172P

Prediction of persistent taxane-induced peripheral neuropathy among early-stage breast cancer survivors using whole-exome sequencing

Kristina Engvall, Niclas Björn, Hanna Uvdal, Elisabeth Åvall-Lundqvist, Henrik Gréen
Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden

BACKGROUND

Persistent taxane-induced peripheral neuropathy (TIPN) among early-stage breast cancer survivors (ESBCS) is common and impacts quality of life. We aimed to explore genetic variants as risk factors.

MATERIALS AND METHODS

A population-based cohort of 884 residual-free ESBCS in Sweden were sent the EORTC chemotherapy-induced PN (CIPN20), 342 agreed to additional whole-exome sequencing for prediction modelling. Analysis focused on the five symptoms that showed highest relative risks compared to controls in our previous studies[1] and are of clinical importance[2]:

- *Numbness in toes/feet*
- *Tingling in toes/feet*
- *Cramps in feet*
- *Difficulty opening a jar because of weakness in hands*
- *Difficulty climbing stairs/getting out of chair because of weakness in legs*

The raw sequencing data was aligned to the human reference genome (GRCh38), quality controls according to standard guidelines using the Genome Analysis Toolkit. The final filtered set included 55 150 common genetic variants (MAF ≥ 1%). We adjusted for age, taxane, cumulative dose, time since treatment, BMI, and diabetes mellitus treatment (DM) (Table 1).

Table 1 . Baseline characteristics.

	All N=337	Training N=237	Testing N=100
Median age at survey (range)	62 (31-86)	62 (35-83)	62 (31-86)
Treatment			
Paclitaxel	150 (44.5%)	97 (40.9%)	53 (53%)
Docetaxel	177 (52.5%)	132 (55.7%)	45 (45%)
Alternating P & D	10 (3.4%)	8 (3.4%)	2 (2.0%)
Mean cumulative dose (mg/m^2)			
Paclitaxel	842 (190)	833 (197)	860 (177)
Docetaxel	263 (61)	261 (67)	271 (34)
BMI at survey (SD)	26.9 (4.7)	27.2 (4.6)	26.1(4.7)
DM treatment	16 (4.7%)	11 (4.6%)	5 (5%)
Mean time (years) since taxane to survey (SD)	4 (1.5)	4.1 (1.6)	3.8 (1.5)

Prediction models (logistic regression) were based on the single-nucleotide variants (SNVs) and insertions /deletions (INDELs) associated with TIPN in a training set of 70% of the ESBCS (N=237) with planned subsequent validation of the remaining 30%.
The clinical risk factors age, taxane, BMI and DM was added to the prediction model (Table 1).

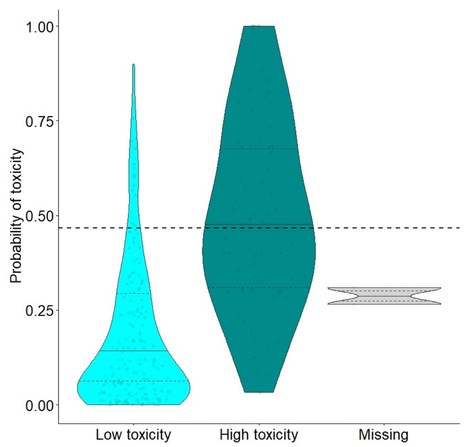

Figure 1.
Violin plot of the probability of numbness in feet toxicity based on genetic risk and clinical factors

Table 2. Performance of prediction models for risk of peripheral neuropathy symptoms based on genetic and clinical risk factors

	Accuracy	Sensitivity	Specificity
Numbness in feet	82%	54%	91%
Tingling in feet	82%	51%	94%
Cramps in feet	77%	35%	95%
Difficulty opening a jar	79%	28%	96%
Difficulty climbing stairs	91%	43%	98%

RESULTS

P-value thresholds for permutations with 50-80% false discovery rates (FDR) was ≤ 0.000875, ≤ 0.001125, ≤ 0.001125, ≤ 0.0005, and ≤ 0.0005 for numbness in feet, tingling in feet, cramps in feet, difficulty opening a jar, and difficulty climbing stairs.
Using these thresholds 71, 79, 69, 33, and 46 genetic variants were identified representing in total 282 unique variants. Prediction models developed, reaches a max accuracy of 75-91% based on genetic risk factors and improved 1-3% with the inclusion of clinical risk factors (Table 2).

CONCLUSION

Genetic prediction models of persistent TIPN may indicate a genetic risk, which could contribute to more individualised adjuvant treatment decisions.
The prediction is improved by adding clinical risk factors.
Further analysis is needed and ongoing.

REFERENCES
[1]Engvall et al. (2021) Persistent neuropathy among early-stage breast cancer survivors in a population-based cohort. Br J Cancer.
[2]Engvall et al (2022) Impact of persistent peripheral neuropathy on health-related quality of life among early-stage breast cancer survivors: a population-based cross-sectional study Breast Cancer Res Treat

First author has no conflicts of interest to declare.

Study sponsored by The Swedish Cancer Society; the Medical Research Council of Southeast Sweden; Futurum - The Academy for Health and Care, Jönköping County Council; Forsknings-ALF.

kristina.engvall@liu.se

LINKÖPING UNIVERSITY