10 <sup>-5</sup>	0.11	4x10 <sup>-6</sup>	27	136	142	2388	7661	5604
rs2748166	38660252	0.38	1.2 (1.0, 1.4)	0.09	0.87	1x10 <sup>-8</sup>	104	152	50	6092	7368	2202
rs2180106	38668193	0.23	1.3 (1.1, 1.6)	0.005	0.14	4x10 <sup>-8</sup>	158	125	22	9380	5482	790
rs1739626	38707544	0.6	1.4 (1.2, 1.7)	5x10 <sup>-5</sup>	0.13	3x10 <sup>-6</sup>	27	137	142	2392	7553	5609
rs1739633	38725698	0.74	1.3 (1.1, 1.6)	0.009	0.57	6x10 <sup>-8</sup>	13	102	190	970	6143	8550
rs1781738	38735257	0.64	1.5 (1.2, 1.8)	6x10 <sup>-5</sup>	0.12	3x10 <sup>-6</sup>	24	122	160	1956	7339	6369
rs13210334	38736260	0.91	1.1 (0.8, 1.5)	0.62	0.57	2x10 <sup>-9</sup>	2	48	255	135	2592	12921
rs1937782	38737208	0.91	1.1 (0.8, 1.4)	0.67	0.62	2x10 <sup>-9</sup>	2	49	255	135	2608	12920
rs6458065	38749332	0.55	1.3 (1.1, 1.5)	0.01	0.77	6x10 <sup>-8</sup>	50	142	114	3141	7812	4709
rs3778443	38762466	0.06	1.4 (1.0, 1.9)	0.04	0.09	4x10 <sup>-9</sup>	254	50	1	13760	1835	61
rs6932648	38766861	0.92	1.0 (0.8, 1.4)	0.90	0.85	2x10 <sup>-9</sup>	2	47	257	104	2449	13103
rs10484854	38772572	0.31	1.0 (0.9, 1.2)	0.78	0.33	1x10 <sup>-9</sup>	141	136	28	7497	6655	1512
rs1781735	38780057	0.48	1.1 (1.0, 1.4)	0.12	0.78	7x10 <sup>-9</sup>	69	158	79	4143	7926	3593
rs1937780	38782428	0.4	1.0 (0.8, 1.2)	0.99	0.33	1x10 <sup>-9</sup>	115	139	52	5666	7548	2439
rs1781731	38790310	0.07	1.4 (1.0, 1.9)	0.03	0.07	5x10 <sup>-9</sup>	253	51	2	13685	1903	72
rs1937781	38797853	0.33	1.2 (1.0, 1.4)	0.07	0.10	3x10 <sup>-9</sup>	128	130	48	7025	6886	1753
rs9296260	38800415	0.76	1.1 (0.9, 1.4)	0.30	0.43	3x10 <sup>-9</sup>	16	106	184	896	5862	8904
rs1698998	38804646	0.83	1.2 (1.0, 1.5)	0.10	0.20	4x10 <sup>-9</sup>	10	69	227	435	4503	10723
rs1623375	38806091	0.53	1.1 (0.9, 1.3)	0.38	0.87	3x10 <sup>-9</sup>	73	133	100	3619	7639	4405
rs1626976	38806558	0.77	1.0 (0.9, 1.3)	0.70	0.29	1x10 <sup>-9</sup>	19	101	185	916	5527	9221

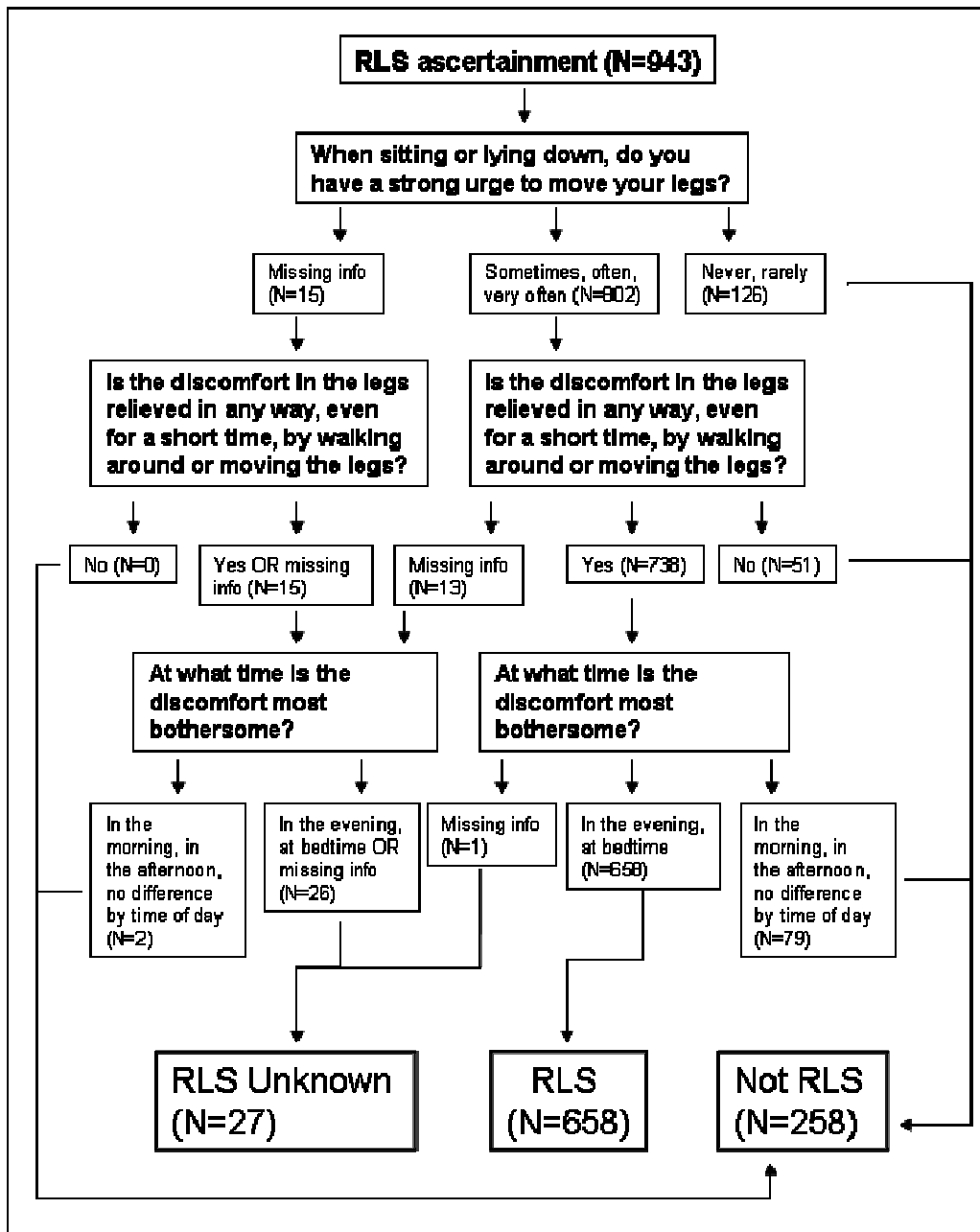
rs17552381	38806755	0.26	1.2 (1.0, 1.4)	0.13	0.18	3x10 <sup>-9</sup>	158	116	31	8539	5997	1110
rs1781726	38812327	0.35	1.1 (0.9, 1.3)	0.17	0.18	2x10 <sup>-9</sup>	124	132	50	6636	7031	1969
rs1937777	38812483	0.06	1.1 (0.8, 1.6)	0.42	0.69	3x10 <sup>-9</sup>	265	37	4	13711	1874	77
rs756405	38814051	0.26	1.1 (0.9, 1.3)	0.36	0.41	2x10 <sup>-9</sup>	161	120	25	8572	6022	1066
rs6458068	38820666	0.17	1.1 (0.9, 1.3)	0.59	0.52	2x10 <sup>-9</sup>	205	92	9	10767	4441	456
rs2206860	38831139	0.47	1.0 (0.9, 1.2)	0.83	0.83	2x10 <sup>-9</sup>	82	157	65	4411	7759	3400
rs1678677	38836120	0.79	1.0 (0.8, 1.3)	0.69	0.48	2x10 <sup>-9</sup>	11	101	194	695	5126	9841
rs13219077	38847145	0.74	1.0 (0.8, 1.2)	0.95	0.75	2x10 <sup>-9</sup>	18	122	165	1040	6068	8550

**Supplementary Table 3.** Genotype frequencies and ORs for full model at rs3923809 in RLS+PLMs cases and controls. P values are for comparing full model to multiplicative model.

<b>Population</b> (N cases/N controls)	<b>AA frequency</b> cases/controls <b>OR (95% CI)</b>	<b>AG frequency</b> cases/controls <b>OR (95% CI)</b>	<b>GG frequency</b> cases/controls <b>OR</b>	<b>P value</b>
Iceland (429/16,866)	0.585 / 0.429 4.3 (2.8, 6.6)	0.378 / 0.454 2.7 (1.6, 4.3)	0.037 / 0.117 1	0.11
U.S. (188/662)	0.596 / 0.465 2.0 (1.1, 3.9)	0.340 / 0.432 1.2 (0.6, 2.5)	0.064 / 0.103 1	0.51

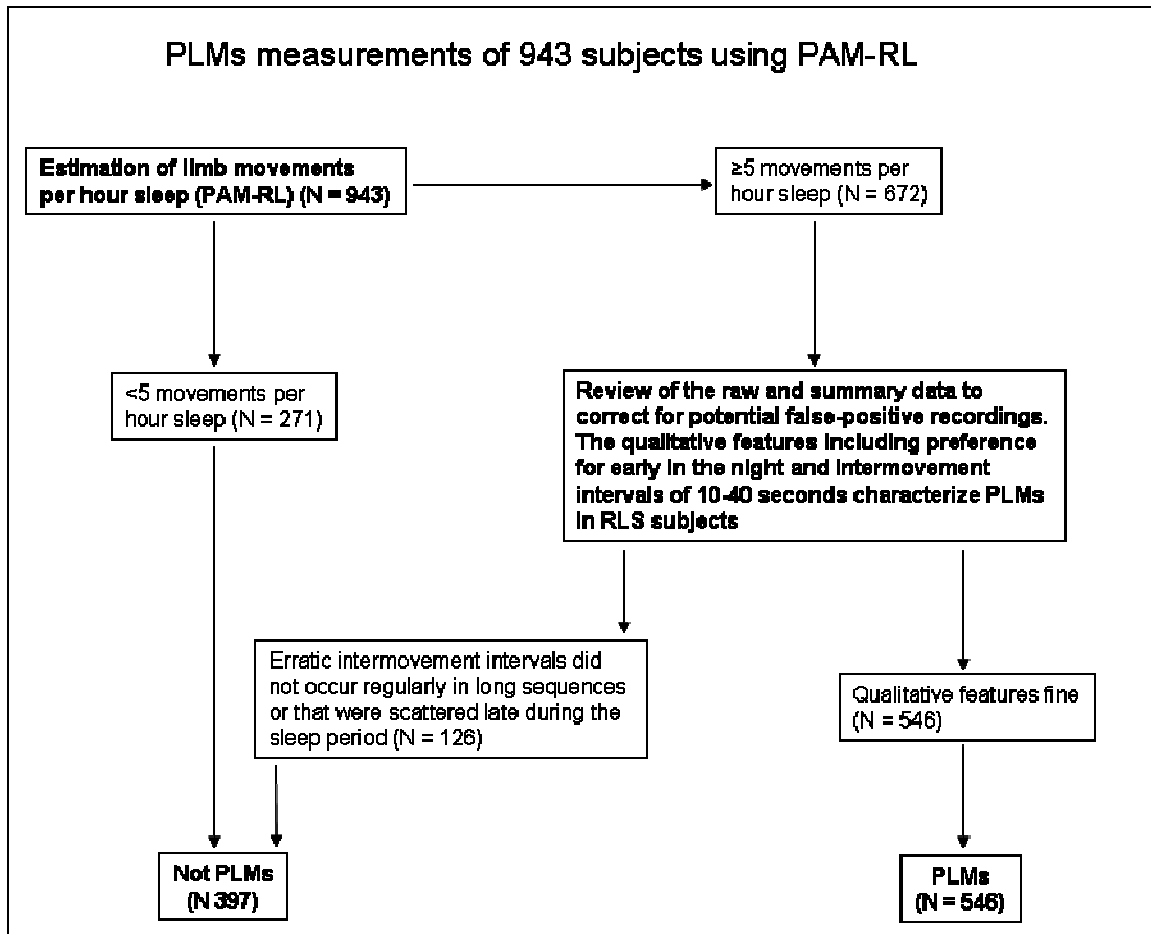
**Supplementary Table 4.** Distribution of the 306,937 P values from the initial genome wide association scan for genes that influence the risk of developing RLS with PLMs. The observed counts are given for both the unadjusted P values ( $P_{\text{obs}}$ ), as well as after applying adjustment factor from genomic controls ( $P_{\text{adj}}$ ). For reference, expected counts of P values per category are also given ( $P_{\text{exp}}$ ).

Category	$P > 0.50$	$0.50 - 0.10$	$0.10 - 0.05$	$0.05 - 0.01$	$0.01 - 0.001$	$0.001 - 0.0001$	$0.0001 - 10^{-5}$	$10^{-5} - 2 \times 10^{-7}$	$P \leq 2 \times 10^{-7}$
$P_{\text{obs}}$	146276	124384	16985	14784	3898	514	71	22	3
$P_{\text{adj}}$	153360	123235	15251	12017	2724	299	33	16	2
$P_{\text{exp}}$	153469	122775	15347	12277	2762	276.2	27.6	3	0.05



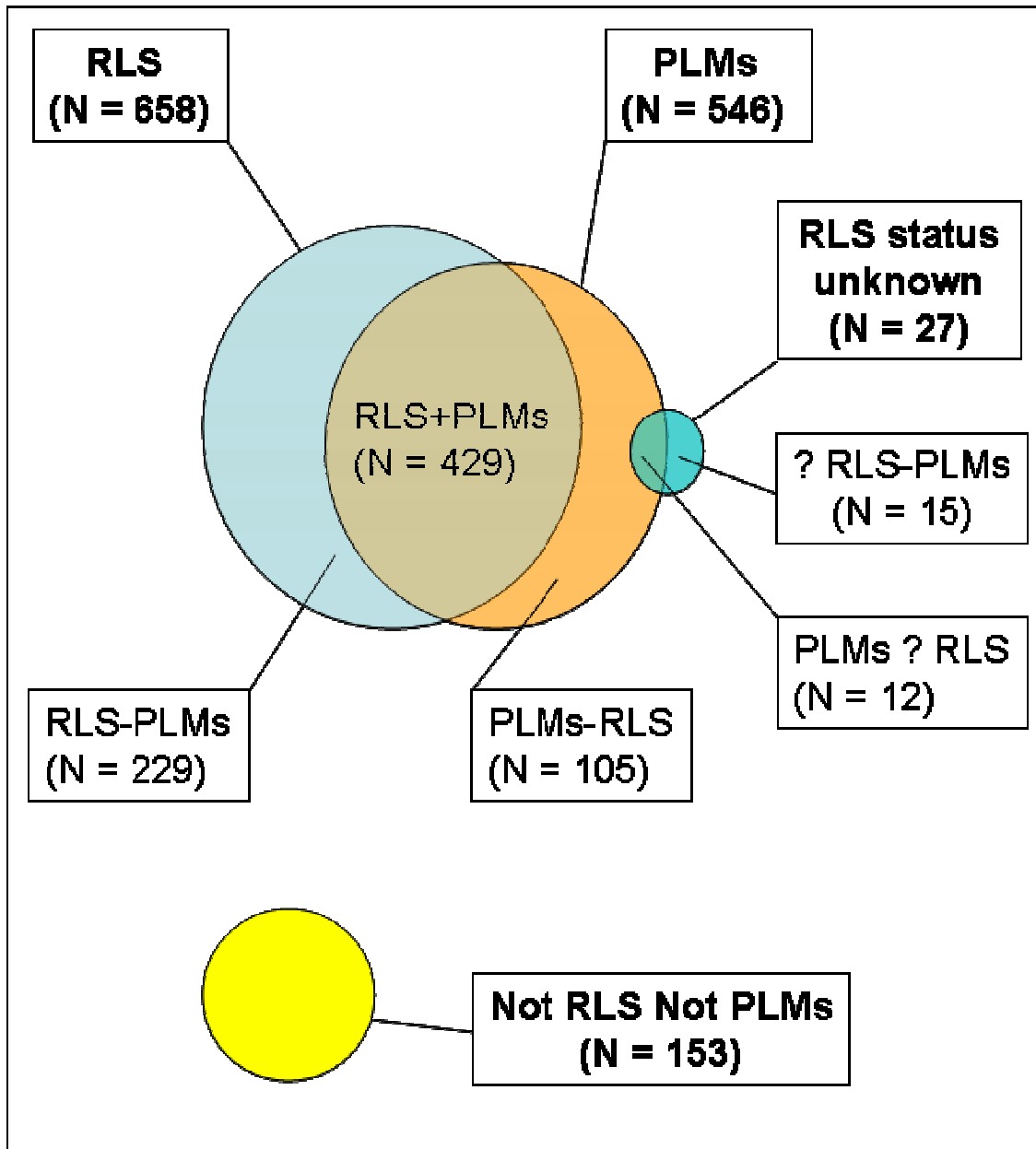
### Supplementary Figure 1. Flow chart – RLS ascertainment

Concept and design of the Icelandic portion of this study began in 2002, so that subjects answered questions that captured the four criteria for RLS established in 1995. (a) Desire to move the extremities, often associated with paresthesias/dysesthesias; (b) motor restlessness; (c) worsening of symptoms at rest with at least temporary relief by activity, and (d) worsening of symptoms in the evening or night. In line with the 2003 revised criteria we use only a, c and d and excluded question b. Thus, we considered subjects to be affected by RLS if they self reported an uncomfortable desire to move their legs with inactivity at least 2-4 times/month that was relieved by movement, and that predominated in the evening or at bedtime.

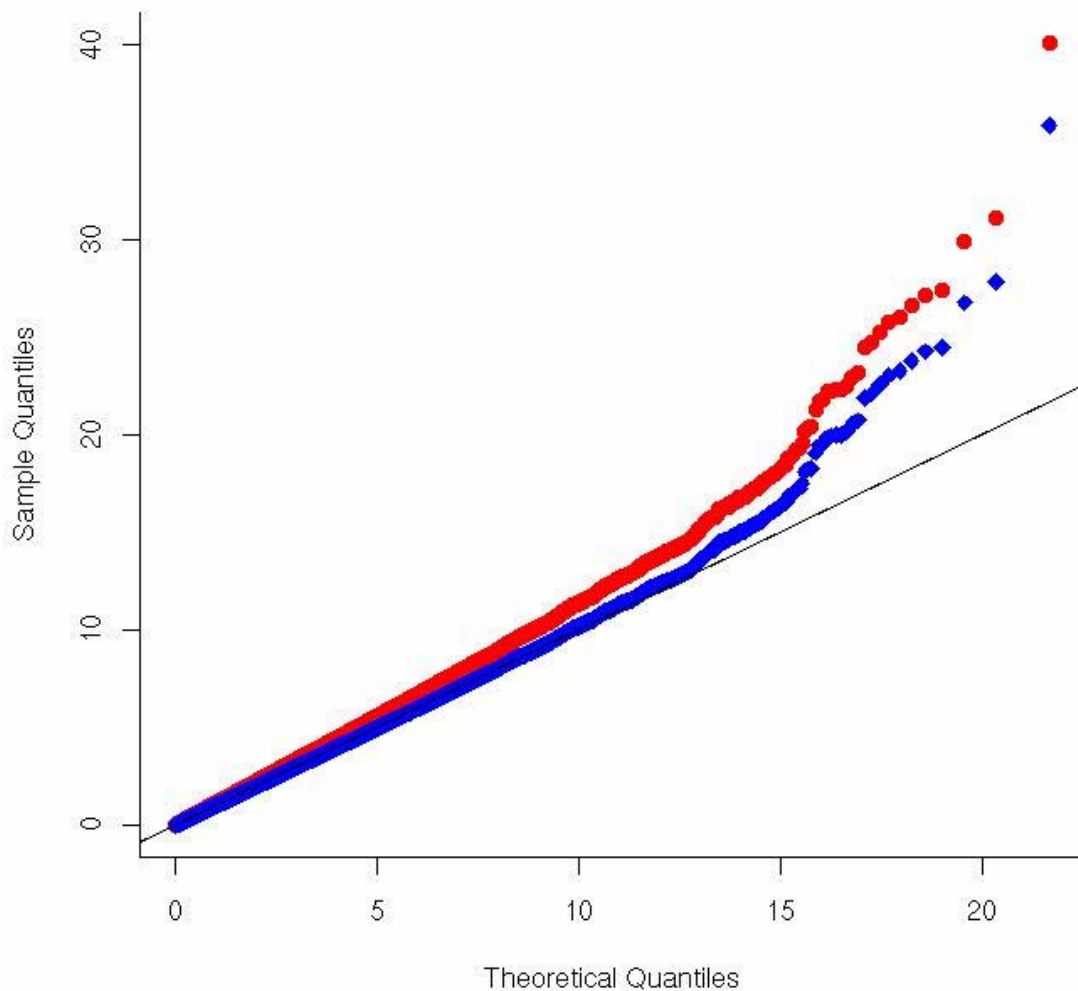


### Supplementary Figure 2. Flow chart – PLMs assessment

Subjects wore small (65gm), wristwatch-sized tri-axial accelerometers with 10Hz sampling (PAM-RL detector, IM Systems, Baltimore, MA) affixed via a Velcro strip to their most affected ankle (default: non-dominant ankle) for five consecutive nights and a nightly frequency of limb movements was derived. The PAM-RL provides an accurate assessment of polysomnographically derived frequencies (Pearson's correlation  $r = 0.87$ ,  $P < 0.0001$ ) (1), discriminates between periodic limb movements and normal nocturnal motor activity (2), and is sensitive to treatment effects in RLS subjects (3, 4). The PAM-RL is unable to discriminate PLMs that occur while awake as opposed to sleep, but can discriminate whether movements occur while recumbent or upright. Thus, individuals who had more than 5 movements/hour for at least one night while recumbent during their major rest period that includes sleep were classified as having PLMs. Of the 943 subjects studied 271 had less than 5 movements per hour sleep and 672 had 5 or more. Of the 672 126 were considered not having PLMs after ambulatory assessment by a single observer, blind to each subject's clinical features, who reviewed the raw and summary data to correct for potential false-positive recordings. 546 subjects were considered having PLMs.



**Supplementary Figure 3.** Diagram depicting the overlap between RLS and PLMs phenotypes. Of the 943 subjects 658 have RLS, 546 have PLMs, 27 have unknown RLS status and 153 have neither RLS nor PLMs. Of the 658 subjects with RLS, 429 have also PLMs whereas 229 do not have PLMs. Of the 546 subjects with PLMs, 429 have also RLS, 105 do not have RLS and for 12 subjects the RLS status is not known. Of the 27 subjects with unknown RLS status, 12 have PLMs and 15 do not have PLMs.



**Supplementary Figure 4.** A Quantile-Quantile plot (Q-Q plot) of the 306,937 chi-square statistics from the initial genome-wide association scan. The results are for the discovery sample of 306 Icelandic RLS+PLMs subjects versus 15,664 control individuals from the Icelandic population. The unadjusted statistics are displayed as filled red circles. The statistics divided by a scaling factor computed from genomic controls are displayed as filled blue diamonds. The equiangular line is displayed for reference purposes.

## Ascertainment

We measured periodic limb movements in 943 Icelanders who had answered the RLS questionnaire (see **Supplementary Table 1** for demographics. Notice that in the Table we only show those who had: complete RLS questionnaires, a genotype for marker rs3923809 and were either diagnosed with RLS, PLMs or both). Periodic limb movements in sleep occur at a frequency of more than 5/h sleep in most RLS subjects on at least one of two nights in a sleep laboratory (5). Given their considerable night-to-night variability (6, 7) we regarded a frequency of periodic limb movements of  $\geq 5/h$  on any one of five PAM-RL recording nights as positively affected. A single observer, blind to each subject's clinical features, reviewed the raw and summary data to correct for potential false-positive recordings. 126 subjects, with complete RLS data and a genotype for marker rs3923809, and frequency of periodic limb movements  $\geq 5/h$  on any one of five PAM-RL recording nights were considered not having PLMs after ambulatory assessment. This determination was made independent of the absolute number and frequency of movements. The qualitative features including preference for early in the night (8), and sleep stage, and intermovement intervals of 10-40 seconds (9) characterize periodic limb movements. The PAM-RL proved to be a durable, simple to use, and reliable device. PLM data was available from 93.7% of the potential nights with 3.2% lost to non-compliance and 3.1% of nights lost due to device malfunction. Data from 5 nights was available on 82% of the subjects, and at least 3 nights of PLM data were available on 98.4% of subjects. Inter-rater reliabilities for estimation of frequency of movement, derived from a sample of 191 subject nights, revealed high correlations (Spearman  $\rho = 0.987$ ;  $P < 0.0001$ ).

The controls used for the study were recruited as a part of various genetic programs at deCODE. The RLS status of the controls was unknown. Individuals with known RLS or PLMs measurements over 5 were excluded as controls. The 15,634 controls used for the genome-wide association scan came from genetic programs in the following diseases (approximate number of participants in brackets): Addiction (3,000), Asthma (350), Breast Cancer (1,450), Chronic Obstructive Pulmonary Disease (200), Colon Cancer (950), Obesity (450), Infectious diseases (1,500), Longevity (1,500), Myocardial Infarction (2,000), Migraine (1,100), Type II diabetes (1,200), Prostate Cancer (1,400), Schizophrenia (550), Stroke (600), and a set of Population Controls (750). The 1,233 controls used for replication in Iceland (Replication I) came from the following programs: Asthma (700), Cardiovascular Diseases (400) and Migraine (150). Since some of the individuals used as controls were participants in more than one program, the numbers of participants in individual programs add up to more than the numbers reported in Tables 1 and 2. No significant differences in frequencies were observed among the groups that make up the controls, neither separately (Discovery vs. Replication I) nor combined ( $P = 0.99$ ).

The US replication sample was recruited through the Emory Program in Sleep in Atlanta, Georgia. Consent for inclusion and blood draws for the proposed analyses occurred under the auspices of an IRB-HIC approved protocol (HIC ID 133-98) Clinical Research in Neurology (CRIN). Patients presenting to other general and subspecialty neurology clinics and their spouses (Alzheimer's patients (N = 188), Parkinson's patients (N = 188) and other less frequent neurological conditions and spouses (N=286)) were chosen as controls.

Ascertainment of RLS in the U.S. sample was derived following personal examination by a RLS specialist. Ambulatory assessment and confirmation of PLMs by the PAM-RL or polysomnography was available for all 188 genotyped subjects.

### **Phenotypic Considerations**

Under the best of circumstances the sensitivities and specificities of subjective and objective measures for RLS do not exceed 0.80-0.90 (10). We therefore assessed the limitations intrinsic to our ascertainment strategy by personally examining a subgroup of 123 Icelanders conforming strictly to the RLS consensus criteria. We assessed the diagnostic accuracy of self-report by comparison to the present diagnostic standard; viz., expert clinical judgement. This derived from face-to-face interviews and physical examinations by 1 of 6 clinicians experienced in the diagnosis and care of RLS patients (11). Assignment of affection status based on endorsement of RLS consensus criteria, revealed a type I error rate of 22.7% (11). Reclassification of the identified false-positives was not performed for the association analysis.

### **Association Analysis**

We tested the association of an allele to RLS using a standard likelihood ratio statistic that, if the subjects were unrelated, would asymptotically have a  $\chi^2$  distribution with 1 degree of freedom under the null hypothesis. Allelic frequencies, rather than carrier frequencies, are presented for the markers. Allele-specific OR values were calculated assuming a multiplicative model for the two chromosomes of an individual (12). Confidence intervals of the ORs were based on the variance-adjusted tests for association, based on a log-normal approximation. Results from the Icelandic and U.S. groups were combined using a Mantel-Haenszel model (13) in which the groups were allowed to have different allelic population frequencies, but were assumed to have common relative risks. For each of the case-control groups, there was no significant deviation from Hardy-Weinberg equilibrium (HWE) in the controls. The same is true for the cases, indicating that the risk resulting from the two chromosomes each person carries is adequately fit by the multiplicative model.

All of the case-control groups included individuals that were related to each other, causing the aforementioned  $\chi^2$  test statistic to have a mean greater than 1 and median greater than 0.675<sup>2</sup>. For the Icelandic discovery sample, for which we had genome-wide association data, we estimated the inflation factor in three ways: (i) using a previously described procedure in which we simulated genotypes through the genealogy of 731,175 Icelanders (14, 15), (ii) by calculating the mean of the 306,937  $\chi^2$  statistics and (iii) by

computing the median of the 306,937  $\chi^2$  statistics and dividing it by 0.675<sup>2</sup>. (ii) and (iii) are methods of genomic control (16) and adjust for both relatedness and potential population stratification. The inflation factors, estimated by (i), (ii) and (iii), were 1.070, 1.114 and 1.117, respectively. Results for the Icelandic samples are based on adjusting the  $\chi^2$  statistics by dividing by 1.117. **Supplementary Figure 4** shows a QQ plot of the  $\chi^2$  statistics, before and after adjustment, against the  $\chi^2$  distribution.

The U.S. replication sample included 3 extended families with a total of 25 affecteds. Using that information to estimate the inflation by method (i) yielded a correction factor of 1.216.

### Calculation and Interpretation of Population Attributable Risk

Population attributable risk is defined as the fraction of cases that would be reduced from the population if the risks of all individuals could be made, e.g. through a treatment, to be the same as non-carriers of the at-risk variant(s). It can be calculated using the following formula:

$$PAR = 1 - (1/W)$$

where

$$W = \text{Frequency}(AA) \times RR(AA) + \text{Frequency}(Aa) \times RR(Aa) + \text{Frequency}(aa).$$

Here ‘A’ denotes the at-risk allele and ‘a’ denotes the wild-type. Frequency is frequency in the general population, which is estimated from the controls assuming Hardy-Weinberg Equilibrium. RR(AA) and RR(Aa) are respectively risks of homozygous (AA) and heterozygous (Aa) carriers of the at-risk allele relative to the risk of the non-carriers (aa). Since RR(aa) = 1 by definition, W is the (average) population risk relative to the risk of aa. Hence 1/W is the fraction of cases remaining if everybody had RR = 1, and 1-1/W is the fraction reduced. Treating the controls as population controls, and assuming a multiplicative model for risks, then it can be shown that RR(AA) and RR(Aa) can be estimated by OR<sup>2</sup>(A) and OR(A) respectively. For example, in Table 1, the PAR for RLS+PLM in the Combined Icelandic cohort, was estimated as

$$1 - [ 1/(0.636^2 \times 1.8^2 + (2 \times 0.636 \times 0.364) \times 1.8 + 0.364^2) ] = 0.57$$

When calculating PAR for Iceland and US combined, the simple average of the control frequencies and the OR computed from the Mantel-Haenszel model is used. Finally, we note that it is possible to have many independent gene variants each having substantial PAR. This is because the joint PAR of two independent variants that follow a log-additive model for risk is not the sum of the individual PARs. Instead,

$$PAR_{\text{joint}} = 1 - (1-PAR_1) \times (1-PAR_2).$$

For example, if two independent variants each have PAR equal to 60%, then the joint PAR is 1 - (1-0.6) × (1-0.6) = 1 - (0.4 × 0.4) = 0.84 = 84%.

Finally, it is noted that PAR is an important measure of the impact of a variant from a public health point of view. It is also relevant to prevalence differences between ethnic groups that have very different frequencies of the variant. It is however not the right measure to evaluate contribution to familial clustering of the disease. For that, the sibling recurrent risk ratio will be more appropriate (17).

## References

1. E. Sforza, M. Johannes, B. Claudio, *Sleep Med* **6**, 407 (Sep, 2005).
2. K. Tuisku, M. M. Holi, K. Wahlbeck, A. J. Ahlgren, H. Lauerma, *Mov Disord* **18**, 442 (Apr, 2003).
3. K. Tuisku, M. M. Holi, K. Wahlbeck, A. J. Ahlgren, H. Lauerma, *Eur J Neurol* **12**, 385 (May, 2005).
4. A. R. Rye D, Carson S and Ritchie S. , *Sleep* **28**, A270 (2005).
5. J. Montplaisir *et al.*, *Mov Disord* **12**, 61 (Jan, 1997).
6. D. L. Bliwise, M. A. Carskadon, W. C. Dement, *Arch Gerontol Geriatr* **7**, 273 (Dec, 1988).
7. E. Sforza, J. Haba-Rubio, *Sleep Med* **6**, 259 (May, 2005).
8. W. J. Culpepper, P. Badia, J. I. Shaffer, *Sleep* **15**, 306 (Aug, 1992).
9. T. Pollmacher, J. Mullington, C. J. Lauer, *Biol Psychiatry* **42**, 713 (Oct 15, 1997).
10. W. A. Hening, *Sleep Med* **5**, 285 (May, 2004).
11. B. D. Rye D, Iranzo A, et al. , *Sleep* **27**, 306 (2004).
12. C. T. Falk, P. Rubinstein, *Ann Hum Genet* **51**, 227 (Jul, 1987).
13. N. Mantel, W. Haenszel, *J Natl Cancer Inst* **22**, 719 (Apr, 1959).
14. S. F. Grant *et al.*, *Nat Genet* **38**, 320 (Mar, 2006).
15. B. Devlin, S. A. Bacanu, K. Roeder, *Nat Genet* **36**, 1129 (Nov, 2004).
16. B. Devlin, K. Roeder, *Biometrics* **55**, 997 (Dec, 1999).
17. N. Risch, *Am J Hum Genet* **46**, 222 (Feb, 1990).