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GST AND MDR1 GENE POLYMORPHISMS IN CHRONIC MYELOID LEUKEMIC PATIENTS

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ABSTRACT

Chronic myeloid leukemia is a myeloproliferative neoplasm characterized by Philadelphia chromosome showing translocation 9:22(q34;q11). Many exogenous and endogenous substances lead to genetic alterations and result in development of cancer including chronic myeloid leukemia. Metabolizing Enzymes (phase1, 2 and 3) offer the first line of defense but multiple polymorphisms seen in these affect the ability of these enzymes to metabolize the carcinogens thereby increasing the individual's chance of suffering from cancer. Major gene polymorphisms are seen in Glutathione-S-Transferase family, Multi Drug Resistance Gene, Cytochrome P450 family, and recently reported Natural Killer Group Receptors Gene Polymorphism in Chronic myeloid leukemia. These gene polymorphisms also have been seen to affect individual's response totherapy. Hence it has now become essential to study this phenomenon of gene polymorphisms as it will show light on the fact as to how some individuals are more susceptible to develop cancer and why every individual has difference response to therapy in CML. This prospective will help in the treatment and follow up of these patients and give a broader picture of importance of these polymorphism in cancers like Chronic myeloid leukemia.

KEYWORDS: Chronic myeloid leukemia, Gene polymorphism, GST, MDR, Cytochrome P450.

INTRODUCTION

Chronic myeloid leukemia is one of most commonest myeloproliferative neoplasm associated with a hallmark rearrangement known as the Philadelphia chromosome formed by presence of translocation t (9;22) (q34; q11) leading to a fusion of the Abelson gene (ABL1) from chromosome 9q34 with the breakpoint cluster region (BCR) gene present on chromosome 22q11.2. The molecular consequence of this translocation is the generation of a BCR ABL1 fusion oncogene, which in turn translates into a BCR ABL1 oncoprotein. It accounts for approximately 15% of newly diagnosed cases of leukemia in adults(1). Being one of the commonest adult leukemia CML accounts for 30% to 60% of all adult leukemias(2). The disease mostly presents with increased leucocyte count, splenomegaly, myeloid hyperplasia in bone marrow and abnormally high level of mature myeloid cells in peripheral blood smear(3). Even though good documentation has been done regarding clinical and biological aspects of this disease still the aspect of individual susceptibility has been less known(4). It is proposed that genetic alterations occur on exposure to endogenous or exogenous toxic substances and hence result in development of cancers (5). One of the first line of defence against these carcinogens are the xenobiotic metabolizing enzymes which play a role in the metabolism, elimination and detoxification of the dangerous compounds which have taken entry into thebody (6).

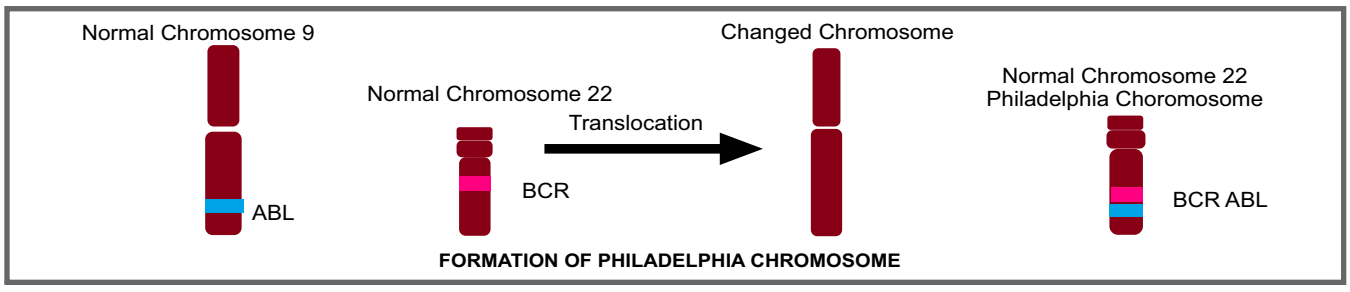

Fig 1: The Translocation Characterised By Insertion Of Abl Gene Into The Bcr Gene Leading To Fusion Of Both Genes Resulting In Defective Function Of Gene,ultimately Resulting In CML

GENE POLYMORPHISM

Genetic polymorphism can be defined as presence of two or more phenotypes which are genetically determined, in a specified population (in proportions that the rarest of the characteristics cannot be maintained just by recurrent mutation). Polymorphism promotes diversity and persists over many generations because no single form has an overall advantage or disadvantage over the others in terms of natural selection. Such gene polymorphism is also seen in many disease including Diabetes Mellitus, Parkinson Disease, Acute myeloid leukemia, Chronic Myeloid Leukemia and also involve the enzymes included in drug metabolism many others (7). Polymorphisms in coding genes of drug-metabolizing enzymes lead to alterations of the metabolism function, affect drug response, and contribute to susceptibility to cancers. These genes encode enzymes capable of catalyzing oxidative metabolism of most drugs, toxic chemicals, and other lipophilic xenobiotic (8).

Major Common Gene Polymorphisms in Chronic Myeloid Leukemia

Major Gene Polymorphisms in Chronic Myeloid Leukemia

- The Glutathione-S-Transferase family
- The Multidrug Resistance Gene
- The Cytochrome P450 family
- Natural Killer Group Receptor Gene

The Glutathione-S-Transferase Family

Glutathione-S-Transferases are a family of enzymes constituting the Phase 2 enzymes. They play major role in detoxification of xenobiotics such as pesticides, antitumoragents and environmental carcinogens. They are divided into two distinct super families: the soluble or cytosolic GSTs and microsomal GSTs. On the grounds of diversity the cytosolic GSTS are further classified as Kappa (*K*), Theta (θ), Omega (*O*), Sigma (ε),Mu (μ), Pi (π), and Zeta (*Z*) and as Alpha (α), (9).

Multiple polymorphisms seen in GST enzyme family changes drastically the ability of these enzymes to metabolize the chemical carcinogens and mutagens and hence the individual's chance of having cancer increases (10). A-G polymorphism at nucleotide 313 in exon 5 of *GSTP*1 gene was the first polymorphism to be identified which leads to an amino acid substitution of isoleucine (IIe) by valine (Val) at 105 amino acid position (Ile105Val). This polymorphism resulted in three*GSTP*1 genotypes comprising of isoleucine/isoleucine (Ile/Ile) homozygous wild type, isoleucine/valine (Ile/Val) heterozygote and valine/valine (Val/Val) homozygous variant. This *GSTP*1 codon 105 polymorphism resulted in increased DNA damage and mutation, playing a crucial role in development of cancer as it alters protein function, diminishing its detoxification ability for certain mutagens and carcinogens (11).

Nahla A. et al (2016) in their study indicated that GSTP1 mutant allele may contribute significantly to susceptibility to CML in sample of Egyptian patients (12). In a study done in Moroccan patients(M),Yaya Kassuogue et al (2015) have concluded that the GSTT1 null genotype is associated with the development of CML in males but not in females (13). In patients of Argentina, Weich N et al (2016) came to conclusion that GSTM1 is significantly linked to poor molecular response to treatment of CML. Not many studies have been done in Indian population (14). Prachi et al(2007) in their case control study done in North Indian population suggested that GSTT1 null genotype projects a 2.67 fold increased risk of CML and also signify that heritable GST status may influence the risk of developing CML (15).

Multidrug Resistance Gene

Imatinib mesylate is a first generation tyrosine kinase inhibitor which has made a paradigm shift in the treatment of CML patients (16). Second generation TKIs nilotinib, dasatinib and bosutinib are usually indicated when resistance or intolerance develops to 1st generation TKIs (16). ABCB1 multidrug resistance 1 gene(MDR1) encodes a drug efflux transmembrane protein called P-glycoprotein (P-gp) which has a major role in extruding drugs from the cells. Organs like intestine, liver, kidneys and circulating leucocytes of CML patients express the ABCB1 gene (16). MDR1 gene polymorphism isassociated to major molecular response to standard dose imatinib. However, the functional relationship between the efflux transporters and nilotinib is highly controversial and needs further studies (17).

Approximately 100 single-nucleotide polymorphisms (SNPs) are located in the coding regions of MDR1 (18). The C3435T polymorphism located in exon 26 is the most SNPs studied in various field of diseases although its frequencydepends on the ethnicities and race (19). It has been seen that the mutated allele of the haplotypes express as major structural modifications leading to conformational change in binding sites and hence the P-glycoprotein activity is diminished and altered (20).Harivansh N etal (2017) in their study suggested that C1236T and C3435T polymorphisms in MDR1 gene and trough levels significantly influence the risk of cytogenetic relapse (21). Omar

Ghallab et al (2015) came to a conclusion that C3435T and G2677T MDR1 polymorphisms might be helpful in planning individualized treatment in CML patients based on the genotype (22). Zu B et al (2014) in their study in Asian CML patients showed that MDR1 C1236T polymorphism might be a risk factor for clinical response to imatinib (23).

Cytochrome P450

Cytochrome P450 is one of the major drug metabolizing enzyme families and plays a significant role in causation as well as response to therapy incancer. Cytochrome P450, family 1, Subfamily A, polypeptide 1 (*CYP1A1*), a polymorphic gene which codes for the important Phase-I XME aryl hydrocarbon hydroxylase has been shown to be involved in drug metabolism and activation of a number of exogenous procarcinogens (24) into highly reactive electrophilic carcinogenic molecules. These electrophiles lead to mutation in tumour suppressor genes and oncogene and if not repaired leads to development of malignancies. Hence this gene plays a vital role in the development of cancerand influences theresponse of therapy. Hence, this gene may play an important role in both the etiology of cancers and as a determinant of cancer therapy response (24, 25).

Presence of A4889G in CYP1A1 initiates enhanced catalytic activity leading to increase in DNA adduct formation leading to tumour formation by causing mutations in tumour suppressor genes. This leads to uncontrolled hematopoietic cell proliferation. Individuals with sequence changes in CYP1A1 have higher risk to develop CML and other malignancies (26).

Taspinar et al (2008)(26) reported a higher distribution of *CYP1A1* Ile/Val heterozygous genotype in the Turkish CML patients (P<0.001) as compared with the controls, suggesting that carriers of *CYP1A1* Ile/Val (AG) genotype had an increased risk of developing CML. Whereas no association between the *CYP1A1*2C* polymorphism and CML risk was reported in the Iranian population (27). Also four-fold risk was seen for ALL in Indian children (28). The differences are supposedly due to differences in ethnicity, environmentalexposure, life style and habits. Samyukta et al (2015) suggested the AG genotype of *CYP1A1*2C* polymorphism may play a protective role against CML and is a good predictor to observe the response to imatinib therapy (29).

Natural Killer Group Receptor Gene

Most recent gene polymorphism suggested regarding CML is in the natural killer group 2D receptor NKG2D; also known as killer cell lectin like receptor K1 (KLRK1)gene. The translocation in CML affects the dendritic cells,hence activating NK cells by increasing the expression of NKG2D ligands(30). The expression of NKG2DL is controlled by the BCR-ABL gene. The anticancer role NK cells is directly dependent on the quantity of NKG2DL on the cellular surface with MICA being the most expressed (31, 31, and 33). Hence in CML, it is by means of the NKG2D/MICA interaction that NK cells exercise their cytotoxic role against tumor cells.

Hara R. et al (2017) in their analysis reported that NKG2D gene polymorphisms may represent patient biomarkers for the prediction of treatment free remission followingdasatinib (new TKI-2) treatment (34).

CONCLUSION

Presence of major gene polymorphisms in Glutathione-S-Transferase family, MultiDrug Resistance Gene, Cytochrome P450 family, and recently reported Natural Killer Group Receptor Gene have been seen to drastically change the susceptibility of an individual to develop Chronic myeloid leukemia. They also to much extent affect the response to therapy. It has now become imperative and challenging to study this phenomenon in larger number of CML patients from wide and varied ethnic and geographical groups (35). A better and more detailed study will be beneficial tounderstand why some individuals develop the risk of CML and also will be a major help in deciding individualized therapy in patients with CML.

REFERENCES

1. American Cancer Society. Cancer Facts & Figures. Atlanta: American Cancer Society; 2017.
2. Bhutani M, Kochupillai V. Hematological malignancies in India. In: Kumar L, editor. New York: Progress in Hematologic Oncology. The Advanced Research Foundation New York; 2003.
3. O'Dwyer ME, Mauro MJ, Druker BJ. Recent advancements in the treatment of chronic myelogenous leukemia. Annu Rev Med. 2002; 53:369-38.
4. Lordelo GS, Miranda-Vilela AL, Akimoto AK, et al. Association between methylene tetrahydrofolate reductase and glutathione S-transferase M1 gene polymorphisms and chronic myeloid leukemia in a Brazilian population. Genet Mol Res. 2012; 11:1013-1026.
5. Hishida, Asahi, Seitaro, et al. GSTT1 and GSTM1 deletions, NQO1 C609T polymorphism and risk of chronic myelogenous leukemia in Japanese. Asian Pacific journal of cancer prevention. 2005; 6:251-255.

6. Omiecinski CJ, Vanden Heuvel JP, Perdew GH, et al. Xenobiotic metabolism, disposition, and regulation by receptors: from biochemical phenomenon to predictors of major toxicities. Toxicol Sci. 2010;120 (1):49-75.
7. Ford E. B., Beer G. De, J. S. Huxley. The new systematics. Oxford: The Clarendon Press; 1940.
8. Uehara S, Uno Y, Inoue T, et al. Novel marmoset cytochrome p450 2c19 in livers efficiently metabolizes human p450 2c9 and 2c19 substrates, s-warfarin, tolbutamide, flurbiprofen, and omeprazole. Drug Metab Dispos. 2015;43: 1408-1416.
9. Mannervik B. The isozymes of glutathione transferase. Adv Enzymol Relat Areas Mol Biol. 1985; 57:357-417.
10. Taspinar M, Aydos SE, Comez O, et al. CYP1A1, GST gene polymorphisms and risk of chronic myeloid leukemia. Swiss Med Wkly. 2008; 138(1-2):12-17.
11. Dunna N.R., Vuree S., Kagita S.,et al. Association of GSTP1 gene (I105V) polymorphism with acute leukaemia. J. Genet. 2012;91: e60-e63.
12. Hamed N., Neanea H., Ghanem A., et al. Polymorphism of human organic cationic transporter1 (c480g) in egyptian chronic myeloid leukemia patients on imatinib. American Journal of Molecular Biology. 2018; 8:83-91.
13. Kassogue Y., Dehbi H., Quachouh M. Association of glutathione S-transferase (GSTM1 and GSTT1) genes with chronic myeloid leukemia. Springerplus. 2015;4: 210.
14. Weich N., Ferri C., Moiraghi B, et al. GSTM1 and GSTP1, but not GSTT1 genetic polymorphisms are associated with chronic myeloid leukemia risk and treatment response. Cancer Epidemiol. 2016.44: 16-21.
15. Bajpai P, Tripathi AK, Agrawal D. Increased frequencies of Glutathione S-transferase (GSTM1 and GSTT1) null genotypes in Indian Patients with Chronic myeloid leukaemia. Leukaemia Research. 2007;31(10):1359-1363.
16. Skoglund K, Moreno SB, Baytar M, et al. ABCB1 haplotypes do not influence transport or efficacy of tyrosine kinase inhibitors in vitro. Pharmgenomics Pers Med. 2013;6:63-72.
17. Agrawal M, Hanfstein B, Erben P, et al. MDR1 expression predicts outcome of Ph+ chronic phase CML patients on second-line nilotinib therapy after imatinib failure. Leukemia. 2014; 28: 1478-1485.
18. Yan Y, Liang H, Xie L, He Y, Li M, Li R, et al. Association of MDR1 G2677T polymorphism and leukemia risk: evidence from a metaanalysis. Tumour Biol. 2014; 35: 2191-2197.
19. Hisham B, Rosline H, Mohd R, et al. Screening for 3435C>T and 2677G>T/A polymorphisms of multi-drug resistance (MDR1) gene in malay patients with leukaemia. Malaysian Journal of Biochemistry and Molecular Biology. 2006;14:18-24.
20. Vivona D, Lima LT, Rodrigues AC, et al. ABCB1 haplotypes are associated with P-gp activity and affect a major molecular response in chronic myeloid leukemia patients treated with a standard dose of imatinib. Oncol Lett. 2014; 7: 1313-1319.
21. Harivenkatesh N, Kumar L, Bakshi S, et al. Do polymorphisms in MDR1 and CYP3A5 genes influence the risk of cytogenetic relapse in patients with chronic myeloid leukemia on imatinib therapy?. Leukemia & lymphoma. 2017;58:1-9.
22. Ghallab O, Hamed N, Shafei E, et al. MDR1 gene polymorphism and outcome in egyptian chronic myeloid leukaemia patients. J Cancer Biol Res. 2015; 3(2): 1062.
23. Bailing Z, Yajuan Li, Xin W, et al. MDR gene MDR1gene polymorphisms and imatinib response in chronic myeloid leukemia: a meta- analysis. Pharmacogenomics. 2014; 15(5): 667-677.
24. Induski JA, Lutz W. Metabolic genotype in relation to individual susceptibility to environmental carcinogens. Int Arch Occup Environ Health. 2000;73(2):71-85.
25. Oyama T, Kagawa N, Kunugita N, et al. Expression of cytochrome P450 in tumor tissues and its association with cancer development. Front Biosci. 2004; 9:1967-1976.
26. Taspinar M, Aydos SE, Comez O, et al. CYP1A1, GST gene polymorphisms and risk of chronic myeloid leukemia. Swiss Med Wkly. 2008;138(1-2):12-17.
27. Razmkhah F, Pazhakh V, Zaker F, et al. Frequency of CYP1A1*2C polymorphism in patients with leukemia in the Iranian population. Lab Med. 2011;42(4):220-223.
28. Joseph T, Kusumakumary P, Chacko P, et al. Genetic polymorphism of CYP1A1, CYP2D6, GSTM1 and GSTT1 and susceptibility to acute lymphoblastic leukaemia in Indian children. Pediatr Blood Cancer. 2004;43(5):560-567.
29. Lakkireddy, Samyuktha. Association of The Common CYP1A1*2C Variant (Ile462Val Polymorphism) with Chronic Myeloid Leukemia

(CML) in Patients Undergoing Imatinib Therapy. Cell journal. 2015;17(3):510-519.

30. Terme M, Borg C, Guilhot F, et al. BCR/ABL promotes dendritic cell-mediated natural killer cell activation. Cancer Res. 2005;65(14):6409-6417.
31. Champsaur M, Lanier LL. Effect of NKG2D ligand expression on host immune responses. Immunol Rev. 2010; 235(1): 267-285 .
32. Boissel N, Rea D, Tieng V, et al. BCR/ABL oncogene directly controls MHC Class I Chain-Related Molecule A expression in chronic myelogenous leukemia. J Immunol. 2006; 176(8):5108-5116 .
33. Coudert JD, Held W. The role of the NKG2D receptor for tumor immunity. Semin Cancer Biol. 2006; 16(5): 333-343.
34. Hara R, Onizuka M, Matsusita E, et al. NKG2D gene polymorphisms are associated with disease control of chronic myeloid leukemia by dasatinib. Int J Hematol. 2017;106(5):666-674.
35. Bănescu, Claudia. CAT, GPX1, MnSOD, GSTM1, GSTT1, and GSTP1 genetic polymorphisms in chronic myeloid leukemia: a case-control study. Oxidative medicine and cellular longevity. 2014; (2014): 875861.

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