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A Study on the Relationship between UGT2B7 Gene Polymorphism and Clinical Prognosis

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Abstract: *Breast cancer (BC) is the most common cancer diagnosis in women, often referred to as the "pink killer" [1], and its incidence ranks first among female malignancies, accounting for 25% of all cancer cases and 15% of all cancer deaths in the world [2]. With the improvement of medical level, the treatment methods of breast cancer have become relatively mature, including chemical therapy, adjuvant chemotherapy, neoadjuvant chemotherapy (mainly anthracycline and zisanchun drugs), endocrine therapy (tamoxifen, etc.), anti-estrogen drugs, aromatase inhibitors, etc. [3].In recent years, the role of UGT2B7 in drug metabolism and prognosis has been gradually discovered. To summarize the important role of UGT2B7 in prognosis diagnosis in recent years. In this paper, we search for qualified research by searching Pubmed, Uniprot and Chinese knowledge network. The data analysis and conclusion are helpful to the glucuronidation of many therapeutic drugs, including opioid drugs (such as codeine, morphine, naloxone), anticancer drugs (such as antitumor drugs: epirubicin, diclofenac, naproxen, etc.). In each treatment, the prognostic effect of UGT2B7 is gradually reflected, which is expected to be an important prognostic index.*

Keywords: *UGT2B7 gene polymorphism clinical prognosis*

1. Introduction

Uridine diphosphate glucuronyltransferase (UDP-glucuronosyltransferase, UGT) [4] is a detoxification and clearance pathway for many exogenous and endogenous substances. It has high biological function and is the most important enzyme in biotransformation of phase II in vivo. It can make lipophilic substrate glucuronidation, which is beneficial to its participation in metabolic process and then excreted from the body. one important member of the UGT family is that UGT2B7, plays an important role in the expression of the nuclear membrane and endoplasmic reticulum in hepatocytes, and is also widely distributed in other tissue cells such as pancreas, kidney, brain and intestine. Pramod C.Nair studies have found that [5]UGT2B7 genetic polymorphisms may exist through multi-functional forms of enzymes that exhibit differences but often weigh stacked substrate selectivity makes UGT2B7 considered one of the most important enzymes involved in drug glucuronidation. This enzyme contributes to glucuronidation of many therapeutic drugs, including opioids (e.g. codeine, morphine, naloxone), anticancer drugs (e.g., antitumor drugs: epirubicin, diclofenac, naproxen, etc.). In various treatments, the prognostic effect of UGT2B7 is gradually reflected. in this paper, by searching Pubmed, Uniprot and Chinese knowledge net, we look for eligible studies. Summarize the important role of UGT2B7 in prognosis diagnosis in recent years.

2. UGT2B7 gene polymorphisms

UGTs are involved in several physiologically important endogenous compounds, such as steroid hormones, bile acids, and many clinically important drugs, including VPA. In the UGT superfamily [6]. Fragments of UGT2B7 are known as the figure shows. UGT2B7 are thought to play an important role in the oxidation of hepatic glucuronic acid. Gene polymorphisms may exist through multifunctional forms of enzymes that exhibit frequent diverse overlapping substrate selectivity leading to UGT2B7 being considered one of the most important enzymes involved in drug glucuronidation.

UGT2B7 is a member of the UGT2B family, Contains 6 exons and 5 introns, 16 kb, in length 529 amino acid residues can be encoded. UGT2B7 genes have genetic polymorphisms, Coffman and so on by the cDNA cloning method analysis UGT2B7 position 268 allele. The results show, UGT2B7 have two alleles: UGT2B7*1 and UGT2B7*2.Japanese scholars discovered UGT2B7G211T as a new

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mutation site in UGT2B7 in 2003.The frequency of mutation was 18.5. At present ,79 G >A, of mutation sites have been reported -161 C >T, 842 G>A, UGT2B7*1c (>G 735A), UGT2B7*2(802C >T), UGT2B7*71S (>T 211G), UGT2B7*5(1192 G >A), 1062C>T and IVS1+985 AIVS1+G.etc where the missense mutation 211 of exon 1 G >T, it can cause the lysine (Ala) encoded by the 71st codon to become tryptophan (Ser).Since G >T 211 is located in the lipid binding region of the UGT2B7 gene, it can lead to the transition of lipophilicity to hydrophilicity of the UGT2B7 metabolic enzymes, which changes the activity of the UGT2B7 enzymes and thus leads to the metabolic changes of their substrates. Recent studies have shown that UGT2B7 gene polymorphisms are associated with the metabolism and prognosis of a variety of drugs, such as valproic acid, morphine, porphyrin, doxorubicin, epirubicin. etc.

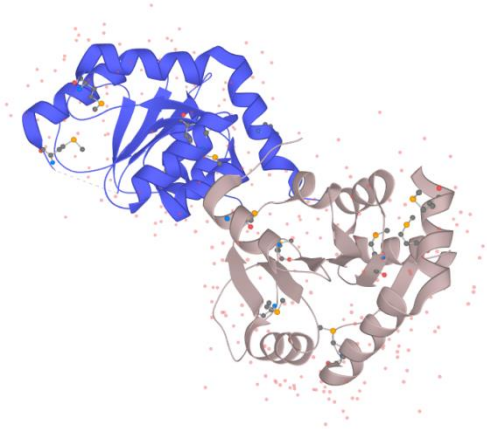

Figure 1: UGT2B7 (285-451)

2.1 Prognosis of opioid therapy

Uridine diphosphate glucuronyltransferase (UGTs) family plays a crucial role in the binding of potentially toxic drugs and endogenous compounds. Ayappa V.Subramaniam[7]propose that morphine is mainly metabolized by a phase II isoenzyme UDP-Glucuronosyltransferase-2B7(UGT2B7), which is used to metabolize morphine. The liver is the main metabolic site, and morphine is metabolized into morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).UGT2B7 is associated with mRNA expression and altered enzyme activity produced by different metabolites. polymorphisms in UGT2B7 may lead to different rates of morphine glucuronidation, leading to higher or lower levels of morphine/metabolic ratios. Genotypic differences in UGT2B7 can affect morphine metabolism to morphine-6-glucuronide and morphine-3-glucuronide, and can affect the therapeutic effect of codeine. Studies suggest that UGT2B7*2/*2 genotypes lead to reduced enzyme function and are associated with higher toxicity.[7,8]

2.2 Prognosis of amorphine therapy

Taxane metabolism and changes in reactive oxygen species and DNA repair, NR1I3 and UGT2B7 interact directly with CYP3A4, CYP3A4 is known to be involved in taxane metabolism. In particular, nr1i3 table a heterodimer and rxr, CYP3A4, of transcription activation And the interaction between proteins and UGT2B7, has a negative regulatory effect on CYP3A4 activity. Of UGT2B7 polymorphic variants found in Mariamena Arbitrio[8] studies, patients (rs7438284,rs7662029,rs7439366 and rs7668258) carrying homozygous allele variant 2 genotypes are "supermetabolites ", Therefore, UGT2B7 enzyme activity may increase taxane glucuronidation/removal, Could be ineffective, And reduce the poison-cold. Which can justify the relevant neuroprotective effects. The protective effects of NPs and NR1I3 and UGT2B7 variants in BC patients with grade 2−3 may provide genetic characteristics for outcome prediction.

2.3 Prognosis in the treatment of anthracycline

Studies have shown that [9] adjuvant chemotherapy with anthracycline can lead to cardiac toxicity events, and the incidence of cardiac toxicity events caused by anthracycline alone is about 8%.The study

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[10] by Hailietal. suggests that UGT2B7-161T allele may be a biomarker for predicting low cardiac toxicity BC patients with adjuvant chemotherapy.Wang Gang's study found that [11] incidence of visceral toxic events in HER-2 positive breast cancer patients receiving EC-TH regimen-assisted chemotherapy was 26.3%, higher than that of anthracycline or trastuzumab monotherapy. Wang Gang divided the UGT2B7—161 into TT ,CT and CC, using statistical analysis to find that homozygous carriers CC lower drug clearance ability and more significant efficacy than CT and TT carriers. This study suggests that UGT2B7-161 gene polymorphism can be used as a potential predictor of the risk of cardiac toxicity events in HER-2 positive breast cancer patients undergoing adjuvant chemotherapy with EC-TH regimen.

2.4 Nitrogen-free broad-spectrum antiepileptic drugs (valproic acid) prognosis

Valproic acid, as a histone deacetylase inhibitor, is widely used in the treatment of epilepsy and psychosis. The study suggests that UGT2B7G211T polymorphism, although its MAF is lower than plasma concentration and age, Wang [12] found that this SNP is significantly associated with regulated VPA plasma concentrations. Patients with variant genotypes (GT and TT) showed lower adjusted plasma VPA concentrations than wild-type (GG), suggesting that patients with variant genotypes may need higher doses of VPA to achieve target blood concentrations. These results may be due to the fact that G211T is an nonsynonymous SNP, which replaces amino acid 71 from alanine (aliphatic nonpolar) to serine (uncharged polarity), thus altering the physicochemical properties of this position. Treatment protocol subgroup analysis in the combined treatment model showed that UGT2B7 gene polymorphism was associated with adjusting plasma VPA concentration in epileptic patients.

3. Results

Uridine diphosphate glucuronyltransferase (UDP-glucuronosyltransferase, UGT) [4] is a detoxification and clearance pathway for many exogenous and endogenous substances. It has high biological function and is the most important enzyme in biotransformation of phase II in vivo.Recent studies have shown that the gene polymorphism of UGT2B7 has a certain correlation with the prognosis of opioids, anthracyclines, echinoids and broad-spectrum antiepileptic drugs without nitrogen, and has the potential to be used as an important indicator of clinical prognosis

4. Discussion and conclusion

Multiple studies have shown that UGT2B7 gene polymorphisms may exist through multifunctional forms of the enzyme, and they exhibit different but often overlapping substrate selectivity, leading UGT2B7 to be considered as one of the most important enzymes involved in drug gluconidization [14]. This enzyme contributes to the gluconation of many therapeutic drugs, including opioids (e.g., codeine, morphine, naloxone), anticancer drugs (e.g., epirubicin), and non-steroidal anti-inflammatory drugs (e.g., diclofenac, naproxen) [15]. However, in the research process of UGT2B7, most of the experiments were conducted by collecting whole blood samples from patients for clinical research [16]. However, because the genetic polymorphism of UGT2B7 is affected by BMI, heredity and smoking, it is difficult to exclude individual specificity. The chronic lack of pure, catalytic human uridine diphosphate glucosaldehyde carbonyl transferases (UGTs) has been an obstacle to the biochemical and biophysical study of the enzyme family associated with this disease. Although UGT2B7 from human body can be extracted and purified to homogenization by Nanodisc technology at present, and shows similar activity to microsomal UGT2B7 [17], it is difficult to be used universally due to the huge cost and high technical level requirements. Therefore, to simplify the purification methods of UGT2B7 and to further explore its important role in clinical prognosis are the directions that we need to continue to explore.

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