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Structural and functional characterization of natural variants of G protein-coupled receptors

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G protein-coupled receptors are the largest superfamily of transmembrane receptors and have vital signaling functions in various organs. Because of their critical roles in physiology and pathology, GPCRs are the most commonly used therapeutic target. It has been suggested that GPCRs undergo massive genetic variations such as genetic polymorphisms and DNA insertions or deletions. Among these genetic variations, non-synonymous natural variations change the amino acid sequence and could thus alter GPCR functions such as expression, localization, signaling, and ligand binding, which may be involved in disease development and altered responses to GPCR-targeting drugs. Despite the clinical importance of GPCRs, studies on the genotype-phenotype relationship of GPCR natural variants have been limited to a few GPCRs such as β-adrenergic receptors and opioid receptors. Here, we analyzed the non-synonymous natural variants of all non-olfactory GPCRs available from a public database, UniProt. The results suggest that the GPCR superfamily undergoes non-synonymous natural variations at a high frequency especially in the N-terminus and TM domains. However, our analysis also suggests that only a few non-synonymous natural variations have been studied in efforts to link the variations with functional consequences. Therefore, we propose to provide insights into understanding the correlation between cellular function, structure and genetic variations.

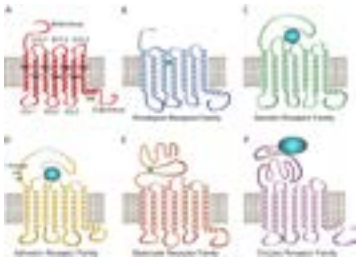

Figure1: *General description of the five families of GPCRs.*

(A) The structural domains of GPCRs. (B-F) Representations of the conserved and various features of the Rhodopsin (B), Secretin (C), Adhesion (D), Glutamate (E), and Frizzled (F) families

Biography

Hee Ryung Kim is doing her PhD in Sungkyunkwan University in Korea. Her interest is to study conformational dynamics of G protein-coupled receptors and its downstream signaling molecules using Hydrogen/Deuterium Exchange Mass Spectrometry. So far, she has been analyzing conformational dynamics of various GPCR-G protein complexes and β-arrestin mutants. Her goal is to elucidate the molecular mechanism of G protein-dependent and independent signaling pathways *via* structural comparison between GPCR-G protein and GPCR-arrestin complexes. As structure plays a key role in protein function, her studies will provide the fundamental information of G protein and arrestin activation. In addition, it may contribute to the development of selective drug with fewer side effects, as an example of Structure-Based Drug Design.

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