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TRACING THE GLUCOCORTICOID RECEPTOR EVOLUTIONARY PEDIGREE: INSIGHTS FROM A COMPREHENSIVE PHYLOGENETIC ANALYSIS OF THE FULL NR SUPER-FAMILY

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BACKGROUND

The nuclear receptor (NR) family comprises three main subfamilies: the steroid hormones receptors, the thyroid/retinoid hormone receptors and the orphan receptors. Proteins within the NR family share a 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.

OBJECTIVE AND HYPOTHESES

To establish an in-depth phylogenetic tree of the full NR family across all species in the tree of life, in an effort to identify molecular and evolutionary traits specific to the glucocorticoid sub-family.

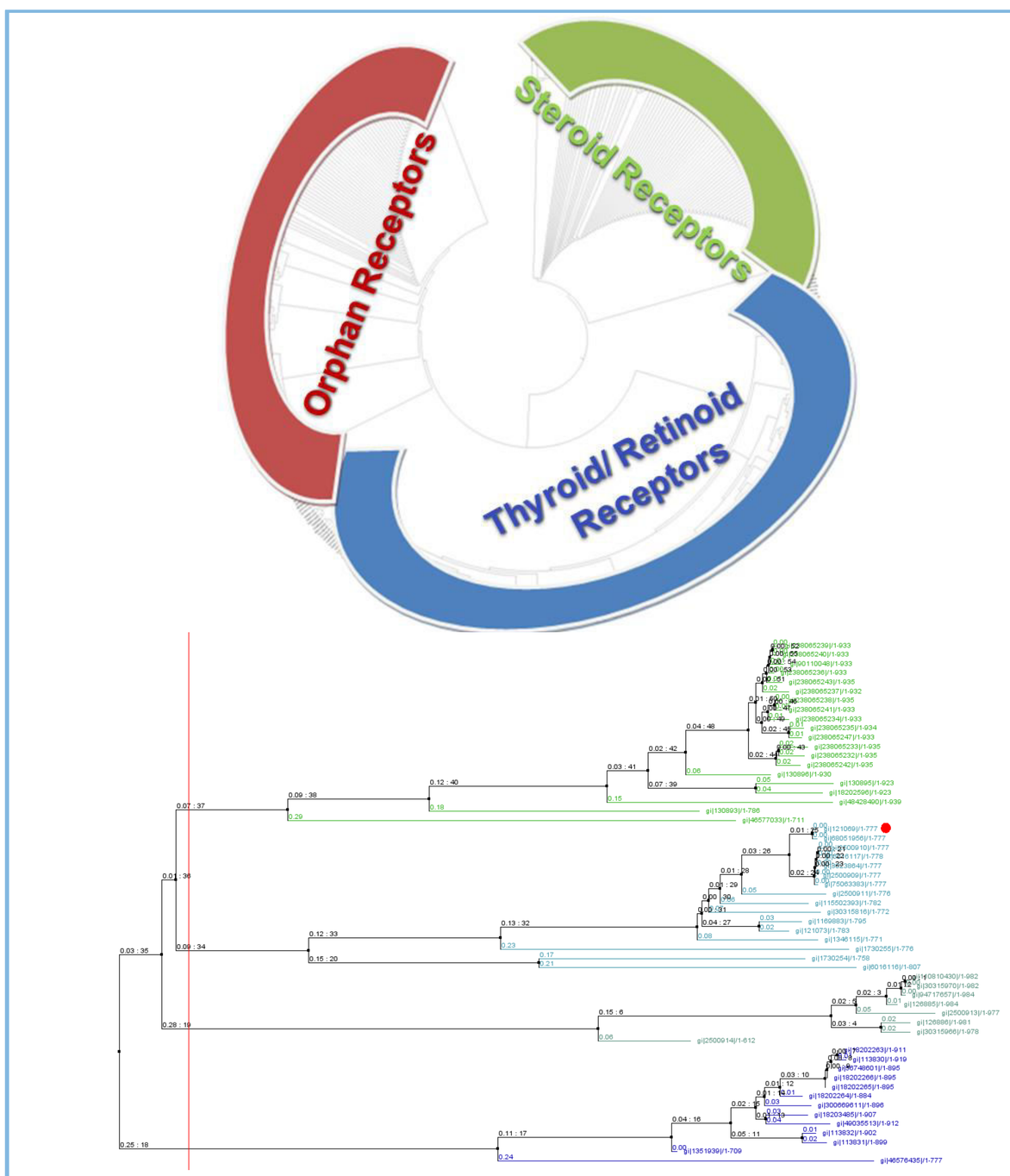

Figure 1. Phylogenetic trees of the nuclear receptor related proteins.
A. The phylogenetic tree confidently separates the Steroid receptors (branch colored Geen), Thyroid / Retinoid receptors (branch colored Blue) and the Orphan receptors (branch colored Red)
B. The steroid receptos representative phylogenetic tree.

Table 1. Dataset results by taxon

A/A	Top organisms	Percentage	A/A	Top organisms	Percentage
1	*Homo sapiens*	15.5	18	*Tupaia chinensis*	0.9
2	*Callithrix jacchus*	4.5	19	*Pteropus alecto*	0.9
3	*Mus musculus*	3.6	20	*Chelonia mydas*	0.9
4	*Rattus norvegicus*	3.2	21	*Tachysurus fulvidraco*	0.8
5	*Pan troglodytes*	3.1	22	*Salmo salar*	0.8
6	*Fundulus heteroclitus*	3	23	*Alligator mississippiensis*	0.8
7	*Danio rerio*	2.7	24	*Trichinella pseudospiralis*	0.8
8	*Macaca mulatta*	1.9	25	*Fukomys damarensis*	0.7
9	*Xenopus laevis*	1.6	26	*Lateolabrax japonicus*	0.6
10	*Larimichthys crocea*	1.6	27	*Daphnia magna*	0.6
11	*Sus scrofa*	1.4	28	*Oncorhynchus mykiss*	0.5
12	*Cricetulus griseus*	1.4	29	*Amazona aestiva*	0.5
13	*Heterocephalus glaber*	1.2	30	*Bos taurus*	0.5
14	*Gallus gallus*	1	31	*Sparus aurata*	0.5
15	*Myotis brandtii*	1	32	*Macaca fascicularis*	0.5
16	*synthetic construct*	1	33	*Capra hircus*	0.5
17	*Poeciliopsis prolifica*	0.9	34	*Other*	40.6

METHODS 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 84566 entries across all known receptor sub-classes. In the second dataset, 217 GR entries were collected and clustered in groups using both evolutionary and physicochemical criteria. The clustered groups were then blasted against the PDB in a query for X-ray solved structures as templates for a holistic 3D homology modelling experiment of the GR family. Both datasets were aligned using progressive methods. The phylogenetic analysis was conducted using the UPGMA distance method and the 3D modelling was performed using MOE. Based on our comprehensive phylogenetic analysis of nuclear receptors, a reliable phylogeny "map" was constructed for GRs. It allowed to pinpoint evolutionary and structurally invariant patches on both the 1D and 3D level of the GR family, which led to the identification of structural 'hotspots' directly related to function that are of great interest as novel pharmacological targets.

CONCLUSION

Based on our comprehensive phylogenetic analysis of nuclear receptors, a reliable phylogeny "map" was constructed for GRs. It allowed to pinpoint evolutionary and structurally invariant patches on both the 1D and 3D level of the GR family, which led to the identification of structural 'hotspots' directly related to function that are of great interest as novel pharmacological targets.

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