ISSN 1682-296X (Print)
ISSN 1682-2978 (Online)

Bio Technology

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

OPEN ACCESS Biotechnology

ISSN 1682-296X
DOI: 10.3923/biotech.2024.1.8

Research Article
Targeting the GLP-1 Receptor in Diabetes Therapy: Insights from a Genetic Perspective

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Abstract

Background and Objective: This study aims to elucidate the genetic underpinnings of GLP-1 receptors, which are pivotal in glucose metabolism regulation. By exploring the evolutionary conservation and structural domains of GLP-1 receptors, the research seeks to underscore their therapeutic potential in diabetes management. **Materials and Methods:** Employing protein sequence alignments and phylogenetic tree analysis, the study investigates the evolutionary trajectory and structural intricacies of GLP-1 receptors across different species and tissues. The experimental design focuses on the comparative genomic approach, while statistical analysis is applied to assess the significance of the findings in the context of diabetes therapy. **Results:** The study revealed a high degree of evolutionary conservation of GLP-1 receptors, highlighting their vital role across species. The structural analysis of GLP-1 receptor domains further clarifies their importance in mediating glucose metabolism. Most notably, the research identifies specific characteristics of GLP-1 receptors that could enhance the efficacy of GLP-1 receptor agonists in diabetes treatment, presenting a compelling case for these receptors as viable therapeutic targets. **Conclusion:** The comprehensive genetic analysis of GLP-1 receptors presented in this study reinforces the concept of utilizing GLP-1 receptor agonists in diabetes therapy. The findings provide valuable genetic insights that could significantly inform and improve the development of targeted diabetes treatments, advocating for a genetic perspective in the ongoing quest for effective diabetes management solutions.

Key words: GLP-1 receptor, phylogeny, *in silico*, laboratory animals, diabetes therapy, genetic analysis

Citation: Tolba, E.A.E.H.T. and H.Z.A. Amer, 2024. Targeting the GLP-1 receptor in diabetes therapy: Insights from a genetic perspective. Biotechnology, 23: 1-8.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The Glucagon-Like Peptide-1 (GLP-1) receptor is a crucial component in the regulation of glucose metabolism and has garnered significant attention for its role in the pathophysiology and treatment of Type 2 Diabetes Mellitus (T2DM)[1,2]. Belonging to the class B family of the G Protein-Coupled Receptors (GPCRs), the GLP-1 receptor is primarily expressed in pancreatic β-cells but it is also found in the brain, heart, kidney, stomach and vascular endothelium, indicating its diverse physiological roles[3,4].

The GLP-1, a hormone produced in the intestines in response to food intake, binds to the GLP-1 receptor on pancreatic β-cells, stimulating insulin secretion in a glucose-dependent manner[5,6]. This process is crucial for lowering postprandial blood glucose levels[7]. The receptor is also expressed in other tissues, including the brain, heart and gastrointestinal tract, where it contributes to a range of metabolic effects, such as inhibiting glucagon secretion, delaying gastric emptying and promoting satiety[5,8].

Genetic variations in the GLP-1 receptor gene, including Single Nucleotide Polymorphisms (SNPs) and mutations can alter receptor expression, ligand binding affinity and signal transduction efficiency[9]. These alterations can lead to variations in the therapeutic efficacy of GLP-1 receptor agonists, differences in susceptibility to developing diabetes and variations in the progression of the disease among individuals.

Activation of the GLP-1 receptor by its endogenous ligand, GLP-1-a peptide hormone secreted by the intestinal L cells in response to nutrient ingestion-triggers a cascade of intracellular signaling events that enhance glucose-dependent insulin secretion, inhibit glucagon release and promote satiety[10]. These actions collectively contribute to the reduction of postprandial glucose levels. Beyond its glycemic control, GLP-1 receptor activation has been linked to a range of beneficial effects on cardiovascular health, including improvements in blood pressure, lipid metabolism and cardiac function, as well as promoting weight loss by decreasing appetite and food intake[11].

The therapeutic potential of GLP-1 receptor agonists has been extensively explored, leading to the development of several synthetic agonists that mimic the action of endogenous GLP-1. These pharmacological agents have proven effective in improving glycemic control in T2DM patients, with additional benefits in weight management and cardiovascular risk reduction[12]. Moreover, research continues to unveil novel aspects of GLP-1 receptor signaling pathways, offering insights into the complex interplay between metabolism and chronic diseases and highlighting the receptor as a promising target for future therapeutic interventions.

To compare and align the sequences of the GLP-1 receptor from humans with various species to identify the most suitable animal model for studying the effects of GLP-1 receptor antagonists in diabetes management.

The primary purpose of this study was to conduct an in-depth genetic analysis of GLP-1 (Glucagon-Like Peptide-1) receptors to elucidate their role and evolutionary conservation in glucose metabolism regulation. This investigation aims to uncover the structural and functional domains of GLP-1 receptors that are critical for their therapeutic action in diabetes management. By examining the genetic and evolutionary aspects of these receptors, the study seeks to highlight their potential as viable targets for diabetes therapy, specifically through the use of GLP-1 receptor agonists. Ultimately, this research endeavors to provide a genetic framework that could inform and enhance the development of novel diabetes treatments, contributing to improved management strategies for this chronic disease.

MATERIALS AND METHODS

Study duration and location: The study was conducted at the Faculty of Science, Jazan University, within the Biology Department, located in Saudi Arabia. The research spanned a period from November, 2023 to January , 2024 allowing for an intensive analysis and investigation into the genetic underpinnings of GLP-1 receptors and their significance in diabetes therapy.

Sequences, alignment and construction of phylogenetic tree: Collect the genetic sequences of the GLP-1 receptor from the National Center for Biotechnology Information (NCBI) database. Focus on a range of species, including common laboratory animals (like mice, rats, rabbits) and others known to have physiological similarities to humans in glucose metabolism. Table 1 lists various tissues from *Homo sapiens*, *Mus musculus*, *Rattus norvegicus* and *Oryctolagus cuniculus*, highlighting their respective GLP-1 gene sequences with accession numbers from GenBank and amino acid (aa) lengths. It illustrates the diverse tissue distribution of GLP-1-ranging from pancreatic and adipose tissues to brain, liver, gastrointestinal tract, kidney and intestine-across

Table 1: Accession numbers of NCBI entries of Glucagon-Like Peptide-1 (GLP-1) receptor from *Homo sapiens* and laboratory animals

Tissue		Accession GenBank	aa	DBSOURCE
Pancreatic	*Homo sapiens*	AAB64013	463	UniProtKB
Adipose tissue	*Homo sapiens*	NP_004114	153	REFSEQ
Brain	*Homo sapiens*	NP_002045	180	REFSEQ
Gastrointestinal tract	*Homo sapiens*	NP_848566	335	REFSEQ
Brain	*Mus musculus*	Q76JU9	300	UniProtKB
Liver	*Mus musculus*	NP_783612	512	REFSEQ
Pancreatic	*Mus musculus*	NP_861416	335	REFSEQ
kidney	*Rattus norvegicus*	NP_036860	463	REFSEQ
Liver	*Rattus norvegicus*	NP_742088	485	REFSEQ
Intestine	*Rattus norvegicus*	NP_068620	550	REFSEQ
Pancreatic	*Oryctolagus cuniculus*	5VAI_R	461	PDB

aa: Arrangement of amino acids in a protein

these species. The sequences are sourced from both UniProtKB and REFSEQ databases, indicating the extensive research and documentation of GLP-1 in different tissues and its importance in physiological processes across species.

A multiple sequence alignment of proteins was performed to reveal evolutionary links and identify shared patterns. This involved aligning the sequences multiple times using Jalview software version 2.8[13]. Phylogenetic trees were constructed with neighbour-joining using MEGA[14,15]. The Jones-Taylor-Thornton model was used to produce a distance matrix. Tom Schneider and Mike Stephens devised a method for graphically expressing and visualising consensus results from amino acid multiple sequence alignments.

The classification of protein families via InterPro involves the integration of predictive models called signatures from various databases. These signatures help in the functional analysis of proteins by identifying family memberships, domain architectures and critical functional sites. InterPro amalgamates these signatures into a unified database, enhancing the accuracy of protein function predictions by utilizing the specific strengths of each member database in the consortium. This method creates a robust diagnostic tool for protein classification[16].

RESULTS

Figure 1 represented an alignment of tested protein sequence using Jalview software. Regarding phylogeny estimation for Glucagon-Like Peptide-1 (GLP-1). Neighbour-joining tree constructed using Mega 10.1.8. The multiple sequence alignments were depicted in Fig. 2. The figure provides a list of Glucagon-Like Peptide-1 (GLP-1) variants from different species and their tissue sources, including *Mus musculus* (mouse) from pancreatic and liver tissues, *Homo sapiens* (human) from gastrointestinal tract, brain, adipose and pancreatic tissues, *Oryctolagus cuniculus* (rabbit) from pancreatic tissue, *Rattus norvegicus* (rat) from intestine, liver and kidney tissues. This highlights the cross-species presence of GLP-1 and its diverse tissue distribution, indicating its significant role in physiological processes across different organisms. Figure 3 represented that GLP-1 sequences from various species, providing a basis for analyzing evolutionary relationships and phylogenetic trees. Such a collection can help in understanding how GLP-1, a peptide important for glucose metabolism and insulin secretion, has evolved across different species. By comparing these sequences, the evolutionary distances and relationships between species can be infer, identifying which species are more closely related based on the similarity of their GLP-1 sequences. This comparison might also reveal how GLP-1's function has been conserved or diversified through evolution, offering insights into its role in different biological processes across species.

Figure 3 and 4 demonstrated the protein families and domains for GLP-1 protein in mouse and rabbit in comparison with human. Figure 3 depicted a comparative chart of G-Protein-Coupled Receptor (GPCR) family expressions across different tissues and species, specifically in the pancreatic tissue of *Mus musculus* and *Oryctolagus cuniculus* and in the gastrointestinal tract and brain of *Homo sapiens*. The GPCRs were categorized into various families such as secretin-like (GPR119, insulinotropic receptor) and rhodopsin-like, indicating the diversity of GPCR types within these tissues. The presence of similar GPCR families across these species and tissues suggests evolutionary conservation and potential similarities in physiological roles, which could be important for translational research and therapeutic targeting. Figure 4 displayed the domain structures of G-protein-coupled receptors (GPCRs) in various tissues across species. In *Mus musculus* pancreatic tissue and *Homo sapiens* gastrointestinal tract, we see domains labeled with GPCR_Rhodpsn_7TM, indicating the presence of rhodopsin-like receptors with seven transmembrane domains. The *Oryctolagus cuniculus* pancreatic tissue shows a GPCR_2_extracellular_dom domain, suggesting the presence

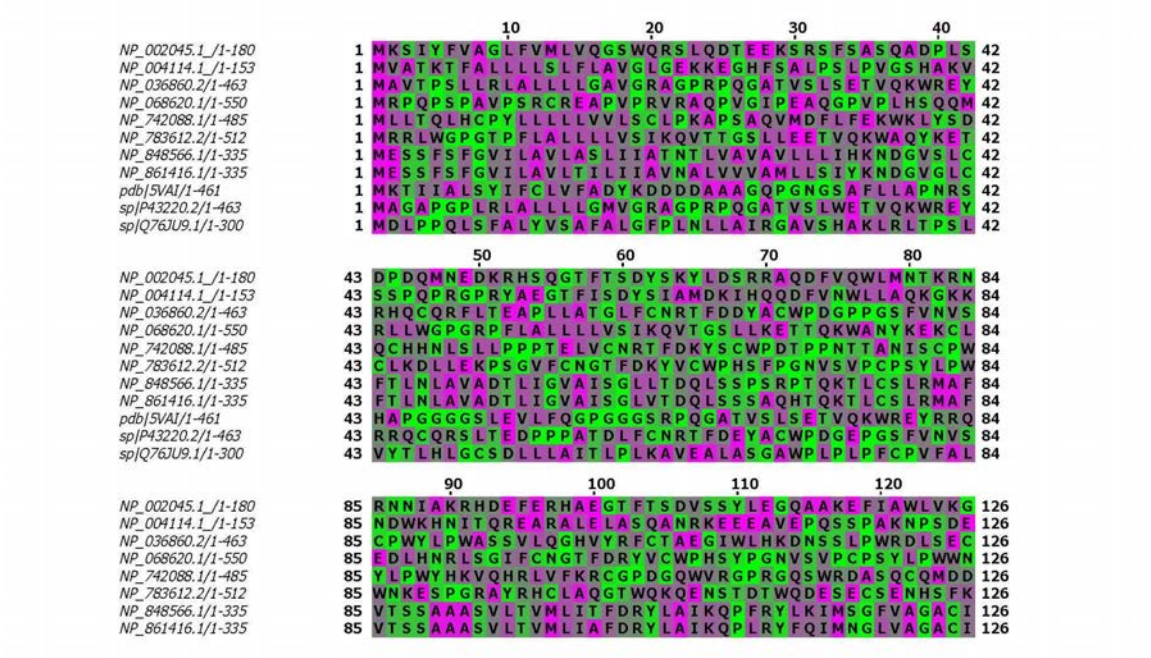

Fig. 1: Multiple sequence alignment of Glucagon-Like Peptide-1 (GLP-1) receptor

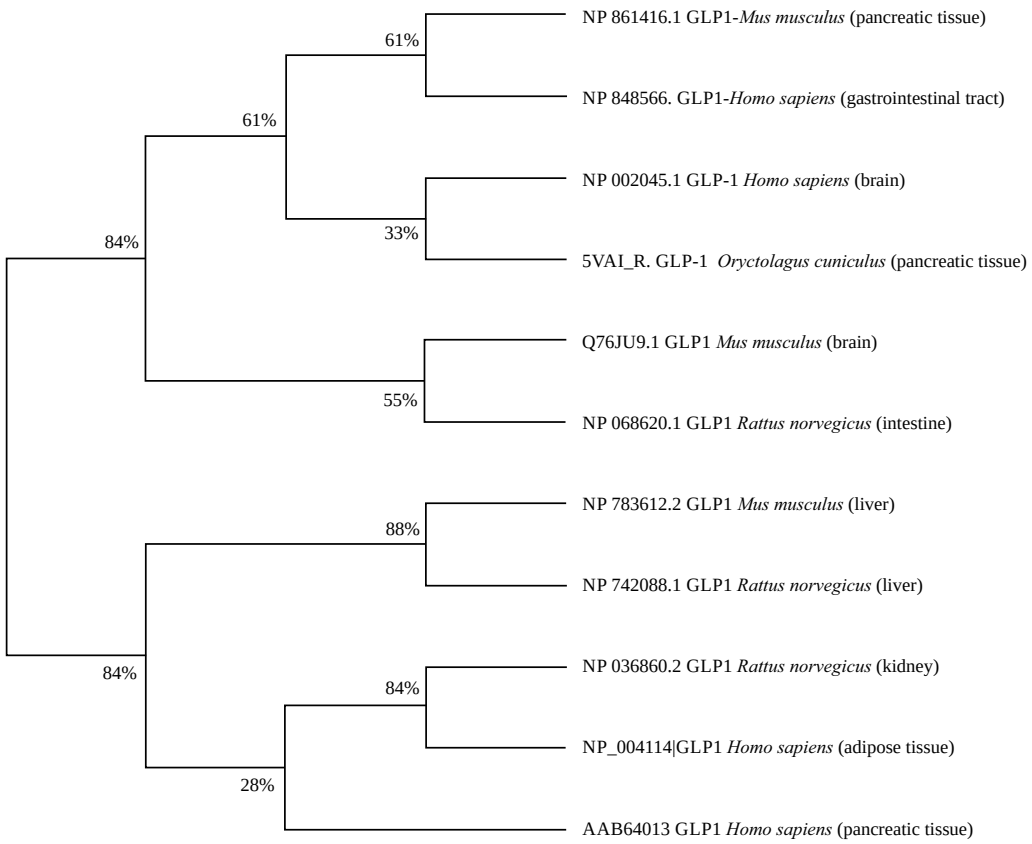

Fig. 2: Phylogenetic analysis of protein sequences of Glucagon-Like Peptide-1 (GLP-1) receptor. The resulting tree is then calculated using two algorithms: Neighbor-Join and BioNJ. These algorithms utilize a matrix of pairwise distances estimated using the Jones-Taylor-Thornton model

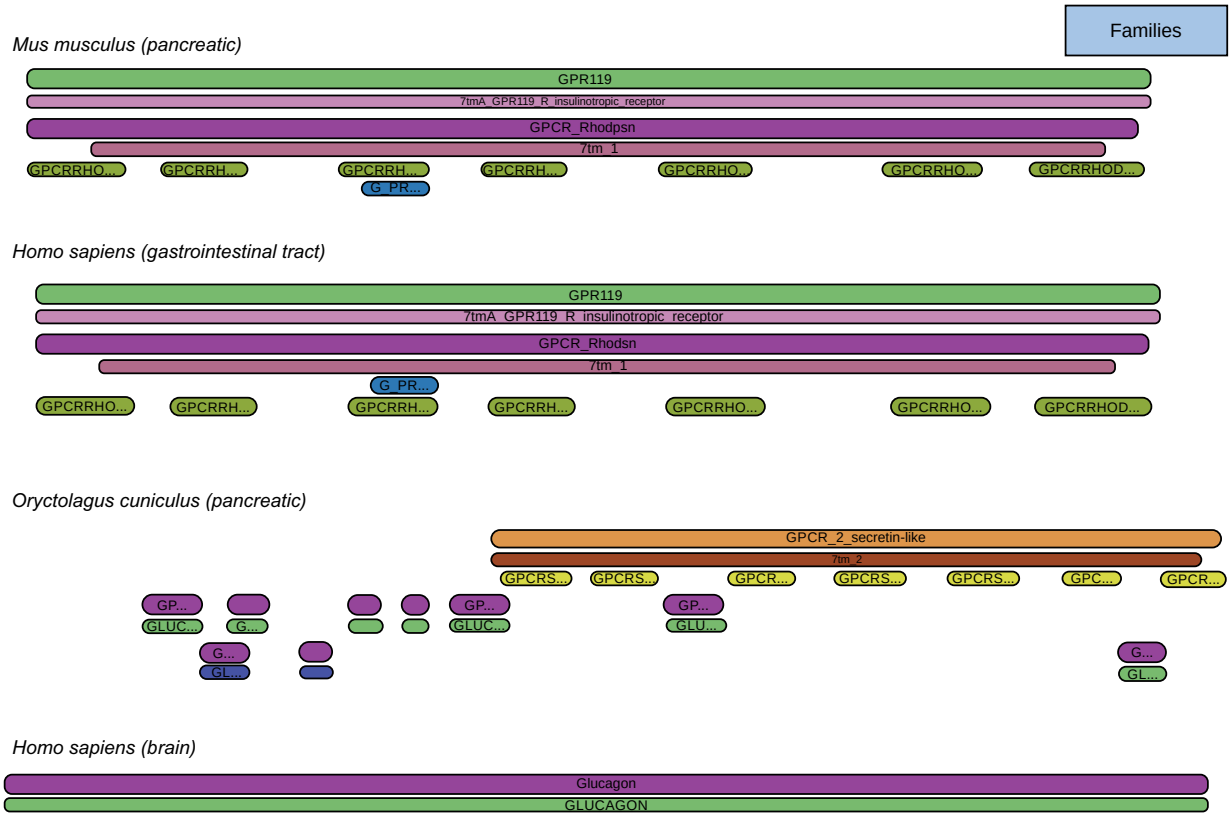

Fig. 3: Functional classification of proteins via subfamily architectures GLP-1 receptors for gastrointestinal tract of *Homo sapiens* and the pancreas of *Mus musculus* and the brain of *Homo sapiens* and the pancreas of *Oryctolagus cuniculus* (rabbit)

of secretin-like GPCR domains, which are important for hormone signaling. In *Homo sapiens* brain tissue, domains associated with glucagon and glucagon-like peptide signaling are depicted, highlighting the diversity and specificity of GPCR domain structures in different biological contexts.

DISCUSSION

Regarding phylogenetic relationship between the expression of GLP-1 receptors in the gastrointestinal tract of *Homo sapiens* and the pancreas of *Mus musculus*. This suggests a conserved evolutionary function of GLP-1 receptors across these tissues and species, highlighting the importance of GLP-1 in regulating metabolic processes in both the digestive system and pancreatic function, despite the evolutionary distance between humans and mice.

The conserved GLP-1 receptor expression in the gastrointestinal tract of *Homo sapiens* and the pancreas of *Mus musculus* suggests related metabolic functionalities across these tissues, reflecting their importance in glucose homeostasis and insulin secretion. This conservation provides a strong rationale for using mouse models to investigate the mechanisms of GLP-1 and develop therapeutic approaches targeting GLP-1 receptors. Animal models can thus offer valuable insights into the efficacy and safety of GLP-1 antagonists, facilitating the translation of research findings into clinical applications for metabolic disorders[17]. More over phylogenetic analysis in the current study highlights GLP-1 receptor expression in the brain of *Homo sapiens* and the pancreas of *Oryctolagus cuniculus* (rabbit), suggesting a strong phylogenetic relationship between these tissues across species. This connection indicates a significant role of GLP-1 receptors in both neurological and metabolic functions[18], underscoring the evolutionary conservation of these receptors. Such findings support the use of cross-species comparisons to understand the biological roles of GLP-1 receptors and their potential therapeutic implications in both metabolic and neurological disorders.

Utilizing animal models in genetic investigations offers invaluable insights into human diseases, enabling researchers to explore disease mechanisms and therapeutic interventions in a controlled environment[19]. These models, particularly when

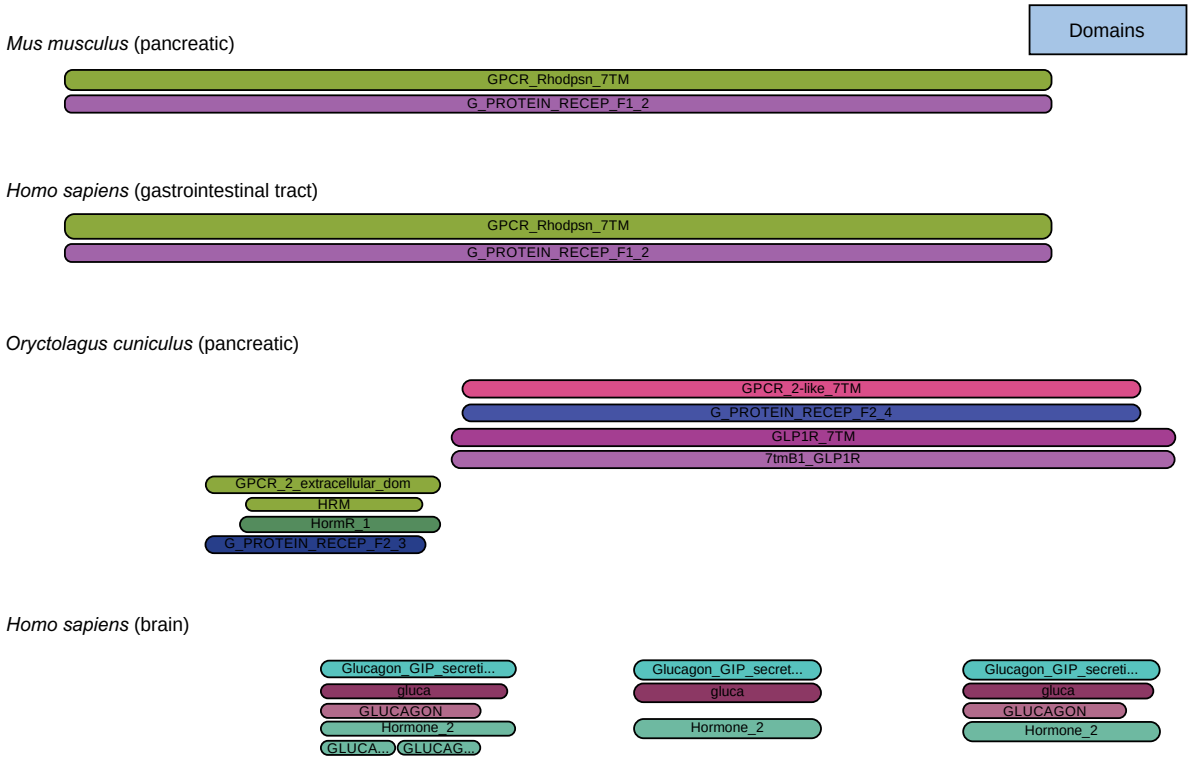

Fig. 4: Functional classification of proteins via domain architectures GLP-1 receptors for gastrointestinal tract of *Homo sapiens* and the pancreas of *Mus musculus* and the brain of *Homo sapiens* and the pancreas of *Oryctolagus cuniculus* (rabbit)

genetic similarities with humans are significant, provide a vital bridge between *in vitro* studies and human clinical trials. By manipulating genes in animal models, scientists can mimic human diseases at the molecular level, allowing for the evaluation of therapeutic efficacy and safety before proceeding to human trials. This approach enhances the predictability and relevance of preclinical studies, making them more effective in translating research into clinical benefits[20].

The observed expression of GLP-1 receptors in the brain of *Homo sapiens* and the pancreas of *Oryctolagus cuniculus* highlights a deep evolutionary link, underscoring the multifaceted roles of GLP-1 receptors beyond metabolic regulation to potentially include neurological functions. This phylogenetic relationship suggests that studies on GLP-1 receptor functions in rabbits could offer insights applicable to humans, particularly in understanding how these receptors influence both brain and pancreatic functions. Such comparative studies are crucial for developing therapeutic strategies targeting GLP-1 receptors for a range of conditions, from diabetes to neurodegenerative diseases.

The domain of a protein refers to a distinct and functional segment or region within the protein's structure[21]. It often possesses specific activities or binding capabilities, contributing to the overall function of the protein. These domains can be crucial for interactions with other molecules or for carrying out particular biological functions. According to current results the rhodopsin-like GPCRs (GPCRA) represent the common family present in gastrointestinal tract of *Homo sapiens* and the pancreas of *Mus musculus*. The GPCRs form an extensive group of proteins that include receptors for hormones, neurotransmitters and light, all functioning to relay external signals through their engagement with guanine nucleotide-binding (G) proteins. While the activating ligands for these receptors vary greatly in their structure and properties, the amino acid sequences of the receptors exhibit significant similarity. This similarity suggests a shared structural blueprint characterized by seven transmembrane (TM) helices. The large family of proteins known as G protein-coupled receptors (GPCRs) is involved in many different autocrine, paracrine and endocrine processes[22]. They exhibit a great deal of variation at the sequence level, which allows for the division of them into various

groupings. The GPCRs are a class of families for which there are signs of an evolutionary relationship but no statistically significant sequence similarity, so the term "clan" can be used to characterize them.

According to current observation the presence of various domain structures in GPCRs across different tissues and species as observed in the study is indicative of the complex evolutionary design of these receptors. The domains identified suggest a significant functional specialization within the GPCR family. For instance, the rhodopsin-like receptors with seven transmembrane domains present in *Mus musculus* and *Homo sapiens* are typically involved in visual and neurological processes[23], while the secretin-like domains in *Oryctolagus cuniculus* relate to hormonal signaling. The diversity of these domain structures reflects the adaptability and specificity of GPCR functions, which can be leveraged for targeted therapeutic interventions, particularly in metabolic and neuroendocrine disorders. The results emphasize the importance of considering both evolutionary conservation and species-specific variations when developing drugs targeting GPCR-related pathways.

CONCLUSION

The study highlights the evolutionary conservation of GLP-1 receptors and their diverse expression across species and tissues. The genetic analysis provided by the sequence alignments and phylogenetic trees opens avenues for targeted diabetes therapies by understanding the structural and functional nuances of GLP-1 receptors. This research reinforces the potential of GLP-1 receptor agonists as a therapeutic strategy, promising advancements in the management of diabetes.

SIGNIFICANCE STATEMENT

The significance of this study lies in its detailed genetic exploration of GLP-1 receptors, which play a crucial role in the regulation of glucose metabolism-a key aspect of diabetes management. By illuminating the evolutionary conservation and structural domains of these receptors, our research provides a foundational understanding that paves the way for the development of more effective diabetes therapies. Specifically, the identification of characteristics that could enhance the therapeutic efficacy of GLP-1 receptor agonists offers a promising avenue for targeted treatment strategies. This work not only expands our genetic knowledge of GLP-1 receptors but also highlights their potential as critical targets in diabetes therapy, underscoring the importance of genetic insights in advancing medical treatments for diabetes.

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