Mutation Prone Point in Progesterone Receptor

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Abstract

Progesterone is an important female hormone. A disorder at progesterone receptor (PR) is a condition that relate to the many female specific disorders. This steroid hormone receptor plays a critical role in the development of breast cancer. Mutation within PR can be seen. Presently, prediction of protein nanostructure and function is a great challenge in the proteomics and structural genomics era. To identify the point vulnerable to mutate is a new trend to expand the knowledge on disorders in genomic and proteomic level of diseases. Here, the author performed a bioinformatics analysis to study the determine positions that tend to comply peptide motifs in the amino acid sequence of PR. To identify the weak linkage in PR, a new bioinformatics tool namely GlobPlot was used. According to this work, the positions resist to mutation are identified. Based on this study, the weak linkages in the PR can be identified and can be good information for the prediction of possible new mutations that can result in phenotype abnormality. In addition, the results from this study can be good information for further research on the diagnosis PR abnormalities and new treatment.

Keywords: progesterone, receptor, weak linkage, mutation

Özet

Progesteron Reseptöründe Mutasyona Açık Nokta

Progesteron önemli bir kadınlık hormonudur. Progesteron reseptöründeki bir bozukluk, pek çok sağlık sorunu ile ilişkili bir durum oluşturmaktadır. Bu steroid hormon reseptörü, meme kanseri gelişiminde kritik rol oynamaktadır. Bazı klinik durumlarda progesteron reseptöründe mutasyon gözlenebilmektedir. Günümüzde protein nanoyapısının tayini ve fonksiyonu proteomik ve yapısal genetik alanının önemli ilgi alanıdır. Mutasyona hassas noktayı tanımlamak, hastalıkların genomik ve proteomik seviyesini belirlemek hastalık konusundaki bilgilerin artmasına yönelik izlenen yeni eğilimdir. Bu yazıda, araştırmacı progesteron reseptöründe aminoasit motiflerinin pozisyonlarını tayin edecek biyoinformatik analize gitmiştir. Bu amaçla, progesteron reseptörlerinde zayıf bağı tayin etmek için 'GlobPlot' adında yeni bir biyoinformatik araç kullanılmıştır. Bu çalışmaya göre mutasyona dirençli noktalar belirlenmiş, zayıf bağlar tanımlanabilmiş ve fenotipte farklılık yaratabilecek yeni mutasyonlar hakkında yeni bilgiler edinilmiştir. Ayrıca, bu çalışma, progesteron reseptör anormallikleri ve bunların tedavilerine ışık tutulabilir.

Anahtar sözcükler: progesteron, reseptör, zayıf bağlantı, mutasyon

Introduction

Progesterone is an important female hormone. It has a lot of meaning in gynecology and obstetrics. The ovarian steroid hormone progesterone is a major regulator of uterine function (1). The action of this hormone is mediated through its cognate receptor, the progesterone receptor (1). A disorder at progesterone receptor (PR) is a condition that relate to the many female specific disorders. This steroid hormone receptor plays a critical role in the development of breast cancer (2). Most importantly, the expression PR by tumor cells provides important information that is critical for the selection of treatment (2).

PR gene has been limited studied in clinical conditions. Pathological alterations of PR structure and function are major cause of progesterone insensitivity in female and a possible underlying of the breast cancer (3,4). Gao et al. proposed that the mutation or aberrant expression of this steroid receptor co-regulator would affect the normal function of the sex steroid receptors and hence may participate in the development and progression of the cancers (5). Analysis on the PR in depth helps better understand the pathogenesis of progesterone receptor disorder. The prevalence of mutations in

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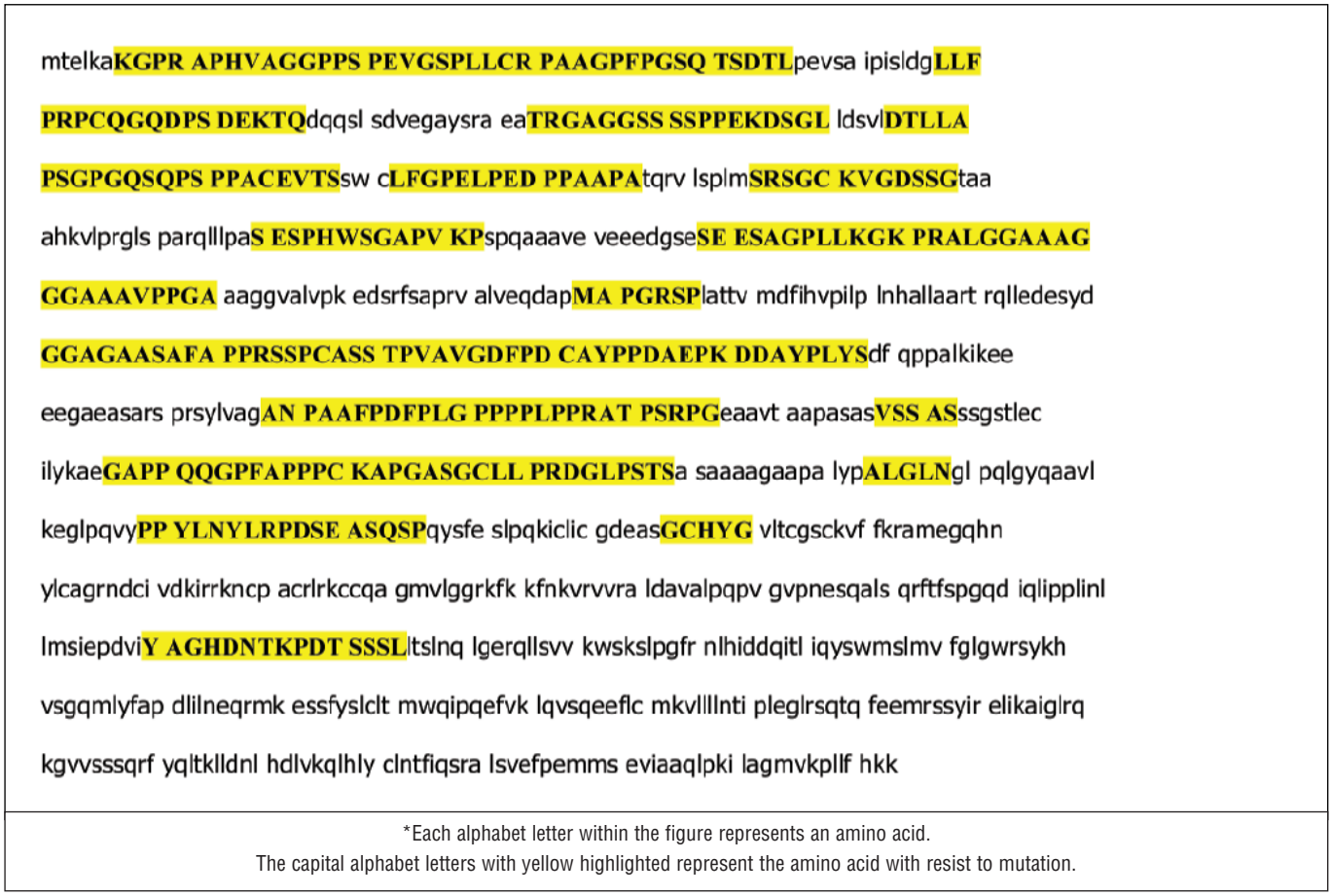
the progesterone receptor gene is not exactly known. Analysis for PR mutated prone points is the first step for further research on the PR mutation. The next step is the study the functional characterization.

Materials and Methods

Presently, prediction of protein nanostructure and function is a great challenge in the proteomics and structural genomics era. To identify the point vulnerable to mutate is a new trend to expand the knowledge on disorders in genomic and proteomic level of diseases (6,7). Generally, disordered regions in proteins often contain short linear peptide motifs that are important for protein function. Identification of the peptide motifs in the amino acid sequence can give a good prediction for the weak linkages in a protein (6,7). Fortunately, this analysis is possible based on the advancement of bioinformatics. Here, the author performed a bioinformatics analysis to study the determine positions that tend to comply peptide motifs in the amino acid sequence of PR.

The database Expert Protein Analysis System (ExPASy) (8) was used for searching for the amino acid sequence of PR. Briefly, the ExPASy is a proteomics server of the Swiss Institute of Bioinformatics (SIB) dedicated to the analysis of protein sequences and structures as well as 2-D PAGE (8). ExPASy also poses a curated protein sequence database which strives to provide a high level of annotation (such as the description of the function of a protein, its domains structure, post-translational modifications, variants, etc.) (8). Then the derived sequences were used for further study on weak linkage.

To identify the weak linkage in PR, a new bioinformatics tool namely GlobPlot (9) was used. Briefly, GlobPlot is a web service that allows the user to plot the tendency within the query protein for order/globularity and disorder (9). The input query protein in this work is the previous derived PR amino acid sequence. The interface is straight forward to use, the user can paste a sequence or enter the SWISS-PROT/SWALL accession or entry code (9). The GlobPlot server fetches the sequence and description of the polypeptide from an ExPASy server using Biopython.org software (9). Putative globular and disorder segments are selected using a simple computational algorithm for determination, putative globular and disorder segments are selected using a simple peak finder algorithm known as PeakFinder (9). PeakFinder enables flexible, automated identification and annotation of binding peaks in query data. The peaks are chosen when the first derivative shows positive (disorder) values over a continuous stretch of the minimum length (9). With the described process, it successfully identifies inter-



*Each alphabet letter within the figure represents an amino acid.
The capital alphabet letters with yellow highlighted represent the amino acid with resist to mutation.

Figure 1. Identified positions (in capital) that comply peptide motifs peptide motifs in amino acid sequence of PR.

domain segments containing linear motifs, and also apparently ordered regions that do not contain any recognized domain (9). The output is manipulated sequence with identified motifs or weak linkages, which are any positions in a protein which are prone for mutation. Each identified position can be clinical important mutated point. The identified motifs are the weak linkages in a protein which are prone for mutation (6,7). In this work, PR (NP_000917) was used for further study. The identified motifs are presented in Figure 1. The positions 7-45, 58-75, 93-110, 116-138, 142-156, 166-177, 200-212, 229-260, 289-295, 331-378, 409-435, 448-452, 467-499, 514-518, 539-555, 576-580, 700-714 are identified as the motif positions which are resist to mutation.

Results

Identification of the mutation points within PR can be useful for further researches to understand the pathogenesis of progesterone disorder. However, the finding on the mutation points with classical in vitro experiments requires a long time and bases on the low possibility to get the positive case. To solve this problem, the advance bioinformatics technology can be applied (10). In this work, the author used an algorithm to identify the position in the amino acid sequences of PR that can be mutated. This is a study by computational medicine technique. There is no need for human subjects and this in silico study required no ethical committee approval. The standard protein database tool ExPASy was use for data mining. This tool was verified as a high reliable database (11). For searching of the mutation, the GlobPlot was used. This new technique is acceptable and used for identification of mutation in globins in a previous research (12). A reliable result can be derived (12,13).

Discussion

In this work, the author can identify many positions. Some are known positions and the others are newly discovered. Based on this study, many weak linkages in the PR can be identified and can be good information for the prediction of possible new mutations that might result in phenotype abnormality. With a low prevalence of low predictability in terms of phenotype expression based on the data of mutation prone positions of PR, further translational application of the finding should be mentioned. Huse et al. observed that a PR deleted of its entire amino domain was incapable of transrepressing glucocorticoid receptor, suggesting that a negative modulation domain should be contained in the region between position 165 and 538 (14). Of interest, there are also a number of identified mutated prone points in the mentioned region in this study. This can confirmed the clinical important of the GlotPlot determined results in this work. In our hands, transrepression of estrogen receptor could not be substantiated, and, under our conditions, at least an equimolar concentration of PRA expression plasmid is required for transrepression. The mutant analysis data in this study will be useful for further functional characterization prediction, which can be presently performed by gene ontology technology technique (15,16). The functional significance of identified mutation-resisting locations should also be further tested on its possible functional characterization. A further research on this area is recommended.

Declaration on conflict of interest

The author hereby would like to declare for no confliction of interest in this work.

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