A data mining and semantic analysis reveals novel insights into the genetic characteristics of the glucocorticoid receptor interactome

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Abstract. The availability of single nucleotide polymorphisms (SNPs) that have been identified in a given gene and have been related to several diseases provides the opportunity to study complex biological pathways and can assist researchers in better associating genes and disease-linked terms in the areas of genetics, genomics and epigenetics. The study of the glucocorticoid receptor (GR) interactome through SNP observations in 'key-player' genes will provide researcher with the opportunity to draw the 'genomic grammar' of the complex biological mechanisms associated with GR function and will open new horizons in biology, medicine, pharmacology and even extend to personalized medicine. The GR interactome is extensive, and is involved in several physiological and pathological processes of the organism. Glucocorticoids are the final product of the hypothalamic-pituitary-adrenal axis and an inextricable part of the stress system. These hormones are implicated in various critical systems and processes for the human organism, such as the immune system, development, metabolism and several others. GR is the protein that mediates their actions and is involved in several interactions with specific genes and proteins. In the present study, in order to unravel new beneficial knowledge on genetic targets regarding the GR interactome, a data mining and semantic pipeline was performed using the available literature. More specifically, through bioinformatics tools and methods, the most relevant SNPs and genes connected to the GR interactome were extracted. Subsequently, the outcome SNPs were filtered, annotated, classified and evaluated in order to create the 'genomic grammar' and identify the related disease with the interactome of GR. Genomic background and heredity play a significant role in the GR interactome. A more in-depth understanding of the biological pathways and complex actions of the GR may lead to the design and development of more effective treatments for inflammatory and autoimmune diseases, as well as cancers.

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Introduction

All living organisms need to maintain an internal dynamic equilibrium for proper biological function. This complex dynamic equilibrium is known as homeostasis and it is constantly threatened by internal or external forces called stressors (1). The state of threatened or perceived as such homeostasis is known as stress, while the response system organisms have developed to combat stress and maintain or reinstate homeostasis is known as the stress system. The stress system includes complex neuroendocrine responses and functions through the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the locus coeruleus (LC)/norepinephrine (NE)-autonomic nervous system (2). The HPA axis consists of neurons located in the paraventricular nucleus of the hypothalamus (PVN) that secrete mainly corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), endocrine cells in the anterior pituitary that secrete adrenocorticotropic hormone (ACTH), and endocrine cells in the adrenal cortex that secrete glucocorticoids (GCs), specifically cortisol in humans and corticosterone in rodents (Fig. 1). CRH and AVP stimulate ACTH secretion in the anterior pituitary, and ACTH in turn, stimulates GC secretion in the adrenal cortex. Lastly, glucocorticoids can inhibit axis function by suppressing CRH

and ACTH secretion (Fig. 1) (3). The LC is a NE-producing nucleus that is located in the posterior portion of the rostral pons. The LC is characterized by numerous efferent NE projections to the entire neuraxis and modulates neuronal function in both the sympathetic and parasympathetic nervous systems (4). This neuromodulatory system has long been associated with synaptic plasticity and is considered to help local circuits dynamically adapt to new circumstances (5). Stress differs among individuals and, based on the basal activity and time course of the neuroendocrine responses, can either help an organism overcome certain challenges or lead to an excessive or inadequate response to stressors with pathological results (6,7).

The principal effectors of the stress system are located in the HPA axis (8). GCs, as the final product of the HPA axis, can be considered the most critical stress-associated hormones. The action of GCs is mediated by two receptors, the GC receptor (GR) and the mineralocorticoid receptor (MR), with both receptors belonging to the nuclear receptors (NRs) superfamily of transcription factors. Binding assays have demonstrated that the MR has a 10-fold higher affinity for GCs than the GR, indicating that the MR is activated at basal levels, while the GR is activated during the circadian peak of GC secretion or during stress (9). Thus, GR signaling is of paramount importance in the stress system.

GR structure and function are characteristic of its NR status. NRs are relatively similar structure-wise, and apart from the main functional domains, also feature regions which interact with cofactors, such as activation function (AF)-1 and AF-2 (Fig. 2) (10). Function-wise, NRs are ligand-dependent transcription factors, with the majority of mentioned receptors being regulated by small lipophilic ligands with ligand-binding, leading to receptor conformational changes and subsequent translocation to the nucleus and the binding of specific DNA sequences. Once a NR is bound to its target DNA sequence, various receptor cofactors are recruited to the site in order to activate or repress target gene expression (11).

GR signaling is relatively similar to other nuclear receptors, and more specifically, the steroid hormone receptor subcategory of NRs (Fig. 3). In the absence of GCs, the GR is located in the cytoplasm, where it is bound to a number of cofactors, termed chaperone proteins, that render it inactive. Specifically, following translation, heat-shock protein (Hsp)70 binds the unfolded receptor in the cytoplasmic matrix, a process accelerated by Hsp40, and promotes the folding of the GR. A cofactor known as BAG family molecular chaperone regulator 1 may inhibit the folding of the mentioned receptor, either directly or by assisting the degradation of the unstable folded GR complex with Hsp70 and Hsp40. The Hsp40/Hsp70-GR complex is later recruited by the Hsp70-Hsp90 organizing protein (Hop) to interact with Hsp90 (12). Hsp90 binding of ATP leads to the dislodgement of Hop, Hsp40 and Hsp70 and sets in motion the subsequent interaction of the Hsp90-GR complex with cochaperone proteins, such as FK506-binding protein (FKBP)51 and prostaglandin E synthase 3, which gives rise to a complex conformation with a high affinity for corticosteroids (13,14). Ligand binding leads to conformational changes in the ligand-binding domain (LBD) that alter the proteins which comprise the heterocomplex, a prime example being the replacement of FKBP51 by FKBP52, leading, mostly, to GR dimerization and nuclear translocation, where the receptor may now regulate transcription (14-16). The nuclear import of the GR is a rapid and active process that relies on GR association with the Hsp90, FKBP52 and importin-α. The GR complex is transported into the nucleus along the cytoskeleton and through the nuclear pore complex (NPC) with the help of dynein (16). Once in the nucleus, the activated GR can modulate gene transcription. Specifically, transactivation can be achieved directly through GR homodimer binding to distinct DNA sequences known as GC response elements (GREs) or indirectly, where GR acts as a monomer and co-operates with other transcription factors to induce transcription (17,18). Transrepression can also be direct, via GR homodimer or, preferably, monomer binding to a negative GRE, or indirect, where GR acts as a monomer and binds to a pro-inflammatory transcription factors, such as NF-κB (17-19). It should also be mentioned that a large part of the receptor's action is also exerted through protein-protein interactions (20). The time length GR remains bound to DNA depends on the bound ligand (21). Following ligand disengagement, GR disconnects from DNA and is either degraded by the proteasome or exported from the nucleus, an inactive process possibly occurring through passive diffusion (16).

As a main mediator of the stress response, the GR also plays a role in numerous biological processes. Beginning from the embryonic phase, the GR influences development and organ maturation (22,23). The pulmonary and cardiovascular systems are interconnected and are both connected to high-stress levels and GR (24). The GR itself has been shown to be associated with several cardiovascular diseases (25). GCs are also known to be essential for metabolism, influencing insulin signaling and gluconeogenesis (26,27), while an abnormal GR regulation has been found to be associated with obesity and diabetes mellitus type II (20). GR also plays a critical role in the immune system, where it downregulates pro-inflammatory transcription factors and cytokines (28-30). It is also known that GCs produced under pathological circumstances are capable of disrupting immune function, an effect that results in susceptibility to infections from viruses and neoplasm development (31). GCs also have the ability to cross the blood-brain barrier, thus affecting various aspects of the nervous system. GR regulates behavioral, emotional and physical responses and can alter synapses (32) and appears to play a role in mood disorder pathology (33).

The GR and its interactome can regulate numerous pathways and systems in humans. Literature on these pathways and systems has accumulated over the decades and since several of the associated studies do not focus on the GR, lesser findings associated with this receptor may have been overlooked by researchers studying the GR. To the best of our knowledge, the present study is novel in that it may provide further information regarding the GR that has not been reported thus far, namely crucial information on GR function and GR-related pathologies. Specifically, a main aim of the present study was to identify the most associated single nucleotide polymorphisms (SNPs) and their genetic variants, gaining information that in the future can potentially support a better understanding of the GR interactome. The general pipeline of the integrated bioinformatics approach is presented in Fig. 4.

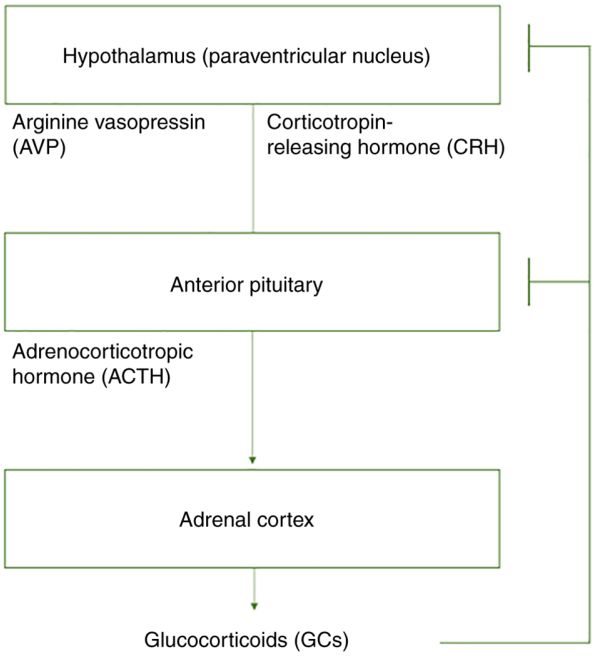

Figure 1. Schematic representation of the HPA axis. Arginine-vasopressin and CRH are secreted by the paraventricular nucleus of the hypothalamus and stimulate the secretion of ACTH from the anterior pituitary. ACTH, in turn, stimulates the release of GCs from the adrenal cortex. GCs can inhibit the function of the HPA axis by suppressing CRH and ACTH release. HPA axis, hypothalamic-pituitary-adrenal axis; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; GCs, glucocorticoids.

Figure 2. Typical structure of a nuclear receptor. NTD, N-terminal domain; AF-1, activation function-1; DBD, DNA-binding domain; HR, hinge region; LBD, ligand-binding domain; AF-2, activation function-2; CTD, C-terminal domain.

Data and methods

Data collection. The main regulators of GR signaling, as described in the text above, along with the receptor itself, were the starting point for a literature search. Specifically, 10 genes of interest were used as key words for an in-depth search on the PubMed database (Table I) (34,35). After using a filtering algorithm, duplicates were removed, and the study focused on the identification of SNPs that have been found to be associated with the GR and the main regulators of its signaling. Information regarding GR-related SNPs and the other genes of interest was also extracted and merged from the genome-wide association studies (GWAS) Catalog database. Last, but not least, all the identified SNP terms were stored in a structured database and all the available entries were associated with the SNP ID number as referred to in the dbSNP database (36).

Data mining. All identified SNPs of interest were annotated with relevant information from the ClinVar (37), LitVar (38), dbSNP (36) and GWAS Catalog (34) databases. Specifically, the dbSNP database was used to find the genomic location of the SNP and their position in a gene, the ClinVar database to find potential associations with human pathological conditions, the GWASCatalog database to find associations with specific traits, and the LitVar database to find the most co-occurred entities in a sentence featuring the aforementioned designated key words, with a focus on diseases, chemicals and genomic variants.

Semantics and terms analyses. Semantics and terms analyses were conducted towards extracting beneficial knowledge, including the genomic grammar, disease ontologies and the most common key words that are presented in the studied literature. Subsequently, all the extracted results were displayed in WordCloud representations in order to summarize the final output.

Results

Based on the results, >127,000 publications were found to be related to GR and its genes of interest (Table I). A total of 274 related GR interactome-related SNPs of utmost interest were identified (Table SI). The annotation of the mentioned SNPs revealed an association with 247 diseases (Tables SI and SII) and 118 genes (Tables SI and SIII). The SNPs found in the GR were associated with specific key words in the scientific literature (Fig. 5). The vast majority of these keywords can be separated into distinct groups as follows: i) The stress system-related group, with entries such as the HPA axis, stress and chronic stress; ii) the gene regulation-related group, with entries such as DNA methylation and epigenetics; iii) the immune system-related group with entries such as inflammation and NF-κB; iv) the development-related group with entries such as fetal programming; v) a group featuring other steroid hormone receptors, with entries such as MR, androgen receptor and progesterone receptor; vi) a group highlighting the role of the receptor in metabolism with entries such as insulin resistance and obesity; vii) a group showcasing the role of GR role in neuropsychiatric disorders with entries such as depression, post-traumatic stress disorder (PTSD) and schizophrenia; viii) a group highlighting the role of the GR in brain architecture and neuronal plasticity, with entries such as hippocampus, prefrontal cortex and microglia; ix) a group featuring members of the GR interactome, with entries such as FKBP5 and serum/glucocorticoid regulated kinase 1; and x) a group featuring agonists and antagonists of the GR, such as dexamethasone and aldosterone. Apart from the mentioned groups, several unique key words associated with various pathological conditions emerge, such as osteoporosis, asthma and Alzheimer's disease. Apoptosis is also present as a unique key word, an inclusion which may be due to the ability of the GR to promote pro-apoptotic protein expression (39).

The SNPs found in the GR were studied in conjunction with several pathological conditions (Fig. 6). The most commonly studied pathological conditions are, as expected, neuropsychiatric disorders, such as depression and PTSD, and metabolic disorders, such as diabetes mellitus and obesity (40). Pathologies, such as asthma, rheumatoid arthritis, or systemic erythematosus lupus are also associated with the study of the GR, which may be due to the fact that these conditions are mainly treated through the use of synthetic GCs (41,42). Cardiovascular diseases are also associated with GR research, possibly due to the aforementioned influence of the stress

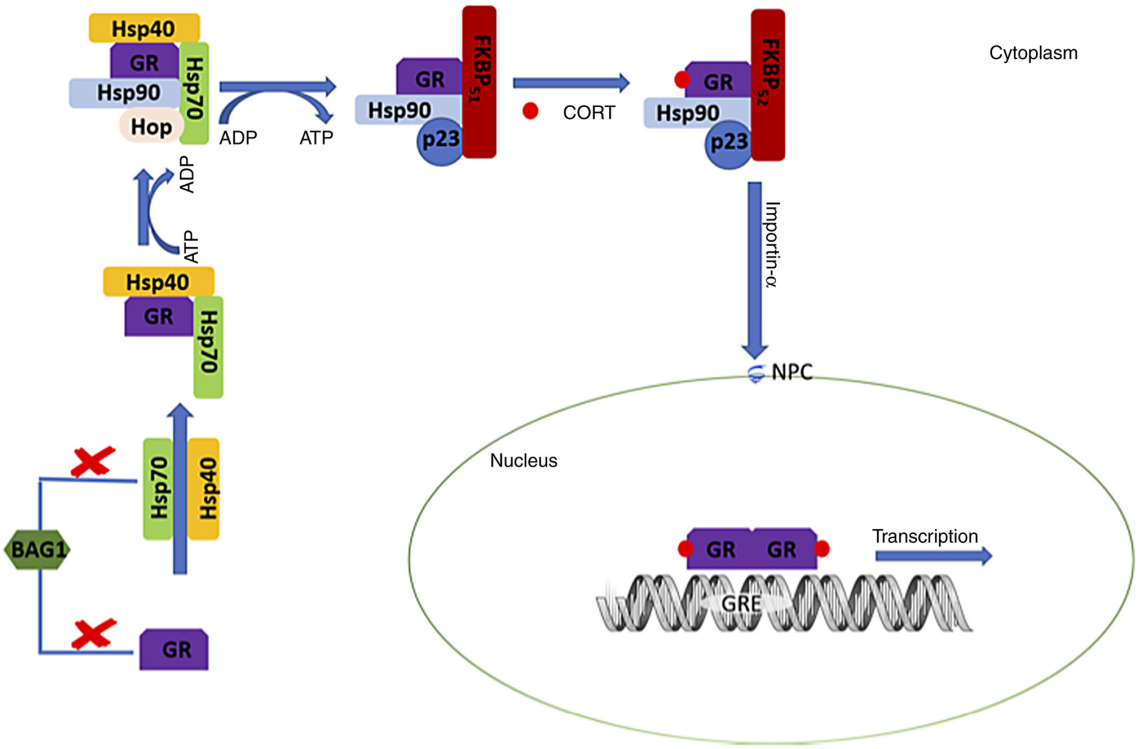

Figure 3. Schematic representation of GC signaling resulting in GR homodimerization and transcription initiation. Hsp70 binds the unfolded receptor in the cytosol, a process accelerated by Hsp40 binding, and leads to the folding of the GR. BAG-1 is a cofactor that may directly impair receptor folding, while it may also aid in the degradation of the unstable folded GR complex with Hsp70 and Hsp40. The interaction of GR with the Hsp40/Hsp70-GR complex is then recruited by Hop, in an ATP-dependent manner, to interact with Hsp90. Hop, Hsp40 and Hsp70 are dislodged from the Hsp90-GR complex upon Hsp90 binding ATP, and the subsequent interaction of the Hsp90-GR complex with FKBP51 and p23 give rise to a complex conformation with a high affinity for corticosteroids. Ligand binding leads to the replacement of FKBP51 by FKBP52, mainly leading to GR dimerization and nuclear translocation through the NPC with the aid of importin-α. Finally, the GR homodimer binds to glucocorticoid response elements to promote gene transcription. GC, glucocorticoid; GR, glucocorticoid receptor; Hsp70, heat-shock protein70; Hsp40, heat shock protein 40; BAG1, BAG family molecular chaperone regulator 1; Hop, Hsp70-Hsp90 organizing protein; p23, prostaglandin E synthase 3 protein; FKBP51, FK506-binding protein 51; CORT, cortisol; FKBP52, FK506-binding protein 51; NPC, nuclear pore complex; GRE, glucocorticoid response elements.

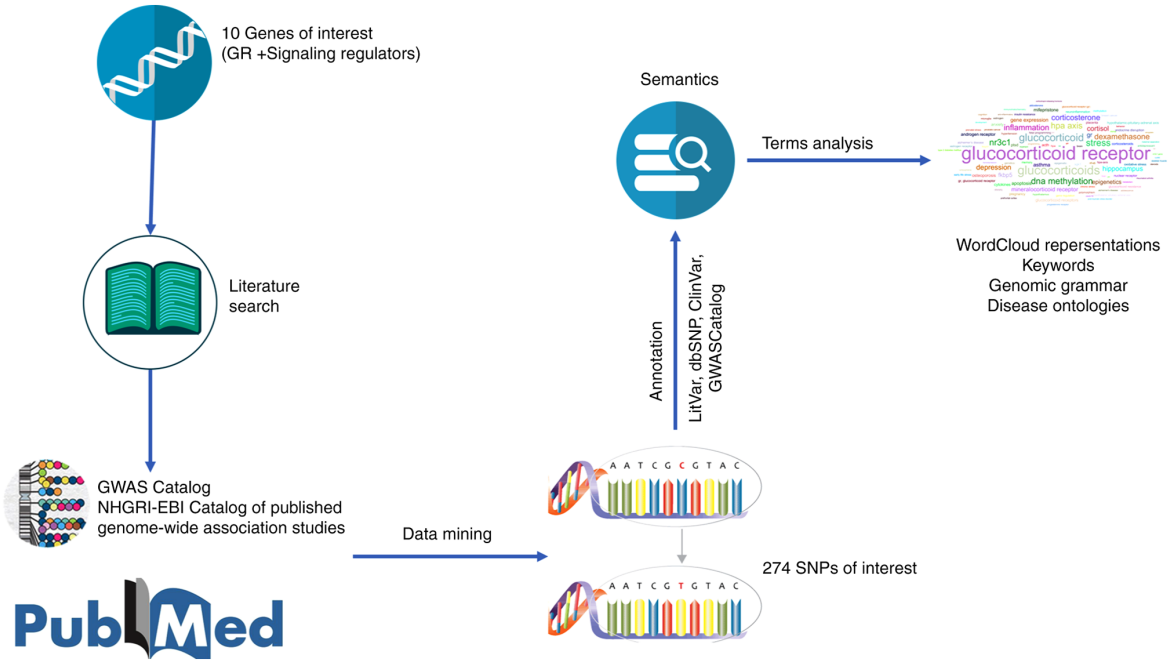

Figure 4. General pipeline workflow. Ten genes of interest were studied in the available literature to find information regarding GR-related SNPs and additional genes of interest. The literature information was extracted from the PubMed database and was later merged with additional information from the GWAS Catalog database. The identified SNPs of interest were annotated with relevant information from the ClinVar, LitVar, dbSNP and GWASCatalog databases. Finally, a semantics and terms analyses were conducted towards extracting beneficial knowledge with the results being presented in a WordCloud presentation format. SNPs, single nucleotide polymorphisms; GR, glucocorticoid receptor; GWAS, genome-wide association studies.

Table I. Genes used and the corresponding PMID of articles reporting their interaction with the GR.

Serial no.	Gene name	PMID: Interaction with GR
1	GR	-
2	FKBP5	19560279
3	FKBP4	32557257
4	HSP90 (AA1)	28224564
5	PTGES3 (p23)	24345775
6	STIP1 (HOP)	32612187
7	HSP70	32612187
8	HSP40	30585227
9	NR3C2	28686058
10	BAG1	30585227

GR, glucocorticoid receptor.

response system on the cardiovascular system. Somewhat unexpected, though, is the study of wounds and injuries, plus various neoplasms in conjunction with GR. The role of GCs in various mechanisms underlying cancer has been largely unexplored. Although the GR is not considered an oncogene, GCs have been shown to arrest growth and induce apoptosis in lymphoid tissue via GR signaling in certain patients (43). The attempt to elucidate the mechanisms regulating the effects of GCs on cancer may be the reason for which numerous neoplasms have been studied in conjunction with GR. Wounds and injuries are markedly associated with inflammation, since inflammation is a phase of the wound healing process (44). The effects of GCs on inflammation may affect the healing process, and thus studies focus on the role of GR in wounds and injuries.

The SNPs found in the regulators of GR signaling have also been studied along with specific genes in the literature (Fig. 7). The vast majority of these genes are the regulators themselves (FKBP5 and HSPA1L). Other genes studied along with regulators of GR signaling include genes coding for regulators of the HPA axis, such as CRHR1, genes coding for main regulators of the immune system, such as complement factor H (CFH) and nuclear factor kappa B subunit 2 (NFKB2), genes coding for various factors influencing brain architecture, such as brain derived neurotrophic factor antisense RNA (BDNF-AS) and neurotrophic receptor tyrosine kinase 2 (NTRK2), genes coding for factors influencing metabolism, such as apolipoprotein E (APOE) and fat mass and obesity-associated protein (FTO), and the MR which also binds GCs. Several genes which produce non-coding mRNAs are also present, such as miR-4761. Non-coding RNAs are known to play a crucial role in gene regulation (45), which is in accordance with the action of GR as a transcription factor. Additional genes included are vascular endothelial growth factor A (VEGFA) and RNA polymerase I and III subunit c (POLR1C). VEGFA codes for the vascular endothelial growth factor, which plays a critical role in physiological and pathological angiogenesis (46), while POLR1C codes for the C subunit of RNA polymerases I and III. GCs exert an angiostatic effect and glucocorticoid treatment has been shown to influence the VEGF mRNA levels (47). The inclusion of POLR1C though, is of interest, and will be discussed in-depth below.

Lastly, the SNPs found in the regulators of GR signaling have been studied for their role in several diseases (Fig. 8) (48). The diseases associated with GR signaling regulator SNPs almost completely overlap with the diseases studied in conjunction with GR SNPs. Several diseases associated with metabolism or the healing process are unique to GR signaling regulators, implying that GR may influence the mentioned mechanisms indirectly through its interactome. It is also intriguing that neoplasm studies are more present in GR signaling regulators SNPs, possibly displaying that the GR may play a more complex role in cancer than what was originally thought. As regards disease studies which are unique to GR signaling regulators, these include Parkinson's disease, Alzheimer's disease and epilepsy, highlighting the role of GR signaling in proper brain function, and polycystic ovary syndrome (PCOS). The inclusion of PCOS may be due to the effect GCs have on the hypothalamic-pituitary-gonadal axis, whose products play a key role in the pathophysiology of this disease (49).

Discussion

Glucocorticoids are essential mediators of the stress system, being the final product of the HPA axis activation (8,18). Following their excretion from the adrenal glands, they enter the blood circulation, find the target cells and exert multiple actions. The majority of their actions are carried out through gene regulation, after pairing with their receptor; their actions also known as the genomic effects of GCs (19). Through the transactivation of anti-inflammatory functions and the transrepression of pro-inflammatory genes, GCs exert their anti-inflammatory effects, taking part in regulating inflammation and other immune system processes (17). Among the target genes of GR regulating attributes, one can also find pro-apoptotic genes, mainly used in the treatment of lymphoid malignancies and other neoplasms (50,51). During developmental phases, GCs are involved in several fetal programming processes, resulting in differences between treated and untreated subjects in adult life. Embryos treated with GCs have been shown to develop earlier and present with several physical and behavioral differences in adulthood, compared to the untreated embryos (23). GR plays a role in several metabolic pathways, participating in the signaling pathway of insulin in the liver, skeletal muscles and adipose tissue (26), and are responsible for metabolic diseases, such as diabetes and obesity (20). Other steroid receptors, biological relatives of GR, have been studied along with GR as putative targets for glucocorticoids, in an attempt to identify the associated diseases (52).

As participants of the HPA axis, GCs are associated with structural and alterations in different parts of the brain and subsequently also associated with several neuropsychiatric disorders. PTSD is a disorder in which GR can be used as a potential therapeutic target, as GCs may be able to lower the hippocampal-mediated trauma memories. Changes in GC sensitivity of the hippocampus could determine the risk of developing PTSD in later life. Abnormal GC circulation and mitigated circadian cortisol fluctuations may cause sleep

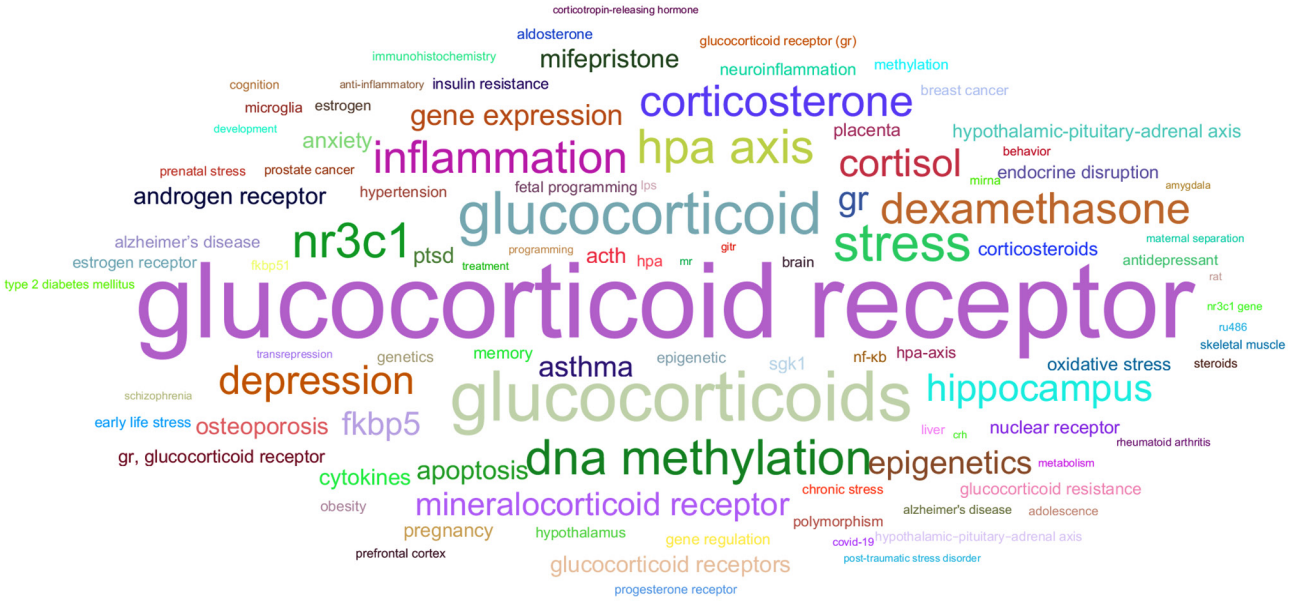

Figure 5. WordCloud representation of the extracted keywords from the glucocorticoid receptor-related publications. Larger words represent more commonly found key words in the literature.

Figure 6. WordCloud representation of the related diseases based on the extracted single nucleotide polymorphisms from the glucocorticoid receptor-related publications. Larger words represent more commonly found diseases in the literature.

disturbances observed in PTSD cases, and morphological and functional alterations in the hippocampus (53). It is also known that chronic stress is a crucial factor in the development of disorders, such as depression and it was recently proven that neuroinflammation in the hippocampus and depression-like behavior is mediated by activation of the GR pathway in hippocampal microglia (54). GCs exert various effects on prefrontal cortex functions, depending on whether the stress is chronic or acute (55). Acute stress can actually enhance working memory via a GR-dependent mechanism (56). Following the ultradian rhythm, GCs can induce changes at synapses throughout the cortex which are involved in motor learning and other functions (57,58). Exposure to high levels of GCs, chronic stress and stress-related disorders may also increase the risk of developing Alzheimer's disease (59). It has been shown that when the GR is blocked due to stress early on in life, mice exhibit lower cognitive flexibility and higher levels of amyloid-β in the hippocampus. Treatment with a GR antagonist in middle-aged mice has been shown to result in lower amyloid-β levels and recovery from the cognitive defects (60).

GCs have been used in clinical practice for a number of years, tapped into their ability to alleviate symptoms of certain pathologies. Such treatments mainly involve the GC immunosuppressive attitudes and are being administered to patients with conditions, such as systemic erythematosus lupus, asthma and rheumatoid arthritis (61-63). Moreover, in cases of asthma exacerbations, GCs are used to combat inflammation (63,64),

Figure 7. WordCloud representation of the glucocorticoid receptor interactome 'genomic grammar' of the based on the extracted single nucleotide polymorphisms from the final analyzed dataset of publications. Larger words represent more commonly found genes and genomic regions in the literature.

Figure 8. WordCloud representation of the associated diseases with glucocorticoid receptor signaling regulators based the extracted single nucleotide polymorphisms from the final analyzed dataset of publications. Larger words represent more commonly found diseases in the literature.

and possibly even to induce lung tissue regeneration (65). However, as previously demonstrated, patients suffering from asthma with GC resistance, were not responsive to GC treatments (63). Some mechanisms that the GR uses are the regulation of hematopoietic cell apoptosis and the suppression of pro-inflammatory cytokine expression (66). Sadly, several other pathologies have emerged as adverse effects of GC use in clinical practice. The excess of GCs in bones causes osteoporosis, as GCs activate pro-apoptotic molecules that reduce osteocyte viability and osteoclast apoptosis (67). Increased GR signaling affects factors that are involved in bone formation and calcium metabolism, finally leading to an increased risk of fractures (68,69). Due to the adverse effects inhibiting their unhampered prevalence, there has been extensive research about putative agonists and antagonists that attenuate or even eliminate these effects (70).

SNPs found in GR studies are associated with several already mentioned pathologies, including neuropsychiatric disorders, metabolic disorders and autoimmune diseases. Cardiovascular diseases have also been shown, defining the role of GR in stress and the importance of stress for coronary heart disease. Emotional stress is a usual trigger of cardiac events and there is even a syndrome known as stress cardiomyopathy that supports this evidence (24). Wounds and injuries

also surfaced following the analysis of GR SNPs, connecting the anti-inflammatory properties of GCs to another not so obvious target. GCs can suppress the migration of endothelial progenitor cells (EPCs) and impair wound healing, something that should be considered before using EPCs for autologous cell transplantation (71). On the other hand, dexamethasone has been shown to be of assistance to wound healing in animal models of frostbite (72). Therefore, further studies are required to define the factors implicated in changing the GC wound healing properties.

The role of GCs in cancer pathology and pathogenesis is still under evaluation. The effects of GCS on tumor progression appear to heavily rely on the cells targeted. In the case of lymphocytic malignancies, dexamethasone, a synthetic GC, is used to promote apoptotic cell death, while in epithelial cell tumors, GCs mostly exert the opposite effect (73). *In vitro* research has demonstrates that GCs suppress cell migration and invasion via the downregulation of Ras homolog family member A, matrix metalloproteinase (MMP)2, MMP9 and IL-6, or via the induction of E-cadherin (74). On the other hand, cancer research has also shown that an excess of GCs enhances the proliferation of tumor cells *in vitro* and *in vivo* (75). A poor immune system response and a poor prognosis have also been found to be associated with GC hypersecretion (76). GCs have been proven to deplete T cells that infiltrate tumors of adrenocortical carcinomas, while tumor-infiltrating lymphocytes were more effective against tumors in other cancer types (73). Cancer signaling is extremely complex and transcription factors, such as the GR display complex effects (77).

The GR signaling regulators appear to play a critical role in determining the various actions of the receptor. The SNPs of GR regulator analysis (Fig. 7) resulted in genes that revolved around the HPA axis, immune system, metabolism and brain architecture. Several brain-related diseases, including Parkinson's disease, Alzheimer's disease and epilepsy appear to be connected to GR signaling as well. Chronic inflammation places the immune system on alert and activates the HPA axis, producing GCs. High levels of GCs for a long period of time activate a pro-inflammatory environment in microglia and subsequently increase dopamine neuron degeneration, leading to clinical manifestations of Parkinson's disease (78). Stress is also referred to as a possible cause for epilepsy in several patients. Research using model mice has demonstrated that corticosterone administration to epileptic mice results in more epileptic episodes (79). PCOS also appears to be connected to impaired GC signaling. GC resistance was found in almost 67% of patients with PCOS in the study by Panayiotopoulos *et al* (80). Corticosteroids have also been used in the treatment of certain cancer types, such as hemangiomas, taking advantage of their ability to inhibit angiogenesis. The mechanism of dexamethasone in this case is the inhibition of the expression of VEGFA in hemangioma cells (81). Apart from its anticancer VEGFA-regulating effect, GR can also inhibit the secretion of VEGFA in endochondral ossification, thus disrupting the normal entrance of blood vessels and creating bone growth issues in children that have been administered GCs (82).

Of note, despite having no direct connection to GR or its interactome, a specific subunit of RNA polymerases I and III was identified in the analysis in the present study. POLR1C is a gene that codes for the RPAC1 subunit of ribosomal RNA polymerases I and III. Studies from over three decades ago have shown that GCs stimulate the production of rRNA in rat livers (83), probably making use of proteins activating the idle form of RNA polymerase I (84), although having no particular connection to the RPAC1 subunit. Perhaps the connection between GR and POLR1C is indirect and involves a few mediators. Bruna *et al* (85) demonstrated that the GR inhibits the c-Jun N-terminal kinase (JNK) pathway. Upon stress, JNK2 inactivates the TIF-IA transcription factor downstream the JNK pathway, which makes it impossible for TIF-IA to interact with RNA polymerase I and the initiation complex cannot be formed (86). The individual mechanisms through which the GR can inhibit the formation of RNA polymerase I complex, under conditions of stress are as follows: The GR LBD contains a hormone-regulated JNK docking site. Naturally, GR in the cytoplasm is associated with a protein complex. When GCs bind to the GR, the ligand-receptor couple unbinds the protein complex, and the JNK docking site is exposed. The GC-GR complex then travels to the nucleus and binds with JNK; thus, the consequent JNK deficiency does not allow proper signal transduction, causing the inhibition of the pathway (85). Under stress conditions, JNK phosphorylates TIF-IA at Thr200, inhibiting its interaction with Pol I, resulting to inability of RNA polymerase I to transcribe (86). An alternative path that could connect GR to RNA polymerase I is the mammalian target of rapamycin (mTOR) signaling pathway. The GR in skeletal muscles targets and mainly inhibits the mTOR pathway (87). With this pathway blocked, mTOR is unable to activate the transcription factor TIF-IA, altering its phosphorylation pattern, leading to no recruitment of Pol I to the rDNA promoter (88), and thus, to no rRNA synthesis. Additional research is required however, to clarify the exact mechanisms underlying the complex association of GR to RNA polymerase activity.

In conclusion, the present study established that SNPs found in the GR interactome participate in numerous biological processes of high importance, such as immune regulation, metabolism, development and proper brain function. Moreover, pathological conditions, such as autoimmune diseases, neuropsychiatric diseases, metabolic disorders and even cancer, appear to, in one way or another, be related with SNPs found in the GR interactome. The study of the mentioned SNPs may provide information on the mechanisms through which such diseases emerge and may help to promote personalized healthcare, where therapy can be selected based on an individual's genetic background for maximum effectiveness. A prime example would be using the SNPs of interest identified in the present study as diagnostic or prognostic markers for GR-related pathologies.

Another interesting observation of the present study was the underreported effect GR may have on rRNA synthesis through its indirect effect on the POLR1C gene. Since rRNA synthesis dysregulation has been associated with a broad range of diseases, further research may expand the network of pathologies influenced by glucocorticoids.

On the whole, the results obtained in the present study may prove to be useful both in a clinical and a research setting. It should be mentioned, though, that all information presented was extracted from the currently available literature where many articles may hold contradictory results. Moreover, as

the literature expands, specific associations may weaken or strengthen, affecting the importance of GR in several of the mechanisms analyzed. Nevertheless, since several associations mentioned appear to be have been hinted at previously, the present study appears to be in accordance with the current view of the functions of GR.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors (MS, TM, LP, EP, ID, KP, KD, DAS, FB, GPC, EE and DV) contributed to the conceptualization, design, writing, drafting, revising, editing and reviewing of the manuscript. All authors confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

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DAS is the Managing Editor of the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. GPC is an Editorial Advisor of the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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