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ABCC9/SUR2 in the brain: implications for hippocampal sclerosis of aging and a potential therapeutic target

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Abstract

The *ABCC9* gene and its polypeptide product, SUR2, are increasingly implicated in human neurologic disease, including prevalent diseases of the aged brain. SUR2 proteins are a component of the ATP-sensitive potassium ("K_{ATP}") channel, a metabolic sensor for stress and/or hypoxia that has been shown to change in aging. The K_{ATP} channel also helps regulate the neurovascular unit. Most brain cell types express SUR2, including neurons, astrocytes, oligodendrocytes, microglia, vascular smooth muscle, pericytes, and endothelial cells. Thus it is not surprising that *ABCC9* gene variants are associated with risk for human brain diseases. For example, Cantu syndrome is a result of *ABCC9* mutations; we discuss neurologic manifestations of this genetic syndrome. More common brain disorders linked to *ABCC9* gene variants include hippocampal sclerosis of aging (HS-Aging), sleep disorders, and depression. HS-Aging is a prevalent neurological disease with pathologic features of both neurodegenerative (aberrant TDP-43) and cerebrovascular (arteriolosclerosis) disease. As to potential therapeutic intervention, the human pharmacopeia features both SUR2 agonists and antagonists, so *ABCC9*/SUR2 may provide a "druggable target", relevant perhaps to both HS-Aging and Alzheimer's disease. We conclude that more work is required to better understand the roles of *ABCC9*/SUR2 in the human brain during health and disease conditions.

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Keywords

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Introduction

Hippocampal sclerosis of aging (HS-Aging) (Nelson, et al., 2014,Nelson, et al., 2015) is a common age related brain disorder, characterized by cognitive deterioration that mimics Alzheimer disease (AD) clinically but has a different brain histopathology, a distinctive genetic predisposition, and a later age range for maximal risk (Brenowitz, et al., 2014,Murray, et al., 2014,Nelson, et al., 2013,Zarow, et al., 2012). Although HS-Aging and AD are challenging to distinguish in a living patient (Brenowitz, et al., 2014,Pao, et al., 2011,Yu, et al., 2015), it is likely that each disease will require different strategies for prevention or treatment. The underlying pathogenesis of HS-Aging is unknown currently, but there are indications that the *ABCC9* gene may play a key role. This review will summarize what is known about the *ABCC9* gene in the human brain and describe our hypothesis linking *ABCC9* with HS-Aging. We consider the relevant genetic and evolutionary biologic literature, along with current understanding of *ABCC9* function and how the gene may be related to other human diseases.

ABCC genetic phylogeny and the role of ABCC9 paralogs in human diseases

ABCC9 (ATP-binding cassette, sub-family C member 9) gene products are referred to as sulfonylurea receptor 2 (SUR2) proteins. The term “sulfonylurea receptor” derives from the fact that sulfonylurea drugs bind to and block protein activity. Thus we employ established terminology referring to the *ABCC9* gene, which serves as the template for *SUR2* mRNA and SUR2 protein (Nichols, et al., 2013,Shi, et al., 2012). SUR2 regulates potassium (K+) channels in plasma membrane and intracellular organelles (Fig. 1), and other aspects of genomic regulation and protein function are described in greater detail below.

Themes emerge to shed light on human *ABCC9* from studies in other species. The “ABC” gene cluster encode large transmembrane proteins and members of this gene family have been identified from every biologic phylum including bacteria (Cui and Davidson, 2011,Igarashi, et al., 2004). Each gene encodes polypeptides with the same basic unit being one or two nucleotide binding domains (NBD), each associated with a conserved transmembrane domain (TMD) (Igarashi, et al., 2004). Historically, the ABCC sub-cluster was termed “multidrug-resistant associated proteins” because of the ability of some ABCC proteins to extrude drugs and toxins from cells (Bouige, et al., 2002,S.F. Zhou, et al., 2008). The “SUR”-subclass of ABCC genes contain a pair of TMD-NBD domains, with a unique third TMD (TMD0, Fig. 2). SUR genes encode a subtype of K+ channel regulators, and K+ channels are the most widely expressed ion channel among biologic species (Littleton and Ganetzky, 2000) with a broad range of functions.

Absent in plants and fungi, direct SUR gene orthologs are numerous in invertebrate species (Frey, et al., 1998,Sturm, et al., 2009), and these genes provide clues about the evolutionarily ancient SUR gene functions. In *D. melanogaster*, for example, a direct SUR ortholog was identified (Dermauw and Van Leeuwen, 2014). This “dSUR” gene has been implicated in aging, metabolism (including lipid processing and insulin signaling), sleep, and survival after infection or stress (Akasaka, et al., 2006,Allebrandt, et al., 2013,Croker, et al., 2007,Nasonkin, et al., 1999,Ocorr, et al., 2007). There are intriguing results that indicate that dSUR plays a role in aging; the gene is important in the cardiac hypoxic stress response but downregulated in aging (Akasaka, et al., 2006,Nishimura, et al., 2011,Ocorr, et al., 2007). The spider *T. urticae* harbors the largest number of ABCC subfamily member genes of any animal known, including a SUR gene (Dermauw, et al., 2013). The expansive “burst” of ABCC genes in this agricultural pest species may help explain this species’ ability to resist pesticidal strategies (Dermauw, et al., 2013). By contrast, some invertebrate species (silkworms) appear to lack direct SUR homologs (Xie, et al., 2012).

Among vertebrate species, two SUR-type paralogs are relatively well conserved -- termed *ABCC8*/SUR1 and *ABCC9*/SUR2 in humans (Fig. 1). Protein sequence homology between human and zebrafish SUR2 is 79–80% (Fig. 3). It is clear from genetic manipulation that these SUR genes play phylogenetically durable roles in multiple organs and tissues, including stress response, metabolism, and regulation of blood vessel function (Babenko, et al., 1998,Bryan, et al., 2007,Flatt, et al., 1994,Seino, et al., 2000,Seino and Miki, 2003,Solbach, et al., 2006). Interestingly, there have been shown to be age-dependent changes in KATP channels in a number of species including humans (Bao, et al., 2013,Du, et al., 2013,Kawano, et al., 2010,Toyoda, et al., 1997,Tricarico, et al., 1997,Vajapey, et al., 2014). As discussed below, the molecular basis of their function is understood to be primarily as K+ channel regulators(Nichols, 2006), but there are multiple studies suggesting additional actions that may contribute to the wide physiological impact. *ABCC8*/SUR1 function is best understood in its role in the vertebrate pancreas and central neuronal tissue, as a controller of insulin secretion and neuronal excitability. In non-mammalian vertebrates, the *ABCC9*/SUR2 orthologs (sur2), in both goldfish (*Carassius auratus*), and in yellowtail flounder (*Limanda ferruginea*), are reported to participate in those species’ cardiac hypoxic stress response (Cameron, et al., 2013,MacCormack and Driedzic, 2002). Some neurobiological functions have also been implicated for SUR2 in non-mammalian vertebrates. For example, experiments in frogs showed that SUR modifying drugs impacted the neuromuscular junction presynaptically (Salgado, et al., 1993). In chickens, an opioid signaling cascade includes SUR2 modulation (Tu, et al., 2008).

Additional clues about potential physiological and pathogenetic roles are provided by *ABCC9* paralogs in the human genome, presumed to have evolved from a common ancestral gene, that are associated with altered risk for human diseases. For example, mutations of *ABCC7*/CFTR cause cystic fibrosis, the most common fatal genetic disease in Americans (Riordan, et al., 1989). In comparison to *ABCC7*, *ABCC8/SUR1* is far more homologous to *ABCC9/SUR2* (Fig. 3). *ABCC8* is considered to be more highly expressed in the human brain than *ABCC9* (Shi, et al., 2005), and *ABCC8*/SUR1 has been implicated in neuropathologic processes (Jiang, et al., 2007,Mehta, et al., 2013,Simard, et al.,

2008a,Simard, et al., 2008b,Simard, et al., 2012,Tosun, et al., 2013). Mutations in *ABCC8* are associated with congenital hyperinsulinism and diabetes (Bonfanti, et al., 2015,Bryan, et al., 2007,Efferth, 2003,Haghverdizadeh, et al., 2014,Remedi and Nichols, 2009,Smith, et al., 2007). In the latter case, more severe mutations are associated with a complex syndrome (Developmental delay, Epilepsy and Neonatal diabetes, DEND), in which CNS excitability is aberrant, as a result of hyperactivity of the SUR1-regulated K_{ATP} channel activity. That the same disease can result both from mutations in ABCC8 and in the associated K+ channel pore gene, *KCNJ11*/Kir6.2, located nearby in Chromosome 11p (Fig. 1)(Busiah, et al., 2013,Florez, et al., 2004,Gloyn, et al., 2003,Koster, et al., 2008,Laukkanen, et al., 2004,Nielsen, et al., 2003,van Dam, et al., 2005) underscoring the complex interconnectedness of the SUR genes with their K+ channels (Bonfanti, et al., 2015,Inoue, et al., 1997,Olson and Terzic, 2010).

We can summarize three themes relevant to human *ABCC9* functions, based on studies of other genes and organisms. First, *bona fide* SUR genes expressed in invertebrates have been associated with diverse functions including resistance to various stressors and neurotoxins. Second, multiple genes of the ABCC cluster, that share characteristics with *ABCC9*, are associated with human disease conditions including neuropathological outcomes. And finally, among vertebrates, 2 SUR and 2 Kir proteins are strongly conserved, widely expressed, and closely interconnected in function.

ABCC9/SUR2 function: biochemistry and physiology

SUR proteins provide regulatory subunits of K_{ATP} channels which respond to metabolic perturbations (Minami, et al., 2004,Nichols, 2006). A complex interplay has been characterized between ATP inhibition, via an interaction with the pore-forming subunit, and ADP-dependent activation, via interaction with the NBDs of the SUR subunit. These activities result in channel sensitivity to local metabolic state -- opening when the ratio of ATP/ADP is low. By blocking or enhancing the ADP (activation) effect, the compendium of pharmacologic agonists and antagonists, many of which are used extensively in humans (de Weille, et al., 1989,Isomoto and Kurachi, 1997,Jackson and Bressler, 1981a,Jackson and Bressler, 1981b,Melander, et al., 1989,Misler and Giebisch, 1992,Stowers and Borthwick, 1977), interact directly with the SUR subunits.

Biochemical and biophysical studies indicate that the functional K_{ATP} channel is an octamer consisting of four pore-forming Kir6 proteins, each associated with one SUR subunit (Clement, et al., 1997,Shyng and Nichols, 1997) . The association is necessary for the complex to traffic to the cell membrane: both SUR and Kir6 proteins contain polybasic sequences that act as endoplasmic reticulium retention signals, which are effectively masked when the two proteins are associated (de Araujo, et al., 2011,Lodwick, et al., 2014,Nichols, 2006,Park, et al., 2008,Park and Terzic, 2010). The genes that encode these proteins are shown in Fig. 1, and the understood geometric dispositions of the various proteins depicted in cartoon form. Although biochemical regulation of the K_{ATP} channel function is incompletely understood, particularly in the brain, a number of post-translational modifications have been reported. For example, SUR2 is affected directly by glycosylation, sulfhydration, and protein kinase A phosphorylation (Gade, et al., 2013,Gao, et al.,

2014,Kang, et al., 2014,Light, 1996). The K_{ATP} channel is also regulated via separate phosphorylation event(s) in the Kir6.x channels (Edwards, et al., 2009,Ko, et al., 2008,Sanada and Kitakaze, 2004,Sun, et al., 2008), again showing complex functional interdependence of these proteins.

RNA splicing, producing alternative *SUR2* mRNA transcripts, is a conspicuous feature of *ABCC9/SUR2* regulation (Chutkow, et al., 1999,Shi, et al., 2005,Ye, et al., 2009). Reported *ABCC9*-derived transcripts are presented in Fig. 4. Most prior studies have focused on two important *SUR2* splice variants, which are termed *SUR2A* and *SUR2B*. These transcripts are generated through differential splicing of two *ABCC9* exons which encode the polypeptides' carboxy terminal portions (Chutkow, et al., 1996,Davis-Taber, et al., 2000,Inagaki, et al., 1996,Isomoto, et al., 1996). *SUR2A* has been reported to show relatively high expression in cardiac and skeletal muscle cells, whereas *SUR2B* is more broadly expressed including in smooth muscle cells and brain (Chutkow, et al., 1996,Davis-Taber, et al., 2000,Isomoto, et al., 1996,Ploug, et al., 2010,Shi, et al., 2005).

A poorly understood RNA splicing event skips 25 internal *ABCC9* exons to produce a smaller gene product that is trafficked to the internal mitochondrial membrane (Ye, et al., 2009). This "mitoSUR" protein variant (~55kDa) is approximately one third the size of "full-length" SUR2 (Figs. 2B, 4G) and the pharmacologic properties are profoundly different from the larger daughter proteins of *ABCC9* (Liu, et al., 2001) . The mitoSUR has been described in many contexts including mammalian brain (Aggarwal, et al., 2010,Aggarwal, et al., 2013,Fahrenbach, et al., 2014,Lacza, et al., 2003,Maack, et al., 2009). Genetic lesions in *ABCC9* may also differentially affect the expression/splicing, or function, of mitoSUR, SUR2A, and/or SUR2B depending on sequence location. There are other *SUR2* transcripts for which the protein products' functions are essentially unknown (Fig. 4), and these observations underscore the necessity for obtaining more basic information about *ABCC9*.

Experimental studies have elucidated numerous functions for K_{ATP} channels, varying by cell-specific, developmental, metabolic, and stress related factors. Here we show schematic diagrams depicting current hypotheses that may be relevant to human brain K_{ATP} channels (Figs 5–7). Each figure represents a different paradigm where SUR2 is involved in response to different stimuli and to changes in environment.

In many different cell types, SUR2 may compensate for stress and/or hypoxia by changing membrane hyperpolarization toward a voltage state that attenuates local intracellular Ca^{++} levels (Fig. 5). Much of the published experimental work to date has focused on cardiac myocytes, where K_{ATP} channels are involved in the important paradigm of "ischemic preconditioning" (Rana, et al., 2015,Sanada and Kitakaze, 2004), a term that refers to experimentally induced resistance to the adverse impact of loss of blood supply. Similar paradigm(s) probably occur in human CNS (Alkan, 2009,Busija, et al., 2008,Yuan, et al., 2004). In the vascular smooth muscle cell within the media layer of arterioles (Fig. 6), the K_{ATP} channels transmit signals from blood-borne and local factors to modulate blood flow. Notably, this cartoon ignores other members of the neurovascular unit such as endothelial cells, pericytes, and astrocytes, which express K_{ATP} channels also (see below). Finally, in

the CNS (Fig. 7), multiple cell types express SUR2 (see below) and the pleitropic effects of the gene may include neurotransmitter-responsive excitability (Sun and Hu, 2010). There is a recurrent theme of SUR2 proteins sensing Mg^{++}/ADP levels to promote K_{ATP} channels' opening and local Ca^{++} processing; however, the physiologic result varies widely according to the microenvironment.

ABCC9 in the brain

Specific K_{ATP} channel functions are challenging to define experimentally because of complexity at many levels: the variable components in mature K_{ATP} channels, different splice variants of both SUR proteins, functional changes that may result from altered intracellular trafficking, post-translational modifications, and the idiosyncrasies of channel functions from cell type to cell type. A recent review listed over 50 different K+ channel proteins in the mammalian CNS, and acknowledged formidable "challenges presented by the combined molecular complexity of [K+ channels] and structural complexity of the mammalian brain" (Trimmer, 2015). That review article focused on the pore-forming K+ channel proteins so *ABCC9*/SUR2 was not mentioned. As stated above, K_{ATP} channels may be composed of mixtures of regulatory (SUR1/SUR2) and pore-forming (Kir6.1/Kir6.2) subunits (Wheeler, et al., 2008,Yoshida, et al., 2004) and each combination has different attributes (Cheng, et al., 2008,Yamada, et al., 1997) although there may be constraints on the combinatorial potential of an individual channel complex (Giblin, et al., 2002). A discussion of some of the characteristics of the various K_{ATP} channel assemblages is presented elsewhere (Babenko, et al., 1998). Relatively little is known about the gene regulatory orchestration of the biologically integrated channel components in brain. Interestingly, the human *SUR2* 3'UTR is variable in length (al) which may be a pathway for regulating transcript stability (Nelson and Keller, 2007). Further, mouse *Sur1* and *Sur2* expression can be regulated through promoter DNA methylation (Fatima, et al., 2012).

A fundamental question is -- which cells express the mRNA and proteins? In brief, SUR2 is likely expressed in every cell type of the human brain, including neurons, astrocytes, oligodendrocytes, ependymal cells, microglia, pericytes, vascular smooth muscle, and endothelial cells. It is a common overgeneralization that SUR2A is a skeletal and cardiac muscle protein whereas SUR2B is a vascular smooth muscle protein -- the actual expression pattern of SUR2 isoforms is less straightforward. One of the technical limitations to the study of *ABCC9*/SUR2 is the lack of "gold-standard" molecular probes that could characterize comprehensively the subtypes of *ABCC9*-derived transcripts and polypeptides that are expressed. From the perspective of lab bench researchers that have assessed the results of multiple SUR2 antibodies, we can attest to the imperfect apparent specificity of some of these probes in our hands (see Ref. (Nelson, et al., 2014)). Prior studies of SUR2 gene expression focused on non-human mammals. Zhou et al (Zhou, et al., 2012) studied SUR2 distribution (mRNA and protein) in rat brain and found widespread expression; neurons predominantly expressed SUR2A whereas SUR2B was more expressed in glial cells. Interestingly, arteries from different anatomical areas of pig brains also were reported to show distinctive profiles of SUR2A and SUR2B expression (Jansen-Olesen, et al., 2005,Ploug, et al., 2006,Ploug, et al., 2008). Probes that were not isoform-specific demonstrated SUR2 protein in rat dorsal root ganglia neurons (Zoga, et al., 2010), and, a

study of hippocampal neurons using single-cell PCR showed that SUR2 expression was more common among hippocampal interneurons than pyramidal-type excitatory neurons (Zawar, et al., 1999). Experiments in cultured primary rat neurons also found substantial SUR2 expression (Ma, et al., 2009). A different study of rats showed that neuronal SUR2 expression (both mRNA and protein level) increased following neurotoxin lesions in the prefrontal cortex (S. Wang, et al., 2005).

Looking beyond anatomical and cellular distribution patterns, assessment of the functional roles of *ABCC9*/SUR2 in the mammalian brain is also confounded by the imperfect specificity of many of the experimental approaches. For example, most of the drugs that impact SUR2, including glibenclamide, also affect SUR1. Many prior studies– in the substantia nigra, in the hypothalamus, and elsewhere have focused on SUR1. Single cell RT-PCR indicates that the K_{ATP} channels in those cells are probably comprised primarily of SUR1 and Kir6.2 (Hicks, et al., 1994,Lee, et al., 2011,Liss, et al., 1999,Wu, et al., 1996), but over-reliance on the sulfonylurea marker [3H-Glibenclamide] may detect SUR2 as well as SUR1, and genetic manipulations in rodents have focused on the Kir6.x genes, which do not distinguish between Sur1 or Sur2 partner proteins.

Although there is evidence to indicate *ABCC9*/SUR2-related mechanisms are important for neuron (Ma, et al., 2008,Ma, et al., 2009,Tanner, et al., 2011,Xie, et al., 2010,Zawar, et al., 1999), astrocyte (Wang, et al., 2014,Zhou, et al., 2012,Zhu, et al., 2008), and oligodendrocyte (Fogal, et al., 2010) function, there are presently more bases for a discussion of the published literature regarding the impact of *ABCC9*/SUR2 on brain vasoregulation. SUR2 may contribute in multiple ways to the complicated task of regulating CNS blood flow and neuroinflammation. In particular, K_{ATP} channels have been shown to play important roles in vascular smooth muscle cells (Ko, et al., 2008,Nichols, et al., 2013,Shi, et al., 2012,Standen and Quayle, 1998,Sun and Hu, 2010) including primary effects of vasoactive diffusible factors (nitric oxide and hydrogen sulfide) (Liang, et al., 2011,Shi, et al., 2012,Wang, et al., 2014). SUR2-containing K_{ATP} channels are biochemical substrates partly responsible for vasodilation following oxygen and/or glucose deprivation (Adebiyi, et al., 2011). There have been relatively few study of brain arterioles in association with genetic or pharmacologic manipulations of SUR2 per se. However, smooth muscle cells are not the only cell type of the neurovascular unit that express *ABCC9*; for example, SUR2B was identified as upregulated in rat capillaries of stroke-prone spontaneously hypertensive rats and hypothesized to contribute to their endothelial dysfunction (Kirsch, et al., 2001). Further, in mouse embryo brains, *ABCC9* is robustly expressed in the pericytes (Bondjers, et al., 2006). Finally, there are multiple lines of evidence that K_{ATP} channels help regulate inflammatory signaling in microglia. SUR2B may modulate the microglial release of pro-inflammatory factors including TNF-alpha and reactive oxygen species (Sun and Hu, 2010). Microglia appear to activate a microglial->neuronal precursor mechanism that includes K_{ATP} channel activation (Ortega, et al., 2012,F. Zhou, et al., 2008). However, many of the above studies are confounded by both technical and theoretical complexities that render an “overview” challenging.

A perspective on prior discoveries related to *ABCC9*/SUR2 in the brain, along with insights into therapeutic potential, may be conveyed through a cross-section of the reports that

focused on a particular drug candidate molecule, iptakalim (systematic name: 2, 3–dimethyl-N-[1-methylethyl]-2-butanamine). Iptakalim is an "atypical K_{ATP} channel opener" agent that is administered orally and penetrates the blood-brain barrier, with pharmacologic activation of K_{ATP} channels that varies by SUR protein types: SUR2B>SUR2A>>SUR1 (Costa, 2009,Gao, et al., 2005,Sikka, et al., 2012). Iptakalim has been shown to exert effects that hint at the potential for clinical benefits. The drug is neuroprotective in experimental models of stroke and Parkinson's disease (Hu, et al., 2005,H. Wang, et al., 2005a,H. Wang, et al., 2005b,Wang, et al., 2004,S. Wang, et al., 2005,Wang, et al., 2006,Yang, et al., 2004,Yang, et al., 2005,Yang, et al., 2009,Zhang, et al., 2011,Zhou, et al., 2007). Other experimental results reported for iptakalim in mammals include beneficial neurochemical effects that may help to combat depression or psychoses (Lu, et al., 2014,Volf, et al., 2012). Preliminary clinical trials have indicated lack of adverse side effects in human research volunteers (Cai, et al., 2012,Duan, et al., 2011). Much remains to be learned about the potential therapeutic and/or side effects of iptakalim.

ABCC9 gene variants in human diseases: overview

For iptakalim or any drug, exhaustive biologic characterization is not a necessary prerequisite to developing a therapeutic strategy. There are many examples of drugs whose safety and efficacy were determined prior to full insights into drug mechanism(s). This may be kept in mind as we shift topics, from the incompletely understood *ABCC9* mechanisms of action, and toward a description of human diseases that are linked to the gene.

Multiple *ABCC9* allelic variants are associated with human diseases. A genetic disease condition called hypertrichotic osteochondrodysplasia, or Cantu syndrome (Harakalova, et al., 2012,van Bon, et al., 2012), is caused by heterozygous *ABCC9* mutations that so far are clustered in the exons encoding the core of SUR2 (Czeschik, et al., 2013,Harakalova, et al., 2012,van Bon, et al., 2012) and therefore will be expressed in SUR2A and SUR2B (Grange, et al., 2014,Nichols, et al., 2013). Cantu syndrome is rare with <100 cases reported to date (Scurr, et al., 2011) (see below). The clinical features include disorders of bones, heart, and hair follicles (hirsuitism) with macrocephaly often observed (Cantu, et al., 1982,Nevin, et al., 1996). Whereas the reasons for the manifestations are not known, the mechanism for Cantu syndrome is gene gain-of-function, reducing the sensitivity of channel activation to the ADP/ATP ratio (Nichols, et al., 2013). While ABCC8 or KCNJ8 gene deletion in mice results in a Prinzmetal angina-like phenotype with elevated blood pressures (Chutkow, et al., 2002,Li, et al., 2013,Miki, et al., 2002), no specific human monogenic syndrome has yet been definitively linked to loss-of-function mutations in *ABCC9*.

Of direct relevance to the current review, prior published reports all lack neuropathologic workup, but underscore that this disease often includes neurological complications, with a cerebrovascular component documented in some cases (Table 1). Different reports have noted the presence of "mild" mental retardation, autism, intellectual disability, and/ or neuroimaging-based brain abnormalities – at least one of these conditions was noticed in 28/47 (60%) of Cantu syndrome cases described to date (Table 1). The neurologic developmental delay that can be seen in Cantu syndrome may be partly secondary to skeletal muscle manifestations, i.e. hypotonia (Grange, et al., 2014) or may be related to alterations

in brain blood flow. Importantly, two mutations in *KCNJ8*/Kir6.1 which also result in gain-of-function in expressed K_{ATP} channels, are associated with Cantu syndrome, along with neurological phenotype with tortuous cerebral blood vessels (Brownstein, et al., 2013,Cooper, et al., 2014).

Whereas Cantu syncrome is a congenital defect that may have pleitropic manifestations, a number of exonic *ABCC9* variants have been associated with cardiovascular diseases including atrial fibrillation, vasospasm, dilated cardiomyopathy, and myocardial infarction (Barajas-Martinez, et al., 2012,Beziau, et al., 2014,Bienengraeber, et al., 2004,Kane, et al., 2005,Nichols, et al., 2013,Olson, et al., 2007,Smith, et al., 2013); Table 2. Variants in *ABCC9* have also been reported in association with Brugada (cardiovascular) syndrome and early repolarization syndrome (Barajas-Martinez, et al., 2012,Hu, et al., 2014). In prior studies, as with Cantu syndrome cases, there has not been systematic neuropathological nor neuroimaging-based assessment of blood vessels to date in the brains of patients with disease-associated exonic *ABCC9* polymorphisms.

In contrast to the results of *ABCC9* exonic mutations, intronic single nucleotide polymorphisms (SNPs) have been linked to diverse non-cardiac clinical phenotypes (Table 2). Some genetic associations were reported that are intriguing but did not identify a single particular SNP that met criteria for a statistically significant association with a specific disease. For example, *ABCC9* SNPs were associated with Hirschprung disease (most significant SNP was rs704192) in a genomewide association study (GWAS) of 123 persons with “sporadic” Hirschprung disease, and 432 unaffected controls (Kim, et al., 2014). In a separate GWAS with 281 elderly individuals, a SNP (rs10743430) was associated with entorhinal cortical thinning on magnetic resonance imaging (MRI) (Furney, et al., 2011). Further, 2 reports linked *ABCC9* polymorphism with hypertension. Sato et al (Sato, et al., 2006) identified a combination of SNPs that correlate with essential hypertension in a cohort of 405 individuals, and Kamide et al (Kamide, et al., 2013) found in a cohort of 265 persons that an *ABCC9* SNP is associated with responses to anti-hypertension drugs.

In terms of genomic studies that reported statistically significant associations between *ABCC9* SNPs and human illnesses, these conditions have tended to be brain disorders: sleep problems, depression, and HS-Aging. These SNPs are best considered “risk factors” because the allelic variant shows far lower genetic penetrance than the exonic mutations. The sleep and depression studies come from two separate research groups and the results incompletely overlap. Allebrandt et al (Allebrandt, et al., 2013) found that there is an *ABCC9* SNP (rs11046205) associated with sleep duration. A follow-up study by Parsons et al (Parsons, et al., 2013) failed to replicate the primary SNP association but identified a rare polymorphism nearby (rs11046209) that was associated with altered sleep duration and found that rs11046205 status was associated in that sample with depressive symptoms (Parsons, et al., 2013).

ABCC9 in hippocampal sclerosis of aging (HS-Aging)

The association between *ABCC9* genetic polymorphism and HS-Aging suggest a pathogenetic mechanism with substantial impact on public health. HS-Aging is prevalent

among aged individuals, affecting up to 25% of the “oldest-old” (Kuslansky, et al., 2004,Leverenz and Lipton, 2008,Murray, et al., 2014,Zarow, et al., 2008,Zarow, et al., 2012). HS-Aging mimics AD clinically (Brenowitz, et al., 2014,Nag, et al., 2015,Pao, et al., 2011), and the association between HS-Aging pathology and antemortem cognitive impairment is strong, factoring in all other known pathologies (Nag, et al., 2015,Nelson, et al., 2010). Importantly, HS-Aging tends to occur in individuals older than 85 years of age at death (Dickson, et al., 1994,Murray, et al., 2014,Nelson, et al., 2011,Nelson, et al., 2013).

The neuropathology of HS-Aging is characterized by cell loss and astrocytosis in the hippocampal formation of aged persons that is out of proportion to the Alzheimer’s-type plaques and tangles (Montine, et al., 2012). Focusing on the pathology-based endophenotype, we performed a GWAS and replication experiment that incorporated 363 HS-Aging cases and 2303 controls, from 5 separate large autopsy cohorts, with every case pathologically evaluated (Nelson, et al., 2014). This study yielded only a single statistically significant risk locus for HS-Aging, an *ABCC9* SNP pair (rs704178 and rs704180) that are co-inherited. Subsequently, we performed an additional replication assessment of a separate group of individuals with 51 HS-Aging cases and 561 controls (again, all cases were pathologically verified) that replicated the association between rs704180 risk genotype and HS-Aging pathology (Nelson, et al., 2015). Interestingly, there appears to be genetic “hotspot” with common SNPs associated with HS-Aging pathology and other disease phenotypes. For example, the SNP associated with Hirschprung disease (Kim, et al., 2014) -- rs704192 -- is in relatively close linkage disequilibrium to rs704180 (r^2=0.55, D’ statistic ~0.91). The SNP associated with both sleep duration and depression (Allebrandt, et al., 2013,Parsons, et al., 2013) -- rs11046205 -- is in the same intron as rs704178, <2000 bases away. We also note that the SNP (rs10743430) that showed association (Furney, et al., 2011) with entorhinal cortical thinning (P~1e-7 but not genomewide significant) is not within the *ABCC9* gene itself, but upstream and intergenic. However, evaluation of public access databases indicate that rs10743430 may be an expression quantitative trait locus for *ABCC9* (data not shown).

Prospects for development of therapeutic strategies may be enhanced by better understanding disease mechanisms. A key challenge is determining which disease paradigm best fits for HS-Aging: is it a neurodegenerative disease, or a cerebrovascular disease? Cerebrovascular diseases are characterized by disrupted blood supply, with relatively unpredictable clinical and anatomic disease progression. By contrast, neurodegenerative diseases usually follow a progressive clinical course, with pathognomonic “inclusion bodies” within specific brain areas.

Although the pathogenesis of HS-Aging is incompletely understood, some published findings suggest vascular factors cause or exacerbate the disease. Dickson et al (Dickson, et al., 1994), in a seminal study of 13 aged individuals with hippocampal sclerosis, observed severe “arteriosclerosis” in 12 of the 13 cases, after which others (Reed, et al., 2007,White, et al., 2002,Zarow, et al., 2008) also hypothesized a link between hippocampal sclerosis and cardiovascular risk factors. Subsequent studies have provided a more specific focus. We performed a systematic analysis of multiple large autopsy series and found that among vascular pathologies in the brain, only arteriolosclerosis – dysmorphic changes in small

arterioles (Fig. 8) – is associated with HS-Aging pathology (Neltner, et al., 2014). In HS-Aging cases, arteriolosclerosis was observed in regions outside of the hippocampal formation, indicating a “whole-brain disease” rather than a disease process isolated to the medial temporal lobe. Intriguingly, Montagne and colleagues recently showed that subtle blood-brain barrier dysfunction and “leaky vessels” in the human hippocampus precede cognitive impairment in advanced aging (Montagne, et al., 2015). Winkler et al (Sagare, et al., 2013) reported that pericyte damage could contribute to cognitive impairment through disruption of the neurovascular unit, which may relate to HS-Aging rather than AD. *ABCC9* has also been shown to be expressed in pericytes and its impairment associated with leaky vessels (Bondjers, et al., 2006), and K_{ATP} channels have been shown to be sensitive to cerebral ischemia (Armstead, 1997,Lindauer, et al., 2003,Sun and Hu, 2010).

Alongside the findings linking HS-Aging to cerebrovascular disease, brains of patients with HS-Aging pathology have pathologic features that are indicative of a neurodegenerative condition. A key pathologic biomarker for HS-Aging is aberrant TDP-43 inclusion bodies that may resemble the staining pattern of hippocampal TDP-43 pathology observed in frontotemporal lobar degeneration (FTLD), a neurodegenerative disease (Amador-Ortiz, et al., 2007a,Amador-Ortiz, et al., 2007b,Aoki, et al., 2015,Neumann, et al., 2006). Further, some gene variants (in or near *GRN* and *TMEM106B* genes) that are associated with increased risk for HS-Aging (Dickson, et al., 2010,Murray, et al., 2014,Nelson, et al., 2015,Pao, et al., 2011,Rademakers, et al., 2008) were previously associated with increased risk for FTLD (Deming and Cruchaga, 2014,Van Deerlin, et al., 2007). The clinical course of HS-Aging also tends to follow the trajectory of a neurodegenerative disease (Nelson, et al., 2011).

So how could HS-Aging be related to both cerebrovascular disease and neurodegenerative disease? The *ABCC9* genetic association may be a critical clue to help solve the riddle. Although there are valid reasons to contradistinguish neurodegenerative and cerebrovascular disorders, there is increasing evidence in support of a more nuanced paradigm with “mixed” pathogenetic mechanisms in the aged human brain (Montine, et al., 2014,Snyder, et al., 2014,Weller, et al., 2015). TDP-43 pathology is not specific for neurodegenerative diseases, having been reported in a wide variety of brain disorders including Alexander’s disease, Down syndrome, low-grade glial neoplasms, and chronic brain trauma (Davidson, et al., 2011,Lee, et al., 2008,Ling, et al., 2013,McKee, et al., 2010,Walker, et al., 2014), so there is overlap between pathologic findings that are seen in “reactive” and “neurodegenerative” conditions. Note that in each of the above conditions there is a brain injury or disease that occurs over a long time period, as opposed to an acute condition. It is quite possible that a subtype of chronic vascular insult(s) could induce TDP-43 phosphorylation and misfolding, although acute anoxic or hypoxic changes lack TDP-43 pathology (Amador-Ortiz, et al., 2007b,Lee, et al., 2008,Nelson, et al., 2011,Zarow, et al., 2008). Conversely, many vascular abnormalities have been described in AD brains (Brown and Thore, 2011,Farkas and Luiten, 2001,Hamel, 2014,Hunter, et al., 2012,Kalaria, et al., 2012). The established functions of human *ABCC9*/SUR2 include both regulating arteriolar smooth muscle tone and participating in pathways that have been implicated in neurodegenerative diseases, e.g., hypoxia/ischemia, neuroinflammation, and injury responses. There are also published

studies that support direct connections between *ABCC9*/SUR2 and neurodegenerative diseases, including both HS-Aging and AD. For example, in a study of *Abcc9* knockout mice, the biological pathway most affected (versus wildtype) was “Alzheimer’s disease” (Gao, et al., 2014). Moreover, treatment of mice that model Alzheimer’s-type pathology with SUR2 activators causes attenuation of pathology (Goodman and Mattson, 1996,Heurteaux, et al., 1993,Kong and Ba, 2012,Liu, et al., 2002,Liu, et al., 2010,Liu, et al., 2003). There is as yet unclear understandings of the cross-talk between the normal and disease pathways. A very recent paper found direct evidence for $K_{AT}P$ channels regulating brain Aβ peptide release, and concluded that “the identification of these channels as a link between hyperglycemia and AD pathology creates an avenue for translational research in AD.” (Macauley, et al., 2015)

Data from multiple sources are thus compatible with the novel hypothesis that long-term *ABCC9* dysregulation due to a genetic variant may manifest, in the “oldest-old”, in a pathologic phenotype that combines features of a cerebrovascular disease (arteriolosclerosis) and a neurodegenerative disease (hippocampal TDP-43 pathology and cell loss). The $K_{AT}P$ channels may also be directly relevant to AD pathology. The details of a stereotypical timeline or causal hierarchy of mechanisms are as yet beyond our grasp but Fig. 8 conveys one plausible hypothesis, and a credible molecular pathway for disease modification.

Going forward: prospects for neurotherapeutic strategies

ABCC9/SUR2 is an attractive candidate for therapeutic strategies because it is well-established as a “druggable target”. Pharmacological agents that modify SUR function are well known and prescribed widely around the world. Both agonists (nicorandil, diazoxide, iptakalim) and antagonists (sulfonylurea drugs) have been applied in clinical trials. In addition to treatment of monogenic diseases such as Cantu syndrome, such drugs may be repurposed for other human pathologies including cardiovascular diseases, as well as sleep disorders and depression. Currently we have no perfect animal model for HS-Aging to study with these well-characterized drugs. This is an area of active research in our laboratory. An important point about characterized drugs that affect SUR2 function is that each has different specificity for SUR2A, SUR2B, and SUR1, and each could exert different impact on the brain due to blood-brain barrier penetration and other factors (for example, the sulfonylurea drugs tend to be water-insoluble (Davis, et al., 1982,Miralles, et al., 1982)). The overall impact on an organism and/or disease progression is therefore stochastic and more work may be required to engineer drugs tailored to specific targets, and applicable to particular brain functions or diseases.

In summary, the *ABCC9* gene, and its polypeptide SUR2 product, occupies an intriguing biological niche relevant to stress response and vasoregulation in the brain. The direct implications for human diseases are most sharply defined for Cantu syndrome, characterized by subtle but intriguing neurological manifestations. Potentially more important in terms of human disease prevalence are the associations between *ABCC9* and sleep disorders, depression, and HS-Aging. For now, more understanding of the biology of *ABCC9*/SUR2 and K_{ATP} channels in the human brain is required. Better resources for manipulation and

assay of K_{ATP} channel subcomponents are also needed, in order to realize the potential for positive impact on public health through greater focus on this pathogenetic gene.

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Highlights

- ABCC9 encodes SUR2, a metabolic sensor protein that has been shown to change (expression and function) in aging
- ABCC9 is also strongly implicated in vasoregulation
- ABCC9 has been implicated in neurologic diseases including sleep, depression, and hippocampal sclerosis of aging (HS-Aging)
- HS-Aging is a prevalent and impactful brain disease of advanced old age
- ABCC9/SUR2 is a potentially druggable target that may provide a future therapeutic strategy

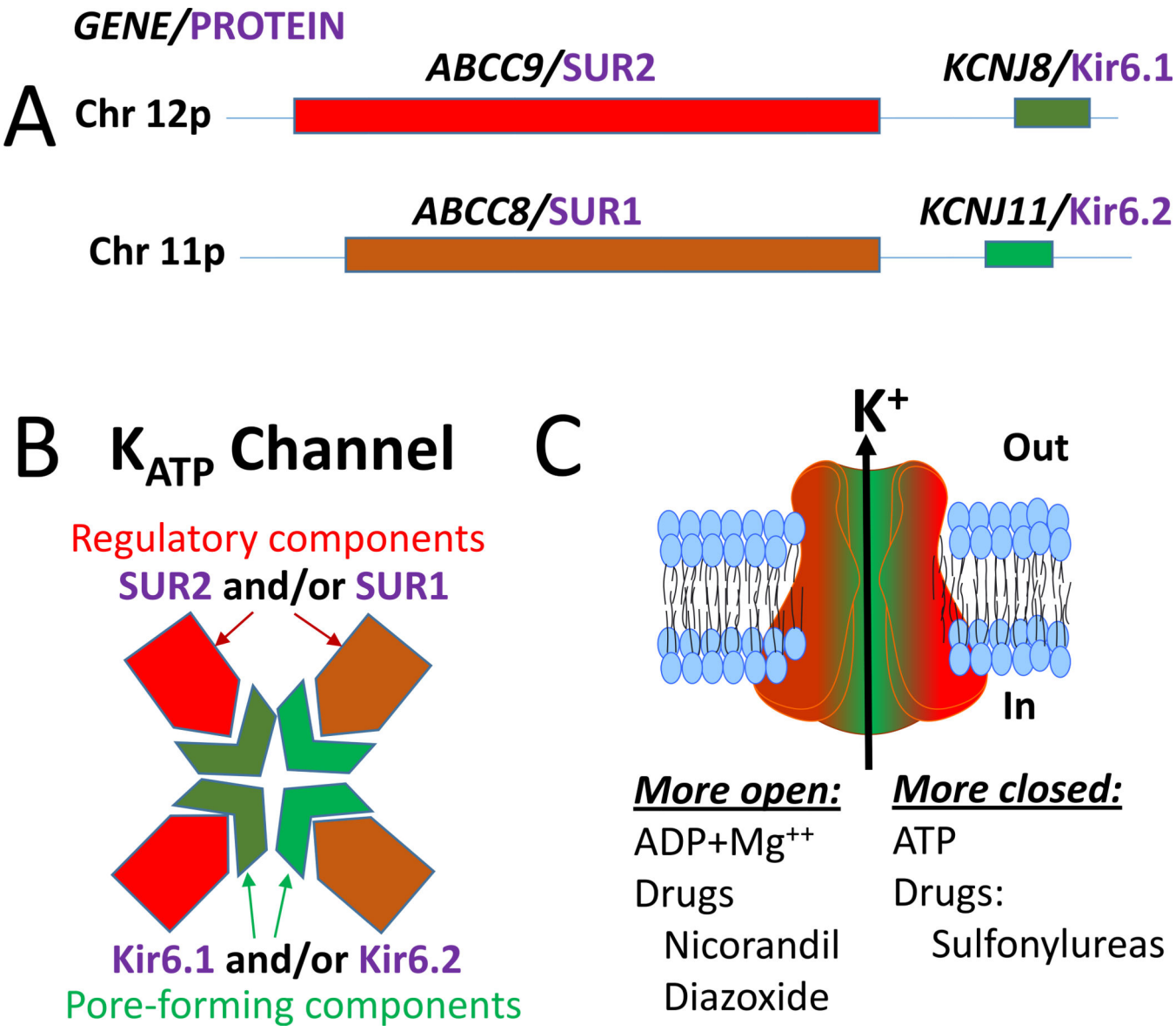

Figure 1. Schematic representation of the genes and proteins that make up the human K_{ATP} channel

A. The *ABCC9* gene resides on chromosome 12p and encodes the SUR2 protein. Approximately 20 kilobases 3' from *ABCC9* is the *KCNJ8* gene that encodes for the Kir6.1 protein. Paralogous genes on chromosome 11p are *ABCC8*, which encodes for SUR1 protein, and *KCNJ11* which encodes for Kir6.2 protein. B. Studies on crystal structure have elucidated how the K_{ATP} channel is organized in the plasma membrane. The K_{ATP} channel constitutes a hetero-octamer that includes combinations of 4 SUR1/SUR2 proteins, and 4 Kir6.1/Kir6.2 proteins, with the Kir6.x proteins forming the channel pore. C. When the K_{ATP} channel is functionally working in the plasma membrane, it allows K+ ions out and is responsive to ATP/ADP ratio and pharmacological agonists (e.g., nicorandil and diazoxide) and antagonists (sulfonylurea drugs).

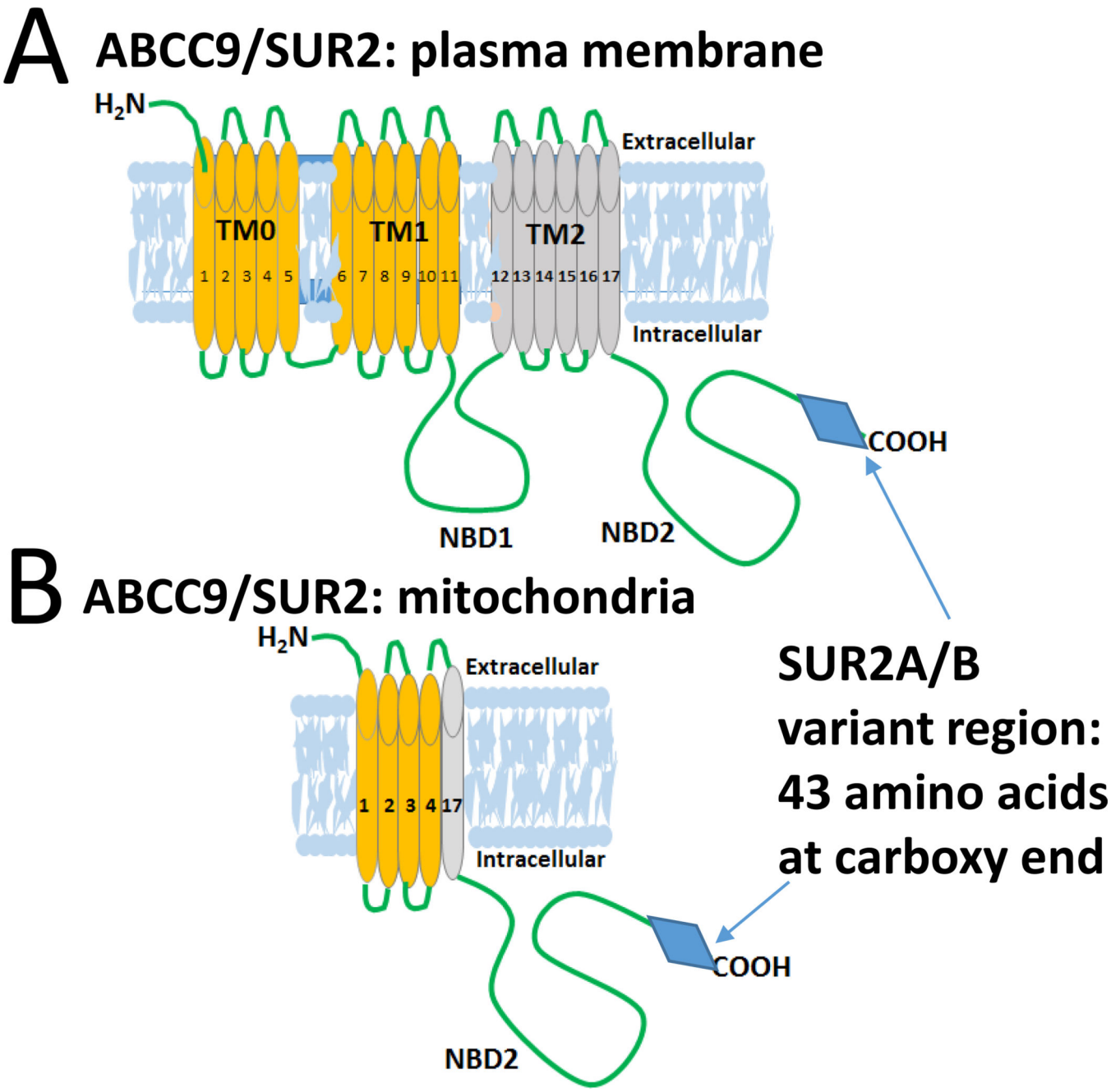

Figure 2. Protein structure of human *ABCC9* encoded SUR2 polypeptides

These are relatively large proteins (~150kDa) with multiple membrane-spanning domains. Like all ABCC gene-encoded proteins, SUR2 has two transmembrane ("TMD") domains, along with two nucleotide-binding ("NBD") domains. A characteristic feature of the sulfonylurea subcategory of ABCC genes is the presence of a third transmembrane domain, TM0. SUR2 has a specialized element in the extreme carboxy end, where two alternatively spliced exons lead to two variants (SUR2A and SUR2B) according to that portion. B. A variant of SUR2 has been described in mitochondria (~55kDa), shortened as a result of alternative splicing as shown.

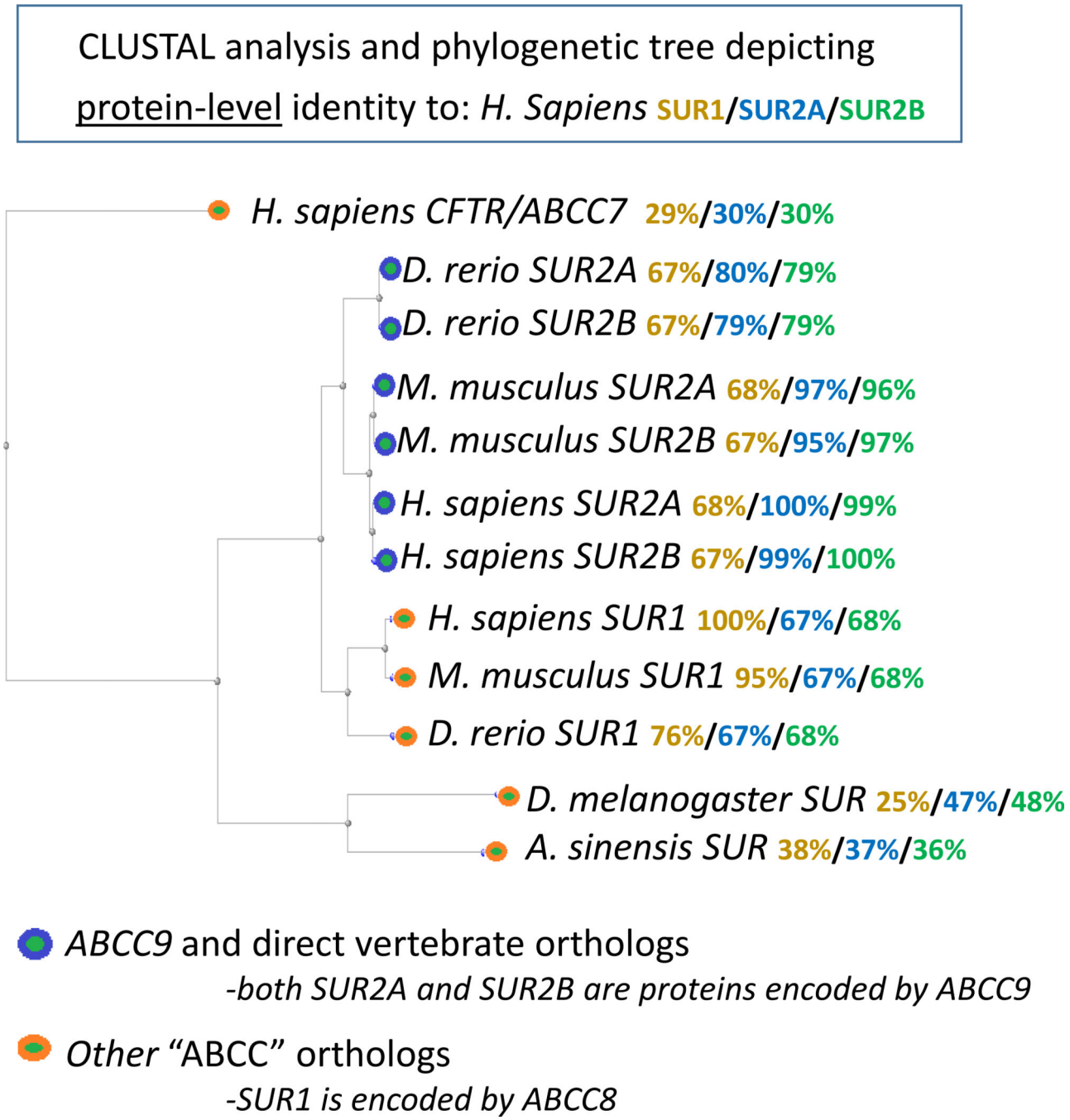

Figure 3. Phylogenetic tree provides background on evolution and protein-level identity with paralogous proteins

Shown is the result of a phylogenetic tree generated by comparing the protein-level sequences of ABCC proteins using the Web-based alignment tool (http://blast.ncbi.nlm.nih.gov/blast). Also shown for each species/gene in the tree is the protein level percent identity for human full-length SUR1/SUR2A/SUR2B proteins. Each of these genes is relatively well-conserved in vertebrate species. Further, there are invertebrate orthologs (shown are SUR protein data related to fruit flies and mosquitos) that appear more homologous to human SUR2 than to SUR1 proteins. For comparison, a presumed ortholog

is included in the phylogenetic tree: the human *ABCC* gene *CFTR*/*ABC7*. This is the gene responsible for the most common lethal human genetic disease, cystic fibrosis (Riordan, et al., 1989).

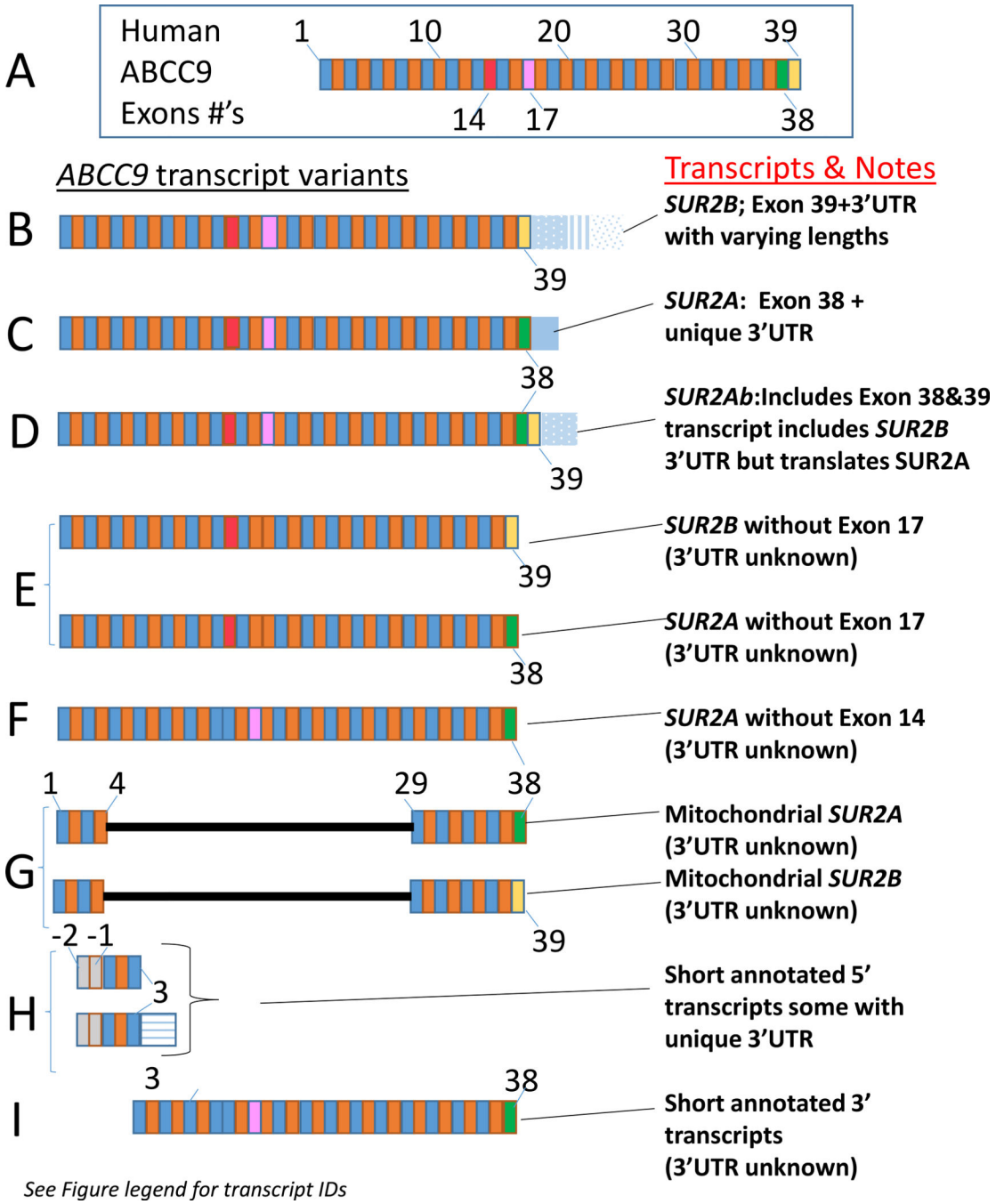

Figure 4. Alternative splicing in humans is complex, leading to multiple variants of SUR2 transcripts and proteins(Shi, et al., 2005)

A. Basic genomic structure of *ABCC9* includes at least 39 potential exons, not including untranslated regions (UTRs). B. Transcript designated "*SUR2B*" (ENST00000261200) includes Exon 39 but not Exon 38. This transcript incorporates 3' UTR regions of varying lengths which may affect transcript(s) stability. C. Transcript designated "*SUR2A*" (ENST0000026120) includes Exon 38 but not Exon 39 and was recently described to have an unique 3'UTR from genomic sequence immediately downstream from Exon 38 (al). D. A separate transcript, designated "SUR2Ab" (not yet annotated) incorporates both Exon 38

and Exon 39; whereas this transcript is translated similar to “SUR2A”, it harbors the 3’UTR that is associated with SUR2B transcript (al). E. Human SUR2A- and SUR2B–like clones have been characterized that do not include Exon 17 (NM_005691 and NM_020297) (Davis-Taber, et al., 2000). F. Human SUR2A–like clones were characterized that do not include Exon 14 (NM_020298). G. Transcripts that produce SUR2-like proteins in mitochondrial lack a large portion (from Exons 4–29) but may incorporate either Exon 38 or Exon 39 (Ye, et al., 2009). Transcripts that have been annotated, but not functionally characterized, which include exons exclusively from either the 5’ portion (H) or the 3’ portion (I) of the *ABCC9* gene (ENST00000544039,ENST00000538350, and ENST00000326684).

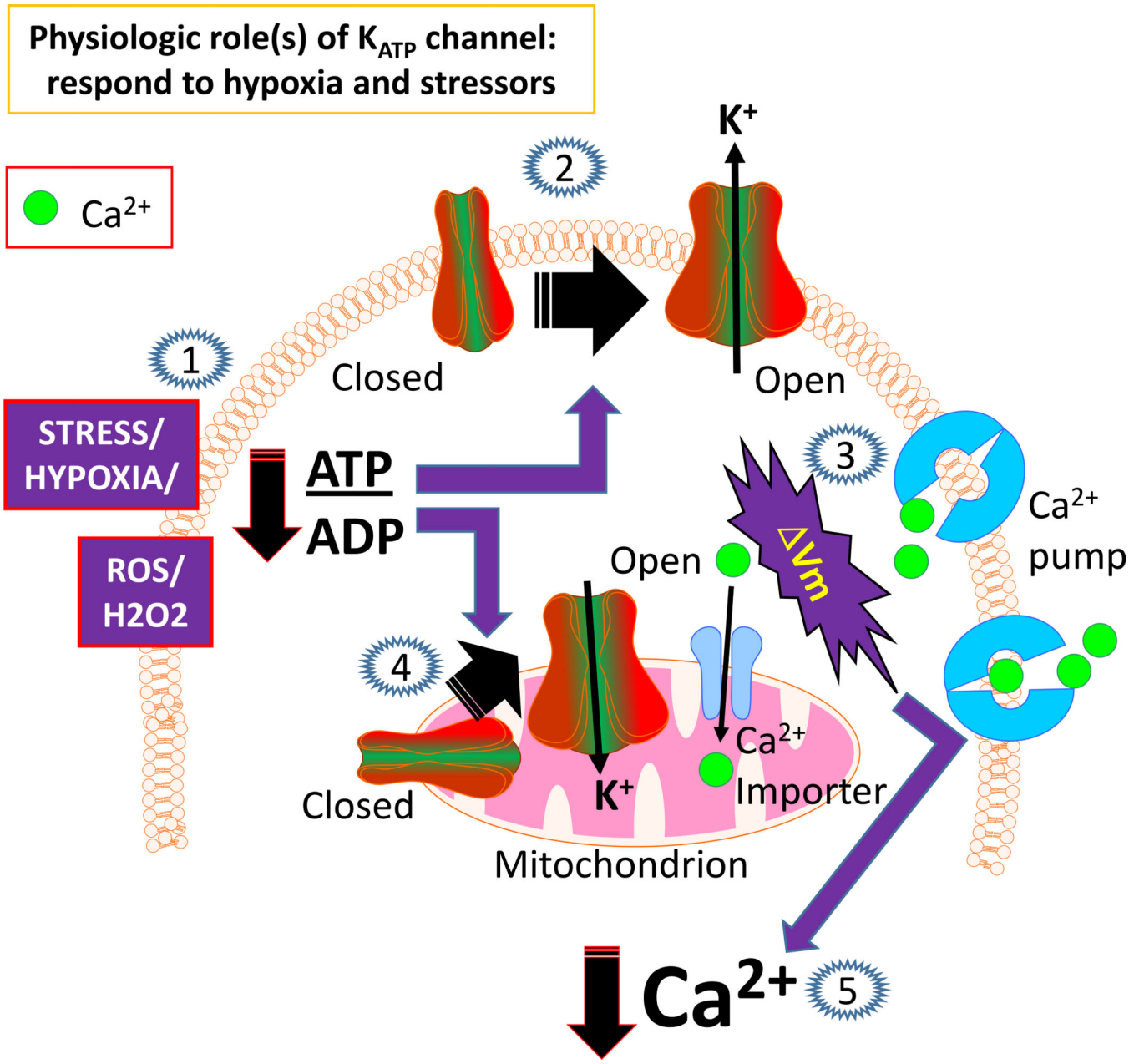

Figure 5. Mechanistic progression associated with SUR2 in a generic cell-type

1. Stressors and/or hypoxia lead to decreased intracellular ATP/ADP ratio. 2. At the plasma membrane, the ATP/ADP ratio, as well as other messengers not shown, can shift the K_{ATP} channel from a closed to open configuration, leading to K+ ions leaving the cell. 3. The K+ ions alter (reduce) the membrane depolarization leading to shift in the voltage-gated Ca++ pump dynamics. 4. In mitochondria, overlapping signals can affect the local mitochondria and mitochondrial SUR2, which is currently imperfectly understood but which also can alter mitochondrial Ca++ processing and energy production. 5. A key net outcome of SUR2 function and K_{ATP} channel opening is to decrease local intracellular Ca++ levels which can buffer the impact of the stress/hypoxic challenge.

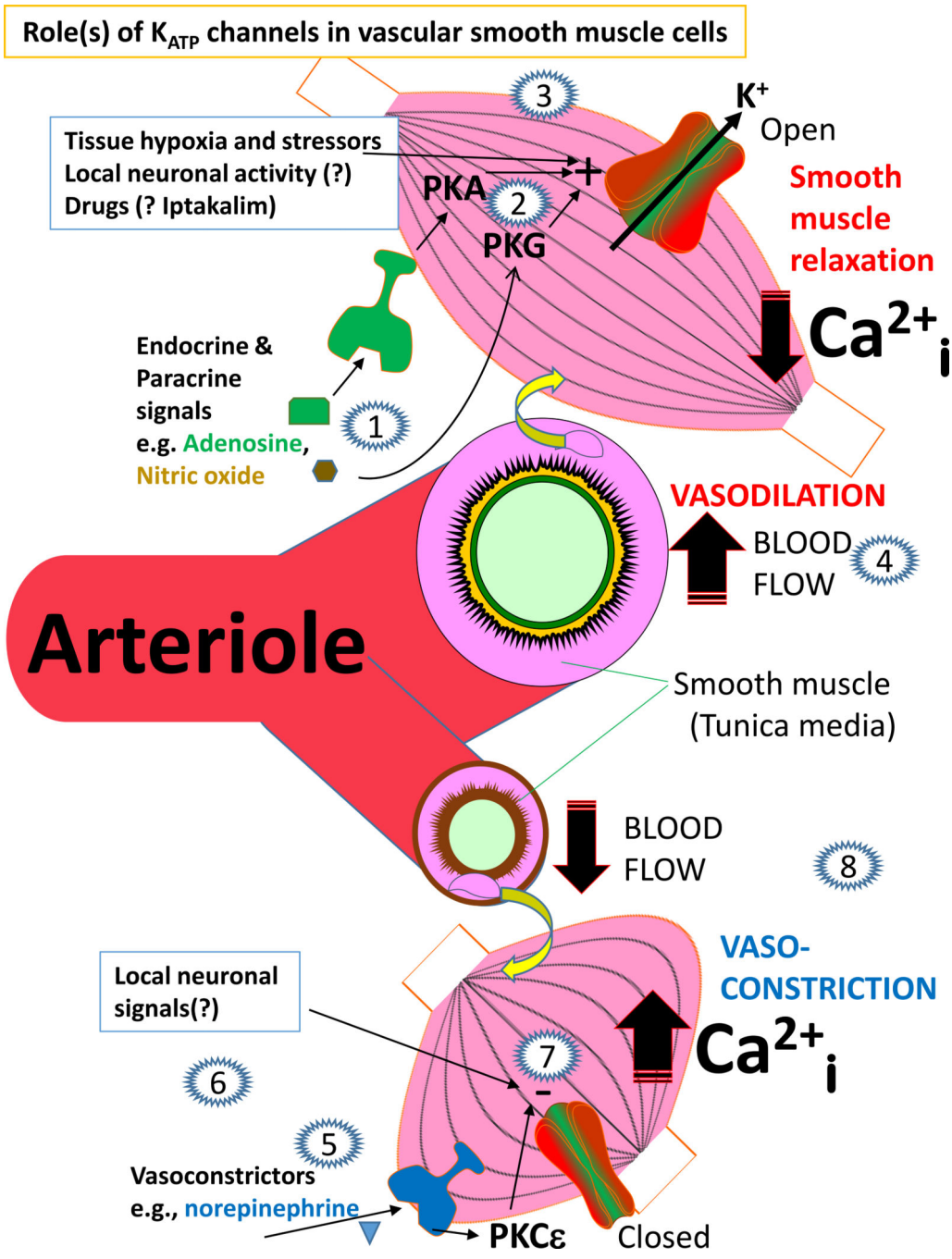

Figure 6. SUR2 and K_{ATP} channels play key roles regulating arteriolar function including vasodilation (1–5) and vasoconstriction (6–8)

1. Blood-borne vasodilatory agents (adenosine, nitric oxide, and others) can function through either membrane receptors (e.g., adenoside) or by diffusible (nitric oxide) mechanisms. 2. Intracellular second messengers including protein kinase A (PKA) can phosphorylate SUR2 and promote K_{ATP} channel opening. 3. It is not well understood how local brain ischemia/hypoxia, or local neuronal excitability, may also promote K_{ATP} channel opening in vivo. 4. The K_{ATP} channel promotes decreased intracellular Ca^{++}, vasodilation, and increased local blood flow. 5. By contrast, other signals can promote vasoconstriction,

including norepinephrine. 6. One pathway to promote smooth muscle contraction through K_{ATP} channel mechanism is the PKCe. 7. Other brain-specific pathways including neuronal signaling may also lead to K_{ATP} channel closing. 8. The net effect of K_{ATP} channel closing is to increase intracellular Ca^{++}, contract smooth muscle in the tunica media of arterioles, and decrease local blood flow. This figure incorporates information from recent reviews (Flagg, et al., 2010,Ko, et al., 2008). Here we show cartoon depiction of the K_{ATP} channel in smooth muscle cells but it should be kept in mind that K_{ATP} channels have also been shown to affect endothelial cells, pericytes, and possibly perivascular astrocytes.

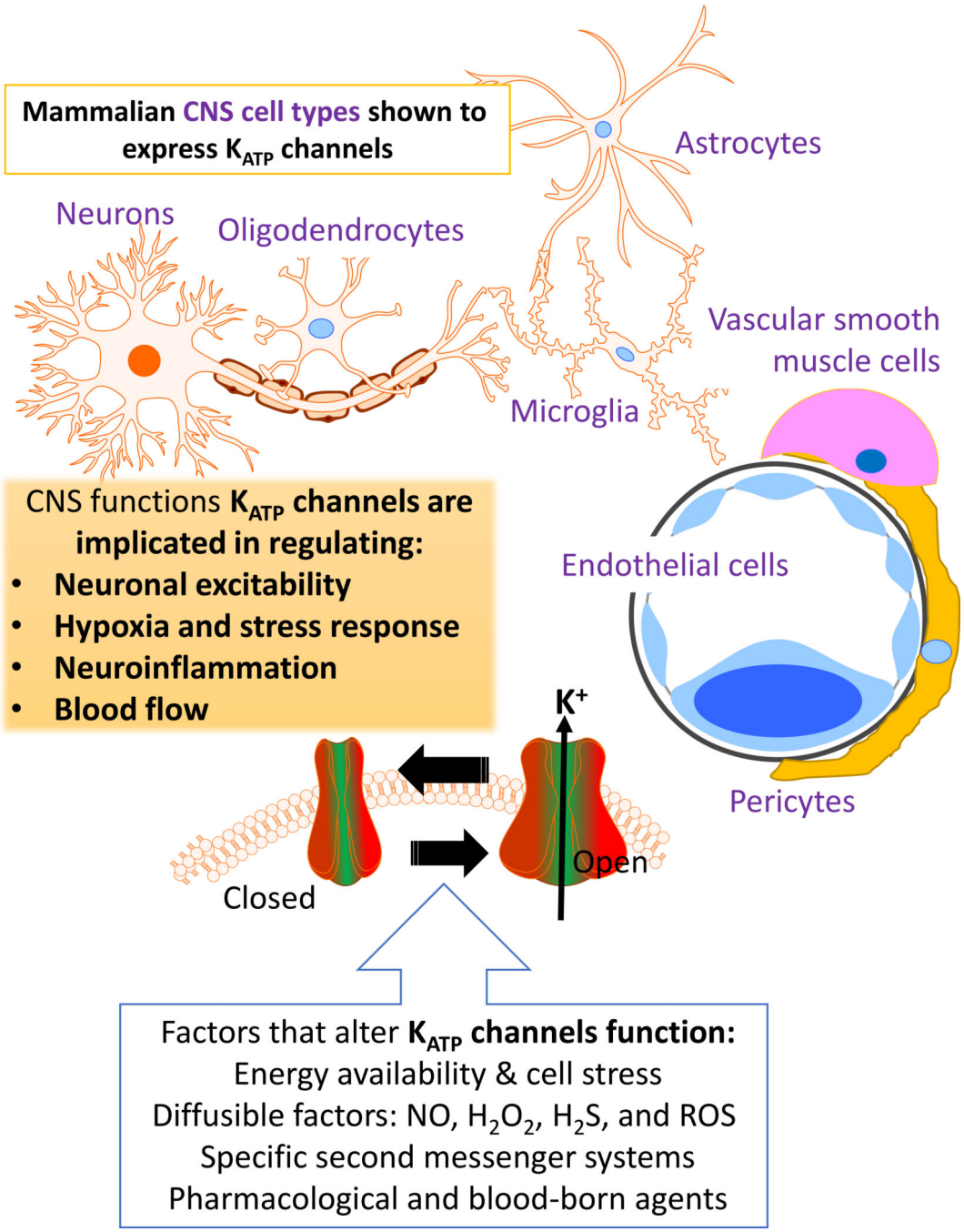

Figure 7. K_{ATP} channels have been described in just about every cell type of the human brain

The interplay of K_{ATP} channels, alongside the many other subtypes of K+ channels, in the human brain is extremely complex. These channels play important roles in regulating neuronal excitability, stress response, neuroinflammation, and blood flow. Thus these K_{ATP} channels are candidates for involvement in human brain diseases when they are dysfunctional. Increasing evidence is accumulating to highlight the brain conditions where K_{ATP} channel may be relevant.

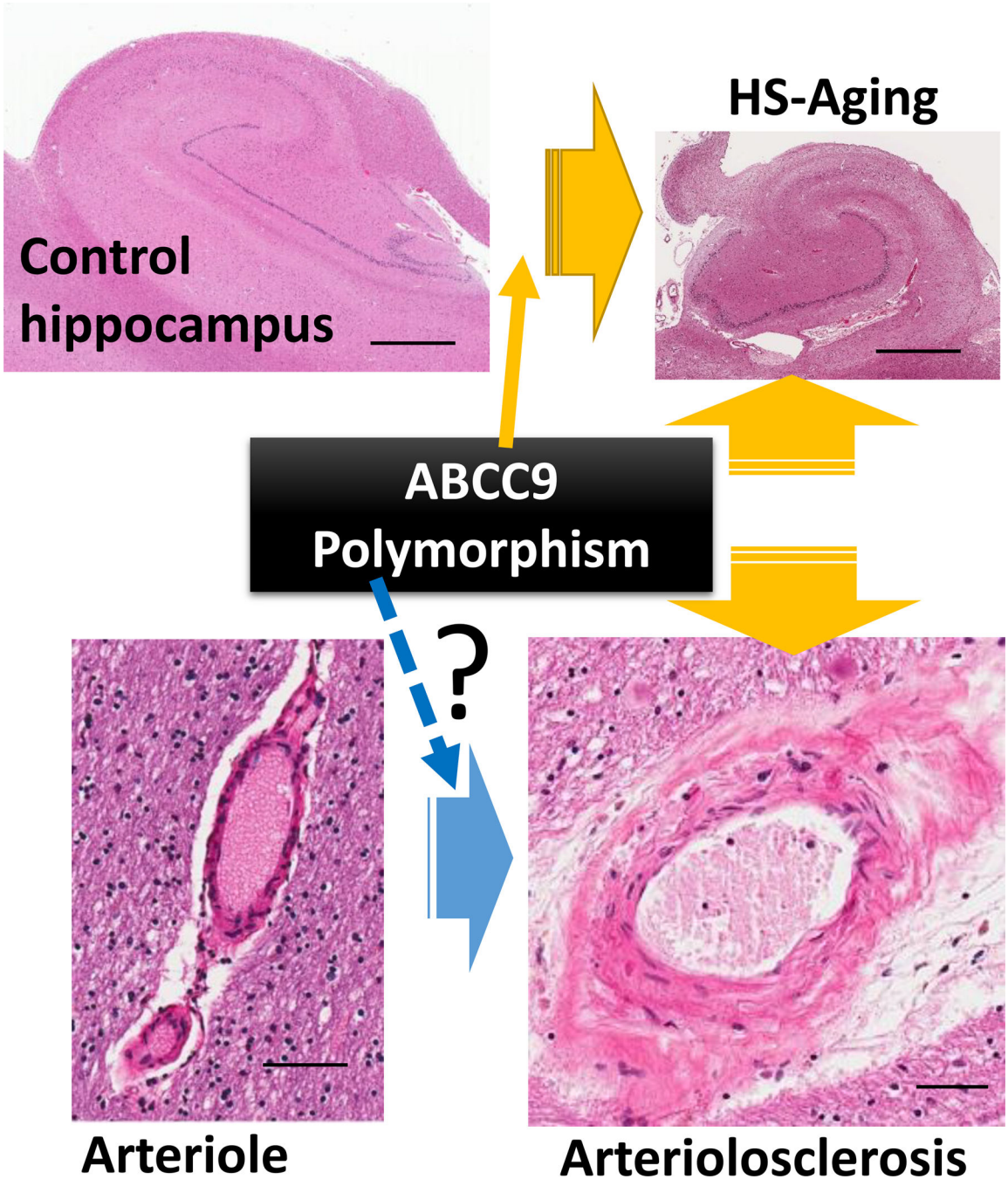

Figure 8. A polymorphism in *ABCC9* showed genome-wide statistically significant association with hippocampal sclerosis of aging (HS-Aging) as a GWAS endophenotype (Haug, et al., 2015,Nelson, et al., 2014)

HS-Aging is a prevalent neurodegenerative condition affecting the “oldest-old” and characterized by cell loss and atrophy in the hippocampal formation not due to Alzheimer’s disease-type pathways. Another factor associated with HS-Aging pathology is arteriolosclerosis, a pathological change where normal arterioles become dysmorphic (as shown in the Figure). Whether and how these observations are connected currently is unknown. Given the known expression of *ABCC9* in vascular smooth muscle cells, a

parsimonious hypothesis is that long-term *ABCC9* dysregulation may contribute to brain arteriolar injury (arteriolosclerosis) which in turns potentiates the manifestation of HS-Aging pathology. Scale bars = 1mm for A, B. 100 microns for C, D.

Table 1

Cantu syndrome cases reported to date, with (n=28) and without (n=19) documented neurological conditions

Paper	# Cases	Notable human CNS findings	(Ref)
Cantu et al, 1982	2	1/2 with mild mental retardation/delay	(Cantu, et al., 1982)
Nevin et al, 1996	1	Developmentally normal boy	(Nevin, et al., 1996)
D. García-Cruz et al, 1997	4	"Mild mental retardation" in 3/4, "enlarged posterior fossa" in 4/4.	(Garcia-Cruz, et al., 1997)
Rosser et al, 1998	3	Developmental delay noted in 2/3 cases	(Rosser, et al., 1998)
S.P. Robertson et al, 1999	2	Developmental delay/mild mental retardation in both cases	(Robertson, et al., 1999)
D Concolino et al, 2000	1	"Psychomotor development was normal"	(Concolino, et al., 2000)
B Lazalde et al, 2000	4	No specific mention of neurological disorders	(Lazalde, et al., 2000)
H. Engels et al, 2002	1	Brain atrophy and ultrasound- confirmed "bilateral calcification of the Arteriae thalamostriatae"	(Engels, et al., 2002)
D.K. Grange et al, 2006	Woman and two daughters	No mention of cognitive or cerebral anomaly	(Grange, et al., 2006)
C. Graziado et al, 2010	1	"mildly delayed psychomotor development"	(Graziadio, et al., 2011)
I. Scurr et al, 2010	9	Motor or speech delay in 9/10 cases	(Scurr, et al., 2011)
Kobayashi et al, 2010	1	Clinical syndrome included "developmental delay"	(Kobayashi, et al., 2010)
J.C. Czeschik et al, 2012	2	Both with ABCC9 mutations, 1/2 with mild developmental delay	(Czeschik, et al., 2013)
C.L. Garcia-Gonzalez et al, 2012	1	Delayed psychomotor development with cerebral cortical atrophy on CT scan	(Garcia-Gonzalez, et al., 2012)
W.M. van Bon Bregjie et al, 2012	9 previously unpublished, 1 father/daughter, 1 sib pair	All with ABCC9 mutations, 3 diagnosed with intellectual disability and/or developmental delay, 8/9 with macrocephaly	(van Bon, et al., 2012)
Y. Hiraki et al, 2013	Father and son	"mild psychomotor delay … and an autistic disorder based on the DSM-IV"	(Hiraki, et al., 2014)
J.Y. Park et al, 2014	1	ABCC9 mutation (p.Ala1462Gly, c.4385C>G) confirmed; atrophic changes of the brain on MRI	(Park, et al., 2014)

Table 2

Clinical conditions and their associations with specific *ABCC9* mutations

Clinical condition/ endophenotype	Mutation Type*	Notes	(Refs)
Cantu syndrome	E, I	Apparent autosomal dominant inheritance of functional gain of toxic function; many mutations identified, mostly in exons coding transmembrane domains of SUR2 protein	(Harak alova, et al., 2012, van Bon, et al., 2012)
Atrial fibrillation	E	Case of mutation [Thr1547Ile] associated with atrial fibrillation originating in the vein of Marshal	(Olson, et al., 2007)
Dilated cardiomyopathy	E	Two cases with distinct mutations [frameshift1524, A1513T] associated with dilated cardiomyopathy	(Bienen graeber , et al., 2004)
Myocardial infarction, early repolarization syndrome (ERS), and Brugada syndrome (BrS)	E	Coronary arterial vasospam and myocardial infarction linked to V734I mutation. Severe cardiac arrhythmias associated with 8 *ABCC9* mutations from 11 BrS probands and 4 ERS probands, the latter with V734I mutations.	(Baraja s-Martine z, et al., 2012, Beziau, et al., 2014, Hu, et al., 2014, Minoretti, et al., 2006, Smith, et al., 2013)
Sleep disorder	I	*ABCC9* SNP rs11046205 and rs11046209 showed some association with sleep duration, but with some variation between studies	(Allebr andt, et al., 2013), (Parsons, et al., 2013)
Depression	I	*ABCC9* SNP rs11046205 was associated with depressive symptoms	(Parsons, et al., 2013)
Hippocampal sclerosis of aging (HS-Aging)	I	GWAS with genome-wide statistical significance and separate replication study show association between HS-Aging and a group of intronic SNPs that include rs704180	(Nelson, et al., 2014, Nelson, et al., 2015)
Blood pressure/hypertension	I	*ABCC9* SNPs were associated with angiotensin II receptor blocker medication response	(Kamide, et al., 2013)
Blood pressure/hypertension	I	A haplotype (*ABCC9* SNP combination) is associated with risk for essential hypertension	(Sato, et al., 2006)
Entorhinal cortex thinning	G	SNP rs10743430 is ~50,000bases upstream from *ABCC9* In GWAS for MRI-detected atrophy; p~6E-7.	(Furney, et al., 2011)
Hirschprung disease	I	Top SNP (rs704192) is in linkage disequilibrium with HS-Aging risk SNPs	(Kim, et al., 2014)

*Exonic (E), Intronic (I), Intergenic (G)