Comparison and analysis Receptor Tyrosine Kinases associated EGFR gene and its variants

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Abstract- Epidermal growth factor receptor (EGFR) is a transmembrane receptor which consists of an extracellular ligand-binding domain, a transmembrane domain and an intracellular tyrosine kinase domain. Several mutations have been resulted due to multiple factors. Patients with EFGR mutations are particularly responsive to the small molecule TKIs. Although it was observed that, the frequency of EGFR mutation is significantly higher in patients who have never smoked. Testing for mutations in EGFR is therefore an important step in the treatment-decision pathway. Several different testing methods offer a more sensitive alternative to direct sequencing for the detection of common EGFR mutations. This study involves, analysis and comparison of EFGR gene variants by using computational biology tools.

Index Terms- Mutation, intracellular receptor, gene variants, TKI.

I. Introduction

Growth factor is a naturally occurring substance or group of proteins that are involved in stimulating growth of cells and tissues. Growth factors are important for regulating a variety of cellular processes. They can actually act as signaling molecules between cells. Growth factors play an important role in promoting cellular differentiation and cell division process. Many examples includes various cytokines and hormones that bind to specific receptors on surface of their target cells. The epidermal growth factor receptor (EGFR) is a transmembrane protein of 170 kD. It consists of a N-terminus extracellular ligand-binding site, a hydrophobic transmembrane domain, and a C terminus intracellular region with tyrosine kinase activity. The downstream signaling pathways of EFGR regulate key cellular events that drive the progression of many neoplasms. Disruption of these pathways was found to cause malignant transformation [1]. Various mutations, gene amplification, and protein overexpression of multiple elements of this pathway lead to carcinogenesis.

II. Classification of EFGR

The epidermal growth factor receptor is the first of the ErbB family of receptor tyrosine kinases (RTKs) [1,2]. The other members include ErbB2, ErbB3 and ErbB4. The EGFR is activated through ligand-induced homo or heterodimerization of the receptor with other receptors of the ErbB family under physiologic conditions. But studies shown it can also be activated due to receptor over-expression, increase of EGFR gene copy number and activating mutations [3]. EGFR activation has been shown to play a key role in tumor cell proliferation, apoptosis, tumor-induced angiogenesis, metastasis, and DNA damage repair after cytotoxic insults [1,4].

The signaling process of EFGR is a complex process that requires proper regulation [5]. Signaling through the EGFR pathway is a complex process that requires tight regulation [5]. The first level of complexity is encountered at the receptor level, where multiple ligands are shared and lateral signaling occurs between members of the ErbB family. Then there are positive and negative feedback loops built into the pathways and differential activation of transcription factors, depending upon the cell type. When this tightly regulated system goes awry, it can contribute to malignant transformation and tumor progression through increased cell proliferation and prolonged survival. [6-7]

III. Role in Lung Cancer

EGFR is expressed on the cell surface of a substantial percentage of some non-small scale lung cancer. Initial studies with the EGFR tyrosine kinase inhibitors (TKIs) demonstrated biologic and clinical activity in only a relatively limited subset of lung cancers. [8] Further investigation demonstrated that the highest response rates to these TKIs were seen in patients with somatic mutations within the EGFR-TK domain, particularly exon 19 deletion, exon 21 L858R, and exon 18 G719X.[9]

IV. EGFR mutation analysis

Analysis of mutations in the gene for epidermal growth factor receptor (EGFR) indicated many mutations in all defined variants. According to previous studies, *EGFR* mutations are more commonly observed in patients with adenocarcinomas and no prior history of smoking, as well as in females and those of Asian descent. Based on the new adenocarcinoma classification, Korean researchers identified *EGFR* mutations in 50.5% of surgically resected lung adenocarcinomas in their center. Mutations were associated with the various types of carcinoma. [10-11] Studies shown data that activating *EGFR* mutations are seen in approximately 50% of Asians and 10% of non-Asians.

V. Material and Methods

The EGFR gene analysis shows its different variants. The results was obtained from gene data repository with NCBI Genbank.

VI. Map Analysis

Transcript maps were obtained through Ensemble software. http://asia.ensembl.org/Homo_sapiens/Gene/Summary?g=ENSG00000146648;r=7:55019021-55256620

Gene Orthologues

Gene orthologues was obtained from reported enteries in HGNC and NCBI gene records. http://www.genenames.org/cgi-bin/hcop?species_a=9606&species_b=all&ortholog=all&column=symbol&Search=Search&query=EGFR

EFGR gene Mutation Analysis

Various mutations were found to be associated with EFGR gene. Analysis was done using COSMIC data repository. http://grch37-cancer.sanger.ac.uk/cosmic/gene/analysis?ln=EGFR&ln1=EGFR&start=1&end=1211&coords=bp%3AAA&sn=&ss=&hn=&sh=&sys=y&fathmm=PATHOGENIC&mut=deletion_frameshift&id=150#

Protein Expression Analysis

Protein expression was analyzed from Ensemble software. **http://asia.ensembl.org/Homo_sapiens/Location/View?r=7:55173990-55174001**

VII. Results

EFGR Map

Analysis of EFGR shown its location with range: Chromosome 7: 55,173,990-55,174,00. Below is the map with known assembly.

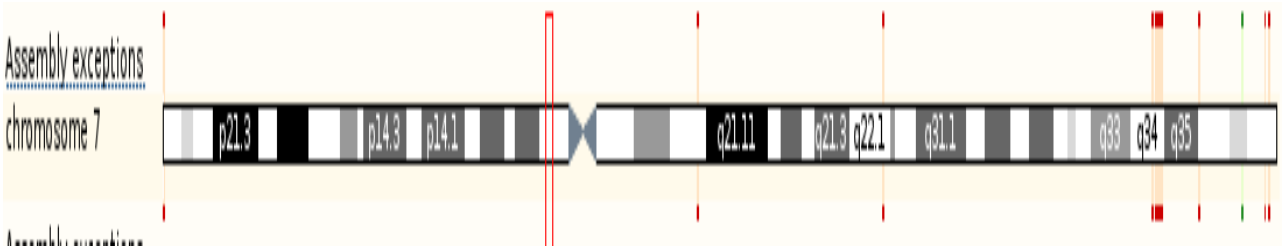

Fig: Shows Chromosome map of EFGR Human gene.

EFGR Gene Orthologues

The table below shows various EFGR gene orthologues in different species.

Gene ID	Gene Name	Description	Location
1956	EGFR	epidermal growth factor receptor *(Homo sapiens*	Chromosome 7
13649	Egfr	epidermal growth factor receptor (*Mus musculus)*	Chromosome 11
24329	Egfr	epidermal growth factor receptor [*Rattus norvegicus*]	Chromosome 14
378478	Egfr	epidermal growth factor receptor a (erythroblastic leukemia viral (v-erb-b) oncogene homolog	Chromosome 2
396494	EGFR	epidermal growth factor receptor [*Gallus gallus* (chicken)]	Chromosome 2

Mutations/Substitutions

The mutation analysis shown various substitutions. The figure below indicates the starting position from 898 and ending position as 1211.

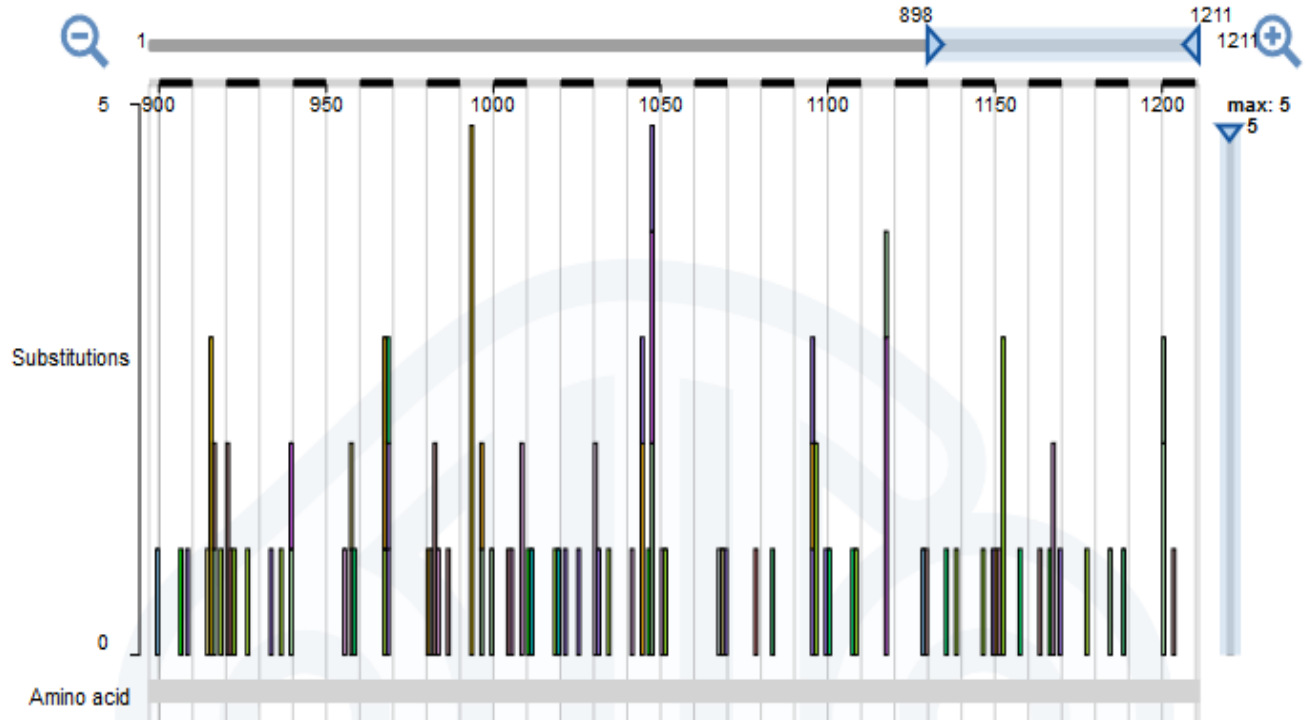

Fig: Shows substitutions starting from position 898 to 1211 in EFGR gene.

VIII. Expression Analysis

Expression studies shown various coding regions of EFGR protein with all its variants.

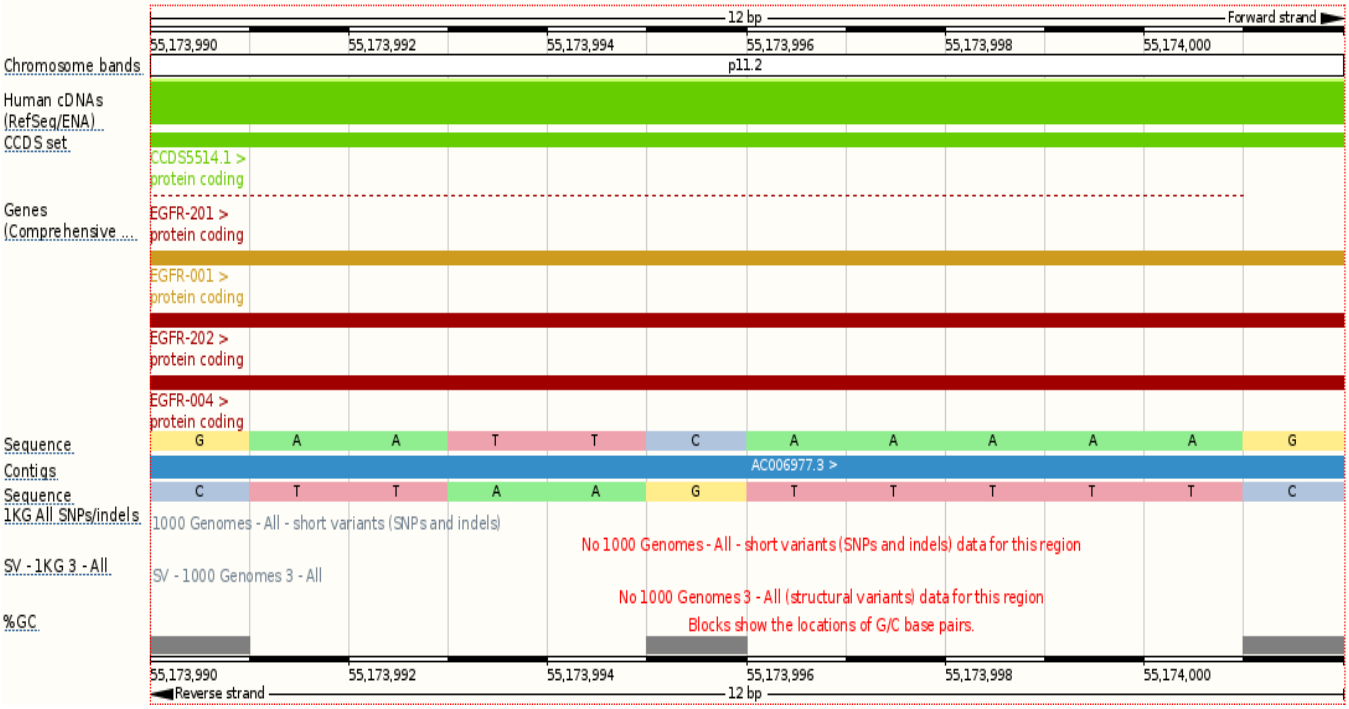

Fig: Shows Protein coding regions of EFGR gene.

IX. Discussion

Growth Factor is a protein molecule which functions to regulate various cellular processes. Growth factors can also be produced by genetic engineering in the laboratory and used in biological therapy. They bind to receptors on the cell surface, with the result of activating cellular proliferation and differentiation. They can help to promote cell growth. EGFR

blocking agents are also routinely used for treatment of metastatic colon cancer and are used with some head and neck cancers. The utility of EGFR inhibitors and their correlation with *EGFR* mutations in different types of cancers has yet to be fully established. The role of testing for certain *EGFR* gene mutations and the mutations' affect on a person's responsiveness to treatment continues to be explored. Finding mutations in EGFR is an important step in the treatment and also for decision. Hence, analysis and comparison of human EFGR, with various other variants shown different expression patterens. Also the mutation including substitutions were analyzed. This help to study their function and role in receptor ligand binding pathways.

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