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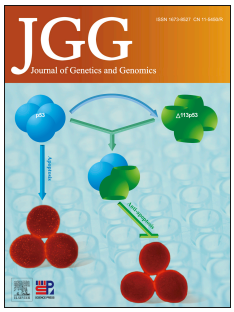

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Genetics and pathophysiology of mammalian sulfate biology

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Abstract

Nutrient sulfate is essential for numerous physiological functions in mammalian growth and development. Accordingly, disruptions to any of the molecular processes that maintain the required biological ratio of sulfonated and unconjugated substrates are likely to have detrimental consequences for mammalian physiology. Molecular processes of sulfate biology can be broadly grouped into four categories: firstly, intracellular sulfate levels are maintained by intermediary metabolism and sulfate transporters that mediate the transfer of sulfate across the plasma membrane; secondly, sulfate is converted to 3'-phosphoadenosine 5'-phosphosulfate (PAPS), which is the universal sulfonate donor for all sulfonation reactions; thirdly, sulfotransferases mediate the intracellular sulfonation of endogenous and exogenous substrates; fourthly, sulfate is removed from substrates *via* sulfatases. From the literature, we curated 91 human genes that encode all known sulfate transporters, enzymes in pathways of sulfate generation, PAPS synthetases and transporters, sulfotransferases and sulfatases, with a focus on genes that are linked to human and animal pathophysiology. The predominant clinical features linked to these genes include neurological dysfunction, skeletal dysplasias, reduced fecundity and reproduction, and cardiovascular pathologies. Collectively, this review provides reference information for genetic investigations of perturbed mammalian sulfate biology.

Key Words

Sulfate; Pathogenetics; Transport; Sulfotransferase; Sulfatase; PAPS

1. Introduction

Sulfate plays an important role in numerous biochemical and cellular processes in mammalian physiology (Fig. 1A) (Dawson, 2011). In most cases, sulfonation leads to the inactivation of steroids, thyroid hormone and neurotransmitters, as well as Phase II metabolism and detoxification of xenobiotics and certain drugs such as paracetamol (Mulder and Jakoby, 1990; Darras et al., 1999; Richard et al., 2001; Yamaguchi, 2001; Stanley et al., 2005; Alnouti, 2009; Dawson, 2012). Sulfonation of glycosaminoglycans is also required to maintain the structure and function of tissues (Habuchi et al., 2004; Klüppel, 2010). Despite the essential roles for sulfate in maintaining healthy growth and development, the physiological importance of sulfate is often underappreciated in clinical settings.

In children and adults, the diet provides approximately one third of daily requirements (Allen et al., 1989; Florin et al., 1991; Florin et al., 1993). Certain foods including brassica vegetables and commercial breads, as well as mineral waters, contain abundant levels of sulfate which is absorbed into circulation *via* active transport in the small intestine (Dawson, 2011). Circulating levels are then maintained at approximately 0.3 mmol/L by the kidneys, which filter sulfate in the glomerulus and then reabsorb sulfate in the proximal tubule (Murer et al., 1992; Cole and Evrovski, 1997). The first step of reabsorption is mediated by the solute linked carrier 13A1 (SLC13A1) sulfate transporter on the apical membrane of renal epithelial cells, and the second step *via* the SLC26A1 sulfate-anion exchanger on the basolateral membrane (Lotscher et al., 1996; Karniski et al., 1998). Circulating sulfate is then taken up by cells throughout the body *via* tissue specific sulfate transporters.

In addition to sulfate provided from circulation, the intracellular needs for sulfate are also supplied *via* intermediary metabolism of sulfur-containing amino acids, methionine and

cysteine (Mulder, 1981; Turner et al., 2006). Methionine is metabolized to cysteine *via* the transsulfuration pathway (Dawson et al., 1996), and cysteine is then oxidized to sulfate *via* two pathways, including a major pathway involving cysteine dioxygenase (Ueki et al., 2011) (Fig. 1B). Sulfur-containing gases, including hydrogen sulfide and sulfur dioxide, can also be oxidized to generate sulfate (Mitsuhashi et al., 2005; Olson, 2015). The removal of sulfate from substrates *via* sulfatases, particularly in the lysozyme, also contributes to the flux of sulfate availability within cells (Dawson et al., 2015a). Together, a sufficient supply of sulfate from circulation and the above mentioned intracellular pathways are required for sulfonation reactions to function effectively.

Sulfate is converted into 3'-phosphoadenosine 5'-phosphosulfate (PAPS), which is the universal sulfonate (SO_3^{2-}) donor for all sulfonation reactions (Fig. 1B) (Klassen and Boles, 1997). In both humans and animals, PAPS synthesis is mediated by PAPS synthetase in two steps: firstly the sulfurylation of ATP to form adenosine 5'-phosphosulfate (APS), followed by phosphorylation to form PAPS (Venkatachalam, 2003). Sulfotransferases (SULT) in the cytoplasm mediate the sulfonation of steroids, thyroid hormone, xenobiotics, neurotransmitters and bile acids, whereas Golgi-membrane bound sulfotransferases (ST) mediate the sulfonation of proteoglycans and lipids (Fig. 1B) (Gamage et al., 2006). ST-mediated sulfonation is reliant on the transport of PAPS into the Golgi *via* the SLC25B2 and SLC35B3 PAPS transporters that are expressed on the Golgi membrane (Sasaki et al., 2009). The required biological ratio of sulfonated to unconjugated substrates is also maintained by the removal of sulfate *via* sulfatases (Hanson et al., 2004).

In recent years, animal models of perturbed sulfate biology have demonstrated the essential roles of numerous genes involved in sulfate biology, leading to increased clinical interest in this field (Dawson, 2011, 2013; Dawson et al., 2015a). This review highlights our

current knowledge of the 91 genes that contribute to maintaining sulfate homeostasis, with a particular emphasis on the pathogenetics of sulfate biology in humans and animal models.

2. Genes involved in maintaining sulfate homeostasis

Over the past decade, numerous studies have focused on individual genes or gene families, and these have been previously summarized elsewhere, including reviews on sulfate transporters (Dawson and Markovich, 2005, 2007), PAPS synthesis and transport (Venkatachalam, 2003; Nishihara, 2014), sulfate generation from amino acids (Mulder, 1981), sulfotransferases (Gamage et al., 2006) and sulfatases (Hanson et al., 2004). This review brings together all of the genes from each functional group, including current nomenclature and all known alias names reported to date (Tables 1–4). In addition, we summarize the chromosomal locations of all listed genes, which show the significance of most autosomes and the X-chromosome in maintaining sulfate homeostasis.

Approximately half of the genes (n = 47/91) are found on six chromosomes (2, 4, 5, 7, 16 and X), whereas none are located on chromosomes 9, 7 and 14 (Fig. 2). Some related genes are located within the same chromosome arm, suggesting a gene duplication event during evolution, including: *SLC13A1* and *SLC13A4* at 7q31-33; *SLC35B2* and *SLC35B3* at 6p21-24; *SULT1A1*, *SULT1A2* and *SULT1A3* at 16p11-12; *SULT1C2*, *SULT1C3* and *SULT1C4* at 2q12; *SULT2A1* and *SULT2B1* at 19q13; *CHST4*, *CHST5* and *CHST6* at 16q22; *STS*, *ARSD*, *ARSE*, *ARSF* and *ARSH* at Xp22.3. These gene clusters are relevant when considering that deletions at these chromosomal locations have been associated with neurological disorders (Lin et al., 2009; Ben Khelifa et al., 2013; Pinto et al., 2014; Rai and Sharif, 2015; Rudd et al., 2015; Urquhart et al., 2015; Fedorenko et al., 2016; Scheps et al., 2016), which is one of the most consistent clinical features of disturbed sulfate biology (Fig. 3) and highlights the important roles of sulfate in brain physiology.

2.1 Sulfate transporter genes

The human genome contains 11 sulfate transporter genes belonging to the solute linked carrier 4 (SLC4), SLC13 and SLC26 gene families. SLC4A1 is an anion exchanger, with chloride and bicarbonate being the predominant substrates, but can also cotransport sulfate and H^+ in exchange for chloride (Jennings, 1976). The contribution of SLC4A1 in maintaining sulfate homeostasis in mammalian physiology is unclear and the major phenotypes linked to mutations in *SLC4A1*, including hereditary spherocytosis in red blood cells and distal renal tubular acidosis in the kidney, have been attributed to perturbed chloride and bicarbonate exchange (Bruce et al., 1997; Bruce et al., 2005).

SLC13A1 and SLC13A4 are Na^+-dependent sulfate transporters that are primarily expressed in the kidney and placenta, respectively (Lotscher et al., 1996; Simmons et al., 2013). Disruption of the *SLC13A1* gene leads to renal sulfate wasting and hyposulfataemia in humans, mice, dogs and sheep (Dawson et al., 2003; Bowling et al., 2012; Neff et al., 2012; Zhao et al., 2012), whereas loss of the *SLC13A4* gene blocks placental sulfate supply to the developing fetus, which causes severe developmental abnormalities and late gestational fetal death in mice (Rakoczy et al., 2015b). Interestingly, disruptions to the *SLC13A1* and *SLC13A4* genes do not cause any major cellular pathology in the tissues where these genes are expressed but rather lead to reduced circulating sulfate levels which in turn decreases sulfonation capacity in cells throughout the body (Dawson et al., 2003; Lee et al., 2006; Rakoczy et al., 2015b). In particular, certain cells such as chondrocytes, endothelial cells and hepatocytes, which have a high sulfate requirement, are linked to skeletal, vascular and hepatic metabolism phenotypes in animals with disrupted *SLC13A1* and *SLC13A4* genes (Table 5).

Eight members of the SLC26 gene family exchange sulfate for other anions including chloride, bicarbonate and oxalate (Dawson and Markovich, 2005). To date, five members of

the SLC26 family have been linked to human pathologies: *SLC26A2* is linked to four types of chondrodysplasias; *SLC26A3* is defective in congenital chloride diarrhea and metabolic acidosis; *SLC26A6* mutations are associated with kidney stones; *SLC26A8* is associated with spermatogenic failure; *SLC26A9* is linked to idiopathic bronchiectasis (Table 5). In addition, *Slc26a1* has been linked to renal stones and paracetamol-enhanced liver toxicity in mice (Dawson et al., 2010b), which may be relevant to genetic variants in the *SLC26A1* genes of certain patients with calcium oxalate urolithiasis (Dawson et al., 2013). Whilst the SLC26 gene family shares significant structural and sequence similarity, the phenotypes linked to each gene are quite distinct which is likely due to the different tissue distribution of each transporter as well as the various anions that are exchanged with sulfate (Dawson and Markovich, 2005).

2.2 Sulfate generation genes

Adults and children have the capacity to metabolise the sulfur-containing amino acids methionine and cysteine to sulfate (Fig. 1B) (Dawson et al., 2015a). The transsulfuration pathway converts methionine to cysteine (Dudman et al., 1996), which is then catabolized to sulfate *via* two pathways (Ueki et al., 2011): a major pathway that relies on cysteine dioxygenase (CDO1) and glutamic-oxaloacetic transaminase 1 (GOT1), and a minor pathway involving cystathionine β-synthase (CBS), γ-cystathionase (CTH), sulfide quinone reductase (SQRDL) and thiosulfate sulfurtransferase (TST). The latter pathway generates hydrogen sulfide from cysteine *via* CBS, either in the cytosol or mitochondria, which is then oxidized *via* SQRDL and TST in the mitochondria (Olson, 2015). Hydrogen sulfide can also be converted to sulfur dioxide, *via* nicotinamide-adenine dinucleotide phosphate oxidase (Mitsuhashi et al., 2005), which is further converted to sulfite and sulfate (Fig. 1B). The final step of both pathways requires sulfite oxidase (SUOX) to generate sulfate. The negligible

CDO1 and *CTH* gene expression in human and rodent fetal tissues (Gaull et al., 1972; Loriette and Chatagner, 1978; Rakoczy et al., 2015a), suggests that the developing fetus lacks the capacity to generate sulfate and likely explains the late gestational fetal death in *Slc13a4* null-mice when placental sulfate supply from mother to fetus is blocked (Rakoczy et al., 2015b).

Whilst previous studies have attributed the pathogenetics of the above genes to excess levels of pathway intermediates (e.g., hyperhomocysteinemia with *CBS*; sulfite and sulfocysteine with *SUOX*) (Dawson et al., 1996; Bosley et al., 2014), the contribution of intracellular sulfate deficiency from blocks in these pathways has not been considered. This is relevant when considering that these pathways contribute approximately 2/3 of intracellular sulfate requirements (Dawson et al., 2015a). Accordingly, the contribution of genetic defects in the *CDO1*, *GOT1*, *CBS*, *CTH*, *SQRDL*, *TST* and *SUOX* genes to altered sulfate homeostasis awaits further investigation.

2.3 PAPS synthetase and transporter genes

All sulfonation reactions in animals require the conversion of sulfate to the universal sulfonate (SO_3^-) donor, PAPS (Klassen and Boles, 1997). PAPS is generated *via* PAPS synthetase in the cytosol, by sulfurylation of ATP to form APS followed by phosphorylation to form PAPS (Fig. 1B) (Venkatachalam, 2003). Mutations in the *PAPSS2* gene have been linked to developmental dwarfism disorders, including spondyloepimetaphyseal dysplasia in humans, and brachymorphism in mice (Table 5). However, disruption of the *PAPSS1* gene has not been reported in any human pathology but is proposed to be embryologically lethal due to its abundant expression in the developing nervous system and bone marrow (Strott, 2002).

The sulfonate group from PAPS is transferred to the target substrate in either the cytosol or the Golgi, with the latter requiring PAPS transporters (SLC35B2 and SLC35B3) to mediate the translocation of PAPS from the cytosol into the Golgi (Sasaki et al., 2009). Cartilage defects and lethal phenotypes have been linked to *Slc35b2* in Zebrafish and *Drosophila* (Kamiyama et al., 2003; Clément et al., 2008), whereas up-regulation of *SLC35B2* mRNA expression is associated with poor prognosis of invasive ductal breast carcinoma in humans (Chim-ong et al., 2014).

The landmark paper reporting sulfate activation to PAPS (Lipmann, 1958) and the following identification of sulfotransferases (Lipmann, 1958; Gamage et al., 2006), as well as the characterisation of animal models of perturbed sulfate homeostasis (Tables 5–7), have led to our current understanding of sulfate biology genetics, and the physiological importance of sulfate in modulating the biological activity of neurotransmitters (Coughtrie et al., 1998; Lee et al., 2007), steroids (Dawson, 2012), thyroid hormone (Richard et al., 2001; Wu et al., 2005), proteoglycans and xenobiotics (Habuchi et al., 2004; Klüppel, 2010).

2.4 Sulfotransferase genes

Sulfotransferases, can be grouped into two classes: (i) SULTs which sulfonate neurotransmitters, bile acids, xenobiotics and steroids; (ii) Golgi-located STs that have proteoglycan and lipid substrates (Gamage et al., 2006). The overlapping substrate specificity and tissue expression of the SULTs suggest they are not individually critical, and most likely explain why pathogenetic defects in this family of cytosolic sulfotransferases have not been reported for humans. However, disruption of the estrogen sulfotransferase gene *Sult1e1* led to mid-gestational fetal loss and placental thrombosis in mice (Tong et al., 2005), indicating that complete loss of certain SULTs can be embryonic lethal but this has

yet to be determined for humans. The potential role of steroid sulfotransferases SULT1E1 and SULT2A1 in the induction and maintenance of hormone-dependent cancers has been reported. Reduced expression of *SULT2A1* is found in hepatocellular carcinoma cells (Huang et al., 2005), whereas SULT1E1 activity is less abundant in breast cancer cell lines when compared to normal breast cell lines (Falany et al., 2002; Tanaka et al., 2003). *SULT2A1* genetic variants have also been associated with a lower ratio of DHEA-sulfate to DHEA in children with premature adrenarche, as well as adrenal androgen excess in some women with polycystic ovary syndrome (Goodarzi et al., 2007; Utriainen et al., 2012). Further studies are required to determine the role of SULTs in certain cancers and altered endocrine profiles.

To date, 37 human Golgi membrane bound STs have been reported, with seven of these genes (*CHST3*, *CHST6*, *CHST8*, *CHST14*, *HS6ST1, GAL3ST4* and *NDST1*) linked to human pathologies (Table 6). These STs mediate the sulfonation of proteoglycans, including chondroitin sulfate, heparan sulfate and keratin sulfate, which are essential for maintaining the structure and function of connective tissues in the body, particularly in the eye, skin and developing skeleton (Habuchi et al., 2004; Klüppel, 2010). Sulfonated proteoglycans are also a component of the mucous barrier which protects the epithelial layer of the gut, lungs and reproductive tract (Nieuw Amerongen et al., 1998; Argüeso and Gipson, 2006; Dawson et al., 2009). Accordingly, the phenotypes associated with disrupted ST genes in humans and mice include conditions affecting the structural integrity of the eye, skin, joints and lungs, as well as reduced fecundity (Table 6).

2.5 Sulfatase genes

The human genome contains 17 sulfatase genes and one sulfatase modifying factor gene, *SUMF1*, which is critical for post-translational modification of all sulfatases (Table 4)

(Cosma et al., 2003; Sardiello et al., 2005). Within the lysosome (Fig. 1B), defective removal of sulfate from sulfoglycolipids (*via ARSA*) and proteoglycans (*via ARSB*, *GALNS*, *GNS*, *IDS* and *SGSH*) leads to lysosomal storage disorders, that have progressive clinical features with late infantile, juvenile or adult onset (Diez-Roux and Ballabio, 2005; Ashworth et al., 2006; Eckhardt, 2008). Steroid sulfatase (*STS*) deficiency leads to X-linked ichthyosis which presents after birth (Honour et al., 1985), whereas *ARSE* is linked to X-linked chondrodysplasia punctata that manifests in the prenatal period (Horikoshi et al., 2010). The SULF1 and SULF2 sulfatases are secreted to the cell surface in numerous fetal tissues, including bone and cartilage, where they mediate the removal of 6-*O*-sulfate from heparan sulfate, which enhances growth factor signaling during development (Ratzka et al., 2010). The human *SULF1* gene has been linked to mesomelia-synostoses syndrome that has clinical features of limb shortening and acral synostoses (Isidor et al., 2010). Similar developmental defects are observed in *Sulf1* and *Sulf2* null mice (Holst et al., 2007). The severe and lethal developmental defects linked to the human and rodent *SUMF1* gene, which causes multiple sulfatase deficiency, highlight the essential roles of sulfatases in maintaining healthy growth and development.

3. Phenotypes of disturbed sulfate biology

In humans, 28 of the listed 91 genes have been linked to pathophysiology (Tables 5–7). This finding suggests that many of the genes reported in this review, may have some redundancy, particularly the sulfotransferases which have overlapping substrate specificities and are expressed in multiple tissues (Gamage et al., 2006). However, of the 63 genes in our list which are not reported in human pathologies, there are 15 genes that are linked to pathologies in animals with most being embryonic lethal. This is relevant to the important roles of sulfate in fetal development and suggests that our list most likely

contains genes yet to be associated with human fetal loss. Importantly, the clinical features linked with the human genes in our list (Tables 5–7) give similar phenotypes in animal models, further supporting their conserved physiological roles across species. Overall, from the 43 genes in our list that are linked to pathophysiology in humans and animals, almost half of those genes are linked to neurological dysfunction (*n* = 16), perturbed skeletal growth and development (*n* = 19), or perturbed reproduction and fecundity (*n* = 16) in humans and/or animals. These features correlate to the relatively high abundance of those genes in brain, skeletal and reproductive tissues (Fig. 3), as well as the essential requirement for sulfate in the developing fetus (Dawson, 2011). In addition, cardiovascular phenotypes are associated with nine genes reported in this review (Fig. 3). Whilst there are numerous pathological features associated with the 43 genes, the following sections focus on predominant features, including neurological dysfunction, skeletal dysplasias, reduced fecundity and reproduction, and cardiovascular pathologies. The potential involvement of several sulfate maintenance genes in cancer has also gained attention from the scientific community in recent years, and those findings have been reviewed elsewhere (Dawson et al., 2010a; Dawson, 2012; Daniels and Kadlubar, 2013; Rižner, 2016).

3.1 Neurological dysfunction linked to sulfate maintenance genes

Disturbances of sulfate metabolism have been linked with several disorders that have neurological dysfunction as a major clinical feature, including *ARSA* with metachromatic leukodystrophy, *ARSB* with Maroteaux–Lamy syndrome, *IDS* with Hunter's syndrome, *SGSH* with Sanfilippo A syndrome, *NDST1* with intellectual disability, and *SUMF1* with multiple-sulfohydrolase deficiency (Tables 6–7). All of these genes are expressed in the brain as well as multiple other tissues (Fig. 3), which likely explains the additional clinical features associated with these disorders. Disruption of these genes in animals also leads to brain

dysfunction phenotypes that closely model the human situation, such as *ARSB* in mouse, rat, cat and dog (Table 7). In addition, neurological features are observed with mouse *Slc13a1* (seizures and behavioural abnormalities) and *Sulf2* (hippocampal and cerebellar neuron deficits, and behavioural abnormalities), as well as *Arsg* in dog (cerebellar ataxia) and mouse (neuronal cell death and behavioural deficits). These findings are relevant to the numerous roles of sulfate in the brain including sulfonation of neurotransmitters, thyroid hormone, neurosteroids, lipids and proteoglycans.

Sulfate is a major component of proteoglycans and cerebroside sulfate, which contributes to maintaining the structure and function of neural tissues (Mulder and Jakoby, 1990), particularly during fetal neurodevelopment (Dawson, 2013). Importantly, the sulfate content of glycoproteins, such as heparan sulfate and chondroitin sulfate, plays an important role in neurogenesis, including the modulation of axonal guidance, neuronal outgrowth, and synapse development (Yamaguchi, 2001; Schwartz and Domowicz, 2004; Carulli et al., 2005). In addition, sulfonation modulates the actions of neurosteroids on glutamatergic, $GABA_A$, N-methyl-D-aspartate and sigma-opioid receptors (Kríz et al., 2008). For example, pregnenolone is a barbiturate-like agonist, whereas pregnenolone-sulfate is a picrotoxin-like agonist. Other examples include sulfonated DHEA which stimulates acetylcholine release from the hippocampus, whereas unconjugated DHEA does not (Kríz et al., 2008). This latter finding is relevant when considering the decreased DHEA-sulfate to DHEA ratio in the hyposulfataemic *Slc13a1* null mouse which also exhibits behavioural abnormalities (Dawson et al., 2004, 2005, 2008).

Studies in sheep showed that radio-tracer [^{35}S]-sulfate administration to pregnant ewes led to the high abundance of [^{35}S]-sulfate in the fetal brain, with levels peaking in the third trimester (Hansard and Mohammed, 1968), demonstrating the incorporation of maternally-derived sulfate into the developing fetal brain. Sulfonated substrates are also actively

supplied to the developing brain. For example, iodothyronines are sulfonated in the placenta *via* the SULT1A1 sulfotransferase, and then transported into fetal circulation where they are taken up by fetal tissues, including the brain (Richard et al., 2001). Local concentrations of sulfonated (active) and unconjugated (inactive) T3 within the brain are regulated *via* the actions of ARSC sulfatase and SULT1A1 sulfotransferase, which provides a means of protecting the fetus from excessive unconjugated active T3 (Richard et al., 2001).

3.2 Skeletal dysplasias linked to sulfate maintenance genes

Skeletal defects are one of the most widely investigated clinical features linked to perturbed sulfate biology (Dawson and Markovich, 2005, 2007). The genetic basis of sulfate biology in the skeletal sulfation disorders is well researched and has been linked to defects in the sulfate transporter *SLC26A2*, synthetase *PAPSS2*, sulfotransferases (*CHST3* and *CHST14*) and several sulfatases (*IDS, GNS, SGSH, NDST1, ARSA, SULF1, ARSB, ARSE* and *STS*) (Tables 5-7).

More than two decades ago, the sulfate transporter gene *SLC26A2* was linked to diastrophic dysplasia (DTD), which is a moderately severe chondrodysplasia that typically presents with short-limbed dwarfism and generalized dysplasias of the joints (Hastbacka et al., 1994). To date, over 30 mutations in the human *SLC26A2* gene have been linked to chondrodysplasias (Dawson and Markovich, 2005), with the underlying metabolic defect being reduced sulfate content of chondroitin in chondrocytes (Cornaglia et al., 2009). The extent of impaired chondroitin sulfonation correlates to clinical severity, with mutations in *SLC26A2* leading to four different chondrodysplasias, ranging from mild to lethal: Multiple epiphyseal dysplasia (MED), DTD, atelosteogenesis Type II (AO2), and achondrogenesis Type IB (ACG1B). The correlation between sulfonation capacity and clinical severity suggests that therapeutic approaches which are aimed at increasing sulfonation capacity in

the skeleton could potentially ameliorate the skeletal pathology linked to *SLC26A2*. This approach is relevant when considering the chondrodysplasia phenotype of the mutant *Slc26a2* mouse can be improved by administration of thiol-containing compounds, such as dietary N-acetyl cysteine that can bolster sulfate supply (Forlino et al., 2005; Pecora et al., 2006; Cornaglia et al., 2009).

In recent years, the skeletal phenotypes linked to *SLC26A2* and *PAPPS2* in humans and animals have expanded to include knee osteoarthritis (Ikeda et al., 2001). In addition, the SLC13A1 sulfate transporter which maintains circulating sulfate level, has been associated with osteochondrodysplasias in sheep and dogs (Neff et al., 2012; Zhao et al., 2012), suggesting that perturbed sulfate biology is likely to be more prevalent than the estimated 2% of all human skeletal dysplasias which is based on live births (Stevenson et al., 2012).

3.3 Reduced reproduction and fecundity linked to sulfate maintenance genes

Interest in sulfate biology during human gestation has expanded following the characterisation of fetal demise in animal models of reduced sulfonation capacity (Tables 5–7). For example, disruption of the sulfate transporter gene *Slc13a1* in pregnant female mice leads to maternal and fetal hyposulfataemia, as well as late gestational fetal loss (Dawson et al., 2003, 2011). A related sulfate transporter in the placenta, *Slc13a4*, which mediates sulfate supply from mother to fetus during pregnancy (Dawson et al., 2012; Simmons et al., 2013), has also been linked to severe fetal developmental defects and death. These animal studies highlight the importance of maintaining high maternal sulfate levels in pregnancy, as well as supplying sulfate to the fetus *via* placental sulfate transporters.

In pregnant women, plasma sulfate levels increase by approximately 2-fold in early pregnancy (10–20 weeks gestation), with levels peaking in late gestation (30–37 weeks) at a time when fetal demands for sulfate are high (Dawson et al., 2015b). Similarly, circulating

sulfate levels are increased in mouse gestation, which is mediated by increased expression of the renal *Slc13a1* and *Slc261* sulfate transporter genes that enhance sulfate reabsorption from the urinary filtrate back into circulation (Dawson et al., 2012). Further research into the potential pathogenetic roles of the *SLC13A1*, *SLC26A1* and *SLC13A4* genes in human pregnancy is warranted based on animal studies, as well as known genetic variants in these human genes (Dawson and Markovich, 2005, 2007; Dawson et al., 2013), particularly those loss-of-function variants leading to hyposulfataemia (Lee et al., 2006; Bowling et al., 2012).

Steroid sulfonation also contributes to maintaining pregnancy and healthy fetal growth and development. Sulfonated steroids are the major form of steroids supplied to fetal tissues. For example, estradiol is sulfonated in the placenta (E2-3-S) and then taken up by the fetal brain where it is de-sulfonated by STS sulfatase to E2, which is a potent stimulator of fetal adrenocorticotropin (ACTH) secretion and the hypothalamus-pituitary-adrenal (HPA) axis (Wood, 2005). These findings are relevant to the role of the SULT1E1 estrogen sulfotransferase which is abundantly expressed in the placenta where it mediates sulfonation of E2, as well as estrone (E1) and estriol (E3) (Dawson, 2012). Disruption of the *Sult1e1* gene in pregnant female mice leads to placental thrombosis and mid-gestational fetal loss (Tong et al., 2005). *Sult1e1* is also expressed in the testis, where its disruption leads to reduced sperm motility, seminiferous tubule damage, Leydig cell hypertrophy/hyperplasia, and reduced fecundity of male mice. Spermatogenic failure is also linked to a mutation found in the human *SLC26A8* anion sulfate transporter (Dirami et al., 2013), which is most abundantly expressed in the testis (Fig. 3). Similar phenotypes are observed in the male *Slc26a8* null mouse, with the proposed molecular dysfunction being attributed to perturbed chloride and bicarbonate fluxes during sperm capacitation (Rode et

al., 2012a). Accordingly, the contribution of altered sulfate homeostasis to disrupted SLC26A8 function requires further investigation.

Endocrine disruption has also been linked to *Chst8* in mice, which exhibits increased sex hormones, testosterone and luteinizing hormone (LH) (Mi et al., 2008b). These hormonal disturbances cause precocious sexual maturation and an increase in litter numbers and fecundity. *Chst8* is highly expressed in the pituitary gland and the disturbance of this sulfotransferase leads to increased levels of non-sulfonated LH (the active form of LH), which up-regulates the hypothalamic-pituitary-gonad axis *via* increased testosterone and estrogen levels in male and female mice, respectively (Mi et al., 2008a).

Sulfate also contributes an important role in fertilization, particularly during oocyte maturation when sulfonated zona pellicida glycoproteins contribute to the process of accepting sperm (Lay et al., 2011). In addition, sulfonated tyrosine residues on sperm-expressed proteins, such as MFGE8, contribute to the capacity of sperm to adhere to the oocyte plasma membrane. For example, the tyrosylprotein sulfotransferase-2 (*Tpst2*) deficient male mouse lacks tyrosine sulfonation of MFGE8 leading to infertility (Borghei et al., 2006). In addition, tyrosine sulfonation of the follicle-stimulating hormone and luteinizing hormone receptors is required for optimal reproductive function (Costagliola et al., 2002; Mi et al., 2002).

3.4 Role of sulfate maintenance genes in the cardiovascular system

Nine sulfate-related genes (*IDS*, *SULF1*, *GALNS*, *SUMF1*, *ARSE*, *ARSB*, *CBS*, *CHST14* and *CHST3*), which are expressed in blood, vascular and/or heart tissues (Fig. 3), are associated with cardiovascular pathologies. Six of these genes encode sulfatases which are linked to accumulation of glycosaminoglycans in the heart, leading to cardiac valve dysplasia or cardiomyopathy (Rigante and Segni, 2002; Diez-Roux and Ballabio, 2005). In one reported

case, acute heart failure from valve disease was the predominant phenotype associated with the *ARSB* gene (Jurecka et al., 2011), although the clinical spectrum of sulfatase deficiencies usually includes neurological and/or skeletal pathologies as the major phenotype. Mutations in the *CBS* gene are also associated with cardiovascular disease (Dawson et al., 1996, 1997), although this has been attributed to hyperhomocysteinemia as a consequence of impaired homocysteine metabolism (Dudman et al., 1996) rather than reduced intracellular sulfate generation (Fig. 1B). Cardiovascular features of atrial septal defects, patent ductus arteriosus, coarctation of the aorta, and cardiac valve dysplasia are within the differential diagnosis of *CHST14* deficient Ehlers-Danlos syndrome (Miyake et al., 2013). *CHST3* has also been linked to cardiovascular phenotypes, including mitral, tricuspid and/or aortic regurgitations (Tuysuz et al., 2009). The cardiac involvement of the *CHST14* and *CHST3* sulfotransferase genes is proposed to be a consequence of reduced sulfate content of glycosaminoglycans which impairs extracellular collagen bundling and function (van Roij et al., 2008; Miyake et al., 2013). The endogenously generated sulfur-containing gases H_2S and SO_2 that are intermediates of the sulfate generating pathways (Fig. 1B), also contribute to numerous physiological and pathophysiological roles in the mammalian body (Medani et al., 2011; Wang et al., 2011; di Masi and Ascenzi, 2013; Wang et al., 2014; Guo et al., 2016; Huang et al., 2016). In particular, both H_2S and SO_2 modulate vascular tone and cardiac function, and have cardioprotective effects in animal models of systemic and pulmonary hypertension, atherosclerosis and cardiac ischemia-reperfusion injury (Elrod et al., 2007; di Masi and Ascenzi, 2013; Wang et al., 2014). These animal studies are relevant to the clinical situation when considering the genes involved in endogenous H_2S and SO_2 generation from sulfur-containing amino acids (Fig. 1B and Table 1) are conserved across mammalian species. Collectively, cardiovascular phenotypes are linked to several genes in

this review, demonstrating the importance for maintaining sulfate homeostasis in the cardiovascular system.

4. Role of sulfate in the metabolism of pharmacological drugs

Sulfate is conjugated to numerous pharmacological drugs, including acetaminophen, tamoxifen, apomorphine, butesonide and ethinylestradiol (Kauffman, 2004). In most cases, sulfonation increases the water solubility and renal excretion of the drug. However, certain drugs such as minoxidil, which is an antihypertensive agent and hair growth stimulant, are activated upon sulfonation (Buhl et al., 1990; Strott, 2002). Sulfonation is a low-capacity but high-affinity Phase II metabolic pathway which accounts for approximately 35% of drug metabolism at therapeutic doses in adults, together with 50% *via* glucuronidation and 15% *via* oxidative pathways (McGill and Jaeschke, 2013; Lancaster et al., 2015). Overdoses of certain drugs can saturate the sulfonation pathway and place more pressure on the oxidative pathway. For example, acetaminophen overdose leads to excess levels of the oxidative pathway intermediate, N-Acetyl-p-Benzoquinone Imine (NAPQI), which is a reactive toxic product that can cause hepatotoxicity and death (Jan et al., 2014). Studies in mice have shown that low blood sulfate levels, due to disruption of the renal sulfate transporter genes *Slc13a1* and *Slc26a1* (Table 5), can reduce hepatic sulfonation capacity and enhance acetaminophen-induced hepatotoxicity (Lee et al., 2006; Dawson et al., 2010b). This may be relevant to loss-of-function variants in the human *SLC13A1* gene which lead to hyposulfatemia (Bowling et al., 2012), as well as the *SULT1A1*, *SULT1A3* and *SULT1C4* sulfotransferase genes that sulfonate acetaminophen (Yamamoto et al., 2015). Taken together, these studies warrant investigations into the consequences of gene variants, that reduce sulfonation capacity (Tables 1and 2), on drug toxicity in humans.

Summary

The diverse roles of sulfate in mammalian physiology, together with the impact of sulfate-related genes on health outcomes, cannot be underestimated. The number of genes associated with sulfate biology is a testament to the significance of sulfate in many tissues and physiological functions. Further studies are required for translating the past few decades of animal research into the clinic, particularly for those genes which yield significant pathologies in animals but have yet to be linked to human health. While interest in sulfate-related genes continues to expand, particularly in the fields of bone, neuroscience, reproduction and cardiovascular research, there is still much to be done. Expanding the list of clinically reportable genes opens up the possibility for genetic counselling, as well as developing therapeutic approaches towards treatments. In summary, this review provides a list of all known human genes that encode sulfate transporters, PAPS synthetases and transporters, enzymes involved in intracellular sulfate generation, cytosolic and membrane-bound sulfotransferases and sulfatases. Collectively, this review provides reference information for future genetic studies of sulfate biology in human health.

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Figure legends

Fig. 1. Physiological roles of sulfate and pathways of sulfate homeostasis. A: Sulfate contributes to numerous biochemical and cellular processes in mammalian physiology. B: Intracellular sulfate levels are maintained by uptake of extracellular sulfate *via* sulfate transporters (T) on the plasma membrane, removal of sulfate from substrates *via* sulfatases in the cytosol and lysosome, and intermediary metabolism of methionine and cysteine *via* cystathionine β-synthase (CBS), γ-cystathionase (CTH), cysteine dioxygenase (CDO1), glutamic-oxaloacetic transaminase 1 (GOT1), sulfide quinone reductase (SQRDL), thiosulfate sulfurtransferase (TST), sulfite oxidase (SUOX) and nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase. Sulfate is converted into PAPS *via* PAPS synthetase (PAPSS2) which is used in the cytosol by sulfotransferases (SULT) or transported into the Golgi *via* PAPS transporters (SLC35B2 and SLC35B3) and used by Golgi membrane-bound sulfotransferases (ST).

Fig. 2. Distribution of 91 human genes that are involved with sulfate biology. An ideogram of all chromosomes with lines plotted to the corresponding location of each gene. Lines connect to coloured circles representing the major groups of genes involved in sulfate biology, as defined by the colour key. Diagrams were constructed using the online Phenogram tool (Wolfe et al., 2013) and chromosomal locations of genes from the online NCBI Gene database (http://www.ncbi.nlm.nih.gov/gene/ accessed on 25 February 2016).

Fig. 3. Tissue distribution and pathologies linked to 28 human genes involved in sulfate biology. From the 28 genes linked to human pathologies (Tables 5–7), we generated a heat map of approximate mRNA expression levels (as identified by the colour key) in 45 human tissues using data obtained from the online NCBI UniGene EST database http://www.ncbi.nlm.nih.gov/est/ accessed on 25 February 2016 (top). Organ systems with predominant pathologies for the 28 genes (bottom) were obtained by searching PubMed, Medline and the online NCBI OMIM database http://www.ncbi.nlm.nih.gov/omim/. Those pathologies reported to be associated with each gene were confirmed from the full text of identified publications.

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Table 1. Genes encoding sulfate transporters, PAPS synthetases and transporters, and key enyzmes in the pathway of sulfate generation from amino acids.

Gene	ID	Location	Aliases
Sulfate transporters			
SLC4A1	109270	17q21.31	*AE1*, *EPB3*, *DI*, *FR*, *SW*, *WD*, *WR*, *CHC*, *SAO*, *WD1*, *BND3*, *CD233*, *EMPB3*, *RTA1A*
SLC13A1	6561	7q31.32	*NAS1*, *NaSi-1*
SLC13A4	26266	7q33	*NAS2*, *SUT1*, *SUT-1*
SLC26A1	10861	4p16.3	*EDM4*, *SAT-1*, *SAT1*
SLC26A2	1836	5q31-34	*DTD*, *DTDST*, *EDM4*, *MST153*, *MSTP157*, *D5S1708*
SLC26A3	1811	7q31	*CLD*, *DRA*
SLC26A6	65010	3p21.3	
SLC26A7	115111	8q23	*SUT2*
SLC26A8	116369	6p21	*TAT1*, *RP11-482O9.1*, *SPGF3*
SLC26A9	608481	1q32.1	
SLC26A11	610117	17q25.3	
PAPS synthetases			
PAPSS1	9061	4q24	*ATPSK1*, *PAPSS*, *SK1*
PAPSS2	9060	10q24	*ATPSK2*, *RP11-77F13.2*, *BCYM4*, *SK2*
PAPS transporters			
SLC35B2	610788	6p21.1	*PAPST1*, *SLL*, *UGTre14*
SLC35B3	610845	6p24.3	*PAPST2*, *CGI-19*, *C6orf196*
Key enzymes in the pathways of sulfur-containing amino acid catabolism			
CBS	875	21q22.3	*HIP4*
CDO1	1036	5q23.2	*CDO*, *CDO-I*
CTH	1491	1p31.1	
GOT1	2805	10q24.1-25.1	*ASTQTL1*, *GIG18*, *AST1*, *cAspAT*, *cCAT*
SQRDL	58472	15q15	*SQOR*, *CGI-44*, *PRO1975*
TST	7763	22q13.1	*LL22NC01-146D10.3*, *RDS*
SUOX	6821	12q13.2	

Information was obtained from the online NCBI Gene database http://www.ncbi.nlm.nih.gov/gene/ accessed from 25 October 2015 to 25 February 2016.

Table 2. Genes encoding cytosolic sulfotransferases

Gene	ID	Location	Aliases
SULT1A1	6817	16p12.1	*HAST1/2*, *P-PST*, *PST*, *ST1A1*, *ST1A3*, *STP*, *STP1*, *TSPST1*
SULT1A2	6799	16p12.1	*HAST4*, *P-PST*, *ST1A2*, *STP2*, *TSPST2*
SULT1A3	6818	16p11.2	*HAST*, *HAST3*, *M-PST*, *ST1A3/ST1A4*, *ST1A5*, *STM*, *TL-PST*
SULT1A4	445329	16	*HAST3*, *M-PST*, *ST1A3/ST1A4*, *TL-PST*
SULT1B1	27284	4q13.3	*ST1B1*, *ST1B2*, *SULT1B2*
SULT1C2	6819	2q12.3	*ST1C1*, *ST1C2*, *SULT1C1*, *humSULTC2*
SULT1C3	442038	2q12.3	*ST1C3*
SULT1C4	27233	2q12.3	*SULT1C*, *SULT1C2*
SULT1E1	6783	4q13.1	*EST*, *EST-1*, *ST1E1*, *STE*
SULT2A1	6822	19q13.3	*DHEA-ST*, *DHEAS*, *HST*, *ST2*, *ST2A1*, *ST2A3*, *STD*, *hSTa*
SULT2B1	6820	19q13.3	*HSST2*
SULT4A1	25830	22q13.2	*BR-STL-1*, *BRSTL1*, *DJ388M5.3*, *NST*, *SULTX3*, *hBR-STL-1*
SULT6B1	391365	2p22.2	

Information was obtained from the online NCBI Gene database http://www.ncbi.nlm.nih.gov/gene/ accessed from 25 October 2015 to 25 February 2016.

Table 3 . Genes encoding membrane bound sulfotransferases

Gene	ID	Location	Aliases
CHST1	8534	11p11.2	*C6ST*, *KSST*, *GST-1*, *KS6ST*, *KSGal6ST*
CHST2	9435	3q24	*C6ST*, *GST-2*, *GST2*, *Gn6ST-1*, *glcNAc6ST-1*
CHST3	9469	10q22.1	*C6ST*, *C6ST1*, *HSD*
CHST4	10164	16q22.2	*GST3*, *GlcNAc6ST2*, *HECGLCNAC6ST*, *LSST*
CHST5	23563	16q22.3	*I-GlcNac-6-ST*, *I-GlcNAc6ST*, *glcNAc6ST-3*, *gn6st-3*, *hlGn6ST*
CHST6	4166	16q22	*MCDC1*
CHST7	56548	Xp11.23	*RP1-71L16.8*, *C6ST-2*
CHST8	64377	19q13.1	*GALNAC4ST1*, *GalNAc4ST*
CHST9	83539	18q11.2	*UNQ2549/PRO6175*, *GALNAC4ST-2*
CHST10	9486	2q11.2	*HNK-1ST*, *HNK1ST*
CHST11	50515	12q	*C4ST*, *C4ST-1*, *C4ST1*, *HSA269537*
CHST12	55501	7p22	*UNQ500/PRO1017*, *C4S-2*, *C4ST-2*, *C4ST2*
CHST13	166012	3q21.3	*C4ST3*
CHST14	113189	15q15.1	*UNQ1925/PRO4400*, *ATCS*, *D4ST1*, *HNK1ST*
CHST15	51363	10q26	*BRAG*, *GALNAC4S-6ST*, *RP11-47G11.1*
GAL3ST1	9514	22q12.2	*CST*
GAL3ST2	64090	2q37.3	*hCG_31746*, *GAL3ST-2*, *GP3ST*
GAL3ST3	89792	11q13.1	*GAL3ST-3*, *GAL3ST2*
GAL3ST4	79690	7q22.1	*PP6968*, *GAL3ST-4*
HS2ST1	9653	1p22.3	*dj604K5.2*
HS3ST1	9957	4p16	*3OST*, *3OST1*
HS3ST2	9956	16p12	*3OST2*, *30ST2*
HS3ST3A1	9955	17p12	*UNQ2551/PRO6180*, *30ST3A1*, *3OST3A1*
HS3ST3B1	9953	17p12	*30ST3B1*, *30ST3B1*
HS3ST4	9951	16p11.2	*30ST4*, *30ST4*, *3-OST-4*, *h3-OST-4*
HS3ST5	222537	6q21	*3-OST-5*, *3OST5*, *HS3OST5*, *NBLA04021*
HS3ST6	64711	16p13.3	*HS3ST5*
HS6ST1	9394	2q21	*HH15*, *HS6ST*
HS6ST2	90161	Xq26.2	*RP3-435D1.3*
HS6ST3	266722	13q32.1	*HS6ST-3*
NDST1	3340	5q33.1	*HSST*, *NST1*
NDST2	8509	10q22	*NST2*, *HSST2*
NDST3	9348	4q26	*HSST3*
NDST4	64579	4q26	*NDST-4*, *NHSST4*
TPST1	8460	7q11.21	*TANGO13A*
TPST2	8459	22q12.1	*CTA-445C9.10-003*, *TANGO13B*
UST	10090	6q25.1	*2OST*

Information was obtained from the online NCBI Gene database http://www.ncbi.nlm.nih.gov/gene/ accessed from 25 October 2015 to 25 February 2016.

Table 4 . Genes encoding sulfatases and sulfatase modifying factors

Gene	ID	Location	Aliases
Sulfatases			
ARSA	410	22q13.33	*MLD*
ARSB	411	5q14.1	*ASB*, *G4S*, *MPS6*
STS	412	Xp22.32	*ARSC*, *ARSC1*, *ASC*, *ES*, *SSDD*, *XL1*
ARSD	414	Xp22.3	*ASD*
ARSE	415	Xp22.3	*ASE*, *CDPX*, *CDPX1*, *CDPXR*
ARSF	416	Xp22.3	*ASF*
ARSG	22901	17q24.2	*ASG*, *UNQ839/PRO1777*, *KIAA1001*
ARSH	347527	Xp22.33	*ASH*, *sulfatase*, *arylsulfatase H*
ARSI	340075	5q32	*Arylsulfatase I*
ARSJ	79642	4q26	*Arylsulfatase J*
ARSK	153642	5q15	*TSULF*
GALNS	2588	16q24.3	*GALNAC6S*, *GAS*, *MPS4A*, *GALN6S*
GNS	2799	12q14	*G6S*
IDS	3423	Xq28	*MPS2*, *SIDS*
SGSH	6448	17q25.3	*HSS*, *MPS3A*, *SFMD*
SULF1	23213	8q13.1	*HSULF-1*, *SULF-1*
SULF2	55959	20q12-13.2	*HSULF-2*, *RP5-1049G16.1*
Sulfatase Modifying Factors			
SUMF1	285362	3p26.1	*UNQ3037*, *AAPA3037*, *FGE*
SUMF2	607940	7q11.1	*PSEC0171*, *pFGE*

Information was obtained from the online NCBI Gene database http://www.ncbi.nlm.nih.gov/gene/ accessed from 25 October 2015 to 25 February 2016.

Table 5. Pathophysiology linked to sulfate transporters, PAPS synthetases and transporters, and the enzymes involved in sulfate generation from amino acids

Gene	Species	Condition	Reference
SLC4A1	Human	Hereditary spherocytosis/stomatocytosis, Southeast Asian ovalocytosis, distal renal acidosis, developmental delay	Bruce et al., 1997; Bruce et al., 2005
	Cow	Hereditary spherocytosis, growth retardation, mild acidosis	Inaba et al., 1996
	Mouse	Spherocytosis and hemolysis	Peters et al., 1996
	Zebrafish	Dyserythropoiesis	Paw et al., 2003
SLC13A1	Human	Hyposulfataemia, renal sulfate wasting	Bowling et al., 2012
	Mouse	Hyposulfataemia, growth retardation, late gestational fetal loss, seizures, behavioural abnormalities	Dawson et al., 2003, 2004, 2005, 2011
	Sheep	Hyposulfataemia, osteochondrodysplasia, growth retardation	Zhao et al., 2012
	Dog	Hyposulfataemia, osteochondrodysplasia, growth retardation	Neff et al., 2012
Slc13a4	Mouse	Fetal abnormalities, including skeletal defects, vascular haemorrhaging, craniofacial malformations and embryonic death	Rakoczy et al., 2015b
Slc26a1	Mouse	Hyposulfataemia, hyperoxaluria, renal stones	Dawson et al., 2010b
SLC26A2	Human	Skeletal dysplasias	Dawson and Markovich, 2005
	Mouse	Growth retardation, skeletal dysplasia, joint contractures, delay in formation of secondary ossification centre and osteoporosis of long bones	Forlino et al., 2005
SLC26A3	Human	Congenital chloride diarrhoea	Hoglund et al., 2001
	Mouse	Fatal infectious diarrhoea	Borenshtein et al., 2009
SLC26A6	Human	Increased kidney stone risk	Lu et al., 2016
	Mouse	Hyperoxaluria, elevated plasma oxalate, defective oxalate secretion (Bird's disease – kidney stones)	Jiang et al., 2006
Slc26a7	Mouse	Distal renal tubular acidosis, impaired gastric acid secretion	Xu et al., 2009
SLC26A8	Human	Spermatogenic failure	Dirami et al., 2013
	Mouse	Reduced sperm motility, capacitation defect	Rode et al., 2012b
SLC26A9	Human	Diffuse idiopathic bronchiestasis	Bakouh et al., 2013
	Mouse	Gastric hypochlorhydria, airway mucus obstruction in inflammatory condition, elevated systemic arterial pressure	Xu et al., 2008; Amlal et al., 2013
Slc35b2	*Drosophila*	Pupal lethality	Kamiyama et al., 2003
	Zebrafish	Cartilage defects	Clément et al., 2008
PAPSS2	Human	Brachyolmia type 4 with mild epiphyseal and metaphyseal changes, premature pubarche, androgen excess	Faiyaz ul Haque et al., 1998; Noordam et al., 2009; Oostdijk et al., 2015
	Mouse	Brachymorphic, shortened limbs, dome shaped skull, short thick tail, 25% reduction in axial skeleton	Faiyaz ul Haque et al., 1998
CBS	Human	Hyperhomocysteinemia, neurological deficits, dislocation of the optic lens, increased bone fracture risk, premature arteriosclerosis and thromboembolism	Dawson et al., 1996, 1997
	Mouse	Mod-severe homocysteinemia, post-natal death within 1 month of age, abnormal lipid metabolism	Watanabe et al., 1995
Cdo1	Mouse	High postnatal mortality, growth retardation, male infertility, kyphosis, irregular shaped cranium	Ueki et al., 2011
CTH	Human	Cystathioninuria, neurological deficits	Wang and Hegele, 2003
	Mouse	Hydrogen sulfide reduction, hypertension, diminished endothelium-dependent vasorelaxation	Yang et al., 2008; Ishii et al., 2010
SUOX	Human	Sulfite oxidase deficiency, neurological impairment	Kisker et al., 1997
	Cow	Arachnomelia	Drögemüller et al., 2010

Information was obtained from PubMed, Medline and the online NCBI OMIM http://www.ncbi.nlm.nih.gov/omim/ and OMIA http://omia.angis.org.au/home/ databases accessed from 25 October 2015 to 25 February 2016.

Table 6. Pathophysiology linked to sulfotransferase genes

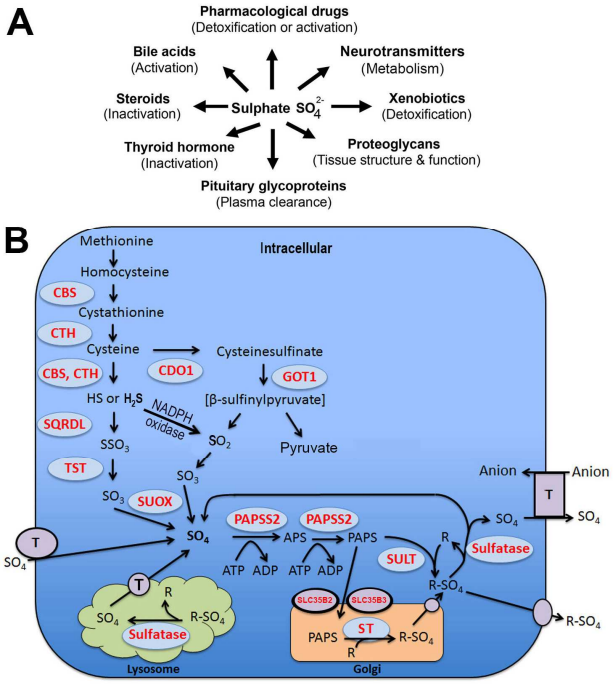
Gene	Species	Condition	Reference
Sult1e1	Mouse	Placental thrombosis and spontaneous fetal loss.	Tong et al., 2005
Chst2	Mouse	Peripheral lymph node addressin (PNAd) elimination and reduced lymphocyte homing	Uchimura et al., 2002
CHST3	Human	Joint dislocations, vertebral changes, heart valve abnormalities, brachydactyly, spondyloepiphyseal dysplasia, bilateral mixed hearing loss	Thiele et al., 2004; Tuysuz et al., 2009; Unger et al., 2010; Waryah et al., 2016
Chst5	Mouse	Thin corneas	Hayashida et al., 2006
CHST6	Human	Macular corneal dystrophy	Akama et al., 2000; El-Ashry et al., 2002
	Dog	Macular corneal dystrophy	Tetas Pont et al., 2015
CHST8	Human	Peeling skin syndrome	Cabral et al., 2012
	Mouse	Increased luteinizing hormone, testosterone, estrogen	Mi et al., 2008b
CHST11	Human	Skeletal malformation, malignant lymphoproliferative disease	Chopra et al., 2015
	Mouse	Chondrodysplasia	Klüppel et al., 2005
CHST14	Human	Ehlers-Danlos syndrome	Malfait et al., 2010; Miyake et al., 2010
GAL3ST4	Human	Pectus excavatum	Wu et al., 2012
Hs2st	Mouse	Eye and skeletal defects, kidney agenesis, neonatal death	Bullock et al., 1998
Hs3t1	Mouse	Reduced fecundity delayed placental development	de Agostini, 2006
Hs3st1	Mouse	Reductions in anticoagulant heparan sulphate, genetic background-specific lethality, intrauterine growth retardation	HajMohammadi et al., 2003
HS6ST1	Human	Hypogonadotrophic hypogonadism with and without anosmia	Tornberg et al., 2011
	Mouse	Reduced fecundity, perturbed placental development	Habuchi et al., 2007
NDST1	Human	Intellectual disability, epilepsy, muscular hypotonia	Reuter et al., 2014
	Mouse	Respiratory distress and atalectasis and neonatal death	Fan et al., 2000
	Drosophila	Impaired long-term memory	Reuter et al., 2014
Ndst2	Mouse	Altered mast cell morphology, reduced histamine, inability to synthesise sulfated heparin	Forsberg et al., 1999; Humphries et al., 1999
Tpst1	Mouse	Fetal loss and reduced body weight	Ouyang et al., 2002

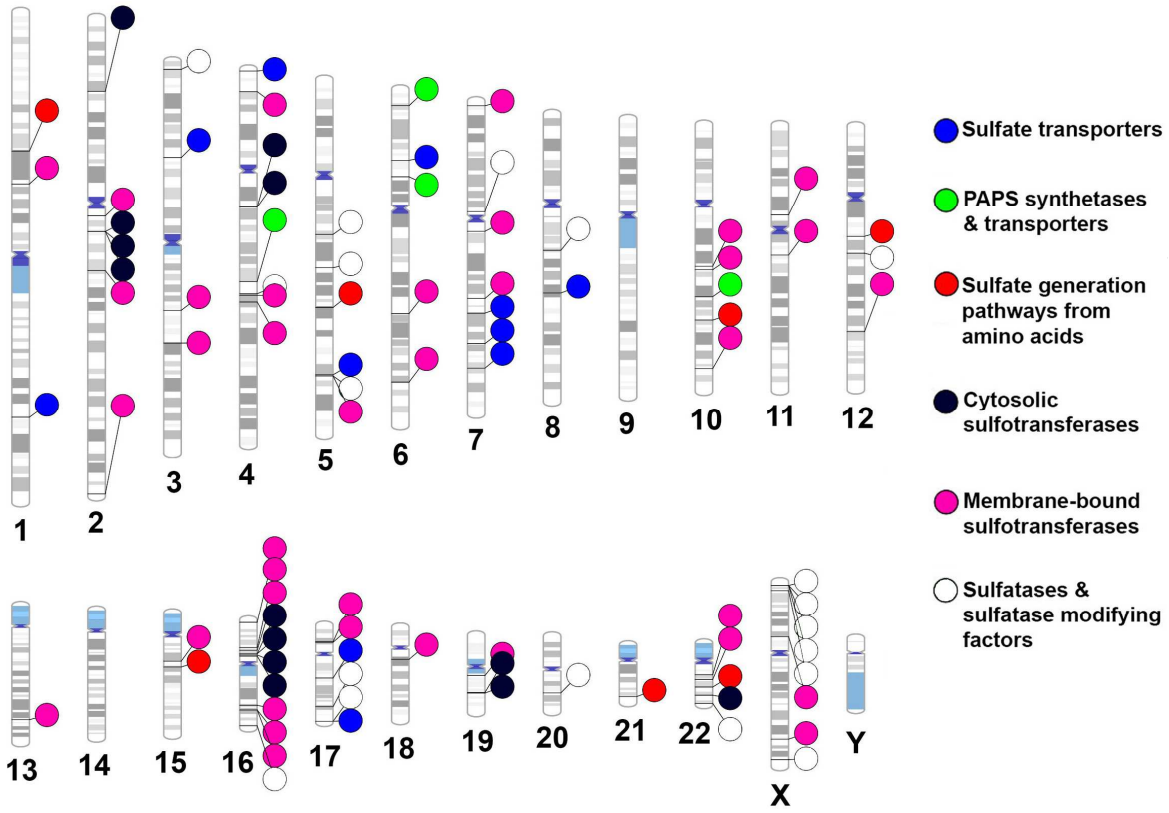
Information was obtained from PubMed, Medline and the online NCBI OMIM http://www.ncbi.nlm.nih.gov/omim/ and OMIA http://omia.angis.org.au/home/ databases accessed from 25 October 2015 to 25 February 2016.

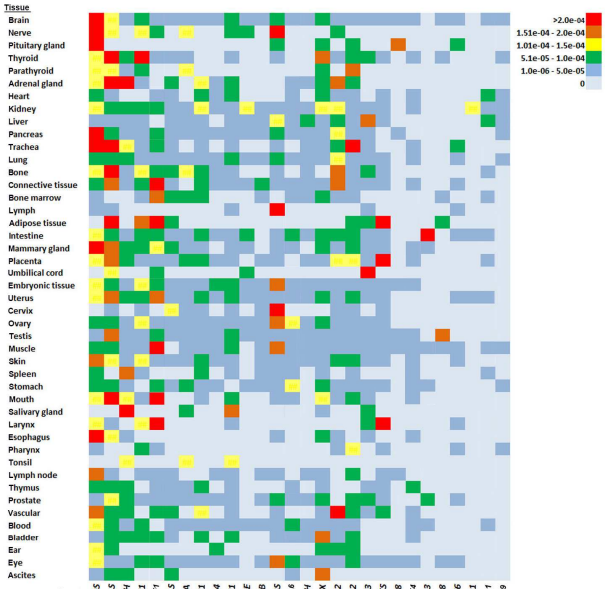
Table 7. Pathophysiology linked to sulfatase and sulfatase modifying factor genes

Gene	Species	Condition	Reference
ARSA	Human	Metachromatic leukodystrophy	Diez-Roux and Ballabio, 2005; Sardiello et al., 2005
ARSB	Human	Maroteux-Lamy syndrome	Diez-Roux and Ballabio, 2005; Sardiello et al., 2005
	Mouse	Facial dysmorphia, dystosis multiplex, GAG build up in connective tissue, reticuloendothelial cells and cartilage	Evers et al., 1996
	Rat	Facial dysmorphia, dysostosis multiplex, increased urinary excretion of glucosaminoglycans	Yoshida et al., 1994
	Cat	Dwarfism, facial dysmorphia, dermatan sulfaturia, lysosomal inclusions in most tissues, corneal clouding, degenerative joint disease, abnormal leukocyte inclusions.	Crawley et al., 1998
	Dog	Epiphyseal dysplasia, malformed vertebral bodies, luxation / subluxation of appendicular and lumbosacral joints with hypoplasia of the odontoid process and hyoid apparatus.	Jolly et al., 2012
ARSE	Human	Chondrodysplasia punctata 1 (X-linked recessive)	Franco et al., 1995
Arsg	Dog	Cerebellar ataxia, neuronal ceroid lipofuscinoses	Abitbol et al., 2010
	Mouse	Mucopolysaccharidosis, behavioural deficits	Kowalewski et al., 2012
STS	Human	X-linked ichthyosis	Ballabio et al., 1987
GALNS	Human	Morquio A syndrome – metabolic syndrome	Diez-Roux and Ballabio, 2005
	Mouse	Accumulated glycosaminoglycans in tissues – skeletal, neurological, ocular, skin and connective tissue problems	Tomatsu et al., 1993
GNS	Human	Sanfilippo D syndrome	Diez-Roux and Ballabio, 2005
	Goat	Neurological manifestations	Thompson et al., 1992; Cavanagh et al., 1995
IDS	Human	Hunter syndrome	Diez-Roux and Ballabio, 2005
SGSH	Human	Sanfilippo A syndrome	Diez-Roux and Ballabio, 2005
	Dog	Progressive neurologic disease, pelvic limb ataxia and spinocerebellar ataxia	Fischer et al., 1998
SULF1	Human	Mesomelia-synostoses syndrome	Isidor et al., 2010
	Mouse	Developmental defects, neonatal lethality	Holst et al., 2007
Sulf2	Mouse	Developmental defects, neonatal lethality	Holst et al., 2007
SUMF1	Human	Multiple sulfatase deficiency	Dierks et al., 2003
	Mouse	Skeletal abnormalities, congenital growth retardation	Settembre et al., 2007

Information was obtained from PubMed, Medline and the online NCBI OMIM http://www.ncbi.nlm.nih.gov/omim/ and OMIA http://omia.angis.org.au/home/ databases accessed from 25 October 2015 to 25 February 2016.







Pathology	IDS	GNS	SGSH	NDST1	SULF1	GALNS	ARSA	SUMF1	CHST14	HS6ST1	ARSE	ARSB	CBS	SLC26A6	CTH	SUOX	PAPSS2	SLC26A2	CHST3	ST5	CHST8	GALNS74	SLC26A3	SLC26A8	CHST6	SLC13A1	SLC4A1	SLC26A9
Neurological	X	X	X	X	X	X	X	X		X		X	X	X		X	X				X							
Skeletal	X	X	X		X	X	X	X	X		X	X	X	X				X	X	X		X	X					
Eye		X				X			X			X	X							X					X			
Skin	X							X	X			X								X	X							
Renal					X									X													X	X
Intestine	X	X	X									X								X			X					
Reproductive										X							X							X				
Cardiovascular	X				X	X		X	X		X	X	X						X									
Respiratory	X					X						X																X
Liver	X	X				X		X				X																
Connective tissue									X													X						
Blood													X							X							X	
Auditory																			X									