



Thymidylate Synthase Polymorphisms for Use in Screening for Cancer Susceptibility (*Robert Ladner, SOM 02-52*) *Diagnostic/Therapeutic*

Background

Thymidylate Synthase (TS) is an important enzyme in the nucleotide synthesis pathway and converts dUMP to dTMP. TS is a target for a variety of chemotherapeutic agents such as 5-FU, raltitrexed (Tomudex and pemetrexed (Alimta)) and inhibition of TS leads to cytotoxicity due to depletion of dTTP pool, a phenomenon dubbed as “thymine-less death.” TS also plays a critical role in cardiovascular diseases and other defects. TS and methylenetetrahydrofolate reductase (MTHFR) compete for folate in the generation of homocysteine. Folate and homocysteine have been associated with cardiovascular risk. Polymorphisms consisting of 28 base pair repeats in the 5’-untranslated region of the TS gene have been identified in certain African and Asian populations and have been shown to predict patient response to 5-FU chemotherapy. **The present invention discloses a novel single nucleotide polymorphism which could be added to existing screening tests thereby enhancing the predictive value of the tests.**

Description of the Technology

A novel single nucleotide polymorphism (SNP) in the 5’ tandem repeats of the TS gene has been discovered. Individuals with wild-type form had higher transcription of TS than those with the variant form. In addition, the present invention also discloses a six base pair deletion in the 3’ gene of TS which results in mRNA instability and decreased production of TS. It has been shown that in cancer tissues, the reduced production of TS prevents the growth and metastasis of cancerous cells. Taken together, these studies demonstrate that identification of these polymorphisms would enable the prediction of a patient’s response to chemotherapy and cardiovascular disease treatments.

Applications

- To assess the risk of cancer and cardiovascular diseases
- To develop screening methods for the base pair deletion in the 3’ gene of TS
- To predict the clinical outcome of chemotherapy and anti-cardiovascular treatments

Patent Status

PCT application filed.

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