Differences in Germline Mutations Affecting Platinum Chemotherapy Sensitivity Between Male and Female Non-Small Cell Lung Cancer Patients

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Abstract

Platinum-based drugs (e.g., cisplatin, carboplatin, and oxaliplatin) are standard chemotherapy agents for the treatment of advanced non-small cell lung cancer (NSCLC), but their efficacy varies depending on the patient's genetic background. Currently, it remains unclear whether sex influences the genetic mutations associated with platinum drug sensitivity, and systematic studies are lacking. This study included 432 NSCLC patients undergoing platinum-based chemotherapy (341 males, 78.94%; 91 females, 21.06%), with chemotherapy sensitivity evaluated using RECIST 1.1 criteria. Whole-genome sequencing (WGS) and genome-wide association studies (GWAS) were performed to identify genetic mutations associated with platinum chemotherapy efficacy in male and female cohorts, aiming to uncover the molecular mechanisms of sex differences in lung cancer treatment.

Introduction

Platinum-based drugs (e.g., cisplatin, carboplatin, and oxaliplatin) are standard chemotherapy agents for lung cancer treatment, especially for patients with advanced non-small cell lung cancer (NSCLC). However, the efficacy and resistance to platinum-based drugs vary significantly among patients, which is closely associated with their genetic background. Genomic studies provide powerful tools to uncover the molecular mechanisms underlying platinum drug sensitivity. By analyzing the mutational profiles of lung cancer patients, researchers can identify key genetic variants associated with platinum sensitivity. Nonetheless, **it remains unclear whether sex-specific differences exist in the genetic mutations affecting platinum sensitivity.** Systematic investigations in this area are still lacking. Addressing this gap will not only enhance our understanding of the molecular roles of sex in lung cancer treatment but also provide valuable insights for optimizing personalized therapeutic strategies.

Methods and Materials

This study included a total of 432 non-small cell lung cancer (NSCLC) patients undergoing platinum-based chemotherapy, all recruited from Xiangya Hospital of Central South University. Among them, 341 were male patients (78.94%) and 91 were female patients (21.06%). Chemotherapy sensitivity was evaluated and classified according to RECIST 1.1 criteria. To investigate the genetic factors associated with platinum chemotherapy sensitivity, whole-genome sequencing (WGS) was performed for all patients. Genome-wide association studies (GWAS) were conducted separately for male and female cohorts to systematically analyze genetic mutations influencing platinum chemotherapy efficacy. A significance threshold of 1e-4 was applied to identify significant loci.

Results

The GWAS results revealed that, using a significance threshold of 1e-4, 297 loci were significantly associated with platinum drug sensitivity in the male cohort, while 60 loci were identified in the female cohort.

Among these, the most significant loci in the male cohort were rs257109, rs921686, rs3872723, rs4012172, and rs10801135. In the female cohort, the most significant loci were rs8060234, rs11642340, rs17549909, rs7271555, and rs66863549.

Figure 1. Patient distribution.

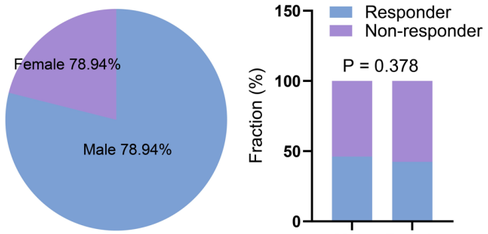


Figure 2. Manhattan map of the male cohort.

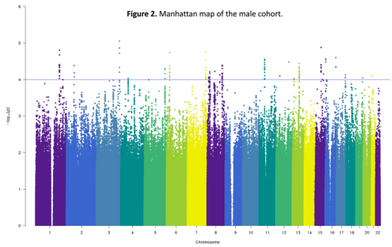
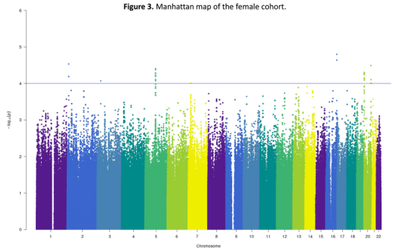


Figure 3. Manhattan map of the female cohort.



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铂类药物（如顺铂、卡铂和奥沙利铂）是治疗晚期非小细胞肺癌（NSCLC）的标准化疗药物，但其疗效因患者遗传背景而异。目前，性别是否影响铂类药物敏感性的基因突变位点尚不明确，缺乏系统性研究。本研究共纳入432例接受铂类化疗的NSCLC患者（男性341例，78.94%；女性91例，21.06%），化疗敏感性根据RECIST 1.1标准评估。通过全基因组测序和全基因组关联分析（GWAS），分别对男性和女性群体中与铂类化疗疗效相关的基因突变位点进行了分析，以揭示影像铂类化疗疗效的胚系突变中的性别差异。