IOCPM 2025 Conference

The 1st International Online Conference on Personalized Medicine

29–31 October 2025 | Online

MDPI

Association of the TYMS 2R/3R Variant (rs45445694) with Chemotherapy Response in Breast Cancer Patients

Martha Patricia Gallegos-Arreola[1],Adriana Ramos-Silva[1], Ingrid Patricia Dávalos-Rodríguez[1], Josefina Yoaly Sánchez-López[1], Luis E. Figuera[1], Asbiel Felipe Garibaldi-Ríos[1, 2], Ana María Puebla-Pérez[3], Belinda Claudia Gómez-Meda[4], Guillermo Moisés Zúñiga-González[5].

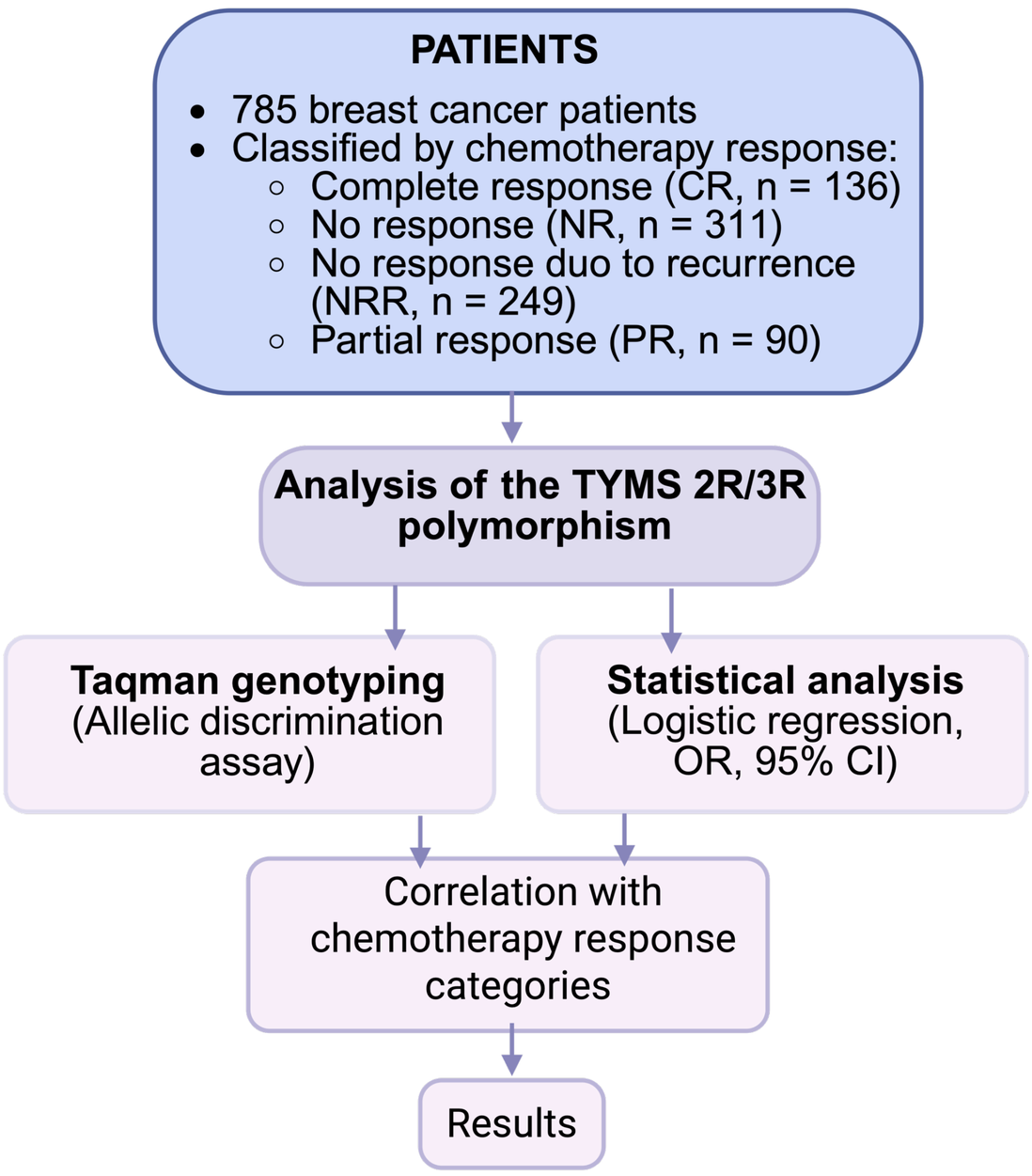
[1]División de Genética, Centro de Investigación Biomédica de Occidente, Centro Médico Nacional de Occidente, Instituto Mexicano del Seguro Social, Guadalajara 44340, Jalisco, México.[2]Centro Universitario de Ciencias de la Salud (CUCS), Universidad de Guadalajara (UdeG), Guadalajara 44340, Jalisco, México.[3]Laboratorio de Inmunofarmacología, Departamento de Farmacología, Centro Universitario de Ciencias Exactas e Ingenierías, Universidad de Guadalajara, Guadalajara, Jalisco, México. [4]Departamento de Biología Molecular y Genómica, Instituto de Genética Humana "Dr. Enrique Corona Rivera", Centro Universitario de Ciencias de la Salud (CUCS), Universidad de Guadalajara (UdeG), Guadalajara 44340, Jalisco, México. [5]División de Medicina Molecular, Centro de Investigación Biomédica de Occidente, Centro Médico Nacional de Occidente, Instituto Mexicano del Seguro Social, Sierra Mojada 800, Col. Independencia, Guadalajara 44340, Jalisco, México

INTRODUCTION & AIM

Thymidylate synthase (TYMS) is an essential enzyme in DNA synthesis and the main target of fluoropyrimidine-based chemotherapy such as 5-fluorouracil (5-FU) and capecitabine[1]. Variations in TYMS expression can influence drug efficacy and toxicity, making it a key pharmacogenetic marker. The rs45445694 (2R/3R) polymorphism, located in the 5′UTR region, alters transcriptional activit, where the 3R allele is often linked to higher TYMS expression and reduced chemotherapy sensitivity. Previous studies have shown inconsistent associations between this variant and treatment response across different populations [3,4].

This study aimed to determine the frequency of rs45445694 in Mexican breast cancer (BC) patients and evaluate its association with chemotherapy response, contributing to the identification of genetic predictors of therapeutic outcomes in this population.

METHOD



RESULTS & DISCUSSION

The 2R/3R genotype was the most frequent across all groups, especially among responders (68%), compared to 57.7% in NR, 62% in NRR, and 58% in PR. The 3R/3R genotype was more prevalent in NR (29.5%) and PR (41%) than in responders (13%). In contrast, the 2R/2R genotype was relatively uncommon, showing similar frequencies in responders (16%) and NR (12.5%), with slightly lower proportions in NRR (11%) and PR (10%). The 3R/3R genotype was significantly associated with increased risk of NR (OR=2.94; 95% CI: 1.67–5.16; p=0.0002), NRR (OR=2.57; p=0.0014), and PR (OR=4.88; p<0.00001). Conversely, the 2R/3R genotype was protective in NR (OR=0.64; p=0.045) and PR (OR=0.45; p=0.005) (Table 1).

Table 1. Distribution of *TYMS* 2R/3R genotypes and alleles according to treatment response.

Genotype	CR (n=136)	NR (n=311)	NRR (n=249)	PR (n=90)	Total (N=785)	OR (vs CR)	95% CI	p-value
2R/2R	22 (16.0%)	39 (12.5%)	27 (11.0%)	9 (10.0%)	97 (12.4%)	Reference	–	–
2R/3R	92 (68.0%)	179 (57.7%)	154 (62.0%)	52 (58.0%)	477 (60.8%)	0.64 (NR) 0.45 (PR)	0.42–0.97 0.28–0.71	**0.045** **0.000**
3R/3R	18 (13.0%)	92 (29.5%)	68 (27.0%)	37 (41.0%)	215 (27.4%)	2.94 (NR) 2.57 (NRR) 4.88 (PR)	1.67–5.16 1.44–4.58 2.51–9.47	**0.0002** **0.001** **<0.00001**
Allele 2R	136 (50.0%)	257 (41.3%)	208 (41.8%)	70 (38.9%)	671 (42.7%)	–	–	–
Allele 3R	136 (50.0%)	363 (58.7%)	290 (58.2%)	110 (61.1%)	901 (57.3%)	–	–	–

CONCLUSION

The *TYMS* rs45445694 variant influences chemotherapy response in breast cancer. The 3R/3R genotype was associated with poorer outcomes, while 2R/3R showed a protective effect. These results suggest *TYMS* genotyping could serve as a predictive marker for fluoropyrimidine response in Mexican patients.

FUTURE WORK / REFERENCES

1. Marsh S. Thymidylate synthase pharmacogenetics. Invest New Drugs. 2005 Dec;23(6):533-7. doi: 10.1007/s10637-005-4021-7. PMID: 16267625.
2. Torres RP, Santos FP, Branco JC. Methotrexate: Implications of pharmacogenetics in the treatment of patients with Rheumatoid Arthritis. ARP Rheumatol. 2022 Oct 1;1(3):225-229. English. PMID: 35724450.
3. Jennings BA, Kwok CS, Willis G, Matthews V, Wawruch P, Loke YK. Functional polymorphisms of folate metabolism and response to chemotherapy for colorectal cancer, a systematic review and meta-analysis. Pharmacogenet Genomics. 2012 Apr;22(4):290-304. doi: 10.1097/FPC.0b013e328351875d. PMID: 22388795.
4. Castro-Rojas CA, Esparza-Mota AR, Hernandez-Cabrera F, Romero-Diaz VJ, Gonzalez-Guerrero JF, Maldonado-Garza H, Garcia-Gonzalez IS, Buenaventura-Cisneros S, Sanchez-Lopez JY, Ortiz-Lopez R, Camacho-Morales A, Barboza-Quintana O, Rojas-Martinez A. Thymidylate synthase gene variants as predictors of clinical response and toxicity to fluoropyrimidine-based chemotherapy for colorectal cancer. Drug Metab Pers Ther. 2017 Dec 20;32(4):209-218. doi: 10.1515/dmpt-2017-0028. PMID: 29257755.