UNIVERSITI TEKNOLOGI MARA

GENETIC RISKS OF CHILDHOOD LYMPHOBLASTIC LEUKAEMIA AND THE INTERPATIENT VARIATION OF METHOTREXATE RESPONSES AMONG PATIENTS

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

Acute lymphoblastic leukaemia is the most prevalent cancer in children under 14 years of age in Malaysia, with an incidence rate of approximately 35 per one million children. Several potential environmental and lifestyle factors associated with the risk of childhood leukaemia have been investigated, such as infections, pesticides, traffic air pollution, industrial pollutant, diet, parental occupation and smoking habit. The study aimed to determine relationships between two SNPs; rs10821936 (*ARID5B*) and rs25487 (*XRCC1),* and risk associated in childhood ALL, as well as four SNPs; rs717620 (*ABCC2*), rs4948496 (*ARID5B*), rs1801133 (*MTHFR*) and rs4149056 (*SLCO1B1*), with the serum levels and toxicity of MTX. The study also sought to investigate the metabolic alterations associated with MTX and to determine the potential metabolic markers and pathway for drug responses. Genomic DNA was isolated from blood, and the polymerase chain reaction analysis was performed for the genotyping study. The variants were then annotated and analysed utilising Variant Effect Predictor (VEP), Sorting Intolerant from Tolerant (SIFT) and Polymorphism Phenotyping version 2 (PolyPhen-2). In addition, the Agilent 1200 Infinity HPLC system coupled with the Agilent 6460 triple-quadrupole (QQQ) and Agilent 6520 Accurate-Mass (Q-TOF) mass spectrometers were employed to measure serum concentrations of MTX and to identify the potential metabolic markers, respectively. Eighty-one per cent of the patients have genotypes CC and CT of rs10821936 (*ARID5B*) were associated with 2.5 – 2.1 increase in the risk of developing ALL. The rs717620 *ABCC2* genotype was significantly associated with MTX serum levels at 48 hours post-treatment (p = 0.017, Kruskal-Wallis Test). Patients with CT and TT of rs717620 (*ABCC2*) and TC and CC of rs4948496 (*ARID5B*) were significantly associated with grade I – IV leukopenia (Fisher Exact Test; p = 0.03 and 0.02, respectively). The metabolomics study found that thirteen metabolites significantly discriminated the pre- and post-MTX group. Out of the thirteen metabolites identified, the four metabolites with VIP scores of more than 1 were xanthine, alpha-linolenic acid, (9Z)-hexadecenoic acid and cholic acid. The findings revealed that xanthine was the most significant metabolic marker in childhood ALL with an AUC value of 0.88 (95%, CI = 0.84 – 0.92). Our results demonstrate that by pre-screening of ALL patients would identify whose patients at risk and therefore help a paediatric oncologist to personalize chemotherapy drugs for precision health.

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