AN UPDATED EVOLUTIONARY STUDY IN GLUCOCORTICOID RECEPTORS; INSIGHTS FROM A COMPREHENSIVE PHYLOGENETIC, SNP'S AND MUTATION'S ANALYSIS OF THE NUCLEAR RECEPTORS FAMILY.

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The authors have no financial relationship(s) to disclose relevant to this poster presentation

BACKGROUND

Nuclear receptor (NR) family comprises three main subfamilies; the steroid hormones receptors, the thyroid/ retinoid hormone receptors and the orphan receptors. Proteins within the nuclear receptors family share common domain architecture. These closely related receptors and their cognate ligand compounds play a key role in homeostasis, reproduction, growth, and development. Despite their biological significance, their evolution and diversification remains to be elucidated. SNPs and mutations are characterized by the permanent alteration of the nucleotide sequence of the genome of an organism. These alterations can be used as biomarkers of genetic variation within a population. Genetic variation is of extreme importance in the evolutionary process, since it may lead to both structural and functional differentiation in gene products.

OBJECTIVE AND HYPOTHESES

To update in-depth the phylogenetic tree of the full Nuclear Receptor family across all species in the tree of life, in an effort to identify molecular and evolutionary traits specific to the glucocorticoid sub-family. To study mutations and SNPs as Nuclear Receptor points of interest, directly associated with the structure and function of this specific protein family. sub-family.

METHOD AND RESULTS

Combinations of key terms were employed in order to identify relative NR and GR protein sequences on both primary and tertiary/quaternary structural levels. Sequence data were collected from the NCBI Database. Two distinct datasets were prepared for the purposes of this study. The first dataset comprised of all NRs, which involved 117080 (308 GR) entries across all known receptor sub-classes. In the second dataset, entries were collected 400 3D structures of the NR ligand binding domain and clustered in groups using both evolutionary and structural features. Both datasets were aligned using progressive methods. The phylogenetic analysises were conducted using the UPGMA distance method and the distance matrix in the structural tree were performed using a hyprid function. Finally, 29 natural occurring mutations and 10 SNPS were chosen and study on human GR predicted 3D model. The selection was made based on their impact on the receptor's structure and function.

CONCLUSION

Based on our comprehensive evolutionary study in nuclear receptors, a reliable phylogeny "map" was constructed for NRs with more emphasis in GRs. It allowed to pinpoint evolutionary and structurally invariant patches on both the 1D and 3D level of the NR/GR, which led to the identification of structural 'hotspots' directly related to function that are of great interest as novel pharmacological targets. A strong case can be presented for both natural occurring mutations and SNPs being used as structural 'hotspots'.

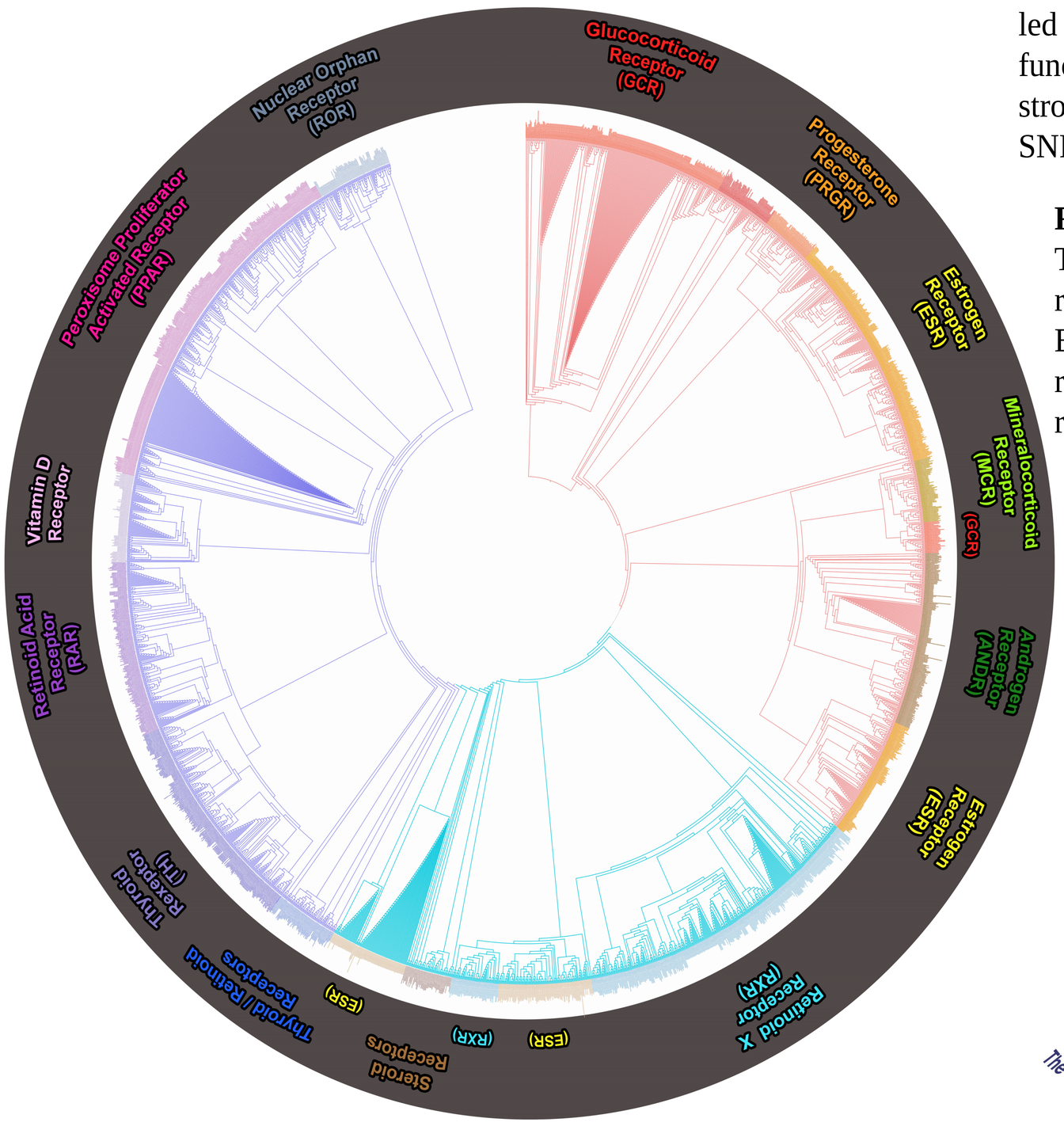

Figure. Phylogenetic tree of the nuclear receptor related proteins. The phylogenetic tree confidently separates the Glucocorticoid receptors, Progesterone receptors, Mineralocorticoid receptors, Estrogen receptos, Androgen receptos,, Thyroid / Retinoid receptors, Vidamin D receptors, Peroxisome Proliferator-activated receptor and the Orphan nuclear.