ABSTRAK

ANALISIS *RHO GTP-ASE ACTIVATING PROTEIN 35* (*ARHGAP35*) PADA KANKER PAYUDARA MENGGUNAKAN PENDEKATAN BIOINFORMATIKA

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Latar Belakang: Kanker payudara merupakan kanker kedua yang paling banyak menyebabkan kematian setelah kanker paru-paru. Kanker payudara berkembang karena adanya kerusakan DNA dan mutasi genetik. Sebuah studi menyatakan bahwa *ARHGAP35* memiliki potensi sebagai *driver gene* kanker payudara, suatu gen yang mendukung pertumbuhan kanker payudara saat mengalami mutasi. Penelitian ini bertujuan untuk menganalisis peran *ARHGAP35* pada pertumbuhan dan perkembangan sel kanker payudara.

Metodologi: Penelitian ini menggunakan pendekatan secara bioinformatika. Analisis tingkat ekspresi *ARHGAP35* dilakukan menggunakan Oncomine (*fold change* > 2; *p-value* < $1E^{-4}$; *gene rank top* 10%). Analisis *overall survival* (OS) dan *disease free survival* (DFS) kanker payudara dilakukan menggunakan GEPIA (titik potong median; HR ditampilkan dengan 95% CI). Analisis jejaring interaksi protein-protein dilakukan menggunakan STRING. Analisis KEGG *pathway* dan *gene ontology* (GO) ARHGAP35 dan protein terkait dilakukan menggunakan WEBGESTALT menggunakan metode *Over Representation Analysis* (ORA). cBioPortal digunakan untuk analisis tingkat mutasi gen dengan jumlah sampel sebanyak 9502 dari 16 studi yang tersedia.

Hasil Penelitian: Hasil analisis menunjukan adanya ekspresi berlebih *ARHGAP35* pada beberapa jenis kanker payudara yaitu *invasive ductal breast carcinoma* (IDC), *invasive ductal and lobular breast carcinoma* (IDLC), *invasive lobular breast carcinoma* (ILC), *male breast carcinoma*, dan *mixed ductal and lobular carcinoma* (MDLC). Ekspresi tinggi ARHGAP35 memiliki OS yang lebih rendah secara signifikan (p = 0,045) dibandingkan dengan ekspresi rendah ARHGAP35 dan perbedaan DFS yang tidak signifikan (p = 0,98). Jejaring interaksi protein-protein yang terbentuk menggambarkan ARHGAP35 beinteraksi dengan RHOA, RHOB, RHOC, RHOD, RASA1, RND1, RAC1, CDC42, FYN dan SRC. Hasil analisis KEGG *pathway* dan GO menunjukan protein-protein tersebut banyak terlibat dalam proses berbasis aktin melalui jalur *adheren junction, axon guidance, focal adhesion, regulation of actin cytoskeleton,* dan *tight junction*. Analisis tingkat mutasi menunjukan adanya 34 *missense*, 29 *truncating,* 3 *fusion*, dan 1 *inframe* pada *ARHGAP35*.

Kesimpulan: *ARHGAP35* terlibat dalam pertumbuhan dan perkembangan kanker payudara melalui jalur pengaturan sitoskeleton aktin.

Kata Kunci: *ARHGAP35*, kanker payudara, *overall survival*, KEGG *pathway*, tingkat mutasi

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ABSTRACT

ANALYSIS THE ROLE OF *RHO GTP-ASE ACTIVATING PROTEIN 35* (*ARHGAP35*) IN BREAST CANCER BY THE BIOINFORMATICS APPROACH

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Background: Breast cancer is the second most common cause of death after lung cancer. Breast cancer develops due to DNA damage and genetic mutations. A study states that *ARHGAP35* has the potential to be a breast cancer driver gene, a gene that supports the growth of breast cancer when mutated. This study aims to analyze the role of *ARHGAP35* in the growth and development of breast cancer cells.

Methods: This study uses a bioinformatics approach. ARHGAP35 expression level analysis was performed using Oncomine (fold change> 2; p-value <1E-4; gene rank top 10%). Analysis of overall survival (OS) and disease free survival (DFS) of breast cancer was performed using GEPIA (median cutoff; HR displayed with 95% CI). Protein-protein interaction network analysis was performed using STRING. Analysis of KEGG pathway and gene ontology (GO) of ARHGAP35 and associated proteins was performed using WEBGESTALT using the Over Representation Analysis (ORA) method. cBioPortal was used for gene mutation analysis with a total sample size of 9502 from 16 available studies.

Results: The analysis showed that there was an overexpression of ARHGAP35 in several types of breast cancer, namely invasive ductal breast carcinoma (IDC), invasive ductal and lobular breast carcinoma (IDLC), invasive lobular breast carcinoma (ILC), male breast carcinoma, and mixed ductal and lobular carcinoma (MDLC). High expression of ARHGAP35 had significantly lower OS ($p = 0.045$) compared to low expression of ARHGAP35 and the difference in DFS was not significant ($p = 0.98$). The protein-protein interaction network formed described that ARHGAP35 is interacting with RHOA, RHOB, RHOC, RHOD, RASA1, RND1, RAC1, CDC42, FYN and SRC. The results of the KEGG pathway and GO analysis show that these proteins are highly involved in actin-based processes through adherent junction, axon guidance, focal adhesion, regulation of actin cytoskeleton, and tight junction. Mutation rate analysis showed 34 missense, 29 truncating, 3 fusion, and 1 inframe on ARHGAP35.

Conclusion: *ARHGAP35* is involved in the growth and development of breast cancer through regulation of actin cytoskeleton pathway.

Keywords: *ARHGAP35*, breast cancer, overall survival, KEGG pathway, mutation rate

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