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An Expert Review of Pharmacogenomics of Sickle Cell Disease Therapeutics: Not Yet Ready for Global Precision Medicine

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Abstract

Sickle cell disease (SCD) is a blood disease caused by a single nucleotide substitution (T > A) in the beta globin gene on chromosome 11. The single point mutation (Glu6Val) promotes polymerization of hemoglobin S (HbS) and causes sickling of erythrocytes. Vaso-occlusive painful crises are associated with recurrent and long-term use of analgesics/opioids and hydroxyurea (HU) by people living with SCD. The present analysis offers a state-of-the-art expert review of the effectiveness of pharmacogenomics/genetics of pain management in SCD, with specific focus on HU and opioids. The literature search used the following keywords: SCD, pharmacogenomics, pharmacogenetics, pain, antalgics, opioids, morphine, and HU. The literature was scanned until March 2016, with specific inclusion of targeted landmark and background articles on SCD. Surprisingly, our review identified only a limited number of studies that addressed the genetic/genomic basis of variable responses to pain (e.g., variants in *OPRM1*, *HMOX-1*, *GCH1*, *VEGFA COMT* genes), and pharmacogenomics of antalgics and opioids (e.g., variants in *OPRM1*, *STAT6*, *ABCB1*, and *COMT* genes) in SCD. There has been greater progress made toward identifying the key genomic variants, mainly in *BCL11A*, *HBS1L-MYB*, or *SAR1*, which contribute to response to HU treatment. However, the complete picture on pharmacogenomic determinants of the above therapeutic phenotypes remains elusive. Strikingly, no study has been conducted in sub-Saharan Africa where majority of the patients with SCD live. This alerts the broader global life sciences community toward the existing disparities in optimal and ethical targeting of research and innovation investments for SCD specifically and precision medicine and pharmacology research broadly.

Introduction

Sickle Cell Disease (SCD) is a multisystem disease, which is associated with episode pain (chronic and acute illness) and organ damage, and commonly occurs in sub-Saharan African countries. SCD is a genetic blood disease caused by a single nucleotide substitution (T > A) in the beta globin gene on chromosome 11 (Brousseau et al., 2007). The resulting HbS leads to polymerization and precipitation of hemoglobin during deoxygenation or dehydration. This results in sickling of red blood cells, abnormal adhesion of leukocytes and platelets, inflammation, hemolysis, and hypercoagulation, which could lead to vaso-occlusive crisis and hypoxia and ultimately organ damage (Bartolucci and Galacteros, 2012).

There is a strong association between the frequency of the HbS mutation and endemicity of malaria (Charache et al., 1995; Williams et al., 2005). It is estimated that 305,800 babies are born each year with SCD worldwide with nearly 75% of the births occurring in sub-Saharan Africa (SSA) (Piel et al., 2013). However, as a result of migration, there is a reported increasing burden of SCD in other countries where it was not initially prevalent, such as South Africa (Wonkam et al., 2012), Ireland (Gibbons et al., 2015), Italy (Colombatti et al., 2013), Germany (Kunz et al., 2015; Zur, 2016), England (Pizzo et al., 2015), and France (Dzierzynski et al., 2016), with, for example, 1300–2600 affected newborns annually in France. SCD is now an accepted worldwide health problem and comparable with other major global noncommunicable diseases such as diabetes and hypertension (Weatherall and Clegg, 2008).

Despite the high incidence, there is currently no effective public health program in any SSA country focused on SCD (Rahimy et al., 2009; Tekola-Ayele and Rotimi, 2015;

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Wonkam et al., 2014b). As a consequence, up to 90% of infants with SCD in SSA are believed to die by the age of 5 years (Grosse et al., 2011; Makani et al., 2013). While there have been recent efforts in selected African countries to implement newborn screening (McGann et al., 2013; Rahimy et al., 2009; Tshilolo et al., 2009; Tubman et al., 2016), to use hydroxyurea (HU) more frequently (Makubi et al., 2012; Olabode and Shokunbi, 2006; Ware, 2013), and to initiate genetic studies (Cox et al., 2014; Mmbando et al., 2015; Mtatiro et al., 2014; Pule et al., 2015; Rumaney et al., 2014; Wonkam et al., 2014a, 2014b, 2014c), there is still a lack of integration and coordination of these emerging research efforts.

In sharp contrast to SSA, comprehensive clinical care programs have reduced SCD-related premature childhood deaths by 70% in high-income nations such as the United State of America (Vichinsky, 1991; Yanni et al., 2009). This evidence from the West indicates that the institution of interventions such as newborn screening and penicillin prophylaxis can reduce the horrendous disease burden in SSA (Rahimy et al., 2003). Therefore, there is a major need for research to help develop effective therapies across the life span of SCD patients in all parts of the world (Chaturvedi and DeBaun, 2016; Hamideh and Alvarez, 2013), including the incorporation of personalized medicine and pharmacogenomics.

Indeed, environmental and multiple genetic factors influence many pathophysiological aspects of SCD that contribute to a highly variable clinical expression in individual patients. Fetal hemoglobin (HbF) has emerged as a central disease modifier and genetic variants at three principal loci, *BCL11A*, *HBS1L-MYB*, and *HBB* cluster, which account for 10–20% of HbF variation among SCD patients in USA, Brazil, and the United Kingdom (Lettre et al., 2008; Thein and Menzel, 2009). These studies have been replicated in patients living with SCD in Tanzania and Cameroon (Makani et al., 2011; Mtatiro et al., 2014; Pule et al., 2015; Wonkam et al., 2014a). Interestingly, the expression of these modifiers is amenable to therapeutic manipulation (Bukar et al., 2013; Canver et al., 2015; Xu et al., 2011), leading to new hope for treatment routes for SCD (Orkin, 2016).

HU is the only Food and Drug Administration (FDA)-approved treatment of SCD in adults and children (Shenoy, 2011). HU is a ribonucleotide reductase inhibitor that increases the fetal hemoglobin level, a known ameliorator of the disease. Patients respond differently to HU due to genetic variations (Bockaert and Pin, 1999; Charache et al., 1995; Steinberg et al., 1997; Zimmerman et al., 2004).

Nevertheless, the common medications used by SCD patients are antalgics to manage pain. Pain in SCD is classified as acute, chronic, and mixed pain, which varies in severity (Ballas, 2015; Ballas et al., 2012; Steinberg et al., 2010). Genetic differences are suggested to be the reason for inter-individual variability in pain perception and experience and variable responses to anti-inflammatory (Chou et al., 2006) and opioid drugs (Chou et al., 2006). Individuals who are homozygous for 118A>G polymorphism in the *OPRM1* (a major site of action for most opioid analgesics) have more pain and need more morphine to subdue the pain (Klepstad et al., 2004). Single-nucleotide polymorphisms (SNPs) in the *COMT* gene affected pain sensitivity and with low *COM*T activity lead to increased levels of norepinephrine and epinephrine, which resulted in more pain sensitivity (Slade et al., 2007).

The aim of the present analysis was to provide an expert literature review of the effectiveness of pharmacogenomics/genetics for pain management in SCD, with specific focus on pharmacogenetics/pharmacogenomics of pain, HU, and opioids.

Methods

A comprehensive literature search was conducted by the authors covering the subject until March 2016, with specific addition of landmark and background articles on SCD published articles. We used the PubMed® (National Library of Medicine), Medline®, and Google Scholar®. Keywords included individual use or a combination of the following: ''Pharmacogenomics,'' ''Pharmacogenetics,'' ''Hydroxyurea,'' ''Sickle Cell Disease,'' ''Pain,'' ''Painkillers,'' and ''Morphine'' and ''Opioids.'' Additionally, specific expert authors' names that are active in the field of SCD and its therapeutics were also used to complement the literature searches.

Selection criteria

The inclusion criteria were confined to articles written in English, with major emphasis being focused on research articles and review articles describing pharmacogenomics of pain, particularly on SCD patients, and effectiveness of pharmacogenomics of drug therapies for HU and pain management. Prior knowledge of research groups working on HU, pain episodes, and SCD in Africa globally further facilitated the identification and selection of research articles. Only available full-length articles, in English, with the use of ''HU,'' ''Painkillers,'' ''Morphine,'' and ''Opioids'' were selected. In cases where multiple studies reported a similar pathway, the most recent report with the most detailed associations' studies was included. The main search was conducted, separately, by an MSc student and a PhD student (First and Second authors) in Human Genetics working on SCD (to maximize the inclusion of potentially relevant articles) and reviewed successively by a medical geneticist and a human geneticist, with expertise in SCD and pharmacogenomics (Fourth and Third authors), respectively.

A total of 316 articles were consulted after the search from Google Scholar (of which 47 were from PubMed); exclusion criteria were performed based on the article title and its relevance to the scope of the review; additional study performed on the same cohort for the same experiment; and studies that were not clearly stated were excluded. Subsequently, 158 articles were fully retrieved and their abstract and result sections perused for further elimination, of which a final total of 125 articles were selected for inclusion in the review (Fig. 1 and Supplementary Table S1).

Data collection

Data were collected using an extraction form to summarize the following information: type of study, year of publication, patients' sample, study country, title, and author names (Supplementary Table S1).

Results

Pharmacogenomics of pain susceptibility in SCD

Acute pain acts as a protective mechanism in response to tissue injury (Ballas and Lusardi, 2005; Bergman, 2005) and

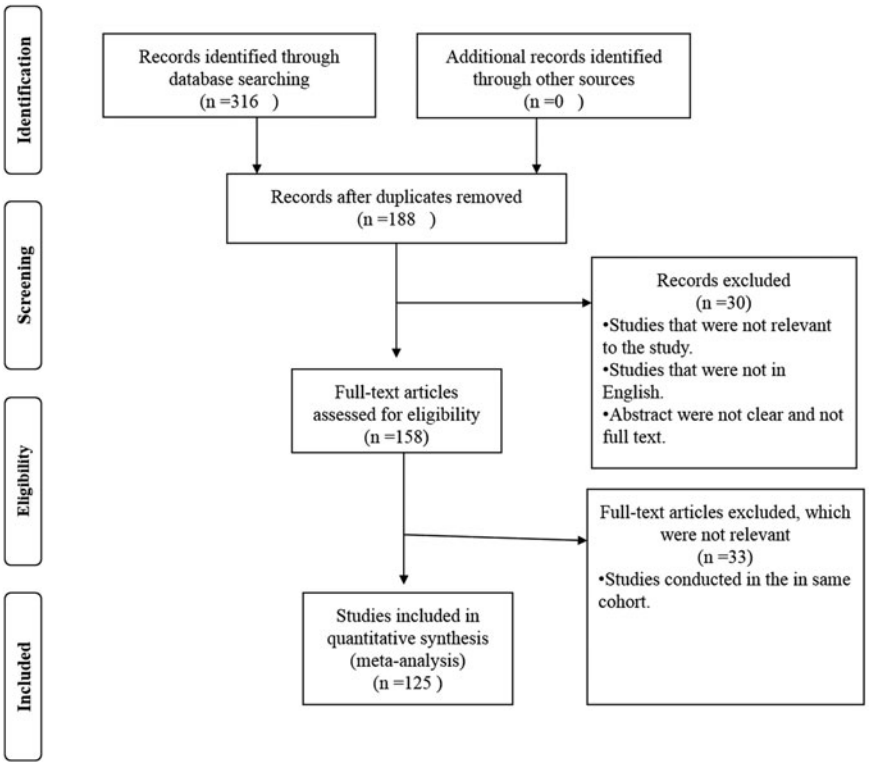

FIG. 1. Flowchart of the literature review employed in the present expert review.

can worsen and prolong to a chronic state, which results in mixed pain. Chronic pain persists longer than acute pain (Todd, 2005; Todd et al., 2006). Chronic pain can result in psychopathology disorders such as depression, anxiety, and personality disorder (Dersh et al., 2002), which is called chronic pain syndrome (Knorring, 1989). Chronic Pain in SCD has a direct impact on the quality of life of patients (Kanter and Kruse-Jarres, 2013; Platt et al., 1991; Rees et al., 2010).

A few studies have been conducted to establish the difference in pain perception and response to opioids (Stamer and Stuber, 2007). It was found that genomic variations influence both perception and vulnerability to chronic pain (Mogil, 2004; Mogil and Devor, 2004; Stamer and Stuber, 2007). Furthermore, SNPs of specific genes were associated with variable degrees of pain perception (Diatchenko et al., 2005), leading to the hypothesis that some variants were located in genes related to the inflammatory process of vaso-occlusive painful crises, resulting in nerve and tissue damage and thus the development of secondary pain (Mogil, 2004). Table 1 summarizes the selected genes that have been associated with pain susceptibility in SCD.

HMOX-1 codes for heme oxygenase-1, which is a rate-limiting step in the catalysis of heme. It exhibits a GT dinucleotide repeat in the promoter region, and long repeat lengths (>25 repeats) are associated with decreased activity and inducibility, and therefore higher rates of SCD patient hospitalization, but not directly associated with pain (Bean et al., 2013). It is reported that among African-Americans, a polymorphism in the GTP cyclohydrolase (*GCH1*) on chromosome 14 (rs8007267) is significantly associated with pain crises (Belfer et al., 2014). *GCH1* catalyzes the rate-limiting step for tetrahydrobiopterin synthesis, thus variation in its gene is likely to have pathophysiological roles in pain. Acute pain has been a subject of some studies with the most relevant to SCD referring to an SNP (rs614803) located in a region about 8 kb from the COMM domain-containing protein COMMD7. This polymorphism is significantly associated with painful crises.

COMMD7 modulates many proteins and is associated with NF-kappa-B complex, suppressing its transcriptional activity (Galarneau et al., 2013). Investigations among Egyptians reported the *GSTM1* null allele to be significantly associated with increased risk of severe vaso-occlusive crises (Shiba et al., 2014). *GSTM1* is located on chromosome 1 and catalyzes the addition of glutathione on molecules to increase the antioxidant status, while the *GSTM1* null refers to deletion of this gene. A higher incidence of pain was observed among SCD patients who were carriers of the methylenetetrahydrofolate reductase (*MTHFR*; C677T) polymorphism as well as Factor V Leiden *(FVL*; G191A) polymorphism (Nishank et al., 2013). The vascular endothelial growth factor gene (*VEGFA*) has several mutations of which three, rs2010963, rs833068, and rs3025020, have been associated with vaso-occlusive crisis when inherited in a homozygous state (Al-Habboubi et al., 2012).

Morphine metabolism

Morphine is a member of the opioid family and is mostly used because it is globally available and shows successful clinical efficacy (Adegbola, 2009). Morphine is derived from codeine through the action of *CYP2D6*-catalyzed demethylation. Through the actions of UDP-glucuronosyltransferases, 2B7 and 1A1 (*UGT2B7* and *UGT1A1*), morphine is converted to morphine-3-glucuronide (M3G) and morphine-6-

Table 1. Genomic Variants that Influence Pain in Sickle Cell Disease

Gene	*SNPS*	*Chromosomes locus*	*Association*	*References*
OPRM1	rs1799971	6:154039662	Pain	Joly et al. (2012); Jhun et al. (2015)
HMOX-1	A(GT) VNTR	Chromosome 22	Vaso-occlusive crises	Bean et al. (2013)
GCH1	rs8007267	14:54912273	Pain	Belfer et al. (2014)
COMMD7	rs614803	18:79389574	Painful crisis	Galarneau et al. (2013)
GSTM1	GSTM1 null allele	Chromosome 1	Severe vaso-occlusive crisis	Shiba et al. (2014)
MTHFR	rs1801133 (C677T)	1:11796321	Pain	Nishank et al. (2013)
FVL	rs6025 (G1691A; R506Q)	1:169549811	Pain	Nishank et al. (2013)
VEGFA	rs833068 (G398A)	6:43774790	Vaso-occlusive crisis	Al-Habboubi et al. (2012)
VEGFA	rs2010963	6:43770613	Vaso-occlusive crisis	Al-Habboubi et al. (2012)
VEGFA	rs3025020	6:43781373	Vaso-occlusive crisis	Al-Habboubi et al. (2012)
CYP2D6	rs1065852	22:42130692	Pain and drug metabolism	Joly et al. (2012); Jhun et al. (2015)
COMT	rs4633	22:19962712	Pain	Joly et al. (2012); Jhun et al. (2015)
	rs6269	22:19962429	Pain	
	rs737865	22:19942598	Pain	
CPY3A	rs1057868	7:75985688	Pain	Joly et al. (2012); Jhun et al. (2015)
UGTB7	rs1799971	6:154039662	Pain	Joly et al. (2012); Jhun et al. (2015)
ABCB1	rs1045642	7:87509329	Pain	Jhun et al. (2015)

glucuronide (M6G) through glucuronic acid conjugation. Ultimately, the glucuronidated morphine is effluxed by transporters such as *ABCB1*, *ABCC2*, *ABCC3*, and *SLC01B1*. M6G is responsible for analgesia contribution by binding to μ-opioid receptor; there are arguments about the role of M6G in analgesia that results from morphine (Höllt, 2002; Murthy et al., 2002; Osborne et al., 1990; Smith et al., 1990). M3G has small pull force for opioid receptors (Smith et al., 1990) and it might be responsible for the excitatory effect of morphine (Smith et al., 1990). Blood plasma concentration of morphine and its metabolites is a function of morphine dose and renal clearance, which might be affected by genetic variations, and it is therefore anticipated that variants in the above genes could be associated with variable response to the drug treatment in patients living with SCD. This is supported by evidence from a population study, indicating that the allele variation in genes that are involved in morphine mechanism might regulate the response of opioid analgesic (Lotsch and Geisslinger, 2006).

Genetic variations and morphine metabolism

Patients respond differently to drugs due to variations in genes coding for metabolizing enzymes (Table 2). *UGT2B7* (rs7438135), *OPRM1* (rs1799971), and *ABCB1* (rs1045642) influence the pharmacokinetic and pharmacodynamic measurements and affect the clinical effectiveness of morphine (Adegbola, 2009). *COMT* (rs4633) is not directly involved in the metabolism, but can improve the productivity of morphine. This can occur by influencing μ-opioid receptors and its concentration in different areas of the brain by affecting the neuronal activity; with reduction in *COMT* activity then resulting in sensitivity to pain and morphine (Bockaert and Pin, 1999; Bohn et al., 1999; Kraus et al., 2001; Loh et al., 1998; Matthes et al., 1996; Meineke et al., 2002; Rakvåg et al., 2005; Weinshilboum and Raymond, 1977; Zubieta et al., 2003). Individuals who have the lowest *COMT* activity (met/met variant) have higher sensory and higher effective rates of pain, as well as a more effective state, as the met/met variant reduces the ability to activate the μ-opioid receptor system (Zubieta et al., 2003). This also causes upregulation of the opioid receptors and low concentrations of morphine are required to produce sufficient analgesia to ease the pain (Rakvåg et al., 2005).

ABCB1, which is also known as the *MDR1* transporter gene (Weinshilboum and Raymond, 1977), contributes to the variability in morphine metabolism to produce analgesia by moving the efflux of morphine and M6G across the blood–brain barrier (Darbari et al., 2008). *OPRM1* is the major site

Table 2. Genetic Variants Associated with Morphine Metabolism

Gene	*SNPS*	*Chromosome locus*	*Effect of variant allele*	*References*
UGT2B7	rs7438135	4:69095621	Drug metabolism	Höllt (2002); Duguay et al. (2004)
OPRM1	rs1799971	6:154039662	Pain and mediates analgesic effect of morphine.	Lötsch et al. (2002); Zubieta et al. (2003); Jhun et al. (2015)
ARRB2	rs1045280	17:4719343	Drug metabolism	Ross et al. (2005)
STAT6	rs167769	12:57109992	Drug metabolism	Ross et al. (2005); Jhun et al. (2015)
	rs841718	12:57099213	Drug metabolism	
	rs3024971	12:57099944	Drug metabolism	
COMT	rs4633	22:19962712	Drug metabolism and pain	Zubieta et al. (2003); Jhun et al. (2015)
ABCB1	rs1045642	7:87509329	Responsible for analgesia	Meineke et al. (2002); Jhun et al. (2015)

of action for most opioid analgesics, including morphine (Adegbola, 2009; Beyer et al., 2004; Lotsch and Geisslinger, 2006). This gene is responsible for both pain response and opioid addiction (Adegbola, 2009; Compton et al., 2003). Each individual has different responses to morphine due to polymorphisms in *OPRM1*, which affect the functioning and expression of the binding site (Adegbola, 2009; Chou et al., 2006; Klepstad et al., 2004; Lotsch and Geisslinger, 2006; Mantione et al., 2005; Stamer and Stuber, 2007); and *OPRM1* has two SNPS; A118G and C17T, with A118 being the one that is a commonly identified SNP (Adegbola, 2009; Bond et al., 1998). There is therefore an urgent need to explore the knowledge on pharmacogenomics on morphine metabolism among the population of people affected by SCD.

Pharmacogenomics of HU

HU is the only available treatment for induction of HbF in patients living with SCD that has been approved by both the FDA in 1998 and by the European Medicines Agency in 2007. It was also mentioned as an effective treatment for both adult and children with SCD by the National Institutes of Health (Officer of Medical Applications of Research) (NIH-OMAR) and the Agency of Healthcare Research and Quality (AHRQ) (Herrick, 2000; Loh et al., 1998; Weatherall et al., 2005). HU is an oral, S-phase-specific cytotoxic, antimetabolic, and antineoplastic drug treatment. It is a strong inhibitor of a universal enzyme called ribonucleotide reductase (Elford, 1968; Modell and Darlison, 2008). In 1984, the first clinical application of HU in hemoglobinopathies successfully demonstrated a swift and vivid increase in HbF concentration within immature red blood cells called reticulocytes (Platt et al., 1984).

Besides increasing HbF, HU also plays an important clinical role by increasing the concentration of hemoglobin and simultaneously decreasing white blood cells, absolute neutrophil count, absolute reticulocyte count, and platelets (Charache et al., 1992; de Montalembert et al., 2006; Kinney et al., 1999; Thornburg et al., 2009; Zimmerman et al., 2004). Treatment of HU is associated with a decrease in the frequency of pain episodes, acute chest syndrome, hospitalization, and the need for a blood transfusion (Charache et al., 1995).

The reduction of the clinical phenotype results in increase of efficiency in survival rates and life expectancy among SCD patients (Nagel et al., 1985; Voskaridou et al., 2010; Zago et al., 2000). It may also provide protection against cerebrovascular disease (Zimmerman et al., 2007), long-term drug safety, capacity to prevent organ damage, and reduced morbidity and mortality in school-age children (Kinney et al., 1999), toddlers (Hankins et al., 2005; Thornburg et al., 2009), and infants (Alvarez et al., 2012). HU also helps with related complications of SCD such as stroke prevention, priapism, and pulmonary hypertension (DeBaun, 2014). Maximum tolerated dose for various phenotypes was observed to be different for patients using HU, showing that patients respond differently to HU (Charache et al., 1992; Heeney and Ware, 2008; Ware et al., 2011).

Genetic variation in HU treatment response

Induced HbF levels range from 10% to greater than 30% (Kinney et al., 1999; Zimmerman et al., 2004) among patients with SCD, highlighting the variation in response to HU. This is due to pharmacogenomic interactions (Steinberg et al., 2003). Previous studies have shown that haplotypes in the *HBB* gene cluster that are associated with SCD could possibly affect the clinical response to HU, likely refereed by their genetically determined effect on the HbF level (Adekile, 2011; Friedrisch et al., 2008). *XMNL-HHBG2* (rs7482144) is associated with high level of HbF in response to HU drug treatment in both SCD and β-thalassemia individuals

Table 3. Genomic Variants Associated with Hydroxyurea-Induced HbF Level

Gene	*SNPs*	*Chromosome: locus*	*References*
HBB	rs7482144	11:5254939	Friedrisch et al. (2008); Adekile (2011)
BCL11A	rs1427407	2:60490908	Ware et al. (2011); Ware (2013); Friedrisch et al. (2008); Adekile (2011)
	rs4671393	2:60491212	
	rs7606173	3:60493111	
	rs7557939	2:60494212	
	rs1186868	2:61764103	
ARG1/2	rs2295644	14:67599842	Friedrisch et al. (2008); Adekile (2011)
	rs17599586	6:131583579	
	rs28384513	6:135055071	
HBS1L-MYB	rs9399137	6:135097880	Friedrisch et al. (2008); Adekile (2011)
SAR1	rs2310991	3:142444839	Kumkhaek et al. (2008); Zhu et al. (2014)
	rs4282891	10:70171890	
	rs76901216	10:70170313	
SALL2	rs61743453	14:21523209	Sheehan et al. (2013)
FLT1	rs2182008	13:28412924	Ma et al. (2007)
	rs8002446	13:28423263	
	rs9319428	13:28399484	
	rs3751395	13:28384818	
	rs2387634	13:28416291	
TOX	rs826729	8:58826354	Ma et al. (2007)
	rs765587	8:58878344	
	rs9693712	8:59034864	
	rs172652	8:59045582	
	rs380620	8:59069973	
	rs2693430	8:58812489	
	rs12155519	8:58936271	
ARG2	rs10483801	14:67650289	Ma et al. (2007)
	rs10483802	14:67650704	
NOS1	rs816361	12:117217326	Ma et al. (2007)
	rs7977109	12:117292535	
	rs7309163	12:117291469	
NOS2A	rs1137933	17:27778906	Ma et al. (2007)
	rs944725	17:27782545	
MAP3K5	rs9376230	6:136781227	Ma et al. (2007)
	rs9483947	6:136784262	
PDE7B	rs11154849	6:136032167	Ma et al. (2007)
	rs9376173	6:136038308	
	rs1480642	6:136178390	
	rs487278	6:136180690	
HAO2	rs10494225	1:119375480	Ma et al. (2007)
KLF10	rs3191333	8:102649991	Borg et al. (2012)

SNP, single-nucleotide polymorphism.

(Alebouyeh et al., 2004; Dixit et al., 2005; Yavarian et al., 2004). Research provides some evidences that the effect of HU on HbF level could act through other HbF-promoting loci such as *BCL11A* (Ware et al., 2011). *BCL11A* is central to the fetal switch. It is coexpressed with *SOX-6* as well as directly interacting and co-occupying the β-globin loci. It also has an association with the Mi-2/nucleosome remodeling and deacetylase (NuRD) complex for long-range reconformation of the β-globin cluster for the transcriptional silencing of γ-globin (Xu et al., 2010).

Besides *BCL11A*, from DNA structural alteration to sequence modification, the secretion-associated and ras-related protein (SAR-1) has been shown to play a significant role in γ-globin regulation (Zhu et al., 2014) and three SNPs in the *SAR-1a* promoter sequence have been associated with HbF level in the peripheral blood of SCD patients on HU (Kumkhaek et al., 2008). In addition, in relation to HU responses, it was reported that 17 SNPs are associated with HbF and 20 SNPs with response to HU (Solovieff et al., 2010). It was shown that the absence of *KLF10* (rs3191333) was found to be significantly associated with induction of HbF level in β-thalassemia intermedia compared with the majority patients with β-thalassemia and healthy individuals (Borg et al., 2012). Additional variants, which have been less consistently associated with HU-induced HbF level, are summarized in Table 3.

Discussion

There are emerging data summarized in the present article that indicate that genetic differences in SCD individuals influence the sensitivity to pain (Table 1). There are also a few studies indicating variability in analgesic response that is produced by morphine treatment with some considerable overlap with variants in genes also associated with pain sensitivity (Table 2). However, there are limited data on genetic interindividual variants and responses to morphine treatment in SCD that is directly associated with morphine metabolism. Surprisingly, there are very few data on pharmacogenetics of antalgics and analgesics and specifically opioids used in managing SCD and no data from SSA. Understanding the pharmacogenomics of pain medication in SCD could potentially improve personalized medicine and explore new routes for therapeutic intervention.

Besides antalgics and analgesics, HU drug treatment, which is prescribed for SCD patients, has produced successful results in both children and adults by decreasing pain, blood transfusions, and hospitalization. There is more consistent evidence of the association between several SNPs and HbF levels in response to HU treatment (Table 3). Again, none of the studies were conducted in SSA where the disease burden is highest, further supporting a call for action if the wide use of HU is to be implemented in Africa. Fortunately, there are emerging clinical data from multiple sites on the implementation of HU in Africa in an effort to close this gap, and they have taken the opportunity to perform association studies that could hopefully provide new insight into pharmacogenomics of HU in SCD.

Expert Commentary

Vaso-occlusive painful crises are the main clinical events of SCD and are associated with recurrent and long-term use of antalgics/opioids and HU. The present article has provided evidence of the scarcity of studies investigating the variable response to pain in SCD patients. More consistent studies have addressed the various mechanisms to understand genomic variation affecting the response to HU, but the full understanding of the variable HU-mediated HbF production among individuals affected by SCD remains elusive. Therefore, more research is needed to understand their various mechanisms and pharmacogenomics of both painkiller/opioids and HU to improve the management of people living with SCD.

Five-Year View

The global burden of SCD is anticipated to increase due to an increase in the life expectancy of people living with SCD in the West as well as in Africa. This is due to the emerging implementation of newborn screening and the use of HU treatment and the global migration that is associated with the increase in SCD incidence in countries where this condition was not initially prevalent. The improvement in the treatment of SCD will continue to contribute toward an increase in the global burden of the disease as well as dependency on chronic medications. Therefore, it is expected that most patients living with SCD will have access to pain and HU treatment worldwide, including in SSA. Thus, it could be anticipated in the coming years to observe more global interest in the field of pharmacogenetics of SCD, especially for antalgics and HU.

It is expected that future studies will also give potential explanations regarding the regulatory mechanism level of these drugs and associated gene expression, which could reveal additional pathways to explore novel therapeutic interventions that could maximize benefits while avoiding side effects. As the level of science advances, it is also suspected that there will be more medications that will be developed that are outside HbF induction, for example, to induce stress hematopoiesis, endothelial nitric oxide release, the reduction of leucocyte counts, the reduction of red blood cell adhesion to the endothelium, the reduction in inflammation processes, or medication aiming to reduce blood viscosity to name a few.

There are also topics of SCD pharmacogenomics in need of more research that have not been discussed in the current article, such as those related to recurrent blood transfusions and associated immunogenic issues, and chronic use of antibio-prophylaxy with penicillin in SCD. More research on pharmacogenomics in various aspects of treatment of SCD will result, hopefully, in a complete profile and possible algorithm that could be usable for a successful personalized medicine in SCD.

Key Issues

- Vaso-occlusive painful crises are associated with the recurrent pain and long-term use of antalgics/opioid by people living with SCD. Surprisingly, the present article has provided evidence of limited number of studies to understand the variable responses to pain and pharmacogenomics of antalgics and opioids in people living with SCD.
- There has been great progress made toward understanding and identifying key genomic variants in *BCL11A*, *HBS1L-MYB*, or *SAR1* that predispose the response to the HU treatment; however, the complete picture remains elusive.
- The global burden of SCD is anticipated to increase due to increase of the life expectancy of patients in the

West, emerging implementation of newborn screening and the use of HU treatment in Africa, and the global migrations. Therefore, it could be anticipated to see, in the coming years, more global interest in the field of pharmacogenetics of SCD.

- Strikingly, no study has been conducted in SSA where majority of the patients with SCD live. This alerts the broader global life sciences community toward the existing disparities in optimal and ethical targeting of research and innovation investments for SCD specifically and precision medicine and pharmacology research broadly.

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Abbreviations Used

FDA = Food and Drug Administration
HbS = hemoglobin sickle
HU = hydroxyurea
SCD = sickle cell disease
SNP = single-nucleotide polymorphism
SSA = sub-Saharan Africa