MEIS1 variant as a determinant of autonomic imbalance in Restless Legs Syndrome

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Running title: Heart rate variability in RLS patients

Supplementary figures and tables:

Supplementary Figure S1: Box-whisker plots showing RRmean, SDNN and RMSSD in control subjects (a), RLS patients (b), RLS TT patients (c) and RLS GG patients (d) during N2, N3 and REM sleep stages. Data are represented as lower quartile, median and upper quartile (boxes), and minimum and maximum ranges (whiskers). Red dashed lines indicate the median values for RRmean, SDNN and RMSSD in control patients during N2. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.005$ following Student's or Wilcoxon's tests. # $p_a \leq 0.05$; ### $p_a \leq 0.005$ following statistical test adjusted for age and gender (Control *vs* RLS) or for PLMS (RLS TT *vs* RLS GG). RRmean= mean normal-to-normal R-R length; SDNN=standard deviation of normal-to-normal R-R intervals; RMSSD=root mean square of successive differences.
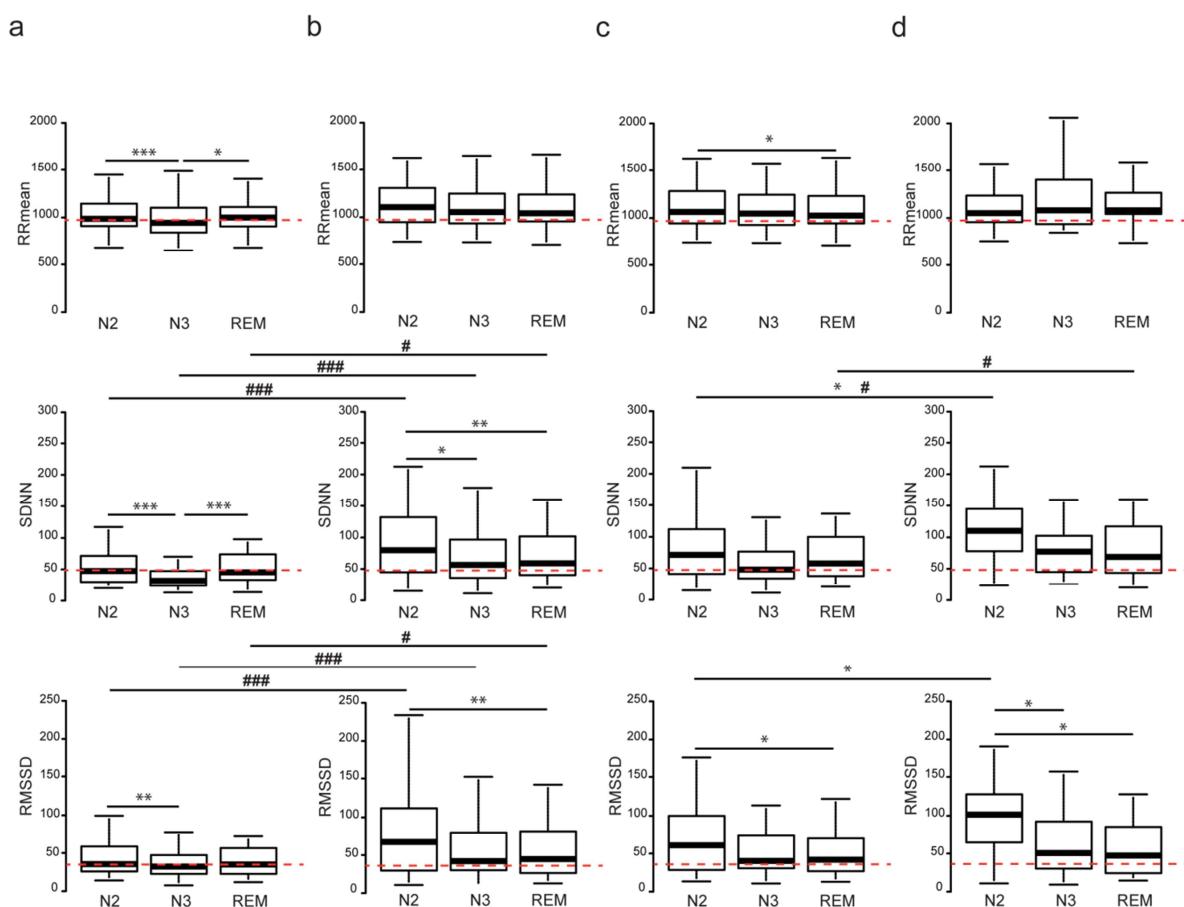
Supplementary Figure S2: Box-whisker plots showing SD1 and SD2 in control subjects (a), RLS patients (b), RLS TT patients (c) and RLS GG patients (d) during N2, N3 and REM sleep stages. Data are represented as lower quartile, median and upper quartile (boxes), and minimum and maximum ranges (whiskers). Red dashed lines indicate the median values for SD1 or SD2 in control patients during N2. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.005$ following Student's or Wilcoxon's tests. [#] $p_a \leq 0.05$; [###] $p_a \leq 0.005$ following statistical test adjusted for age and gender (Control *vs* RLS) or for PLMS (RLS TT *vs* RLS GG). SD1=standard deviation of instantaneous beat-to-beat interval variability; SD2=standard deviation of continuous long-term R/R interval variability.
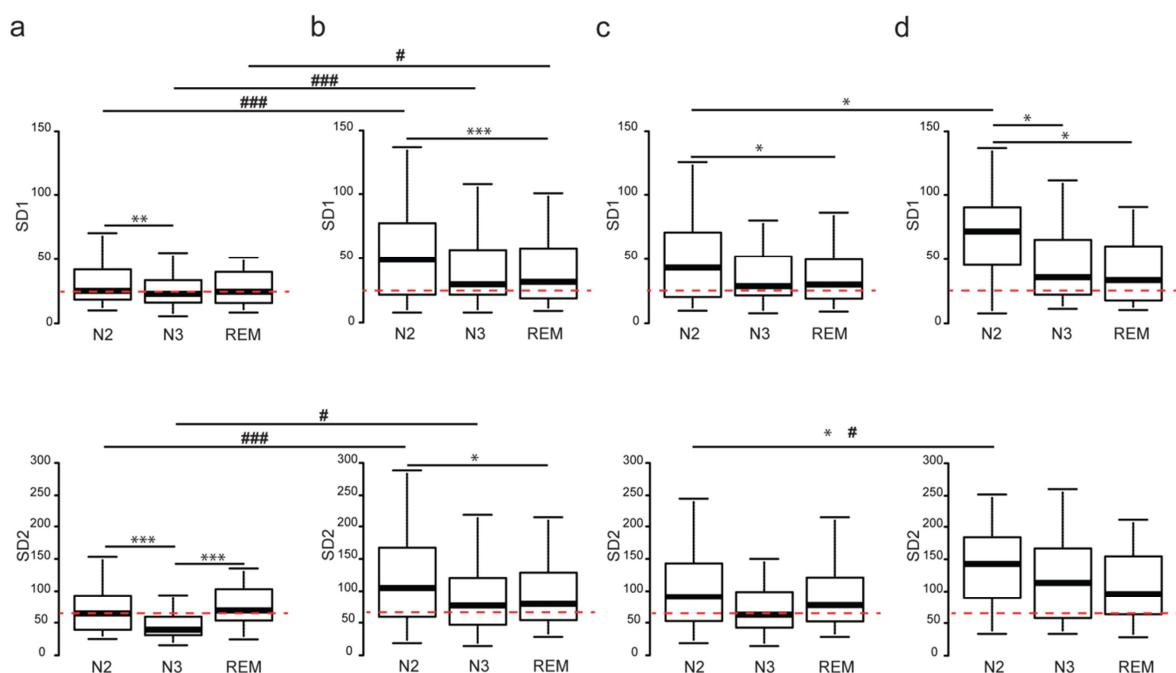
Supplementary Table S1: Results of heart rate variability analysis in the time-domain in the different sleep stages in RLS patients and healthy controls, and in RLS patients sorted according to the *MEIS1* SNP rs2300478 genotype (GG or TT). Data are presented as Median ± MAD. *p*=p value following Student or Wilcoxon's test; p_a= p value adjusted for age and gender. * $p \leq 0.05$; ** $p \leq 0.01$ *** $p \leq 0.005$. RRmean= mean normal-to-normal R-R length; SDNN=standard deviation of normal-to-normal R-R intervals; RMSSD=root mean square of successive differences.

			N2	N3	REM
Control	Mean RR	Median±MAD	988.3±123.9	945.9±155.8	1000.1±109.2
	SDNN	Median±MAD	47.6±19.5	32.3±10.4	45.8±19.7
	RMSSD	Median±MAD	35.5±16.3	32.0±10.5	34.7±18.2
RLS	Mean RR	Median±MAD	1060.6±172.4	1057.0±161.0	1042.1±123.8
	SDNN	Median±MAD	83.6±42.4	56.7±24.0	58.9±25.5
	RMSSD	Median±MAD	68.6±38.6	41.6±19.2	44.6±21.4
Non adjusted	Mean RR	*p*	0.034*	0.003***	0.042*
	SDNN	*p*	0.0003***	2.10^{-5}***	0.047*
	RMSSD	*p*	6.10^{-4}***	9.10^{-4}***	0.035*
Adjusted	Mean RR	p_a	0.36	0.12	0.40
	SDNN	p_a	0.003***	4.10^{-4}***	0.03*
	RMSSD	p_a	2.10^{-4}***	0.0026***	0.017*
RLS TT	Mean RR	Median±MAD	1062.7±176.0	1048.3±158.9	1026.3±159.7
	SDNN	Median±MAD	71.5±35.3	48.2±19.5	58.0±24.6
	RMSSD	Median±MAD	60.7±35.2	40.3±15.8	42.0±18.8
RLS GG	Mean RR	Median±MAD	1049.9±117.8	1081.5±155.9	1082.3±90.2
	SDNN	Median±MAD	109.9±37.4	77.0±28.8	68.9±26.4
	RMSSD	Median±MAD	101.1±29.8	50.3±27.6	47.1±24.8
	Mean RR	*p*	0.72	0.20	0.22
	SDNN	*p*	0.025*	0.06	0.42
	RMSSD	*p*	0.02*	0.78	0.59
	Mean RR	p_a	0.83	0.38	0.26
	SDNN	p_a	0.024*	0.58	0.038*
	RMSSD	p_a	0.056	0.48	0.39

Supplementary Table S2: Poincare plot geometry analysis of heart rate variability in the different sleep stages in RLS patients and healthy controls, and in RLS patients sorted according to the *MEIS1* SNP rs2300478 genotype (GG or TT). Data are presented as Median ± MAD. *p*=p value following Student or Wilcoxon's test; p_a= p value adjusted for age and gender. * $p \leq 0.05$; ** $p \leq 0.01$ *** $p \leq 0.005$. SD1=standard deviation of instantaneous beat-to-beat interval variability; SD2=standard deviation of continuous long-term R/R interval variability.

			N2	N3	REM
Control	**SD1**	**Median**±MAD	**25.2**±11.6	**22.7**±7.4	**24.6**±12.9
	SD2	**Median**±MAD	**64.3**±25.8	**39.4**±12.4	**69.1**±24.5
RLS	**SD1**	**Median**±MAD	**48.9**±27.5	**29.5**±13.6	**31.6**±15.2
	SD2	**Median**±MAD	**105.1**±52.8	**76.3**±33.6	**79.4**±31.5
Non adjusted	**SD1**	*p*	**6.10^{-4}****	**0.002*****	**0.036***
	SD2	*p*	**4.10^{-4}****	**0.012***	**0.080**
Adjusted	**SD1**	p_a	**2.10^{-4}****	**4.10^{-3}****	**0.017***
	SD2	p_a	**8.10^{-3}****	**0.019***	**0.08**
RLS TT	**SD1**	**Median**±MAD	**43.0**±25.2	**28.6**±11.2	**29.9**±13.5
	SD2	**Median**±MAD	**90.4**±41.9	**62.4**±27.0	**77.2**±30.1
RLS GG	**SD1**	**Median**±MAD	**71.6**±21.2	**35.7**±18.5	**33.5**±17.6
	SD2	**Median**±MAD	**142.7**±48.8	**113.3**±54.4	**95.9**±33.6
	SD1	*p*	**0.021***	**0.099**	**0.59**
	SD2	*p*	**0.036***	**0.50**	**0.44**
	SD1	p_a	**0.057**	**0.44**	**0.39**
	SD2	p_a	**0.028***	**0.94**	**0.37**