Chapter 7

Pharmacogenetics of Cardiovascular Disease: Genetic Variation and Statin Intolerance

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Abstract

Statins are very effective for lowering low-density lipoprotein cholesterol for primary and secondary cardiovascular disease prevention. While statins are usually well tolerated, individual response to statin therapy varies and intolerance, predominantly muscle symptoms, may appear in a significant proportion of patients. Besides clinical factors, variation in genes coding for proteins with drug transporting, immune or enzymatic function have been implicated in the pathogenesis of statin intolerance. In this review, we will characterise the candidate gene variants for development of statin intolerance, describe their population distribution and summarise current knowledge on their biological plausibility. Clinical relevance and current guidelines/recommendations will be also discussed.

Keywords: genetic variation, pharmacogenetics, *SLCO1B1*, statin, statin-induced myopathy

1. Introduction

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase) inhibitors are highly effective drugs lowering plasmatic concentration of LDL-C cholesterol by 30–50% [1]. Despite the fact that they are usually considered safe and very well tolerated, a significant proportion of the treated patients does not tolerate the drug: they suffer from side effects, which may result in non-compliance of patients, drug dose-lowering and even discontinuation of therapy [2–4]. Undesirable effects of statins restrict their administration or reaching LDL-C cholesterol target values and limits effective treatment of patients at risk. Non-adherence or discontinuation of therapy is associated with an increased risk of cardiovascular events [5–7].

By analogy to individual nature of patients´ response to treatment [8–10] there are also inter-individual differences in occurrence and extent of statin intolerance and its symptoms. The knowledge of the risk factors predisposing for intolerance development including characteristic genetic background is crucial for its understanding and prevention. In this chapter we will review the polymorphic gene variants implicated in development of statin intolerance, briefly describe their biological plausibility and characterise clinical relevance.

2. Statin intolerance

Statin intolerance is the inability to tolerate sufficient dose of statin needed to reduce cardiovascular risk due to side effects or intolerance to treatment [11]. The most frequent are muscle symptoms characterised bellow.

2.1. Statin-associated muscle symptoms

Statin-induced muscle symptoms range from myalgia to mild or severe myopathy and even to rare rhabdomyolysis [12]. The symptoms appear in about 75% in the first 10–12 weeks and in 90% of cases in the first 6 months after treatment initiation or dose up titration [13]. The true frequency muscle related side effects has been widely debated: while an observational study reported as much as about 20% of patients on statins [14], clinical trial data suggests frequencies to be equal or lower than 5% [15], however there was a study reporting that clinical trials did not use a standard definition for statin myalgia [16], which may result in underestimated occurrence of statin-induced muscle symptoms. In any case, given very high usage of statins (the third most frequently prescribed drug), even lower relative frequency numbers would mean substantial absolute number of symptomatic patients.

2.2. Clinical-related risk factors

The available data shows that the side effects of statin therapy are group-dependent, time-dependent and dose-dependent; their frequency is greater at a higher statin dose [17].

Endogenous factors known to increase occurrence of side effects are as follows: another lipid-lowering therapy, alcohol abuse, surgery, heavy exercise. Importantly, interactions with medication may be serious [18]; particularly drug interactions likely contribute the susceptibility to statin related muscle symptoms [19].

Further factors predisposing to statin intolerance are: advanced age (>70 year), female sex, race/ethnicity, family history of muscle disorders, vitamin D deficiency, history of creatine elevation, hepatic and renal impartment, hypothyroidism, low body mass index [20].

2.3. Genetic factors

Besides the above characterised factors, genetic "make-up" of a given patient is important component in susceptibility to statin intolerance. Indeed, genetic variation represents the major factor responsible for inter-individual differences in patient responsiveness and their inclination towards undesirable side effects of statins.

3. Genes responsible for statin intolerance

The following section characterises the gene variants that have been implicated in mechanisms of statin intolerance represented by statin-induced myopathy. These are listed in the **Table 1**.

3.1. *SLCO1B1* gene

SLCO1B1 gene encodes the OATP1B1 (organic anion transporting polypeptide), which has been reported to regulate the hepatic uptakes of statins [27, 28]. Strong support for its nomination as a risk factor for statin intolerance came from the GWAS study which investigated genetic variation in 85 subject with myopathy and 90 controls, all taking 80 mg of simvastatin [21]: strong association was identified between statin-induced myopathy and single nucleotide polymorphism (SNP) rs4363657 located within the *SLCO1B1* gene. This noncoding SNP was in nearly complete linkage disequilibrium with the nonsynonymous rs4149056 SNP variant, which has been linked to statin metabolism: the odds ratio for myopathy was 4.5% per one copy of the C allele and 16.9% in CC homozygotes compared with homozygotes for standard allele (TT). More than 60% of observed myopathy cases could be attributed to this particular genetic variation, [21], which is also due to its relatively high population prevalence - rs4149056 C allele frequency is 15%.

3.2. *LILRB5* gene

A potential role for immune system genetic variation in development of statin-induced myopathy has been recently reported for a variant in leukocyte immunoglobulin-like receptor subfamily-B, *LILRB5* gene (rs12975366:T > C:Asp247Gly) [25]. The missense variant Asp247Gly has been associated with serum creatine kinase (CK) levels; the mean levels of this enzyme were elevated in Asp247 homozygotes (TT). The *LILRB5* Asp247 homozygous genotype has, therefore, been associated with increased risk of statin intolerance [25]. No independent replication data on this plausible new variant has been available so far.

Gene	Chromosome	Allele	rs number	Coding variation	Study
SLCO1B1	12p12.2	*5 ≠	rs4149056	521 T > C	[21]
CYP2D6	22q13.1	*3	rs35742686	2549delA	[22]
		*4	rs3892097	splicing defect, G > A	
		*5		gene deletion	
CYP3A4	7q21.1	*1B	rs2740574	-392A > G transition	[23]
GATM	15q15.3	—	rs9806699	G > A, cis-e QTL	[24]
LILRB5	19q13.4	—	rs12975366	T > C: Asp247Gly	[25]
COQ2	4q21.22-q21.23	—	rs6335454	synonymous	[26]
		—	rs4693075	non-coding	

Note: rs, reference sequence; ≠ denotes haplotype (not allele) designation, see Section 4, second paragraph.

Table 1. Gene and their variants implicated in development of statin intolerance presented as statin myopathy.

3.3. *GATM* gene

Glycine amidinotransferase, *GATM* gene encodes a mitochondrial enzyme, which is involved in creatine biosynthesis. SNP rs9806699 within the *GATM* gene has been associated with statin induced myopathy, specifically minor allele A conferring a protective effect and reduced risk of myopathy [24]. However, as this result was not replicated [29], further investigations are required before a possible role for this variation in statin tolerance is clarified.

3.4. Family of cytochrome P450 genes

The cytochrome P450 family is a group of izoenzymes important for catalysing oxidation of xenobiotics. There is a wide spectrum of polymorphic variants affecting various pharmacogenetics aspects. Regarding cardiovascular setting, CYP gene variation plays role in warfarin and clopidogrel metabolism with clear clinical relevance (e.g. [30]). In context of statin adverse drug reaction, Mulder et al. [22] reported higher incidence of statin intolerance in the group of patients who carried two of the less effective *CYP2D6* *3,*4,*5 alleles. Regarding another gene within cytochrome P450 system, namely *CYP3A5*, an association was observed between nonfunctional *CYP3A5**3 allele and the magnitude of CK elevation in case of patients experiencing myalgia during atorvastatin treatment [23]. Importantly, patients who develop myalgia while taking atorvastatin were more likely to experience a greater degree of muscle damage if they express two copies of *CYP3A5**3.

3.5. Other plausible gene variants

COQ2 gene encodes Coenzyme Q2, involved in synthesis of ubiquinon (Coenzyme Q10, CoQ10), a redox carrier in the mitochondrial respiratory chain and a lipid-soluble antioxidant. Two variants within the *COQ2* gene (**Table 1**) have been associated with increased odds of statin intolerance, defined primarily through muscle symptomatology [26]. This observation has been subsequently replicated [31].

From other molecules functioning as drug transporters, *ABCB1* gene variation may also participate in development of statin muscle symptoms. This gene encodes the P-glycoprotein, an independent efflux pump. From its variants, the 1236 T, 2677non-G, and 3435 T alleles were less frequent in cases undergoing statin therapy than in the control group [32]. The authors also demonstrated a reduced T-non-G-T haplotype frequency (20.0%) in patients in whom myalgia developed during simvastatin treatment, as compared with the control, non-myalgia group (41.4%).

Most recently, a variant of a *UGT1* gene coding for uridine diphosphate glucuronosyltransferase, specifically *UGT1A1**28 variant allele (rs8175347), was reported to possess plausible protective effect in development of statin intolerance [33], however again this finding must be replicated.

In the following text we will concentrate on the *SLCO1B1* gene variation and describe its population distribution and clinical relevance. The reason for our focus is that to date, the rs4149056 *SLCO1B1* variant has been repeatedly evidenced to possess the strongest effect in response to statin therapy.

4. Genetic variability and population distribution of *SLCO1B1*

More than 45 nonsynonymous variants in *SLCO1B1* gene have been identified [34]. Some of the variants have altered function [35]. Genotypic frequencies of *SLCO1B1* variants depend on ethnicity, and genetic difference between populations correlated with the geographical distances [34, 36, 37]. In particular, single nucleotide polymorphism the 521 T > C (rs4149056) appeared more commonly in European-Americans while it was less frequent in African-Americans. In opposite, single nucleotide polymorphism the 388A > G (rs2306283) was detected predominantly in African-Americans. Pasanen et al. [38] investigated the frequencies of 12 SNPs in *SLCO1B1* in 941 persons from 52 populations across Europe, Asia, Africa, Middle East, Oceania and the Americas (Amerindians).

SLCO1B1 single nucleotide polymorphisms 521 T > C and 388A > G form four haplotypes: *1A (388A/521 T), *1B (388G/521 T), *5 (388A/521 T) and *15 (388G/521C) [38, 39]. The low activity haplotypes–*5 (388A/521C) and *15 (388G/521C) occur with combined haplotype frequency of approximately 15–20% in Europeans, 10–15% in Asians, 2% in sub-Saharian Africans. The *1B (388G/521 T) haplotype occurs in approximately 26% Europeans, in 39–63% Asians and in 77% sub-Saharian Africans. The haplotypes *5 and *15 are associated with significant reductions of statin hepatic uptake [40], resulting in increase of systemic substrates exposure.

5. Clinical relevance of the variation in the *SCLO1B1* gene

Clinical relevance of the *SCLO1B* variation is based on biological role of its gene products in hepatic transport of statins. Statins are mainly delivered within hepatocytes to their site of actions by uptake transporters and eliminated into the bile by eflux transporters [41]. Many statins are substrates of hepatic uptake transporters including OATP1B1, OATP2B1 and OATP1B3 [28] with OATB1B1 as the main one. The loss of function the *SLCO1B1*5 (Val174Ala, 521 T > C, rs4149056), located in exon 5, downregulates OATB1A1 transporter cell membrane and protein expression [42] which leads to decreased hepatic uptake, greater systemic statin plasma concentrations, and therefore greater muscle statin exposure, all these resulting in adverse effects [20, 36, 43–45].

Importantly, the impact of the rs4149056 variant on statin metabolism appears to differ between distinct statins. The effect of rs4149056 genotypes was much greater for simvastatin, less for atorvastatin and rosuvastatin in healthy volunteers [46, 47]: For simvastatin the area under curve, AUC (0-infinity) was increased by 221% in genotype CC individuals in compared with wild-type TT individuals. For atorvastatin this parameter was increased by 145% and for rosuvastatin by 62%. Individuals carrying C allele also reached maximum concentration (Cmax) earlier, and its value was 200% higher compared with TT individuals of rs4149056 [47]. Further, the rs4149056 polymorphism was significantly associated with simvastatin treatment cases of severe statin induced myopathy, which did not occur after atorvastatin [45] or pravastatin [48] treatment. Similar conclusions regarding simvastatin

Study	Simvastatin dose	Outcome	Reference
SEARCH	80 mg	OR 4.5 per C allele	[21]
		OR 16.9 for CC homozygotes	
Heart protection study	40 mg	OR 2.6 per C allele	[21]
Brunham	10-80 mg	OR 2.3 per C allele	[45]

Note: OR, odds ratio.

Table 2. Basic studies that have reported a strong association between the rs4149056 single nucleotide polymorphism and simvastatin induced myopathy.

were obtained in animal model, again for simvastatin however not for pravastatin or atorvastatin [49]. **Table 2** lists main studies investigating effect of simvastatin on statin intolerance/myopathy in humans.

It is crucial that in agreement with the rules for performing association studies [50] the data obtained in the SEARCH study has been independently replicated within the Heart Protection Study, in 10,000 patients who received 40 mg Simvastatin [21]. The meaningful data obtained in this way provided starting point for reflection of the observations from genetic and pharmacokinetic studies into clinical practice, including formulation of treatment recommendations which will be subject of the next section of our chapter.

6. Testing for statin intolerance in clinic–current status and treatment recommendations

The spectrum of evidence supporting the association between the lead SNP rs4149056 and statin, namely simvastatin-induced myopathy prompted application of the *SLCO1B1* genotyping for clinical usage. This translation to diagnostics aims mainly at reducing risk of simvastatin induced muscle toxicity and at increased adherence to therapy [43, 51, 52]. Another possible outcome of genotyping is the option to use alternate agents of the statin class.

In clinical practice, the adverse effect of *SLCO1B1* polymorphism depends on the genotype (being highest in homozygotes), statin dose and statin type. This has been reflected in the guidance for prescribers provided primarily by the Clinical Pharmacogenetics Implementation Consortium (CPIC); the working group produces guidelines for simvastatin use in individual carriers risk allele in SLCO1B1 gene [43]; the guidelines have been recently updated [53]. In patients with one or two copies of *SLCO1B1* rs4149056 C allele, simvastatin should be avoided or reduced dosage should be considered, pravastatin or rosuvastatin are preferred alternatives according to the CPIC guidelines, however other clinical and patients specific factors should be taken into account [43, 53].

Apart from this general, non-compulsory guidance, there have been more systematic efforts to apply *SLCO1B1* genotyping into practice. This direction is represented e.g. by pre-emptive programs performed from the initiative by U.S. Pharmacogenetics Research Network at eight sites [54]. Similarly, aiming of introducing genotype-guided prescribing, pre-emptive genotyping has

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KEY MESSAGE

- Statins are the basis of dyslipidemia treatment in patients with increased cardiovascular risk.
- Genetic factors may predispose to statin intolerance.
- *SCLO1B1* gene variation has strong association with statin-induced myopathy.
- Guidance for prescribers reflects individual risk for *SLCO1B1* rs4149056 C allele carriers.
- Investigations of clinical relevance of other plausible gene variants are ongoing.

also been investigated in Europe by the EU Horizon 2020-funded Ubiquitous Pharmacogenomics (U-PGx) Consortium (http://upgx.eu) in seven European countries [55]. Last but not least, recommendations were formulated also on a national level - in France: the French National Network of Pharmacogenetics (RNPGx) [56] is in favour of rs4149056 testing before starting therapy or early after treatment onset in patients with one or more risk factors. If the genotype is not known early, the RNPGx considers that a polymorphism test is potentially useful also in the event of already occurring muscle toxicity in patients treated with statins, in order to rule out or confirm a genetic cause. From the above examples it is clear that pharmacogenetic genotyping for prediction/confirmation of statin intolerance undergoes ongoing development and progress; further updates of the recommendations are expected. It should be noted that there have been opinions as well that the current status of knowledge has not been yet sufficient to allow clinical application of genotyping for risk of statin intolerance [52]. There have been several arguments, however especially those economical ("the tests are too costly") are not substantiated; some "con" opinions have been also "traditionalistic", from conservative point of view on doubting any new test or medical management measure including pharmacogenetics. However, this reluctant or at least "sceptical" attitude about pharmacogenetic contribution to routine statin usage, well known also from other applications of pharmacogenetics, has been gradually changing–it only takes time, systematic information on the evidence and particularly education to overcome it [57].

7. Future perspectives including economic aspects of genetic test for statin intolerance

Implementation of a genetic test for statin intolerance into routine practice definitely requires analysing its benefits not only for patients but also for health care providers. In this context, pharmacoecomic data on genetic testing statin intolerance have been scarce. The existing literature on cost-effectiveness of pharmacogenetic testing has been either general [58] or described economic savings solely due to hypolipidemic effect of statins [59]. The first specific data for statin intolerance and its genetic testing appeared only very recently [60]–the authors estimated 356 Canadian dollars as the cost limit for economic feasibility and at the same time dominant health effect for cardiovascular prevention. In extension of this very first report [60], this topic should be, therefore, addressed more intensively and also from other angles in the future. This has been the case with other pharmacogenetic applications (e.g. [61]), it will be also innovative to use new approaches which utilise alternative parameters for assessing effectiveness (e.g. [62–64]).

Though important, inclusion of economic criteria is the only one part of the future priorities in the field of application of genetic variation for testing statin intolerance. Other avenues for future may address (1) further search for and verification of other genetic markers than *SLCO1B1* including providing pharmacokinetic data [65, 66], (2) reflection of ethnic differences in distribution of genetic markers between populations [64, 67], (3) inclusion of the results of genetic test into electronic medical records [68], (4) performing meta-analyses of studies reported so far, and last but not least, (5) performance of well-designed clinical studies implementing also other non-genetic criteria in order to propose a risk-score or clinically applicable algorithm. The existing examples from other pharmacogenetic applications (e.g. [69]) and above described initiatives such as U-PGX [55], RNPGX [56], or the recent idea to provide patients with their DNA (pharmacogenetic) passport [70], allow us to expect further developments targeted at patient benefit and innovation of medical care.

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Conflict of interest

The authors do not report any conflict of interest.

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