Informative gene network for chemotherapy-induced peripheral neuropathy

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Abstract

Background: Host genetic variability has been implicated in chemotherapy-induced peripheral neuropathy (CIPN). A dose-limiting toxicity for chemotherapy agents, CIPN is also a debilitating condition that may progress to chronic neuropathic pain. We utilized a bioinformatics approach, which captures the complexity of intracellular and intercellular interactions, to identify genes for CIPN.

Methods: Using genes pooled from the literature as a starting point, we used Ingenuity Pathway Analysis (IPA) to generate gene networks for CIPN.

Results: We performed IPA core analysis for genes associated with platinum-, taxane- and platinum-taxane-induced neuropathy. We found that IL\(_6\), TNF, CXCL8, IL1B and ERK1/2 were the top genes in terms of the number of connections in platinum-induced neuropathy and TP53, MYC, PARP1, P38 MAPK and TNF for combined taxane-platinum-induced neuropathy.

Conclusion: Neurotoxicity is common in cancer patients treated with platinum compounds and anti-microtubule agents and CIPN is one of the debilitating sequela. The bioinformatic approach helped identify genes associated with CIPN in cancer patients.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating condition. CIPN is a dose-limiting toxicity for chemotherapy agents, such as oxaliplatin, cisplatin, and platinum [1–4]. Chemotherapeutic agents may cause structural damage to peripheral nerves, which can result in aberrant somatosensory processing by the peripheral and/or central nervous system. The symptoms of CIPN vary depending on the type of chemotherapy administered and which nerve fibers are affected. Unusual sensations (paresthesia), numbness, balance problems or pain may result from chemotherapies that affect the sensory nerve fibers. When motor nerves are affected, patients may report weakness of the muscles in the feet and hands.

Patients who suffer from CIPN have a higher risk (as much as threefold higher) of developing neuropathic pain (NP) [5]. Defined as “pain initiated or caused by primary lesion or dysfunction in the nervous system,” NP occurs in nearly 40 % of patients who experience cancer pain [6, 7]. Patients with NP experience higher pain intensity and less effective control of their pain with conventional analgesia [8]. Further, patients with NP rate their level of pain relief to be significantly lower than those with nociceptive pain (defined as pain caused by activation of primary afferents in somatic or
visceral tissues) in response to a single dose of an opioid [8, 9]. Patients with NP report twice as many visits to their health care provider \( (p = 0.02) \) and take more prescription (50 % versus 19 %; \( p = 0.001 \)) and over-the-counter medications (62.5 % versus 45 %; \( p = 0.08 \)) for pain than those without NP [5].

Published guidelines for the initial treatment of NP include the use of gabapentin, pregabalin, carbamazepine, tricyclic antidepressants, oxycodone, morphine, methadone, tramadol, duloxetine, and venlafaxine [10, 11]. However, placebo-controlled trials have shown that medications such as gabapentin [12] and glutamine [13] have no statistically significant effects on NP. Animal and human studies have been conducted to identify the best ways to treat and manage NP [14–20]. Because CIPN is a risk factor for the development of NP in cancer patients, a better understanding of the potential biological mechanisms underlying CIPN has huge clinical significance.

Host genetic variability has been implicated in many pain conditions, including neuropathy. Each of these studies assessed different therapeutic agents and different genetic mechanisms. However, it is understood that as a complex trait, several genes are implicated in CIPN. Bioinformatics provides tools for using large-scale information to produce comprehensive networks of genes and the underlying biological pathways implicated in a phenotype. Therefore, in this study, we used the Ingenuity Pathway Analysis (IPA), a bioinformatic tool for analyzing biological data, and performed a comprehensive network-based approach to identify genes implicated in neuropathy induced by chemotherapy agents. Compared to traditional regression approaches, network-based approaches can provide a holistic picture that captures the complexity of intracellular and intercellular interactions in diseases [21]. Furthermore, the network-based approaches can identify genes and pathways related to a disease or phenotype, which will lead to a better understanding of the underlying biological mechanisms [22]. Further, networks generated from IPA core analysis may suggest new candidate genes for future studies of CIPN.

**Methods**

With the goal of identifying a comprehensive list of genes and potentially novel genes associated with CIPN, we first conducted a literature search as described below. Using genes pooled from the literature as a starting point, we used IPA to generate gene networks for CIPN.

**Literature review**

Using the PubMed database, we performed a comprehensive literature review, limiting our search to human studies and articles published in English before July 2014. The primary purpose of the literature search was to identify genes associated with CIPN in cancer patients. The terms we used were “cancer neuropathy SNP,” “cancer neuropathy SNPs,” “cancer neuropathy gene,” “cancer neuropathy genes,” “cancer neurotoxicity SNP,” “cancer neurotoxicity SNPs,” “cancer neurotoxicity gene” and “cancer neurotoxicity genes.” We then screened the resulting articles based on the title, abstract, and the full text, and excluded duplicate articles. Next, we manually searched the reference lists of the articles identified in our initial search and those in related review articles to identify additional relevant articles (Table 1). From these studies, we retrieved the information about genes...
harboring or close to the significantly associated genetic variants (SNPs or haplotypes) and included those genes in the IPA. In particular, we included only those genes for IPA analysis that (1) have been replicated in an independent study or meta-analysis, (2) have at least one SNP that reached the genome-wide significance level, or (3) have a known biological functional significance (e.g., multi-drug resistance, drug metabolism, and mediating developmental events in the nervous system). We also summarized the information based on the different chemotherapy agents used for cancer patients.

### Ingenuity pathway analysis

IPA (Ingenuity Systems, www.ingenuity.com) is a software that connects a list of molecules in a set of networks based on the scientific information contained in the Ingenuity Knowledge Base of biological interactions and functional annotations from millions of relationships between proteins, genes, complexes, cells, tissues, drugs, and diseases [23, 21]. In the networks, nodes are used to represent molecules (e.g., genes, chemicals, protein families, complexes, microRNA species and biological processes) [24] and lines connecting two molecules are used to represent the relationship between them. Many different types of relationships are considered in the IPA analyses, including activation, binding, causation, chemical-chemical interaction, expression enzyme catalysis, inhibition, biochemical modification, protein-protein binding and transcription.

In this study, we utilized the IPA core analysis function to generate relevant networks that identify additional genes that interact with the genes identified from the literature review (denoted as focus genes in IPA). The IPA core analysis function is a process to create networks on the basis of the focus genes [25]. The working hypothesis for network generation is that the biological function involves locally dense interactions; thus, IPA uses an algorithm to attempt to generate networks that are as densely connected as possible [26]. The network generation process first ranks the focus genes in decreasing order on the basis of triangular connectivity, which measures the number of triangular connections in which a gene functions (or pairs of genes to which a gene is connected). The most connected focus gene (the top ranked gene) is considered to be the starting seed gene. Next, the remaining focus genes that are in the neighborhood of the starting seed gene are added to generate the first seed gene network. A neighborhood is defined as a gene plus the genes exactly one connection away from that gene. Then the second seed gene network is identified from the focus genes that are not included in the first seed gene network. The process continues until all focus genes are

### Table 1: Number of articles obtained using different search terms

| Search terms            | # of articles by PubMed search | # of articles by initial screen | # of articles from references | # of articles included |
|-------------------------|---------------------------------|---------------------------------|------------------------------|------------------------|
| cancer neuropathy SNPs(SNP) | 30                              | 20                              | 28                           | 36                     |
| cancer neuropathy genes(gene) | 266                             | 1                               | 0                            | 1                      |
| cancer neurotoxicity SNPs(SNP) | 37                              | 6                               | 0                            | 6                      |
| cancer neurotoxicity genes(gene) | 349                             | 1                               | 0                            | 1                      |
| Total                   | 682                             | 28                              | 36                           | 64                     |
represented in a relevant network. Subsequently, all smaller networks are combined to make larger networks by connecting seed gene networks through an additional non-focus gene. If the gene network does not reach the maximum network size (140 genes in this study), IPA will then connect additional genes/networks from its database to any of the genes involved in the gene network. Specifically, given a network, to identify additional genes to be added, IPA gives priority to the genes that have the largest overlap with the existing network and have the least number of neighbors. This property is measured using a metric called specific connectivity, which is calculated by dividing the number of genes in the intersection of the neighborhood and the existing network by the union of the number of genes in the neighborhood and the existing network. The gene with the highest specific connectivity score is included in the existing network. Importantly, the IPA analysis can exclude a focus gene from the resulting network if such a gene is less likely to have connections (i.e., biological relationships) with the network.

The resulting functions/pathways/networks are evaluated using the right-tailed Fisher’s exact test, which provides $p$ values based on the null hypothesis that the association between a set of focus genes and a given function/pathway/network is due to random chance [25]. Specifically, if the final network includes $n$ genes and $n_f$ of them are focus genes, the $p$ value is the probability of finding $n_f$ or more focus genes in a set of $n$ genes randomly selected from the IPA pre-specified database [26]. A score, which is assessed as $-\log_{10}(p\text{ value})$, is used to rank the resulting functions/pathways/networks. We used a significance level of $<10^{-5}$ in our study (score $>5$) when selecting networks [21].

We limited the IPA analysis to human studies. In the IPA core analysis, we used the Ingenuity Knowledge Base as the reference set. In order to generate networks in the core analysis, we used the settings of a maximum of 140 genes per network and 25 networks per analysis, because the networks for up to 140 genes allow for the possibility that the same network can include all focus genes [27]. We reported the most interconnected genes in the networks as the key genes of interest, because highly connected molecules (called hubs) are typically associated with biological functions or diseases [22, 24, 21, 26, 27].

Results

Literature review

From our search of the PubMed database, we initially identified 682 articles. After screening the title, abstract and full text, we excluded 654 articles for the following reasons (Table 1): (1) not human studies; (2) not published in English; (3) meta-analysis study, review or letter to the editor; (4) clinical trial studies; (5) not genetic association studies; (6) not neuropathy-related phenotypes studies; (7) not cancer studies; and (8) duplicate articles from different searches. We then manually searched the reference lists from the resulting 28 articles and from related review articles about genetic neuropathy studies, and identified 36 more articles. As a result, we had a total of 64 articles from which we extracted information to identify the focus genes and perform the analyses through IPA.

Table 2 lists the information we retrieved from each of the studies, including the year of publication, first author, ethnicity of patient population, cancer type, sample size,
| Year | First author | Ethnicity | Cancer type | Sample size | Phenotype | Significant genes |
|------|--------------|-----------|-------------|-------------|-----------|-------------------|
| 2003 | Aplenc R [41]| W, AA, H  | Acute lymphoblastic leukemia | 533 | Peripheral neuropathy | CYP3A4, CYP3A5 |
| 2004 | Isla D [42] | W         | Lung        | 62          | Docetaxel-cisplatin-treated neurological neuropathy | None |
| 2006 | Lecomte T [43]| W         | Gastrointestinal solid tumors | 64 | Oxaliplatin-related cumulative neuropathy | GSTP1 |
| 2006 | Sissung TM [44]| W         | N/A         | 26          | Paclitaxel-induced neuropathy | ABCB1 |
| 2007 | Gamelin L [45]| W         | Colon, rectum | 145 | Oxaliplatin-induced neurotoxicity | AGXT |
| 2007 | Marsh S [46] | N/A       | Ovarian     | 914         | Paclitaxel/docetaxel-induced neuropathy | None |
| 2007 | Oldenburg J [47]| W         | Testicular  | 238         | Self-reported chemotherapy-induced long-term toxicities | GSTP1 |
| 2007 | Ruzzo A [48] | W         | Colorectal  | 166         | Oxaliplatin-induced neurotoxicity | GSTP1 |
| 2008 | Keam B [49] | A         | Gastric     | 73          | Peripheral sensory neuropathy | None |
| 2008 | Pare L [50] | W         | Colorectal  | 126         | Cumulative oxaliplatin-induced neuropathy | None |
| 2008 | Sissung TM [51]| N/A       | Prostate    | 73          | Docetaxel-induced neuropathy | ABCB1 |
| 2009 | Argyriou AA [52]| W         | Colorectal  | 62          | Oxaliplatin-induced peripheral neuropathy | None |
| 2009 | Goekkurt E [53]| W         | Gastric     | 134         | Neurotoxicity | GSTP1 |
| 2009 | Green H [54] | W         | Ovarian     | 38          | Sensory/motor neuropathy | None |
| 2009 | Kim HS [55] | A         | Epithelial ovarian | 118 | Taxane/platinum-induced neurotoxicity | ERCC1 |
| 2009 | Kweekel DM [56]| W         | Colorectal  | 91          | Neurotoxicity | None |
| 2009 | Mir O [57] | W         | Breast, lung, prostate | 58 | Docetaxel(Taxotere)-induced peripheral neuropathy | GSTP1 |
| 2009 | Seo BG [58] | A         | Gastric     | 94          | Neuropathy | None |
| 2010 | Antonacopoulou AG [59]| W         | Colorectal  | 55          | Chronic oxaliplatin-induced peripheral neuropathy | ITGB3 |
| 2010 | Boige V [60] | W         | Colorectal  | 349         | FOLFOX-induced severe neurologic toxicity | None |
| 2010 | Chen YC [61] | A         | Colorectal  | 166         | Oxaliplatin-induced chronic cumulative neuropathy | GSTP1 |
| 2010 | Cho HJ [62] | A         | Diffuse large B-cell lymphoma | 94 | Chemotherapy-related neurotoxicity | None |
| Year | First Author | Location | Study Type | Symptoms | Genes Associated |
|------|--------------|----------|------------|----------|------------------|
| 2010 | Inada M [63] | Colorectal | Oxaliplatin-induced peripheral neuropathy | ERCC1, GSTP1 |
| 2010 | Kanai M [64] | Colorectal | Early-onset oxaliplatin-induced neuropathy | None |
| 2010 | Khrunin AV [65] | Ovarian | Cisplatin-based neuropathy | GSTM1, GSTM3 |
| 2010 | Li QF [66] | Gastric | Neurological toxicity | GSTP1 |
| 2010 | McLeod HL [67] | Metastatic colorectal | Diarrhea, vomiting, paresthesia, febrile neutropenia and neutropenia | GSTP1 |
| 2010 | Ofverholm A [68] | Breast, ovarian | Occurrence and degree of neurotoxicity | None |
| 2010 | Rizzo R [69] | Breast | Taxane-induced hypersensitivity and sensory neuropathy | None |
| 2010 | Basso M [70] | Colorectal, pancreatic, bile ducts | Acute oxaliplatin neurotoxicity | SK3 |
| 2010 | Bergmann TK [71] | Ovarian | Sensory neuropathy | None |
| 2010 | Bergmann TK [72] | Ovarian | Sensory neuropathy | None |
| 2011 | Broyl A [73] | Multiple myeloma | Bortezomib/vincristine-induced peripheral neuropathy | RHOB1B2, CPT1C, SOX8, caspase 9, ALOX12, IGF1R, SOD2, MYOSA, MBL2, PPAR, ERCC4, ERCC3, AURKA, MKI67, GLI1, DPYD, ABCC1 |
| 2011 | Cibeira MT [74] | Multiple myeloma | Thalidomide-induced peripheral neuropathy | GSTT1 |
| 2011 | Corthals SL [75] | Multiple myeloma | Bortezomib induced peripheral neuropathy | CYP17A1 |
| 2011 | Favis R [76] | Myeloma | Bortezomib-induced peripheral neuropathy | CTLA4, PSMB1, CTSS, GJE1, DYNC111, TCF4 |
| 2011 | Hong J [77] | Colorectal | Sensory neuropathy | GSTP1 |
| 2011 | Johnson DC [78] | Multiple myeloma | Thalidomide-related peripheral neuropathy | ABCA1, ICAM1, PPAR, SERPINB2, SLC12A6 |
| 2011 | Leskela S [79] | Lung, breast, ovary, uterus, head and neck | Neurotoxicity | CYP2C8, CYP3A5 |
| 2011 | Sucheston LE [80] | Breast | Taxane-induced neurotoxicity | FANCD2 |
| 2011 | Baldwin RM [81] | Breast | Paclitaxel induced peripheral sensory neuropathy | FG5D4, FZD3, EPHA5 |
Table 2 List of genetic association studies for chemotherapy-induced neuropathy in cancer patients, sorted by publication year and name of first author (Continued)

| Year | First Author | Type of Cancer | Tissue Type | Chemotherapy-Induced Neurotoxicity | Genes |
|------|--------------|----------------|-------------|-----------------------------------|-------|
| 2012 | Braunagel D [82] | W Acute myeloid leukemia | Acute myeloid leukemia | Cytarabine-induced neurotoxicity | NME1 |
| 2012 | Fung C [83] | W, A, AA, H Testicular germ cell tumor | Testicular germ cell tumor | Cisplatin-induced neurotoxicity, peripheral neuropathy | None |
| 2012 | Hasmats J [84] | W Ovarian, lung, carcinoma in uteri/peritoneal/breast | Ovarian, lung, carcinoma in uteri/peritoneal/breast | Paclitaxel/carboplatin-induced neuropathy | ABCA1 |
| 2012 | Hertz DL [85] | W, AA Breast | Breast | Peripheral neuropathy | CYP2C8 |
| 2012 | Leandro-Garcia LJ [86] | W Ovary, lung, breast | Ovary, lung, breast | Paclitaxel-induced peripheral neuropathy | TUBB2A |
| 2012 | Won HH [87] | A Colon | Colon | Severe oxaliplatin-induced chronic peripheral neuropathy | TAC1, FOXC1, GMDS, ITGA1, PELO, ACYP2, TSPYL6, DLEU7, BTG4, POU2AF1, CAMK2N1, FARS2, LYRM4 |
| 2013 | Argyriou AA [88] | W Colorectal | Colorectal | Oxaliplatin-induced peripheral neuropathy | SCN4A, SCN10A |
| 2013 | Bergmann TK [89] | W Ovarian | Ovarian | Paclitaxel-induced neuropathy | None |
| 2013 | Cecchin E [90] | W Colorectal | Colorectal | Oxaliplatin neurotoxicity | ABCC1, ABCC2 |
| 2013 | de Graan AJ [91] | W Esophagus, ovary, cervix, endometrial, breast, lung, head/neck | Esophagus, ovary, cervix, endometrial, breast, lung, head/neck | Paclitaxel-induced neurotoxicity | CYP3A4 |
| 2013 | Hertz DL [92] | W, AA Breast | Breast | Paclitaxel-induced neuropathy | CYP2C8 |
| 2013 | Kumamoto K [93] | A Colorectal | Colorectal | Oxaliplatin-induced sensory peripheral neuropathy | GSTP1, GSTM1 |
| 2013 | Leandro-Garcia LJ [94] | W Ovary, fallopian tube, peritoneum, lung, uterus, breast | Ovary, fallopian tube, peritoneum, lung, uterus, breast | Paclitaxel induced peripheral sensory neuropathy | EPHA4, EPHA6, EPHA5, XKR4, LIMK2 |
| 2013 | Lee KH [95] | A Colon | Colon | Sensory neuropathy | XRCC1 |
| 2013 | Liu YP [96] | A Gastric | Gastric | Oxaliplatin-induced neurotoxicity | GSTP1 |
| 2013 | McWhinney-Glass S [97] | N/A Ovarian | Ovarian | Platinum/taxane-induced neurotoxicity | SOX10, BCL2, OPRM1, TRPV1 |
| 2013 | Oguri T [98] | A Colorectal | Colorectal | Oxaliplatin-induced chronic peripheral neurotoxicity | ACYP2, FARS2, ERCC1, TAC1 |
| 2014 | Abraham JE [99] | W Breast | Breast | Taxane-related sensory neuropathy | ABCB1, TUBB2A, CYP2C8, ABCC2, CYP1B1, KIAA0146-PRKD, SLC01B1, EPHA6 |
| 2014 | Bhojwani D [100] | N/A | | | ASTN2, PKDC1, IYD |
phenotypes, and significant genes. These studies included different cancer sites and patients of different ethnic groups. Neuropathy (or neurotoxicity) in cancer patients is usually induced by the chemotherapy agents used in cancer treatment, such as oxaliplatin, cisplatin, and platinum, and is usually measured according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events or Common Toxicity Criteria.

In Table 3, we summarize the focus genes from the literature review with respect to neuropathy induced by different chemotherapy agents, including platinum, taxane, platinum/taxane, Bortezomib, bortezomib/vincristine, thalidomide, methotrexate, cytarabine, platinum/fluorouracil, platinum/S-1 (i.e., oral fluoropyrimidine consists of tegafur, 5-chloro-2,4 dihydroxypyrimidine, and potassium oxonate), taxane/gemcitabine, platinum/fluorouracil/leucovorin, platinum/fluorouracil/irinotecan, prednisone/vincristine/methotrexate, platinum/capecitabine, platinum/fluorouracil/irinotecan/leucovorin and rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone. Among the different (or combined) chemotherapy agents, those studied most frequently in relation to drug-induced neuropathy were platinum, taxane and the combination of platinum/taxane, for which our literature search respectively produced 21, 19 and 5 related papers.

Among the focus genes reported in the articles, GSTP1, CYP2C8 and ABCB1 were studied the most frequently (Table 4). ABCC2 and GSTP1 were associated with both platinum- and taxane-induced neuropathy; CYP2C8 was associated with both taxane- and platinum/taxane-induced neuropathy; and ERCC1 was associated with platinum- and platinum/taxane-induced neuropathy. Besides platinum-, taxane- and platinum/taxane-induced neuropathy, neuropathy induced by other chemotherapy agents were not frequently studied. Therefore, we focused on the genes associated with platinum-, taxane- and platinum/taxane-induced neuropathy in our analyses.

**Table 2** List of genetic association studies for chemotherapy-induced neuropathy in cancer patients, sorted by publication year and name of first author (Continued)

| Year | Authors | Disease | Chemotherapy | Genes |
|------|---------|---------|--------------|-------|
| 2014 | Custodio A [101] | Colon | Oxaliplatin-induced peripheral neuropathy | CCNH, ABCG2 |
| 2014 | Hertz DL [102] | Breast | Paclitaxel-induced peripheral neuropathy | CYP2C8, ABCG1 |
| 2014 | Khrunin AV [103] | Ovarian | Cisplatin-based neurotoxicity | None |
| 2014 | Lee SY [104] | Breast | Paclitaxel and gemcitabine combination chemotherapy neurotoxicity | RRM1 |

W: White; A: Asian; AA: African American; H: Hispanic

**IPA core analysis**

We performed the IPA core analysis for the focus genes reported to be associated with platinum-, taxane- and platinum/taxane- induced neuropathy. The significant networks revealed from the IPA core analyses are shown in Figs. 1, 2 and 3 for the focus genes...
Table 3  Summary of genes associated with chemotherapy agent-specified neuropathy from the literature review. Number of papers for each agent-specified neuropathy, number of genes associated with each agent-specified neuropathy and number of agent-specified neuropathies associated with each gene are shown. For the association between a gene and an agent-specified neuropathy, the number of relating papers is listed.

| Genes          | # of papers | # of genes | # of agents |
|----------------|-------------|-------------|-------------|
| (IPA symbols)  | 26          | 19          | 7           |
| GSTP1          | 6           | 7           | 1           |
| ERCC1          | 2           | 2           | 1           |
| ACYP2          | 1           | 2           |             |
| FARS2          | 1           | 2           |             |
| GSTM1          | 1           | 2           |             |
| TAC1           | 1           | 2           |             |
| ABCC2          | 2           | 1           | 1           |
| ABCC1          | 2           | 1           |             |
| ABCG2          | 1           | 1           |             |
| AGXT           | 1           | 1           |             |
| BTG4           | 1           | 1           |             |
| CAMK2N1        | 1           | 1           |             |
| CCNH           | 1           | 1           |             |
| DLEU7          | 1           | 1           |             |
| FOXC1          | 1           | 1           |             |
| GMDS           | 1           | 1           |             |
| GSTM3          | 1           | 1           |             |
| ITGA1          | 1           | 1           |             |
| ITGB3          | 1           | 1           |             |
| KCNN3          | 1           | 1           |             |
| LYRM4          | 1           | 1           |             |
| PEO1           | 1           | 1           |             |
| POU2AF1        | 1           | 1           |             |
| SCN10A         | 1           | 1           |             |
| SCN4A          | 1           | 1           |             |
| TSPYL6         | 1           | 1           |             |
| CYP2C8         | 2           | 5           | 1           |
| ABCB1          | 1           | 3           |             |
| EPHA5          | 1           | 2           |             |
| EPHA6          | 1           | 2           |             |
| TUBB2A         | 1           | 2           |             |
| CYP3A4         | 2           | 1           |             |
| CYP3A5         | 2           | 1           |             |
| ABCG1          | 1           | 1           |             |
Table 3 Summary of genes associated with chemotherapy agent-specified neuropathy from the literature review. Number of papers for each agent-specified neuropathy, number of genes associated with each agent-specified neuropathy and number of agent-specified neuropathies associated with each gene are shown. For the association between a gene and an agent-specified neuropathy, the number of relating papers is listed (Continued)

| Gene   | Papers | Genes | Neurpathies |
|--------|--------|-------|-------------|
| CYP1B1 | 1      | 1     | 1           |
| EPHA4  | 1      | 1     | 1           |
| FANCD2 | 1      | 1     | 1           |
| FGD4   | 1      | 1     | 1           |
| FZD3   | 1      | 1     | 1           |
| LIMK2  | 1      | 1     | 1           |
| SLCO1B1| 1      | 1     | 1           |
| SPI2D  | 1      | 1     | 1           |
| XR4    | 1      | 1     | 1           |
| ABCA1  | 2      | 1     | 1           |
| BCL2   | 1      | 1     | 1           |
| OPRM1  | 1      | 1     | 1           |
| SOX10  | 1      | 1     | 1           |
| TRP1   | 1      | 1     | 1           |
| CTLA4  | 1      |       |             |
| CTSS   | 1      |       |             |
| CYP17A1| 1      |       |             |
| DYNC1I1| 1      |       |             |
| GJC3   | 1      |       |             |
| PSMB1  | 1      |       |             |
| TCF4   | 1      |       |             |
| PPARD  | 2      | 1     | 1           |
| ALOX12 | 1      | 1     | 1           |
| AURKA  | 1      | 1     | 1           |
| CASP9  | 1      | 1     | 1           |
| CPT1C  | 1      | 1     | 1           |
| DPDY   | 1      | 1     | 1           |
| ERCC3  | 1      | 1     | 1           |
| ERCC4  | 1      | 1     | 1           |
| GLI1   | 1      | 1     | 1           |
| IGF1R  | 1      | 1     | 1           |
| MBL2   | 1      | 1     | 1           |
| MK667  | 1      | 1     | 1           |
| MYOSA  | 1      | 1     | 1           |
| RHOBT2 | 1      | 1     | 1           |
| SOD2   | 1      | 1     | 1           |
| SOX8   | 1      | 1     | 1           |
| GSTT1  | 1      |       |             |
| ICAM1  | 1      | 1     | 1           |
| SERPINB2| 1    | 1     | 1           |
| SLC12A6| 1      | 1     | 1           |
Table 3  Summary of genes associated with chemotherapy agent-specified neuropathy from the literature review. Number of papers for each agent-specified neuropathy, number of genes associated with each agent-specified neuropathy and number of agent-specified neuropathies associated with each gene are shown. For the association between a gene and an agent-specified neuropathy, the number of relating papers is listed (Continued)

| Gene  | Platinum | Taxane | Platinum/Taxane |
|-------|----------|--------|----------------|
| ASTN2 | 1        | 1      |                |
| IYD   | 1        | 1      |                |
| PXDC1 | 1        | 1      |                |
| NME1  | 1        |        |                |
| RRM1  | 1        |        | 1              |
| XRCC1 | 1        |        |                |

P: Platinum; T: Taxane; P/T: Platinum/Taxane; B: Bortezomib; B/V: Bortezomib/Vincristine; Th: Thalidomide; M: Methotrexate; Cyt: Cytarabine; P/F: Platinum/Fluorouracil; P/S: Platinum/S-1; T/G: Taxane/Gemcitabine; P/F/L: Platinum/Fluorouracil/Leucovorin; P/F/I: Platinum/Fluorouracil/Irinotecan; P/F/L: Platinum/Fluorouracil/Leucovorin; R/Cyc/D/V/Pr: Rituximab/Cyclophosphamide/Doxorubicin/Vincristine/Prednisone

Table 4  Focus genes* associated with platinum-, taxane-, and platinum/taxane- induced neuropathy, as identified through the literature review

| Platinum-induced neuropathy | Taxane-induced neuropathy | Platinum/Taxane-induced neuropathy |
|-----------------------------|---------------------------|-----------------------------------|
| ABC1                        | ABCB1                     | ABCA1                             |
| ABC2                        | ABC2                      | BCL2                              |
| ABCG2                       | ABCG1                     | CYP2C8                            |
| ACYP2                       | CYP1B1                    | ERCC1                             |
| AGXT                        | CYP2C8                    | OPRM1                             |
| BTG4                        | CYP3A4                    | SOX10                             |
| CAMK2A1                     | CYP3A5                    | TRPV1                             |
| CCNH                        | EPHA4                     |                                   |
| DLEU7                       | EPHA5                     |                                   |
| ERCC1                       | EPHA6                     |                                   |
| FARS2                       | FANCD2                    |                                   |
| FOXC1                       | FGD4                      |                                   |
| GMDS                        | FZD3                      |                                   |
| GSTM1                       | GSTP1                     |                                   |
| GSTM3                       | LIMK2                     |                                   |
| GSTP1                       | SLCO1B1                   |                                   |
| ITGA1                       | SPIDR                     |                                   |
| ITGB3                       | TUBB2A                    |                                   |
| KCNN3                       | XK84                      |                                   |
| LYRM4                       |                           |                                   |
| PEL0                        |                           |                                   |
| POU2AF1                     |                           |                                   |
| SCN10A                      |                           |                                   |
| SCN4A                       |                           |                                   |
| TAC1                        |                           |                                   |
| TSPYL6                      |                           |                                   |

*Genes shown to be significant based on the literature
reported to be associated with platinum-, taxane- and platinum/taxane- induced neuropathy, respectively. In the networks, the solid and dashed edges or arrows indicate direct and indirect interactions, respectively. In Table 5, we report the genes that had at least 15 connections (i.e., hubs, suggesting biological importance) in the networks, ranked by the number of connections for each gene.

**Platinum-induced neuropathy**

The IPA core analysis revealed six networks associated with platinum-induced neuropathy. Using a nominal significance level of $10^{-5}$, of the 6 networks, we found only one network to be significant ($p$ value of $10^{-12}$; Fig. 1. We note that 66 genes (one focus gene and 65 “novel” genes) out of 121 genes in the network have at least 15 connections (Table 5), suggesting the potential biological importance of these genes in CIPN associated with platinum-based chemotherapy. The gene ITGB3 was the only focus gene in the network, and the top 5 “novel” genes were IL6, TNF, CXCL8, IL1B and ERK1/2.

**Taxane-induced neuropathy**

The IPA core analysis for taxane-induced neuropathy revealed eight networks, two of which were significant, with $p$ values of $10^{-9}$ and $10^{-8}$ (Fig. 2). There is no hub in the network.

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**Fig. 1** The most significant network ($p$ value $= 10^{-12}$) generated by IPA core analysis for 26 focus genes associated with platinum-induced neuropathy. Green: focus genes; red: genes with at least 15 connections; yellow: focus genes with at least 15 connections. Dashed and solid lines represent indirect and direct interactions, respectively.
The IPA core analysis for platinum/taxane-induced neuropathy identified three networks, one of which was significant, with a \( p \) value of \( 10^{-8} \) (Fig. 3). We note that 6
genes (one focus gene and 5 additional “novel” genes) out of 48 genes in the network have at least 15 connections. The gene BCL2 is the only focus gene included in the network that has more than 15 connections. The 5 additional genes that directly or indirectly interact with the corresponding focus genes associated with platinum/taxane-induced neuropathy based on the literature are TP53, MYC, PARP1, P38 MAPK and TNF.

Discussion
In this study, we performed a comprehensive literature review to identify genes implicated in CIPN and then used IPA bioinformatic tools to conduct comprehensive pathway and network analyses of the known genes identified in the literature. Neurotoxicity is common in cancer patients who are treated with platinum compounds and anti-microtubule agents, and the development of CIPN is a potentially debilitating sequela. From the literature review, we found that neuropathy induced by platinum compounds and taxanes (and a combination of these two agents) has been studied most frequently. Neuropathy induced by chemotherapy agents other than platinum, taxane and platinum/taxane combinations has not been adequately studied.

Among the focus genes identified from our literature search, GSTP1, CYP2C8 and ABCB1 were most frequently assessed as candidates for CIPN. From the literature review, we also found that the genomic variations of genes associated with neuropathy
Table 5 List of genes with at least 15 connections (i.e., hubs*) in the networks, ranked by the number of connections for each gene

| Platinum-induced CIPN | IPA Symbol | # of connections | Platinum/taxane-induced CIPN | IPA Symbol | # of connections |
|-----------------------|------------|------------------|-----------------------------|------------|------------------|
| IL6                   | 70         |                  | TPS3                        | 42         |                  |
| TNF                   | 69         |                  | BCL2**                      | 28         |                  |
| CXCL8                 | 56         |                  | MYC                         | 16         |                  |
| IL1B                  | 55         |                  | PARP1                       | 16         |                  |
| ERK1/2                | 54         |                  | P38 MAPK                    | 15         |                  |
| VEGFA                 | 52         |                  | TNF                         | 15         |                  |
| MAPK1                 | 51         |                  |                             |            |                  |
| NFKB (complex)        | 46         |                  |                             |            |                  |
| P38 MAPK              | 45         |                  |                             |            |                  |
| TGFbeta               | 43         |                  |                             |            |                  |
| COL18A1               | 42         |                  |                             |            |                  |
| CCL2                  | 39         |                  |                             |            |                  |
| IFNG                  | 38         |                  |                             |            |                  |
| PTGS2                 | 37         |                  |                             |            |                  |
| ERK                   | 34         |                  |                             |            |                  |
| TP53                  | 34         |                  |                             |            |                  |
| MAPK3                 | 33         |                  |                             |            |                  |
| Akt                   | 32         |                  |                             |            |                  |
| STAT3                 | 30         |                  |                             |            |                  |
| CD3                   | 29         |                  |                             |            |                  |
| JUN                   | 29         |                  |                             |            |                  |
| P38 (complex)         | 29         |                  |                             |            |                  |
| EGFR                  | 28         |                  |                             |            |                  |
| MMP1                  | 28         |                  |                             |            |                  |
| HGF                   | 27         |                  |                             |            |                  |
| Jnk                   | 27         |                  |                             |            |                  |
| CCL5                  | 26         |                  |                             |            |                  |
| CD40                  | 26         |                  |                             |            |                  |
| IL1A                  | 26         |                  |                             |            |                  |
| ITGB1**               | 26         |                  |                             |            |                  |
| MMP2                  | 25         |                  |                             |            |                  |
| Cg                    | 24         |                  |                             |            |                  |
| FN1                   | 24         |                  |                             |            |                  |
| RELA                  | 24         |                  |                             |            |                  |
| TLR4                  | 23         |                  |                             |            |                  |
| Vegf                  | 23         |                  |                             |            |                  |
| CXCL10                | 22         |                  |                             |            |                  |
| EGF                   | 21         |                  |                             |            |                  |
| ITGB3                 | 21         |                  |                             |            |                  |
| MAPK14                | 21         |                  |                             |            |                  |
| NFKBIA                | 21         |                  |                             |            |                  |
induced by platinum versus taxane compounds were different. For example, GSTP1, ERCC1, ACYP2, FARS2, GSTM1 and TAC1 were found to be associated with platinum-induced neuropathy in more than one study but were not associated with taxane-induced neuropathy. On the other hand, CYP2C8, ABCB1, EPHA5, EPHA6 and TUBB2A were found to be associated with taxane-induced neuropathy in more than one study, but not to be associated with platinum-induced neuropathy (Table 3). The overall theme is that these CIPN-associated genes are related to the networks that regulate intracellular drug concentrations (e.g., GSTP1, GSTM1 and ABCB1), response to DNA damage (e.g., ERCC1, FANCD2, BCL2, and SOX10), cellular stress response pathways (e.g., BCL2), inflammation (e.g., ABCC1, ABCC2, ABCG2, ITGA1, ITGB3, TAC1, ABCB1, ABCC2, EPHA4, EPHA6, SLC01B1, TUBB2A, ABCA1, BCL2, OPRM1 and TRPV1), and neuronal plasticity (e.g., ERCC1 and TAC1).

We performed IPA core analysis for the genes associated with platinum-, taxane- and platinum/taxane-induced neuropathy. We found that IL6, TNF, CXCL8, IL1B and ERK1/2 were the top genes in terms of the number of connections in platinum-induced neuropathy, suggesting either direct or indirect interactions with nervous tissue leading to CIPN after exposure to platinum compounds. It is particularly interesting that studies of

**Table 5** List of genes with at least 15 connections (i.e., hubs*) in the networks, ranked by the number of connections for each gene (Continued)

| Gene  | Connections |
|-------|-------------|
| SP1   | 21          |
| STAT1 | 21          |
| AKT1  | 20          |
| HIF1A | 20          |
| SRC   | 20          |
| TERT  | 20          |
| Pkc(s) | 19        |
| CTNNB1| 18          |
| Focal adhesion kinase | 18 |
| FOS   | 18          |
| HDAC1 | 18          |
| IgG   | 18          |
| ITGAV | 18          |
| NFKB1 | 18          |
| CD44  | 17          |
| FGF2  | 17          |
| Lh    | 17          |
| MAPK8 | 17          |
| SYK   | 17          |
| Ap1   | 16          |
| CCND1 | 16          |
| IGF1  | 16          |
| PKCD  | 16          |
| TREM1 | 16          |
| OSM   | 15          |

*Suggests biological importance  
**Focus genes
pain in cancer patients have shown the importance of cytokine genes [28–37] including IL6, TNF and IL1B polymorphisms. These studies hypothesized that cytokines associated with inflammation or tissue damage modify the activity of nociceptors, which contributes to pain hypersensitivity. Studies also suggest that hyperexcitability in pain transmission neurons may also be caused by proinflammatory cytokines produced by glial cells that respond to inflammation or other cancer-produced cytokines. Substance P and excitatory amino acids released from presynaptic terminals result to an exaggerated pain response [38, 39]. In patients with lung cancer, polymorphisms in TNF and IL6 were significantly associated with pain severity (for TNF, GG = 4.12; GA = 5.38; AA = 5.50; \( p = 0.04 \)) and with morphine-equivalent daily dose (IL-6, GG = 69.61; GC = 93.6; CC = 181.67; \( p = 0.004 \)) [36]. An additive effect of mutant alleles in IL1B T-31C (odds ratio = 0.55, 95 % confidence interval = (0.31, 0.97)) was also found to be associated with high intensity of pain, depressed mood and fatigue in lung cancer patients [31].

In addition to the top connections in the networks, the overall biological processes involved in the networks help us to better understand the gene-phenotype association. The IPA core analysis is a process for creating molecule networks on the basis of focus genes, which are genes associated with the phenotypes of interest. Because all the focus and non-focus genes in the network have inter-connected relationships, it provides a list of novel candidate genes associated with the phenotype. The network also provides a clearer picture of the (possibly interacting) genes that might be directly or indirectly associated with chemotherapy-induced peripheral neuropathy. The most significant network generated by IPA core analysis for the focus genes associated with platinum-induced neuropathy (Fig. 1) contains genes for inflammation (multiple interleukins, TNF, IFNG, STAT3, STAT1), DNA damage response (TP53) and cell survival (MAPK, JUN, ERK, NFkB). Network 2, which relates to taxane-induced neuropathy (Fig. 2b), includes many genes that are involved in the DNA damage response. The network related to neuropathy induced by combined platinum and taxane therapy (Fig. 3) resembles Fig. 1 in terms of the cellular functions involved, i.e., inflammation, DNA damage response and cell survival. The major commonality among Figs. 1, 2b and 3 is TP53, which is a central hub in these three networks. Network 1, which relates to taxane-induced neuropathy (Fig. 2a), primarily involves drug metabolizing enzymes and transporter proteins that will affect the intracellular concentration of taxanes. These analyses suggest that genetic variations in the DNA damage response are associated with the risk of developing CIPN, and that taxane-induced neuropathy is also affected by genetic variations that regulate intracellular drug levels while this aspect may not be important for platinum compounds.

This bioinformatic approach to expanding gene networks and identifying connection hubs has limitations. First, many proteins do not interact, while others may connect to major hubs that interact with hundreds of genes and proteins. Therefore, it is believed that the degree of connectivity obeys a power law, which means that the network is scale-free, a desired property. However, we found that the IPA metric/algorith that generates networks does not guarantee that the resulting networks are scale-free, even though the networks may exhibit certain scale-free behavior in which the major hubs are closely followed by smaller ones that have less connectivity, and the smaller hubs are then followed by other nodes with an even smaller degree of connectivity, and so on (see Figs. 1 and 3). Furthermore, the IPA algorithm that
generates networks will not continue if the network reaches the pre-specified maximum network size (i.e., 140 genes), which might rule out many nodes with small degrees of connectivity and impact the scale-free behavior. We employed a widely used log-log plot to investigate whether the networks in Figs. 1 and 3 follow the power law [24, 40]. The log-log plot should appear as a decaying straight line if the network obeys the power law, which was not observed in our plot. Therefore, we cannot conclude that the resulting networks are scale-free.

Further limitations could be that the connections may be specific to certain tissues or physiological contexts that are not applicable to CIPN. Many of the connections have not been demonstrated in neural tissue. Nevertheless, this network analysis identified biological processes that are relevant to the mechanism of neuropathy induced by platinum compounds and taxanes, thus providing the basis for future studies of the genes involved in these biological processes. Our study has not discovered any pathways involved in pain perception. Perhaps, due to the fact that many studies in the literature were done as focused search for SNP associations in a relatively small set of genes in pre-selected pathways, such as glutathione, DNA repair, cell cycle, apoptosis, cell signaling, and metabolism. Whether new gene sequencing technology can discover genetic markers associated with differences in neuropathic pain perception remains to be seen. In conclusion, our study has shown putative genes associated with CIPN. Future studies will include the selection of pharmacogenomic panel tests that will help identify patients at risk for CIPN and the routine incorporation of such panels into clinical practice.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
All co-authors are justifiably credited with authorship, according to the authorship criteria. Final approval is given by each co-author. In details: CCR and SS conceptualized the study. JW performed the literature review and pathway analysis. JW and CCR drafted the manuscript. SS and SJY provided advice and revised the manuscript. All authors read and approved the final manuscript.

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