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REVIEW

Genetic determinants of neuronal vulnerability to apoptosis

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Abstract Apoptosis is a common mode of cell death that contributes to neuronal loss associated with neurodegeneration. Single-nucleotide polymorphisms (SNPs) in chromosomal DNA are contributing factors dictating natural susceptibility of humans to disease. Here, the most common SNPs affecting neuronal vulnerability to apoptosis are reviewed in the context of neurological disorders. Polymorphic variants in genes encoding apoptotic proteins, either from the extrinsic (*FAS*, *TNF-α*, *CASP8*) or the intrinsic (*BAX*, *BCL2*, *CASP3*, *CASP9*) pathways could be highly valuable in the diagnosis of neurodegenerative diseases and stroke. Interestingly, the *Arg72Pro* SNP in *TP53*, the gene encoding tumor suppressor p53, was recently revealed a biomarker of poor prognosis in stroke due to its ability to modulate neuronal apoptotic death. Search for new SNPs responsible for genetic variability to apoptosis will ensure the implementation of novel diagnostic and prognostic tools, as well as therapeutic strategies against neurological diseases.

Keywords Genetic · Polymorphism · p53 · Neuron · Apoptosis · Neurodegeneration

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Abbreviations

AD	Alzheimer's disease
AIF	Apoptosis-inducing factor
ALS	Amyotrophic lateral sclerosis
Apaf-1	Adaptor protein apoptotic peptidase-activating factor
APOE ε4	Apolipoprotein E ε4
Bad	Bcl-2-associated death promoter
Bak	Bcl-2 antagonist/killer-1
Bax	Bcl-2-associated X protein
Bcl-xL	Bcl-2-like 1
Bcl-2	B-cell lymphoma-2
BH	Bcl-2 homology
Bid	BH3-interacting domain death agonist
Bim	Bcl-2-interacting mediator of cell death
CASP3	Caspase-3
CASP8	Caspase-8
CASP9	Caspase-9
CNS	Central nervous system
DISC	Death-inducing signaling complex
FAF1	Fas-associated protein 1
FasL	Fas ligand
HDM2	Human double minute-2
HLA	Human leukocyte antigen
LRRK2	Leucine-rich repeat kinase 2
Mcl-1	Myeloid cell leukemia-1
MDM2	Murine double minute-2
MS	Multiple sclerosis
Noxa	NADPH oxidase activator 1
OMM	Outer mitochondrial membrane
PCD	Programmed cell death
PD	Parkinson disease
PUMA	p53-upregulated modulator of apoptosis
SNP	single-nucleotide polymorphisms
tBid	Truncated Bid

Sp1	Stimulatory protein 1
TNF	Tumor necrosis factor
TRADD	TNFR-associated death domain protein

Introduction

Programmed cell death (PCD) is an essential and genetically regulated process of cell elimination that maintains the physiological function of all organs and tissues, including the brain [1–3]. Type I or apoptotic cell death is one of the modes of PCD that can contribute to the pathogenesis of many diseases, including cancer, ischemic vascular disease, and neurodegenerative disorders [4, 5]. In neurological diseases, the relative contribution of apoptosis to the degenerative process is yet controversial; however, it appears to be a contributing factor [5, 6]. This review specifically focuses on the genetic determinants to apoptosis as an attempt to better understand the human variability to neurological disorders.

Human natural variability and vulnerability to disease can be determined by single-nucleotide polymorphisms (SNPs) in chromosomal DNA. In this context, SNPs located within pro-apoptotic and antiapoptotic genes have been identified, and their function in tumor susceptibility widely investigated [7, 8]. Notably, cancer is associated with enhanced resistance to cell death, whereas neurodegeneration is caused by premature cell death [2, 9]. It is therefore conceivable that SNPs of genes involved in the negative regulation of apoptotic (i.e., with oncogenic potential) and pro-apoptotic (i.e., with tumor suppression potential) pathways might dictate the risk of developing certain neurological diseases. Here, the most common SNPs affecting neuronal vulnerability to apoptosis are reviewed. Interestingly, variants in genes encoding apoptotic proteins are highly associated with neurodegeneration and stroke. Unraveling novel associations of SNPs responsible for genetic variability to apoptosis with neurological disorders will help in identifying new targets and therapeutic strategies against these devastating diseases.

Neuronal apoptotic pathways

Apoptotic cell death is executed by cysteinyl aspartyl proteases (called caspases) that trigger a coordinated cascade of events leading to the cleavage of crucial substrates, which rapidly dismantle the cell. Caspases are present as inactive pro-enzymes in healthy cells, and are converted into their active forms by proteolytic cleavage at internal aspartic acid residues. This cleavage splits the caspase protein into a small and a large subunit. The caspase cascade involves: the initiator caspases and the executioner caspases. Initiator caspases contain a long pro-domain that provides a protein–protein interaction platform that allows the recruitment of pro-caspases into an activating protein complex. Long pro-domain caspases include caspases-1, -2, -4, -5, -9, -11, and -12 (with an N-terminal caspase-activating recruitment domain), and caspases-8 and -10 (with an N-terminal death effector domain). Executioner caspases-3, -6, and -7, which lack the large N-terminal non-enzymatic domain but posses a short pro-domain, are responsible for most of the cell destruction during apoptosis. Initiator caspases are activated in response to particular stimuli, whereas executioner caspases are particularly important for the ordered dismantling of vital cellular structures [10, 11].

Apoptosis typically proceeds through one of the two signaling cascades, known as extrinsic and intrinsic pathways, both of which converge to activate the executioner caspases-3 and -7 (Fig. 1). The extrinsic pathway is initiated by binding of death receptors, such as Fas or tumor necrosis factor (TNF), with their respective ligands [Fas ligand (FasL) and TNF-α]. This ligand-receptor binding causes receptor trimerization and recruitment of several adaptor proteins at the cytosolic death-domain receptor. FAS recruits FAS-associated death domain protein (FADD), whereas TNF receptor recruits TNFR-associated death domain protein (TRADD), which then recruits FADD. These proteins further bind initiator pro-caspase-8 (or -10) and form the death-inducing signaling complex (DISC) thus enabling their autoactivation [5, 12, 13]. Depending on the efficiency of DISC formation, activated caspase-8 can either directly activate the downstream executioner caspases-3 and -7 [14], or initiate the cleavage of the pro-apoptotic BH3-interacting domain death agonist (Bid), which in turn engages the mitochondrial apoptotic cascade [15, 16] (Fig. 1).

The intrinsic (mitochondrial) pathway is activated by stimuli that trigger the permeabilization of the outer mitochondrial membrane (OMM) followed by the release of proapoptotic proteins from the mitochondrial intermembrane space, leading to executioner caspase activation [17, 18]. This pathway is regulated by members of the Bcl-2 family of proteins that contain one or more Bcl-2 homology (BH) domains [3, 19, 20]. The anti-apoptotic subfamily comprises proteins that contain BH domains 1–4, such as Bcl-2, Bcl-2-like 1 (Bcl-xL), and myeloid cell leukemia-1 (Mcl-1), whereas the pro-apoptotic Bax and Bak contain BH domains 1–3 [21, 22]. A larger group of pro-apoptotic proteins, including Bcl-2-associated death promoter (Bad), Bcl-2-interacting mediator of cell death (Bim), and Bid, among others, contain only the BH3 domain.

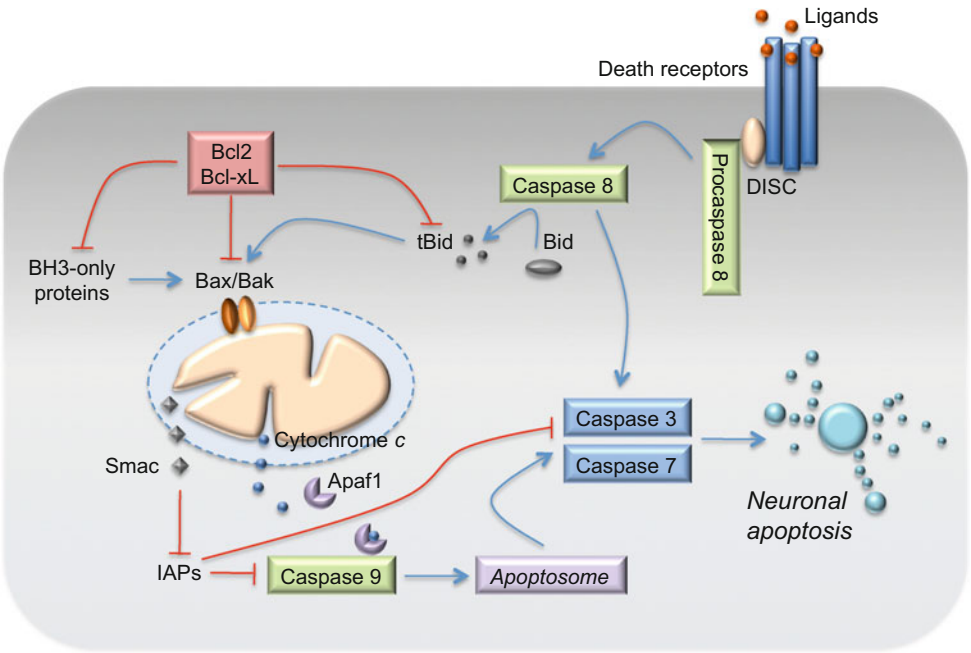

Fig. 1 The extrinsic and mitochondrial (intrinsic) apoptotic pathways. Apoptosis proceeds through one of two signaling cascades termed the extrinsic and mitochondrial (intrinsic) pathways. The extrinsic pathway is initiated by the ligation of transmembrane death receptors with their ligands, leading to the recruitment of adaptor molecules and to the formation of the pro-caspase-8 DISC. This results in the dimerization and activation of caspase-8, which can either directly cleave and activate caspase-3 and caspase-7, or cleave BH3-interacting domain death agonist (Bid), which in turn engages mitochondrial apoptotic signaling. Truncated Bid promotes the activation of Bax (Bcl-2-associated X protein) and Bak (Bcl-2 antagonist/killer-1), causing outer mitochondrial membrane (OMM) permeabilization. Antiapoptotic proteins, Bcl-2 (B cell lymphoma-2) and Bcl-xL (Bcl-2-like1), prevent OMM permeabilization by sequestering BH3-only proteins, or active Bax and Bak. BH3-only proteins promote Bax and Bak activation. The mitochondrial (intrinsic) pathway is activated by stimuli that trigger the OMM permeabilization and the release of proapoptotic proteins, such as Smac and cytochrome *c*, from the mitochondrial intermembrane space into the cytosol. Cytochrome *c* binds to apoptotic protease-activating factor 1 (Apaf-1), inducing its heptamerization and forming the apoptosome that recruits and activates caspase-9. Caspase-9 cleaves and activates the executioner caspase-3 and caspase-7. Smac inhibits the inhibitors of apoptosis proteins (IAPs). See text for a detailed description

Activator proteins, including truncated Bid (tBid), Bim, and other factors, such as p53, directly interact with and activates Bax and Bak, resulting in OMM permeabilization [23]. However, antiapoptotic proteins bind and sequester BH3-only proteins, and also bind any monomeric, activated Bax and Bak proteins that might be present [24]. BH3-only proteins provoke death by either binding to antiapoptotic proteins [22] or displacing activators and Bax and Bak from anti-apoptotic proteins, permitting progression of the death signal [25].

Following activation, Bax and Bak form homo-oligomers and participate in the formation of pores in the OMM The OMM permeabilization promotes the release of pro-apoptotic proteins from the mitochondria, including cytochrome *c* [26]; second mitochondria-derived activator of caspase (Smac) and HtrA2/Omi; and apoptosis-inducing factor (AIF) and endonuclease G, which can induce caspase-independent chromosomal DNA cleavage [27]. Once in the cytosol, cytochrome *c* joins the adaptor protein apoptotic peptidase-activating factor (Apaf-1) and deoxyATP, and form the apoptosome that recruits pro-caspase-9, resulting in the allosteric activation of caspase-9 and the subsequent activation of effector caspases-3 and -7 [28]. In parallel, cytosolic Smac neutralizes the inhibitors of apoptosis proteins, the key inhibitor of caspases-9, -3, and -7 [29] (Fig. 1).

Although neurological disorders are clinically and neuropathologically very different, studies in transgenic mouse models and in vitro have revealed that neuronal loss by apoptosis is one of the pathological hallmarks of neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), HD, amyotrophic lateral sclerosis (ALS), stroke, brain trauma, spinal cord injury, and diabetic neuropathy [5, 6]. However, its relative importance and role in human disease is still controversial, since other modes of cell death, including type II or autophagy and type III or necrotic cell death, also participate to neuronal loss, in some cases even with higher quantitative relevance than apoptosis [4, 5, 30]. In addition, it is difficult to demonstrate apoptosis convincingly in the

brains of patients because of methodological limitations and the imposition of strict criteria for the recognition of apoptosis. Despite these limitations, it is widely accepted that apoptosis participates in neuronal cell death and in the neurodegenerative process [5, 6].

In this context, different proteins involved in the mitochondrial apoptotic pathway have been detected in the brain of patients suffering from several neurological disorders [5]. Activated caspases-9 and -3, or their specific proteolytic products, have been reported in degenerating nerve cells of brain tissue affected by PD [31, 32], AD [33, 34], and ischemic stroke [35, 36]. Moreover, the down-regulation of antiapoptotic members of the Bcl-2 family (Bcl-2 and Bcl-xL), and/or the upregulation of their pro-apoptotic counterparts (Bax and Bak), have been documented in patients affected by distinct neurodegenerative disorders, including AD and PD [11, 32, 37–39].

The Fas–FasL system is expressed in the CNS, including glial cells and neurons, and is associated with the maintenance of the immune suppressed status in normal brain [40]. In developing brains, the Fas system participates in neurite branching through its death domain without caspase activation [41]. On the other hand, expression of Fas and FasL is significantly elevated in a variety of neurologic disorders, suggesting that this system may play roles in neurodegenerative and neuroinflammatory responses [40, 42, 43]. Disruption of Fas signaling pathways attenuates neurological damage in experimental cellular and animal models of neuropathological diseases by limiting cell death, including traumatic brain injury [44, 45], multiple sclerosis (MS) [46, 47], stroke [48, 49], ALS [50], AD [51, 52], and PD [53–55].

In the CNS, TNF-α is produced by astrocytes, microglia, and neurons in response to several extrinsic and intrinsic stimuli. Exogenous signals triggered by experimental exposure to bacterial and viral proteins induce inflammatory responses within the CNS and stimulates the expression of TNF-α, among other cytokines [56, 57]. TNF-α expression is also induced by cell-intrinsic stimuli relating to acute brain injury, including cerebral ischemia and trauma, and abnormal release and/or uptake of neurotransmitters, such as glutamate [57], which occurs in several neurodegenerative diseases and stroke [58]. Under these pathological conditions, elevated TNF-α production and TNF-α receptor expression were shown to contribute to neuronal cell death [57, 59, 60].

Polymorphisms in apoptotic genes

SNPs are genetic variations in chromosomal DNA sequences in which a single nucleotide is substituted by one of the other three nucleotides. To be considered a SNP, the least common allele should have a ≥1 % frequency in the human population. The human genome contains about 10–20 million SNPs. The protein coding sequences contain approximately 100,000–300,000 common SNPs, and additional SNPs lie within putative regulatory regions of genes that might be relevant for human health and disease. Although only 1 % of SNPs have the potential to affect directly gene function, this can account for the wide natural genetic diversity of humans [61].

The ability to execute apoptosis is subjected to interindividual variations in humans, which is attributed to genetic factors [8, 62]. Studies in twin pairs support the role of genetic portrait in determining the activity of apoptotic pathways [63, 64]. There are only a limited number of known coding SNPs within PCD pathways; however, numerous non-coding gene polymorphisms should also be considered due to their possible regulatory role. Several of these SNPs have potential functional significance in apoptotic cell death [8]. It is important to note that genetic determinants of apoptotic susceptibility may not be limited to protein-coding genes. The recently described involvement of microRNAs in major apoptosis-mediated pathological processes, including cancer and neurodegeneration [65–67], makes SNPs located within microRNAs and their binding sites to be considered as genetic determinants of disease risk. In this sense, the expression of miRNA molecules is altered in the brain of patients with neurodegenerative diseases, such as AD, PD, HD, and ALS, suggesting that microRNAs might have a crucial regulatory role in these disorders. Thus, polymorphisms in microRNA target sites may constitute an important determinant of neurodegenerative disease risk. The function of microRNA and miRNA target sites SNPs in neurodegeneration has been recently reviewed [65, 68, 69] hence will not be further discussed in this review. Here we review the most common SNPs in genes encoding proteins that modulate neuronal vulnerability to apoptosis. Interestingly, theses SNPs are associated with neurodegenerative diseases and stroke. SNPs with functional significance and clinical association with neurological disorders are summarized in Table 1.

Fas polymorphisms

Fas and FasL are expressed in the normal CNS, and their expression is increased in inflamed and degenerated brains. Therefore, the FasL–Fas system has a dual function in the CNS: maintaining the immune suppressed status in normal brain, and inducing neuronal cell death and inflammation in a variety of neurological disorders [40, 42, 43].

The *FAS* gene is placed in the 10q24 locus, which is involved in the risk of AD [70, 71] and MS [72], as judged by several linkage studies. Interestingly, activation of the

Table 1 Clinical association with neurological disorders and functional significance of single-nucleotide polymorphisms in apoptotic genes

Gene, SNP	Molecular description	Functional significance	Clinical association
FAS, −670A > G	A to G substitution within signal transducers and activators of transcription binding sites in the *FAS* promoter [73]	The −670 *A* allele is associated with higher level of gene transcription [73]	Associated with AD risk [74, 75]; other studies failed to show this association [78, 79, 83] Associated with MS risk [72, 80, 81]; Niino et al. [82] failed to show this association
FAS, −1377G > A	G to A substitution within Sp1 binding site in the *FAS* promoter [73]	The −1377 *G* allele is associated with higher level of gene transcription [73]	Associated with AD risk [83]
TNF-α, −308G > A	G to A substitution in the *TNF-α* promoter	The −308 *A* allele has higher transcriptional activity and gene expression than the *G* allele [113]	Associated with AD risk; however, data have led to disparate results [105, 109, 110] Increases the risk to develop early onset of sporadic PD [119]. Other studies failed to find this association [118] Associated with ischemic stroke risk, but the results have not been consistent across populations [121–125]
TNF-α, −850C > T	C to T substitution in the *TNF-α* promoter	The −850 *T* allele is associated with a higher level of gene transcription [113]	The *TNF* −850 *T* allele synergistically with carriage of the *APOE* ε4 alleles increase the risk of AD [105, 106]. No positive associations were found in an Italian population [113]
TNF-α, −1031C > T	C to T substitution in the *TNF-α* promoter	The −1031 *C* allele increases TNF expression [105]	Increases the risk of developing an early onset of sporadic PD [120]
CASP8, −652 6N ins/del	Six-nucleotide insertion/deletion in the *CASP8* promoter region	The −652 *6N del* variant destroys the Sp1-binding site and decreases RNA expression and caspase-8 apoptotic activity [130]	Not studied in neurological disorders
CASP9, −1263A > G	A to G substitution in the promoter of *CASP9*	The −1263 *GG* genotype enhances the transcriptional activity [141]	Not studied in neurological disorders
BCL2, −938C > A	C to A substitution in the inhibitory P2 *BCL2* promoter	The −938 *C* allele increases promoter activity and binding of nuclear proteins [147]	Not studied in neurological disorders

Table 1 continued

Gene, SNP	Molecular description	Functional significance	Clinical association
BCL2, rs956572A > G	A to G substitution in the intronic region of *BCL2*	The *AA* genotype is associated with lower Bcl-2 mRNA, protein concentrations and greater cellular sensitivity to stress-induced apoptosis [148]	Modulates grey matter volume in the ventral striatum of healthy subjects [148] Increases the risk to develop bipolar disorder [149]
BAX, −248G > A	G to A substitution in the 5′-UTR of *BAX*	The *−248 G* variant decreases constitutive Bax expression and increases the Bcl-2/Bax ratio [151, 152]	Not studied in neurological diseases
TP53, Arg72Pro	Codon 72 of human *TP53* has either the sequence *CCC*, which encodes proline, or *CGC*, which encodes arginine within a segment that encodes the proline-rich domain, which is important for p53-induced apoptosis [177, 206]	The Arg72 variant has enhanced capacity to trigger apoptosis in neurons [185] and proliferating cells [208–210] and increases neuronal vulnerability to ischemia-induced apoptosis [185]	The *Arg*/*Arg* genotype is associated with poor functional outcome after stroke [185] and traumatic brain injury [212] The *Arg*/*Arg* genotype is associated with higher risk for HD [214]; however, a replication study contradicts this association [215]
MDM2, 309T > G	T to G substitution in the first intron of *MDM2*, which acts as a transcriptional enhancer region [216]	The *309 T* allele increase the affinity of the transcriptional activator Sp1, resulting in higher levels of MDM2 RNA and protein and the subsequent attenuation of the p53 pathway [216, 218]	Not studied in neurological disorders

SNP single-nucleotide polymorphism

FasL–Fas signaling pathway participates in both neuronal and immune cell apoptosis of AD and, as a negative regulator, in the inflammatory component of MS. Moreover, FasL-mediated apoptosis may balance immune cell access to the brain of patients suffering from AD and MS [42]. The *FAS* promoter is polymorphic, including a G to A substitution at −1,377 bp (−1377G > A, rs2234767) and an A to G substitution at −670 bp (−670A > G, rs1800682), which occur within Sp1 and signal transducers and activators of transcription 1 transcription factor binding sites, respectively, thus modulating gene expression and apoptotic signaling [73]. The most widely studied *FAS* polymorphism is the −670A > G SNP. Several studies have shown a significant association between this polymorphism and AD risk; but others have not. An association between this polymorphism and non-familial early onset AD was reported in a Scottish population [74] and in subjects from Scotland and Sweden [75], the homozygous *GG* genotype being enriched in the AD patients. In both studies, the strongest association occurs in carriers of the apolipoprotein E ε4 (*APOE* ε4) allele, which is strongly associated with age at onset, risk, and unfavorable outcome in AD [76, 77]. These results imply that −670A > G SNP, in interaction with *APOE* ε4, is a genetic risk factor for sporadic early onset AD. However, other studies failed to validate these findings [78, 79].

Several population studies have also associated the −670A > G SNP with the risk of developing MS. In particular, the *FAS* −670 *G* allele decreases the risk of MS, but does not affect the course of the disease [72, 80]. Whereas Katarci et al. [81] described that the association of *FAS* −670A > G SNP with MS risk is restricted to women, other studies failed to show any association [82].

Sibley et al. [73] demonstrated that the −1377 *A* allele has reduced ability to bind transcription factor Sp1, while the −1377 *G* allele is associated with a higher level of gene transcription. One study in subjects from Italy reported an association between −1377G > A SNP and risk of developing AD and a differential rate of cognitive decline during a 2-year follow-up. However, this study did not show an association with either AD risk or rate of cognitive decline and the *FAS* −670A > G SNP [83].

Recently, Erten-Lyons et al. [84] described that a 3′UTR SNP in *FAS* gene (rs1468063) is associated with progression of AD and brain volume. In particular, the *CT* genotype was significantly associated with faster disease progression, smaller total brain, and larger ventricular volumes. While authors speculated that this SNP could cause functional changes in the mRNA structure or its stability, they do not show experimental data demonstrating a functional effect of this SNP. In the study, the authors concluded that rs1468063 SNP might modulate the response to Alzheimer's pathology by controlling Fas-mediated neuronal apoptosis.

The function of *FAS* SNPs on PD risk and outcome has been poorly explored. Fas-associated protein 1 (FAF1) was originally identified as a member of the Fas DISC that enhances apoptosis initiated through FasL [85]. FAF1 participates in diverse biological processes, including brain development and neural cell death [86]. *FAF1* gene is placed at *PARK10* locus on human chromosome 1p32, which is associated with late-onset PD [87]. Recently, Betarbet et al. [88] described that FAF1 levels are increased in the frontal cortex of PD patients, and increased FAF1 levels induces cell death and significantly potentiates the toxic effects of PD-related stressors, including oxidative stress and inhibitors of the mitochondrial complex I and the proteasome. Functional loss of FAF1 may provide a pro-survival signal to cells in a disease state, such as cancer and PD [89]. In this sense, SNP testing has revealed that *FAF1* is associated with a genetic locus implicated in susceptibility to Crohn's disease, increased risk for colorectal cancer [90], and papillary thyroid cancer [91]. However, the effect on PD risk remains unknown.

Dominant missense mutations in leucine-rich repeat kinase 2 (LRRK2) are the most common genetic cause of PD [92]. LRRK2 interacts with FADD and triggers neuronal death through the extrinsic apoptotic pathway. This pathway is activated by disease-triggering mutations, which strengthens the LRRK2–FADD association and the consequent recruitment and activation of caspase-8. The kinase domain of LRRK2 is essential for LRRK2–FADD interaction, since inhibition of the kinase function eliminates the increased FADD binding caused by PD mutations [93], and prevents neurodegeneration [94, 95]. In this context, PD patients have a higher frequency of a common recurrent mutation (G2019S, a glycine-to-serine substitution at codon 2019) located in the kinase domain of LRRK2 [96–98]. However, the effect of this mutation on LRKK2–FADD interaction is currently unknown.

TNF-α polymorphisms

The *TNF-α* gene, which maps within the class III region of human leukocyte antigen (HLA), is an important mediator of apoptotic and inflammatory responses. In humans, constitutive TNF-α and stimulated TNFR expression depend on two genetic biallelic polymorphisms in the *TNF* gene locus, localized in the promoter region and in the first intron. In one study, no relationship was found between *TNF-α* polymorphisms and elevated circulating TNF-α [99]; however, others demonstrated that SNPs of the promoter region of *TNF-α* gene affect binding to nuclear factors and influence the rate of transcription [100]. Nonetheless, it is unclear whether these variations are relevant for the in vivo regulation of gene activity [29, 100–102].

Circulating TNF-α levels are increased in the brain of AD patients [57, 103], and in vitro studies demonstrated that TNF-α induces the generation of the neurotoxic β-amyloid [104]. It has also been hypothesized that SNPs affecting levels of TNF-α affect the risk of developing AD [105]. Although several TNF-α SNPs have been described, only two promoter gene SNPs, −308G > A (rs1800629) and −850C > T (rs1799724), which modulates binding to transcription factors and affects gene expression, have been associated with increased risk of AD [105–110]. The *TNF-α −850 T* allele, synergistically with carriage of the *APOE ε4* alleles, increase the risk of AD in Caucasian Australians and Northern Europeans [105, 106]. Laws et al. [111] corroborated the interaction of *TNF-α −850 T* allele with *APOE ε4* alleles and its association with AD risk, and further reported an association with lower cerebrospinal fluid β-amyloid levels. However, no positive associations between TNF-α promoter haplotypes and AD disease were found in Italian population [112]. Regarding the TNF-α −308G > A SNP, the *A* allele has a higher transcriptional activity than the −308 *G* allele [113] and increases susceptibility for developing AD [108]. Although some case–control studies have associated −308G > A SNP with AD risk, data have led to disparate results [105, 109, 110]. It was suggested that discordant findings might indicate linkage with another locus nearby, different in the diverse population studied. In fact, the TNF-α −308G > A SNP is linked to different transcriptional activities depending on the different HLA haplotypes carrying this SNP [114]. In centenarians, the *TNF* −308G > A SNP has also been associated with the risk in age-related dementia and longevity. The few centenarians with *AA* genotype had increase prevalence of dementia and higher mortality risk and tended to show higher plasma levels of TNF-α than *GA* or *GG* genotypes. However, these findings need to be validated due to the low number of subjects with *AA* genotype included in the study [115]. Other SNPs of TNF-α, such as −863C > A, −238G > A, and −1031T > C, were also found to modulate transcriptional activity of *TNF-α* gene and to be associated with the risk of developing AD in different populations. However, the results have shown a high degree of heterogeneity, probably due to racial differences; besides that they were drawn from a limited number of studies. Thus, further investigations will be required to validate the impact of these SNPs on the risk of AD [105, 116].

Inflammatory processes play an important role in the pathogenesis of PD. Mogi et al. [117] demonstrated that TNF-α levels were enhanced in CSF and in the striatum of PD patients. Thus, genetically determined differences in cytokine production might influence the risk of developing sporadic PD [57, 118]. A significant increase in the frequency of *TNF* −308 *A* allele is found in PD patients, and the TNF −308 *AA* genotype increases the risk to develop early onset sporadic PD [119]. However, other studies failed to find this association [118]. Other genetic analysis of PD patients revealed that the occurrence of the −1031 *C* allele within the *TNF-α* promoter was markedly predictive of the early onset form of sporadic PD [120]. These findings suggest that modulation of TNF-α expression enhances the risk of developing PD, and further support the implication of dysfunctional TNF-α signaling in neurodegeneration [57].

The *TNF-α* gene has also been studied in stroke genomics. Several studies have reported a *TNF* −308G > A SNP association with ischemic stroke risk, but the results have not been consistent across populations [121–125]. While some studies found that the −308 *A* allele confers an increased risk of ischemic stroke in young patients [122] and in patients with a preceding febrile episode [124], other studies reported a protective role in adults with ischemic stroke [121] and lacunar infarcts [123]. Moreover, two case–control studies have documented that *TNF* −308 *A* allele is associated with resistance against ischemic stroke in males [126, 127]. However, Karahan et al. [128] found no association between the *TNF* −308G > A SNP and stroke. Whether population-specific differences in *TNF* −308 allelic frequencies, allelic heterogeneity, and variability in stroke classification criteria explain these contradictory results remains to be elucidated. Nevertheless, together, theses results suggest that *TNF-α* promoter region polymorphisms are responsible for the susceptibility against stroke and neurodegenerative diseases, but further studies are required to validate these findings.

Polymorphisms in the *CASP8* gene

Caspase-8 is an effector protein of the death receptor family pathway, thus mediating neuroinflammatory and neurodegenerative processes. Immunohistochemistry studies revealed that activated caspase-8-positive sites were localized in the brains of AD [129, 130] and PD [131] patients. The *CASP8* gene resides on chromosome 2q33. The most frequent references to *CASP8* SNPs in literature are (1) the *CASP8* promoter region six-nucleotide deletion/insertion (*−652 6N ins/del*; rs3834129) variant, and (2) a *D302H* SNP (rs1045485) coding region that results in aspartic acid-to-histidine substitution at codon 302. The *−652 6N del* variant in the *CASP8* promoter destroys the Sp1-binding site that results in decreased RNA expression and lower caspase-8 apoptotic activity [130]. While *CASP8* SNPs are strongly associated with the risk of developing several types of cancer [132–136], their association with neurological disorder development is yet unknown.

Gene expression profiling studies revealed that the *CASP8* gene is found in close proximity to a susceptibility region for MS located in chromosome 2 [137, 138]. Furthermore, the caspase-8 gene is differentially expressed in studies performed in MS, as well as in the experimental autoimmune encephalomyelitis animal model of MS [138]. Recently, Camiña-Tato et al. [139] described that *GG* homozygosity for the intronic SNP rs2037815 and *CT* heterozygosity for the intronic SNP rs12990906 are associated with primary progressive MS when compared with relapse-onset MS and control groups. Moreover, the *G* allele for SNP rs2037815 was associated with a trend towards faster disease progression in primary progressive MS patients. The authors [139] concluded that *CASP8* SNPs are not only associated with increased risk but also with disease susceptibility in primary progressive MS patients. However, Sand [140] described contradictory findings in this study, thus further studies remain to fully support the role of rs2037815 SNP on MS risk and progression.

Polymorphism in genes involved in the mitochondrial apoptotic pathway

Only a few mitochondrial apoptotic genes (*BAX*, *BCL2*, *CASP3*, *CASP9*) with potential functional significance have been genotyped in cancer patients versus healthy controls. Unfortunately, the majority of theses apoptosis-related SNPs have not yet been tested in appropriate case–control investigations [8].

Polymorphisms in the promoter region of the *CASP9* gene may influence the promoter activity of this gene, thereby modulating susceptibility to apoptotic cell death. In particular, the A to G substitution at −1,263A bp (rs4645978) in the promoter region of *CASP9* enhances the transcriptional activity of this gene [141]. The functionality of this SNP has been established in cancer risk and intervertebral disc degeneration. In this context, the *CASP9* −1263 *GG* genotype, with lower transcriptional activity, was associated with a decreased risk of lung cancer when compared to that of −1263 *AA* [141]. On the other hand, subjects with the −1263 *GG* genotype have a higher risk of developing lumbar disc disease than those with the −1263 *AA* genotype [142, 143].

Polymorphisms in the *CASP3* gene also influence caspase-3 production and/or activity, thereby modulating the susceptibility to lung cancer [144, 145]. Accordingly, Jang et al. recently reported, in a case–control study, an association of *G*-containing genotype for −928A > G, *A*-containing genotype for 77G > A, and *C*-containing genotype for 17532A > C SNPs with reduced risk for lung cancer.

The *BCL2* gene, located on chromosome 18q21.3, consists of one large intron, three exons and two promoters with different functional properties. The second promoter (P2) is located 1,400 bp upstream of the translation initiation site and decreases the activity of the P1 promoter, thus functioning as a negative regulatory element [146]. Nückel et al. [147] described that the regulatory −938C > A SNP in the inhibitory P2 *BCL2* promoter affects promoter activity, binding of nuclear proteins, and Bcl-2 protein level in B cells from chronic lymphocytic leukemia patients. The *C* allele displayed significantly increased *BCL2* promoter activity and binding of nuclear proteins compared with the *A* allele. Concomitantly, the *AA* genotype is associated with increased Bcl-2 protein expression and unfavorable prognosis and overall survival in patients with chronic lymphocytic leukemia. Thus, the −938C > A SNP could be a good candidate to modulate neuronal survival.

Salvadore et al. [148] recently described an intronic SNP (rs956572) in the *BCL-2* gene that exerts functional effects on Bcl-2 expression, since the *AA* homozygous genotype is associated with lower Bcl-2 mRNA, protein concentrations and greater cellular sensitivity to stress-induced apoptosis in human lymphoblasts. The *A* allele directly affects the brain by significantly reducing grey matter volume in the ventral striatum of healthy subjects [148]. In addition, the rs956572 SNP has been associated with the risk of developing bipolar disorder. Machado-Vieira et al. [149] reported in a recent study that bipolar disorder patients carrying the *AA* genotype exhibited elevated basal cytosolic Ca^{2+}, in comparison to *GG* homozygotes, and suggested that it might be a good candidate for a risk allele in mood disorders.

Finally, experiments in mice have revealed a link between a SNP in the *BAX* promoter (−515 SNP) with the quantitative difference in Bax expression that affects neuronal cell death. Neurons harboring the −515 *T* polymorphic variant have twice the level of endogenous Bax protein and higher susceptibility to apoptosis than −515 *C* neurons [150]. Interestingly, a similar phenotype has been described in humans. Saxena et al. [151] demonstrated that high Bcl-2/Bax protein ratio contributes to death resistance in chronic lymphocytic leukemia. They described a novel −248G > A SNP in the 5′-UTR of the human *BAX* gene that decreases constitutive Bax expression and increases the Bcl-2/Bax protein ratio. In consequence, chronic lymphocytic leukemia patients that possess the −248G > A SNP (*GA*/*GG* genotype) show higher resistance to treatment, and a shorter overall survival, than those patients with a wild-type genotype [151, 152]. Given the relatively high prevalence in the normal population [152] and the central role of Bax in neuronal apoptosis [153–155], the *BAX* −248G > A SNP might also

contribute to susceptibility of neurons in genetically complex neurodegenerative diseases.

Bcl-2 protein levels are modulated by the nuclear transcription factor p53. In particular, p53 trans-activate Bax [156], among other pro-apoptotic proteins, leading to Bcl-2 downregulation and apoptotic cell death. Furthermore, p53 mediates neuronal apoptosis in acute and chronic neurological disorders, including experimental cerebral ischemia [157–160], ischemic stroke [161, 162], AD [163–165], and PD [166, 167]. Due to the high impact of p53 in the control of cell survival, the role of *TP53* polymorphisms on neuronal susceptibility to apoptosis is discussed in a separate section below.

Polymorphisms in the *TP53* gene

The TP53 is a tumor suppressor gene encoding the nuclear transcription factor p53 that regulate several major cellular functions including gene transcription, DNA synthesis, DNA repair, cell cycle regulation, senescence, and cell death. In neurons, p53 mediates apoptosis induced by a range of insults including DNA damage, hypoxia/ischemia, trophic withdrawal, hypoglycemia, oxidative stress, and viral infections [168].

The p53 is short-lived and constitutively expressed, at low levels, in most cell types including neurons [169]. The levels of p53 protein are key for its activity, and are tightly controlled in the cell by covalent modifications [170]. Under unstressed conditions, the interaction of p53 with murine double minute-2 (MDM2) or the human homolog (HDM2) regulates continuous and rapid p53 degradation [171]. In the nucleus, HDM2/MDM2 binds to the transactivation domain of p53, ubiquitylates the protein and mediates its transport into the cytosol, where it is ubiquitylated and then degraded by the proteasome [172, 173]. In turn, p53 transcriptionally regulates MDM2 expression and hence the levels of both p53 and MDM2 are balanced through a negative feedback loop [174]. The related MDM4 protein, also known as MDMX, also modulates p53 activity [175]. The relationship between p53, MDM2 and MDM4 at the molecular level is complex; MDM2 binds to *TP53* mRNA, controlling the rate of translation [176], and MDM2 regulates its own levels as well as those of MDM4 and p53 [177].

Under stress conditions, including DNA damage, p53 is stabilized and activated by phosphorylation or acetylation of p53, uncoupling p53 from its negative regulators, mainly the HDM2/MDM2 system, and by proteasome inhibition [178]. The activation of p53 triggers apoptosis by transcriptional activation of pro-apoptotic genes, and by transcriptional-independent mechanisms. On the one hand, p53 can mediate apoptosis by inducing the expression of Bax [156] and other pro-apoptotic proteins, including Bid [179], NADPH oxidase activator 1 (Noxa) [180], and p53-upregulated modulator of apoptosis (PUMA) [181], among other pro-apoptotic proteins that directly act on mitochondria and induce apoptosis. Furthermore, p53 can promote apoptosis through transcription-independent pathways that may involve translocation to mitochondria and direct protein–protein interactions [182, 183]. Recent studies have shown that p53 directly induces OMM permeabilization either by forming an inhibitory complex with protective Bcl-2 or Bcl-xL [160, 184, 185] or by transcriptionally independent activating of Bax, resulting in cytochrome *c* release and apoptosis [186].

Accumulation of p53 is essential for neuronal apoptosis in response to DNA damage, oxidative damage, cellular calcium overload, and excitotoxicity. In vivo and in vitro studies reveals that increased expression of p53 is associated with neuronal apoptosis following stroke [157–159, 187, 188] and traumatic brain injury [189–191]. Inhibition of p53 activity by systemic administration of pifithrin-α increases brain resistance to ischemic and excitotoxic injury [160, 192, 193]. Accordingly, mice lacking the *TP53* gene show decreased neuronal damage after ischemic injury [194].

In addition to acute neurological disorders, progressive neuronal death associated with enhanced p53 levels has been detected in chronic neurodegenerative diseases including AD [165] and PD [167]. Accumulation of p53 in brain tissue has been detected in toxin-induced animal models of PD [195, 196] and in AD patients [197, 198]. Moreover, inhibition of p53 either with pharmacological inhibition or dominant negative constructs is neuroprotective against PD and AD [192, 198, 199].

Most of SNPs in the *TP53* gene occur in non-coding sequences. The best characterized intronic *TP53* polymorphism is a 16 base pair insertion in intron 3 (*Ins16bp*, rs17878362), which has been associated with an increase in the risk of several types of cancer; however this association might be a consequence of the close proximity of this polymorphism to the codon 72 polymorphism in exon 4 (*Arg72Pro*; rs1042522) [177, 200]. So far, the *Arg72Pro* SNP of *TP53* gene is the only apoptosis-associated SNP that has been validated and subjected to a systematic analysis.

The TP53 codon 72 polymorphism (Arg72Pro)

Codon 72 is located in exon 4 in the segment of *TP53* that encodes the proline-rich domain, which is important for p53 function, particularly for its ability to induce apoptosis [201, 202]. This domain contains the common polymorphic site, specific to humans, and has either the CCC sequence,

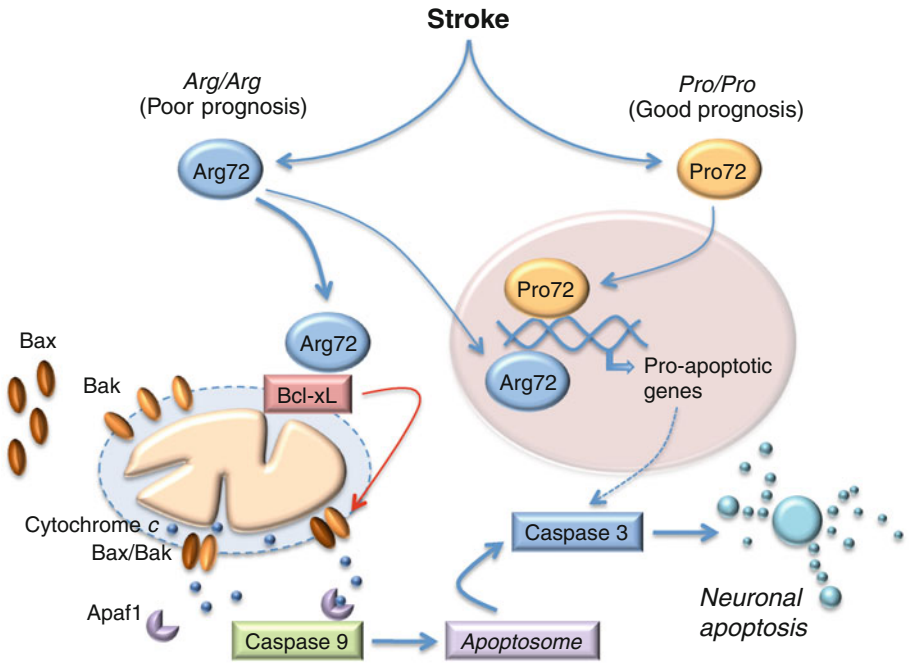

Fig. 2 The human *TP53 Arg72Pro* SNP modulates neuronal susceptibility to ischemia-induced neuronal apoptosis and dictates functional prognosis after stroke. Functional prognosis after stroke is associated with *TP53 Arg72Pro* SNP. The *Arg/Arg* genotype is associated with poor functional prognosis after either ischemic or hemorrhagic stroke; the good prognosis is mainly restricted to stroke patients harboring the *Pro* allele. While both Arg72 and Pro72 polymorphic variants can identically transactivate p53-downstream pro-apoptotic genes, Arg72, but not Pro72, translocates to the mitochondria, where it directly binds to, and inactivates, Bcl-xL, thus inducing mitochondrial outer membrane permeabilization. Subsequent cytochrome *c* release from the mitochondria to the cytosol promotes the activation of caspase-9 and -3, leading to neuronal apoptosis

which encodes proline (Pro72), or CGC, which encodes arginine (Arg72) [177, 203].

The SNP in codon 72 (*Arg72Pr*) was first described as a non-tumor-derived amino-acid change that altered the mobility and affected the structure of the proline-rich domain [204, 205]. In 1999, Thomas et al. [206] described for the first time that the Arg72 variant of p53 was more efficient than the Pro72 one at both suppressing transformation by oncogenes and initiating apoptosis. Noteworthy, the frequency of the *Pro* allele changes with latitude, the areas with intense exposure to the sunlight being the highest, and northern European territories the lowest [207]. All these observations demonstrate that the two alleles might produce functionally distinct proteins. It has been repeatedly demonstrated by different groups that the *Pro* allele is associated with reduced apoptotic potential of the protein in proliferating normal and tumor cells. Thus, the Arg72 variant of p53 is more effective at inducing apoptosis and protecting stressed cells from neoplastic development than the Pro72. This determines that *Arg72Pro* SNP has been associated to cancer progression, the age of its onset, and the overall survival of individuals [177, 203, 208–210].

Although one study presented data supporting a transcriptional-dependent mechanism to explain the different apoptotic potentials of the p53 polymorphic variants [211], most studies have reported the absence of differences in specific DNA binding or transcriptional activity between them. This led to demonstrate that the enhanced apoptotic capacity of the Arg72 variant was a consequence of its transport to the mitochondria, resulting to cytochrome *c* release to the cytosol and caspase-dependent apoptotic cell death [185, 209, 210].

Recently, we [185] revealed that the Arg72 variant of p53 has a higher capacity to trigger neuronal apoptosis than the Pro72 one. Moreover, Arg72 increased the vulnerability of neurons to ischemia-induced apoptotic cell death through the activation of the mitochondrial pathway. We found that Arg72 translocates to the mitochondria and directly binds to, and inactivates, Bcl-xL, thus inducing cytochrome *c* release to promote caspase-9 activation and neuronal apoptosis (Fig. 2). Moreover, in two independent hospital-based prospective cohorts of patients we also described that the *TP53 Arg72Pro* SNP strongly determines functional outcome after stroke, regardless whether the origin is ischemic or hemorrhagic [185]. The *Arg/Arg* genotype was strongly associated to poor functional outcome after stroke, good prognosis being mainly restricted to stroke patients harboring the *Pro* allele (Fig. 2). Thus, *Arg/Arg* genotype governs neuronal vulnerability to apoptosis and can be considered as a genetic marker predicting

poor functional outcome after either ischemic or hemorrhagic stroke [185].

Similarly, Martinez-Lucas et al. [212] found that *TP53 Arg72Pro* SNP is linked to functional outcome after traumatic brain injury in humans. They found that the *TP53 Arg/Arg* genotype is associated with increased risk of a bad outcome at discharge from the surgical intensive care unit.

The association of *Arg72Pro* SNP with the risk and progression of chronic neurodegenerative diseases is less clear. A case–control association study between sporadic AD and this SNP found no association between this locus and the risk, age of onset, and progression for AD [213]. Chattopadhyay et al. [214] conducted a case–control study for *Arg72Pro* SNP and found the *Arg/Arg* genotype in the *TP53* gene to be a significant risk factor for HD. However, in a replication study, Arning et al. [215] contradicted this finding and found no association between *Arg72Pro* SNP and the age of onset in HD.

The MDM2 309T > G polymorphism

The E3 ubiquitin ligase MDM2 directly binds to and inhibits p53 by regulating its location, stability, and activity as a transcriptional activator [173, 176]. The essential role of MDM2 in the regulation of p53 activity argues that SNPs at this locus should be considered as a potential modulation of p53 function. In fact, polymorphisms in the *MDM2* gene have been reported to influence cancer risk, or synergize with, p53 SNPs—or mutations—to modify cancer risk [177]. Although several polymorphisms have been identified in the *MDM2* gene, the most intensively characterized SNP is a *T* to *G* substitution found at position 309 (309T > G, rs2279744) in the first intron of the MDM2 oncogene, which serves as a transcriptional enhancer region [216]. This SNP increases the affinity of the transcriptional activator Sp1, resulting in higher levels of MDM2 RNA and protein, with the subsequent attenuation of the p53 pathway [216–218]. Furthermore, the elevated levels of MDM2 in cells carrying the homozygous 309 *GG* genotype result in the inability to properly stabilize p53 and the attenuation of the p53 response to cellular stresses like DNA damage. Although the 309T > G SNP has been extensively associated with accelerated tumor formation in both hereditary and sporadic cancers in humans [216–218], its possible role in stroke and neurodegenerative diseases is largely unknown.

Concluding remarks

Apoptosis regulates selective cell elimination, and SNPs in genes encoding apoptosis regulatory proteins contributes to individual vulnerability to both cancer and neurological disease. Polymorphic variants in genes encoding apoptotic proteins that are associated with high risk of developing neurodegenerative diseases and stroke can reduce the risk of cancer. An interesting example is the *Arg72Pro* SNP of *TP53*, the gene encoding tumor suppressor p53, a key regulatory protein in apoptosis. Humans harboring the *Arg/Arg* allele of *TP53* are more vulnerable to poor prognosis in stroke, and less susceptible to cancer, than those bearing the *Pro/Pro* allele. Thus, unraveling new associations between the SNPs dictating genetic variability to apoptosis and neurological diseases may help to identify novel diagnostic and prognostic tools, targets and therapeutic strategies against these disorders.

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