Targeted sequencing reveals low-frequency variants in *EPHA* genes as markers of paclitaxel-induced peripheral neuropathy

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Translational Relevance

Paclitaxel treatment frequently cause peripheral neuropathy, an adverse event that can limit treatment course and lead to permanent symptoms drastically decreasing quality of life. Our group has contributed to the identification and validation of common polymorphisms in *EPHA* genes associated with paclitaxel neuropathy, but a large part of the inter-individual variation in neuropathy remains unexplained. We hypothesized that low-frequency variants with strong effects may contribute to the neuropathy variability in patients. By performing targeted exon sequencing of candidate genes we found for the first time that patients carrying low-frequency non-synonymous coding variants in *EPHA5/6/8* contribute to paclitaxel-induced neuropathy susceptibility. Furthermore, these genes might also be relevant neuropathy markers for other neurotoxic drugs due to the involvement of Eph receptors in neuronal functions.

ABSTRACT

Purpose: Neuropathy is the dose limiting toxicity of paclitaxel and a major cause for decreased quality of life. Genetic factors have been shown to contribute to paclitaxel neuropathy susceptibility; however, the major causes for inter-individual differences remain unexplained. In this study we identified genetic markers associated with paclitaxel-induced neuropathy through massive sequencing of candidate genes.

Experimental Design: We sequenced the coding region of 4 *EPHA* genes, 5 genes involved in paclitaxel pharmacokinetics and 30 Charcot-Marie-Tooth genes, in 228 cancer patients with no/low neuropathy or high grade neuropathy during paclitaxel treatment. An independent validation series included 202 paclitaxel-treated patients. Variation-/ gene-based analyses were used to compare variant frequencies among neuropathy groups and Cox regression models were used to analyze neuropathy evolution along treatment.

Results: Gene-based analysis identified *EPHA6* as the gene most significantly associated with paclitaxel-induced neuropathy. Low frequency non-synonymous variants in *EPHA6* were present exclusively in patients with high neuropathy and all affected the ligand binding domain. Accumulated dose analysis in the discovery series showed a significantly higher neuropathy risk for *EPHA5/6/8* low-frequency non-synonymous variant carriers (HR=14.60, 95%CI=2.33-91.62, P=0.0042) and an independent cohort confirmed an increased neuropathy risk (HR=2.07, 95%CI=1.14-3.77, P=0.017). Combining the series gave an estimated 2.50-fold higher risk of neuropathy (95%CI=1.46-4.31; $P=9.1x10^{-4}$).

Conclusion: This first study sequencing *EPHA* genes revealed that low frequency variants in *EPHA6, EPHA5* and *EPHA8* contribute to the susceptibility to paclitaxel-induced neuropathy. Furthermore, EPHAs neuronal injury repair function suggests that these genes might constitute important neuropathy markers for many neurotoxic drugs.

INTRODUCTION

The anticancer agent paclitaxel is a microtubule inhibitor widely used in the treatment of many solid tumors (1). Peripheral neuropathy is its dose-limiting toxicity (2), and severe neuropathy cases with an important reduction in the quality of life of the patients are not rare (3, 4). The lack of effective treatments for the neuropathy creates an urgent need to identify markers that can help to personalize treatment and avoid severe neuropathy events. The patient genetic background has been proposed to play a relevant role in the susceptibility for suffering neuropathy (5). In this regard, paclitaxel pharmacokinetic (6, 7) and pharmacodynamic (8, 9) pathways have been included in studies of candidate genes and, more recently genome-wide association studies (GWAS) have been performed (10, 11).

Candidate gene studies, by us and other groups, have demonstrated that common variants in paclitaxel metabolizing enzymes and paclitaxel target (i.e. *CYP2C8*3* (12-14), *CYP3A4*22* (7), *TUBB2A* rs909964 and rs909965 (8, 9)) influence neuropathy risk, while genome wide genotyping has uncovered novel genes (10, 11). A GWAS by our group (11) suggested that the *EPHA* gene family, which plays a key role in the development of nervous system and in nerve injury repair (15-17), was a key player for paclitaxel neuropathy susceptibility. Meta-analysis of GWAS top hits showed that *EPHA5* rs7349683 reached genome-wide significance (11), and follow-up studies further supported that this variant (18), *EPHA6* rs301927 (9, 18) and *EPHA8* rs209709 (18) moderately increased paclitaxel-induced neuropathy risk. However, large part of the variation in paclitaxel-induced neuropathy remains unexplained.

Low-frequency variants with strong effects may contribute to the neuropathy variability observed in patients. To investigate this hypothesis sequencing technologies are required and, so far, only two exploratory studies following different strategies have been performed. In one we applied whole exome sequencing to few extreme neuropathy patients,

and identified defective *CYP3A4* variants associated with the neuropathy (19). The second study sequenced genes causative of familial polyneuropathies (Charcot-Marie-Tooth, CMT), and suggested *ARHGEF10* and *PRX* as chemotherapy-induced neuropathy markers (20). These initial studies are promising, however, the statistical power for a whole exome sequencing study is low and in the CMT analysis key genes were excluded.

Here, we performed targeted exome sequencing of genes with common variants associated with paclitaxel-induced neuropathy (*EPHA4, EPHA5, EPHA6* and *EPHA8*) plus genes involved in paclitaxel pharmacokinetics and in CMT. In total we sequenced 39 genes in 228 selected patients with high or no/low paclitaxel-induced neuropathy. The strongest association corresponded to *EPHA6*, and the relevance of low frequency *EPHA5/6/8* non-synonymous coding variants was validated in an independent cohort of 202 paclitaxel-treated patients. These results reveal *EPHA* genes as key players in chemotherapy-induced neuropathy and stress the importance of gene sequencing for identifying genetic risk factors of neuropathy.

PATIENTS AND METHODS

Patients

The discovery series was derived from a set of 449 breast or ovarian cancer patients treated with paclitaxel (97% in first line), with DNA available, no previous neurotoxic drug treatments and with clinical data and neuropathy assessment; some have already been reported (18, 19, 21). In these patients the neuropathy was homogenously graded (19), and 228 were selected for whole or targeted exon deep-sequencing, based on extreme-neuropathy phenotype. Among them, 131 were high-neuropathy patients that fulfilled the following criteria: grade 3 or 2 neuropathy (NCI-CTC v4) during paclitaxel treatment, no neuropathy risk factors (diabetes, alcoholism, AIDS or previous neuropathies), and treatment modifications due to neuropathy (dose reduction or treatment suspension) or neuropathy that lasted >6 months after paclitaxel treatment finished. The remaining 97 patients were no/low-neuropathy patients with no neuropathy signs or grade 1 neuropathy after receiving paclitaxel (Table 1).

The validation of results was performed in an independent series of 202 paclitaxel-treated patients with neuropathy data recorded cycle by cycle. Most patients had breast or ovarian tumors, 109 were Spanish (54%) and 93 Swedish (46%). 129 samples corresponded to a previous GWAS study (11), 37 to Spanish patients already described (18) and 36 samples were new cases collected in Spain. From all patients cumulative paclitaxel dose up to grade 2 (NCI_CTC v2/4) neuropathy was available (Table 1).

All individuals participating in the study were over 18 years of age, had been diagnosed of cancer with histological confirmation, a life expectancy of ≥12 weeks and ECOG performance status ≤2, adequate bone marrow and renal and hepatic function. The recruitment of patients and collection of samples was approved by local internal ethical review committees and all patients gave written informed consent to participate in the study.

Next generation sequencing (NGS)

From the 228 patients used in the discovery series, 196 samples were processed using the TruSeq Custom Amplicon Kit (Illumina) covering the coding plus 25 bp intronic flanking region of 39 genes that included: *EPHA4, EPHA5, EPHA6* and *EPHA8* (10, 11) plus additional genes involved in paclitaxel metabolism and transport (*ABCB1, CYP2C8*, *CYP3A4*, *SLCO1B1*, *SLCO1B3*) and a selection of 30 genes associated with CMT hereditary peripheral neuropathies (Fig. 1). Very conserved CMT genes with no/very few variants reported were not selected for sequencing (e.g. *ATL1, EGR2, GDAP1, GJB1, LMNA, PRPS1, RAB7A, YARS*). In brief, 150 ng of DNA extracted from peripheral blood (FlexiGene DNA Kit, Qiagen) was used to construct libraries and sequenced in a MiSeq sequencer (Illumina, Spain) with a paired-end mode using MiSeq Reagent Kit V3 (Illumina, Spain) and 600 cycles. In addition, whole exome sequencing was performed on the remaining 32 patients (16 with high neuropathy (8 have been reported (19)) and 16 patients with no neuropathy), as previously described (19). For the validation of the results, a TruSeq Custom Amplicon Kit (Illumina) including the coding and intronic flanking region of *EPHA5*, *EPHA6* and *EPHA8* was used.

Variant identification

Targeted NGS data was demultiplexed with MiSeq Reporter (Illumina). Alignment was performed using Smith-Waterman algorithm (22) using GRCh37/hg19 assembly as reference and Genome Analysis Toolkit v2 (GATK, (23)) was used for raw variant calling. For the 32 samples with whole exome sequencing data, alignment and variant calling were performed by RUbioSeq software v3.7 (24). In this software the alignment was performed using Burrows-Wheeler alignment (25), unmapped reads are realigned using BFAST (26) and for variant calling, GATK v2 was used (23). Variants were annotated with Snp Eff (http://snpeff.sourceforge.net/) and Variant Effect Predictor

(http://www.ensembl.org/info/docs/tools/vep/index.html), and only non-synonymous coding variants and those altering canonical splice sites, with P>0.001 for Hardy Weinberg Equilibrium were considered in subsequent steps. Supplementary Table 1 indicates gene and transcript references.

Variants included in the analysis were: i) those previously described in public databases (dbSNP, http://www.ncbi.nlm.nih.gov/SNP/; Exome Aggregation Consortium (ExAC), http://exac.broadinstitute.org), and ii) variants not previously described with: high variant call quality (Q>30), read depth >10X and alternative variant frequency higher than 0.3 in at least one individual. Sequencing artefacts, defined as nucleotide changes detected in >20 samples in the sequencing panel but never described in ExAC, were omitted from the analysis. We defined loss of function (LOF) variants as those introducing stop codons (nonsense), variants disrupting canonical splice sites and indels disrupting the reading frame. Template and configuration files for alignment and scripts are available at https://github.com/htejero/PaclitaxelNeuropathy.

Validation of variants was performed by Sanger sequencing with an ABI PRISM 3700 DNA Analyzer capillary sequencer (Applied Biosystems) on 3% of the LOF and missense variants included in the analysis.

Data analysis

Variants were classified as "common variants" if they had a minor allele frequency (MAF) ≥0.5% in the more than 30.000 sequenced non-Finnish Europeans from ExAC. Variants were classified as "low frequency variants" if they had a MAF <0.5% in the non-Finnish Europeans from ExAC and MAF <1% in 578 Spanish exomes from the CIBERER Spanish Variant Server (http://csvs.babelomics.org/). The purpose of including the Spanish data was to detect population specific variants, because of the small sample size (n<600) the

MAF threshold in this population was less stringent. For common variants, the frequency of each variant in the high versus no/low neuropathy group was compared with a Chi^2 or Fisher test. For low frequency variants, the association with paclitaxel-induced neuropathy was assessed with the gene-based Burden test (27) using the SKAT package and R statistical software (http://www.R-project.org/). Scripts are available at https://github.com/htejero/PaclitaxelNeuropathy. Based on statistical power calculations, only genes with ≥ four rare variants were included in the analysis.

The study followed a 2-step design in which the best candidates from the discovery phase were selected for validation in an independent cohort of paclitaxel-treated patients (Table 1 shows discovery and validation series). No correction for multiple testing was performed. For samples with cycle by cycle neuropathy data, the association between *EPHA* variants and paclitaxel neuropathy risk was tested using Kaplan-Meier analysis, modelling the cumulative dose of paclitaxel up to the development of neurotoxicity grade ≥2. Patients with no or low neuropathy (grade 0/1) were censored at total administered cumulative dose. We also evaluated the association using univariate and multivariable Cox regression analysis (14). Country of origin and treatment schedule (1h versus 3h infusion) were included as covariates in the multivariate analyses. SPSS software package v.19 was used for these analyses. P values less than 0.05 were considered statistically significant.

RESULTS

Study population and NGS

NGS was performed on selected cases: 131 patients with high neuropathy (grades 2/3 that lasted a mean of 55 months) despite low accumulated paclitaxel dose (median= 1295 mg) and 97 patients with no/low neuropathy (grades 0/1) despite high accumulated paclitaxel dose (median= 1485 mg) (Table 1). In addition, 33% of patients in the high neuropathy group had paclitaxel dose reductions or treatment suspensions caused by the neuropathy.

Sequencing of 39 candidate genes in the 228 patients identified 277 coding non-synonymous or canonical splice site variants (266 missense, 3 in-frame deletions, 8 LOF; Suppl. Table 1). From these, 86 were common variants and 191 low-frequency variants.

At least one common variant was identified in each sequenced gene, except for *CYP3A4*, *EPHA4*, *HSPB1*, *HSPB8*, *NEFL*, *NDRG1* and *SPTLC2*. When the presence of these common variants was compared among the neuropathy groups, association with paclitaxel neuropathy was found for only 2 SNPs located in *CYP2C8* and *PRX* ($P<0.05$; Suppl. Table 2).

The 191 low frequency variants were distributed among all sequenced genes, except for *NEFL* and *NGF*. Of these 191 variants, 8 were loss of function (3 altered canonical splice sites, 2 were nonsense variants and 3 were indels causing frameshifts leading to premature stop codons; Table 2).

Gene-based analysis of paclitaxel-induced neuropathy in the discovery series

Analysis of the low frequency variants identified *EPHA6* as the gene most significantly associated with paclitaxel-induced neuropathy (Table 3). The 5 carriers of these variants were all high neuropathy patients with an amino acid change in the ephrin receptor ligand binding domain of the protein. Remarkably, no *EPHA6* variant carriers were present in the no/low-neuropathy group, suggesting a strong effect on neuropathy. One additional gene

had this characteristic (*SEPT9*), but results did not reach statistical significance level. The other two *EPHA* genes analyzed, *EPHA5* and *EPHA8*, have a similar biological function as *EPHA6* (15-17) and also belonged to the high-neuropathy risk group of genes (Table 3). In *EPHA5*, 5 carriers had high neuropathy versus 1 with low neuropathy; and in *EPHA8,* 9 carriers were in the high neuropathy and 6 in the no/low neuropathy group (Fig. 2; Suppl. Table 1). The highly conserved *EPHA4,* with only 2 carriers, one in each group, could not be analyzed.

Some of the discovery series patients had cycle by cycle neuropathy data available and among these, 3 were carriers of low-frequency variants in *EPHA5/6/8* genes (one variant in each gene). Accumulated paclitaxel dose analysis revealed that these patients had a significantly higher risk to suffer from neuropathy than patients without *EPHA* low frequency variants (HR=14.60, 95%CI=2.33-91.62, P=0.0042; Fig. 3A).

Low frequency variants in *EPHA6, EPHA5* and *EPHA8* confirmed as neuropathy risk factor in the validation series

Sequencing *EPHA5/6/8* in an independent cohort of 202 patients treated with paclitaxel and detailed cycle by cycle neuropathy data (Table 1), revealed 15 carriers of low frequency missense variants in these genes (one corresponded to *EPHA6,* one to *EPHA5* and 13 to *EPHA8*). These variants were combined and an accumulated paclitaxel dose analysis revealed that low frequency *EPHA5/6/8* variants conferred increased risk of neuropathy (HR=2.07, 95%CI=1.14-3.77, P=0.017; Fig. 3B).

Combining discovery and validation series, resulted in a HR of 2.50 (95%CI=1.46-4.31) with a P value of 9.1×10^{-4} (Fig. 3C).

DISCUSSION

Paclitaxel induced-neuropathy is a clinically relevant toxicity affecting large number of cancer patients. Genetic variation has been shown to influence susceptibility to paclitaxel-induced neuropathy, however, a large part of the variation remains unexplained. Low-frequency variants with strong effects may explain part of the variability. To investigate this hypothesis, we performed massive sequencing of candidate genes in patients selected based on extreme-neuropathy phenotype. Gene-based analysis identified, for the first time, low frequency genetic variants in *EPHA5/6/8* as risk factors of chemotherapy induced neuropathy. These results may provide a basis for personalizing paclitaxel treatment and decreasing the incidence of severe chemotherapy-induced neuropathies.

GWAS studies have identified common variants in *EPHA* genes with moderate effects on paclitaxel-induced neuropathy (E*PHA5*-rs7349683, *EPHA6*-rs301927, *EPHA8*-rs209709 and *EPHA4*-rs17348202) (10, 11) and subsequent studies further supported the association of *EPHA5, EPHA6* and *EPHA8* polymorphisms (9, 18). Non-synonymous coding variants, potentially affecting protein function, are expected to have stronger effects on neuropathy than common regulatory variants (28). Following this idea, we performed a NGS study in *EPHA* genes, together with paclitaxel pharmacokinetics and hereditary peripheral neuropathy related genes. Gene-based analysis of our data revealed that low frequency missense variants in *EPHA6* increased paclitaxel-induced neuropathy risk. All these variants were located in the ephrin receptor ligand binding domain, suggesting an alteration of the protein function and further supporting the association. *EPHA5* and *EPHA8* followed a similar trend (Fig. 2). In total, 15% (19 of 131) of patients in the high neuropathy group carried low frequency non-synonymous coding variants in *EPHA5/6/8* genes. In the 202 patients of the validation series, 13 *EPHA8* variant carriers were identified but only one *EPHA6* and one *EPHA5* carriers were detected, suggesting that *EPHA6* and *EPHA5* variants (present in 5 out of the 131 patients

with high-neuropathy of the discovery) are less frequent in an unselected patient population, including many moderate-neuropathy patients (not represented in the discovery set). Thus, *EPHA6* and *EPHA5* variant carriers were scarce in the validation series, and the calculated EPHA-effect mainly derived from *EPHA8*. Despite this, the accumulated dose analysis is a sensitive approach (18, 21) and was able to detect a statistically significant association. Altogether, these data suggest a relevant role for *EPHA5/6/8* genes in paclitaxel-induced neuropathy and indicates a high impact of low frequency variants missed in GWAS.

Eph receptors are tyrosine kinases involved in neural development (15) and nerve regeneration after damage (17, 29) among other functions: EphA4 controls axon sprouting/ nerve regeneration after spinal cord injury (30-32); EphA5 plays an important role in the initiation of the early phases of synaptogenesis (33) and it has been found upregulated in mice with injured sciatic nerve (34); EphA6 is involved in neural circuits underlying aspects of learning and memory (35); and EphA8 induces neurite outgrowth through induction of sustained MAPK activity (36) while lack of this gene produces aberrant axonal projections (37). Knocking out EphA4, EphA5, Eph6 and EphA8 genes in mice, results in viable and fertile animals with different neurological phenotypes. EphA4 knockout mice have gross motor dysfunction (38-40) and altered axonal regeneration and functional recovery following spinal cord injury (41). Knocking-out the tyrosine kinase domain of EphA5 results in axon aberrations in topographic mapping and altered behavioral patterns (42, 43). EphA8 knockout mice have abnormal axonal projections in the spinal cord (37) and EphA6 knockout mice experienced behavioral deficits in learning and memory tests (35). Thus, these are crucial genes for neural development and nerve regeneration with a plausible link for the association found with paclitaxel-induced neuropathy.

In ExAC database 0.1% of the European non-Finish population are carriers of LOF variants in either *EPHA5, EPHA6* or *EPHA8,* and on >100,000 Islandic individuals, two

complete human knockouts for *EPHA5* and one for *EPHA6* were identified (44). So far, no phenotype has been assigned to these individuals who are apparently healthy subjects. However, based on the literature and on our results, a high susceptibility to drug-induced neuropathy would be expected.

Concerning other genes potentially associated with the neuropathy, in line with Beutler *et al* (20) we postulated that variants moderately affecting the function of CMT genes, while not being pathogenic, may increase the susceptibility to drug-induced neuropathy. We did not find low frequency variants in *PRX* and common variants in *ARHGEF10* associated with paclitaxel-induced neuropathy, although the 2nd and 3rd top protective genes were these two, similarly to Beutler *et al*. For the *ARHGEF10* common variant rs9657362 we also found a trend towards protection (20, 45). We also observed a trend towards increased neuropathy risk for other CMT genes (*SEPT9* and *SH3TC2*). Variability in results among studies may be related to differences in neuropathy definitions/ assessments, in tumor types and patient treatments, or in the distribution of low-frequency variants, which have shown to be population-specific. Thus, results need to be further explored and validated in large independent series.

With regards to the LOF variants detected in this study, three occurred in CMT genes (*ARHGEF10*, *IKBKAP* and *DHTKD1).* The patients with variants in *ARHGEF10* and *IKBKAP* belonged to the no/low neuropathy group, in agreement with the fact that activating rather than LOF mutations in *ARHGEF10* cause CMT (46) and that no phenotype is observed for *IKBKAP* heterozygous individuals (47). The variant in *DHTKD1* was present in two patients with different neuropathy, but recent data question the role of this gene in CMT disease (48, 49). Among the remaining LOF variants, two affected *EPHA* genes *(EPHA5* and *EPHA8)* and corresponded to high-neuropathy patients. One LOF variant occurred in the paclitaxel uptake transporter *SLCO1B1,* in a high neuropathy patient. Two occurred in

CYP3A4, a gene in which we have demonstrated that defective variants increased neuropathy risk (19). Two patients were carriers of the *CYP3A4*20* frameshift allele and belonged to the high-neuropathy group, but one patient with a splicing defect affecting the last exon belonged to the no/low neuropathy group. The effect of this latter variant on the splicing of the gene and how it affects function remains to be studied.

Although the main goal of this study was to identify neuropathy associated low-frequency coding variants, we also found two common polymorphisms associated with the neuropathy: *CYP2C8* rs1058930 (*CYP2C8*4*), for which previous studies have found contradictory results (9, 14), and *PRX* rs268674, which was associated with neuropathy risk here for the first time. Further studies should evaluate the relevance of these results.

Limitations of this study include gene selection, since relevant genes not yet connected with neuropathy susceptibility may have been excluded. There are also differences in the selection of patients in the discovery and validation series. In the discovery series, patients were mainly treated with paclitaxel as single agent whereas in the validation cohort, the majority of the patients were treated with paclitaxel in combination with carboplatin. No major differences in neuropathy development between paclitaxel/carboplatin therapy versus paclitaxel as single agent exist (50, 51). In addition, we adjusted the analysis using treatment schedule as covariate. Nevertheless, using a more homogenous series may have resulted in stronger association results. Detection of low/ moderate effects on neuropathy may require even larger samples sets, although the number of patients in this study is substantial and the neuropathy assessment was homogenously performed to reduce subjectivity (11, 19). On the whole, additional studies validating the results in extensive and well characterized series of patients, the development of a model integrating all different risk markers identified, and providing with a standardized methodology to perform the genetic testing would be required to implement these risk factors into the clinics.

In conclusion, this study proves a relevant role of *EPHA5*, *EPHA6* and *EPHA8* genes in paclitaxel-induced neuropathy susceptibility and suggests that sequencing studies, rather genotyping, would be adequate approaches to study genetic markers of neuropathy. Moreover, taking into account the role of these proteins in neural development and injury repair, *EPHA* variants may also confer increased neuropathy risk to many additional neurotoxic drugs. The final goal is to identify genetic risk factors that can help to personalize neurotoxic drug treatments and avoid severe chemotherapy-induced neuropathies that can seriously affect patients' quality of life.

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TABLES

Table 1. Characteristics of the patients in the discovery series (n=228) and validation series (n=202).

Characteristics	Discovery series		Validation series
	High neuropathy	No/ low neuropathy	Cycle by cycle neuropathy data
Number of patients	131	97	202
Age (years)			
Median (min-max)	54 (35-82)	48 (32-73)	60 (34-82)
Gender			
Female	131 (100%)	97 (100%)	187 (93%)
Male	0 (0%)	0 (0%)	15 (7%)
Tumor type			
Breast	121 (92%)	82 (85%)	47 (23%)
Ovary	10 (8%)	15 (15%)	120 (60%)
Others	0 (0%)	0 (0%)	35 (17%)
Type of paclitaxel treatment			
First line	129 (99%)	95 (98%)	192 (95%)
Second line[a]	2 (1%)	2 (2%)	10 (5%)
Paclitaxel treatment[b]			
FEC+T	81 (62%)	23 (24%)	0 (0%)
AC+T	18 (14%)	18 (19%)	35 (17%)
T+FEC	14 (11%)	29 (30%)	0 (0%)
C+T	10 (7%)	15 (15%)	156 (77%)
Others	8 (6%)	12 (12%)	11 (6%)
Number of paclitaxel cycles			
Median (min-max)	8 (3-13)	10 (6-27)	7 (2-44)
Paclitaxel accumulated total dose (mg)			
Median (min-max)	1295 (450-1600)	1485 (900-4059)	1225 (114-3150)
Maximum sensory neuropathy grade[c]			
Grade 0	0 (0%)	56 (58%)	32 (16%)
Grade 1	0 (0%)	41 (42%)	42 (21%)
Grade 2	30 (23%)	0 (0%)	78 (38%)
Grade 3	101 (77%)	0 (0%)	50 (25%)
Dose modifications due to neuropathy[d]			
Paclitaxel dose reduction	14 (11%)	0 (0%)	21 (10%)
Paclitaxel treatment suspension	29 (22%)	0 (0%)	23 (11%)

[a] Patients with second line paclitaxel treatment and no previous neurotoxic drugs in first line therapy.

[b] Some patients receiving chemotherapeutic drugs in combination with targeted therapy (bevacizumab, trastuzumab, denosumab or pertuzumab) are included in the table according to

the chemotherapy agents received. FEC+T: 5-fluorouracil 600 mg/m^2, epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2, every 21 days, followed by paclitaxel 100 mg/m^2, every 7 days. AC+T: doxorubicin 60mg/m^2 and cyclophosphamide 600 mg/m^2, every 21 days, followed by paclitaxel 80mg/m^2, every 7 days. T+FEC: paclitaxel 80 mg/m^2, every 7 days, followed by 5-fluorouracil 600 mg/m^2, epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m2, every 21 days. C+T: carboplatin AUC5-6 and paclitaxel 175mg/m^2, every 21 days.

[c] NCI-CTC v2/4.

[d] When in the same patient paclitaxel dose was first reduced and later on paclitaxel treatment was suspended, the patient is included in the table as “treatment suspension”.

Table 2. Loss of function variants in the discovery series.

Gene	Type of gene	Variant[a]	Protein change	Nr individuals, Status	Discovery series group	Variant ID[b]	ExAC browser MAF[c]
ARHGEF10	CMT	c.1521_1522delAT[c]	p.Ala509His fs*515	1, Heterozygous	No/low NP	rs765378810	0.000066
IKBKAP		c.150+1G>A[c]	Splicing defect	1, Heterozygous	No/low NP	-	-
DHTKD1		c.1160-1G>C[c]	Splicing defect	2, Heterozygous	Both	rs760767010	0.000017
EPHA5	GWAS	c.2722dupT	p.Tyr908Leu fs*921	1, Heterozygous	High NP	-	-
EPHA8		c.1822C>T	p.Gln608*	1, Heterozygous	High NP	-	-
CYP3A4	PK	c.1461_1462insA (*CYP3A4*20*)	p.Pro488Thr fs*494	2, Heterozygous	High NP	rs67666821	0.00028
CYP3A4		c.1417-1G>C	Splicing defect	1, Heterozygous	No/low NP	rs141749477	0.0000083
SLCO1B1		c.1738C>T	p.Arg580*	1, Heterozygous	High NP	rs71581941	0.0016

[a] Genomic position and reference transcript are indicated in Supplemental Table 1.
[b] Variants not present in ExAC browser are indicated by "-".
[c] Variants not present in CMT databases (Inherited Peripheral Neuropathies Mutation Database http://www.molgen.vib-ua.be/CMTMutations/Mutations/MutByGene.cfm and OMIM http://www.omim.org/).
CMT: Charcot-Marie-Tooth; GWAS: Genome Wide Association Study; PK: pharmacokinetics; NP: neuropathy; MAF: minor allele frequency.

Table 3. Genes associated with paclitaxel-induced neuropathy using the gene-based burden test in the discovery series.

Gene	P-value	Number of variants carriers (variants)[a]	
		High neuropathy group, n=131	No/ low neuropathy group, n=97
Neuropathy risk			
EPHA6	0.041	5 (T72A,N127H,R162T,V196L)	0
SEPT9	0.072	4 (S96L,T235I,D348N,R355W)	0
SH3TC2	0.081	14 (T27A,V230A,T366A,S433L,Y510S,A590T,R658H,H696R,T755I,S831N,T1098P,D1229V)	4 (V230A,P251S,T1098P,D1229V)
EPHA5	0.219	5 (A49S,R494C,A611T,E678V,Y908fs)	1 (R238Q)
DHTKD1	0.271	9 (E42G,N107I,S114P,Q138K,A210S,c.1160-1G>C,T461K,I762del)	3 (I386V,c.1160-1G>C,G729R)
MFN2	0.323	6 (N63H,G298R,T423A,R468H,R663C)	2 (R468H,R707W)
LRSAM1	0.596	6 (I228M,F253V,Q409E,L500F,Q573K,L639P)	3 (S183L,R594C,Q697R)
SLCO1B3	0.737	5 (R23C,S64T,N145S,V235M)	3 (F36L,N145S,T414I)
ABCB1	0.752	5 (N183S,I261V,K624R,V835L)	3 (I261V,S1141T,R1225P)
EPHA8	0.785	9 (P321L,V365M,V444M,E462G,E464G,L559F,Q608*,A791V,D940H)	6 (G160S,I360V,V365M,E462G,Q525R,R679Q)
SBF2	0.787	7 (E304K,P339L,S730A,G775S,R890G,E1401K,K1672del)	3 (D289E,T1253S,A1849V)
SLCO1B1	0.800	4 (T10I,L193I,R580*,I656V)	3 (L193I,G210V)
Neuropathy protection			
TRPV4	0.082	1 (A293D)	4 (R160Q,R391W,T504A,S824L)
PRX	0.138	3 (M670V,P756L,D1013N)	6 (M670V,S751P K1062N,G1257R,E1360del,E1394D)
ARHGEF10	0.154	4 (S688N,H733Y,T811N,H1197Y)	7 (A509Hfs,S688N,H733Y,H834R,P956L,A960P)
NTRK1	0.261	2 (L79Q,G192A)	4 (L247P,Q570R,G714S,A779G)
SCN9A	0.456	4 (K40E,K655R,V1428I,L1916F)	5 (P74H,T152N,K655R,D1219E,L1267V)
IKBKAP	0.571	3 (M182K,R629H,G1013S)	4 (c.150+1G>A,M182K,S339R,R629H)
GARS	0.654	4 (C41R,R101H,S470F,T587M)	5 (T268I)
FAM134B	0.701	3 (P6L,V156F,S382T)	4 (M185V,V203M,Q379E,S382T)
Equal risk and protection			
AARS	0.650	5 (P234S,G275D,I579M)	5 (K81E,P234S,G275D,I579M)
FIG4	0.693	3 (I41T,K278N)	3 (I51V,A397P,E734K)
FGD4	0.712	3 (T79I,S392T,V717M)	3 (R275Q,V461A,D521G)
CYP3A4	0.795	4 (T185S,P389S,P488fs)	4 (R130Q,R162Q,T363M,c.1417-1G>C)

[a] Genomic position and reference transcript are indicated in Supplemental Table 1.

FIGURE LEGENDS

Figure 1. Genes selected for targeted NGS.

The NGS panel included 39 genes classified into two categories: 1) four *EPHA* genes involved in neural processes and found to be associated with taxane-induced neuropathy through GWAS; 2) 35 additional genes selected for an exploratory study, involved in paclitaxel pharmacokinetic (PK) or causative of Charcot-Marie-Tooth. Variants previously described to be associated with paclitaxel-induced neuropathy are included in the graph and the corresponding references provided.

Figure 2. Non synonymous *EPHA* coding variants in the discovery series.

The low frequency variants in *EPHA6*, *EPHA5* and *EPHA8* are represented along the protein sequences. In red variants in the high neuropathy group; in green variants in the no/low neuropathy group of patients. Protein domains are depicted according to Pfam database. Illustrator for Biological Sequences was used to create the graphs (http://ibs.biocuckoo.org/).

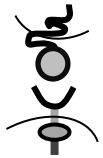
Figure 3. Kaplan-Meier analysis of paclitaxel-induced neuropathy.

Patients were grouped according to the absence (Without) or presence (With) of low-frequency variants in *EPHA5*, *EPHA6*, and *EPHA8,* and the cumulative dose of paclitaxel up to the development of grade 2 peripheral sensory neuropathy was compared. A) Discovery series (n=25). B) Validation series (n=202). C) Analysis combining patients from discovery and validation series (n=227). P values correspond to multivariable Cox regression analyses including country of origin and treatment schedule as covariates.

Figure 1

1) GWAS nerve repair

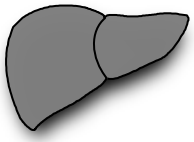
EphA receptors



Gene	(variant [ref])
EPHA4	(rs17348202 [11])
EPHA5	(rs7349683 [10,11,18])
EPHA6	(rs301927 [9,11,18])
EPHA8	(rs209709 [11,18])

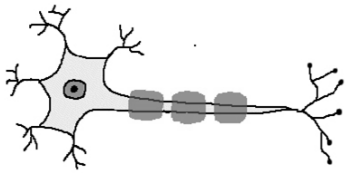
2) Exploratory study

Paclitaxel PK



Gene	(variant [ref])
CYP2C8	(**3* rs11572080 [12-14])
CYP3A4	(**20* rs67666821 [19]; **22* rs35599367 [7])
ABCB1	
SLCO1B1	
SLCO1B3	

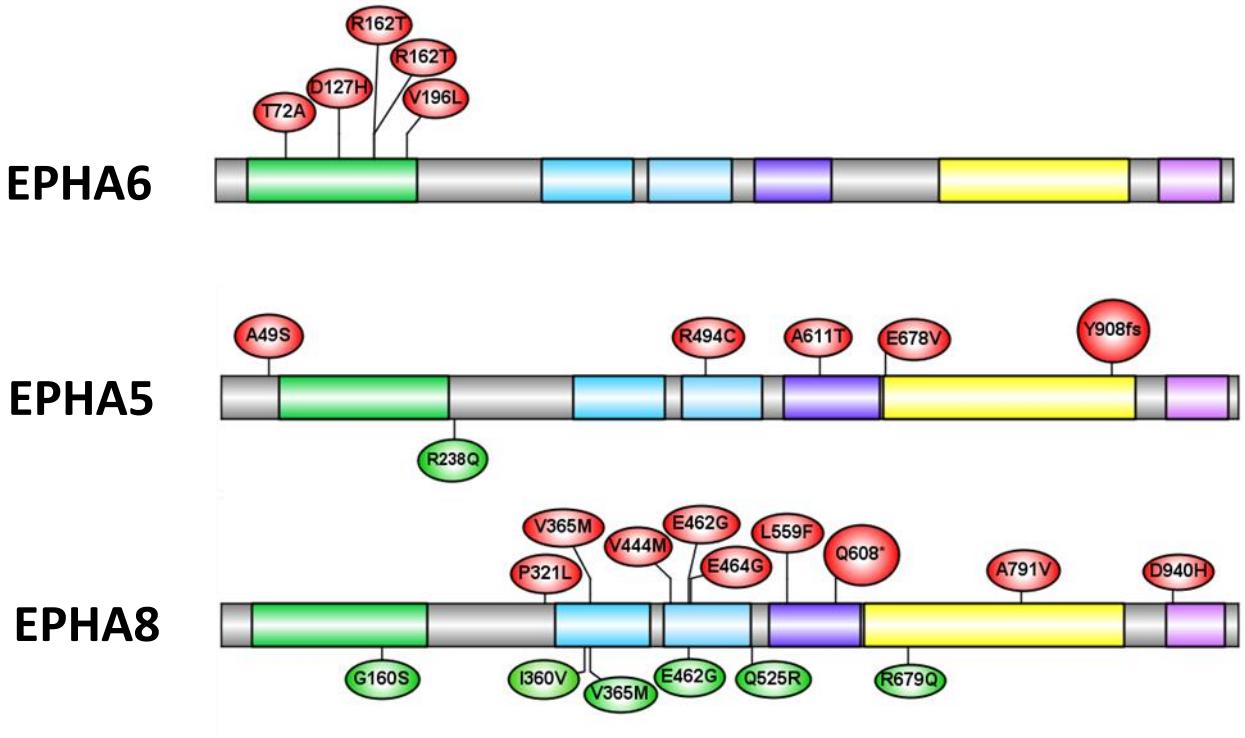
Charcot Marie Tooth genes



Gene	(ref)				
AARS	*FGD4*	*IKBKAP*	*MFN2*	*NTRK1*	*SEPT9*
ARHGEF10 [20]*	*FIG4*	*KIF1B*	*MTMR2*	*PMP22*	*SH3TC2*
CCT5	*GARS*	*LITAF*	*NDRG1*	*PRX* [20#]	*SPTLC1*
DHTKD1	*HSPB1*	*LRSAM1*	*NEFL*	*SBF2*	*SPTLC2*
FAM134B	*HSPB8*	*MED25*	*NGF*	*SCN9A*	*TRPV4*

*rs9657362, rs2294039 & rs17683288. # *PRX* rare variants

Figure 2



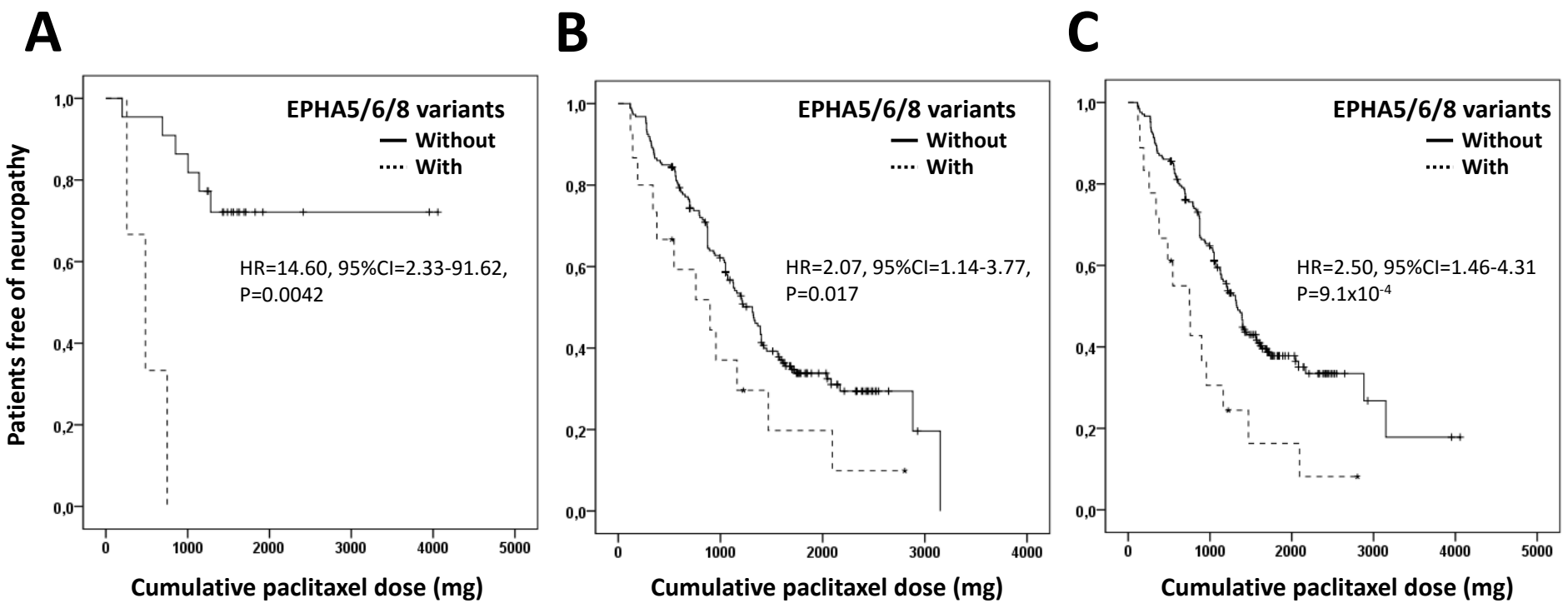
Neuropathy group

- High neuropathy
- No/ low neuropathy

Protein domains

- Ephrin receptor LB domain
- Fibronectin type III domain
- EphA2 TM domain
- Protein tyrosine kinase
- SAM domain

Figure 3


A
B
C
Patients free of neuropathy
EPHA5/6/8 variants
Without
With
HR=14.60, 95%CI=2.33-91.62,
P=0.0042
HR=2.07, 95%CI=1.14-3.77,
P=0.017
HR=2.50, 95%CI=1.46-4.31
P=9.1x10-4
1,0
0,8
0,6
0,4
0,2
0,0
0
1000
2000
3000
4000
5000
Cumulative paclitaxel dose (mg)

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Non synonymous coding and splicing site variants in the discovery series targeted sequencing.

Gene (Gene ID)	Chr:position	Variant ID	Ref	Alt	Transcript ID	Consequence	Protein change	MAF ExAC[a]	MAF Spanish[b]	High Neuropathy group (nr.)			No/Low Neuropathy group (nr.)			HWE (Yes /No) [a]
										wt wt	wt var	var var	wt wt	wt var	var var	
AARS (ENSG00000090861)	16:70286631	rs35744709	T	A	ENST00000261772	missense	Lys967Met	0.01467	0.014	124	7	0	93	4	0	Yes
	16:70286740	rs149377346	C	T		missense	Gly931Ser	0.01102	0.010	128	3	0	94	3	0	Yes
	16:70287883	rs147319762	T	C		missense	Lys820Arg	0.00182	0.014	129	2	0	94	3	0	Yes
	16:70294995	rs144323646	G	C		missense	Ile579Met	0.00009	0.004	130	1	0	96	1	0	Yes
	16:70303659	rs11537667	C	T		missense	Gly275Asp	0.00038	0.004	130	1	0	96	1	0	Yes
	16:70304215	rs141840552	G	A		missense	Pro234Ser	0.00171	0.007	128	3	0	95	2	0	Yes
	16:70310961	-	T	C		missense	Lys81Glu	-	-	131	0	0	96	1	0	Yes
ABCB1 (ENSG00000085563)	7:87133728	rs779103120	C	G	ENST00000265724	missense	Arg1225Pro	-	-	131	0	0	96	1	0	Yes
	7:87138659	rs2229107	A	T		missense	Ser1141Thr	0.00009	-	131	0	0	96	1	0	Yes
	7:87138760	rs55852620	T	G		missense	Gln1107Pro	0.00582	0.002	129	2	0	97	0	0	Yes
	7:87160792	-	C	G		missense	Val835Leu	-	-	130	1	0	97	0	0	Yes
	7:87175195	rs141018820	T	C		missense	Lys624Arg	0.00007	0.001	130	1	0	97	0	0	Yes
	7:87179809	rs2229109	C	T		missense	Ser400Asn	0.04316	0.023	124	7	0	87	10	0	Yes
	7:87190625	rs36008564	T	C		missense	Ile261Val	0.00120	0.002	129	2	0	96	1	0	Yes
	7:87195540	rs60419673	T	C		missense	Asn183Ser	0.00167	0.002	130	1	0	97	0	0	Yes
	7:87229440	rs9282564	T	C		missense	Asn21Asp	0.11199	0.053	112	19	0	80	16	1	Yes
ARHGEF10 (ENSG00000104728)	8:1833801	rs9657362	G	C	ENST00000349830	missense	Leu370Phe	0.13846	0.119	110	19	2	71	26	0	Yes
	8:1844578	rs765378810	CAT	C		**frameshift**	Ala509Hisfs	0.00000	-	131	0	0	96	1	0	Yes
	8:1857556	rs143290224	G	A		missense	Ser688Asn	0.00105	0.007	130	1	0	96	1	0	Yes
	8:1857591	rs2294039	G	A		missense	Val700Ile	0.04063	0.055	123	7	1	88	8	1	Yes
	8:1871183	rs147531758	C	T		missense	His733Tyr	0.00176	0.003	130	1	0	96	1	0	Yes
	8:1871984	-	C	A		missense	Thr811Asn	0.00000	-	130	1	0	97	0	0	Yes
	8:1873461	rs142973221	A	G		missense	His834Arg	0.00006	-	131	0	0	95	2	0	Yes

	8:1876707	rs61752020	G	A		missense	Val938Ile	0.00817	0.011	129	2	0	94	3	0	Yes
	8:1876762	rs201570359	C	T		missense	Pro956Leu	0.00000	-	131	0	0	96	1	0	Yes
	8:1876773	-	G	C		missense	Ala960Pro	0.00003	-	131	0	0	96	1	0	Yes
	8:1877480	rs17683288	T	G		missense	Ser984Ala	0.07288	0.057	111	20	0	87	10	0	Yes
	8:1904983	rs200779877	C	T		missense	His1197Tyr	0.00055	-	130	1	0	97	0	0	Yes
CCT5 (ENSG00000150753)	5:10256172	rs11557652	A	T	ENST00000280326	missense	Glu146Val	0.02393	0.012	128	3	0	95	2	0	Yes
	5:10256175	rs118203986	A	G		missense	His147Arg	0.00002	-	131	0	0	96	1	0	Yes
	5:10256192	rs563305570	G	A		missense	Asp153Asn	0.00002	-	130	1	0	97	0	0	Yes
	5:10261764	rs141675330	C	G		missense	Ile362Met	0.00511	0.004	130	1	0	96	1	0	Yes
CYP2C8 [c] (ENSG00000138115)	10:96797034	rs143038562	G	A	ENST00000371270	missense	Arg442Cys	0.00008	-	130	1	0	97	0	0	Yes
	10:96798749	rs10509681 (*3)	T	C		missense	Lys399Arg	0.11299	0.152	87	39	5	64	29	4	Yes
	10:96818106	rs11572103 (*2)	T	A		missense	Ile269Phe	0.00397	0.003	129	2	0	97	0	0	Yes
	10:96818119	rs1058930 (*4)	G	C		missense	Ile264Met	0.05429	0.059	116	15	0	76	19	2	Yes
	10:96824658	rs41286886	C	T		missense	Val181Ile	0.00762	0.001	130	1	0	96	1	0	Yes
	10:96827030	rs11572080 (*3)	C	T		missense	Arg139Lys	0.11287	0.137	92	35	4	67	27	3	Yes
CYP3A4 [c] (ENSG00000160868)	7:99355806	rs67666821 (*20)	G	GT	ENST00000336411	**frameshift**	Pro488fs	0.00034	-	129	2	0	97	0	0	Yes
	7:99355852	rs141749477	C	G		**splice accept**	c.1417-1G>C	0.00000	-	131	0	0	96	1	0	Yes
	7:99359752	rs749459749	G	A		missense	Pro389Ser	0.00002	-	130	1	0	97	0	0	Yes
	7:99359829	rs67784355 (*11)	G	A		missense	Thr363Met	0.00022	-	131	0	0	96	1	0	Yes
	7:99366093	rs12721627 (*16)	G	C		missense	Thr185Ser	0.00000	-	130	0	1	97	0	0	Yes
	7:99367427	rs4986907 (*15)	C	T		missense	Arg162Gln	0.00019	0.002	131	0	0	96	1	0	Yes
	7:99367788	rs72552799 (*8)	C	T		missense	Arg130Gln	0.00164	0.001	131	0	0	96	1	0	Yes
DHTKD1 (ENSG00000181192)	10:12111090	rs1279138	T	C	ENST00000263035	missense	Phe20Leu	0.00020	0.363	18	0	113	10	0	87	No
	10:12111157	-	A	G		missense	Glu42Gly	-	-	130	1	0	97	0	0	Yes
	10:12123525	rs34644609	C	G		missense	Ala70Gly	0.00684	0.008	128	3	0	96	1	0	Yes
	10:12126548	-	A	T		missense	Asn107Ile	-	-	130	1	0	97	0	0	Yes
	10:12126568	-	T	C		missense	Ser114Pro	-	-	130	1	0	97	0	0	Yes
	10:12126640	-	C	A		missense	Gln138Lys	-	-	130	1	0	97	0	0	Yes
	10:12129639	rs146741810	G	T		missense	Ala210Ser	0.00403	-	129	2	0	97	0	0	Yes
	10:12131081	rs3740015	T	G		missense	Tyr272Asp	0.59906	0.427	23	53	55	14	56	27	Yes
	10:12133603	rs147571909	T	C		missense	Val360Ala	0.00558	0.003	130	1	0	96	1	0	Yes
	10:12133680	-	A	G		missense	Ile386Val	-	-	131	0	0	96	1	0	Yes

	10:12136071	rs760767010	G	C		**splice accept**	c.1160-1G>C	0.00002	-	130	1	0	96	1	0	Yes
	10:12139706	rs201559023	C	A		missense	Thr461Lys	0.00005	0.001	130	1	0	97	0	0	Yes
	10:12143105	rs2062988	C	G		missense	Ile607Met	0.81243	0.168	5	41	85	3	31	63	Yes
	10:12154929	rs117225135	G	A		missense	Gly729Arg	0.00233	0.004	131	0	0	96	1	0	Yes
	10:12155027	-	CATT	C		inframe del	Ile762del	-	-	130	1	0	97	0	0	Yes
EPHA4 (ENSG00000116106)	2:222294690	rs142860268	G	A	ENST00000281821	missense	Thr893Met	0.00007	0.003	131	0	0	96	1	0	Yes
	2:222365859	rs200225096	G	A		missense	Thr286Met	0.00010	-	130	1	0	97	0	0	Yes
EPHA5 (ENSG00000145242)	4:66201779	-	T	TA	ENST00000273854	**frameshift**	Tyr908fs	-	-	130	1	0	97	0	0	Yes
	4:66231667	-	T	A		missense	Glu678Val	-	-	130	1	0	97	0	0	Yes
	4:66231686	rs36050417	C	T		missense	Ala672Thr	0.02758	0.038	124	7	0	91	6	0	Yes
	4:66242741	rs777294375	C	T		missense	Ala611Thr	0.00002	-	130	1	0	97	0	0	Yes
	4:66286206	rs138678484	G	A		missense	Arg494Cys	0.00034	0.004	130	1	0	97	0	0	Yes
	4:66467556	rs147719164	C	T		missense	Arg238Gln	0.00016	-	131	0	0	96	1	0	Yes
	4:66509085	rs33932471	T	G		missense	Asn81Thr	0.06647	0.065	115	16	0	88	9	0	Yes
	4:66535316	rs138631715	C	A		missense	Ala49Ser	0.00033	0.001	130	1	0	97	0	0	Yes
EPHA6 (ENSG00000080224)	3:96533681	rs373432052	A	G	ENST00000389672	missense	Thr72Ala	0.00015	-	130	1	0	97	0	0	Yes
	3:96533846	rs200313366	A	C		missense	Asn127His	0.00037	-	130	1	0	97	0	0	Yes
	3:96706208	rs192891419	G	C		missense	Arg162Thr	0.00319	0.003	129	2	0	97	0	0	Yes
	3:96706309	-	G	T		missense	Val196Leu	-	-	130	1	0	97	0	0	Yes
	3:97311483	rs4857276	C	T		missense	Ala805Val	0.00742	0.011	129	2	0	97	0	0	Yes
EPHA8 (ENSG00000070886)	1:22895820	rs45498698	G	A	ENST00000166244	missense	Gly45Ser	0.00821	0.004	126	5	0	95	2	0	Yes
	1:22903028	rs370843084	G	A		missense	Gly160Ser	0.00003	-	131	0	0	96	1	0	Yes
	1:22913111	rs56656925	C	T		missense	Pro321Leu	0.00035	0.003	130	1	0	97	0	0	Yes
	1:22915462	rs762631777	A	G		missense	Ile360Val	0.00002	-	131	0	0	96	1	0	Yes
	1:22915477	rs369589341	G	A		missense	Val365Met	0.00011	-	130	1	0	96	1	0	Yes
	1:22919833	rs2295021	G	A		missense	Val444Met	0.00000	-	130	1	0	97	0	0	Yes
	1:22919888	rs77608596	A	G		missense	Glu462Gly	0.00150	-	130	1	0	96	1	0	Yes
	1:22919894	rs777499719	A	G		missense	Glu464Gly	0.00000	-	130	1	0	97	0	0	Yes
	1:22920150	rs149084883	A	G		missense	Gln525Arg	0.00308	0.002	131	0	0	96	1	0	Yes
	1:22921794	rs200214765	C	T		missense	Leu559Phe	0.00088	0.001	130	1	0	97	0	0	Yes
	1:22923859	rs144329757	C	A		missense	Pro607His	0.00844	0.004	128	3	0	97	0	0	Yes
	1:22923861	-	C	T		**stop gained**	Gln608*	-	-	130	1	0	97	0	0	Yes

	1:22923873	rs999765	G	C		missense	Glu612Gln	0.10359	0.078	109	20	2	82	11	4	Yes
	1:22924274	rs562829959	G	A		missense	Arg679Gln	0.00000	-	131	0	0	96	1	0	Yes
	1:22925524	-	C	T		missense	Ala791Val	-	-	130	1	0	97	0	0	Yes
	1:22927503	rs62618734	G	A		missense	Arg884His	0.00930	0.006	129	2	0	95	2	0	Yes
	1:22927881	rs374945795	G	C		missense	Asp940His	0.00000	-	130	1	0	97	0	0	Yes
FAM134B (ENSG00000154153)	5:16475199	rs61733811	C	G	ENST00000306320	missense	Ser382Thr	0.00070	0.004	130	1	0	96	1	0	Yes
	5:16475209	rs34432513	G	C		missense	Gln379Glu	0.00015	0.004	131	0	0	96	1	0	Yes
	5:16481181	rs143878016	C	T		missense	Val203Met	0.00425	-	131	0	0	96	1	0	Yes
	5:16483487	rs756538225	T	C		missense	Met185Val	0.00002	-	131	0	0	96	1	0	Yes
	5:16483574	rs758377163	C	A		missense	Val156Phe	0.00002	-	130	1	0	97	0	0	Yes
	5:16572153	rs78314670	G	A		missense	Arg127Cys	0.01020	0.004	130	1	0	93	4	0	Yes
	5:16617064	-	G	A		missense	Pro6Leu	-	-	130	0	1	97	0	0	Yes
FGD4 (ENSG00000139132)	12:32735037	rs145115430	C	T	ENST00000427716	missense	Thr79Ile	0.00006	0.002	130	1	0	97	0	0	Yes
	12:32754345	rs756169087	G	A		missense	Arg275Gln	0.00002	-	131	0	0	96	1	0	Yes
	12:32763752	rs781528826	G	C		missense	Ser392Thr	-	-	130	1	0	97	0	0	Yes
	12:32772675	-	T	C		missense	Val461Ala	-	-	131	0	0	96	1	0	Yes
	12:32777929	rs141237776	A	G		missense	Asp521Gly	0.00013	-	131	0	0	96	1	0	Yes
	12:32778663	rs144693221	C	A		missense	Pro571Thr	0.00619	0.002	130	1	0	96	1	0	Yes
	12:32793315	rs61753359	G	A		missense	Val717Met	0.00189	0.001	130	1	0	97	0	0	Yes
FIG4 (ENSG00000112367)	6:110036336	rs121908287	T	C	ENST00000230124	missense	Ile41Thr	0.00155	0.001	129	2	0	97	0	0	Yes
	6:110036365	-	A	G		missense	Ile51Val	-	-	131	0	0	96	1	0	Yes
	6:110062705	rs138048706	A	T		missense	Lys278Asn	0.00049	0.001	130	1	0	97	0	0	Yes
	6:110064928	rs2295837	A	T		missense	Met364Leu	0.03636	0.038	123	8	0	92	5	0	Yes
	6:110081504	-	G	C		missense	Ala397Pro	-	-	131	0	0	96	1	0	Yes
	6:110107517	rs9885672	T	C		missense	Val654Ala	0.15789	0.148	92	34	5	74	23	0	Yes
	6:110112598	rs372846619	G	A		missense	Glu734Lys	0.00014	-	131	0	0	96	1	0	Yes
GARS (ENSG00000106105)	7:30634548	rs62636572	C	T	ENST00000389266	missense	Pro4Leu	0.02812	0.003	126	5	0	94	2	1	Yes
	7:30634658	rs762605231	T	C		missense	Cys41Arg	0.00000	-	130	1	0	97	0	0	Yes
	7:30634661	rs1049402	C	G		missense	Pro42Ala	0.76849	0.261	25	31	75	20	21	56	No
	7:30638491	rs200887429	G	A		missense	Arg101His	0.00061	0.001	130	1	0	97	0	0	Yes
	7:30649268	rs2230310	C	T		missense	Thr268Ile	0.00475	0.005	131	0	0	92	5	0	Yes
	7:30661058	-	C	T		missense	Ser470Phe	-	-	130	1	0	97	0	0	Yes

	7:30668236	rs750292154	C	T		missense	Thr587Met	0.00002	-	130	1	0	97	0	0	Yes
HSPB1 (ENSG00000106211)	7:75932237	-	G	A	ENST00000248553	missense	Ala70Thr	-	-	131	0	0	96	1	0	Yes
HSPB8 (ENSG00000152137)	12:119617202	rs748320300	C	T	ENST00000281938	missense	Arg29Cys	0.00002	-	131	0	0	96	1	0	Yes
IKBKAP (ENSG00000070061)	9:111641825	rs1538660	G	A	ENST00000374647	missense	Pro1158Leu	0.17074	0.166	101	28	2	68	26	3	Yes
	9:111651620	rs3204145	A	T		missense	Cys1072Ser	0.17022	0.181	96	33	2	65	29	3	Yes
	9:111653606	rs2230795	C	T		missense	Gly1013Ser	0.00013	0.001	130	1	0	97	0	0	Yes
	9:111656228	rs2230798	T	A		missense	Lys952Ile	0.01692	0.008	130	1	0	95	2	0	Yes
	9:111659439	rs2230794	T	C		missense	Ile830Met	0.04604	0.057	114	17	0	91	6	0	Yes
	9:111659483	rs2230793	T	G		missense	Ile816Leu	0.18077	0.211	81	42	8	60	34	3	Yes
	9:111660851	rs2230792	C	T		missense	Gly765Glu	0.18670	0.207	81	42	8	60	34	3	Yes
	9:111663930	rs148378319	C	T		missense	Arg629His	0.00277	0.002	130	1	0	96	1	0	Yes
	9:111668652	rs838827	C	T		missense	Arg525Gln	0.06139	0.089	113	14	4	84	12	1	Yes
	9:111674716	rs56053149	G	T		missense	Ser339Arg	0.00004	-	131	0	0	96	1	0	Yes
	9:111678508	rs1140064	C	T		missense	Glu312Lys	0.02805	0.017	128	3	0	95	2	0	Yes
	9:111679940	rs17853166	T	C		missense	Ser251Gly	0.02803	0.016	129	2	0	95	2	0	Yes
	9:111685129	rs10521092	A	T		missense	Met182Lys	0.00018	0.002	130	1	0	96	1	0	Yes
	9:111693276	-	C	T		**splice donor**	c.150+1G>A	-	-	131	0	0	96	1	0	Yes
KIF1B (ENSG00000054523)	1:10292415	-	T	C	ENST00000263934	missense	Val10Ala	-	-	130	1	0	97	0	0	Yes
	1:10381802	rs551543997	T	C		missense	Trp703Arg	0.00009	-	131	0	0	96	1	0	Yes
	1:10397567	rs2297881	A	G		missense	Tyr1087Cys	0.02518	-	121	10	0	87	10	0	Yes
	1:10425683	rs779756425	C	G		missense	Arg1531Gly	0.00000	-	130	1	0	97	0	0	Yes
	1:10428570	rs77172218	G	A		missense	Val1554Met	0.01600	-	129	2	0	96	1	0	Yes
LITAF (ENSG00000189067)	16:11643394	rs149712652	G	A	ENST00000571688	missense	Pro196Ser	0.01258	0.011	128	3	0	96	1	0	Yes
	16:11647492	rs4280262	T	C		missense	Ile92Val	0.20581	0.164	83	43	5	61	31	5	Yes
	16:11650441	rs141862602	G	A		missense	Thr49Met	0.00077	0.003	130	1	0	96	1	0	Yes
	16:11650487	rs759905004	G	T		missense	Pro34Thr	0.00002	-	130	1	0	97	0	0	Yes
LRSAM1 (ENSG00000148356)	9:130230038	rs75690855	C	T	ENST00000323301	missense	Ser183Leu	0.00047	0.001	131	0	0	96	1	0	Yes
	9:130236144	rs376671005	C	G		missense	Ile228Met	0.00002	-	130	1	0	97	0	0	Yes
	9:130241219	rs762870327	T	G		missense	Phe253Val	-	0.001	130	1	0	97	0	0	Yes
	9:130242166	rs1539567	A	G		missense	Asn318Asp	0.78166	0.343	18	47	66	10	37	50	Yes

	9:130248080	rs149540339	C	G		missense	Gln409Glu	0.00078	-	130	1	0	97	0	0	Yes
	9:130253569	rs749192098	C	T		missense	Leu500Phe	0.00006	-	130	1	0	97	0	0	Yes
	9:130258261	rs150882646	C	A		missense	Gln573Lys	0.00017	-	130	1	0	97	0	0	Yes
	9:130258324	rs150062009	C	T		missense	Arg594Cys	0.00033	-	131	0	0	96	1	0	Yes
	9:130263292	rs745672498	T	C		missense	Leu639Pro	0.00002	-	130	1	0	97	0	0	Yes
	9:130265096	-	A	G		missense	Gln697Arg	-	-	131	0	0	96	1	0	Yes
MED25 (ENSG00000104973)	19:50321695	-	G	C	ENST00000312865	missense	Glu33Gln	-	-	131	0	0	96	1	0	Yes
	19:50334047	rs145770066	C	T		missense	Ala335Val	0.00604	-	131	0	0	95	2	0	Yes
	19:50338843	rs193291405	C	G		missense	Ala576Gly	0.02446	0.002	130	1	0	96	1	0	Yes
MFN2 (ENSG00000116688)	1:12052623	rs761216583	A	C	ENST00000235329	missense	Asn63His	0.00003	-	130	1	0	97	0	0	Yes
	1:12061533	rs41278630	G	A		missense	Gly298Arg	0.00316	0.005	130	1	0	97	0	0	Yes
	1:12064155	rs765921889	A	G		missense	Thr423Ala	0.00000	-	130	1	0	97	0	0	Yes
	1:12064892	rs138382758	G	A		missense	Arg468His	0.00325	0.009	129	2	0	96	1	0	Yes
	1:12067224	rs369762154	C	T		missense	Arg663Cys	0.00012	-	130	1	0	97	0	0	Yes
	1:12069692	rs142271930	G	A		missense	Val705Ile	0.00628	0.002	130	1	0	96	1	0	Yes
	1:12069698	rs119103267	C	T		missense	Arg707Trp	0.00055	0.001	131	0	0	96	1	0	Yes
MTMR2 (ENSG00000087053)	11:95568531	rs116750638	A	G	ENST00000346299	missense	Ser619Pro	0.00255	0.002	130	1	0	96	1	0	Yes
	11:95571347	rs61735578	C	G		missense	Glu502Gln	0.02432	0.023	127	4	0	95	2	0	Yes
	11:95578167	rs146572467	C	T		missense	Glu446Lys	0.00055	0.002	130	1	0	97	0	0	Yes
	11:95590766	rs186380748	G	C		missense	Pro202Ala	0.00047	0.002	129	2	0	97	0	0	Yes
	11:95657111	rs3824874	T	G		missense	Lys3Thr	0.42441	0.222	53	51	27	49	30	18	No
NDRG1 (ENSG00000104419)	8:134251197	rs367925853	G	A	ENST00000414097	missense	Ala370Val	0.00052	-	131	0	0	96	1	0	Yes
	8:134251215	rs767058269	G	C		missense	Ser364Trp	-	-	131	0	0	96	1	0	Yes
	8:134296524	rs145871479	C	T		missense	Ala11Thr	0.00139	0.004	131	0	0	94	3	0	Yes
NGF (ENSG00000134259)	1:115829178	rs11466111	C	T	ENST00000369512	missense	Arg80Gln	0.01634	0.008	127	4	0	95	2	0	Yes
	1:115829313	rs6330	G	A		missense	Ala35Val	0.44519	0.443	47	62	22	32	44	21	Yes
NTRK1 (ENSG00000198400)	1:156830779	rs1007211	G	A	ENST00000524377	missense	Gly18Glu	0.01562	0.002	130	1	0	96	1	0	Yes
	1:156834169	rs139140006	T	A		missense	Leu79Gln	0.00006	-	130	1	0	97	0	0	Yes
	1:156838297	rs201185829	G	C		missense	Gly192Ala	0.00133	-	130	1	0	97	0	0	Yes
	1:156841437	-	T	C		missense	Leu247Pro	-	-	131	0	0	96	1	0	Yes
	1:156846268	-	A	G		missense	Gln570Arg	-	-	131	0	0	96	1	0	Yes
	1:156848918	rs6336	C	T		missense	His604Tyr	0.05491	0.046	120	10	1	89	8	0	Yes
	1:156848946	rs6339	G	T		missense	Gly613Val	0.05483	0.047	120	10	1	89	8	0	Yes

	1:156849884	rs770727871	G	A		missense	Gly714Ser	0.00002	-	131	0	0	96	1	0	Yes
	1:156851379	-	C	G		missense	Ala779Gly	-	-	131	0	0	96	1	0	Yes
	1:156851382	rs35669708	G	A		missense	Arg780Gln	0.00722	0.003	129	2	0	93	4	0	Yes
PMP22 (ENSG00000109099)	17:15134308	rs755551524	T	C	ENST00000395938	missense	Ile137Val	0.00000	-	130	1	0	96	1	0	Yes
	17:15134364	rs104894619	G	A		missense	Thr118Met	0.00736	0.003	123	0	0	83	1	0	Yes
PRX (ENSG00000105227)	19:40900077	-	C	A	ENST00000324001	missense	Glu1394Asp	-	-	131	0	0	96	1	0	Yes
	19:40900179	-	TTCC	T		inframe del	Glu1360del	-	-	131	0	0	96	1	0	Yes
	19:40900490	rs200332462	C	T		missense	Gly1257Arg	0.00002	0.002	131	0	0	96	1	0	Yes
	19:40900865	rs268674	C	T		missense	Gly1132Arg	0.94233	0.279	2	16	113	0	4	93	Yes
	19:40901011	rs3745202	G	C		missense	Pro1083Arg	0.17537	0.160	124	4	3	89	6	2	No
	19:40901073	rs139188673	C	A		missense	Lys1062Asn	0.00152	0.006	131	0	0	96	1	0	Yes
	19:40901222	rs548086012	C	T		missense	Asp1013Asn	0.00003	0.001	130	1	0	97	0	0	Yes
	19:40901496	rs268673	T	C		missense	Ile921Met	0.39123	0.350	46	61	24	33	49	15	Yes
	19:40901614	rs268671	A	G		missense	Val882Ala	0.51248	0.379	28	63	40	27	48	22	Yes
	19:40901647	rs201389706	A	G		missense	Val871Ala	0.04189	0.003	116	15	0	87	10	0	Yes
	19:40901992	rs749585237	G	A		missense	Pro756Leu	0.00006	-	130	1	0	97	0	0	Yes
	19:40902008	-	A	G		missense	Ser751Pro	-	-	131	0	0	96	1	0	Yes
	19:40902251	rs757467172	T	C		missense	Met670Val	-	-	130	1	0	96	1	0	Yes
	19:40902776	rs146789340	C	G		missense	Glu495Gln	0.00393	0.011	130	1	0	97	0	0	Yes
	19:40903528	rs118071705	G	A		missense	Ala244Val	0.03438	0.004	129	2	0	94	3	0	Yes
SBF2 (ENSG00000133812)	11:9801969	-	G	A	ENST00000256190	missense	Ala1849Val	-	-	131	0	0	96	1	0	Yes
	11:9809201	-	CTTT	C		inframe del	Lys1672del	0.00061	-	130	1	0	97	0	0	Yes
	11:9830504	rs758191255	C	T		missense	Glu1401Lys	-	-	130	1	0	97	0	0	Yes
	11:9850939	-	T	A		missense	Thr1253Ser	-	-	131	0	0	96	1	0	Yes
	11:9853777	rs12574508	G	C		missense	Gln1216Glu	0.10937	0.086	106	23	2	76	18	3	Yes
	11:9861208	rs117957652	G	C		missense	Leu1098Val	0.02703	0.025	128	3	0	92	5	0	Yes
	11:9871708	-	G	C		missense	Arg890Gly	-	-	130	1	0	97	0	0	Yes
	11:9878045	rs141330687	C	T		missense	Gly775Ser	0.00409	0.002	130	1	0	97	0	0	Yes
	11:9878180	-	A	C		missense	Ser730Ala	-	-	130	1	0	97	0	0	Yes
	11:9879838	rs7102464	C	T		missense	Glu679Lys	0.10425	0.102	107	24	0	78	19	0	Yes
	11:10015505	rs149794117	G	A		missense	Pro339Leu	0.00003	-	130	1	0	97	0	0	Yes
	11:10019878	-	C	T		missense	Glu304Lys	0.00002	-	130	1	0	97	0	0	Yes

	11:10019921	rs775319050	A	C		missense	Asp289Glu	0.00000	-	131	0	0	96	1	0	Yes
SCN9A (ENSG00000169432)	2:167055370	rs111558968	G	A	ENST00000409672	missense	Leu1916Phe	0.00015	0.002	130	1	0	97	0	0	Yes
	2:167055393	rs3750904	T	C		missense	Asp1908Gly	0.00320	0.011	131	0	0	96	1	0	Yes
	2:167083160	rs149346064	C	T		missense	Val1428Ile	0.00286	0.001	130	1	0	97	0	0	Yes
	2:167089942	rs180922748	G	C		missense	Leu1267Val	0.00220	0.006	131	0	0	96	1	0	Yes
	2:167094638	rs141268327	T	C		missense	Asn1245Ser	0.00809	0.012	127	4	0	95	2	0	Yes
	2:167094715	rs750397053	G	C		missense	Asp1219Glu	0.00000	0.002	131	0	0	96	1	0	Yes
	2:167099158	rs6746030	A	G		missense	Trp1150Arg	0.87293	0.215	19	17	95	17	22	58	No
	2:167108385	rs74401238	C	T		missense	Arg1110Gln	0.02084	0.012	130	1	0	95	2	0	Yes
	2:167136962	rs182650126	T	C		missense	Ile739Val	0.00626	0.004	130	1	0	96	1	0	Yes
	2:167138296	rs121908919	T	C		missense	Lys655Arg	0.00290	0.008	130	1	0	96	1	0	Yes
	2:167141109	rs41268673	G	T		missense	Pro610Thr	0.03443	0.029	119	12	0	91	6	0	Yes
	2:167142979	rs58022607	C	T		missense	Ser490Asn	0.00546	0.008	130	1	0	94	3	0	Yes
	2:167163032	rs761441210	G	T		missense	Thr152Asn	-	-	131	0	0	96	1	0	Yes
	2:167168046	rs201992546	G	T		missense	Pro74His	-	-	131	0	0	96	1	0	Yes
	2:167168149	rs371565974	T	C		missense	Lys40Glu	0.00004	0.001	130	1	0	97	0	0	Yes
SEPT9 (ENSG00000184640)	17:75398351	-	C	T	ENST00000427177	missense	Ser96Leu	-	-	130	1	0	97	0	0	Yes
	17:75398498	rs34587622	C	T		missense	Pro145Leu	0.12237	0.130	90	33	8	71	26	0	Yes
	17:75398768	rs528907798	C	T		missense	Thr235Ile	0.00000	-	130	1	0	97	0	0	Yes
	17:75483634	rs201560726	G	A		missense	Asp348Asn	0.00021	-	130	1	0	97	0	0	Yes
	17:75484342	rs199557573	C	T		missense	Arg355Trp	0.00055	-	130	1	0	97	0	0	Yes
	17:75494705	rs2627223	A	G		missense	Met576Val	0.93855	0.215	38	8	85	21	3	73	No
SH3TC2 (ENSG00000169247)	5:148384455	rs146920285	T	A	ENST00000515425	missense	Asp1229Val	0.00367	0.006	128	3	0	96	1	0	Yes
	5:148388420	rs55853803	C	T		missense	Val1158Ile	0.03139	0.029	123	8	0	93	4	0	Yes
	5:148389868	rs77636085	T	G		missense	Thr1098Pro	0.00188	-	130	1	0	96	1	0	Yes
	5:148406803	rs375034766	C	T		missense	Ser831Asn	0.00007	-	130	1	0	97	0	0	Yes
	5:148407031	-	G	A		missense	Thr755Ile	-	-	130	1	0	97	0	0	Yes
	5:148407208	rs17109261	T	C		missense	His696Arg	0.00013	0.003	130	1	0	97	0	0	Yes
	5:148407322	rs138040787	C	T		missense	Arg658His	0.00009	-	130	1	0	97	0	0	Yes
	5:148407527	rs149244124	C	T		missense	Ala590Thr	0.00004	-	130	1	0	97	0	0	Yes
	5:148407766	rs757294130	T	G		missense	Tyr510Ser	0.00000	-	130	1	0	97	0	0	Yes
	5:148407893	rs6875902	C	A		missense	Ala468Ser	0.21292	0.210	78	49	4	67	27	3	Yes

	5:148407997	rs200967041	G	A		missense	Ser433Leu	0.00074	-	130	1	0	97	0	0	Yes
	5:148411156	rs772832716	T	C		missense	Thr366Ala	0.00003	-	130	1	0	97	0	0	Yes
	5:148420221	rs144963732	G	A		missense	Pro251Ser	0.00027	-	131	0	0	96	1	0	Yes
	5:148421021	rs148634904	A	G		missense	Val230Ala	0.00081	0.003	130	1	0	96	1	0	Yes
	5:148422274	rs17722293	C	T		missense	Gly171Glu	0.01443	0.020	128	3	0	95	2	0	Yes
	5:148431777	rs141649676	T	C		missense	Thr27Ala	0.00167	-	130	1	0	97	0	0	Yes
SLCO1B1 (ENSG00000134538)	12:21294537	rs766950888	C	T	ENST00000256958	missense	Thr10Ile	0.00002	-	130	1	0	97	0	0	Yes
	12:21329738	rs2306283	A	G		missense	Asn130Asp	0.41084	0.384	49	60	22	33	40	24	Yes
	12:21329813	rs11045819	C	A		missense	Pro155Thr	0.16647	0.142	102	27	2	68	27	2	Yes
	12:21331549	rs4149056	T	C		missense	Val174Ala	0.16052	0.124	96	29	6	70	27	0	Yes
	12:21331605	rs376996580	C	A		missense	Leu193Ile	0.00000	-	130	1	0	95	2	0	Yes
	12:21331856	rs766417954	G	T		missense	Gly210Val	0.00000	-	131	0	0	96	1	0	Yes
	12:21375289	rs71581941	C	T		**stop gained**	Arg580*	0.00141	0.002	130	1	0	97	0	0	Yes
	12:21391976	rs34671512	A	C		missense	Leu643Phe	0.05201	0.054	119	11	1	84	12	1	Yes
	12:21392013	rs757219127	A	G		missense	Ile656Val	0.00002	-	130	1	0	97	0	0	Yes
SLCO1B3 (ENSG00000111700)	12:20968739	rs369736559	C	T	ENST00000381545	missense	Arg23Cys	0.00011	-	130	1	0	97	0	0	Yes
	12:21007985	rs79042365	C	G		missense	Phe36Leu	0.00000	-	131	0	0	96	1	0	Yes
	12:21008067	rs151295214	T	A		missense	Ser64Thr	0.00000	-	130	1	0	97	0	0	Yes
	12:21011480	rs4149117	T	G		missense	Ser112Ala	0.85331	0.190	6	27	98	4	20	73	Yes
	12:21014025	rs146623116	A	G		missense	Asn145Ser	0.00248	0.002	129	2	0	96	1	0	Yes
	12:21015760	rs7311358	G	A		missense	Met233Ile	0.85329	0.104	2	27	102	1	22	74	Yes
	12:21015764	-	G	A		missense	Val235Met	-	-	130	1	0	97	0	0	Yes
	12:21028208	rs60140950	G	C		missense	Gly256Ala	0.16225	0.170	101	27	3	69	25	3	Yes
	12:21032475	rs146940490	C	T		missense	Thr414Ile	0.00045	0.001	131	0	0	96	1	0	Yes
SPTLC1 (ENSG00000090054)	9:94800624	rs119482084	C	G	ENST00000262554	missense	Gly387Ala	0.00050	0.004	129	2	0	97	0	0	Yes
	9:94830356	rs45461899	C	A		missense	Arg151Leu	0.03106	0.021	127	4	0	94	3	0	Yes
	9:94830357	rs146548058	G	A		missense	Arg151Cys	0.00003	-	130	1	0	97	0	0	Yes
	9:94843240	rs76962472	G	T		missense	Pro89Gln	0.00063	-	131	0	0	96	1	0	Yes
SPTLC2 (ENSG00000100596)	14:77987874	rs747168398	G	A	ENST00000216484	missense	Arg452Cys	0.00002	-	131	0	0	96	1	0	Yes

TRPV4 (ENSG00000111199)	12:110221524	rs55728855	C	T	ENST00000418703	missense	Glu840Lys	0.00885	0.004	129	2	0	97	0	0	Yes
	12:110221571	rs764622721	G	A		missense	Ser824Leu	0.00005	-	131	0	0	96	1	0	Yes
	12:110230597	rs56177950	C	T		missense	Val562Ile	0.01019	0.015	128	3	0	93	4	0	Yes
	12:110231809	rs762000967	T	C		missense	Thr504Ala	0.00000	-	131	0	0	96	1	0	Yes
	12:110234491	rs775385702	G	A		missense	Arg391Trp	0.00000	-	131	0	0	96	1	0	Yes
	12:110236693	-	G	T		missense	Ala293Asp	-	-	130	1	0	97	0	0	Yes
	12:110246181	rs139300843	C	T		missense	Arg160Gln	0.00003	-	131	0	0	96	1	0	Yes
	12:110252547	rs3742030	G	A		missense	Pro19Ser	0.03914	0.023	127	4	0	89	7	1	Yes

[a] MAF in ExAC for Europeans non-Finish (>33.000 indiv).

[b] MAF in Spanish population (578 indiv).

[c] For *CYP2C8* and *CYP3A4* variants, the *-allele name is shown, when available, after variant ID.

Supplementary Table 2. Association of common non-synonymous coding variants with paclitaxel-induced neuropathy.

Gene	Variant ID	Protein change	MAF ExAC[a]	MAF Spanish[b]	Nr carriers		OR, 95% CI (inf-sup)	P value
					High neuropathy	No/low neuropathy		
AARS	rs35744709	Lys967Met	0.01467	0.014	7	4	1.30 (0.33-6.16)	0.766
	rs149377346	Gly931Ser	0.01102	0.010	3	3	0.74 (0.10-5.57)	0.703
	rs147319762	Lys820Arg	0.00182	0.014	2	3	0.49 (0.04-4.33)	0.655
ABCB1	rs55852620	Gln1107Pro	0.00582	0.002	2	0	1.01 (0.99-1.02)	0.510
	rs2229109	Ser400Asn	0.04316	0.023	7	10	0.51 (0.16-1.50)	0.257
	rs9282564	Asn21Asp	0.11199	0.053	19	17	0.76 (0.37-1.59)	0.542
ARHGEF10	rs9657362	Leu370Phe	0.13846	0.119	21	26	0.62 (0.33-1.18)	0.155
	rs2294039	Val700Ile	0.04063	0.055	8	9	0.66 (0.23-1.83)	0.502
	rs61752020	Val938Ile	0.00817	0.011	2	3	0.49 (0.04-4.33)	0.655
	rs17683288	Ser984Ala	0.07288	0.057	20	10	1.52 (0.66-3.73)	0.387
CCT5	rs11557652	Glu146Val	0.02393	0.012	3	2	1.11 (0.13-13.44)	1.000
	rs141675330	Ile362Met	0.00511	0.004	1	1	0.74 (0.01-58.32)	1.000
CYP2C8[c]	rs10509681 (*3)	Lys399Arg	0.11299	0.152	44	33	0.98 (0.59-1.62)	1.000
	rs1058930 (*4)	Ile264Met	0.05429	0.059	15	21	0.45 (0.21-0.93)	**0.030**
	rs41286886	Val181Ile	0.00762	0.001	1	1	0.74 (0.01-58.32)	1.000
	rs11572080 (*3)	Arg139Lys	0.11287	0.137	39	30	0.96 (0.57-1.63)	0.966
DHTKD1	rs34644609	Ala70Gly	0.00684	0.008	3	1	2.23 (0.18-117.89)	0.640
	rs3740015	Tyr272Asp	0.59906	0.427	76	70	0.80 (0.54-1.18)	0.275
	rs147571909	Val360Ala	0.00558	0.003	1	1	0.74 (0.01-58.32)	1.000
	rs2062988	Ile607Met	0.81243	0.168	46	34	1.03 (0.62-1.70)	1.000
EPHA5	rs36050417	Ala672Thr	0.02758	0.038	7	6	0.86 (0.24-3.15)	1.000
	rs33932471	Asn81Thr	0.06647	0.065	16	9	1.34 (0.54-3.51)	0.636
EPHA6	rs4857276	Ala805Val	0.00742	0.011	2	0	1.01 (0.99-1.02)	0.510

EPHA8	rs45498698	Gly45Ser	0.00821	0.004	5	2	1.87 (0.30-19.78)	0.704
	rs144329757	Pro607His	0.00844	0.004	3	0	1.01 (0.99-1.03)	0.265
	rs999765	Glu612Gln	0.10359	0.078	22	15	0.93 (0.47-1.85)	0.947
	rs62618734	Arg884His	0.00930	0.006	2	2	0.74 (0.05-10.28)	1.000
FAM134B	rs78314670	Arg127Cys	0.01020	0.004	1	4	0.18 (0.00-1.86)	0.168
FGD4	rs144693221	Pro571Thr	0.00619	0.002	1	1	0.74 (0.01-58.32)	1.000
FIG4	rs2295837	Met364Leu	0.03636	0.038	8	5	1.19 (0.34-4.70)	0.986
	rs9885672	Val654Ala	0.15789	0.148	39	23	1.50 (0.85-2.71)	0.181
GARS	rs62636572	Pro4Leu	0.02812	0.003	5	3	0.92 (0.20-4.72)	1.000
IKBKAP	rs1538660	Pro1158Leu	0.17074	0.166	30	29	0.70 (0.40-1.24)	0.244
	rs3204145	Cys1072Ser	0.17022	0.181	35	32	0.75 (0.44-1.28)	0.315
	rs2230798	Lys952Ile	0.01692	0.008	1	2	0.37 (0.01-7.13)	0.577
	rs2230794	Ile830Met	0.04604	0.057	17	6	2.17 (0.80-6.86)	0.155
	rs2230793	Ile816Leu	0.18077	0.211	50	37	1.09 (0.68-1.77)	0.783
	rs2230792	Gly765Glu	0.18670	0.207	50	37	1.09 (0.68-1.77)	0.783
	rs838827	Arg525Gln	0.06139	0.089	18	13	1.18 (0.56-2.56)	0.774
	rs1140064	Glu312Lys	0.02805	0.017	3	2	1.11 (0.13-13.44)	1.000
	rs17853166	Ser251Gly	0.02803	0.016	2	2	0.74 (0.05-10.28)	1.000
KIF1B	rs2297881	Tyr1087Cys	0.02518	-	10	10	0.73 (0.27-2.00)	0.647
	rs77172218	Val1554Met	0.01600	-	2	1	1.48 (0.08-87.99)	1.000
LITAF	rs149712652	Pro196Ser	0.01258	0.011	3	1	2.23 (0.18-117.89)	0.640
	rs4280262	Ile92Val	0.20581	0.164	48	36	0.95 (0.58-1.54)	0.905
LRSAM1	rs1539567	Asn318Asp	0.78166	0.343	65	47	1.11 (0.73-1.71)	0.672
MED25	rs145770066	Ala335Val	0.00604	-	0	2	0.00 (0.00-3.94)	0.180
	rs193291405	Ala576Gly	0.02446	0.002	1	1	0.74 (0.01-58.32)	1.000
MFN2	rs142271930	Val705Ile	0.00628	0.002	1	1	0.74 (0.01-58.32)	1.000
MTMR2	rs61735578	Glu502Gln	0.02432	0.023	4	2	1.49 (0.21-16.61)	1.000

NGF	rs11466111	Arg80Gln	0.01634	0.008	4	2	1.49 (0.21-16.61)	1.000
	rs6330	Ala35Val	0.44519	0.443	84	65	0.85 (0.58-1.26)	0.464
NTRK1	rs1007211	Gly18Glu	0.01562	0.002	1	1	0.74 (0.01-58.32)	1.000
	rs6336	His604Tyr	0.05491	0.046	11	8	1.12 (0.41-3.21)	0.997
	rs6339	Gly613Val	0.05483	0.047	11	8	1.12 (0.41-3.21)	0.997
	rs35669708	Arg780Gln	0.00722	0.003	2	4	0.37 (0.03-2.58)	0.409
PMP22	rs104894619	Thr118Met	0.00736	0.003	0	1	0.00 (0.00-28.88)	0.425
PRX	rs268674	Gly1132Arg	0.94233	0.279	18	4	3.92 (1.28-16.01)	**0.015**
	rs268673	Ile921Met	0.39123	0.350	85	64	1.04 (0.70-1.54)	0.926
	rs268671	Val882Ala	0.51248	0.379	103	70	1.33 (0.90-1.97)	0.156
	rs201389706	Val871Ala	0.04189	0.003	15	10	1.12 (0.46-2.85)	0.955
	rs146789340	Glu495Gln	0.00393	0.011	1	0	1.00(0.99-1.01)	1.000
	rs118071705	Ala244Val	0.03438	0.004	2	3	0.49 (0.04-4.33)	0.655
SBF2	rs12574508	Gln1216Glu	0.10937	0.086	25	21	0.81 (0.44-1.53)	0.588
	rs117957652	Leu1098Val	0.02703	0.025	3	5	0.44 (0.07-2.29)	0.294
	rs7102464	Glu679Lys	0.10425	0.102	24	19	0.93 (0.47-1.85)	0.947
SCN9A	rs141268327	Asn1245Ser	0.00809	0.012	4	2	1.49 (0.21-16.61)	1.000
	rs74401238	Arg1110Gln	0.02084	0.012	1	2	0.37 (0.01-7.13)	0.577
	rs182650126	Ile739Val	0.00626	0.004	1	1	0.74 (0.01-58.32)	1.000
	rs41268673	Pro610Thr	0.03443	0.029	12	6	1.50 (0.51-4.97)	0.573
	rs58022607	Ser490Asn	0.00546	0.008	1	3	0.24 (0.00-3.07)	0.317
SEPT9	rs34587622	Pro145Leu	0.12237	0.130	41	26	1.49 (0.86-2.60)	0.167
SH3TC2	rs55853803	Val1158Ile	0.03139	0.029	8	4	1.49 (0.39-6.88)	0.720
	rs6875902	Ala468Ser	0.21292	0.210	53	30	1.36 (0.82-2.26)	0.254
	rs17722293	Gly171Glu	0.01443	0.020	3	2	1.11 (0.13-13.44)	1.000
SLCO1B1	rs2306283	Asn130Asp	0.41084	0.384	82	64	0.79 (0.54-1.18)	0.265
	rs11045819	Pro155Thr	0.16647	0.142	29	29	0.71 (0.40-1.25)	0.255
	rs4149056	Val174Ala	0.16052	0.124	35	27	1.15 (0.66-2.02)	0.704
	rs34671512	Leu643Phe	0.05201	0.054	12	13	0.67 (0.28-1.58)	0.419

SLCO1B3	rs4149117	Ser112Ala	0.85331	0.190	33	24	1.04 (0.59-1.83)	0.999
	rs7311358	Met233Ile	0.85329	0.104	29	23	0.95 (0.52-1.76)	0.977
	rs60140950	Gly256Ala	0.16225	0.170	30	28	0.76 (0.43-1.34)	0.372
SPTLC1	rs45461899	Arg151Leu	0.03106	0.021	4	3	0.99 (0.16-6.82)	1.000
TRPV4	rs55728855	Glu840Lys	0.00885	0.004	2	0	1.01 (0.99-1.02)	0.510
	rs56177950	Val562Ile	0.01019	0.015	3	4	0.55 (0.08-3.30)	0.465
	rs3742030	Pro19Ser	0.03914	0.023	4	8	0.32 (0.07-1.17)	0.091

[a] MAF in ExAC for Europeans non-Finish (>33.000 indiv).

[b] MAF in Spanish population (578 indiv).

[c] For *CYP2C8* variants, the *-allele name is shown, when available, after variant ID.