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Non-Synonymous Snps in The Human Erbb2 Gene: Insilico Prediction and Functional Analysis

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ABSTRACT

Introduction: ERBB2 is altered by mutations and amplifications in a variety of cancer types. A small number of drugs have been approved by the Food and Drug Administration (FDA) to treat ERBB2 variants. Determining the expected impact of gene mutations and the protein-protein interactions involved in various cancer types was the aim of the in silico study, which evaluated the ERBB2 gene using bioinformatics techniques.

Methods: The single nucleotide polymorphisms (SNPs) of the ERBB2 gene were investigated in silico using the accession IDs and FASTA amino acid sequences obtained from the National Center for Biotechnology Information (NCBI). Scale-Invariant Feature Transform (SIFT), Polymorphism Phenotyping version 2 (Polyphen-2), Combined Annotation Dependent Depletion (CADD) score, meta-analytic logistic regression (MetaLR), and mutation assessor were among the bioinformatics tools utilized for the study. Protein-protein interactions were evaluated using a string database.

Results: 8298 SNPs are examined. According to SIFT analysis of the SNPs in the ERBB2 gene, 35.7% of the mutations were acceptable and 63.3% were detrimental. The Polyphen study found that 54.1% of SNPs were dangerous mutations and 45.1% were benign. According on metaLR analysis, 63.5% of the SNPs were tolerated, while 36.1% had detrimental mutations. A total of 10.8%, 33.4%, 35%, and 20.3% of the mutations were classified as high, low, medium, and neutral respectively, based on the mutation assessor tool.

Conclusion: The current in silico investigation aims to elucidate the significance of ERBB2 gene variants and their correlation with various disease states. According to our study majority of the SNPswere found to be deleterious. Future studies on pathological conditions connected to ERBB 2 may consider this analysis of detrimental nsSNPs. This study may have significant implications for precision medicine as well.

Keywords: HER-2- neu, Gene, SNPs, Computational analysis

1. INTRODUCTION

The human epidermal growth factor receptor (HER) family of receptors plays a central role in the pathogenesis of several human cancers[1]. The family is made up of four main members: HER-1, HER-2, HER-3, and HER-4, also called ErbB1, ErbB2, ErbB3, and ErbB4 respectively. Epidermal growth factor receptors (also known as ErbBs) and their ligands exist in all higher eukaryotes[2]. ERbB stands for its origin in the Erb-b gene responsible for avian erythroblastosis virus. The HER 2 neu oncogene (also known as HER2, ERBB2, or p185) was discovered by a group of scientists at Massachusetts Institute of Technology, Rockefeller, and Harvard University[3,4]. ERBBs are type 1 transmembrane proteins that have a single transmembrane helix, a ligand binding extracellular portion with four domains (I, II, III, and IV), a tyrosine kinase domain that is most closely related to Janus kinases and belongs to the same family as other receptor tyrosine kinases, and a C-terminal tail (which varies in length among family members) that has several tyrosine phosphorylation sites that act as a scaffold for adaptor molecules and enzymes to allow downstream signaling[5].

Function:

The Her2neureceptor is a proto-oncogene with intracellular tyrosine kinase activity that is found on chromosome 17q12[6]. It is unique because it does not have a known ligand that activates directly. The HER2 receptor is activated by forming homodimers or heterodimers with other ERBB family receptors particularly, it forms the most stable heterodimer with EGFR[7].Instead, HER2 is primarily activated through heterodimerization with other EGFR family members, particularly HER3 and HER4. This dimerization leads to the formation of an active receptor complex, which triggers a cascade of intracellular signaling pathways that regulate fundamental cellular processes such as cell proliferation, survival, differentiation, and migration[8,9,10,11]. Therefore, HER2 can enhance EGFR signaling and promote the continuous differentiation and proliferation of tumor cells[12]. Many tissues express HER2, and its primary function in these tissues is to promote carcinogenesis and excessive/uncontrolled cell proliferation.

ERBB2 Overexpression and Its Role in Cancer:

The HER2 gene is amplified or overexpressed in 15–30% of breast cancer situations[13]. Numerous malignancies, such as breast, colorectal, bladder, gastric, oesophageal, endometrial, and ovarian cancers, have been found to overexpress and have mutations in HER2. The treatment and treatment-associated outcomes of various tumors can be influenced by the existence of somatic mutations or overexpression that results in HER2 deregulation[14]. Apart from its role in development of various cancers, it has also been intensely evaluated as a therapeutic target.

Single nucleotide polymorphisms (SNPs):

The most basic type of DNA variation between individuals is the replacement of one nucleotide with a different one is known as Single nucleotide polymorphisms (SNPs)[15] which are residing in regulatory or functionally relevant gene regions may affect protein function[16]. SNPs are found throughout the 3 billion-base human genome, spaced between 100 to 300 bases apart. These SNPs influence both coding and non-coding regions of the genome. SNPs may modify drug interactions within the body, have no impact on cellular functions, or contribute to diseases, among various other effects[17]. Various studies on genotyping have correlated HER2 Ile655Val (rs1136201 variant) polymorphism and breast cancer risk[18,19,20]. To clarify the role of ERBB2 in the predisposition to breast cancer, we tested the association of SNPs with the disease by the help of in silico Study.

Breast cancer is one type of cancer that affects a huge number of people globally and is associated with a very high level of disability in the world. Of its many forms, overexpression and amplification of a receptor tyrosine kinase, especially ERBB2 (Her2) is crucial to tumorigenesis and other related diseases. About fifteen to twenty percent of breast cancer patients show ERBB2 amplification, and this is known to correlate with invasive tumours, greater chances of relapses and a poor prognosis. As such, ERBB2 acts as both a therapeutic target and a prognostic biomarker.

Many targeted therapies such as monoclonal antibodies like trastuzumab and tyrosine kinase inhibitors have already been sanctioned by the FDA for use against women with ERBB2 positive breast cancer. Despite these advancements, the correlation between the abnormal expression of the ERBB2 gene with the tumor immune microenvironment is still extremely unclear. Such a gap in knowledge highlights the need for more extensive exploration of the role of ERBB2 on cancer biology.

This study involves the use of in silico bioinformatics tools to analyze the SNPs, mutations and the proteins of the ERBB2 gene This research seeks to explain the involvement of ERBB2 in breast cancer and how this gene may possibly function through determining the deleterious effects of its variations on protein structure and function. Such an understanding opens up possibilities on how changes in the genetic make-up of the ERBB2 mediate the progression of breast cancer and the response to treatment, hence may provide bases for new treatment strategies.

2. MATERIALS AND METHODS:

Inclusion criteria: Data regarding the ERBB2 gene's SNPs was sourced from the NCBI database, after which the SNPs underwent analysis using bioinformatics tools such as SIFT, Polyphen, CADD, META LR, and Mutation accessor.

Exclusion criteria:SNPs for which the computational scores are not available were excluded.

Ethical Considerations: This study has no ethical concerns as the data taken from public domain.

Access SIFT at sift.jcvi.org to analyze query sequences and predict harmful substitutions using alignment information. This includes searching for related sequences for a specific protein sequence, picking closely related sequences that might share similar functions, and then combining these chosen sequences. The process involves multiple steps to determine alignments and ultimately calculate the standardized probabilities for each possible permutation. Substitutions that are intolerant or damaging are expected to happen if the normalised probability is below 0.05, while substitutions that are tolerated are expected to happen if the normalised probability is above 0.05.The SIFT technique evaluates the effect of alterations in amino acids on protein functionality. It works by exploiting the similarity in genetic sequences and amino acid properties between related genes and domains.

Evaluation of single nucleotide polymorphisms using PolyPhen.

PolyPhen-2, short for Polymorphism Phenotyping v2, utilizes basic physical and comparative rules to predict how amino acid changes impact human protein structure and function.Both the SIFT and Polyphen tools are utilized protein amino acid sequences for analysis in our study.

Combined Annotation Dependent Depletion (CADD)

CADD is a method used to assess the impact of insertions, deletions, and single nucleotide variants on the human genome. Although there are many alternative annotation and scoring systems available, most annotations typically concentrate on a particular information category (such as conservation) and/or have a limited scope of application. Therefore, there is a need for a comprehensive statistic that fairly represents multiple data points. The CADD system combines various annotations into a single metric by comparing surviving variations from natural selection with simulated mutations. C-scores provide a ranking for causal changes within certain genome sequences, which are linked to experimentally measured regulatory impacts, as well as the pathogenicity and allelic diversity of coding and non-coding variants. In GWAS, trait-associated variant C-scores were higher than control C-scores and correlated with sample size, suggesting improved accuracy in larger studies.

MetaLR

MetaLR uses logistic regression to merge allele frequency information and nine separate variant risk scores to forecast the virulence of missense variants. Different versions are classified as either "damaging" or "acceptable." Moreover, it is rated on a scale of 0 to 1, with versions scoring higher being more probable to cause harm.

Mutation assessor

Software for assessing mutations predicts how functional changes in amino acids in proteins will impact their function. This is determined by looking at how conserved the affected amino acids are in protein homologues. Protein-protein interaction was conducted utilizing the String database, with enrichment achieved through GO enrichment.

3. RESULTS:

A total of 8298 SNPs were filtered and analysed.

Table:1 SIFT analysis of SNPs of ERBB2 gene

sift_class	Frequency	Percent
Not available	2	.0
Deleterious	5281	63.3
Tolerated	3015	35.7
Total	8298	100.0

SIFT analysis of the ERBB2 gene's SNPs found that 63.3% of the mutations were harmful while 35.7% were tolerable. **(Table: 1)**

Table:2 Polyphen analysis of SNPs of ERRB2 gene

Polyphen class	Frequency	Percent
Not available	2	.0
Benign	3735	45.0
possibly damaging	1244	15.0
probably damaging	3246	39.1
Unknown	71	.9
Total	8298	100.0

According to Polyphen study, 45% of SNPs were benign mutations whereas 54.1% of them were harmful. **(Table: 2)**

Table:3 CADD analysis of SNPs of ERBB2 gene

Cadd class	Frequency	Percent
Not available	16	.2
likely benign	7373	88.9
likely deleterious	909	11.0
Total	8298	100.0

The ERBB2 gene showed 11% likely deleterious and 97.32% likely benign according to CADD scores. **(Table: 3).**

Table:4 META Lr analysis of SNPs of ERBB2 gene

Meta lr class	Frequency	Percent
Not available	37	.4
Damaging	2995	36.1
Tolerated	5266	63.5
Total	8298	100.0

On the basis of the metaLR analysis, 36.1% of the SNPs were determined to have harmful mutations, whereas 63.5% of them were tolerated. **(Table: 4)**

Table:5 Mutation assessor class analysis of SNPs of ERBB2 gene.

Mutationassessorclass	Frequency	Percent
Not available	39	.5
High	897	10.8
Low	2774	33.4
Medium	2906	35.0
Neutral	1682	20.3
Total	8298	100.0

According to the mutation assessor tool, a total of 10.8%, 33.4%, 35%, and 20.3% of the mutations were determined to be high, low, medium, and neutral. **(Table: 5)**

String data base analysis show number of nodes: 11, number of edges: 52, average node degree: 9.45, avg. local clustering coefficient: 0.958, expected number of edges: 28, PPI enrichment p-value: 4.03e-05. Network nodes represent proteins i.e. each node represents all the proteins produced by a single, protein-coding gene locus. Edges represent protein-protein associations. Eight different colored lines representing the existence of the eight different categories of evidence that were taken into consideration while predicting the linkages were drawn on an edge in evidence mode. **(Figure:1)**

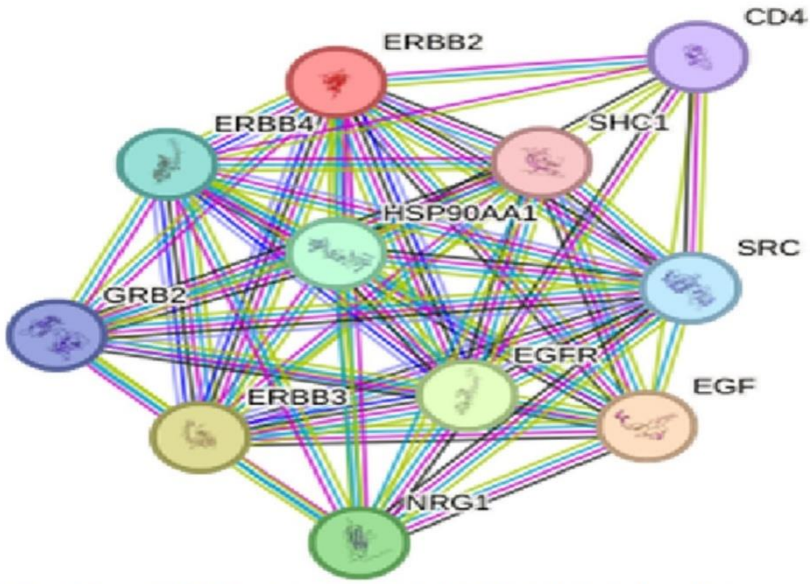

Figure:1 – protein – protein interaction by string base.

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- Navy blue line: from curated databases
- Purple line: experimentally determined
- Green line: gene neighbourhood
- Red line: gene fusions
- Blue line: gene co-occurrence
- Yellow line: textmining
- Black line: co-expression
- Light blue line: protein homology

The range of the SIFT scale is 0 to 1. When a single nucleotide polymorphism's SIFT score is less than or equal to 0.05, it is considered hazardous; when it is greater than 0.05, it is considered tolerated. 2.75 to 3.5 is the ideal range for the median information. The variety of the prediction sequences is measured in this way. A number greater than 3.25 indicates that the prediction was based on closely related sequences. The number of sequences at prediction is the number of sequences at a particular location. Since SIFT software selects sequences on its own, it may only display a limited number of sequences if the change takes place at the beginning or end of the protein, as this column illustrates.

The PolyPhen tool examined the SNPs as well. A benign mutation is indicated by a score of 0.0-0.15, probable damage is indicated by a score of 0.15 to 1.0, and certain, predicted damage is indicated by a score of 0.85 to 1.0.

4. DISCUSSION:

Despite many studies showing a correlation between SNPs in this gene and various diseases, there have been no computational studies done on the functional impacts of these SNPs. SIFT technology uses sequence homology and the physico-chemical properties of amino acid residues among related genes and domains over time to assess the impact of amino acid changes on protein function. Nevertheless, SIFT and PolyPhen are highly useful in assessing the impact of mutations on protein function and in the evaluation of gene polymorphisms using wet lab techniques. MetaLR shows the probability, ranging from "neutral," "low," "medium," or "high," in addition to the rank score, which falls between 0-1, where

higher scores suggest changes that are more likely to have adverse impacts. CADD Scores below 30 are seen as "probably not harmful," while scores above 30 are viewed as "probably harmful." It is estimated that the variants with scores > 30 will comprise 0.1% of the most detrimental potential substitutions in the human genome. The mutation assessor scale goes from 0 to 1, with higher scores suggesting greater potential for harm.

A variety of ligands, such as amphiregulin, betacellulin, epiregulin, transforming growth factor α (TGFα), heparin-binding epidermal growth factor, epidermal growth factor (EGF), and neuregulins, have the ability to activate ErbB receptors. In both healthy and pathological situations, including embryonic development, these ligands cause a wide range of ErbB receptor homo- and heterodimerization, which results in a complex cell transduction signaling[21]. This implies that even small alterations in the receptor's structure caused by single nucleotide polymorphisms (SNPs) can affect both ErbB kinase activity and the way ErbB receptor interacts with ligands, downstream partners, or inhibitors like anti-ErbB monoclonal antibodies[22].

The ERBB2 gene, recognized for its involvement in a multitude of malignancies, especially breast carcinoma, has been correlated with numerous single nucleotide polymorphisms (SNPs) that affect both cancer predisposition and therapeutic responses. Empirical studies demonstrate that the presence of both prevalent and uncommon variants in ERBB2 can profoundly influence cancer risk among diverse populations and various forms of cancer.

Key SNPs in ERBB2 and Cancer Risk are I654V and I655V Variants showing comprehensive investigation revealed the infrequent variant I654V (rs1801201) within a lineage exhibiting various cancer phenotypes, indicating an elevated cancer susceptibility (OR = 1.40) when associated with the prevalent I655V variant (rs1136201)[23]. Among Chinese females possessing a hereditary predisposition to breast cancer, the R113Q variant (c.338G>A) was detected in 6.8% of the patient cohort, a figure significantly surpassing that of controls (1.2%), thereby implying its potential function as a risk determinant[24].

The frequency of single nucleotide variants (SNV) in the ERBB2 gene across various cancers was found to be 9% in pan-cancer, with breast cancer having the highest rate at 22.4%, followed by gastric adenocarcinoma at 18.3%[25]. Variations within the ERBB family, encompassing ERBB2, have been associated with divergent reactions to trastuzumab therapy, thereby suggesting their prospective significance in the realm of personalized medicine[26].

The present in silico investigation, aimed at elucidating the significance of ERBB2 gene polymorphisms and their interactions with various disease states, strongly indicates that the deleterious consequences of mutations within this gene, alongside protein-protein interactions, significantly affect various human disorders. Although ERBB2 variants play a significant role in elucidating cancer predisposition and therapeutic effectiveness, the intricate nature of their interplay with additional genetic determinants and environmental factors continues to necessitate further investigation.

This in silico research points to the possible significance of ERBB2 polymorphisms and mutations in the clinical aspects of breast cancer pathology and possibly in the pathologies of other cancers as well. The investigation of the single nucleotide polymorphisms (SNPs) of the ERBB2 gene also served to explain the biological consequences and structural changes accompanying such alterations at the DNA level.

Genetic Landscape of ERBB2 Variations

When these results were analyzed based on CADD scores it was observed that 97.32% of the mutations were benign basing on CADD scores indicating most ERBB2 SNPs are likely not to have a major negative impact on protein function. However, the rest of the mutations 11% of the mutations that were classified as likely to be deleterious could perhaps be important in inducing changes in the shape of the protein which in turn may result in it becoming oncogenic. Even the SIFT in which 63.3% of the SNPs were classified as deleterious support the position that some other variants of ERBB2 are likely important in disrupting the normal functions of proteins. These mutations of concern are likely to affect the receptor’s signaling pathways which are vital for the growth and survival aspects that are characteristic of cancer cells.

MetaLR and PolyPhen-2 analyses presented analyses that were mutual pointers, where PolyPhen-2 suggests that 54.1% of the supposed harmful SNPs are so, while MetaLR puts 36.1% in that category. This makes them emphasize the changes in predictions as the outcome of use of more than one computational algorithm and presents the case for more than one tool use to improve evaluation. It was also valuable to note that mutation assessor tool on granules pegged at 10.8% the portion of mutations that had a high functional impact, and under this assumption of functional importance, some SNPs in ERBB2 can be considered to be oncogenic.

ERBB2 in Breast Cancer Pathophysiology

Breast tumors that are Hormone receptor positive Type 2 (HER2) have over expression of four genes that include epidermal growth factor receptor 2 and also show amplification of these four genes. This cancer is one of the most lethal and with limited treatment options until the targeted therapy approach emerged. Increase in the gene mutation of ERBB2 has the potential of increasing the kinase activity of the receptor thus altering signaling pathways identified as the PI3K/AKT and the MAPK pathways. This dysregulation encourages excessive cell division without sex-cell apoptosis while supporting a tumor micro-environment ideal for metastasis.

The conclusions of the investigation in question, especially the discovery of deleterious mutations, indicate that ERBB2

alterations may not only contribute to the development of neoplasia but also impact the relationship of the neoplasm with the immune system. Abnormal expression of ERBB2 oncogenes has been associated with mechanisms of immune suppression, including decreased expression of antigen and the enlistment of immunosuppressive cells that can limit the success of immunotherapies.

Protein-Protein Interactions and Therapeutic Implications

ERBB2 was demonstrated to be part of a network of interacting proteins through analysis, provided by the-string database, that links ERBB2 with numerous functions that include cell growth, differentiation and survival. Important interactions with proteins outline such as EGFR, ERBB3 and ERBB4 were also reported, underscoring the role played by the HER family in the regulation of complex signalling pathways. Genetic changes or therapeutics that disrupt these interactions can dramatically change how cells behave.

From a clinical viewpoint, the concern with such interactions is critical. The currently available treatments targeting ERBB2, Imo, trastuzumab and pertuzumab in particular, have shown impressive clinical effects. On the other hand, the problem of resistance to these therapies is an important issue to be overcome. The deleterious SNPs for the development of new generation drugs or drug combinations that could defeat this resistance mechanisms may be found in ERBB2. Furthermore, results of this work combined with efforts made in the field of immunotherapy may suggest ways of improving immune response in patients with breast cancer HER2+.

Conclusion and Future Directions: The current investigation justifies the importance of ERBB2 polymorphisms in the progression of breast cancer.

Rationale of the study: This study has helped in providing information on deleterious mutations as well as specific important protein conflicts that allows researchers to formulate a reasonable hypothesis of tumorigenesis and therapy resistance.

Outcome of the study: From this point on, one way to validate the results is to conduct experiments, also further studies can involve the exploration of ERBB2 in immune modulation and testing new therapies that would aim to target the effects of ERBB2 mutations. Therefore, extending the scope of the investigation is like merging heuristic predictions with experimentation, integrating such two dimensions will notably elevate the prospects of effective and personalized treatment for HER2 positive breast cancer.

Limitations of the study:

In biological analysis there are some challenges that must be considered, unjustified assumptions and poorly constructed models are some of them. All bioinformatics tools that predict certain outcomes are based on databases and algorithms, which without question do not provide complete information and understanding of protein structure and function correlations, or even the tumor microenvironment. Furthermore, this work also does not take into consideration post translational modifications nor the effect that ERBB2 could pose as a result of epigenetic factors

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