

<b>GSK Medicine:</b> Ropinirole	
<b>Study Number:</b> ROP115168 (PGx366)	
<b>Title:</b> PGx366 Pharmacogenetics study of sleep-related phenotypes in subjects from ropinirole clinical studies RRL100013, 101468/204, 101468/205, ROX104805, ROR104836, ROP106064, 108862, ROX107846	
<b>Start Date (FPA actual):</b> 02-JUL-2010	<b>Completion Date (CSR actual):</b>
<p><b>Rationale:</b> Ropinirole is approved for the treatment of Parkinson’s Disease (PD) and Restless Legs Syndrome (RLS). Prescriber information for ropinirole carries a warning for sudden onset of sleep (falling asleep during activities of daily living). The frequency of somnolence, as recorded in the ropinirole Global Data Sheet, is very common in patients with PD in monotherapy studies (<math>\geq 1/10</math>), and common in patients with PD in adjunct therapy studies (<math>\geq 1/100</math>, <math>&lt; 1/10</math>). In patients with RLS, the frequency of somnolence is common (<math>\geq 1/100</math>, <math>&lt; 1/10</math>). Post-marketing data demonstrates that ‘extreme somnolence, SOS’ is very rare (<math>&lt; 1/10,000</math>).</p> <p>Sleep-related events were observed within eight GSK clinical studies carried out in patients with PD or RLS. Three of the studies (108862, ROP106064, ROX107846) were in Japanese patients only, and the other five studies (ROR104836, RRL100013, 101468/204, 101468/205, ROX104805) were in non-Japanese patients (<math>\geq 94\%</math> White Caucasians). When pooling patients across clinical studies, somnolence was observed in 32% of patients with PD treated with ropinirole, and 12% of patients with RLS treated with ropinirole. While the rate of somnolence observed in placebo-treated patients with RLS was 6%, no placebo-treated patients with PD were included in these GSK clinical studies. In addition, cases of investigator reported sudden onset of sleep (SOS) and fatigue were also observed.</p> <p>Certain features of both drug-related somnolence and SOS appear to be similar to naturally occurring human sleep disorders; hypersomnia (sleep of excessive depth and duration) and narcolepsy (sleep disorder characterized by brief and sudden attacks of deep sleep often occurring with cataplexy and hypnagogic hallucinations). The well known genetic susceptibility factors for narcolepsy have also been shown in recent studies to be associated with hypersomnia, thereby pointing to a potential pathophysiological overlap between these conditions.</p> <p>Genetic susceptibility to narcolepsy and hypersomnia may be associated with common genetic variation at these loci: <i>HLA-DRB1</i> (major histocompatibility complex, class II, DR beta-1), <i>TCRA</i> (T-call antigen receptor, alpha subunit) and a region containing the <i>CPT1B</i> and <i>CHKB</i> (carnitine palmitoyltransferase 1, muscle/choline kinase, beta) genes<sup>1,2,3,4,5</sup>. In addition, one report suggests that a variant (rs2858884) near <i>HLA-DQA2</i> (major histocompatibility complex, class II, DR beta-1), which is strongly linked to <i>HLA-DRB1*03-HLA-DQB1*02</i> (major histocompatibility complex, class II, DQ beta-1) and <i>HLA-DRB1*1301-HLA-DQB1*0603</i>, may have a protective effect against narcolepsy<sup>6</sup>. These genes/gene regions were therefore considered as candidates for evaluation in patients treated with ropinirole displaying sleep-related phenotypes (SOS, somnolence and fatigue) and in patients treated with ropinirole not displaying sleep-related phenotypes.</p>	
<p><b>Objectives:</b> The objectives of this exploratory Pharmacogenetic (PGx) experiment were to investigate whether genetic variation within the candidate genes/gene regions (<i>HLA-DRB1</i>, <i>TCRA</i>, <i>HLA-DQA2</i> and <i>CPT1B/CHKB</i>) is associated with SOS, somnolence and fatigue in patients with PD or RLS treated with ropinirole in GSK clinical studies ROR104836, RRL100013, 101468/205, 101468/204, ROX104805, 108862, ROP106064 and ROX107846.</p>	
<b>Indication:</b> Parkinson’s Disease and Restless Legs Syndrome	

**Study Investigators/Centers:** GSK conducted the experiment using DNA samples and clinical data collected in ROR104836, RRL100013, 101468/205, 101468/204, ROX104805, 108862, ROP106064 and ROX107846 clinical trials.

**Research Methods:** Genomic DNA was extracted from peripheral blood in patients treated with ropinirole: cases who experienced sleep events (n=7 SOS; n=158 somnolence; n=113 fatigue) and controls who received ropinirole without exhibiting any sleep events (n=853). Some patients experienced more than one type of sleep event, and therefore were included in more than one case group in the analysis. All case and control patients provided written informed consent and provided a blood sample for PGx research. Single nucleotide polymorphisms (SNPs) that tag the two *HLA* variants of interest were genotyped for these analyses. For *HLA-DR15*, a haplotype defined by the *HLA-DRB1\*1501* and *HLA-DQB1\*0602* alleles, four tagging SNPs (rs6901830, rs7773756, rs6919855, rs2647012) were genotyped in Japanese patients and one SNP (rs3135388) was genotyped in the predominantly White (non-Japanese) patients. For a subset of 24 Japanese patients, who, on the basis of SNP data, carried either the *HLA-DRB1\*1501* or *HLA-DRB1\*1302* allele, Labtype SSO (One Lambda Inc., Canoga Park, CA, USA) *HLA-DRB1* genotyping data was generated to determine the actual *HLA-DRB1* genotypes. *HLA-DQA2* was tagged by SNP rs2859090 in both Japanese and predominantly White (non-Japanese) populations. In addition the candidate SNPs in *TCRA* and *CPT1B/CHKB* (rs1154155 and rs5770917, respectively), were also genotyped.

The SNPs tagging *HLA-DQA2* and the *HLA-DR15* haplotype plus SNPs in the *TCRA* and *CPT1B/CHKB* genes were genotyped by KBioScience (Hoddesdon, Herts, UK) using fluorescence resonance energy transfer (FRET) based platforms. High resolution HLA data for Japanese SOS cases was generated by Histogenetics (Ossining, NY, USA) for *HLA-DRB1* and *HLA-DQB1* using Sequenced Based Typing (SBT). Labtype SSO *HLA-DRB1* genotyping data was generated by GSK Genetics (RTP, NC, USA).

*HLA-DR15*, *HLA-DQA2*, *TCRA* and *CPT1B/CHKB* genetic variants were evaluated for association with sleep events observed in patients treated with ropinirole.

**Data Source:** ROR104836, RRL100013, 101468/205, 101468/204, ROX104805, 108862, ROP106064 and ROX107846 clinical study data.

**Study Design:** This was a retrospective, exploratory PGx investigation to identify genetic variants associated with sleep events observed in patients with PD or RLS treated with ropinirole. Association analysis was performed in all patients on active ropinirole treatment, within each of the eight individual clinical studies to determine study-specific genetic effects. Meta-analysis was also performed to combine effects across more than one study.

**Study Population:** All patients treated with ropinirole within clinical studies ROR104836, RRL100013, 101468/205, 101468/204, ROX104805, 108862, ROP106064 and ROX107846 who gave a blood sample and consent for genetic research, who were successfully genotyped for at least one genetic marker under evaluation and for whom clinical end-point data was available.

**Study Exposures, Outcomes:** Patients treated with ropinirole from ROR104836, RRL100013, 101468/205, 101468/204, ROX104805, 108862, ROP106064 and ROX107846 clinical trials; sleep events were defined as SOS, somnolence and fatigue.

**Data Analysis Methods:** Analysis was performed using penalized logistic regression for three endpoints: the presence/absence of SOS, somnolence or fatigue. Study-specific covariates were included, as appropriate. The p-values as well as estimated odds ratios with 95% confidence intervals are reported. All single marker analyses were performed using SAS 9.2. Study-wide significance thresholds were pre-determined for each genotype-phenotype association test to maintain an overall alpha of 0.05: more weight was given to the somnolence and SOS end-points and the *HLA-DR15* and *TCRA* genes/gene regions, as there is stronger evidence in the scientific literature supporting their involvement in sleep-related phenotypes:

**Pre-specified Thresholds for Statistical Significance (Correction for Multiple Testing)**

Genetic Marker	Somnolence or SOS	Fatigue
<i>HLA-DR15</i> or <i>TCRA</i>	P<0.008	P<0.004
<i>CPT1B/CHKB</i> or <i>HLA-DQA2</i>	P<0.002	P<0.001

Single studies were evaluated individually, and meta-analyses were conducted to combine effects across studies. Both fixed effect and random effects meta-analysis models were used. A fixed effect meta-analysis model was fitted using the Mantel-Haenzel method. This model allows for within study variability but assumes one true effect size shared by all studies. This method is recommended for rare events, and so was considered more appropriate for evaluation of the SOS events observed, as it does not assume that trial estimates are normally distributed. A random effects model was fitted using the DerSimonian-Laird method<sup>7</sup>. This model allows for within and between study variation allowing the true effect to vary from study to study. Meta-analysis was performed using the R meta library and metagen function<sup>8</sup>.

**Limitations:** This exploratory PGx analysis was conducted using clinical data and DNA obtained during the conduct of clinical studies ROR104836, RRL100013, 101468/205, 101468/204, ROX104805, 108862, ROP106064 and ROX107846, none of which considered PGx analyses in their design. The experiment was well-powered to detect the potential effect of *HLA-DR15* and *TCRA* on somnolence, assuming odds ratios greater than 2 and 4, respectively, as have been reported with hypersomnia. However, the experiment was under-powered to detect any genetic effects on SOS of the size reported between *HLA-DR15* and narcolepsy (odds ratio ~15). In addition, these studies were undertaken in different disease populations, different ethnic groups and varied by formulation, treatment group, duration and whether they were randomised double-blind or open-label. Therefore, any results suggesting a positive or negative association between a genetic variant and any sleep event would require validation in an independent sample.

**Study Results:** No statistically significant associations were observed meeting pre-determined thresholds between any of the genetic markers tested (*HLA* and candidate gene variants) and any of the sleep phenotypes (SOS, somnolence and fatigue) evaluated in the single study analysis or the meta-analysis, in patients treated with ropinirole:

**Meta-analysis P values using the Fixed Effects Model and All Clinical Studies**

Genetic Marker	SOS	Somnolence	Fatigue
<i>HLA-DR15</i>	0.760	0.196	0.100
<i>TCRA</i>	0.962	0.880	0.565
<i>HLA-DQA2</i>	0.573	0.399	0.259
<i>CPT1B/CHKB</i>	0.135	0.814	0.622

Data were similar when applying the random effects model. Performing the analysis in either only Japanese or Non-Japanese clinical studies did not reveal any statistically significant associations.

**Conclusion:** In this retrospective, exploratory PGx analysis, no genetic evidence has been identified to indicate that the variants (HLA and candidate gene) included in this experiment predispose patients with PD or RLS, treated with ropinirole, to sleep-related events. As this PGx experiment was well-powered to detect the effects of *HLA-DR15* and genetic variation within *TCRA* on somnolence, we can conclude that in this sample set *HLA-DR15* and genetic variation within *TCRA* do not influence the somnolence events observed with ropinirole treatment. This study cannot rule out the effects of the genetic markers tested on SOS events observed in patients treated with ropinirole, as the study was not well-powered to detect them.

**Publications (list full citation of all manuscripts):**

**References:**

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