Clinical Biochemistry 124 (2024) 110707

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Atorvastatin-associated myotoxicity: A toxicokinetic review of pharmacogenetic associations to evaluate the feasibility of precision pharmacotherapy

Emilia Hoste [a,b], Vincent Haufroid [b,c], Louise Deldicque [d], Jean-Luc Balligand [e], Laure Elens [a,b,*]

[a] Integrated PharmacoMetrics, pharmacoGenomics and Pharmacokinetics, Louvain Drug Research Institute (LDRI), Université Catholique de Louvain (UCLouvain), Brussels 1200, Belgium
[b] Louvain Center for Toxicology and Applied Pharmacology, Institut de recherche expérimentale et clinique (IREC), Université Catholique de Louvain (UCLouvain), Brussels, Belgium
[c] Department of Clinical Chemistry, Cliniques Universitaires Saint-Luc, Brussels, Belgium
[d] Institute of Neuroscience (IoNS), Université Catholique de Louvain (UCLouvain), Louvain-la-Neuve 1348, Belgium
[e] Pole of Pharmacology and Therapeutics (FATH), Institute of Experimental and Clinical Research (IREC), Université Catholique de Louvain (UCLouvain), Brussels, Belgium

ARTICLE INFO

Keywords:
Atorvastatin
Statin-related myotoxicities
Pharmacogenetics
Pharmacokinetics
Drug transporters

ABSTRACT

Atorvastatin (ATV) and other statins are highly effective in reducing cholesterol levels. However, in some patients, the development of drug-associated muscle side effects remains an issue as it compromises the adherence to treatment. Since the toxicity is dose-dependent, exploring factors modulating pharmacokinetics (PK) appears fundamental. The purpose of this review aims at reporting the current state of knowledge about the singular genetic susceptibilities influencing the risk of developing ATV muscle adverse events through PK modulations. Multiple single nucleotide polymorphisms (SNP) in efflux (*ABCB1*, *ABCC1*, *ABCC2*, *ABCC4* and *ABCG2*) and influx (*SLCO1B1*, *SLCO1B3* and *SLCO2B1*) transporters have been explored for their association with ATV PK modulation or with statin-related myotoxicities (SRM) development. The most convincing pharmacogenetic association with ATV remains the influence of the rs4149056 (c.521 T > C) in *SLCO1B1* on ATV PK and pharmacodynamics. This SNP has been robustly associated with increased ATV systemic exposure and consequently, an increased risk of SRM. Additionally, the SNP rs2231142 (c.421C > A) in *ABCG2* has also been associated with increased drug exposure and higher risk of SRM occurrence. *SLCO1B1* and *ABCG2* pharmacogenetic associations highlight that modulation of ATV systemic exposure is important to explain the risk of developing SRM. However, some novel observations credit the hypothesis that additional genes (e.g. *SLCO2B1* or *ABCC1*) might be important for explaining local PK modulations within the muscle tissue, indicating that studying the local PK directly at the skeletal muscle level might pave the way for additional understanding.

1. Introduction

Cardiovascular diseases (CVD) are responsible for about 45 % of overall European mortality. In total, it has been estimated that CVD have caused the death of 4.1 million European females and males in 2019, according to the report of the European Society of Cardiology [1]. Elevated low density (LDL) and very low density (VLDL) lipoprotein levels constitute one of the major predisposing factors in the development of CVD [1,2]. 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, have revolutionized the treatment of hypercholesterolemia and the management of patients with increased CVD risk. Decreasing elevated LDL-cholesterol levels has proved to be an effective strategy to reduce the risk of CVD in general and fatal or nonfatal stroke in primary prevention [3,4].

Among the five commercialized statins in the European Union, atorvastatin (ATV) is the most prescribed in the context of primary and secondary prevention of cardiovascular events because of its high efficacy at low doses [3]. Even though the treatment is relatively well-tolerated, 7 to 15 % of patients suffer from statin-induced skeletal muscle abnormalities or complaints, ranging from benign myalgia to

* Corresponding author at: Avenue Emmanuel Mounier 72, B1.72.02, 1200 Brussels, Belgium.
E-mail address: laure.elens@uclouvain.be (L. Elens).

https://doi.org/10.1016/j.clinbiochem.2024.110707
Received 11 October 2023; Received in revised form 2 January 2024; Accepted 2 January 2024
Available online 3 January 2024

rare but potentially life-threatening rhabdomyolysis [5,6]. As a lipophilic statin, the use of ATV is associated with a higher risk of myotoxicities compared to hydrophilic statins [7,8]. Despite its lipophilicity, ATV undergoes extensive transport across membranes through influx and efflux transporters, which justifies the focus of this review on this drug. Commonly reported muscular side-effects, subsumed under the umbrella of statin-related myotoxicity (SRM) or statin-associated myopathy (SAM), appear in various forms. In practice, the most frequent muscular event observed with statin use consists of myalgia or moderate myopathy (Table 1). If signs of intolerance are experienced, it is advised to switch therapy. Nonetheless, switching therapy is not always enough to improve symptoms and, in the worst scenario, this can lead to necrotizing autoimmune myotoxicities [9].

There is, at present, no real consensus on the definition of SAM or SRM. According to the American College of Cardiology (ACC), the term myopathy stands for any muscular disease while myalgias are commonly defined by muscle aches, cramps, or complaints with normal creatine kinase (CK) levels. Myositis refers to muscular symptoms with an elevation in CK but not higher than 10 times the upper limit of normal (ULN) range [10]. Finally, rhabdomyolysis is diagnosed by the presence of the precited symptoms with a CK elevation above 10 times the ULN and creatinine elevation with brown urine and urinary myoglobin [11,12]. The Food and Drug Administration (FDA) definitions do not include myositis as a separate category and define rhabdomyolysis as CK of >50 times the ULN with renal function alterations [13]. The European Phenotype Standardization Project (EPSP) has also defined SRM phenotypes with slight differences compared to ACC or FDA definitions (Table 1). For the sake of clarity and because there is no real consensus on the definition of the toxicity endpoints investigated in clinical studies, the term SRM will be used throughout the review to reflect any muscular event/outcome whatever the original definition used in the original study considered. Even if this oversimplification does not reflect the exact EPSP definition of SRM, most clinical studies evaluate SRM based on self-reported muscle symptoms or symptomatology only and CK levels are rarely measured. Thereby, our review mainly focuses on common muscular side-effect and considers mainly myalgia (SRM1 and 2) and possibly moderate and few severe myopathy (SRM 3 and 4).

As for any chronic treatment, the effectiveness of statin therapy largely depends on patients' adherence. Adherence to statin therapy is suboptimal in both primary and secondary prevention of CVD. The exact rate of non-adherence is difficult to determine. However, a *meta*-analysis highlighted a global adherence rate to statins of 49 % among observational studies and of 90.3 % in randomized trials in patients after 1 year of treatment [14]. Several sources of non-adherence have been identified, among which side-effects are one of the leading causes [4]. As SRM is the most common statin side-effect and represents an important cause of statin intolerance or patient discomfort, it can lead to poor adherence and/or spontaneous drug discontinuation, which increases the risk of treatment failure [15,16].

Apart from impacting patients' adherence, SRM also impact patient quality of life, which is particularly inconvenient considering chronic medications. Unfortunately, the risk of side-effects for a given *de novo* patient remains at present unpredictable. There are multiple risk factors for SRM including patient-specific (age, genetics, weight, etc.) or drug-related (metabolism, transport, dose, drug-drug interaction, etc.) factors but the associations are not always well-defined. It is, however, established that SRM are dose- and concentration-dependent and reversible upon discontinuation, suggesting that differences in patients' tolerance would have a pharmacokinetic (PK) basis [7,17]. Deciphering the reasons for PK variabilities and more particularly, local PK within the muscle tissue might help in modulating the risk of muscle side effects in each patient and has the potential to optimize patient adherence and quality of life in the long term. This review aims at reporting the current state of knowledge about the singular genetic susceptibilities influencing the ATV toxicity through PK modulations (i.e. toxicokinetics). More specifically, this paper will discuss the potential impact of genetic variability in pharmacogenes and the influence of genetic polymorphisms on drug PK, with a special focus on the consequences of these genetic polymorphisms on the risk of SRM. More specifically, the role of drug transporters in driving the drug across membranes and determining drug accumulation within the muscle cell and the functionality of selected polymorphisms will be addressed.

Table 1
Statin-related myotoxicity phenotype classification. Distinction of the six levels of SRM characterized by the patients' phenotype and the clinical assessment.

SRM classification	Phenotype	Clinical assessement
SRM 0	CK elevation < 4 x ULN	No muscle symptoms
SRM 1	Myalgia, tolerable	Muscle symptomsNo CK elevation
SRM 2	Myalgia, intolerable	Muscle symptoms, complete resolution on dechallenge CK < 4 x ULN
SRM 3	Myopathy	Muscle symptoms, complete resolution on dechallenge CK elevation > 4 x ULN < 10 x ULN
SRM 4	Severe myopathy	Muscle symptoms, complete resolution on dechallenge CK elevation > 10 x ULN < 50 x ULN
SRM 5	Rhabdomyolysis	Muscle symptoms + CK elevation > 10 x ULN with evidence of renal impairment OR CK > 50 x ULN
SRM 6	Autoimmune-mediated necrotizing myositis	HMGCR antibodies, HMG-CoA reductase expression in muscle biopsy, incomplete resolution on dechallenge

Adapted with permission from Alfirevic et al. [108].

2. Putative mechanisms of atorvastatin-associated myotoxicity

There are numerous hypotheses to explain the muscular toxicity observed with statins, but none is sufficient to elucidate the underlying physiopathology, which remains speculative at this stage. Discussion regarding novel hypotheses and unresolved roles of factors affecting SRM is beyond the scope of the present review. However, outlining the general pathophysiologic basis of SRM appears important to understand the role of PK modulations in the development of muscle side effects.

Basically, statins competitively inhibit the HMG-CoA reductase with an affinity of 1000 to 10,000-fold more than that of the endogenous substrate. This inhibition leads to a depletion of the mevalonate pathway intermediate metabolites such as dolichols, prenylated proteins, isoprenoids and ubiquinone or coenzyme Q10 (Fig. 1) [18,19].

The most convincing hypothesis on the etiology of SRM suggests that the inhibitory effect of ATV on the mevalonate pathway within the

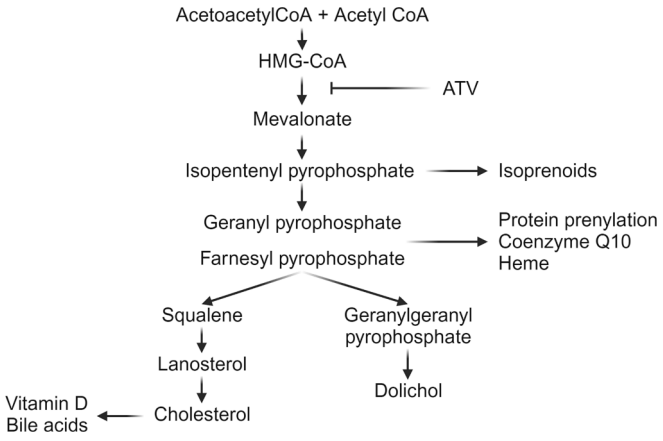

Fig. 1. Figure 1: Overviexw of the mevalonate pathway and HMG-CoA reductase inhibition by Atorvastatin (ATV).

muscle and the subsequent depletion in intermediate derived metabolites are responsible for the observed muscle toxicity. *In vitro* studies show that blocking cholesterol synthesis by inhibiting squalene production (which appears distally in the pathway) does not cause muscle toxicity [20]. In rat skeletal muscle cells, squalene supplementation is not able to reverse muscle toxicity caused by statins whereas statin-induced myotoxicity is reversed when precursors of upper isoprenoid intermediaries are given [20]. This assumption is further supported by the fact that muscle-related side effects of statins are dose-, potency- and concentration-dependent. The vulnerability of skeletal muscle compared to other tissues is explained by the higher sensitivity of muscle cells to the statin-induced inhibition of cholesterol synthesis [17,21]. Indeed, it has been demonstrated that human skeletal muscle cells are 44.5 times more sensitive than human primary hepatocyte cells to ATV HMG-CoA reductase inhibition (IC_{50} of 4.7 nM and 209 nM, respectively) [21]. Among intermediate metabolites, isoprenoid compounds like geranylgeranyl pyrophosphate and farnesyl pyrophosphate are responsible for protein prenylation [22], including small GTPases like Rho, Ras and Rab. Rho, Ras and Rab are activated upon isoprenylation and further regulate vital cell functions such as cell integrity, division, differentiation, fusion and trafficking, therefore playing key roles in cell survival [23,24]. On the contrary, a reduced isoprenylation of these GTPases induces atrogin-1 synthesis. This ubiquitin ligase increases protein degradation which indirectly decreases protein synthesis processes that can potentiate myotoxicities [8,25–28]. Further evidence that isoprenylation may be responsible for the observed muscle toxicity of statins comes from the observation that rare inborn mevalonate kinase deficiency is associated with, among other congenital defects, myopathy whereas mutations in distal enzymes of cholesterol synthesis (that do not affect prenylation) are not [29]. The inhibition of the HMG-CoA reductase has also the consequence of reducing the generation of intermediary products such as dolichols and ubiquinone, also known as coenzyme Q. The former is implicated in oligosaccharides N-glycosylation [30] while the latter is critical for the electron transport chain of mitochondrial respiration [31]. Statins may thus interfere with mitochondrial function, causing impaired muscle performance, resulting in muscle damage observed in patients suffering from SRM [22,32].

In summary, the pathophysiology of SRM is inevitably complex because of the long list of affected intermediaries in the mevalonate pathway and the subsequent changes in cellular functions. Most of the elaborated scenarios link SRM events to the inhibition of the mevalonate pathway within the muscle cell, highlighting the importance of local drug exposure for explaining SRM individual susceptibility.

3. Pharmacokinetics and ADME overview

The daily recommended ATV dose is 10–80 mg taken orally as a calcium salt of the active acid form. It is rapidly and well absorbed but

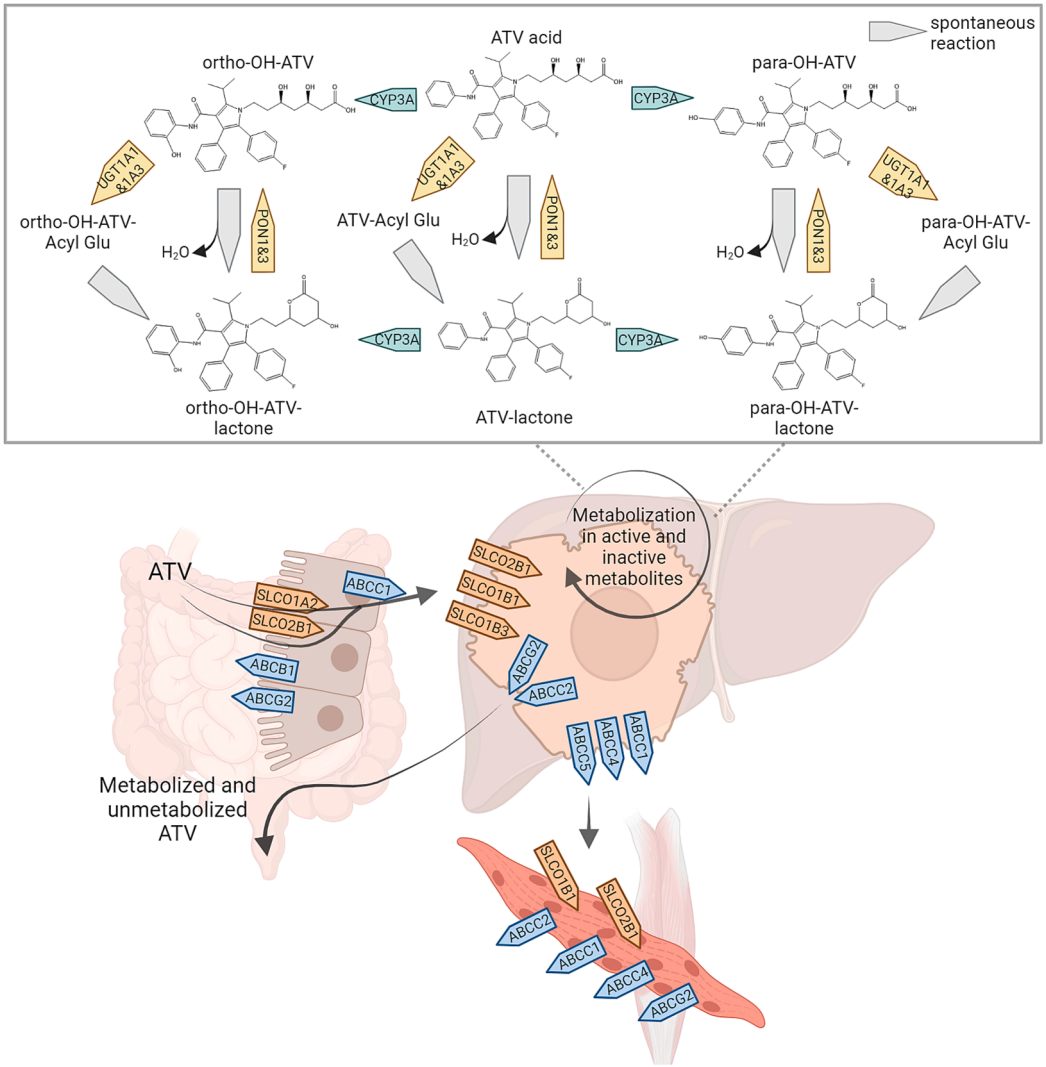

Fig. 2. Figure 2: Overview of Atorvastatin (ATV) transport and metabolization in the intestine, liver and skeletal muscle tissue.

has a weak and variable oral bioavailability of approximately 12 % due to substantial first-pass metabolism [33]. The pharmacologically active ATV acid is biotransformed to its corresponding lactone form and both are further metabolized into OH-metabolites by the cytochrome P450 (CYP) 3A isoenzymes, as depicted in Fig. 2. The main metabolite, 2-OH-ATV (ortho-), is pharmacologically active and significantly contributes to the inhibitory activity on HMG–CoA reductase [34]. By contrast, little is known about its potential involvement in myotoxicity. Once ingested, ATV crosses the gut barrier mainly by passive diffusion with only a small fraction (30 %) of this lipophilic drug permeating via uptake transporters from the solute carrier organic anion (*SLCO*) family coding for organic anion-transporting polypeptide (OATP) [33]. ATV is known to be a substrate for *SLCO1A2* (OATP1A2), *SLCO1B1* (OATP1B1), *SLCO1B3* (OATP1B3) and *SLCO2B1* (OATP2B1) [35,36]. However, their localization varies since OATP1A2 is mainly expressed at the blood brain barrier (BBB), OATP1B1 and OATP1B3 in the liver whereas OATP2B1 is ubiquitously expressed and has been detected in the skeletal muscle tissue (Fig. 2) [37–40]. ATV absorption and cellular uptake are also favored by the activity of two pumps, the oligopeptide transporter (PepT1) expressed along the gastrointestinal tract and the liver and the H^+-monocarboxylic acid transporter (MCT) ubiquitously expressed. With MCT1 (*SLC16A1*) and MCT4 (*SLC16A3*) being mostly expressed in the oxidative fibers and the glycolytic fibers of skeletal muscle tissue [41,42]. ATV PK is also modulated by ATP-binding cassette transporter (*ABC*) superfamily members [34] including *ABCB1* (P-glycoprotein or P-gp), *ABCC1* (MRP1), *ABCC2* (MRP2), *ABCC4* (MRP4), *ABCC5* (MRP5) and *ABCG2* (BCRP). *ABCB1* is ubiquitously expressed but chiefly in the intestine where it limits the bioavailability of its substrate, in the liver and the kidney, participating in the excretion of drugs/metabolites, or at the BBB for protecting the tissue from potential toxicants. *ABCC1* is also ubiquitously expressed however less importantly in the liver, *ABCC2* is mostly found in the hepatocytes, *ABCC4* in the male gonads, *ABCC5* at the BBB and *ABCG2* in the gastrointestinal tract (Fig. 2); see section 'Pharmacogenetics, atorvastatin PK and muscular toxicity' for detailed transporter expression [43–48]. To get into myocytes, where toxicity occurs, ATV (and possibly its metabolites) undergoes passive diffusion but also active and facilitated transport mechanisms. The activity of transporters is thus assumed to modulate drug concentrations directly within myocytes through both drug efflux and influx. Interestingly, *ABCC1*, *ABCC2*, *ABCC4*, *ABCG2*, *SLCO2B1* and *SLCO1B1* are expressed in the skeletal muscle and might play an important role in protecting and sensitizing myocytes from ATV toxicity [39,43–45]. On the other hand, some of these transporters are expressed in the liver where the drug acts on cholesterol synthesis. Whereas OATP transporters (*SLCO1B1*, *1B3* ad *2B1*) drive the influx of drug within the hepatocyte and by such, increase the fraction of the drug reaching its target, *ABC* transporters will either limit the access to the liver at the basolateral pole (*ABCC1* and *ABCC4*) or increase drug excretion when expressed apically (*ABCB1* and *ABCC2*) [49]. Depending on the localization of the different transporters but also the likelihood of compensation for a potential loss of activity, functional genetic defects would not have the same impact on systemic versus local muscle drug exposure. For instance, whereas most transporters are substantially expressed in the liver, only a few of them are expressed at a significant level in the muscle tissue. The net consequence of this consideration is that, even if a change in the activity does not show any association with the systemic exposure because other transporters might compensate for the decreased activity in excretory organs, it does not mean that it cannot impact on the susceptibility of muscle toxicity by directly modulating the local exposure where other transporters are not (or less) expressed.

Chemically, ATV is composed of a dihydroxy heptanoic side chain where a lactone group can be added by phase II glucuronidases (*UGT1A3* and *UGT1A1*) or through spontaneous deconjugation. Conversely, ATV lactone can be hydrolyzed back to the active acid form by esterases such as paraoxonases (*PON1* and *PON3*) [34,50–52]. As stated above, in the liver, ATV biotransformation is driven by CYP enzymes into 2- (ortho) and 4- (para) OH metabolites. It has been reported that more than 85 % of the oxidative metabolism is catalyzed by CYP3A4, whereas it is estimated that CYP3A5 contributes to less than 15 % of the phase I metabolism [53]. 98 % of ATV is bound to plasma proteins but, given its lipophilicity, it is characterized by a large volume of distribution (381L) [54,55], indicating that a high proportion of ATV is found in extravascular compartments [56]. ATV is mainly eliminated through biliary excretion (70 %) after hydroxylation of its lactone form [33,57]. Despite its inability to inhibit the HMG-CoA reductase, the lactone has been shown to be up to 14-fold more potent than the acid form to induce myotoxicities *in vitro*. This discovery is based on the decreased viability of the myotubes in presence of the lactone form compared to the acid one [7]. This phenomenon is presumed to be due to the 1000-fold more lipophilic property of the lactone form when compared to its acid counterpart, allowing the molecule to cross the skeletal muscle cells more easily where it is then converted back into the acid form that is myotoxic [58]. The manifestation of myalgia might thus be indirectly triggered by the lactone form but imputable to ATV acid intramuscular accumulation due to this interconversion. Because of its lower lipophilicity compared to the lactone, ATV acid is further modulated by influx and efflux transporters expressed on the cell membranes. Their expression levels and/or the presence of single nucleotide polymorphisms (SNP) could therefore influence the ATV acid intracellular content hence modulating the individual risk to develop muscle symptoms. To a further extent, the nature of other statins also defines the development of adverse events, with the lipophilic statins (e.g. fluvastatin) being more toxic than the hydrophilic statins (e.g. pravastatin) [59].

4. Pharmacogenetics; atorvastatin pharmacokinetics and muscular toxicity

4.1. Drug transporters

Genes coding for transporter proteins are highly polymorphic and their genetic sequences can be affected by SNP. Depending on the functionality of the SNP, the transporter activity, transporter localization as well as its affinity for ATV, SNP can be associated with either increased/decreased or no change in ATV systemic and/or local exposure with potential impact on the response to the drug (see Table 2).

4.1.1. Efflux transporters

4.1.1.1. ABCB1. ABCB1, formerly referred as P-glycoprotein (P-gp) or multidrug resistance 1 (MDR1), mainly protects the organism from an excessive substrate accumulation due to its ubiquitous expression. Depending on its location, ABCB1 restricts drug bioavailability when expressed in the intestinal lumen, limits the access to potential toxic substances in some fragile tissues (e.g. BBB) or controls systemic drug exposure by eliminating substrates via the corporeal fluids through its expression in excretory organs [47]. An altered transport activity can thus modulate drug disposition and consequently modify the drug efficiency and/or toxicity. Several pharmacogenetic studies have attempted to determine whether *ABCB1* variants impact ATV PK. Kajinami et al. studied the SNP rs2032582 (c.2677G > T/A, p.Ala893Ser/Thr) and rs1045642 (c.3435C > T, p.Ile1145 =), both in strong linkage disequilibrium, in a cohort of 344 hypercholesterolemic patients treated with low dose ATV (10 mg per day). They showed that women carrying the wild-type haplotype (2677G-3435C) were characterized by a lower LDL-cholesterol reduction when compared to the 2677 T/3435 T variant haplotype carriers resulting from lower circulating ATV concentrations. This observation was not replicated in men. The higher ATV exposure and the consequent better LDL-cholesterol decrease in variant haplotype carriers might be explained by a lower efflux pump activity when the SNP is present [60]. Also, when considering the rs1045642 SNP only,

Table 2
Summary of the SNP with the reported effects on ATV influx and efflux transporters as well as on the phase-I and -II metabolization enzymes. Minor allele frequency (MAF) data from gnomAD v2.1.1 and Ensembl [109–112]. AFR: African, EAS: East Asian, SAS: South Asian, EUR: European and AMR: American.

	Genes	SNP reference	MAF	Nucleotide modification	Consequences		
					Physiological		Observed
Efflux transporters	*ABCB1*	rs2032582	AFR: 0.02-0 EAS: 0.37-0.06 SAS: 0.59-0.05 EUR: 0.41-0.02	c.2677G>T/A p.Ala893Ser/Thr	GC haplotype : ATV less efficient to ↓ LDL-cholesterol in women [60] Women c.3435C homozygous : lower LDL-cholesterol ↓ [60]		PK modulation and ATV efficacy
		rs1045642	AFR: 0.799 EAS: 0.632 SAS: 0.395 EUR: 0.466	c.3435C>T p.Ile1145=	Consequences of lower ATV circulating concentrations. In 3435T : greater ↓ in LDL [61] and ↑ of C_{max} [62]		
		rs2373588	AFR: 0.170 EAS: 0.387 SAS: 0.000 EUR: 0.041	g.194405C>T	Variant more frequent in cases experiencing SRM [63]		SRM
	ABCC1	rs45511401	AFR: 0.011 EAS: 0.000 SAS: 0.016 EUR: 0.056	c.2012G>T p.Gly671Val	No association with LDL reduction [65], no effect on ATV clearance [6]. *In vitro*, counteraction of SLCO2B1 influx and increase ABCC1 activity with SNP [66]		PK modulation and ATV efficacy
	ABCC2	rs717620	AFR: 0.058 EAS: 0.212 SAS: 0.113 EUR: 0.200	c.-24C>T in 3' UTR			SRM
		rs2273697	AFR: 0.183 EAS: 0.088 SAS: 0.278 EUR: 0.197	c.1249G>A p.Val417Ile	H12 haplotype (–24T/1249G/3972T) is at ↑ risk than H2 haplotype (–24C/1249A/3972C) to switch statin therapy [69]		
		rs3740066	AFR: 0.259 EAS: 0.230 SAS: 0.325 EUR: 0.370	c.3972C>T p.Ile1324=			
	ABCC4	rs3742106	AFR: 0.322 EAS: 0.511 SAS: 0.494 EUR: 0.388	c.*38T>G in 3' UTR	↓ plasma concentration of ATV and ATV metabolites due to ↓ efflux activity [70]		PK modulation
	ABCG2	rs2231142	AFR: 0.027 EAS: 0.307 SAS: 0.093 EUR: 0.104	c.421C>A p.Gln141Lys	In variant carriers: ↑ $AUC_{0-\infty}$ and C_{max} [72,73], ↑ ATV bioavailability [74]	No significant effect on PK [75] No change in LDL-C response [76]	PK modulation and ATV efficacy
					In homo- and heterozygous, 2.9 more risks of developing SRM [77]		SRM
Influx transporters	*SLCO1B1*	rs4149056	AFR: 0.030 EAS: 0.125 SAS: 0.050 EUR: 0.159	c.521T>C p.Val174Ala	In variant carriers: ↑ ATV, 2-OH ATV concentrations [81], ↑ AUC and C_{max} [73,82]	No association of variant carriers and LDL response [83]	PK modulation and ATV efficacy
					↑ of the risk to develop SRM [6,81,84,85]		SRM
		rs2306283	AFR: 0.774 EAS: 0.752 SAS: 0.476 EUR: 0.403	c.388A>G p.Asn130Asp	No significant impact on ATV PK [83]		PK modulation
		rs11045818	AFR: 0.036 EAS: 0.000 SAS: 0.043 EUR: 0.161	c.411G>A p.Ser137=	No significant impact on ATV PK [83]		PK modulation
	SLCO1B3	rs57585902	AFR: 0.031 EAS: 0.000 SAS: 0.000 EUR: 0.000	c.439A>G p.Thr147Ala			PK modulation
		rs60140950	AFR: 0.026 EAS: 0.001 SAS: 0.070 EUR: 0.157	c.767G>C p.Gly228Ala	No impact of the haplotype on ATV transport [88]		
		rs2043949386	na	c.1559A>C p.His520Pro			
		rs4149117	AFR: 0.426 EAS: 0.725 SAS: 0.905 EUR: 0.851	c.334T>G p.Ser112Ala	No effect on ATV clearance, SRM development or LDL reduction [6]		PK modulation, ATV efficacy and SRM
	SLCO2B1	rs12422149	AFR: 0.091 EAS: 0.326 SAS: 0.218 EUR: 0.104	c.935G>A p.Arg312Gln	In 935A : slight [90] to significant [66] ↓ of *SLCO2B1* with variant. Tendency of ↓ ATV concentrations in muscle [87]	No effect on ATV clearance [6]	PK modulation

(*continued on next page*)

Table 2 (*continued*)

	Genes	SNP reference	MAF	Nucleotide modification	Consequences	
					Physiological	Observed
Phase-I metabolization enzymes	*CYP3A4*	rs35599367 (**22*)	AFR: 0.009 EAS: 0.000 SAS: 0.000 EUR: 0.044	c.522-191C>T (in intron 6)	↓ metabolization activity leading to ↓ ATV doses [91–94]	PK modulation
	PPARA	rs4253728	AFR: 0.062 EAS: 0.001 SAS: 0.000 EUR: 0.254	c.209-1003G>A (in intron 4)	↑ in unmetabolized circulating ATV [93]	PK modulation
		mi-21, miR-27b, miR-206	na	Na	Associated with SRM development [95–99]	SRM
	POR	rs1057868 (**28*)	AFR: 0.183 EAS: 0.374 SAS: 0.354 EUR: 0.288	c.1508C>T p.Ala503Val	↑ CYP3A activity [100] with a tendency ↓LDL-C and cholesterol [101]. In homozygous, ↑ cholesterol levels [102]	ATV efficacy
	CYP3A5	rs776746 (**3*)	AFR: 0.702 EAS: 0.286 SAS: 0.000 EUR: 0.071	c.219-237A>G (6986A>G) (in intron 3)	Homozygous at risk of SRM, reduction in CYP3A5 activity [103,104]	PK modulation and SRM
	CYP2D6	rs3892097 (**4*)	AFR: 0.080 EAS: 0.003 SAS: 0.104 EUR: 0.196	c.506-1G>A	Variant carriers are at ↑ risk of SRM [105]	SRM
Phase-II metabolisation enzymes	*UGT1A1*	rs3064744 (**28*)	AFR: 0.45 EAS: 0.13 SAS: 0.41 EUR:0.32	c.868-6787_868-6786ins(Tan)	↓ of ATV lactonization, protection against ↑ lactones levels [49–51,106]	PK modulation and SRM
	UGT1A3	rs4663969 (**2*)	AFR: 0.541 EAS: 0.338 SAS: 0.000 EUR: 0.397	c.867+16674C>A	↑ of ATV lactonization, ↑ risks of SRM [49–51,106]	PK modulation and SRM

women with the homozygous wild-type (3435CC) experienced significantly lower LDL-cholesterol reduction but increased HDL-cholesterol levels indicating that the 3435C > T SNP might be responsible for the haplotype association [60]. Those results were later supported by the research team of Kadam et al. who also showed a greater reduction of LDL-cholesterol blood levels in 3435 T variant carriers when compared to the wild-type *ABCB1* expressors, but they did not assess ATV PK [61]. In another PK study performed on 60 male volunteers taking one single 80 mg ATV dose, it was shown that the variant allele (3435 T) was associated with a significant increase of C_{max} compared to homozygous wild-type allele carriers (3435CC) [62]. To our knowledge, none of the studies reported to date have evidenced that this increased systemic exposure in variant allele carriers translates into an increased risk of developing SRM.

Another less commonly studied intronic SNP rs2373588 (g.194405C > T) in the efflux transporter *ABCB1* has been investigated for its impact on ATV toxicity in a large case-control study including 1102 acute ischemic stroke patients receiving 80 mg ATV/day *de novo* and experiencing or not myopathy, as defined by CK levels > 10 times the ULN. In that study, it was reported that the *ABCB1* rs2373588 194405 T variant allele was more frequent in the cases than in the controls but, again, no PK endpoint was assessed [63]. To our knowledge, no other study has evaluated the robustness of this association.

4.1.1.2. ABCC1. The ATP-binding cassette family member 1 (*ABCC1*) is ubiquitously expressed in the human body with some tissues expressing more (e.g. kidneys, gonads) or less (e.g. liver, endocrine tissues) importantly the protein [43]. In polarized cells, the protein is localized on the basolateral plasma membrane [64]. Its substrates are thus expelled in the interstitial spaces instead of extracorporeal fluids (Fig. 2).

In 2017, Behdad et al. showed, in a cohort of 179 Iranian patients with primary hypercholesterolemia, no significant association between the *ABCC1* rs45511401 (c.2012G > T, p.Gly671Val) polymorphism and LDL-cholesterol reduction after four weeks of treatment with different ATV dosages [65]. This SNP was also evaluated for its effect on ATV PK in a population PK study investigating the effect of SNP on ATV apparent clearance and clinical response in 70 ATV treated patients. No effect of the c.2012G > T was observed on ATV clearance and, therefore, the association with clinical response endpoints was not tested [6]. In a recent *in vitro* study using HEK293 recombinant cell lines over-expressing *ABCC1* alone or in combination with *SLCO2B1*, it was observed that increased ATV intracellular accumulation driven by *SLCO2B1* influx was partially counteracted by *ABCC1* efflux and that the c.2012G > T SNP in *ABCC1* was associated with increased *ABCC1* efflux activity towards ATV [66], indicating a potential importance of this SNP to modulate the activity of *ABCC1* and protect against excessive drug accumulation within the cell. Future more powerful studies are needed to make conclusions about the clinical relevance of this functional effect and the potential consequence of this *in vitro* observation on SRM occurrence.

4.1.1.3. ABCC2. The ATP-binding cassette family member 2 (*ABCC2*) efflux protein is located on the apical plasma membrane of the hepatocytes, the BBB, the kidneys and the intestinal tract (Fig. 2) [44,67]. It transports endogenous substrates like taurolithocholate sulfate and also exogenous substances such as statins and HIV drugs [26,68]. In 2013, Becker et al. analyzed, in a cohort of 225 ATV users (10 mg, 20 mg and 40 mg daily), whether the common SNPs rs717620 (c.-24C > T), rs2273697 (c.1249G > A, p.Val417Ile) and rs3740066 (c.3972C > T, p.Ile1324 =) in the *ABCC2* gene were associated with a dose decrease or switch to another cholesterol-lowering drug. They highlighted that H12 haplotype (–24 T/1249G/3972 T) carriers were at higher risk for these events compared to carriers of the H2 haplotype (–24C/1249A/3972C). Although non-significant for ATV users, this association might indirectly reflect that patients have developed adverse muscular reactions needing dosage or therapy adjustments [69]. The fact that the difference was not significant might be due to the imprecise outcome definition as the switch or dose decrease might have multiple causes other than drug side effects. As, to our knowledge, the impact of *ABCC2* SNP on ATV PK or *in*

vitro transport has not yet been assessed, it is difficult to conclude on the relevance of this observation and further studies are needed.

4.1.1.4. ABCC4. Multidrug resistance-associated protein 4 (MRP4) is also a member of the ATP-binding cassette family transporting ATV out of the cells [26]. It is mainly found at the basolateral membrane of the hepatocytes, the gastrointestinal tract and the male and female sexual organs (Fig. 2) [45]. Very few research groups investigated the impact of SNP in *ABCC4* on ATV PK. However, Jiang et al. recently highlighted in a cohort of 212 out- and in-patients suffering from chronic kidney disease (CKD) treated with 20 mg of ATV/day for 6 weeks, through univariate and multivariate analysis, that carriers of the variant rs3742106, located in the 3′UTR (c.*38 T > G), was associated with reduced ATV and its metabolites plasma concentrations compared to the wild-type carriers. This would indicate decreased efflux transporter activity. Indeed, as ABCC4 is expressed at the basolateral membrane of cells, a decreased activity would thus theoretically lead to a reduced recirculation of the drug and thus lower plasma levels. However, as the study includes CKD patients only, it is difficult to conclude whether these results can be extended to other less specific patient populations [70].

4.1.1.5. ABCG2. ABCG2, also known as breast cancer resistance protein (BCRP), is one of the efflux transporters that is the most studied for its impact on ATV PK modulation mainly due to its location. It is indeed expressed at the apical membrane of the hepatocytes, the enterocytes, the renal proximal tubule cells and at the BBB (Fig. 2) [48,71]. Among *ABCG2* SNP, the rs2231142 (c.421C > A, p.Gln141Lys) has received much attention. In a cohort of 32 healthy individuals receiving a single 20-mg ATV oral dose, Keskitalo et al. highlighted that the area under the curve ($AUC_{0-\infty}$) in patients expressing the variant genotype (c.421AA) was 72 % greater than in those with the wild-type genotype (c.421CC) [72]. The observation that the $AUC_{0-\infty}$ of ATV is affected by the *ABCG2* genotype, with no effect on its elimination half-life (t½), suggests that *ABCG2* function mainly affects ATV absorption or distribution with limited influence on elimination rate [72]. Going in the same direction, Birmingham et al. carried out a study on 93 Chinese, Japanese and Caucasian volunteers receiving 40 mg of ATV per day. They also highlighted an increased ATV $AUC_{0-\infty}$ and C_{max} in *ABCG2* c.421AA compared to c.421CC carriers [73]. Along the same line, a population PK study performed with rich PK data collected in 27 Japanese individuals taking 10 mg ATV once daily has shown a 55 % increase in ATV bioavailability in carriers of the variant allele compared to non-carriers [74]. As the rs22431142 SNPs is more frequent in Asians, these observations might explain why ethnicity plays a modulating role in ATV PK. However, the recent study of Lee et al. failed to replicate this observation in a two-period crossover study involving 47 statin-naïve Japanese patients receiving an oral micro dose (100 μg) of ATV followed by a low therapeutic dose (10 mg). Contrarily to the other studies, it was observed that, even if the differences did not reach statistical significance, ATV exposure in patients with the *ABCG2* c.421AA variant genotype tended to be reduced when compared to patient carriers of the c.421CC or c.421CA genotypes either after 100 μg or 10 mg ATV dosing [75]. Regarding the ATV efficacy, in a study enrolling 127 hypercholesterolemic patients treated with 10 mg of ATV for 4 weeks, Prado et al. did not find any change in the LDL-cholesterol response to ATV between the c.421CC carriers and the c.421AC or AA carriers but no PK data were reported [76]. Interestingly, a case-control study comparing data from 60 patients who experienced ATV dose-related side effects with 90 matched control patients without side-effects, showed that patients with *ABCG2* 421CA or AA genotypes had 2.9 times greater odds of developing ATV side-effects compared to patients with the *ABCG2* 421CC genotype [77]. All in all, because the impact of the SNP rs2231142 (c.421C > A) in *ABCG2* on ATV PK is still unclear, there is no guideline considering the rs2231142 variant regarding the use of ATV [78]. However, taken together, reported associations suggest that the rs2231142 SNP in *ABCG2* is associated with decreased efflux activity towards ATV and impacts on either the drug absorption or distribution with little or no effect on drug excretion. As the SNP is associated with differences in the odds of suffering from side-effects but not with drug efficacy, it might indicate that the transporter impacts more on the local drug accumulation in specific tissues rather than on the systemic/liver drug accumulation because of potential compensatory mechanisms present in the liver. Further mechanistic studies are needed to evaluate the impact of this SNP on ATV muscle intracellular PK.

4.1.2. Influx transporters.

4.1.2.1. SLCO1B1. OATP1B1 encoded by *SLCO1B1* is involved in the hepatic uptake of the drug and is the influx transporter in the center of all attention when studying ATV PK or pharmacodynamic modulations. OATP1B1 is expressed at the basolateral membranes of hepatocytes only, where it facilitates the hepatic extraction of the drug, thereby favoring its therapeutic effect, but, paradoxically, also its hepatic excretion and thus limiting systemic drug exposure (Fig. 2). This exclusive location together with the known functional defect associated with the most studied SNP rs4149056 (c.521 T > C, p.Val174Ala) probably explains why the associations observed with ATV PK are more clearcut than for other genes/SNPs [37]. The missense variant rs4149056 has been largely studied for its impact on statin PK [79]. It has been shown *in vitro* that the c.521 T > C SNP is the key SNP that determines the functional polymorphic activity of the transporter and is associated with decreased activity [80]. Turner et al. performed a genome-wide association recruiting 590 acute coronary syndrome hospitalized patients treated with high doses of ATV (40 or 80 mg/day). The variant 521C minor allele was clearly associated with higher ATV and 2-OH ATV concentrations. By contrast, after adjustment for multiple testing, this was not observed for ATV lactone and for 2-OH ATV lactone [81]. Confirming this observation, two independent research groups demonstrated that both c.521CC variant homozygous and c.521TC heterozygous genotypes were associated with increased ATV AUC and C_{max} compared to the c.521TT wild-type genotype [73,82]. Indeed, Birmingham et al. associated the variant in a mixed cohort of 93 Chinese, Japanese and Caucasian subjects receiving 40 mg of ATV once a day with higher exposure to the drug with the effect consistent across ethnic groups [73]. Pasanen et al. studied 32 healthy volunteers treated with a single ATV 20 mg dose. Variant homozygous (c.521CC) had a 144 % ($P > 0.001$) greater AUC_{0-48h} than the homozygous wild-type individuals (c.521TT) and a 61 % ($P = 0.049$) greater AUC_{0-48h} than heterozygous (c.521TC) [82]. Surprisingly, Giannakopoulou et al. conducted a study on 201 Greek adults treated for primary hypercholesterolemia with ATV (5–80 mg/day) and found that the polymorphism (c.521 T > C) had no significant association with the ATV-lowering response, suggesting that even if the SNP impacts on ATV exposure, it has no or little impact on its therapeutic efficacy. They also investigated two other *SLCO1B1* variants; rs2306283 (c.388A > G, p.Asn130Asp) and rs201149584 (c.411G > A, p.Ser137 =) but, again, did not observe any significant impact on the ATV PK [83]. This observation is corroborated by the genome wide association study of Turner et al. where they showed that even if the c.521 T > C SNP was associated with ATV PK, it was not linked to the efficacy endpoints as assessed by the development of myocardial infarction, ischemic stroke, cardiovascular death or all-cause mortality. By contrast, when considering muscular toxicity endpoints, they observed that *SLCO1B1* rs4149056 increased the risk of muscular complaints and ATV intolerance [81].

Other studies also demonstrated an increased susceptibility of this variant to develop ATV toxicity. Indeed, Stillemans et al. studied the impact of the SNP c.521 T > C in *SLCO1B1* and highlighted, based on a population PK model, that ATV clearance was reduced in variant carriers (521C) compared to the wild-type carriers (521 T). It was shown that a reduction of ATV clearance below 414.67 $L{\cdot}h^{-1}$ put the patients at

risk of experiencing SRM. The results were acquired on 132 PK samples from a cohort of 70 patients taking 10 to 80 mg of ATV [6]. A retrospective survey data from 379 genotyped Caucasian subjects highlighted an association between the variant c.521 T > C and ATV discontinuation due to the development of muscle side-effects [84]. Even if few studies failed to associate this *SLCO1B1* SNP with myotoxicity endpoints [81,83], a *meta*-analysis combining data extracted from 15 studies consistently showed that 521C heterozygous and homozygous carriers are at up to ~ 2.0 and 4.0 times higher odds of SRM compared to 521TT wild-type genotype [85]. The apparent discrepancy between some studies might potentially be attributed to the different ATV doses administered or the composition of the population. Indeed, the different results indicate that the genetic association between SRM and *SLCO1B1* is mostly observed with high ATV doses and only when the cohort includes enough patients taking ATV. For instance, in a less recent *meta*-analysis, the rs4149056 was significantly associated with simvastatin but not with ATV SRM. However, in the included studies, fewer participants took ATV relative to simvastatin for which the risk of developing side-effects is higher [86]. Very recently, in a double blinded study including 28 coronary patients with self-perceived SRM treated with 40 mg ATV or placebo in a randomized order for 7 to 8 weeks, Lauritzen et al. examined whether ATV metabolites exposure in blood reflects the local exposure in the skeletal muscle and whether genetic variants in transporters modulate this relationship. The authors concluded that ATV metabolite levels in skeletal muscle and plasma are strongly correlated, implying that plasma measurements are suitable proxies of ATV exposure in muscle tissue. However, when looking at the data, they showed that the correlation between the sum of ATV acid metabolites in the muscle and in the plasma was characterized by a rho value (spearman correlation) of 0.7 which is considered as a moderate to strong correlation (but not very strong as stated in their conclusions). Visually, among the 26 eligible patients for PK analysis, several points were far from the identity line, indicating that the correlation, despite being statistically significant, was not verified for all patients. They showed that the *SLCO1B1* 521C carriers had higher median levels of acid and lactone ATV metabolites in the muscle which was probably a consequence of a less efficient liver excretion and higher ATV plasma exposure. This is in line with *meta*-analysis linking this SNP with SRM susceptibility. However, given the small number of patients included in their study, despite being informative, it is difficult to draw any definitive conclusion about the correlation between ATV muscle and blood concentrations or SRM and the impact of other SNPs that could affect the local exposure without impacting systemic ATV concentrations [87].

4.1.2.2. SLCO1B3. Solute carrier organic anion transporter family member 1B3 (*SLCO1B3*) encodes for OATP1B3, an influx transporter mainly localized in the liver but less importantly than *SLCO1B1* which remains the most highly expressed (Fig. 2) [38]. Belonging to the same subfamily, their substrate spectrum is similar without being identical. *In vitro*, Schwarz et al. showed by transient plasmid expression that, even if rs57585902 (c.439A > G, p.Thr147Ala), rs60140950 (c.767G > C, p.Gly228Ala) and rs2043949386 (c.1559A > C, p.His520Pro) *SLCO1B3* variant haplotype results in altered expression, substrate specificity and pH-dependent activity, it does not seem to impact ATV transport significantly [88]. Accordingly, Stillemans et al. did not find any significant association between the *SLCO1B3* rs4149117 (c.334 T > G, p.Ser112Ala) SNP and ATV clearance, self-reported muscle toxicity or LDL-cholesterol lowering response in a cohort of 70 ATV users [6]. These results indicate that, even if OATP1B3 transports ATV, the functionality of natural SNP is not strong enough to impact on ATV PK, especially given the fact that OATP1B1 can eventually compensate for OATP3B1 activity alteration.

4.1.2.3. SLCO2B1. The solute carrier organic anion transporting polypeptide 2B1 (*SLCO2B1)* is mostly expressed in the hepatocytes at comparable RNA levels as *SLCO1B3* but less importantly than *SLCO1B1*. Interestingly, by contrast to other SLCO carriers transporting ATV, *SLCO2B1* is the only one that has been described as being expressed on the membrane of skeletal muscle tissues (Fig. 2) [39]. It mediates the Na ($^{+}$) independent transport of organic anions and endogenous substances such as taurocholate, estrone 3-sulfate, and of many xenobiotics [89]. Knauer et al. have originally demonstrated that OATP2B1 is expressed on the membrane of human skeletal muscle cells and that its expression increases intracellular accumulation and toxicity of statins at supra-physiological drug exposure [26]. *In vitro*, as explained above, using HEK293 recombinant cell lines over-expressing OATP2B1 alone or in combination with ABCC1, it was observed that ATV intracellular accumulation was boosted by OATP2B1 overexpression over a range of ATV concentrations from 25 to 500 nM [66]. Also, in that study, it was shown that this boosting effect on ATV cellular accumulation was decreased by the introduction of the rs12422149 (c.935G > A, p.Arg312Gln) SNP in the *SLCO2B1* coding sequence. Similarly, Yang et al. 2020, studied the impact of 14 nonsynonymous variants in *SLCO2B1* towards ATV in a recombinant HEK293 cell system, including the common c.935G > A SNP. They showed consistently a slightly decreased ATV accumulation in variant cell lines compared to the wild types [90]. In line with this, in the above-mentioned study, despite the low number of patient carriers of the variant allele, Lauritzen et al. observed non-significant lower muscle concentrations of ATV lactone metabolites in *SLCO2B1* variant carriers [87]. By contrast, Stillemans et al. did not find any influence of this SNP on ATV clearance in their population PK model. They however observed that patients co-medicated with an inhibitor of OATP2B1 had lower clearance values than the rest of the population, suggesting a potential importance of OATP2B1 in ATV PK [6]. Again, further studies are needed to confirm the role of the c.935G > A SNP in *SLCO2B1*, if any, in modulating the susceptibility to develop SRM.

4.2. Biotransformation enzymes

4.2.1. Phase I metabolic enzymes

As explained above, ATV is primarily metabolized by CYP3A4 into less active metabolites, see Fig. 2. The evidence of variants influencing ATV PK at the biotransformation step is frequent. Such is the case with the *CYP3A4*22* allele (rs35599367, c.522-191C > T) that has been associated with lower *CYP3A4* hepatic expression and activity and might thus account for differences in ATV PK [91,92]. In line with that hypothesis, Wang et al. evidenced that *CYP3A4*22* carriers required significantly lower doses of statins for optimal lipid control and Klein et al. that healthy *CYP3A4*22* carriers showed 35 % decreased metabolite to parent compound ratio [91,93]. This influence of the *CYP3A4*22* allele on ATV PK was further confirmed by Kitzmiller et al. who showed that statin (including ATV) dose requirement for optimal lipid control was significantly associated with the *CYP3A4/5* combined genotype grouping [94].

Klein et al. also associated CYP3A4 decreased ATV-2-hydroxylation with another deleterious polymorphism (rs4253728, c.209-1003G > A) in the peroxisome proliferator-activated receptor-α (*PPARA*). This genetic variation induces an increase of the unmetabolized circulating ATV, leading to higher systemic exposure to the drug. This was investigated *in vitro* using 150 samples based on a candidate-gene approach from a human liver bank and the results were validated *in vivo* on a cohort of 56 genotyped volunteers [93]. Since *CYP3A* is regulated by *PPARA* which is itself controlled by microRNAs in the liver, research groups identified genetic variations in the microRNAs miR-21, miR-27b and miR-206 that impact their efficiency to regulate *PPARA*. This phenomenon was associated with the development of SRM in several studies [95–99].

As a member of the P450 superfamily, *CYP3A4* activity is modulated by the P450 oxidoreductase (POR) protein activity which is responsible for the transfer of electrons from NADPH to CYP450, thereby promoting ATV metabolism. In a clinical trial using CYP3A phenotyping probes, the

variant rs1057868 (c.1508C > T, p.Ala503Val) defining the *POR*28* allele has been associated with increased CYP3A activity [100]. Ragia et al. showed a non-significant tendency of the *POR*28* variant towards an increased reduction of LDL-cholesterol and total cholesterol after 6 months of treatment of 207 adults with hypercholesterolemia [101]. This observation is counterintuitive as the *POR*28* is associated with CYP3A increased activity; thus higher ATV metabolism, lower drug exposure and decreased efficacy would be expected. As they did not assess ATV PK in their study, we cannot conclude on the causality of their observation. By contrast, and in agreement with the increased CYP3A activity associated with the *POR*28* allele, Drogari et al. showed in a cohort of 123 children and adolescents with familial hypercholesterolemia that, after 6 months of treatment with ATV (10, 20 or 40 mg/day), patients with homozygous *POR*28/POR*28* had significantly higher total cholesterol levels when compared to heterozygous or wild-type *POR*28* genotypes [102]. Again, no PK assessment was performed, and they did not register the occurrence of muscular side-effects in their study. Consequently, it is not yet known if the *POR*28* impact on PK, if any, is affecting the risk of developing SRM.

It is established that CYP3A5 is not the main phase I metabolic enzyme implicated in ATV biotransformation but there are indications that the variant *CYP3A5*3* (rs776746, c.219-237A > G) might influence ATV-induced muscle side-effects. Indeed, in a balanced case-control study involving 137 individuals, Wilke et al. investigated the impact of the *CYP3A5*3* allele on ATV SRM occurrence. They highlighted that adults expressing two copies of this variant allele have a greater likelihood to experience myotoxicities but, no PK data were available to confirm the causative association. The observation is in line with the functionality of the SNP as this intronic variant induces alternative splicing, introducing a stop codon that leads to a loss of *CYP3A5* activity and thus lower metabolism and possibly higher SRM occurrence [103,104].

Although ATV is not supposed to be metabolized by CYP2D6, studies have surprisingly evidenced associations between the development of SRM and functional *CYP2D6* SNP. Frudakis et al. evaluated the frequency of the nonfunctional *CYP2D6*4* allele (defined by the rs3892097, c.506-1G > A) in a case-control study ($n = 263$ samples, $n = 388$ SNPs) where 263 patients were followed for the possible development of a "muscle event". In their study, they highlighted that the frequency of the *CYP2D6*4* allele was about 50 % in patients developing SRM but only 28 % in controls. Even though poorly implicated in ATV metabolism, the authors suggested a possible implication of CYP2D6 in the metabolization of ATV [105].

Paraoxonases play a key role in detoxifying the body from an ATV lactone accumulation (Fig. 2). Following this idea, Riedmaier et al. studied the association of polymorphisms in *PON1* (*−108 T > C*, *−832G > A*, and *− 1741G > A*) and in *PON3* (*−4984A > G*, *−4105G > A*, *−1091A > G*, *−746C > T*, and *F21F*) with an eventual protein function modulation. They showed that *PON1* expression modulation is mainly ruled by the three polymorphisms linked to the gene promoter which significantly influence the ATV lactone hydrolysis. No polymorphism was identified to alter *PON3* activity where its expression appears to be regulated by non-genetic factors [51].

4.2.2. Phase II metabolic enzymes

The reverse reaction of the lactone detoxification is mainly controlled by the UDP glucuronosyltransferases, *UGT1A3* and somewhat by *UGT1A1*, metabolizing ATV-acid in its lactone form. Amongst others, the polymorphisms *UGT1A1*28* (rs3064744, c.868-6787_868-6786ins (Tan)) and *UGT1A3*2* (rs4663969, c.867 + 16674C > A) were highlighted by Riedmaier et al. They showed that both *UGT1A1*28* and *UGT1A3*2* were associated with an increased activity of ATV lactonization catalysis *in vitro* and *in vivo* [50]. Observations on *UGT1A3*2* were supported by Cho et al. on a cohort of 23 healthy volunteers receiving 20 mg of ATV daily. They indeed showed significant increase in ATV lactonization and a lower implication of *UGT1A1*28* mainly because of lower expression levels of the enzyme compared to *UGT1A3* [106] Contrarily, Stormo et al. found that both variants *UGT1A1*28* and *UGT1A3*2* were associated with 41 % and 18 % reduction in ATV lactone plasma concentration compared to the wild-type protein, respectively [107].

5. Conclusion

According to the present review of the literature, all five efflux transporters appear to be more or less implicated in ATV PK modulation and this implication is likely dependent on the localization and the level of expression of the transporter as well as the affinity for ATV. The functionality of the different SNPs detailed so far is not always well described and large studies are lacking to evaluate the potential clinical relevance of the available data. However, more data are available regarding the effect of variants in *ABCG2*, especially the rs2231142 (c.421C > A) that has been more largely studied. Although not all results point in the same direction [75,76], most of them depict the transporter as a key modulator of ATV PK, with increased ATV $AUC_{0-\infty}$ and C_{max} in 421A carriers [72–74]. The variant would then reduce the activity of ATV efflux but, at present, we do not have sufficient data to associate the PK effect with the development of muscle side-effects. One case control study associated this SNP with the odds of developing SRM [77], which might indicate that, even if the PK effect is not always detected at the systemic level, it impacts more on the local drug accumulation in specific tissues rather than on the systemic/liver drug accumulation because of potential compensatory mechanisms present in the liver. Regarding the influx transporters, variants in *SLCO1B3* and *SLCO2B1* are to some extent implicated in ATV PK modulation and impact on the development of SRM but they need further investigation. The variant rs4149056 (c.521 T > C) in *SLCO1B1* on the contrary, has been in the center of all attention. It was demonstrated that heterozygous and homozygous carriers experienced higher ATV and 2-OH ATV concentrations as well as increased ATV AUC and C_{max} compared to the wild-type genotype [73,81,82]. More importantly, the modulation in ATV PK in 521C carriers was, in a few reports, associated with the development of SRM [6,84,85] and further objectivated in *meta*-analysis [85]. Contrarily to ABCG2, this impact on the risk of developing SRM seems to be a direct consequence of a lower drug hepatic clearance and thus higher systemic exposure, rather than a change in the muscle accumulation. Variations in the sequences of phase I (in *CYP3A4* and *CYP2D6*) and phase II (*UGT1A*) metabolic enzymes, also find their importance to better understand ATV PK modulation and SRM development. They indeed directly rule ATV PK, and to a further extent its myotoxicity, as they determine its metabolization into hydroxy- or lactone- metabolites.

Given the lack of prospective studies evaluating the benefit of preemptive genotyping for reducing the risk of developing SRM with statins, at present, pharmacogenetic testing cannot be interpreted alone. Most likely, this proactive approach should be complementary to a reactive therapeutic drug monitoring (TDM) strategy. Indeed, on the one hand, pharmacogenetics has the potential to alert the clinician about the presence of a functional SNP (e.g. in *ABCG2* and/or *SLCO1B1*) while TDM might assist in estimating the patient's actual (apparent) clearance and further improve the therapeutic strategy (dose adjustment or switch). To authenticate the genuine clinical benefit of preemptive pharmacogenetic testing and thereby, advance ATV precision pharmacotherapy, there is a need for prospective studies supporting the credibility of reported associations and evaluating the cost-effectiveness of such a strategy. Essentially, before implementation, a therapy based on the genetic profile of patients should demonstrate its ability to improve the clinical response to the drug compared to the standard of care based on clinical judgement.

Statin pharmacogenetics for explaining muscle adverse symptoms is hampered to some extent by the lack of standardized nomenclature and phenotypic definitions of toxicity outcomes. Indeed, the very broad extent of definitions used and muscle severities considered across

clinical trials/case-control studies render difficult the comparisons and the interpretations of the reported associations. The oversimplification of the SRM definition is thus a limitation of the present review as, in an effort to be exhaustive on the pharmacogenetic associations reported, it was decided to not make the distinction between the different clinical outcomes considered. For instance, it is clear that apparent discrepancies between studies might potentially be explained by a more stringent definition of the muscular toxicity (e.g., a higher SRM grading or re-challenge of the drug) or, alternatively, a less objective definition of the clinical outcome (e.g., any self-reported muscular discomfort).

The conclusions drawn in this review are in line with the recent guidelines published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) regarding the use of statins based on *SLCO1B1*, *ABCG2* and *CYP2D6* genotypes [78]. They indeed highlighted their importance in the modulation of circulating statin levels and the impact on the development of SRM. However, statin therapy should neither be discontinued nor avoided based on *SLCO1B1*, *ABCG2*, or *CYP2C9* genotype results for patients with an indication for statin therapy. All in all, the pharmacogenetic appears to be critical to decipher the inter-individual variability in ATV PK modulation and SRM in patients. It is more than obvious that the research in this field is in a perpetual expansion and has significantly progressed for the past few years but statin adherence remains a major public issue. Most of the studies depicted in this review evaluated the impact of the pharmacogenetic at a systemic level where the effect of transporters that are less expressed could be concealed or compensated by other transporters more importantly expressed. Such is the case of *SLCO2B1*, not highly expressed in the liver compared to *SLCO1B1* and *SLCO1B3*. We understand that a variation in *SLCO2B1* would not be reflected at the systemic level as *SLCO1B1* and *1B3* would take the lead to transport ATV into the hepatocytes. In this situation, studying the pharmacogenetic directly in the skeletal muscle tissue would best reflect the local exposure, erasing the interference with genes that are implicated in the systemic exposure. Indeed, although influx (*SLCO2B1*) and efflux (*ABCC1*, *ABCC2*, *ABCC4*) transporters are expressed at lower levels in the skeletal muscle tissue, a variation could have more impact on the local exposure as less compensatory mechanisms would have to be considered. In an era where genetic information will be more and more available, it is likely that deciphering the individual importance of genetic variants can help in guiding ATV therapy.

Author contributions

EH., LE. And VH. designed and wrote the present review. All authors contributed and approved the last version of the manuscript.

Funding

This work was supported by Fonds pour la Formation à la Recherche dans l'Industrie et dans l'Agriculture (FRIA) under the Grant Number FC33437 to Hoste E.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] ESC, Cardiovascular Realities 2022, 2022, pp. 1-84.
[2] G.A. Roth, S.D. Fihn, A.H. Mokdad, W. Aekplakorn, T. Hasegawa, S.S. Lim, High total serum cholesterol, medication coverage and therapeutic control: an analysis of national health examination survey data from eight countries, Bull. World Health Organ. 89 (2) (2011) 92–101, https://doi.org/10.2471/blt.10.079947.
[3] A. Cordon, C. De Meester, S. Gerkens, D. Roberfroid, C. De Laet, Statins for the primary prevention of cardiovascular events, Belgian Health Care Knowledge Centre (KCE) (2019) 1–225.
[4] E.S. Stroes, P.D. Thompson, A. Corsini, G.D. Vladutiu, F.J. Raal, K.K. Ray, M. Roden, E. Stein, L. Tokgözoğlu, B.G. Nordestgaard, Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society consensus panel statement on assessment, aetiology and management, Eur. Heart J. 36 (17) (2015) 1012–1022.
[5] E. Bruckert, G. Hayem, S. Dejager, C. Yau, B. Bégaud, Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients–the PRIMO study, Cardiovasc. Drugs Ther. 19 (6) (2005) 403–414, https://doi.org/10.1007/s10557-005-5686-z.
[6] G. Stillemans, A. Paquot, G.G. Muccioli, E. Hoste, N. Panin, A. Åsberg, J. L. Balligand, V. Haufroid, L. Elens, Atorvastatin population pharmacokinetics in a real-life setting: Influence of genetic polymorphisms and association with clinical response, Clin Transl Sci 15 (3) (2022) 667–679, https://doi.org/10.1111/cts.13185.
[7] I.B. Skottheim, A. Gedde-Dahl, S. Hejazifar, K. Hoel, A. Asberg, Statin induced myotoxicity: the lactone forms are more potent than the acid forms in human skeletal muscle cells in vitro, Eur. J. Pharm. Sci. 33 (4–5) (2008) 317–325, https://doi.org/10.1016/j.ejps.2007.12.009.
[8] R.M. Turner, M. Pirmohamed, Statin-Related Myotoxicity: A Comprehensive Review of Pharmacokinetic, Pharmacogenomic and Muscle Components, J. Clin. Med. 9 (1) (2019), https://doi.org/10.3390/jcm9010022.
[9] S. Sathasivam, Statin induced myotoxicity, Eur. J. Intern. Med. 23 (4) (2012) 317–324, https://doi.org/10.1016/j.ejim.2012.01.004.
[10] E.J. Kim, A.S. Wierzbicki, Investigating raised creatine kinase, BMJ (clinical Research Ed.) 373 (2021) n1486, https://doi.org/10.1136/bmj.n1486.
[11] M. Tomaszewski, K.M. Stepien, J. Tomaszewska, S.J. Czuczwar, Statin-induced myopathies, Pharmacological Reports : PR 63 (4) (2011) 859–866, https://doi.org/10.1016/s1734-1140(11)70601-6.
[12] A.N. Baer, R.L. Wortmann, Myotoxicity associated with lipid-lowering drugs, Curr. Opin. Rheumatol. 19 (1) (2007) 67–73, https://doi.org/10.1097/BOR.0b013e328010c559.
[13] P.A. Torres, J.A. Helmstetter, A.M. Kaye, A.D. Kaye, Rhabdomyolysis: pathogenesis, diagnosis, and treatment, Ochsner J 15 (1) (2015) 58–69.
[14] M. Lemstra, D. Blackburn, A. Crawley, R. Fung, Proportion and risk indicators of nonadherence to statin therapy: a meta-analysis, Can J Cardiol 28 (5) (2012) 574–580, https://doi.org/10.1016/j.cjca.2012.05.007.
[15] T.T. Abd, T.A. Jacobson, Statin-induced myopathy: a review and update, Expert Opin. Drug Saf. 10 (3) (2011) 373–387, https://doi.org/10.1517/14740338.2011.540568.
[16] M.Y. Wei, M.K. Ito, J.D. Cohen, E.A. Brinton, T.A. Jacobson, Predictors of statin adherence, switching, and discontinuation in the USAGE survey: understanding the use of statins in America and gaps in patient education, J. Clin. Lipidol. 7 (5) (2013) 472–483, https://doi.org/10.1016/j.jacl.2013.03.001.
[17] G.D. Norata, G. Tibolla, A.L. Catapano, Statins and skeletal muscles toxicity: from clinical trials to everyday practice, Pharmacol. Res. 88 (2014) 107–113, https://doi.org/10.1016/j.phrs.2014.04.012.
[18] S.K. Baker, Molecular clues into the pathogenesis of statin-mediated muscle toxicity, Muscle Nerve 31 (5) (2005) 572–580, https://doi.org/10.1002/mus.20291.
[19] G. De Angelis, The influence of statin characteristics on their safety and tolerability, Int. J. Clin. Pract. 58 (10) (2004) 945–955, https://doi.org/10.1111/j.1368-5031.2004.00355.x.
[20] O.P. Flint, B.A. Masters, R.E. Gregg, S.K. Durham, Inhibition of cholesterol synthesis by squalene synthase inhibitors does not induce myotoxicity in vitro, Toxicol. Appl. Pharmacol. 145 (1) (1997) 91–98, https://doi.org/10.1006/taap.1997.8131.
[21] S. Morikawa, T. Murakami, H. Yamazaki, A. Izumi, Y. Saito, T. Hamakubo, T. Kodama, Analysis of the global RNA expression profiles of skeletal muscle cells treated with statins, J. Atheroscler. Thromb. 12 (3) (2005) 121–131, https://doi.org/10.5551/jat.12.121.
[22] P.M. Tricarico, S. Crovella, F. Celsi, Mevalonate Pathway Blockade, Mitochondrial Dysfunction and Autophagy: A Possible Link, Int. J. Mol. Sci. 16 (7) (2015) 16067–16084, https://doi.org/10.3390/ijms160716067.
[23] E.A. Lundquist, Small GTPases, WormBook : the online review of C. elegans biology (2006) 1-18. 10.1895/wormbook.1.67.1.
[24] D.J. Reiner, E.A. Lundquist, Small GTPases, WormBook : the online review of C, in: Elegans Biology 2018, 2018, pp. 1–65, https://doi.org/10.1895/wormbook.1.67.2.
[25] M.D. Gomes, S.H. Lecker, R.T. Jagoe, A. Navon, A.L. Goldberg, Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy, PNAS 98 (25) (2001) 14440–14445, https://doi.org/10.1073/pnas.251541198.
[26] M.J. Knauer, B.L. Urquhart, H.E. Meyer zu Schwabedissen, U.I. Schwarz, C.J. Lemke, B.F. Leake, R.B. Kim, R.G. Tirona, Human skeletal muscle drug transporters determine local exposure and toxicity of statins, Circ. Res. 106(2) (2010) 297-306. 10.1161/circresaha.109.203596.
[27] J. Hanai, P. Cao, P. Tanksale, S. Imamura, E. Koshimizu, J. Zhao, S. Kishi, M. Yamashita, P.S. Phillips, V.P. Sukhatme, S.H. Lecker, The muscle-specific ubiquitin ligase atrogin-1/MAFbx mediates statin-induced muscle toxicity, J. Clin. Invest. 117 (12) (2007) 3940–3951, https://doi.org/10.1172/jci32741.
[28] P. Cao, J. Hanai, P. Tanksale, S. Imamura, V.P. Sukhatme, S.H. Lecker, Statin-induced muscle damage and atrogin-1 induction is the result of a geranylgeranylation defect, FASEB journal : official publication of the Federation

of American Societies for, Exp. Biol. 23 (9) (2009) 2844–2854, https://doi.org/10.1096/fj.08-128843.
[29] D.D. Hinson, R.M. Ross, S. Krisans, J.L. Shaw, V. Kozich, M.O. Rolland, P. Divry, J. Mancini, G.F. Hoffmann, K.M. Gibson, Identification of a mutation cluster in mevalonate kinase deficiency, including a new mutation in a patient of Mennonite ancestry, Am. J. Hum. Genet. 65 (2) (1999) 327–335, https://doi.org/10.1086/302489.
[30] T. Chojnacki, G. Dallner, The biological role of dolichol, Biochem. J. 251 (1) (1988) 1–9, https://doi.org/10.1042/bj2510001.
[31] Y. Wang, S. Hekimi, Understanding Ubiquinone, Trends Cell Biol. 26 (5) (2016) 367–378, https://doi.org/10.1016/j.tcb.2015.12.007.
[32] S. Matzno, S. Yasuda, S. Juman, Y. Yamamoto, N. Nagareya-Ishida, K. Tazuya-Murayama, T. Nakabayashi, K. Matsuyama, Statin-induced apoptosis linked with membrane farnesylated Ras small G protein depletion, rather than geranylated Rho protein, J. Pharm. Pharmacol. 57 (11) (2005) 1475–1484, https://doi.org/10.1211/jpp.57.11.0014.
[33] C.R. Sirtori, The pharmacology of statins, Pharmacol. Res. 88 (2014) 3–11, https://doi.org/10.1016/j.phrs.2014.03.002.
[34] H. Lennernas, Clinical pharmacokinetics of atorvastatin, Clin. Pharmacokinet. 42 (13) (2003) 1141–1160, https://doi.org/10.2165/00003088-200342130-00005.
[35] F. Deng, S.K. Tuomi, M. Neuvonen, P. Hirvensalo, S. Kulju, C. Wenzel, S. Oswald, A.M. Filppula, M. Niemi, Comparative Hepatic and Intestinal Efflux Transport of Statins, Drug Metab. Dispos. 49 (9) (2021) 750–759, https://doi.org/10.1124/dmd.121.000430.
[36] P.T. Ronaldson, H. Brzica, W. Abdullahi, B.G. Reilly, T.P. Davis, Transport Properties of Statins by Organic Anion Transporting Polypeptide 1A2 and Regulation by Transforming Growth Factor-β Signaling in Human Endothelial Cells, J. Pharmacol. Exp. Ther. 376 (2) (2021) 148–160, https://doi.org/10.1124/jpet.120.000267.
[37] The Human Protein Atlas, SLCO1B1. https://www.proteinatlas.org/ENSG00000134538-SLCO1B1, 2023 (Accessed 21 August 2023).
[38] The Human Protein Atlas, SLCO1B3. https://www.proteinatlas.org/ENSG00000111700-SLCO1B3, 2023 (Accessed 21 August 2023).
[39] The Human Protein Atlas, SLCO2B1. https://www.proteinatlas.org/ENSG00000137491-SLCO2B1, 2023 (Accessed 21 August 2023).
[40] The Human Protein Atlas, SLCO1A2. https://www.proteinatlas.org/ENSG00000084453-SLCO1A2, 2023 (Accessed 21 August 2023).
[41] The Human Protein Atlas, SLC16A1. https://www.proteinatlas.org/ENSG00000155380-SLC16A1, 2023 (Accessed 21 August 2023).
[42] The Human Protein Atlas, SLCO16A3. https://www.proteinatlas.org/ENSG00000141526-SLC16A3, 2023 (Accessed 21 August 2023).
[43] The Human Protein Atlas, ABCC1. https://www.proteinatlas.org/ENSG00000103222-ABCC1, 2023 (Accessed 21 August 2023).
[44] The Human Protein Atlas, ABCC2. https://www.proteinatlas.org/ENSG00000023839-ABCC2, 2023 (Accessed 21 August 2023).
[45] The Human Protein Atlas, ABCC4. https://www.proteinatlas.org/ENSG00000125257-ABCC4, 2023 (Accessed 21 August 2023).
[46] The Human Protein Atlas, ABCC5. https://www.proteinatlas.org/ENSG00000114770-ABCC5, 2023 (Accessed 21 August 2023).
[47] The Human Protein Atlas, ABCB1. https://www.proteinatlas.org/ENSG00000085563-ABCB1, 2023 (Accessed 21 August 2023).
[48] The Human Protein Atlas, ABCG2. https://www.proteinatlas.org/ENSG00000118777-ABCG2, 2023 (Accessed 21 August 2023).
[49] V.W. Ma, E.J. Kaleta, S.C. Bryant, G.M. Spears, L.J. Train, S.E. Peterson, V. A. Lennon, S.L. Kopecky, L.M. Baudhuin, Genetic variation in statin intolerance and a possible protective role for UGT1A1, Pharmacogenomics 19 (2) (2018) 83–94, https://doi.org/10.2217/pgs-2017-0146.
[50] S. Riedmaier, K. Klein, U. Hofmann, J.E. Keskitalo, P.J. Neuvonen, M. Schwab, M. Niemi, U.M. Zanger, UDP-glucuronosyltransferase (UGT) polymorphisms affect atorvastatin lactonization in vitro and in vivo, Clin. Pharmacol. Ther. 87 (1) (2010) 65–73, https://doi.org/10.1038/clpt.2009.181.
[51] S. Riedmaier, K. Klein, S. Winter, U. Hofmann, M. Schwab, U.M. Zanger, Paraoxonase (PON1 and PON3) Polymorphisms: Impact on Liver Expression and Atorvastatin-Lactone Hydrolysis, Front. Pharmacol. 2 (2011) 41, https://doi.org/10.3389/fphar.2011.00041.
[52] T. Prueksaritanont, R. Subramanian, X. Fang, B. Ma, Y. Qiu, J.H. Lin, P. G. Pearson, T.A. Baillie, Glucuronidation of statins in animals and humans: a novel mechanism of statin lactonization, Drug Metab. Dispos. 30 (5) (2002) 505–512, https://doi.org/10.1124/dmd.30.5.505.
[53] J.E. Park, K.B. Kim, S.K. Bae, B.S. Moon, K.H. Liu, J.G. Shin, Contribution of cytochrome P450 3A4 and 3A5 to the metabolism of atorvastatin, Xenobiotica 38 (9) (2008) 1240–1251, https://doi.org/10.1080/00498250802334391.
[54] M. Schachter, Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update, Fundam. Clin. Pharmacol. 19 (1) (2005) 117–125.
[55] D. Gibson, R. Stern, R. Abel, L. Whitfield, Absolute bioavailability of atorvastatin in man, Pharm. Res. 14 (2) (1997) 253.
[56] A. Mansoor, N. Mahabadi, Volume of Distribution, StatPearls, StatPearls Publishing StatPearls Publishing LLC., Treasure Island (FL), 2020.
[57] W. Jacobsen, B. Kuhn, A. Soldner, G. Kirchner, K.F. Sewing, P.A. Kollman, L. Z. Benet, U. Christians, Lactonization is the critical first step in the disposition of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor atorvastatin, Drug Metab. Dispos. 28 (11) (2000) 1369–1378.
[58] M. Hermann, M.P. Bogsrud, E. Molden, A. Asberg, B.U. Mohebi, L. Ose, K. Retterstol, Exposure of atorvastatin is unchanged but lactone and acid metabolites are increased several-fold in patients with atorvastatin-induced myopathy, Clin. Pharmacol. Ther. 79 (6) (2006) 532–539, https://doi.org/10.1016/j.clpt.2006.02.014.
[59] K. Sakamoto, H. Mikami, J. Kimura, Involvement of organic anion transporting polypeptides in the toxicity of hydrophilic pravastatin and lipophilic fluvastatin in rat skeletal myofibres, Br. J. Pharmacol. 154 (7) (2008) 1482–1490, https://doi.org/10.1038/bjp.2008.192.
[60] K. Kajinami, M.E. Brousseau, J.M. Ordovas, E.J. Schaefer, Polymorphisms in the multidrug resistance-1 (MDR1) gene influence the response to atorvastatin treatment in a gender-specific manner, Am J Cardiol 93 (8) (2004) 1046–1050, https://doi.org/10.1016/j.amjcard.2004.01.014.
[61] P. Kadam, T.F. Ashavaid, C.K. Ponde, R.M. Rajani, Genetic determinants of lipid-lowering response to atorvastatin therapy in an Indian population, J. Clin. Pharm. Ther. 41 (3) (2016) 329–333, https://doi.org/10.1111/jcpt.12369.
[62] R.B.R. León-Cachón, J.A. Ascacio-Martínez, M.E. Gamino-Peña, R.M. Cerda-Flores, I. Meester, H.L. Gallardo-Blanco, M. Gómez-Silva, E. Piñeyro-Garza, H. A. Barrera-Saldaña, A pharmacogenetic pilot study reveals MTHFR, DRD3, and MDR1 polymorphisms as biomarker candidates for slow atorvastatin metabolizers, BMC Cancer 16 (2016) 74, https://doi.org/10.1186/s12885-016-2062-2.
[63] L. Zhang, H. Lv, Q. Zhang, D. Wang, X. Kang, G. Zhang, X. Li, Association of SLCO1B1 and ABCB1 Genetic Variants with Atorvastatin-induced Myopathy in Patients with Acute Ischemic Stroke, Curr. Pharm. Des. 25 (14) (2019) 1663–1670, https://doi.org/10.2174/1381612825666190705204614.
[64] S.M. He, R. Li, J.R. Kanwar, S.F. Zhou, Structural and functional properties of human multidrug resistance protein 1 (MRP1/ABCC1), Curr. Med. Chem. 18 (3) (2011) 439–481, https://doi.org/10.2174/092986711794839197.
[65] N. Behdad, J. Kojuri, N. Azarpira, A. Masoomi, S. Namazi, Association of ABCB1 (C3435T) and ABCC1 (G2012T) Polymorphisms with Clinical Response to Atorvastatin in Iranian Patients with Primary Hyperlipidemia, Iran Biomed. J. 21 (2) (2017) 120-5. 10.18869/acadpub.ibj.21.2.120.
[66] E. Hoste, A. Paquot, N. Panin, S. Horion, H. El Hamdaoui, G.G. Muccioli, V. Haufroid, L. Elens, Genetic Polymorphisms in SLCO2B1 and ABCC1 Conjointly Modulate Atorvastatin Intracellular Accumulation in HEK293 Recombinant Cell Lines, Ther. Drug Monit. 45 (3) (2023) 400–408, https://doi.org/10.1097/ftd.0000000000001043.
[67] I. Cascorbi, Role of pharmacogenetics of ATP-binding cassette transporters in the pharmacokinetics of drugs, Pharmacol. Ther. 112 (2) (2006) 457–473, https://doi.org/10.1016/j.pharmthera.2006.04.009.
[68] M.T. Huisman, J.W. Smit, K.M. Crommentuyn, N. Zelcer, H.R. Wiltshire, J. H. Beijnen, A.H. Schinkel, Multidrug resistance protein 2 (MRP2) transports HIV protease inhibitors, and transport can be enhanced by other drugs, AIDS 16 (17) (2002) 2295–2301, https://doi.org/10.1097/00002030-200211220-00009.
[69] M.L. Becker, L.L. Elens, L.E. Visser, A. Hofman, A.G. Uitterlinden, R.H. van Schaik, B.H. Stricker, Genetic variation in the ABCC2 gene is associated with dose decreases or switches to other cholesterol-lowering drugs during simvastatin and atorvastatin therapy, Pharmacogenomics J. 13 (3) (2013) 251–256, https://doi.org/10.1038/tpj.2011.59.
[70] Z. Jiang, Z. Wu, R. Liu, Q. Du, X. Fu, M. Li, Y. Kuang, S. Lin, J. Wu, W. Xie, G. Shi, Y. Peng, F. Zheng, Effect of polymorphisms in drug metabolism and transportation on plasma concentration of atorvastatin and its metabolites in patients with chronic kidney disease, Front. Pharmacol. 14 (2023) 1102810, https://doi.org/10.3389/fphar.2023.1102810.
[71] Z. Safar, E. Kis, F. Erdo, J.K. Zolnerciks, P. Krajcsi, ABCG2/BCRP: variants, transporter interaction profile of substrates and inhibitors, Expert Opin. Drug Metab. Toxicol. 15 (4) (2019) 313–328, https://doi.org/10.1080/17425255.2019.1591373.
[72] J.E. Keskitalo, O. Zolk, M.F. Fromm, K.J. Kurkinen, P.J. Neuvonen, M. Niemi, ABCG2 polymorphism markedly affects the pharmacokinetics of atorvastatin and rosuvastatin, Clin. Pharmacol. Ther. 86 (2) (2009) 197–203, https://doi.org/10.1038/clpt.2009.79.
[73] B.K. Birmingham, S.R. Bujac, R. Elsby, C.T. Azumaya, C. Wei, Y. Chen, R. Mosqueda-Garcia, H.J. Ambrose, Impact of ABCG2 and SLCO1B1 polymorphisms on pharmacokinetics of rosuvastatin, atorvastatin and simvastatin acid in Caucasian and Asian subjects: a class effect? Eur. J. Clin. Pharmacol. 71 (3) (2015) 341–355, https://doi.org/10.1007/s00228-014-1801-z.
[74] N. Tsamandouras, Y. Guo, T. Wendling, S. Hall, A. Galetin, L. Aarons, Modelling of atorvastatin pharmacokinetics and the identification of the effect of a BCRP polymorphism in the Japanese population, Pharmacogenet. Genomics 27 (1) (2017) 27–38, https://doi.org/10.1097/fpc.0000000000000252.
[75] N. Lee, K. Maeda, S. Fukizawa, I. Ieiri, A. Tomaru, H. Akao, K. Takeda, M. Iwadare, O. Niwa, T. Masauji, N. Yamane, K. Kajinami, H. Kusuhara, Y. Sugiyama, Microdosing clinical study to clarify pharmacokinetic and pharmacogenetic characteristics of atorvastatin in Japanese hypercholesterolemic patients, Drug Metab. Pharmacokinet. 34 (6) (2019) 387–395, https://doi.org/10.1016/j.dmpk.2019.08.004.
[76] Y. Prado, T. Zambrano, L.A. Salazar, Transporter genes ABCG2 rs2231142 and ABCB1 rs1128503 polymorphisms and atorvastatin response in Chilean subjects, J. Clin. Pharm. Ther. 43 (1) (2018) 87–91, https://doi.org/10.1111/jcpt.12607.
[77] N. Mirošević Skvrce, V. Macolić Šarinić, I. Šimić, L. Ganoci, D. Muačević Katanec, N. Božina, ABCG2 gene polymorphisms as risk factors for atorvastatin adverse reactions: a case-control study, Pharmacogenomics 16(8) (2015) 803-15. 10.2217/pgs.15.47.
[78] R.M. Cooper-DeHoff, M. Niemi, L.B. Ramsey, J.A. Luzum, E.K. Tarkiainen, R. J. Straka, L. Gong, S. Tuteja, R.A. Wilke, M. Wadelius, E.A. Larson, D.M. Roden, T. E. Klein, S.W. Yee, R.M. Krauss, R.M. Turner, L. Palaniappan, A. Gaedigk, K.

M. Giacomini, K.E. Caudle, D. Voora, The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms, Clin. Pharmacol. Ther. 111 (5) (2022) 1007–1021, https://doi.org/10.1002/cpt.2557.

[79] J. König, Y. Cui, A.T. Nies, D. Keppler, A novel human organic anion transporting polypeptide localized to the basolateral hepatocyte membrane, Am. J. Physiol. Gastrointest Liver Physiol. 278 (1) (2000) G156–G164, https://doi.org/10.1152/ajpgi.2000.278.1.G156.

[80] Y. Kameyama, K. Yamashita, K. Kobayashi, M. Hosokawa, K. Chiba, Functional characterization of SLCO1B1 (OATP-C) variants, SLCO1B1*5, SLCO1B1*15 and SLCO1B1*15+C1007G, by using transient expression systems of HeLa and HEK293 cells, Pharmacogenet. Genomics 15 (7) (2005) 513–522, https://doi.org/10.1097/01.fpc.0000170913.73780.5f.

[81] R.M. Turner, V. Fontana, J.E. Zhang, D. Carr, P. Yin, R. FitzGerald, A.P. Morris, M. Pirmohamed, A Genome-wide Association Study of Circulating Levels of Atorvastatin and Its Major Metabolites, Clin. Pharmacol. Ther. (2020), https://doi.org/10.1002/cpt.1820.

[82] M.K. Pasanen, H. Fredrikson, P.J. Neuvonen, M. Niemi, Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin, Clin. Pharmacol. Ther. 82 (6) (2007) 726–733, https://doi.org/10.1038/sj.clpt.6100220.

[83] E. Giannakopoulou, G. Ragia, V. Kolovou, A. Tavridou, A.D. Tselepis, M. Elisaf, G. Kolovou, V.G. Manolopoulos, No impact of SLCO1B1 521T>C, 388A>G and 411G>A polymorphisms on response to statin therapy in the Greek population, Mol. Biol. Rep. 41 (7) (2014) 4631–4638, https://doi.org/10.1007/s11033-014-3334-z.

[84] D.W. Linskey, J.D. English, D.A. Perry, H.M. Ochs-Balcom, C. Ma, P.J. Isackson, G.D. Vladutiu, J.A. Luzum, Association of SLCO1B1 c.521T>C (rs4149056) with discontinuation of atorvastatin due to statin-associated muscle symptoms, Pharmacogenetics and genomics 30(9) (2020) 208-211. 10.1097/fpc.0000000000000412.

[85] S. Turongkaravee, J. Jittikoon, T. Lukkunaprasit, S. Sangroongruangsri, U. Chaikledkaew, A. Thakkinstian, A systematic review and meta-analysis of genotype-based and individualized data analysis of SLCO1B1 gene and statin-induced myopathy, Pharmacogenomics J 21 (3) (2021) 296–307, https://doi.org/10.1038/s41397-021-00208-w.

[86] J. Jiang, Q. Tang, J. Feng, R. Dai, Y. Wang, Y. Yang, X. Tang, C. Deng, H. Zeng, Y. Zhao, F. Zhang, Association between SLCO1B1 -521T>C and -388A>G polymorphisms and risk of statin-induced adverse drug reactions: A meta-analysis, Springerplus 5 (1) (2016) 1368, https://doi.org/10.1186/s40064-016-2912-z.

[87] T. Lauritzen, J. Munkhaugen, K. Peersen, O. Kristiansen, E. Sverre, S.D. Nebauer, M. Villseth, A.M. Andersen, A.C. Svarstad, E.P. Jensen, S. Bergan, E. Husebye, N. T. Vethe, Atorvastatin Metabolite Pattern in Skeletal Muscle and Blood from Patients with Coronary Heart Disease and Statin-Associated Muscle Symptoms, Clin. Pharmacol. Ther. 113 (4) (2023) 887–895, https://doi.org/10.1002/cpt.2844.

[88] U.I. Schwarz, H.E. Meyer zu Schwabedissen, R.G. Tirona, A. Suzuki, B.F. Leake, Y. Mokrab, K. Mizuguchi, R.H. Ho, R.B. Kim, Identification of novel functional organic anion-transporting polypeptide 1B3 polymorphisms and assessment of substrate specificity, Pharmacogenetics and genomics 21(3) (2011) 103-14. 10.1097/FPC.0b013e328342f5b1.

[89] UniProt, OATP2B1_Human. https://www.uniprot.org/uniprotkb/O94956/entry, 2023 (Accessed 22 August 2023).

[90] J. Yang, Z. Wang, S. Liu, W. Wang, H. Zhang, C. Gui, Functional Characterization Reveals the Significance of Rare Coding Variations in Human Organic Anion Transporting Polypeptide 2B1 (SLCO2B1), Mol Pharm 17 (10) (2020) 3966–3978, https://doi.org/10.1021/acs.molpharmaceut.0c00747.

[91] D. Wang, Y. Guo, S.A. Wrighton, G.E. Cooke, W. Sadee, Intronic polymorphism in CYP3A4 affects hepatic expression and response to statin drugs, Pharmacogenomics J. 11 (4) (2011) 274–286, https://doi.org/10.1038/tpj.2010.28.

[92] L. Elens, A. Nieuweboer, S.J. Clarke, K.A. Charles, A.J. de Graan, V. Haufroid, R. H. Mathijssen, R.H. van Schaik, CYP3A4 intron 6 C>T SNP (CYP3A4*22) encodes lower CYP3A4 activity in cancer patients, as measured with probes midazolam and erythromycin, Pharmacogenomics 14 (2) (2013) 137–149, https://doi.org/10.2217/pgs.12.202.

[93] K. Klein, M. Thomas, S. Winter, A.K. Nussler, M. Niemi, M. Schwab, U.M. Zanger, PPARA: a novel genetic determinant of CYP3A4 in vitro and in vivo, Clin. Pharmacol. Ther. 91 (6) (2012) 1044–1052, https://doi.org/10.1038/clpt.2011.336.

[94] J.P. Kitzmiller, D.M. Sullivan, M.A. Phelps, D. Wang, W. Sadee, CYP3A4/5 combined genotype analysis for predicting statin dose requirement for optimal lipid control, Drug Metabol Drug Interact 28 (1) (2013) 59–63, https://doi.org/10.1515/dmdi-2012-0031.

[95] J.E. Liu, B. Ren, L. Tang, Q.J. Tang, X.Y. Liu, X. Li, X. Bai, W.P. Zhong, J.X. Meng, H.M. Lin, H. Wu, J.Y. Chen, S.L. Zhong, The independent contribution of miRNAs to the missing heritability in CYP3A4/5 functionality and the metabolism of atorvastatin, Sci. Rep. 6 (2016) 26544, https://doi.org/10.1038/srep26544.

[96] K. Kida, M. Nakajima, T. Mohri, Y. Oda, S. Takagi, T. Fukami, T. Yokoi, PPARalpha is regulated by miR-21 and miR-27b in human liver, Pharm. Res. 28 (10) (2011) 2467–2476, https://doi.org/10.1007/s11095-011-0473-y.

[97] Y.M. Shah, K. Morimura, Q. Yang, T. Tanabe, M. Takagi, F.J. Gonzalez, Peroxisome proliferator-activated receptor alpha regulates a microRNA-mediated signaling cascade responsible for hepatocellular proliferation, Mol. Cell. Biol. 27 (12) (2007) 4238–4247, https://doi.org/10.1128/mcb.00317-07.

[98] M. Ingelman-Sundberg, S.C. Sim, A. Gomez, C. Rodriguez-Antona, Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects, Pharmacol. Ther. 116 (3) (2007) 496–526, https://doi.org/10.1016/j.pharmthera.2007.09.004.

[99] L. Ekstrom, I. Skilving, M.L. Ovesjo, E. Aklillu, H. Nylen, A. Rane, U. Diczfalusy, L. Bjorkhem-Bergman, miRNA-27b levels are associated with CYP3A activity in vitro and in vivo, Pharmacol. Res. Perspect. 3 (6) (2015) e00192.

[100] B. Oneda, S. Crettol, E. Jaquenoud Sirot, M. Bochud, N. Ansermot, C.B. Eap, The P450 oxidoreductase genotype is associated with CYP3A activity in vivo as measured by the midazolam phenotyping test, Pharmacogenetics and genomics 19(11) (2009) 877-83. 10.1097/FPC.0b013e32833225e7.

[101] G. Ragia, V. Kolovou, A. Tavridou, L. Elens, A.D. Tselepis, M. Elisaf, R.H. Van Schaik, G. Kolovou, V.G. Manolopoulos, Lack of association of the p450 oxidoreductase *28 single nucleotide polymorphism with the lipid-lowering effect of statins in hypercholesterolemic patients, Mol. Diagn. Ther. 18 (3) (2014) 323–331, https://doi.org/10.1007/s40291-013-0082-z.

[102] E. Drogari, G. Ragia, V. Mollaki, L. Elens, R.H. Van Schaik, V.G. Manolopoulos, POR*28 SNP is associated with lipid response to atorvastatin in children and adolescents with familial hypercholesterolemia, Pharmacogenomics 15 (16) (2014) 1963–1972, https://doi.org/10.2217/pgs.14.138.

[103] P. Kuehl, J. Zhang, Y. Lin, J. Lamba, M. Assem, J. Schuetz, P.B. Watkins, A. Daly, S.A. Wrighton, S.D. Hall, P. Maurel, M. Relling, C. Brimer, K. Yasuda, R. Venkataramanan, S. Strom, K. Thummel, M.S. Boguski, E. Schuetz, Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression, Nat. Genet. 27 (4) (2001) 383–391, https://doi.org/10.1038/86882.

[104] R.A. Wilke, J.H. Moore, J.K. Burmester, Relative impact of CYP3A genotype and concomitant medication on the severity of atorvastatin-induced muscle damage, Pharmacogenet. Genomics 15 (6) (2005) 415–421, https://doi.org/10.1097/01213011-200506000-00007.

[105] T.N. Frudakis, M.J. Thomas, S.N. Ginjupalli, B. Handelin, R. Gabriel, H.J. Gomez, CYP2D6*4 polymorphism is associated with statin-induced muscle effects, Pharmacogenet. Genomics 17 (9) (2007) 695–707, https://doi.org/10.1097/FPC.0b013e328012d0a9.

[106] S.K. Cho, E.S. Oh, K. Park, M.S. Park, J.Y. Chung, The UGT1A3*2 polymorphism affects atorvastatin lactonization and lipid-lowering effect in healthy volunteers, Pharmacogenet. Genomics 22 (8) (2012) 598–605, https://doi.org/10.1097/FPC.0b013e3283544085.

[107] C. Stormo, M.P. Bogsrud, M. Hermann, A. Åsberg, A.P. Piehler, K. Retterstøl, M. K. Kringen, UGT1A1*28 is associated with decreased systemic exposure of atorvastatin lactone, Mol Diagn Ther 17 (4) (2013) 233–237, https://doi.org/10.1007/s40291-013-0031-x.

[108] A. Alfirevic, D. Neely, J. Armitage, H. Chinoy, R.G. Cooper, R. Laaksonen, D. F. Carr, K.M. Bloch, J. Fahy, A. Hanson, Q.Y. Yue, M. Wadelius, A.H. Maitland-van Der Zee, D. Voora, B.M. Psaty, C.N. Palmer, M. Pirmohamed, Phenotype standardization for statin-induced myotoxicity, Clin. Pharmacol. Ther. 96 (4) (2014) 470–476, https://doi.org/10.1038/clpt.2014.121.

[109] gnomAD browser v2.1.1. https://gnomad.broadinstitute.org/, 2023 (Accessed 21 August 2023).

[110] K.J. Karczewski, L.C. Francioli, G. Tiao, B.B. Cummings, J. Alföldi, Q. Wang, R.L. Collins, K.M. Laricchia, A. Ganna, D.P. Birnbaum, L.D. Gauthier, H. Brand, M. Solomonson, N.A. Watts, D. Rhodes, M. Singer-Berk, E.M. England, E.G. Seaby, J. A. Kosmicki, R.K. Walters, K. Tashman, Y. Farjoun, E. Banks, T. Poterba, A. Wang, C. Seed, N. Whiffin, J.X. Chong, K.E. Samocha, E. Pierce-Hoffman, Z. Zappala, A. H. O'Donnell-Luria, E.V. Minikel, B. Weisburd, M. Lek, J.S. Ware, C. Vittal, I.M. Armean, L. Bergelson, K. Cibulskis, K.M. Connolly, M. Covarrubias, S. Donnelly, S. Ferriera, S. Gabriel, J. Gentry, N. Gupta, T. Jeandet, D. Kaplan, C. Llanwarne, R. Munshi, S. Novod, N. Petrillo, D. Roazen, V. Ruano-Rubio, A. Saltzman, M. Schleicher, J. Soto, K. Tibbetts, C. Tolonen, G. Wade, M.E. Talkowski, C.A. Aguilar Salinas, T. Ahmad, C.M. Albert, D. Ardissino, G. Atzmon, J. Barnard, L. Beaugerie, E.J. Benjamin, M. Boehnke, L.L. Bonnycastle, E.P. Bottinger, D.W. Bowden, M.J. Bown, J.C. Chambers, J.C. Chan, D. Chasman, J. Cho, M.K. Chung, B. Cohen, A. Correa, D. Dabelea, M.J. Daly, D. Darbar, R. Duggirala, J. Dupuis, P.T. Ellinor, R. Elosua, J. Erdmann, T. Esko, M. Färkkilä, J. Florez, A. Franke, G. Getz, B. Glaser, S.J. Glatt, D. Goldstein, C. Gonzalez, L. Groop, C. Haiman, C. Hanis, M. Harms, M. Hiltunen, M.M. Holi, C.M. Hultman, M. Kallela, J. Kaprio, S. Kathiresan, B.-J. Kim, Y.J. Kim, G. Kirov, J. Kooner, S. Koskinen, H.M. Krumholz, S. Kugathasan, S. H. Kwak, M. Laakso, T. Lehtimäki, R.J.F. Loos, S.A. Lubitz, R.C.W. Ma, D.G. MacArthur, J. Marrugat, K.M. Mattila, S. McCarroll, M.I. McCarthy, D. McGovern, R. McPherson, J.B. Meigs, O. Melander, A. Metspalu, B.M. Neale, P.M. Nilsson, M. C. O'Donovan, D. Ongur, L. Orozco, M.J. Owen, C.N.A. Palmer, A. Palotie, K.S. Park, C. Pato, A.E. Pulver, N. Rahman, A.M. Remes, J.D. Rioux, S. Ripatti, D.M. Roden, D. Saleheen, V. Salomaa, N.J. Samani, J. Scharf, H. Schunkert, M.B. Shoemaker, P. Sklar, H. Soininen, H. Sokol, T. Spector, P.F. Sullivan, J. Suvisaari, E.S. Tai, Y.Y. Teo, T. Tiinamaija, M. Tsuang, D. Turner, T. Tusie-Luna, E. Vartiainen, M.P. Vawter, J.S. Ware, H. Watkins, R.K. Weersma, M. Wessman, J.G. Wilson, R.J. Xavier, B.M. Neale, M.J. Daly, D.G. MacArthur, C. Genome Aggregation Database, The mutational constraint spectrum quantified from variation in 141,456 humans, Nature 581(7809) (2020) 434-443. 10.1038/s41586-020-2308-7.

[111] Ensembl. https://www.ensembl.org/index.html, 2023 (Accessed 21 August 2023).

[112] F.J. Martin, M.R. Amode, A. Aneja, O. Austine-Orimoloye, A.G. Azov, I. Barnes, A. Becker, R. Bennett, A. Berry, J. Bhai, S.K. Bhurji, A. Bignell, S. Boddu, P. R. Branco Lins, L. Brooks, S.B. Ramaraju, M. Charkhchi, A. Cockburn, L. Da Rin Fiorretto, C. Davidson, K. Dodiya, S. Donaldson, B. El Houdaigui, T. El Naboulsi,

R. Fatima, C.G. Giron, T. Genez, G.S. Ghattaoraya, J.G. Martinez, C. Guijarro, M. Hardy, Z. Hollis, T. Hourlier, T. Hunt, M. Kay, V. Kaykala, T. Le, D. Lemos, D. Marques-Coelho, J.C. Marugán, G.A. Merino, L.P. Mirabueno, A. Mushtaq, S. N. Hossain, D.N. Ogeh, M.P. Sakthivel, A. Parker, M. Perry, I. Piližota, I. Prosovetskaia, J.G. Pérez-Silva, I.A. Ahamed, N. Salam, H. Saraiva-Agostinho, D. Schuilenburg, S. Sheppard, B. Sinha, W. Sipos, E. Stark, R. Steed, D. Sukumaran, M.-M. Sumathipala, L. Suner, K. Surapaneni, M.S. Sutinen, F. Tricomi, D. Urbina-Gómez, A. Veidenberg, T.A. Walsh, B. Walts, E. Wass, N. Willhoft, J. Allen, J. Alvarez-Jarreta, M. Chakiachvili, B. Flint, S. Giorgetti, L. Haggerty, G.R. Ilsley, J.E. Loveland, B. Moore, J.M. Mudge, J. Tate, D. Thybert, S.J. Trevanion, A. Winterbottom, A. Frankish, S.E. Hunt, M. Ruffier, F. Cunningham, S. Dyer, R.D. Finn, K.L. Howe, P.W. Harrison, A.D. Yates, P. Flicek, Ensembl, Nucleic Acids Res. 51 (D1) (2023) D941, https://doi.org/10.1093/nar/gkac958.