Title

A review of the literature on the relationships between genetic polymorphisms and chemotherapy-induced nausea and vomiting

Authors

Singh, Komal P

Dhruva, Anand A

Flowers, Elena

et al.

Publication Date

2018

DOI

10.1016/j.critrevonc.2017.11.012

Peer reviewed

Published in final edited form as:

Crit Rev Oncol Hematol. 2018 January ; 121: 51–61. doi:10.1016/j.critrevonc.2017.11.012.

A Review of the Literature on the Relationships Between Genetic Polymorphisms and Chemotherapy-Induced Nausea and Vomiting

Komal P. Singh, RN, MS, PhD(c)[1], **Anand A. Dhruva, MD**[2], **Elena Flowers, RN, PhD**[1], **Kord M. Kober, PhD**[1], and **Christine Miaskowski, RN, PhD**[1]

[1]Schools of Nursing, University of California, San Francisco, California

[2]Medicine, University of California, San Francisco, California

Abstract

Despite current advances in antiemetic treatments, between 30% to 60% of oncology patients experience chemotherapy-induced nausea (CIN) and 13% to 33% report chemotherapy-induced vomiting (CIV). Inter-individual differences are observed in the occurrence and severity of chemotherapy-induced nausea and vomiting (CINV). This review summarizes and critiques studies on associations between occurrence and severity of CINV and polymorphisms in serotonin receptor, drug metabolism, and drug transport pathway genes. Sixteen studies evaluated the associations between the occurrence and/or severity of CINV and single nucleotide polymorphisms (SNPs). Across these studies, three SNPs in 5-hydroxytryptamine receptor (*5-HT3R*) genes, two alleles of the cytochrome P450 family 2 subfamily D member 6 (*CYP2D6*) gene, and three SNPs in ATP binding cassette subfamily B member 1 (*ABCB1*) gene were associated with the occurrence and severity of CINV. Given the limited number of polymorphisms evaluated, additional research is warranted to identify new mechanisms to develop more targeted therapies.

Keywords

nausea; vomiting; serotonin; drug metabolism; drug transport; antiemetics

INTRODUCTION

Despite current advances in antiemetic treatments, between 30% to 60% of oncology patients experience chemotherapy-induced nausea (CIN) and 13.3% to 32.5% report chemotherapy-induced vomiting (CIV).[1–3] Despite the use of guideline directed antiemetic regimens, CIN continues to be one of the most severe side effects of chemotherapy (CTX).[4]

Address correspondence to: Komal Singh, RN, MS, PhD(c), Doctoral Student, Department of Physiological Nursing School of Nursing, University of California, 2 Koret Way – N631Y, San Francisco, CA 94143-0610, 650-575-6504 (phone), 415-476-8899 (fax), komal.singh@ucsf.edu.

Inter-individual differences are observed in the occurrence and severity of chemotherapy-induced nausea and vomiting (CINV). Phenotypic characteristics associated with increased risk of CINV include: age under 50 years, female gender, higher trait anxiety, a history of motion sickness, a history of morning sickness, decreased alcohol intake, dehydration, malnutrition, recent surgery, and receipt of radiation therapy.[5–8]

Treatment characteristics associated with increased risk for CINV include: higher pretreatment expectations for CINV; susceptibility to conditioned responses triggered by odors and tastes in the oncology clinic; occurrence of CINV during a previous CTX treatment; and feelings of warmth, dizziness, or lightheadedness after CTX.[9, 10] In addition, the intrinsic emetogenic potential of the CTX is an important factor that contributes to the occurrence and severity of CINV.[11–14] Finally, lack of adherence with the antiemetic regimen during and following CTX increases the risk for CINV.[8]

While these phenotypic characteristics help to identify high risk patients, they do not explain all of the inter-individual variability in the occurrence and severity of CINV. For example, in a study of risk factors for antiemetic failure,[15] 46% of the patients with three risk factors (i.e., female gender, younger age, no history of alcohol use) and 9% of the patients with no risk factors experienced antiemetic treatment failure. Recent evidence suggests that polymorphisms in genes involved in the nausea and vomiting pathways may influence oncology patients' risk for CINV and/or their responses to antiemetics. To date, four reviews have summarized findings from studies on associations between antiemetic efficacy and genetic polymorphisms in oncology patients receiving CTX.[16–19]

In the first review,[17] findings from six pharmacogenetic studies of antiemetic efficacy were summarized. The specific genes evaluated across these six studies were: 5-hydroxytryptamine 3A receptor (*HTR3A*), *HTR3B*, *HTR3C*, ATP binding cassette subfamily B member 1 (*ABCB1*), and cytochrome P450 family 2 subfamily D member 6 (*CYP2D6*). The second review focused on an evaluation of differences in the efficacy of 5HT3 receptor antagonists associated with a number of genetic polymorphisms.[16] While focused on a single mechanism, this review extended the findings from the previous review[17] with a summary of four additional studies. The third review focused on the phamacogenetics of CINV.[18] This 2015 review was organized using the major mechanisms that contribute to antiemetic efficacy. Across nine studies, seven of which were highlighted in the previous reviews,[16, 17] associations between antiemetic efficacy and polymorphisms in *HTR3B*, *HT3RC*, *HT3RD*, *neurokinin-1 (NK-1) receptor*, *ABCB1*, organic cation transporter protein *(OCT1)*, and *CYP2D6* genes were described.

In the fourth narrative review that focused on the nursing implications of the pharmacogenomic studies of antiemetic efficacy,[19] only one additional study was summarized. The major focus of all four papers was to summarize the pharmacogenomic findings within the context of the major mechanisms that are targeted by antiemetics to decrease CINV, namely: 5HT3, drug transport, and drug metabolism pathways.

However, none of these reviews provided a comprehensive synthesis of these studies that included a detailed description of the associations between genetic polymorphisms and the

occurrence and severity of CINV; a critique of the studies' designs and the methods used to assess CINV; a description of study limitations; and directions for future research. Therefore, the purposes of this review of the relationships between genetic polymorphisms and CINV are to: 1) describe salient study characteristics; 2) summarize and critique the instruments used to assess CINV and the timing of the assessments; 3) synthesize findings on associations between the occurrence and severity of CINV and genetic polymorphisms; and 4) synthesize findings on associations between antiemetic efficacy and genetic polymorphisms.

METHODS

Literature search

A systematic electronic literature search was conducted using three databases: PubMed®, Excerpta Medica Database (EMBASE®), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL®). A combination of keywords used to identify relevant studies were: *chemotherapy-induced nausea and vomiting* or *chemotherapy-induced vomiting* or *chemotherapy-induced nausea* AND *gene* or *genetics* or *polymorphisms* or *gene expression* or *candidate genes*. Studies were included if they met the following criteria: (1) the entire sample had a cancer diagnosis; (2) oncology patients were assessed for CIN and/or CIV; (3) oncology patients were genotyped; and (4) associations between the occurrence and/or severity of CIN and/or CIV, with or without antiemetic drugs, and patient genotype were described. An additional inclusion criterion was that the studies were published in English between 2000 and 2016 because the human genome was sequenced in 2000. Studies were excluded: (1) if the timing of the CIN or CIV assessments was not reported; (2) if they evaluated postoperative nausea and vomiting or radiotherapy-induced nausea and vomiting; and (3) if genotype associations were evaluated only in the context of the pharmacokinetics of the CTX.

As shown in Figure 1, the search strategy yielded 202 studies in PubMed®, 476 studies in EMBASE®, and 12 studies in CINAHL®. A total of 623 studies were excluded because the majority of them did not evaluate CINV. Of the 51 studies that did evaluate CINV, 35 were excluded because: 11 did not report the timing of the CIN or CIV assessment; 4 evaluated postoperative nausea and vomiting or radiotherapy-induced nausea and vomiting; 5 did not have genotype data; 1 evaluated genetic associations in the context of CTX pharmacokinetics; and 14 were review articles.

These review articles had the following foci: one was on associations between postoperative nausea and vomiting and genetic polymorphisms; five focused on the protein structure of receptors involved in CINV; four described the pathophysiology of CINV and pharmacological interventions; and the four summarized above,[16–19] described associations between antiemetic efficacy and genetic polymorphisms. Duplicate articles across the databases were removed and screened based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria.[20] Based on our pre-specified inclusion criteria, sixteen studies are included in this review.[21–36]

Data synthesis

These sixteen studies were summarized using the following prespecified evaluation criteria: author, year, purpose, and study design; emetogenicity of the CTX regimen; major study outcome(s); gene(s) and associated polymorphism(s) classified by function; sample characteristics (i.e., sample size, age, gender, diagnosis, treatment setting, antiemetic treatment); assessment of CINV (i.e., instrument(s), timing of CINV assessments); genotyping methods; statistical analyses; major findings; strengths; and limitations (Supplementary Table 1). Given the heterogeneity of the descriptive data among the studies in terms of sample characteristics, assessment of CINV, timing of CINV assessments, types of genotyping methods, specific polymorphisms evaluated, and the types of CTX, the results are summarized in tabular and narrative form.

RESULTS

Sample and treatment characteristics

Study characteristics—All sixteen studies used a prospective cohort design. While all sixteen studies recruited patients from the outpatient setting, four included hospitalized patients.[21–23, 28] Six studies were conducted in Germany,[21–23, 25, 27, 29] two in the United States,[33, 34] two in Turkey,[24, 36] and one each in China,[32] Japan,[31] Indonesia,[28] Israel,[35] Australia,[26] and Spain.[30]

Patient characteristics—Sample sizes ranged from 64[31] to 2,886[34] patients. Six had less than 200 patients.[25–27, 31, 33, 35] Across twelve studies that reported patients' age, [21–25, 28–32, 35, 36] the weighted grand mean age was 54.8 years. Of the remaining four studies, one did not report the patients' age[26] and three reported an age range,[27] a median age,[33] or both.[34] Across fourteen studies, the weighted grand mean percentage of female patients was 51.1%. Two studies did not report the patients' gender distribution.[26, 29] When the study with 2,886 patients was removed,[34] the grand mean percentage of females was 64.3%.

Across the 16 studies, various cancer diagnosis were included (e.g., breast cancer, lung cancer, non-small cell lung cancer, lymphoma, myeloma, ovarian cancer, nasopharyngeal cancer, vulvar cancer, cervical cancer, colorectal cancer, gastrointestinal cancer, genitourinary cancer). In six studies,[21–24, 29, 36] between 27.6% and 63.0% of the patients had breast cancer. In four studies,[25, 27, 31, 35] 100% of the patients had breast cancer. In two studies,[30, 34] 100% of the patients had stage III or higher colon cancer. In one study,[32] all of the patients had acute myeloid leukemia. In another study,[33] all of the patients had non-small cell lung cancer. One study did not report the patients' cancer diagnoses.[26]

Types of CTX—In nine studies,[21–25, 27, 31, 35, 36] across a total of 1657 patients, 865 received cyclophosphamide alone or a combination CTX regimen that included cyclophosphamide. In seven studies,[21–24, 28, 33, 36] across a total of 1501 patients, 615 received a platinum-based CTX treatment. In two studies,[30, 34] 3903 patients received 5-flurouracil (5-FU) or a 5-FU based CTX regimen (e.g., a combination of folinic acid, 5-FU, and oxaliplatin (FOLFOX); a combination of folinic acid and 5-FU (FOLFIRI)). In one

study of 216 patients,[24] 161 received an anthracycline-based CTX regimen. In another study, [32] all 215 patients received cytarabine.

Emetogenicity of CTX regimens—Of the fourteen studies with available data, the CTX regimens were of moderate to high emetogenicity based on the classification scheme proposed by Hesketh and colleagues.[37, 38] One study did not report on the emetogenicity of the CTX regimen.[26] One did not report the CTX regimen administered.[29]

Antiemetic treatment—Four studies did not report the specific antiemetic regimen administered.[30, 33–35] In twelve studies,[21–29, 31, 32, 36] patients received serotonin antagonists prophylactically. In terms of the specific drugs, in ten studies, patients received a standardized regimen of tropisetron and/or ondansetron.[21–29, 32] In the remaining studies, patients received granisetron,[31, 36], dolasetron,[26] or metoclopramide[28] for delayed CINV. In five studies,[25, 27, 28, 31, 36] dexamethasone was given with a standardized regimen that contained a serotonin antagonist.

Methods used to assess CIN and CIV

Assessment of CIN occurrence—The occurrence of CIN was evaluated in nine studies. [25, 27, 28, 30–34, 36] In three studies,[25, 27, 31] a patient diary was used to assess CIN occurrence. In two of these studies,[25, 27] patients documented the occurrence of CIN on an hourly basis for two days after the first cycle of CTX. In the third study,[31] daily assessments of CIN were done for 5 days following CTX administration.

Four studies[28, 32–34] used the National Cancer Institute Common Toxicity Criteria (NCICTC) to assess CIN occurrence. Three studies[28, 32, 34] used NCICTC version 3 and one study[33] used NCICTC version 4. In two studies,[28, 32] the occurrence of acute CIN was categorized as absent (i.e., grades 1 or 2) or present (i.e., grades 3 or 4). In the same two studies,[28, 32] the occurrence of CIN was assessed using a visual analog scale (VAS) that ranged from 0 mm to 100 mm. CIN occurrence was categorized as absent (i.e., a score of <5 mm on the VAS) or present (i.e., a score of >5 mm on the VAS). In another study that used NCICTC version 3,[34] patients were assessed biweekly for the occurrence of CIN, which was categorized as absent (i.e., grades 1 or 2) or present (i.e., grades 3 or 4).

In one study that used NCICTC version 4,[33] CIN occurrence was self-reported at the oncology clinic prior to CTX administration and before each subsequent cycle and was categorized as absent (i.e., grades 1 or 2) or present (i.e., grade 3). Other instruments used to assess the occurrence of CIN included the World Health Organization (WHO) toxicity grading scale[30, 39] and a daily questionnaire that rated the severity of CIN as none, slight, moderate, or severe.[36] In the study that used the WHO toxicity grading scale,[30] the timing of the CIN assessments was not reported. The occurrence of CIN was categorized as absent (i.e., WHO grades 1 or 2) or present (i.e., WHO grades 3 or 4). For the study that used the daily questionnaire,[36] occurrence of CIN was assessed for five consecutive days from the start of CTX administration.

Of the nine studies that assessed the occurrence of CIN,[25, 27, 28, 30–34, 36] only three reported its occurrence rate.[28, 30, 34] The CIN occurrence rates were: 4.3%,[34] 21.8%,[28] and 23.3%[30] and the grand mean percentage rate was 9.9%.

Assessment of CIN severity: Six studies evaluated the severity of CIN.[21–24, 26, 35] In three studies,[21–23] CIN severity was assessed using a VAS (i.e., no nausea (0 mm) to the most extensive nausea (100 mm)) before CTX administration, between 0 and 4 hours, and between 5 and 24 hours after CTX administration. In one study,[24] the severity of CIN was rated using a Likert scale (i.e., 0 = none, 1 = mild, 2 = moderate, 3 = severe), between 0 and 24 hours and between 2 and 5 days after CTX. While one study used NCICTC version 3 to assess CIN severity,[26] the timing of the assessment was not reported.[26] In one study,[35] the Memorial Symptom Assessment Scale (MSAS) was used to assess the severity of CIN once in seven days for each cycle of CTX administration.

Of the six studies that assessed the severity of CIN,[21–24, 26, 35] four reported its severity.[21–23, 35] Across three studies that used a VAS,[21–23] the weighted grand mean average CIN severity score was 12.7 for the observation period between the 5th hour and the 24th hour after CTX administration. In the study that used the MSAS,[35] the average CIN severity for 105 patients was 1.7.

Assessment of CIV occurrence: Fourteen studies evaluated the occurrence of CIV.[21–28, 30–34, 36] Three of these studies had patients report the number of vomiting and retching episodes in a daily diary immediately before CTX administration, between 0 and 4 hours, and between 5 and 24 hours after CTX administration.[21–23] In the six studies that used a diary to assess the occurrence of CIV,[24, 25, 27, 29, 31, 36] patients completed the diary for 24 hours[29] or for 5 days[24, 31, 36] following CTX administration. In two studies,[25, 27] patients documented any CIV event on an hourly basis for two days following CTX administration.

Of the five studies that used the NCICTC to assess CIV occurrence, four[26, 28, 32, 34] used version 3 and one[33] used version 4. In four of these studies,[26, 28, 32, 34] the occurrence of acute CIV was categorized as absent (i.e., grades 1 or 2) or present (i.e., grades 3 or 4). In two studies,[28, 32] based on patient documentation of any vomiting episode, delayed CIV was dichotomized as “yes” or “no”. In these two studies,[28, 32] the occurrence of CIV was assessed daily for 5 days after CTX administration. In a third study,[26] CIV occurrence was assessed for 24 hours following CTX administration. In the fourth study that used NCICTC version 3,[34] CIV occurrence was assessed biweekly. In the study that used NCICTC version 4,[33] the occurrence of CIV was assessed at the oncology clinic prior to CTX administration and before each subsequent cycle. The occurrence of acute CIN was categorized as absent (i.e., grades 1 or 2) or present (i.e., grade 3).

Of the fourteen studies that evaluated the occurrence of CIV, ten reported its occurrence.[21–28, 30, 34] These occurrence rates ranged from 18.6%[26] to 40.0%[24] and the grand mean percentage was 14.2%.

Assessment of CIV severity: In the one study that used the MSAS to evaluate the severity of CIV,[35] it was assessed once in seven days for each cycle of CTX. CIV severity scores ranged from 0.0 (± 0.0) to 0.3 (± 0.7) with an average score of 0.25.

Analysis of genetic polymorphisms

Genotyping methods and statistical analyses: A variety of methods were used to identify genetic polymorphisms. Eight studies used restriction fragment length polymorphism (RFLP) and real time polymerase chain reaction (PCR) techniques to detect single nucleotide polymorphisms (SNPs).[21, 24, 25, 28, 29, 31, 35, 36] Other techniques used were: automated capillary DNA sequencing,[22, 23] multiplex PCR primer extension,[26] MegaBACE 1000 sequencer,[27] genotyping microarray,[30] and mass spectrometry.[32–34]

Across the sixteen studies, Chi square analysis was the predominant method used to evaluate for associations between a CINV phenotype and genotype.[22–28, 34] For multivariate analyses, logistic regression was used in six studies.[22, 30–32, 34, 36] Three studies used one-way analysis of variance (ANOVA) to evaluate for differences in CINV characteristics with respect to specific polymorphisms.[24, 29, 35] Two studies performed a Kaplan Meier log rank test,[25, 27] two conducted a Cox proportional hazard regression analysis,[25, 33] and one performed the Cochran-Mantel-Haenzel test[31] to determine associations between genetic polymorphisms and antiemetic responses. Fourteen out of the sixteen studies evaluated Hardy Weinberg equilibrium.[22–27, 29–36]

Associations between CIN and genetic polymorphisms

Associations between the occurrence of CIN and genetic polymorphisms: As shown in Table 1, nine studies evaluated for associations between the occurrence of CIN and a number of genetic polymorphisms.[25, 27, 28, 30–34, 36] The specific genes evaluated included: *HTR3A*, *HTR3B*, *HTR3C*, *HTR3D*, and *HTR3E*;[25, 27] *ABCB1*;[28, 31–33, 36] ATP binding cassette subfamily C member 1 (*ABCC1*), ATPase copper transporting beta (*ATP7B*), and ATP binding cassette subfamily G member 2 (*ABCG2*);[33] *CYP2D6*;[28] dihydropyrimidine dehydrogenase (*DPYD*);[34] and general transcription factor IIE subunit 1 (*GTF2E1*).[33] In the two studies that evaluated for associations between the occurrence of CIN and polymorphisms in a number of serotonin receptor genes,[25, 27] no associations were found with any of the SNPs in *HTR3A*, *HTR3B*, *HTR3C*, *HTR3D*, and *HTR3E*.

Five studies evaluated for associations between the occurrence of CIN and polymorphisms in *ABCB1*.[28, 31–33, 36] In the three studies that assessed rs1045642,[31, 32, 36] two found an association with the occurrence of CIN.[32, 36] Compared to patients who were homozygous or heterozygous for the common C allele, patients who were homozygous for the rare T allele had a decreased occurrence of CIN.

In two[32, 36] of the three studies that assessed for an association between the occurrence of CIN and *ABCB1* rs20325282,[31, 32, 36] compared to patients who were homozygous for the common G allele, patients who were heterozygous (GT/A) or homozygous for the rare allele (TT/A) had a decreased occurrence of CIN ($p = 0.012$ and $p = 0.021$, respectively). In the

third study,[31] patients who were homozygous for the rare T allele in this SNP were at increased risk for CIN (p = 0.045).

In the two studies that assessed for associations between the occurrence of CIN and *ABCB1* rs1128503,[33, 36] only one found that being homozygous for the rare C allele was associated with an increased occurrence of acute CIN (p = 0.027).[36] In one of the five studies that assessed *ABCB1*, a haplotype analysis was done.[28] Patients with the CTT haplotype for three SNPs in the *ABCB1* gene (i.e., rs1045642, rs20325282, rs1128503) experienced a decreased occurrence of acute CIN. However, this association did not reach significance (p = 0.07). In addition, compared with other *ABCB1* haplotypes, patients with the CTG haplotype experienced an increased occurrence of delayed CIN (p = 0.02).[28] In one study,[33] no associations were found between the occurrence of CIN and two SNPs in *ABCC1* (i.e, rs246240, rs2238476). However, patients with missense mutations in *ATP7B* rs1801244 (i.e., valine to leucine change) and *ABCG2* rs2231142 (i.e. glutamine to lysine change) were at an increased risk for CIN (p = 0.027 and p = 0.045 respectively).

In the one study that assessed for an association between the occurrence of CIN and polymorphisms in the drug metabolizing enzyme gene *CYP2D6* (i.e., rs16947, rs3892097, rs1065852),[28] no associations were found (p = 0.12). In another study that assessed for an association between the occurrence of CIN and a polymorphism in the *DPYD* enzyme gene, [34] patients with a splice donor variant in *DPYD*2A* rs3918290 (c.1905 + 1 G>A) were at an increased risk for CIN (p = 0.007). In a different study,[33] that assessed for an association between CIN and a polymorphism in the intronic region of the transcription factor *GTF2E1* gene (rs447978, specific allele not reported), patients had a 78% decrease in odds of experiencing CIN (OR (dominant model) = 0.22, 95% CI = −2.52 to −0.49, p = 0.004). In a genome wide association study (GWAS) that evaluated a number of adverse events associated with the administration of CTX,[30] no polymorphisms were found that were associated with the occurrence of CIN.

Associations between the severity of CIN and genetic polymorphisms: As shown in Table 1, six studies evaluated for associations between the severity of CIN and polymorphisms in *HTR3A*,[23] *HTR3B*;[22] *HTR3C*;[26, 35] *ABCB1*;[24] catecholamine-o-methyltransferase enzyme (*COMT*);[35] *CYP2D6*;[21, 22] and guanidine triphosphate cyclohydrolase I (*GCH1*).[35] Of the four studies that evaluated for associations between the severity of CIN and polymorphisms in serotonin receptor genes,[22, 23, 26, 35] three[22, 23, 26] found no associations for any polymorphisms in *HTR3A*, *HTR3B*, and *HTR3C*. In one study,[35] being homozygous for the rare C allele for *HTR3C* rs6766410 was associated with decreased severity of acute CIN (p = 0.04). The association between the severity of CIN and *HTR3C* rs6807362 was not significant (p = 0.08).[35]

In the study that assessed for an association between CIN severity and *ABCB1* rs1045642,[24] being homozygous for the common C allele was associated with more severe acute CIN (p = 0.044). In contrast, no association was found between CIN severity and *COMT* rs4818 (p value not reported).[35] In one[22] of the two studies, that assessed for an association between the severity of CIN and the *CYP2D6* ultrarapid metabolizer (UM) allele, patients who were carriers of this allele had an increased risk for more severe CIN (p = 0.03). In the second

study,[21] a similar trend was found but did not reach statistical significance. In the study that evaluated for associations between CIN severity and polymorphisms in *GCH1* (i.e., rs10483639, rs3783641, rs8007267),[35] the results were not significant (p values not reported).

Associations between CIV and genetic polymorphisms

Associations between the occurrence of CIV and genetic polymorphisms: As shown in Table 1, fourteen studies[21–28, 30–34, 36] evaluated for associations between the occurrence of CIV and a number of polymorphisms in *HTR3A*, *HTR3B*, *HTR3C*, *HTR3D*, and *HTR3E*;[22, 23, 25–27] *ABCB1*;[24, 28, 31–33, 36] *ABCC1*, *ATP7B*, and *ABCG2*;[33] *CYP2D6*;[28] *DPYD*;[34] and *GTF2E1*.[33]

In two studies,[23, 27] no associations were found between the occurrence of CIV and polymorphisms in *HTR3A* (i.e., rs1062613, rs1176722, rs1176719, rs2276303, rs909411, rs1176713). In one study,[22] being homozygous for -100_-102AAG deletion variant in *HTR3B* was associated with increased episodes of CIV ($p < 0.02$). In one[25] of the two studies that evaluated for associations between the occurrence of CIV and polymorphisms in *HTR3C*, patients who were homozygous for rare C allele in rs6766410 had a shorter time to first emetic event. In the second study,[26] none of the seven SNPs in *HTR3C* demonstrated a significant relationship with the occurrence of CIV. In another study,[27] no associations were found between the occurrence of CIV and polymorphisms in *HTR3D* (i.e., rs6443930, rs1000952) and *HTR3E* (i.e., rs5855015, rs7627615, rs56109847).

Six studies evaluated for associations between the occurrence of CIV and polymorphisms in drug transport pathway genes.[24, 28, 31–33, 36] While five studies assessed *ABCB1* rs1045642,[24, 28, 31, 32, 36] only three[24, 32, 36] found an association with the occurrence of CIV. Being homozygous for the rare T allele in rs1045642 was associated with a decreased occurrence of acute CIV ($p = 0.044$, $p = 0.002$, and $p = 0.016$, respectively). Of the three studies that evaluated for an association between the occurrence of CIV and *ABCB1* rs20325282,[31, 32, 36] in only one study,[31] being homozygous for the rare T allele was associated with an increased likelihood of reporting the occurrence of CIV ($p = 0.045$). In contrast, in the other two studies,[32, 36] being homozygous for the rare T allele in rs20325282 was associated with a decreased likelihood of CIV ($p = 0.038$ and $p = 0.021$).

Two studies evaluated for an association between the occurrence of CIV and *ABCB1* rs1128503.[33, 36] While in one study, no association was found,[33] in the second study being homozygous or heterozygous for the rare C allele was associated with an increased number of episodes of vomiting ($p = 0.027$).[36] In another study,[28] patients who were carriers of the CTG haplotype in *ABCB1* (i.e., rs1045642, rs20325282, rs1128503) experienced an increased occurrence of delayed CIV ($p = 0.02$). In another study,[33] no associations were found between the occurrence of CIV and polymorphisms in a number of drug transport pathway genes (i.e., *ABCC1* rs246240 and rs2238476, *ABCG2* rs2231142, *ATP7B* rs1801244).

Two studies evaluated for associations between the occurrence of CIV and polymorphisms in the drug metabolizing enzyme gene *CYP2D6*.[21, 28] While in one study, no association

was found,[28] in the second study,[21] patients who were carriers of the UM allele for *CYP2D6* experienced an increased occurrence of acute CIV ($p < 0.03$).

One study investigated the association between the occurrence of CIV and a *DPYD* polymorphism. Patients with the splice donor variant *DPYD*2A* rs3918290 (c.1905 + 1 G>A) were at an increased risk for the occurrence of CIV ($p = 0.007$).[34] In the only study that evaluated for an association between the occurrence of CIV and a polymorphism in transcription factor gene *GTF2E1*,[33] no association was found with rs447978 (specific allele not reported). In a GWAS study,[30] no significant associations were found with the occurrence of CIV.

Association between the severity of CIV and genetic polymorphisms: One study evaluated for associations between the severity of CIV and a number of genetic polymorphisms in *5-HTR3C*, *COMT*, and *GCH1* genes.[35] No associations were found between the severity of CIV and polymorphisms in *HTR3C* rs6766410 and rs6807362, *COMT* rs4818, and *GCH1* rs10483639, rs3783641, rs8007267.[35]

Associations between antiemetic efficacy and genetic polymorphisms—As shown in Table 2, twelve studies evaluated for associations between the efficacy of antiemetics and polymorphisms *HTR3A*, *HTR3B*, *HTR3C*, *HTR3D*, and *HTR3E*;[22, 23, 25–28] *ABCB1*;[24, 28, 31, 32, 36] *CYP2D6*;[21, 22, 28] and *OCT1*.[29]

In two studies,[23, 27] no associations were found between antiemetic efficacy and polymorphisms in *HTR3A*. In one study that included a haplotype analysis,[23] patients who were carriers of a CT haplotype in *HTR3A* (rs IDs not reported) were less likely to experience CIV and CIN with prophylactic antiemetic treatment ($p = 0.01$). In four studies,[22, 25, 27, 28] no associations were found between antiemetic efficacy and polymorphisms in *HTR3B* (rs1176744, rs45460698, rs4938058, rs7943062). In the two studies that assessed for an association between antiemetic efficacy and polymorphisms in *HTR3C*,[25, 26] only one[25] found that patients who were homozygous for the rare C allele in *HTR3C* rs6766410 had a shorter time to first emetic event within 24 hours of CTX administration ($p = 0.002$).

One study evaluated the association between antiemetic efficacy and polymorphisms in *HTR3D* and *HTR3E*.[27] Being homozygous for the rare C allele for *HTR3D* rs6443930 was associated with an increased likelihood of responding to serotonin antagonists ($p = 0.048$).[27] No associations were found between antiemetic efficacy and polymorphisms in *HTR3E* (rs5855015, rs7627615, rs56109847).

Six studies evaluated for associations between antiemetic efficacy and polymorphisms in drug transport pathway genes.[24, 28, 29, 31, 32, 36] Five studies evaluated for associations between antiemetic efficacy and polymorphisms in *ABCB1*.[24, 28, 31, 32, 36] In one study,[24] granisetron treated patients who were carriers of the rare T allele for *ABCB1* rs1045642 had a higher likelihood of a complete response in the acute phase. In another study of granisetron treated patients,[31] being homozygous or heterozygous for the rare T/A allele for *ABCB1* rs20325282 was associated with a lower complete response rate in the acute phase. In another study of granisetron treated patients,[36] carriers of the TTT haplotype in *ABCB1*

(i.e., rs1045642, rs20325282, rs1128503) had a higher complete response rate. In the same study, this finding was not observed in the ondansetron treated patients.[36] In two studies of patients treated with ondansetron,[28, 32] carriers of the CTG haplotype in *ABCB1* (i.e., rs1045642, rs20325282, rs1128503)[28] or carriers of the CG haplotype in *ABCB1* (i.e., rs1045642, rs20325282)[32] experienced an increased incidence of CIN and CIV.

One study evaluated for an association between antiemetic efficacy and polymorphisms in *OCT1*.[29] An *in vitro* assay demonstrated that polymorphisms in *OCT1* with amino acid substitutions (i.e., R61C, C88R, G401S, M420del, G465R) abolished tropisetron uptake. Plasma concentrations of tropisetron at 3 hours and 6 hours after administration and of ondansetron at 3 hours after administration were highest in patients who lacked a fully active *OCT1* allele ($p < 0.05$). Patients who lacked an active *OCT1* allele demonstrated a greater complete response ($p = 0.007$). This study controlled for the confounding effect of *CYP2D6* allele.

Three studies evaluated for associations between antiemetic efficacy and polymorphisms in the drug metabolizing enzyme gene *CYP2D6*.[21, 22, 28] While in one study,[28] no association was found in the other two studies,[21, 22] patients who were carriers of three active *CYP2D6* alleles (i.e., UMs) experienced decreased complete control of CIN and CIV after tropisetron and ondansetron administration. In one study,[21] patients with no active allele for *CYP2D6* (i.e., poor metabolizers (PMs)) had significantly higher serum concentrations of tropisetron and demonstrated greater complete control of CIN and CIV than patients with three active *CYP2D6* alleles ($p < 0.03$).

DISCUSSION

This comprehensive review summarizes findings from sixteen studies that evaluated for associations between the occurrence and/or the severity of CINV, as well as antiemetic efficacy, and polymorphisms in a variety of candidate genes. As shown in Tables 1 and 2, the majority of these genes were selected because they are involved in the mechanisms of CINV or in the major drug transport or drug metabolism pathways.

Serotonin pathway and CINV

Across the four CINV phenotypes (i.e., CIN occurrence and severity, CIV occurrence and severity), polymorphisms in five serotonin receptor genes were evaluated. This pathway was chosen because serotonin plays a major role in the development of CINV. Serotonin is released from enterochromaffin cells in the visceral mucosa following the administration of CTX. Serotonin activates 5-HT3 receptors on the vagus nerve which stimulates the medial nucleus of the solitary tract (NTS) and the dorsal vagal complex (DVC) in the medulla. This stimulation of the NTS and DVC signals vagal efferent fibers to produce retro-peristaltic contractions in the intestine and contractions in the stomach followed by relaxation of the gastric fundus and the lower esophageal sphincter. This action leads to expulsion of stomach contents.[40]

The 5-HT3 receptor is a ligand gated ion channel that is made up of five subunits (i.e., HTR3A, HTR3B, HTR3C, HTR3D, HTR3E).[41] The serotonin antagonists selectively block

the excitation of presynaptic 5-HT3 receptors on the vagus nerve and act on the area postrema to block afferent signals from the vagus nerve that result in CINV.[40, 42]

As shown in Table 1, across six studies[22, 23, 25–27, 35] that evaluated 22 SNPs in the serotonin receptor pathway, only one found an association between CIN severity[35] and two found an association with CIV occurrence.[22, 25] For CIN severity, patients who were homozygous for rare C allele, in rs6766410 reported less severe CIN. This nonsynonymous SNP causes a change in the amino acid sequence from lysine to arginine which may alter the structure of the HTR3C receptor.[35] In another study,[25] this SNP was associated with an increase in the occurrence of CIV. The other SNP associated with the increased occurrence of CIV was *HTR3B* rs45460698.[22] In one *in vitro* study,[43] this deletion was associated with increased activity in the promoter region of *HTR3B*. However, these results need to be interpreted with caution because only 1.2% of the patients in the study had this polymorphism.

Drug transport pathway and CINV

Across the four CINV phenotypes, polymorphisms in four drug transport genes were evaluated. ABCB1 is a transmembrane glycoprotein that is present on the cell membrane of gastrointestinal (GI) tract enterocytes and on the endothelial cells of the cerebral cortex.[44] ABCB1 limits intracellular absorption of CTX in the GI tract and restricts the entry of CTX into the central nervous system (CNS). Polymorphisms in *ABCB1* may cause conformational changes in its protein structure and affect its function.[45] This alteration may affect the absorption of CTX across the blood brain barrier which affects the occurrence and/or severity CINV.

ABCC1 and ABCG2 are transmembrane proteins that are part of the blood brain barrier and cause the efflux of CTX drugs such as taxanes.[33] ATP7B is an ATPase expressed in the liver and kidney and to a lesser extent in the brain. Higher levels of *ATP7B* mRNA expression are correlated with higher rates of efflux and accumulation of CTX agents (i.e., carboplatin, cisplatin, oxaliplatin) in the bloodstream.[46] Polymorphisms in *ABCC1*, *ABCG2*, and *ATP7B* may change the rate of efflux of CTX drugs that enter the blood brain barrier and cause variations in occurrence and/or severity of CINV.

As shown in Table 1, across six studies,[24, 28, 31–33, 36] that evaluated seven SNPs and one haplotype in the drug transport pathway, five found associations with CIN occurrence,[28, 31–33, 36] one found an association with CIN severity,[24] and five found associations with CIV occurrence.[24, 28, 31, 32, 36] The most consistent finding across the CINV phenotypes were for the *ABCB1* gene. For *ABCB1* rs1045642, patients who were homozygous for the rare T allele had a decrease in CIN[32, 36] and CIV[24, 32, 36] occurrence, as well as CIN severity,[24]. While this synonymous SNP does not change the amino acid sequence, it significantly decreases *ABCB1* function.[36]

The findings regarding *ABCB1* rs20325282 are inconsistent. In two studies,[32, 36] the occurrence of both CIN and CIV were decreased in patients who were homozygous for the rare T allele. In another study,[31] the exact opposite associations were found. *ABCB1* rs203252832 is a tri-allelic polymorphism where G is the common allele and A or T are the two possible rare variants. This nonsynonymous SNP causes a change in amino acid

sequence from alanine to serine in the case of the rare A allele or threonine in the case of the rare T allele which may alter ABCB1 protein structure and/or function.[44]

Only one study found a positive association between *ABCB1* rs1128503 and the occurrence of CIN and CIV.[36] While this synonymous SNP does not change the amino acid sequence of the protein, it may be in linkage disequilibrium with another SNP that affects ABCB1 function. In one study,[28] patients with the CTG haplotype in *ABCB1* had an increase in the number of delayed CINV episodes. In a single study,[33] that evaluated two nonsynonymous SNPs in different genes (i.e., *ATP7B* rs1801244, *ABCG2* rs2231142), both SNPs were associated with an increase in CIN occurrence. While one SNP (*ATP7B* rs1801244) changes the amino acid sequence with no functional consequence,[33] the other SNP (*ABCG2* rs2231142) reduces ABCG2 efflux activity.[47]

Drug metabolism pathway and CINV

Across the four CINV phenotypes, only one drug metabolizing gene (i.e., *CYP2D6*) was evaluated. CYP2D6 belongs to a family of cytochrome P450 isoenzymes that bio-transforms drugs through oxidation. CYP2D6 is a heme containing membrane protein that is expressed in the liver, kidneys, and GI tract.[48] Approximately 5% to 10% of Caucasians lack the active *CYP2D6* allele and as a result are PMs of drugs. Approximately 2% of Caucasians have more than 2 copies of active *CYP2D6* allele and are UMs.[21]

As shown in Table 1, across three studies,[21, 22, 28] that evaluated three SNPs and an UM polymorphism with more than two active copies of the gene as a result of duplication in *CYP2D6*, one found an association with CIN severity[22] and one with CIV occurrence[21]. Patients who had the UM *CYP2D6* allele reported an increased severity of CIN and an increased occurrence of CIV. This finding suggests that these patients may have metabolized their antiemetics more rapidly.[21]

Antiemetic efficacy and genetic polymorphisms

As shown in Table 2, across twelve studies,[21–29, 31, 32, 36] associations between antiemetic efficacy and 24 SNPs and one haplotype in serotonin receptor genes, eight SNPs and one haplotype in two drug transport genes, and five alleles (i.e., including PM and UM) in drug metabolism pathways were evaluated. Three studies found associations between antiemetic efficacy and two SNPs and one haplotype in serotonin receptor genes.[23, 25, 27]

Most of the patients who had a CT haplotype in *HTR3A* and who were treated with tropisetron and ondansetron reported no CINV episodes. These two SNPs located in the intronic region of *HTR3A* have no known function.[23] In one study,[25] patients who were homozygous for the rare C allele in *HTR3C* rs6766410 and were treated with ondansetron and dexamethasone were non-responders. This nonsynonymous SNP changes the amino acid sequence from lysine to asparagine in the cysteine-loop of the HTR3C receptor and may impair ondansetron binding to the serotonin receptor.[25] In another study,[27] patients who were homozygous for the rare C allele in *HTR3D* rs6443930 and treated with ondansetron and dexamethasone demonstrated increased antiemetic efficacy. This nonsynonymous SNP causes a change in the amino acid sequence from glycine to alanine near the N-terminus of the protein and may alter HTR3D protein structure.[27]

Five studies found an association between drug transport pathway genes and antiemetic efficacy.[24, 28, 29, 32, 36] Patients who were homozygous for the rare T allele in *ABCB1* rs1045642 and treated with granisetron reported a decrease in CINV.[24] In another study,[31] patients who were homozygous for the rare T allele in *ABCB1* rs20325282 and treated with granisetron reported increased CINV events. In one study,[36] patients who were homozygous for rare C allele in *ABCB1* rs1128503 and treated with granisetron reported increased CINV episodes. These SNPs may affect the level of *ABCB1* gene expression or alter the structure of ABCB1 causing a change in granisetron binding to ABCB1.[36]

Patients with CG haplotype in *ABCB1* rs1045642 and rs20325282[32] or with TTT haplotype in *ABCB1* rs1045642, rs20325282, and rs1128503[36] and treated with granisetron demonstrated less complete control in the case of the CG haplotype and higher complete control for the TTT haplotype. Patients with the CTG[28] or the TTT[36] haplotypes in *ABCB1* and treated with ondansetron experienced less complete control. Given that the half-life of ondansetron is shorter than granisetron this difference may contribute to the findings for carriers of TTT haplotype.[49] The role of CG and CTG haplotypes in decreased complete control is not clear.[32, 36]

One study investigated the role of *OCT1* in the cellular uptake of tropisetron and ondansetron and its influence on the drug's therapeutic efficacy.[29] *OCT1* is one of the most abundantly expressed drug transport genes in the liver. It synthesizes OCT1, a plasma membrane protein that is critical for the elimination of many endogenous small organic cations, drugs, and toxins.[50] Polymorphisms in the exon region of *OCT1* were analyzed to determine if changes in the amino acid sequence could impact drug transport function and influence cellular uptake of these antiemetics.[29] The *in vitro* and *in vivo* data suggest that concentrations of ondansetron were highest in patients who lacked the active *OCT1* allele and concentrations of ondansetron decreased with increases in the number of active *OCT1* alleles. Patients who lacked an active *OCT1* allele had higher plasma concentration of ondansetron and tropisetron. Patients who had active *OCT1* alleles vomited more frequently.

Drug-drug interactions may influence OCT1 function and contribute to inter-individual variability in hepatic uptake of tropisetron and ondansetron. CTX drugs like oxaliplatin but not carboplatin are substrates for OCT1.[29] Additional SNPs in *OCT1* discovered recently may influence the loss of function of OCT1.[50] Further investigation is required to understand the role of *OCT1* in antiemetic efficacy.

In the two studies that found an association between drug metabolizing pathway genes and antiemetic efficacy, patients with three active *CYP2D6* alleles referred to as the UM group who were treated tropisetron and ondansetron reported an increase in CINV episodes. In one study,[21] patients with no active *CYP2D6* alleles, (i.e., PMs) and treated with tropisetron and ondansetron, reported a decreased number of CINV episodes. Since serum concentrations of tropisetron were highest in the PM group, it was considered a protective allele.[21]

Limitations of the sixteen studies

Sample size—Across the sixteen studies, the sample sizes ranged from 64 to 2886, with the majority of studies having a sample size of approximately 200 patients. None of the

studies reported a power analysis based on the number of SNPs evaluated. Sample size selection for a candidate gene analysis depends on the number of SNPs analyzed, effect size of the SNPs, their allelic frequency, and the extent to which the SNPs are in linkage disequilibrium.[51] Of the 49 SNPs and one haplotype evaluated for associations with CINV, only 11 were statistically significant. Of the 37 SNPs and two haplotypes evaluated for associations with antiemetic efficacy, only 10 were statistically significant. One reason for the lack of consistent findings across the sixteen studies is the relatively small sample sizes.

Allelic frequencies for *HTR3A*, *HTR3B*, *HTR3C*, *HTR3D*, *HTR3E*, *ABCB1*, and *CYP2D6* genes differ among various ethnic populations. While these sixteen studies were conducted in nine different countries, most of them did not report patients' ethnicity and none reported if ancestry informative markers (AIMs) were used to control for these differences. Again, the failure to control for genomic estimates of race/ethnicity may contribute to the inconsistent findings. Most studies did not control for differences in phenotypic characteristics prior to the evaluation of associations between the various CINV phenotypes and genetic polymorphisms. In addition, most studies did not control for variations in the same gene.

Sample characteristics—Across the sixteen studies, patients varied in their cancer diagnoses. While in some studies, patients had a single cancer diagnosis, in other studies patients were heterogeneous in terms of their cancer diagnoses. Some studies recruited only female patients and one recruited only male patients. Across the sixteen studies, patients' ages ranged from 14 years to 86 years. The studies were rather diverse in the types of CTX, as well as the antiemetic regimens, that were evaluated. Diversity in sample characteristics across these studies may have contributed to the inconsistent findings.

CINV assessment—While a variety of instruments can be used to assess CINV, no gold standard assessment tool is available. While some instruments, like the Morrow Assessment for Nausea and Vomiting (MANE) assess the frequency and severity of acute and anticipatory CINV,[52] others like the MASCC Antiemesis Tool (MAT) evaluate the occurrence and duration of acute and delayed CINV.[53]

While these two valid and reliable CINV tools are available, neither was used in any of the sixteen studies in this review. The majority of the studies used a VAS, the NCICTC and/or a patient diary to assess one or more of the CINV phenotypes. None of the studies reported on the validity and reliability of the VAS or the patient diary. The NCICTC does not evaluate the frequency of CIN. NCICTC version 3 assesses CIN for the first 24 hours and version 4 does not indicate the timing for the CIN assessment.

CONCLUSIONS

To date, between 13% to 60% of oncology patients experience CINV.[1–3] While sixteen studies have attempted to determine associations between various CINV phenotypes and polymorphisms in a number of candidate genes, very few definitive conclusions can be drawn from these data due to the limitations enumerated above. As noted in Table 3, a number of areas warrant consideration in future research including adequately powered

studies for the specific genomic analyses that are purposed; more rigorous phenotyping of CINV; evaluation of additional mechanisms that underlie CINV and antiemetic efficacy; and evaluation of changes in gene expression and epigenetics that contribute to the CINV phenotype and antiemetic efficacy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by a grant from the National Cancer Institute (NCI, CA134900). Dr. Miaskowski is an American Cancer Society Clinical Research Professor and is supported by a grant from NCI (CA168960). Komal Singh is supported by a grant from the American Cancer Society.

References

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Antiemetics Version 2.2017. NCCN Web site. http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed April 14, 2017
2. Cohen L, de Moor CA, Eisenberg P, et al. Chemotherapy-induced nausea and vomiting: incidence and impact on patient quality of life at community oncology settings. Support Care Cancer. 2007; 15:497–503. [PubMed: 17103197]
3. Bloechl-Daum B, Deuson RR, Mavros P, et al. Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. J Clin Oncol. 2006; 24(27):4472–4478. [PubMed: 16983116]
4. Hofman M, Morrow GR, Roscoe JA, et al. Cancer patients' expectations of experiencing treatment-related side effects: A University of Rochester Cancer Center - Community Clinical Oncology Program study of 938 patients from community practices. Cancer. 2004; 101:851–857. [PubMed: 15305419]
5. Janelsins MC, Tejani MA, Kamen C, et al. Current pharmacotherapy for chemotherapy-induced nausea and vomiting in cancer patients. Expert Opin Pharmacother. 2013; 14(6):757–766. [PubMed: 23496347]
6. Warr D, Street J, Carides A. Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of phase 3 trial of aprepitant in patients receiving adriamycin-cyclophosphamide-based chemotherapy. Support Care Cancer. 2011; 19(6): 807–813. [PubMed: 20461438]
7. Hesketh P, Aapro M, Street J, et al. Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of two phase III trials of aprepitant in patients receiving cisplatin-based chemotherapy. Support Care Cancer. 2010; 18(9):1171–1177. [PubMed: 19756774]
8. Molassiotis A, Aapro M, Dicato M, et al. Evaluation of risk factors predicting chemotherapy-related nausea and vomiting: results from a European prospective observational study. J Pain Symptom Manage. 2014; 47(5):839–848. [PubMed: 24075401]
9. Molassiotis A, Lee PH, Burke TA, et al. Anticipatory nausea, risk factors, and its impact on chemotherapy-induced nausea and vomiting: results from the Pan European Emesis Registry Study. J Pain Symptom Manage. 2016; 51(6):987–993. [PubMed: 26891606]
10. Roscoe JA, Morrow GR, Aapro MS, et al. Anticipatory nausea and vomiting. Support Care Cancer. 2011; 19(10):1533–1538. [PubMed: 20803345]
11. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2011; 29:4189–4198. [PubMed: 21947834]
12. Hesketh P, Bohlke K, Lyman G, et al. Antiemetics: American Society of Clinical Oncology Focused Guideline Update. J Clin Oncol. 2016; 34(4):381–386. [PubMed: 26527784]

13. Grunberg SM, Osoba D, Hesketh PJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity–an update. Support Care Cancer. 2005; 13(2):80–84. [PubMed: 15599601]
14. Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J of Clin Oncol. 1997; 15(1):103–109. [PubMed: 8996130]
15. Sekine I, Segawa Y, Kubota K, et al. Risk factors of chemotherapy-induced nausea and vomiting: index for personalized antiemetic prophylaxis. Cancer Sci. 2013; 104(6):711–717. [PubMed: 23480814]
16. Trammel M, Roederer M, Patel J, et al. Does pharmacogenomics account for variability in control of acute chemotherapy-induced nausea and vomiting with 5-hydroxytryptamine type 3 receptor antagonists? Curr Oncol Rep. 2013; 15(3):276–285. [PubMed: 23512709]
17. Perwitasari DA, Gelderblom H, Atthobari J, et al. Anti-emetic drugs in oncology: pharmacology and individualization by pharmacogenetics. Int J Clin Pharm. 2011; 33(1):33–43. [PubMed: 21365391]
18. Sugino S, Janicki P. Pharmacogenetics of chemotherapy-induced nausea vomiting. Pharmacogenomics. 2015; 16(2):149–160. [PubMed: 25616101]
19. Kiernan J. Genetic Influence on chemotherapy-induced nausea and vomiting: a narrative review. Oncol Nurs Forum. 2016; 43(3):389–393. [PubMed: 27105200]
20. Moher D, Liberati A, Tezlaff J, et al. Preffered reporting items for systematic reviews and meta-analyses: The PRISMA Statement. PLoS Medicine. 2009; 6(7):e1000097. [PubMed: 19621072]
21. Kaiser R. Patient-tailored antiemetic treatment with 5-hydroxytryptamine type 3 receptor antagonists according to cytochrome P-450 2D6 genotypes. J of Clin Oncol. 2002; 20(12):2805–2811. [PubMed: 12065557]
22. Tremblay PB, Kaiser R, Sezer O, et al. Variations in the 5-hydroxytryptamine type 3B receptor gene as predictors of the efficacy of antiemetic treatment in cancer patients. J Clin Oncol. 2003; 21(11):2147–2155. [PubMed: 12775740]
23. Kaiser R, Tremblay PB, Sezer O, et al. Investigation of the association between 5-HT3A receptor gene polymorphisms and efficiency of antiemetic treatment with 5-HT3 receptor antagonists. Pharmacogenetics. 2004; 14:271–278. [PubMed: 15115912]
24. Babaoglu MO, Bayar B, Aynacioglu AS, et al. Association of the ABCB1 3435C>T polymorphism with antiemetic efficacy of 5-hydroxytryptamine type 3 antagonists. Clin Pharmacol Ther. 2005; 78(6):619–626. [PubMed: 16338277]
25. Fasching PA, Kollmannsberger B, Strissel PL, et al. Polymorphisms in the novel serotonin receptor subunit gene HTR3C show different risks for acute chemotherapy-induced vomiting after anthracycline chemotherapy. J Cancer Res Clin Oncol. 2008; 134(10):1079–1086. [PubMed: 18389280]
26. Ward MB, Kotasek D, McKinnon RA. Investigation of HTR3C mutations for association with 5HT(3) receptor antagonist anti-emetic efficacy. Pharmacogenomics. 2008; 9(8):1027–1033. [PubMed: 18681779]
27. Hammer C, Fasching PA, Loehberg CR, et al. Polymorphism in HTR3D shows different risks for acute chemotherapy induced nausea and vomiting after anthracycline chemotherapy. Pharmacogenomics. 2010; 11:943–950. [PubMed: 20602613]
28. Perwitasari DA, Wessels JA, van der Straaten RJ, et al. Association of ABCB1, 5-HT3B receptor and CYP2D6 genetic polymorphisms with ondansetron and metoclopramide antiemetic response in Indonesian cancer patients treated with highly emetogenic chemotherapy. Jpn J Clin Oncol. 2011; 41(10):1168–1176. [PubMed: 21840870]
29. Tzvetkov MV, Saadatmand AR, Bokelmann K, et al. Effects of OCT1 polymorphisms on the cellular uptake, plasma concentrations and efficacy of the 5-HT(3) antagonists tropisetron and ondansetron. Pharmacogenomics J. 2012; 12(1):22–29. [PubMed: 20921968]
30. Fernandez-Rozadilla C, Cazier JB, Moreno V, et al. Pharmacogenomics in colorectal cancer: a genome-wide association study to predict toxicity after 5- fluorouracil or FOLFOX administration. Pharmacogenomics J. 2013; 13(3):209–217. [PubMed: 22310351]

31. Tsuji D, Kim Y-I, Nakamichi H, et al. Association of ABCB1 polymorphisms with the antiemetic efficacy of granisetron plus dexamethasone in breast cancer patients. Drug Metab Pharmacokinet. 2013; 28(4):299–304. [PubMed: 23358260]
32. He H, Yin JY, Xu YJ, et al. Association of ABCB1 polymorphisms with the efficacy of ondansetron in chemotherapy-induced nausea and vomiting. Clin Ther. 2014; 36(8):1242–1252. [PubMed: 25012726]
33. Lamba JK, Fridley BLT, Ghosh TM, et al. Genetic variation in platinating agent and taxane pathway genes as predictors of outcome and toxicity in advanced non-small-cell lung cancer. Pharmacogenomics. 2014; 15(12):1565–1574. [PubMed: 25340731]
34. Lee AM, Shi Q, Pavey E, et al. DPYD variants as predictors of 5-fluorouracil toxicity in adjuvant colon cancer treatment (NCCTG N0147). J Natl Cancer Inst. 2014; 106(12):1–12.
35. Pud D, Har-Zahav G, Laitman Y, et al. Association between variants of 5-hydroxytryptamine receptor 3C (HTR3C) and chemotherapy-induced symptoms in women receiving adjuvant treatment for breast cancer. Breast Cancer Res Treat. 2014; 144(1):123–131. [PubMed: 24477975]
36. Zoto T, Kilickap S, Yasar U, et al. Improved anti-emetic efficacy of 5-HT3 receptor antagonists in cancer patients with genetic polymorphisms of ABCB1 (MDR1) drug transporter. Basic & Clin Pharmacol Toxicol. 2015; 116:354–360.
37. Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity–state of the art. Support Care Cancer. 2011; 19:S43–47. [PubMed: 20972805]
38. Hesketh P. Chemotherapy-induced nausea and vomiting. N Engl J of Med. 2008; 358(23):2482–2494. [PubMed: 18525044]
39. WHO toxicity grading scale for adverse events. Available at: www.icssc.org/documents/resources/AEManual2003AppendicesFebruary_06_2003%20final.pdf. Accessed 04/14/2017
40. Darmani NA, Ray AP. Evidence for re-evaluation of the neurochemical and anatomical bases of chemotherapy-induced vomiting. Chem Rev. 2009; 109(7):3158–3199. [PubMed: 19522506]
41. Niesler B, Kapeller J, Hammer C, et al. Serotonin type 3 receptor genes: HTR3A, B, C, D, E. Pharmacogenomics. 2008; 9(5):501–504. [PubMed: 18466097]
42. Jordan K, Gralla R, Jahn F, et al. International antiemetic guidelines on chemotherapy induced nausea and vomiting (CINV): content and implementation in daily routine practice. Eur J Pharmacol. 2014; 722:197–202. [PubMed: 24157984]
43. Meineke C, Tzvetkov MV, Bokelmann K, et al. Functional characterization of a -100_-102delAAG deletion-insertion polymorphism in the promoter region of the HTR3B gene. Pharmacogenet Genomics. 2008; 18(3):219–230. [PubMed: 18300944]
44. Ishikawa T, Hirano H, Onishi Y, et al. Functional evaluation of ABCB1 (P-Glycoprotein) polymorphisms: high-speed screening and structure-activity relationship analyses. Drug Metab Pharmacokinet. 2004; 19(1):1–14. [PubMed: 15499164]
45. Vivona D, Lima LT, Rodrigues AC, et al. ABCB1 haplotypes are associated with P-gp activity and affect a major molecular response in chronic myeloid leukemia patients treated with a standard dose of imatinib. Oncol Lett. 2014; 7(4):1313–1319. [PubMed: 24660038]
46. Sprowl JA, Ness RA, Sparreboom A. Polymorphic transporters and platinum pharmacodynamics. Drug Metab Pharmacokinet. 2013; 28(1):19–27. [PubMed: 22986709]
47. Morisaki K, Robey RW, Ozvegy-Laczka C. Single nucleotide polymorphisms modify the transporter activity of ABCG2. Cancer Chemother Pharmacol. 2005; 56:161–172. [PubMed: 15838659]
48. Ogu CC, Maxa JL. Drug interactions due to cytochrome P450. BUMC Proceedings. 2000; 13(4): 421–423. [PubMed: 16389357]
49. Rao KV, Faso A. Chemotherapy-induced nausea and vomiting: optimizing prevention and management. Am Health Drug Benefits. 2012; 5(4):232–240. [PubMed: 24991322]
50. Chen L, Takizawa M, Chen E, et al. Genetic polymorphisms in organic cation transporter 1 (OCT1) in Chinese and Japanese populations exhibit altered function. J Pharmacol Exp Ther. 2010; 335(1):42–50. [PubMed: 20639304]

51. Leschziner GD, Andrew T, Pirmohamed M, et al. ABCB1 genotype and PGP expression, function and therapeutic drug response: a critical review and recommendations for future research. Pharmacogenomics J. 2007; 7(3):154–179. [PubMed: 16969364]

52. Morrow GR. A patient report measure for the quatification of chemotherapy induced nausea and emesis: psychometric properties of the Morrow assessment of nausea and emesis (MANE). Br J Cancer Suppl. 1992; 66(Suppl XIX):S72–S74.

53. Brearley SG, Clements CV, Molassiotis A. A review of patient self-report tools for chemotherapy-induced nausea and vomiting. Support Care Cancer. 2008; 16:1213–1229. [PubMed: 18551323]

Highlights

- Describe salient study characteristics for studies on associations between genetic polymorphisms and chemotherapy-induced nausea and vomiting.
- Summarize and critique the instruments used to assess CINV and the timing of the assessments in the studies.
- Synthesize findings on associations between the occurrence and severity of CINV and genetic polymorphisms.
- Synthesize findings on associations between antiemetic efficacy and genetic polymorphisms.

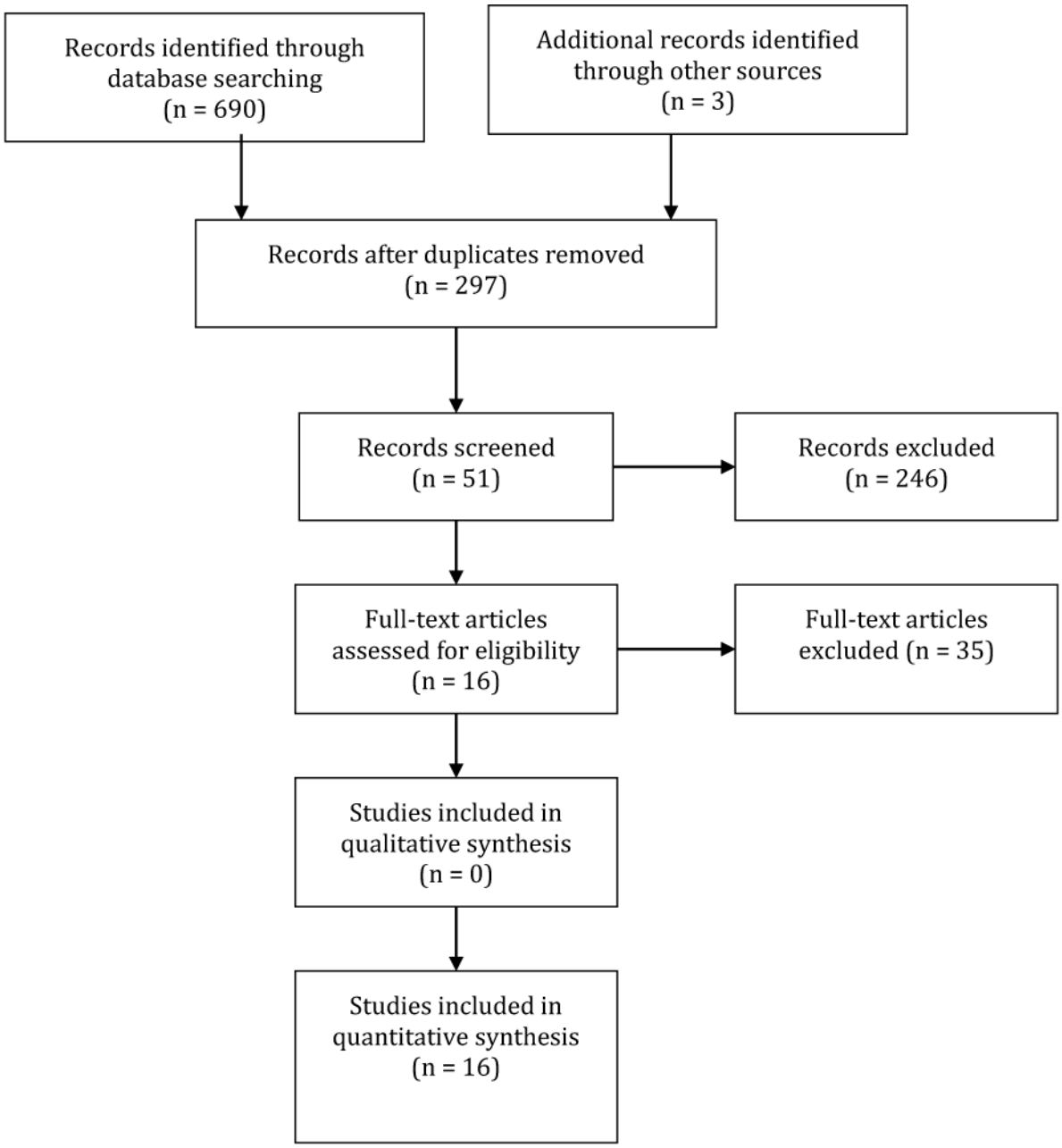

Figure 1.

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram to determine studies on associations between chemotherapy-induced nausea and vomiting phenotypes and candidate gene polymorphisms. Reprinted with permission from.[20]

Table 1

Summary of Findings on Associations Between Chemotherapy-Induced Nausea and Vomiting Phenotypes and Candidate Gene Polymorphisms

Gene	SNP	CIN Occurrence	CIN Severity	CIV Occurrence
		Findings	Findings	Findings
Serotonin receptor genes				
HTR3A	rs1062613	No association[27]	No association[23]	No association[23,27]
	rs1176722	No association[27]	No association[23]	No association[23,27]
	rs1176719		No association[23]	No association[23,27]
	rs2276303		No association[23]	No association[23,27]
	rs909411		No association[23]	No association[23,27]
	rs1176713		No association[23]	No association[23,27]
HTR3B	rs1176744	No association[25]	No association[22]	No association[25]
	rs45460698 (100_102AAG deletion)	No association[27]		↑ for homozygous variants[22]
HTR3C	rs6766410	No association[25]	↓ for rare allele[35]	↑ for rare allele[25]
	rs6807362	No association[25]	No association[35]	No association[25]
	1651 C>T		No association[26]	No association[26]
	3885 C>T		No association[26]	No association[26]
	3894 C>A		No association[26]	No association[26]
	6342 C>T		No association[26]	No association[26]
	7051 G>A		No association[26]	No association[26]
	7082 C>T		No association[26]	No association[26]
	7142 G>C		No association[26]	No association[26]
HTR3D	rs6443930	No association[27]		No association[27]
	rs1000952	No association[27]		No association[27]
HTR3E	rs5855015	No association[27]		No association[27]
	rs7627615	No association[27]		No association[27]
	rs56109847	No association[27]		No association[27]
Drug transport genes				
ABCB1	rs1045642	↓ for rare allele[32, 36] No association[31]	↓ for rare allele[24]	↓ for rare allele[24, 32, 36] No association[28, 31]
	rs20325282	↓ for rare allele[32, 36] ↑for rare allele[31]		↓ for rare allele[32, 36] ↑for rare allele[31]
	rs1128503	↑ for rare allele[36] No association[33]		↑for rare allele[36] No association[33]
	Haplotype rs1045642 + rs20325282 + rs1128503	↓ CTT haplotype NS[28] ↑ CTG haplotype[28]		↑ CTG haplotype[28]
ABCC1	rs246240	No association[33]		No association[33]
	rs2238476	No association[33]		No association[33]

Gene	SNP	CIN Occurrence	CIN Severity	CIV Occurrence
		Findings	Findings	Findings
ABCG2	rs2231142	↑ for Q to K change		No association[33]
ATP7B	rs1801244	↑ for V to L change		No association[33]
Drug metabolizing genes				
CYP2D6	rs16947	No association[28]		No association[28]
	rs3892097	No association[28]		No association[28]
	rs1065852	No association[28]		No association[28]
	(CYP2D6*1 + duplicate allele)		↑ for UM allele[22] ↑ for UM allele NS[21]	↑ for UM allele[21]
Enzyme genes				
COMT	rs4818		No association[35]	
DPYD	rs3918290	↑ for splice variant[34]		↑ for splice variant[34]
GCH1	s10483639		No association[35]	
	rs3783641		No association[35]	
	rs8007267		No association[35]	
Transcription factor gene				
GTF2E1	rs447978	↓ for intronic region SNP[33]		No association[33]
Genome Wide Association Study				
	rs10182133	No association[30]		
	rs2060645	No association[30]		
	rs6815391	No association[30]		
	rs7094179	No association[30]		
	rs9300811	No association[30]		
	rs2389972	No association[30]		
	rs10158985	No association[30]		
	rs851974	No association[30]		
	rs2739171	No association[30]		
	rs724975	No association[30]		

Blank box: Phenotype not studied

Abbreviations: ↑ = measured increased occurrence of CIN/CIV in comparison to reference allele, ↓ = measured decreased occurrence of CIN/CIV in comparison to reference allele, ABCB1 = ATP binding cassette subfamily B member 1, ABCC1 = ATP binding cassette subfamily C member 1, ABCG2 = ATP binding cassette subfamily G member 2, ATP7B = ATPase copper transporting beta, CIN = chemotherapy induced nausea, COMT = catecholamine-o-methyltransferase enzyme, CYP2D6 = cytochrome P450 family 2 subfamily D member 6, DPYD = dihydropyrimidine dehydrogenase, GCH1 = guanidine triphosphate cyclohydrolase I enzyme, GTF2E1 = general transcription factor IIE subunit 1, HTR3A = 5-hydroxytryptamine 3A receptor, HTR3B = 5-hydroxytryptamine 3B receptor, HTR3C = 5-hydroxytryptamine 3C receptor, HTR3D = 5-hydroxytryptamine 3D receptor, HTR3E = 5-hydroxytryptamine 3E receptor, K = Lysine, L = Leucine, NS = not significant, Q = Glutamine, UM = ultrarapid metabolizers, V = valine

Table 2

Summary of Findings on Associations Between Antiemetic Treatment Efficacy and Candidate Gene Polymorphisms

Gene	SNP	Findings
Serotonin receptor genes		
HTR3A	rs1062613	No association[23, 27]
	rs1176722	No association[23, 27]
	rs1176719	No association[23, 27]
	rs2276303	No association[23, 27]
	rs909411	No association[23, 27]
	rs1176713	No association[23, 27]
	CT haplotype (8046 T > C and 10627 G >T)	↓ CINV occurrence in tropisetron and ondansetron treated patients[23]
HTR3B	rs45460698	No association[27, 28]
	rs1176744	No association[25]
	rs4938058	No association[25, 28]
	rs7943062	No association[25, 28]
HTR3C	rs6766410	↑ CIV episodes associated with rare allele in ondansetron and dexamethasone treated patients[25]
	rs6807362	No association[25]
	1651 C>T	No association[26]
	3885 C>T	No association[26]
	3894 C>A	No association[26]
	6342 C>T	No association[26]
	7051 G>A	No association[26]
	7082 C>T	No association[26]
	7142 G>C	No association[26]
HTR3D	rs6443930	↓ CINV occurrence for rare allele in ondansetron and dexamethasone treated patients[27]
	rs1000952	No association[27]
HTR3E	rs5855015	No association[27]
	rs7627615	No association[27]
	rs56109847	No association[27]
Drug transport genes		
ABCB1	rs1045642	↓CINV occurrence in granisetron treated patients with rare allele[24]
	rs20325282	↑CIV occurrence in granisetron treated patients homozygous (TT) or heterozygous (TA) for rare allele[31]
	rs1128503	↑CIV occurrence in granisetron treated patients with rare allele[36]
	Haplotype rs1045642 + rs20325282 + rs1128503	↑CINV occurrence in ondansetron treated patients with CG haplotype[32] ↑ CINV occurrence in ondansetron treated patients with CTG haplotype[28] ↓ CINV occurrence in granisetron treated patients with TTT haplotype[36]

Gene	SNP	Findings
OCT1	R61C	
	C88R	
	G401S	↓CINV occurrence in tropisetron treated patients who lack active *OCT1* allele[29]
	M420del	
	G465R	
Drug metabolizing gene		
CYP2D6	rs16947	No association[28]
	rs3892097	No association[28]
	rs1065852	No association[28]
	UM (CYP2D6*1 + duplicate allele)	↑CINV occurrence in tropisetron and ondansetron treated patients with three active alleles[21, 22]
	PM (Two alleles of CYP2D6*3 CYP2D6*4 CYP2D6*5 CYP2D6*6)	↓CINV occurrence and ↑ serum tropisetron concentration in patients with no active alleles[21]

Abbreviations: ↑ = measured increased antiemetic efficacy, ↓ = measured decreased antiemetic efficacy, A = adenine, ABCB1 = ATP binding cassette subfamily B member 1, C88R = cysteine88-to-arginine, C = Cytosine, CINV = chemotherapy-induced nausea and vomiting, CIV = chemotherapy-induced vomiting, CYP2D6 = cytochrome P450 family 2 subfamily D member 6, G = guanine, G401S = glycine401-to-serine, G465R = glycine465-to-arginine, HTR3A = 5-hydroxytryptamine 3A receptor, HTR3B = 5-hydroxytryptamine 3B receptor, HTR3C = 5-hydroxytryptamine 3C receptor, HTR3D = 5-hydroxytryptamine 3D receptor, HTR3E = 5-hydroxytryptamine 3E receptor, M420del = deletion of methionine420, OCT1 = organic cation transporter protein, PM = poor metabolizers, R61C = arginine61-to-cysteine, T = thymine, UM = ultrarapid metabolizer

Table 3

Directions for Future Research

Sample selection
• Control for genomic estimates of race/ethnicity
• Include sample size that provides adequate power for evaluating selected SNPs
CINV assessment
• Use valid and reliable instruments to characterize the CINV phenotypes (e.g., MANE)
• Determine the optimal timing for CINV measures to capture anticipatory, acute, and delayed CINV phenotypes.
Mechanistic considerations for candidate gene selection
• Evaluate additional pathways involved in the development of CINV (e.g., NK-1 receptor, dopamine receptor activation pathways).
• Evaluate additional pathways involved in antiemetic efficacy (e.g., drug metabolizing enzyme pathways other than CYP2D6)
Other types of genomic analyses
• Evaluate for changes in gene expression that contribute to anticipatory, acute and delayed CINV
• Evaluate for epigenetic changes that contribute to anticipatory, acute and delayed CINV

Abbreviations: CINV = chemotherapy-induced nausea and vomiting, CYP2D6 = cytochrome P450 family 2 subfamily D member 6, = morrow assessment for nausea and vomiting, NK-1 = neurokinin-1, SNPs = single nucleotide polymorphisms