J. Chosun Natural Sci.
Vol.16, No.1 (2023) pp.33-38
https://doi.org/10.13160/ricns.2023.16.1.33

Three-Dimensional Structure Prediction of Follicle-Stimulating Hormone Receptor Transmembrane Domain by Homology Modelling

Priya dharshini B†

Department of Medical Genetics, Chettinad Hospital and Research institute, Kelambakkam, 603103, Chengalpattu District, Tamilnadu, India.

Abstract

The follicle stimulating hormone receptor (FSHR) is a glycoprotein hormone, that belongs to the GPCR superfamily. FSHR plays a major role in reproduction. The aberrant activation of FHS receptor leads to infertility and several reproductive disorders. The recently recognized roles of the FSHR in diverse extragonadal tissues is also closely related to Alzheimer's disease and cancers. Analysing the structural characteristics of the receptor is important in understanding the pathophysiology of diseases associated with the receptor. In this present study, homology modelling of FSHR-TM domain was developed using four different templates. Totally 20 models were developed using single template-based approach and selected three based on the validation of RC plot, RMSD, ProSA, QMEAN and ERRAT values. The developed models would be useful for further research on the structural characteristics and binding characteristics of the FSHR-TM domain.

Keyword: FSHR, Homology Modelling, GPCR

(**Recceived** February 28, 2023; **Revised** March 20, 2023; **Accepted** March 21, 2023)

1. Introduction

The follicle stimulating hormone receptor (FSHR) is a glycoprotein hormone, that belongs to the GPCR superfamily. The Glycoprotein hormone receptor also comprises of luteinizing hormone receptor (LHR/LHCGR) and thyroid-stimulating hormone receptor (TSHR). Follicle stimulating hormone is secreted by the pituitary glands, which promotes the maturation of ovarian follicles, the generation of oestrogen, and the process of spermatogenesis[1-2]. FSHR is characterized by the presence of extracellular N-terminal domain, where its corresponding ligand is recognised and bound. The N-terminal domain of the receptor links the seven transmembrane domains (TMD) with C terminal internal domain[3]. The binding of FSH to its receptor causes conformational changes that result in the transduction of intracellular signals. These changes include the dissociation of G protein complexes into their component parts and the activation of a number of related interacting partners that

† Corresponding author: priyamedigen@gmail.com

cooperatively regulate downstream effectors[4]. Mutation in FSH receptor shows the abnormal signalling that can lead to the significant illnesses, female infertility and reproductive disorders[4]. FSHR is a key therapeutic agent utilised in the treatment of reproductive disorders so targeting FSH receptor will be helpful in understanding the signalling mechanisms[5] The structure of full length FSH receptor is not available, so modelling of Transmembrane domain will be useful in the development of novel therapeutic approaches.

Homology modelling provides the quick method of determining the three-dimensional structure of a protein using sequence data. Since there is no crystal structure available for FSHR- TM domain, single template-based homology modelling was used to develop the structure. In this study we have developed 20 models for FSHR-TM domain and validated with the help of the Ramachandran plot, RMSD, ProSA, QMEAN and ERRAT values. The developed models would be useful for further research on the structural characteristics and binding characteristics of the FSHR-TM domain[6]

2. Materials and methods

2.1. Template selection

The amino acids sequence of human Follicle-stimulating hormone receptor (accession No: P23945) was retrieved from Uniprot. To obtain appropriate templates for modelling the receptor, protein BLAST search against PDB was performed[7] Four distinct templates were chosen based on the sequence identity, query coverage, and E-value. Up to 90% of the polypeptide conformation is prone to being accurately modelled if the amount of sequence identity is greater than 30%. Sequence identity for the selected template was > 30%. We carried out single template-based homology modelling since the identities of the templates were above 30% (Table 1). The selected templates have query coverage of more than 70% and maintained a seven transmembrane domain[7].

2.2. Model generation and Validation of FSH Receptor

The three-dimensional structures of FSH Receptor were modelled using EasyModeller 4.0[8]. Four different templates were used to model the selected protein by using single templated based approach[6]. Twenty models of FSH were generated and validated by Ramachandran plot and ERRAT by SAVES server[9]. The total number of amino acid residues discovered in the favourable, permitted, and prohibited regions is shown by Ramachandran plot. The ERRAT plot was used to calculate the structural error at each amino acid residue in the 3D structural model[10]. The model was further validated by RMSD, ProSA and QMEAN. ProSA is used to detect errors in the protein's three-dimensional structure[11]. QMEAN servers was used to compute the QMEAN score, to assess the model's quality[12].

3. Results and Discussion

3.1 Template Selection

To identify the templates for FSHR protein structure modelling, a BLAST search against the Protein Data Bank (PDB) was performed. Four templates were chosen to model the protein, which include PDB IDs: 7FII, 7XW7,

7UTZ, and 7XW5. The primary criterion for choosing templates for homology modelling is sequence similarity[7]. All the selected templates have sequence identity >40%, query coverage >80% and have seven trans-membrane helices belongs to G-protein-coupled receptors.

3.2. Model Generation and Validation

Easy Modeller 4.0 was used to model the selected protein FSHR-TM domain. 20 models were developed using four templates[8]. The models were validated using different techniques such as RMSD, Ramachandran plot, PROVE, ERRAT plot, QMEAN score, and ProSA[11-12]. Table 2. represents the all the validation results. The optimal model was chosen based on the low RMSD, a high number of residues in preferred and authorised regions, and a high ERRAT quality rating. Model 2, 10 and 16 were selected based on the validation. The selected model was represented in Fig. 1. Fig. 2 represents the RC plot and ERRAT plot was represented by Fig. 3. The ERRAT plot for the selected models was found to be 84.23%, 93.07% and 90.76%[10]. The selected model scored well in the validation and also resembles the seven transmembrane helices.

4. Conclusion

Three dimensional models for follicle stimulating hormone receptor (FSHR) were developed using single template-based approach. Models developed using 7FII, 7XW7 and 7XW5 are found to be consistent. Furthermore, these models could be used for binding site analysis and docking, which could help with rational drug design for FSHR related diseases

Fig. 1. Selected models for FSH Receptor.

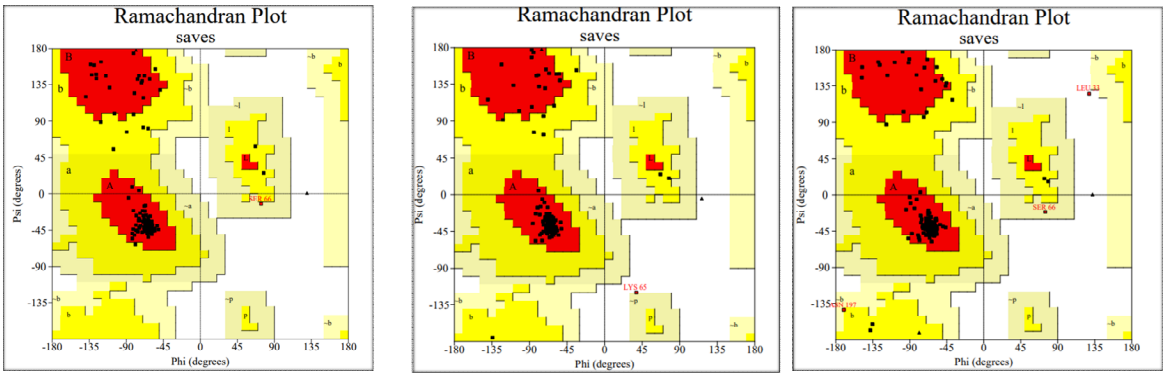

Fig. 2. Ramachandran plot for the selected models.

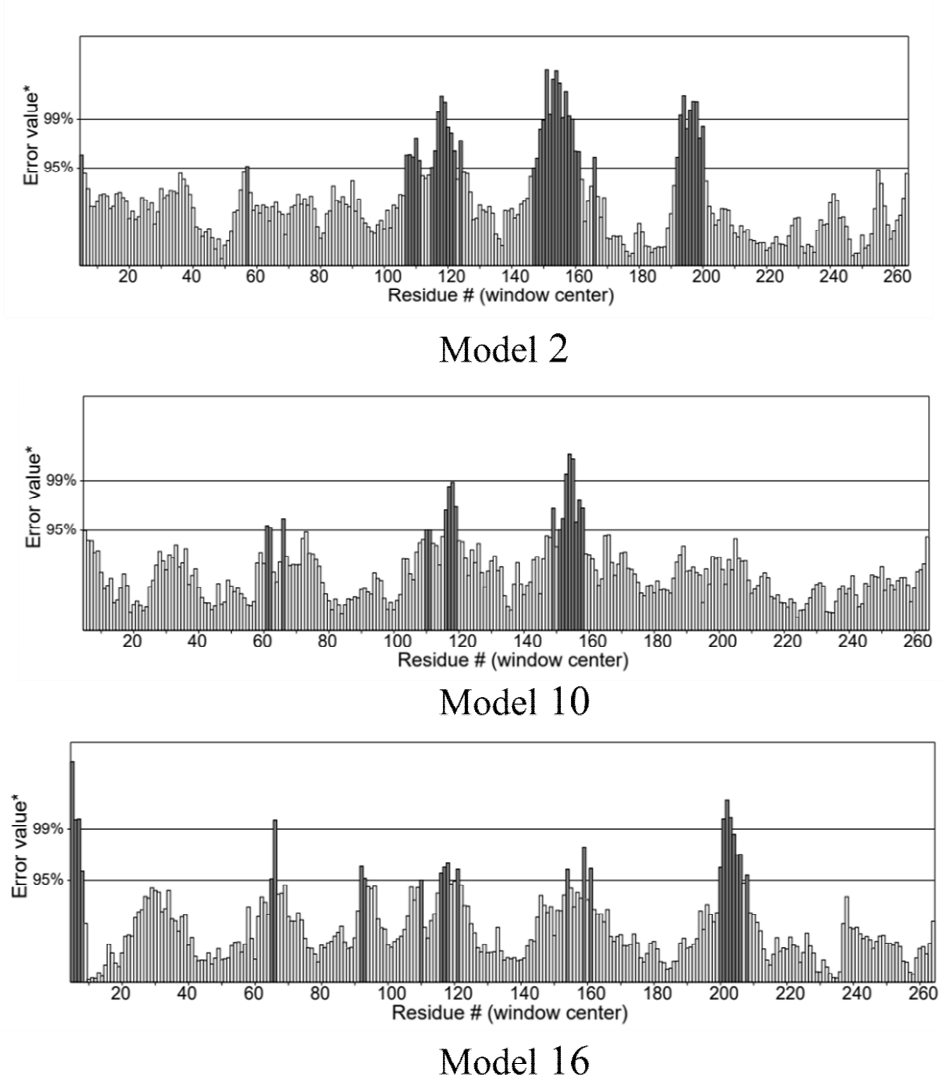

Fig. 3. ERRAT plot for the selected models.

Table. 1. The query coverage and identity values of the templates

PDB ID	Max Score	Total score	Query Coverage %	E Value	Sequence Identity %
7FII	699	699	88%	0.0	56.13 %
7XW7	658	658	92 %	0.0	51.62%
7UTZ	657	657	92 %	0.0	51.62%
7XW5	655	655	92 %	0.0	51.47%

Table. 2. Validation of the generated models using SAVES server

MODEL	TEMPLATE PDB ID	RAMACHANDRA PLOT NUMBER OF RESIDUES IN			ERRAT - overall quality factor	QMEAN global score	ProSA web Z - score Overall model quality	RMSD
		Favoured%	Allowed%	Disallowed%				
1.	7FII	96.0	4.0	0.0	82.69	-3.50	-3.95	0.102
2.	**7FII**	**95.2**	**4.4**	**0.0**	**84.23**	**-3.44**	**-3.99**	**0.134**
3.	7FII	96.4	3.6	0.0	83.84	-3.49	-3.87	0.097
4.	7FII	96.4	3.2	0.0	86.53	-3.40	-3.93	0.160
5.	7FII	95.6	4.4	0.0	80.76	-3.21	-4.01	0.121
6.	7XW7	95.2	4.0	0.0	89.61	-3.32	-3.93	0.107
7.	7XW7	96.0	3.6	0.0	87.30	-2.71	-5.05	0.094
8.	7XW7	96.0	3.6	0.0	84.23	-2.71	-5.02	0.106
9.	7XW7	97.2	2.4	0.0	79.23	-3.01	-5.09	0.090
10.	**7XW7**	**97.2**	**2.4**	**0.4**	**93.07**	**-2.74**	**-5.03**	**0.083**
11.	7UTZ	97.2	2.4	0.4	87.30	-2.97	-5.03	0.146
12.	7UTZ	97.2	2.4	0.0	90.38	-2.62	-5.09	0.113
13.	7UTZ	96.8	2.0	0.4	92.30	-2.78	-4.89	0.095
14.	7UTZ	96.4	3.2	0.0	88.46	-2.53	-4.98	0.091
15.	7UTZ	96.4	2.8	0.4	89.23	-2.79	-5.06	0.093
16.	**7XW5**	**95.6**	**3.2**	**0.4**	**90.76**	**-3.33**	**-4.79**	**0.134**
17.	7XW5	96.0	3.2	0.0	79.23	-2.98	-4.80	0.114
18.	7XW5	95.6	3.2	0.0	85.38	-3.53	-5.03	0.133
19.	7XW5	96.8	2.4	0.0	81.92	-2.79	-4.97	0.112
20.	7XW5	94.8	4.8	0.0	87.30	-2.72	-4.94	0.114

References

[1] Anderson RC, Newton CL, Millar RP. Small Molecule Follicle-Stimulating Hormone Receptor Agonists and Antagonists. Front Endocrinol (Lausanne) 2018;9:757.

[2] Yanofsky SD, Shen ES, Holden F, Whitehorn E, Aguilar B, Tate E, et al. Allosteric activation of the follicle-stimulating hormone (FSH) receptor by selective, nonpeptide agonists. J Biol Chem 2006;281(19):13226-33.

[3] Nataraja SG, Yu HN, Palmer SS. Discovery and Development of Small Molecule Allosteric Modulators of Glycoprotein Hormone Receptors. Front Endocrinol (Lausanne) 2015;6:142.

[4] Ulloa-Aguirre A, Zariñán T, Jardón-Valadez E, Gutiérrez-Sagal R, Dias JA. Structure-Function Relationships of the Follicle-Stimulating Hormone Receptor. Front Endocrinol (Lausanne) 2018;9:707.

[5] Ulloa-Aguirre A, Reiter E, Crépieux P. FSH Receptor Signaling: Complexity of Interactions and Signal Diversity. Endocrinology 2018;159(8):3020-35.

[6] Santhosh Kumar Nagarajan, Thirumurthy Madhavan. 3D Structure Prediction of Thromboxane A2 Receptor by Homology Modeling. J. Chosun Natural Sci.Vol. 8, No. 1 (2015) pp. 75 – 79.

[7] Altschul SF, Gish W, Miller W, Myers EW, Lipman DJ. Basic local alignment search tool. J Mol Biol 1990;215(3):403-10.

[8] Kuntal BK, Aparoy P, Reddanna P. EasyModeller: A graphical interface to MODELLER. BMC Res Notes 2010;3:226.

[9] Pontius J, Richelle J, Wodak SJ. Deviations from standard atomic volumes as a quality measure for protein crystal structures. J Mol Biol 1996;264(1):121-36.

[10] Colovos C, Yeates TO. Verification of protein structures: patterns of nonbonded atomic interactions. Protein Sci 1993;2(9): 1511-9.

[11] Wiederstein M, Sippl MJ. ProSA-web: interactive web service for the recognition of errors in three-dimensional structures of proteins. Nucleic Acids Res 2007;35 (Web Server issue):W407-10.

[12] Benkert P, Tosatto SCE, Schomburg D. QMEAN: A comprehensive scoring function for model quality assessment. Proteins 2008;71(1):261-77.