VŠEOBECNÁ FAKULTNÍ NEMOCNICE V PRAZE

1. LÉKAŘSKÁ FAKULTA Univerzita Karlova

Pomůže genetika ?

Michal Vrablík

ANO !

Pomůže genetika ?

Děkuji za Vaši pozornost

Neexistuje jedno KVO

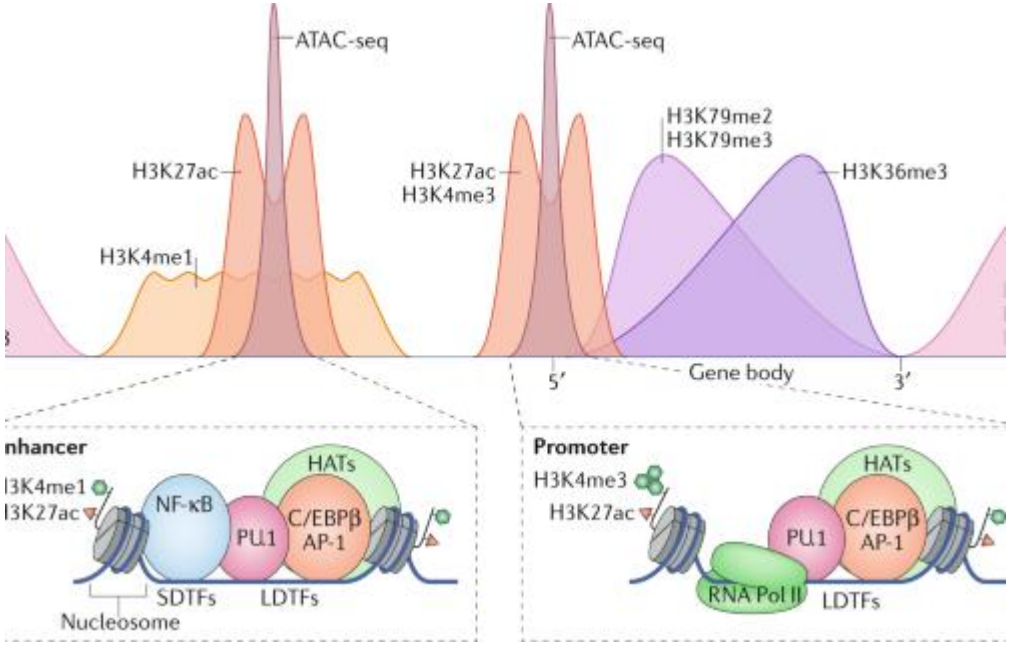
- Behera, Sudhanshu & Pramanik, Krishna & Nayak, Dr. Manasa. (2015). Nedávný pokrok v léčbě kardiovaskulárních onemocnění: konvenční terapie nanotechnologií. Současný farmaceutický design. 21. 10.2174/1381612821666150817104635.

Types of CVD	Description	Symptoms	Risk factors
I. Coronary heart diseases	Ischemic heart disease (IHD); most common type	(i) Heart attack; (ii) Angina at chronic condition	High BP, high BC, tobacco use, unhealthy diet, physical inactivity, diabetes, advancing age, inherited disposition
II. Stroke	Common form of CVD and three categories: (i) Ischemic stroke; (ii) hemorrhagic stroke; (iii) Transient ischemic attack	Brain damage, leading to a sudden impairments; weakness often on one side of the body	High BC, tobacco use, unhealthy diet, physical inactivity, diabetes, and advancing age
III. Rheumatic heart disease and Rheumatic fever	Inflammation of the heart valves and heart muscle caused rheumatic fever (streptococcal bacteria); begins as a sore throat or tonsillitis in children	(i) Shortness of breath, fatigue, irregular heart beats, chest pain and fainting. (ii) Fever, pain and swelling of the joints, nausea, stomach cramps and vomiting	-
IV. Congenital heart disease	Malformations of heart or central blood vessel at birth or during gestation (e.g., hole in heart, abnormal valves, and abnormal heart chambers)	Breathlessness or a failure to attain normal growth and development	Maternal alcohol and medicines use; maternal infection (e.g., rubella); poor maternal nutrition; close blood relationship between parents consanguinity
V. Peripheral vascular disease	Peripheral arterial disease; Two important forms; (i) Atherosclerosis (ii) Abdominal aortic aneurysm	-	Long-standing high BP; Marfan syndrome; tangential heart disorders, syphilis, and other infectious and inflammatory disorders
VI. Deep venous thrombosis (DVT) and pulmonary embolism	The blood clots in the leg veins, which can dislodge and move to the heart and lungs	-	Surgery, obesity, cancer, recent childbirth, use of contraceptive and hormone replacement therapy, long periods of immortality and previous episode of DVT
VII. Other cardiovascular diseases	Tumors of the heart; vascular tumors of the brain; disorders of heart muscle (cardiomyopathy); heart valve diseases	-	-

[BP: Blood pressure; BC: Blood cholesterol]

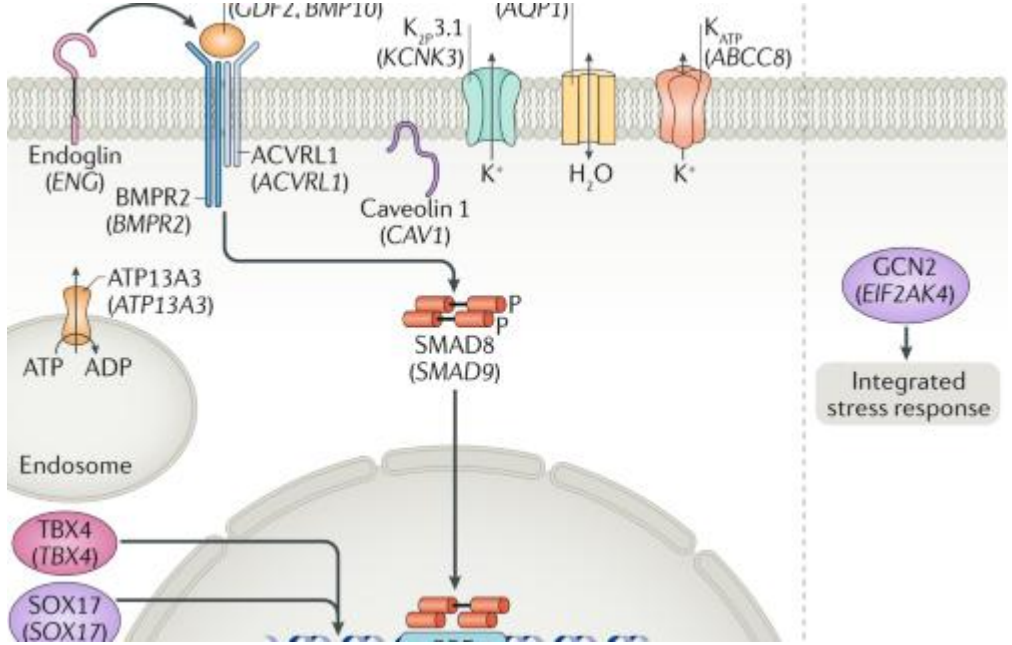
Tedy není ani jedna genetika KVO

Transkripční a epigenetická regulace makrofágů při ateroskleróze



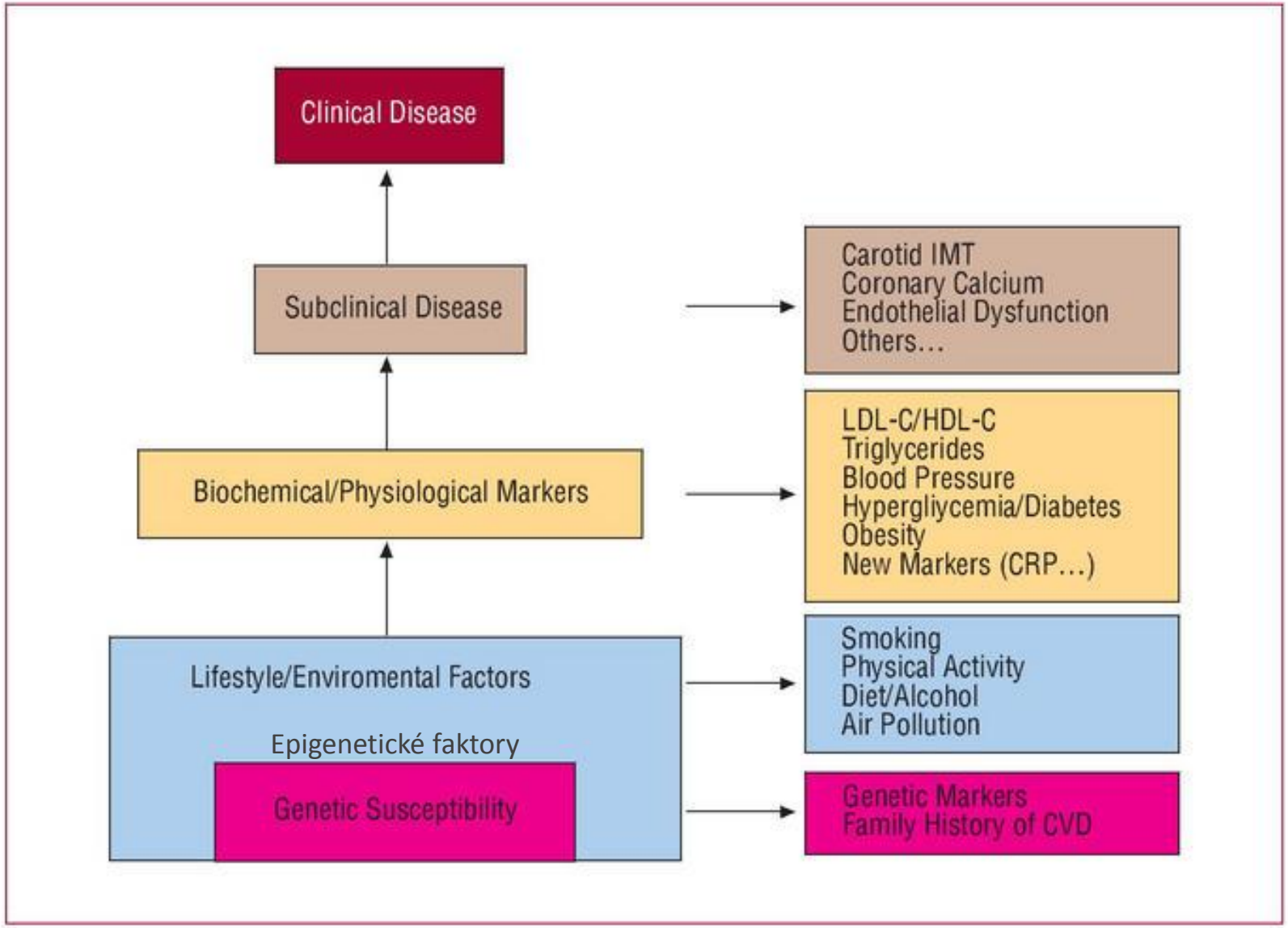
Kuznetsova , T., Prange , KHM, Glass , CK *et al.* Transkripční a epigenetické regulace makrofágů při ateroskleróze . *Nat Rev Cardiol* **17,** 216–228 (2020).

Molekulárně genetický rámec, který je základem plicní arteriální hypertenze



Southgate , L., Machado , RD, Gräf , S. *a kol.* Molekulární základní genetický rámec plicní arteriální hypertenze . *Nat Rev Cardiol* **17,** 85–95 (2020).

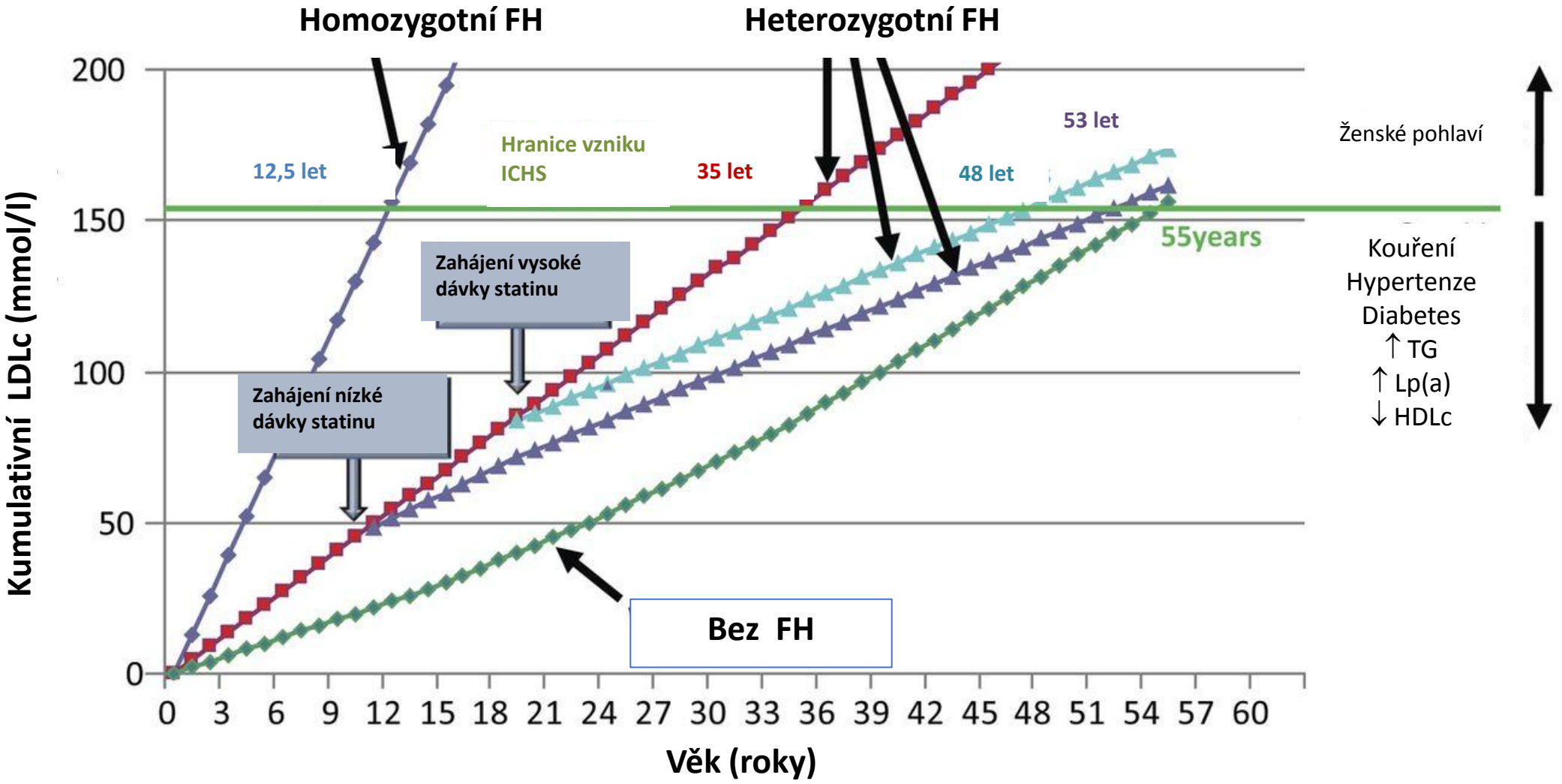
Genetické faktory ve vývoji onemocnění : dlouhá cesta od genotypu k fenotypu



Význam genetických rizik pro cévní zdraví: kumulativní expozice

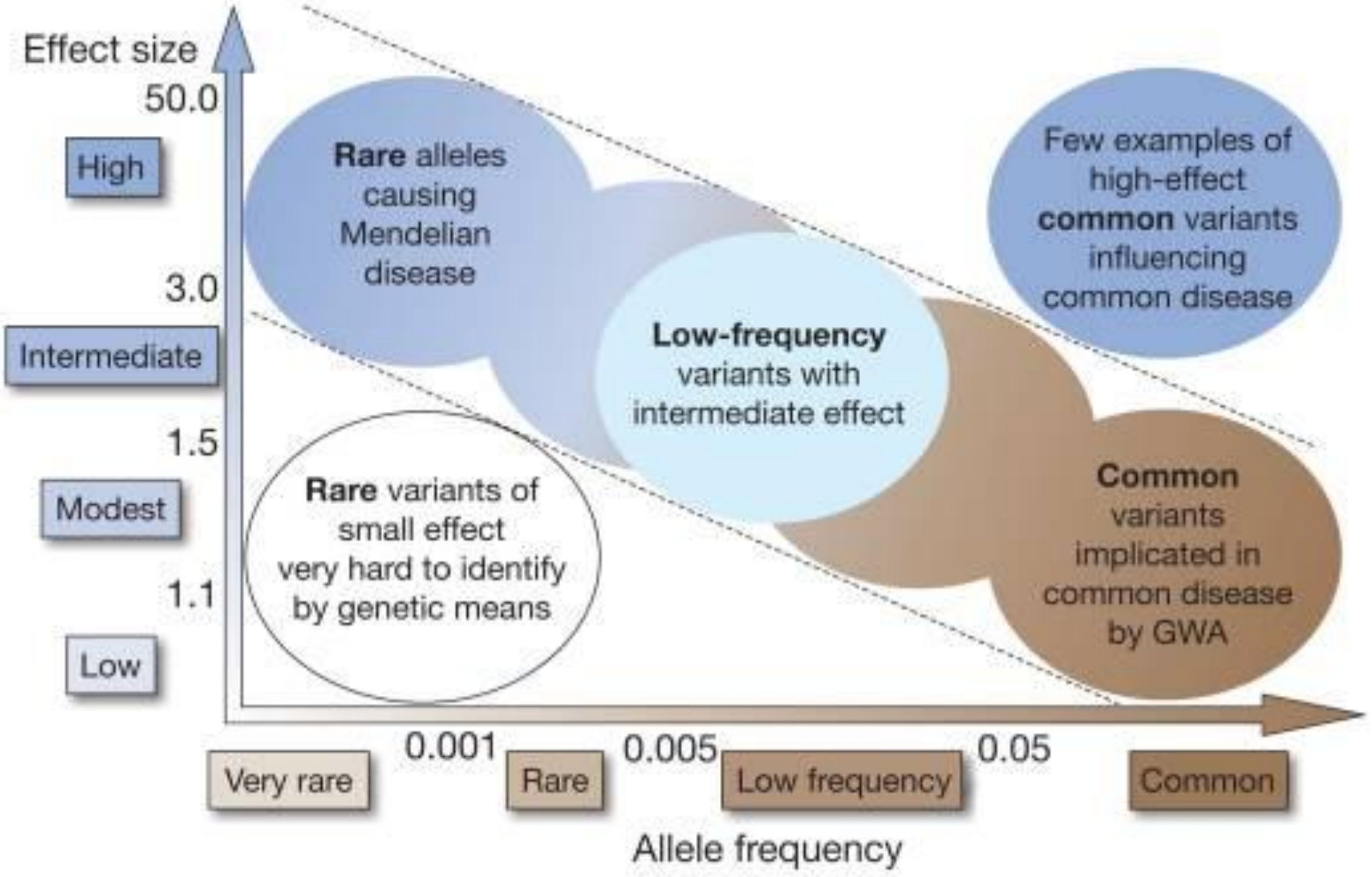
FH = dramatické urychlení cévních změn

Riziko vzniku ICHS při celoživotně velmi vysoké hladině LDLc



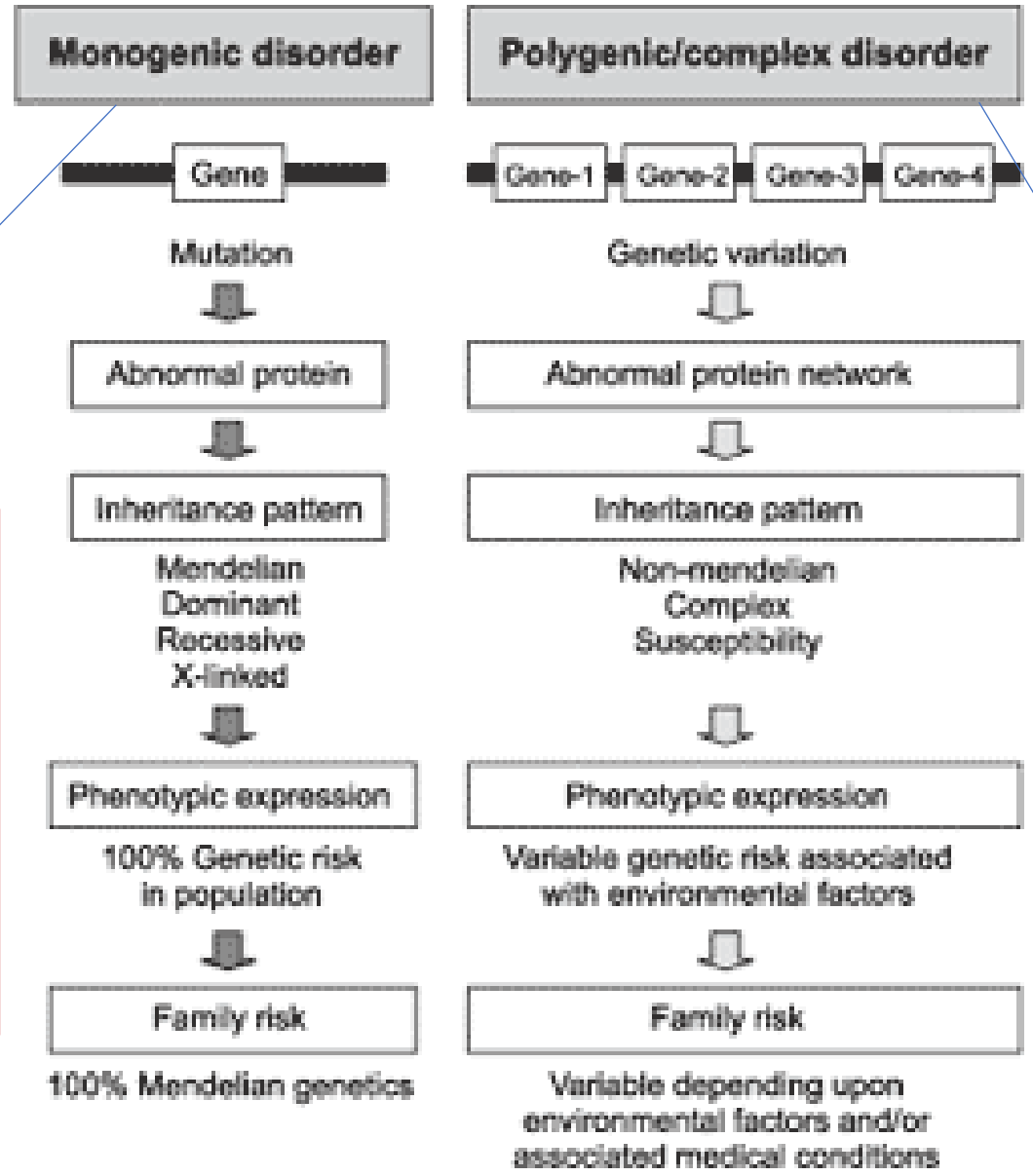
Vrablík M. Hypertenze a KV prevence, 2015, 4: 44-49.

Frekvence rizikových znaků a jejich vliv na fenotyp



Manolio a kol. Příroda 2009. 461(7265): 747–753

Monogenní a polygenní determinace



Vzácný

Penetrance

Variabilita fenotypu

Fenotyp od narození

Environmentální faktory

dopad

Častější

Penetrance

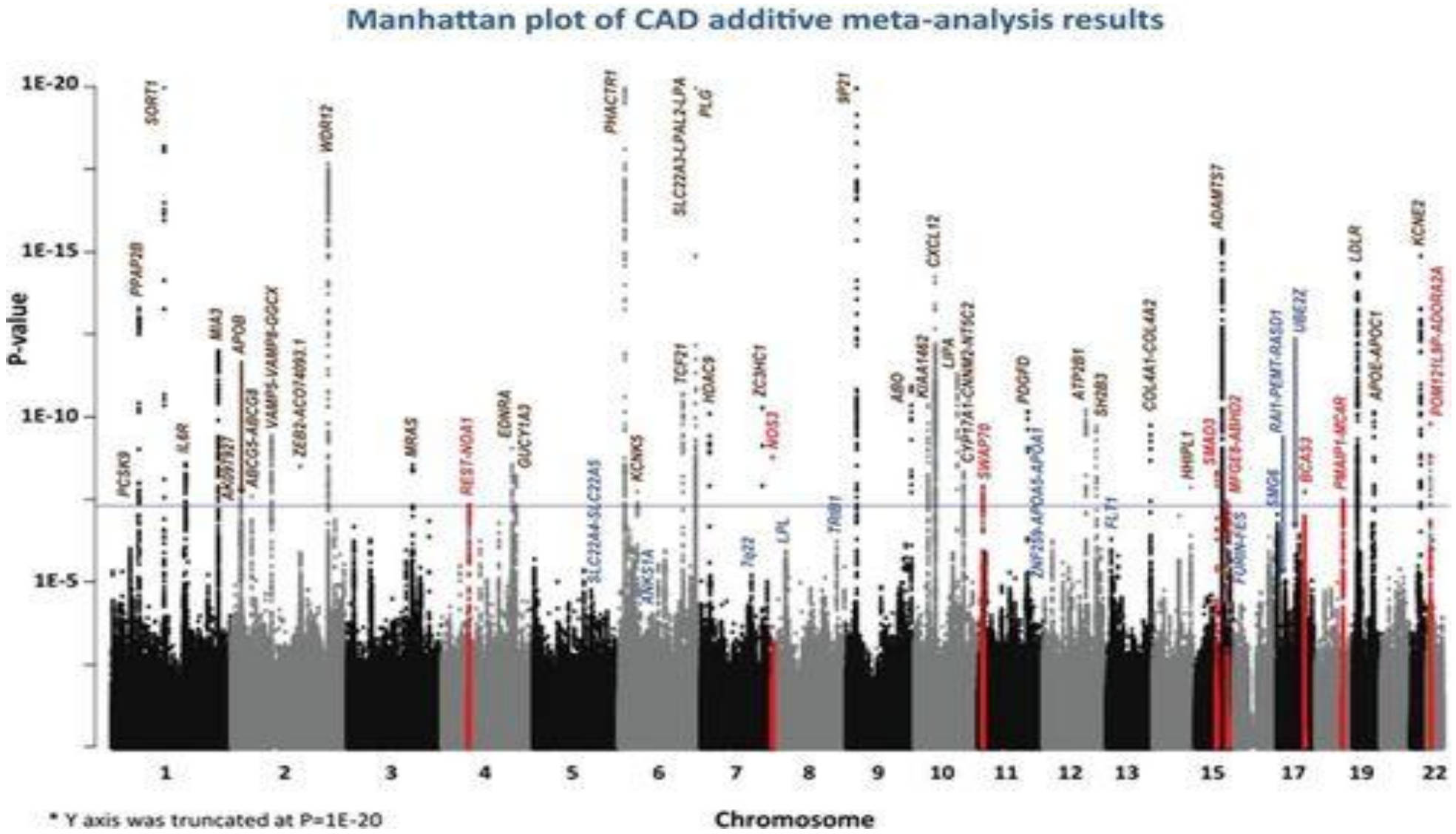
Variabilita fenotypu

Fenotyp během života

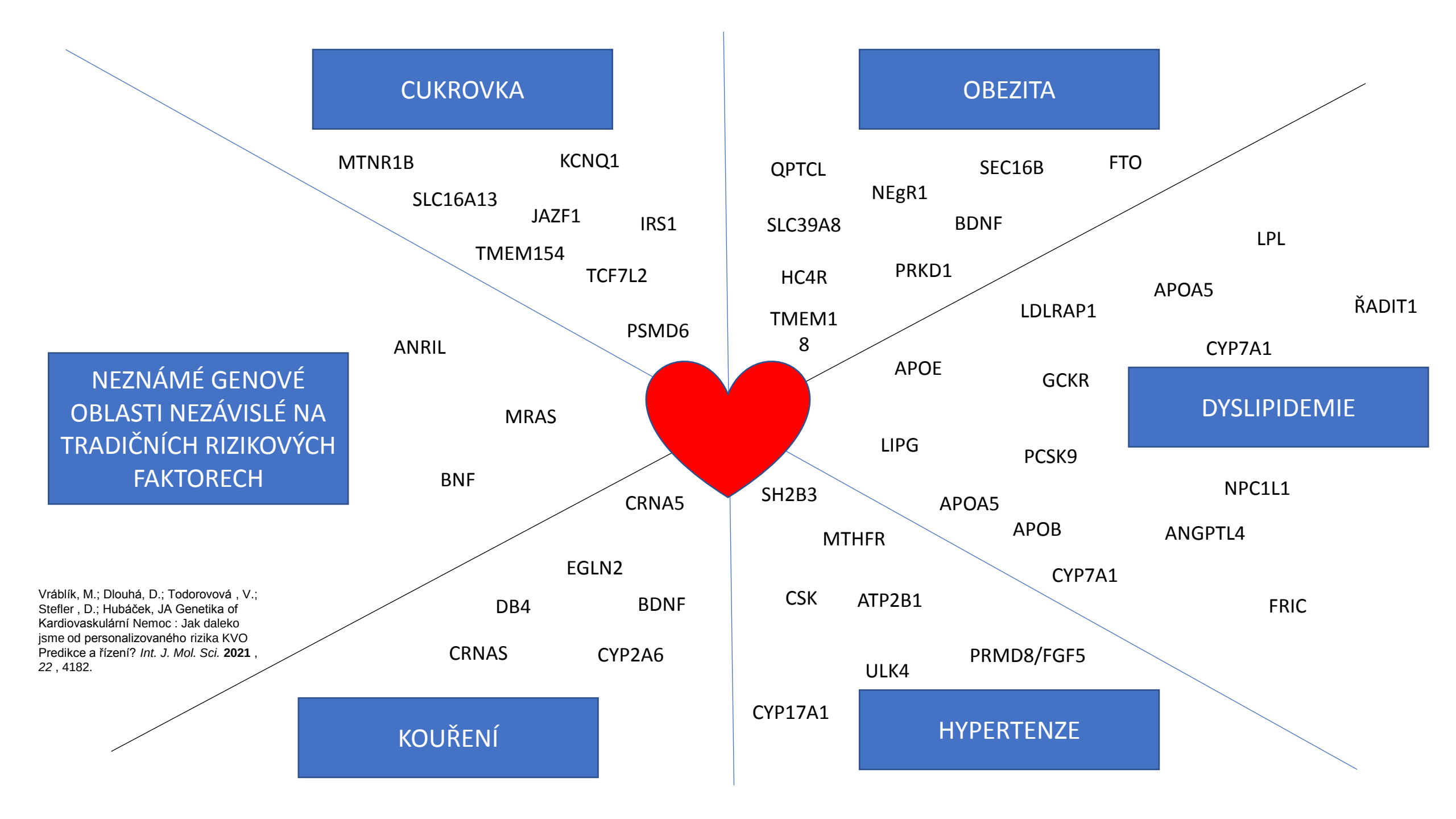
Environmentální faktory

dopad

Které genové lokusy se podílí na vývoji ASKVO?



Ruth McPhersonová. Výzkum krevního oběhu. Genetics of Coronary Artery Disease, svazek: 118, vydání: 4, strany: 564-578, DOI: (10.1161/CIRCRESAHA.115.306566)



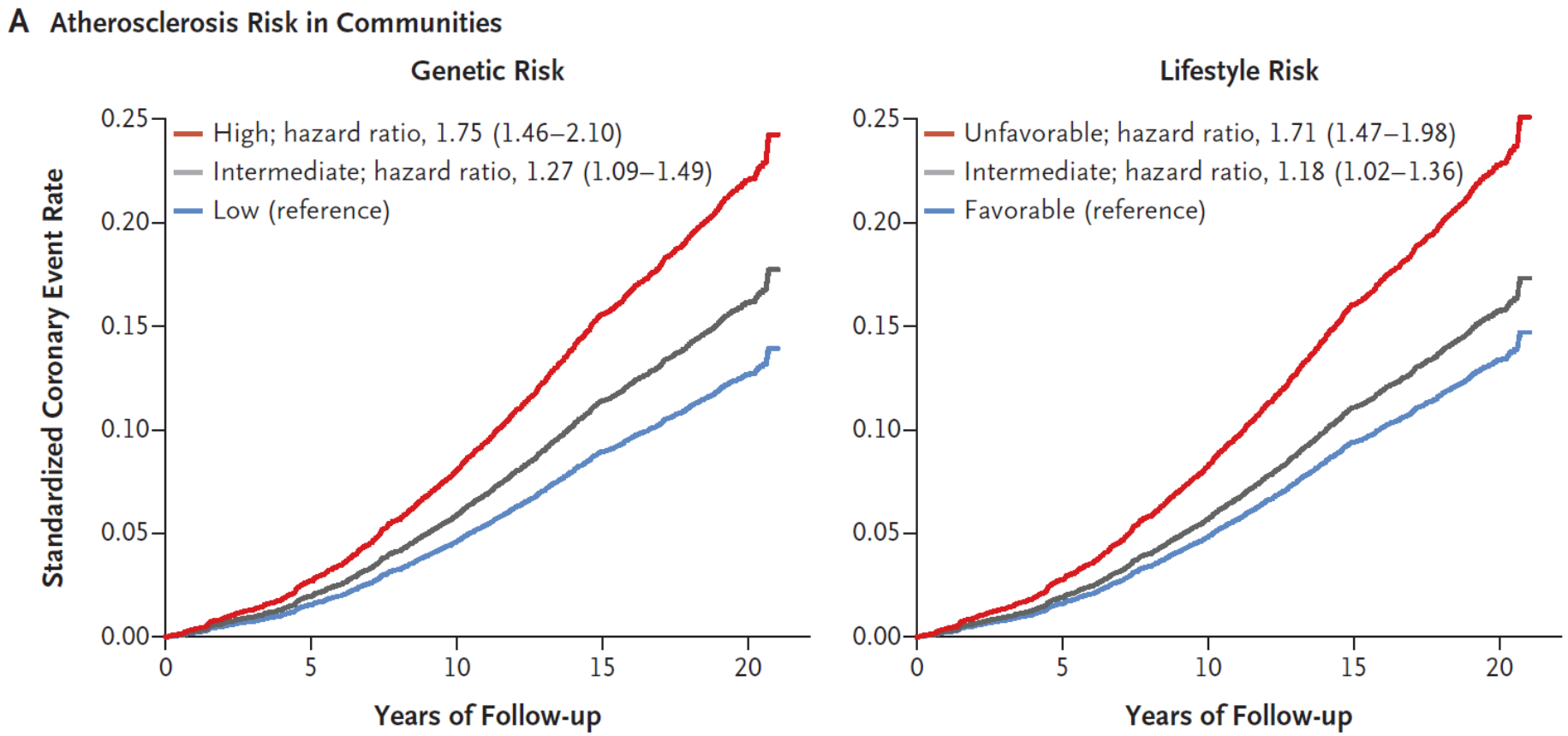
Vráblík, M.; Dlouhá, D.; Todorovová , V.; Stefler , D.; Hubáček, JA Genetika of Kardiovaskulární Nemoc : Jak daleko jsme od personalizovaného rizika KVO Predikce a řízení? *Int. J. Mol. Sci.* **2021** , *22* , 4182.

Epigenetika : vše je ještě složitější...

miRNA	Function
miR-15 family, miR-34 family, miR-499, miR-320, miR-24, miR-1, miR-16, miR-21, miR-92a, miR-375, miR-103/107, miR-133a/b, miR-214	Differently regulated in heart tissue in response to myocardial infarction
miR-34a, miR-217, miR-146a	Endothelial cell senescence
miR-126, miR-31, miR-17-3p	Vascular inflammation
miR-21, miR-221, miR-222, miR-143/145 cluster, miR-1, miR-10a	SMC (smooth muscle cell) differentiation, survival, proliferation, and dedifferentiation
miR-155, miR-125a-5p	Monocytes/macrophages lipid uptake and inflammatory responses
miR-146a, miR-128, miR-365, miR-503	Effect on migration of macrophages
miR-33, miR-302a, miR-122, miR-370, miR-335, miR-378, miR-27, miR-125a-5p, miR-33a/b, miR-144, miR-223, miR-148a, miR-128-1	Cholesterol homeostasis and fatty acid oxidation

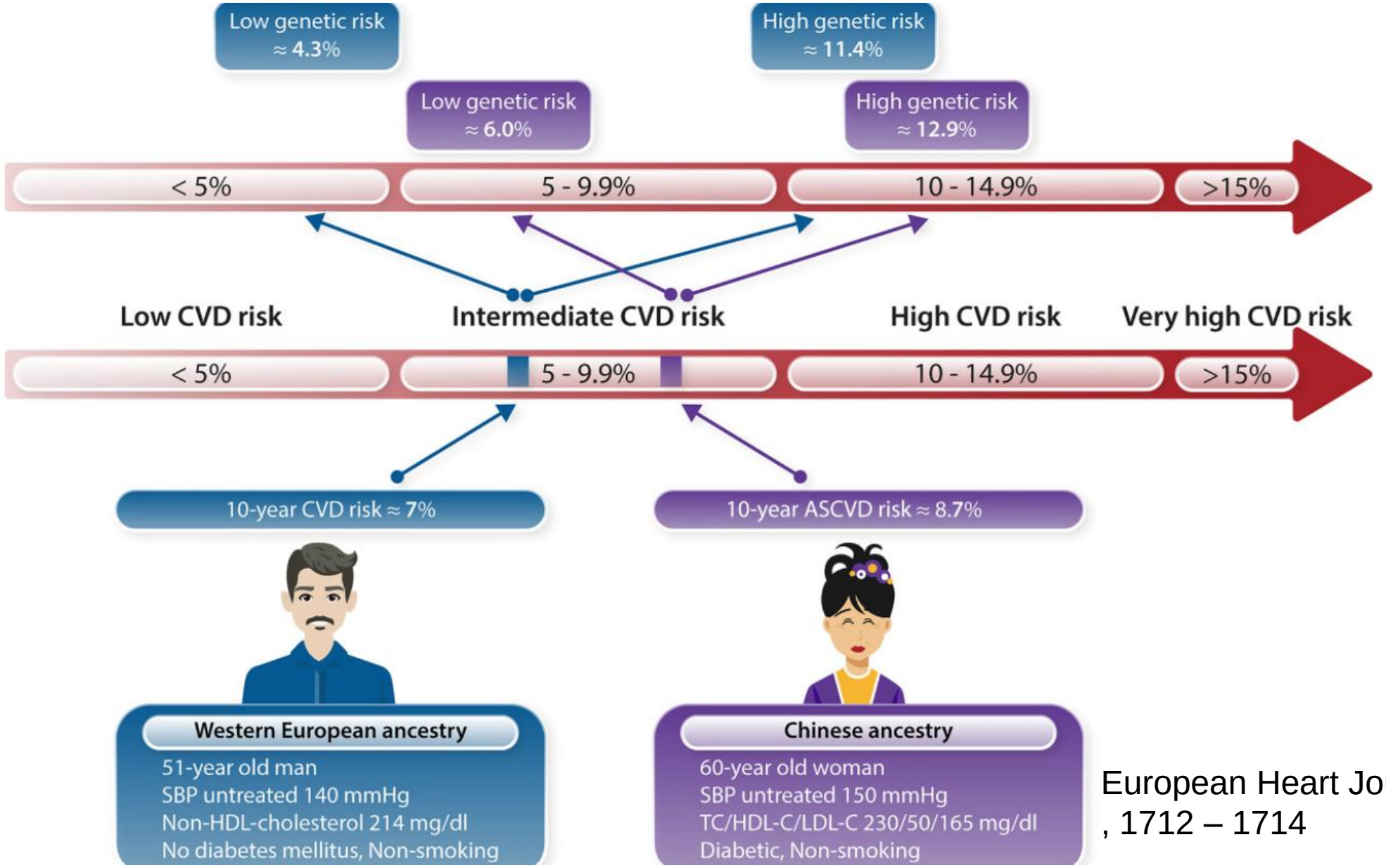
Vráblík, M.; Dlouhá, D.; Todorovová , V.; Stefler , D.; Hubáček, JA Genetika of Kardiovaskulární Nemoc : Jak daleko jsme od personalizovaného rizika KVO Predikce a řízení? *Int. J. Mol. Sci.* **2021** , *22* , 4182.

Genetické faktory a faktory životního stylu stejně důležité při určování rizika ASKVO



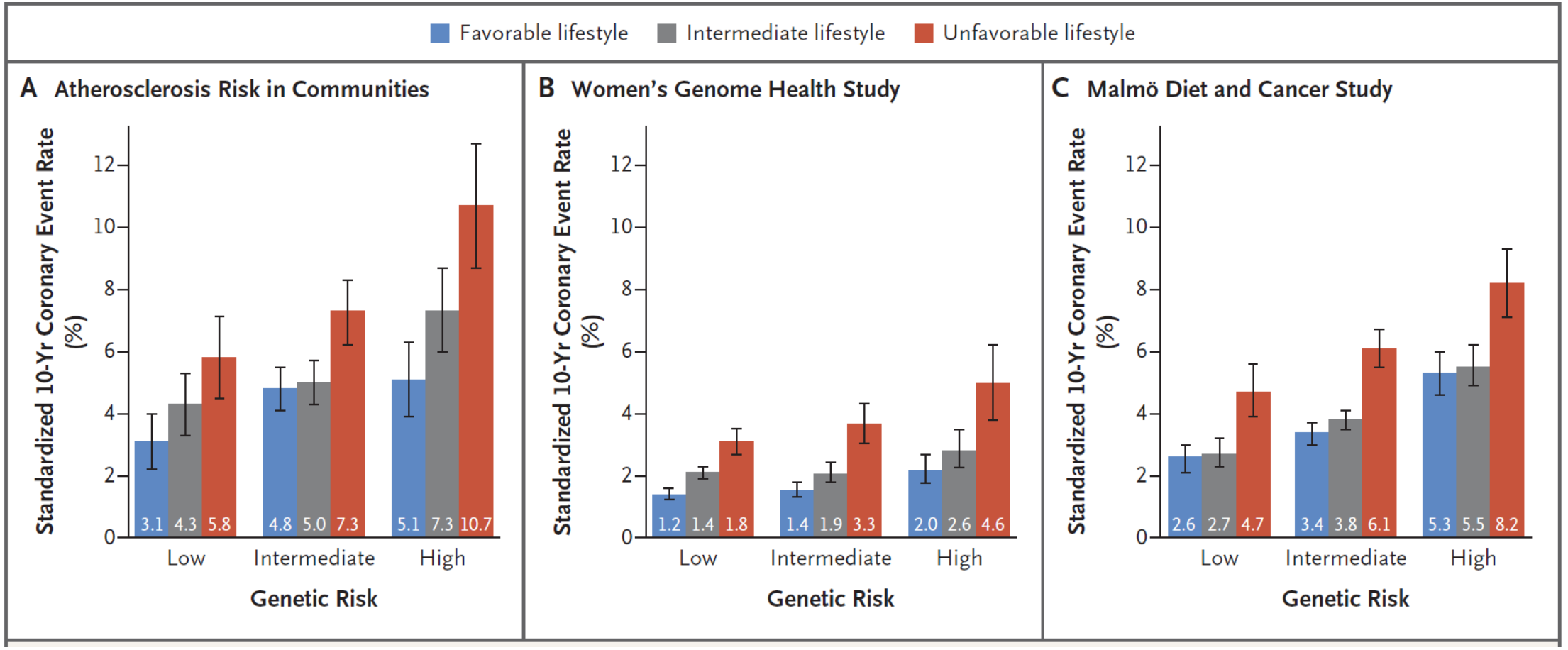
Khera, Emdin a kol. N Engl J Med 2016; 375:2349-2358

Polygenní rizikové skóre (PRS) a KV riziko



European Heart Journal (2022) 4
, 1712 – 1714

Zdravý životní styl: důležitý pro všechny, ale zvláště pro ty s genetickým rizikem ASKVO



Khera, Emdin a kol. N Engl J Med 2016; 375:2349-2358

Veškerý výzkum a uznání genetiky význam v predikci rizika ASCVD měl za následek …

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–111
doi:10.1093/eurheartj/ehab484

ESC GUIDELINES

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

Recommendations for patients with lower extremity artery disease: best medical therapy

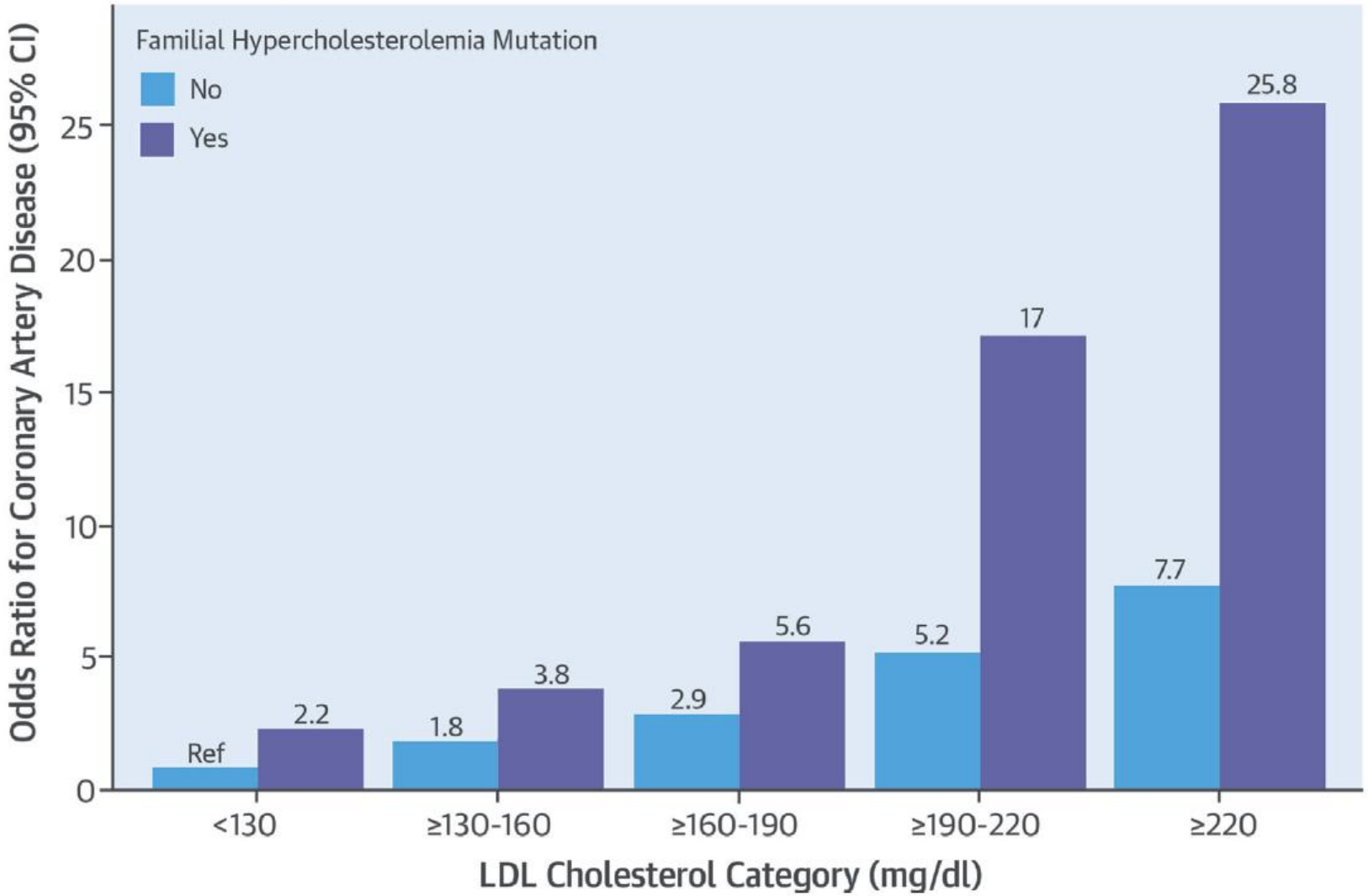
Recommendations	Class[a]	Level[b]
Smoking cessation is recommended in all patients with LEAD.[29,781]	I	B
Healthy diet and PA are recommended for all patients with LEAD.	I	C
In patients with intermittent claudication: • Supervised exercise training is recommended[782–784]	I	A

Risk factors and clinical conditions

2016 CVD Prevention Guidelines	Class	2021 CVD Prevention Guidelines	Class
ABI may be considered as a risk modifier in CVD risk assessment.	IIb	The routine collection of other potential modifiers, such as genetic risk scores, circulating or urinary biomarkers, or vascular tests or imaging methods (other than CAC scoring or carotid ultrasound for plaque determination), is not recommended.	III

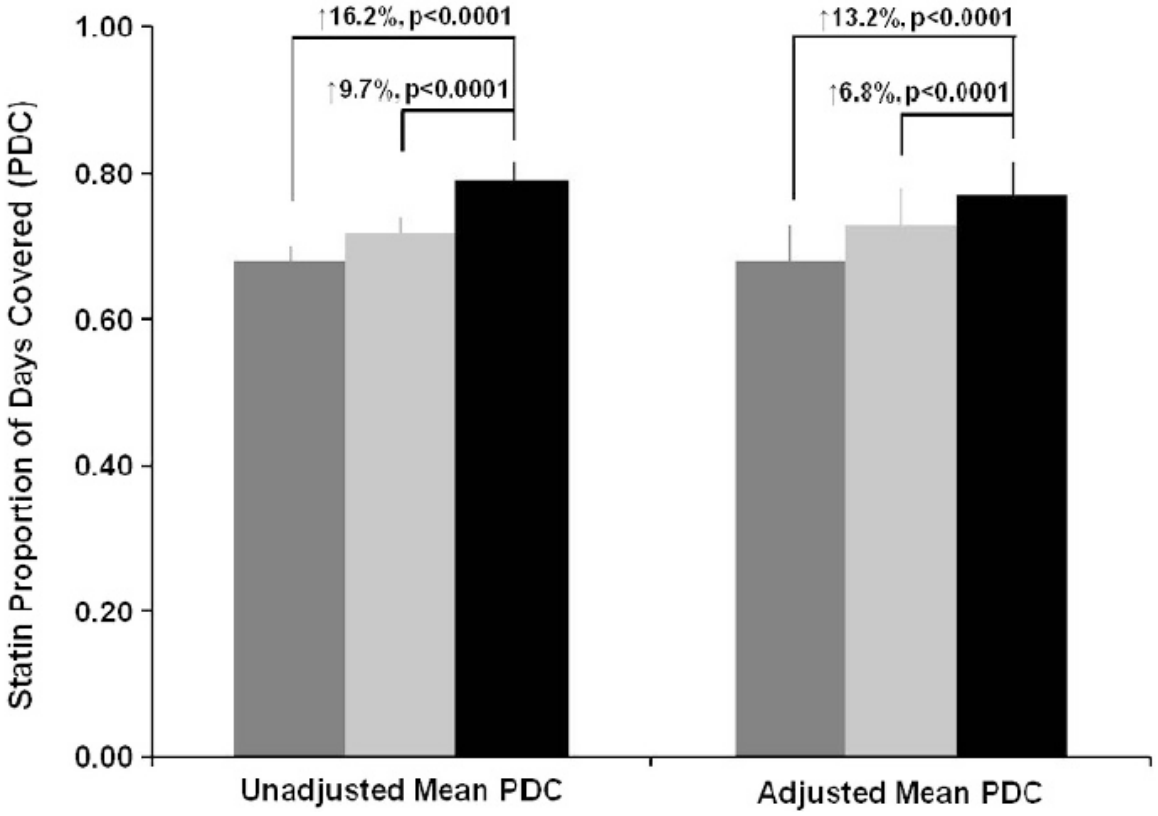
Genetický výsledek pomůže s volbou terapie

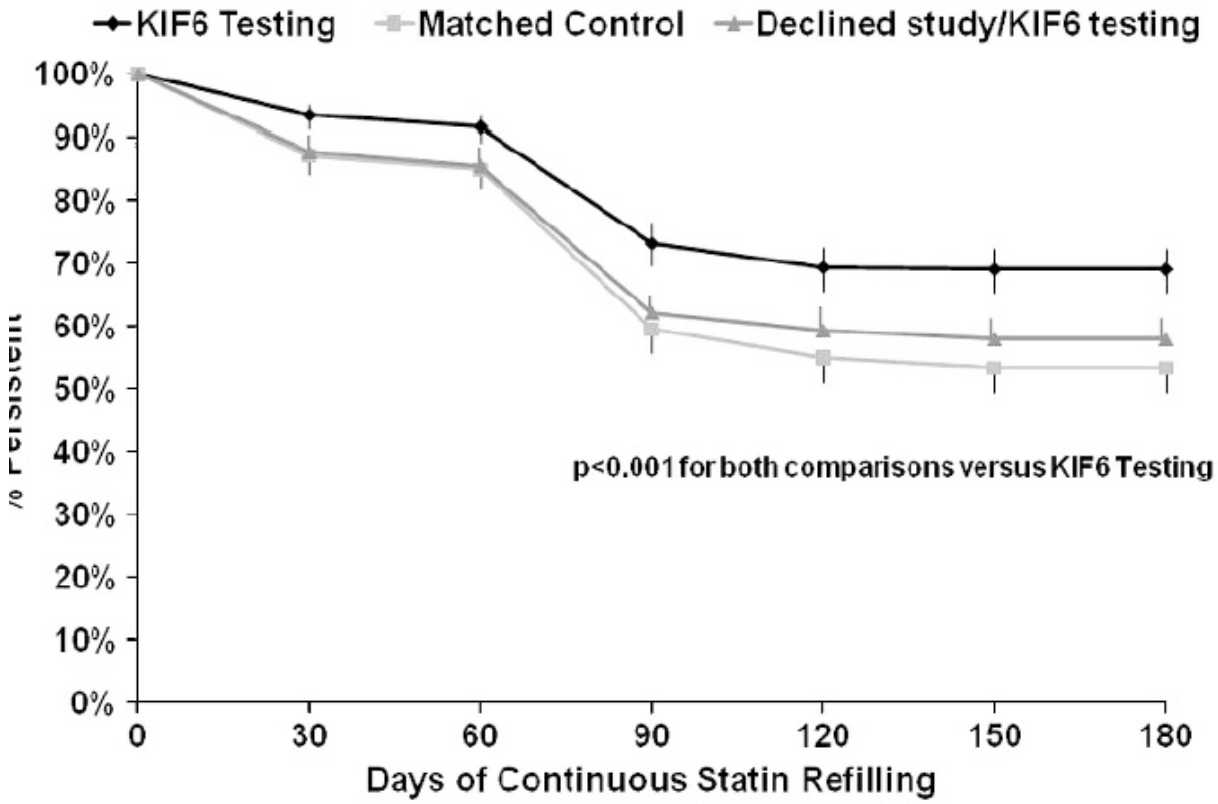
Mutace genu LDL-R nosiče (FH) mají výrazně zvýšené riziko KV příhody bez ohledu na hladinu LDL-C



Khera AV a kol. JACC 2016, 67: 2578-2589

Genetika pomůže prakticky: zlepšení adherence





Charland et al. Pharmacogenomics Journal (2014) 14, 272–280

I nežádoucí účinky léčby podmiňuje genetika

Physiol. Res. 63 (Suppl. 3): S327-S334, 2014 https://doi.org/10.33549/physiolres.932865

REVIEW

Statin-Associated Myopathy: From Genetic Predisposition to Clinical Management

M. VRABLIK[1], L. ZLATOHLAVEK[1], T. STULC[1], V. ADAMKOVA[2], M. PRUSIKOVA[1], L. SCHWARZOVA[1], J. A. HUBACEK[3], R. CESKA[1]

[1]Third Department of Internal Medicine, First Faculty of Medicine, Charles University, Prague, Czech Republic, [2]Department of Preventive Cardiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic, [3]Center for Experimental Medicine, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

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Summary

Statin-associated myopathy (SAM) represents a broad spectrum of disorders from insignificant myalgia to fatal rhabdomyolysis. Its frequency ranges from 1-5 % in clinical trials to 15-20 % in everyday clinical practice. To a large extent, these variations can be explained by the definition used. Thus, we propose a scoring system to classify statin-induced myopathy according to clinical and biochemical criteria as 1) possible, 2) probable or 3) definite. The etiology of this disorder remains poorly understood. Most probably, an underlying genetic cause is necessary for overt SAM to develop. Variants in a few gene groups that encode proteins involved in: i) statin metabolism and distribution (e.g. membrane transporters and enzymes; OATP1B1, ABCA1, MRP, CYP3A4), ii) coenzyme Q10 production (e.g. COQ10A and B), iii) energy metabolism of muscle tissue (e.g. PYGM, GAA, CPT2) and several others have been proposed as candidates which can predispose to SAM. Pharmacological properties of individual statin molecules (e.g. lipophilicity, excretion pathways) and patients' characteristics influence the likelihood of SAM development. This review summarizes current data as well as our own results.

Key words

Statins • Statin associated myopathy • Definition • Risk score • Genetics

Corresponding author

M. Vrablik, Third Department of Internal Medicine, General University Hospital, U Nemocnice 1, 128 08 Prague 2, Czech Republic. Fax: +420 224 966 677. E-mail: michal.vrablik@vfn.cz

Introduction

Statins are an extremely powerful and well-established class of drugs. Numerous experimental and clinical data support their use for a wide range of indications and clinical situations. Most patients treated with statins tolerate statins without difficulty; even long-term treatment has not been associated with deleterious impact to any particular organ system. Given the increasing number of indications for statins and the growing number of users, more attention has been drawn to the side effects of statin therapy. Contrary to randomized clinical trials, where the occurrence of adverse reactions ranges between 1 and 5 %, actual clinical experience, as reported in the literature, suggests that the number of undesirable effects stemming from statin use is much higher (15-20 %).

Statin-associated myopathy (SAM) represents one of the most significant and frequent side effects of these drugs, and it is estimated that up to two thirds of all statin-related side effects involve muscle tissue (Raju *et al.* 2013). Observational studies suggest that 10-15 % of statin users develop some type of muscle problem (Abd and Jacobson 2011). It is estimated that almost 30 % of statin discontinuations occur within the first year of treatment and are most likely due to adverse side effects (Kamal-Bahl *et al.* 2007). Despite the literature being relatively rich on this topic, uncertainty continues and ranges from its definition and underlying

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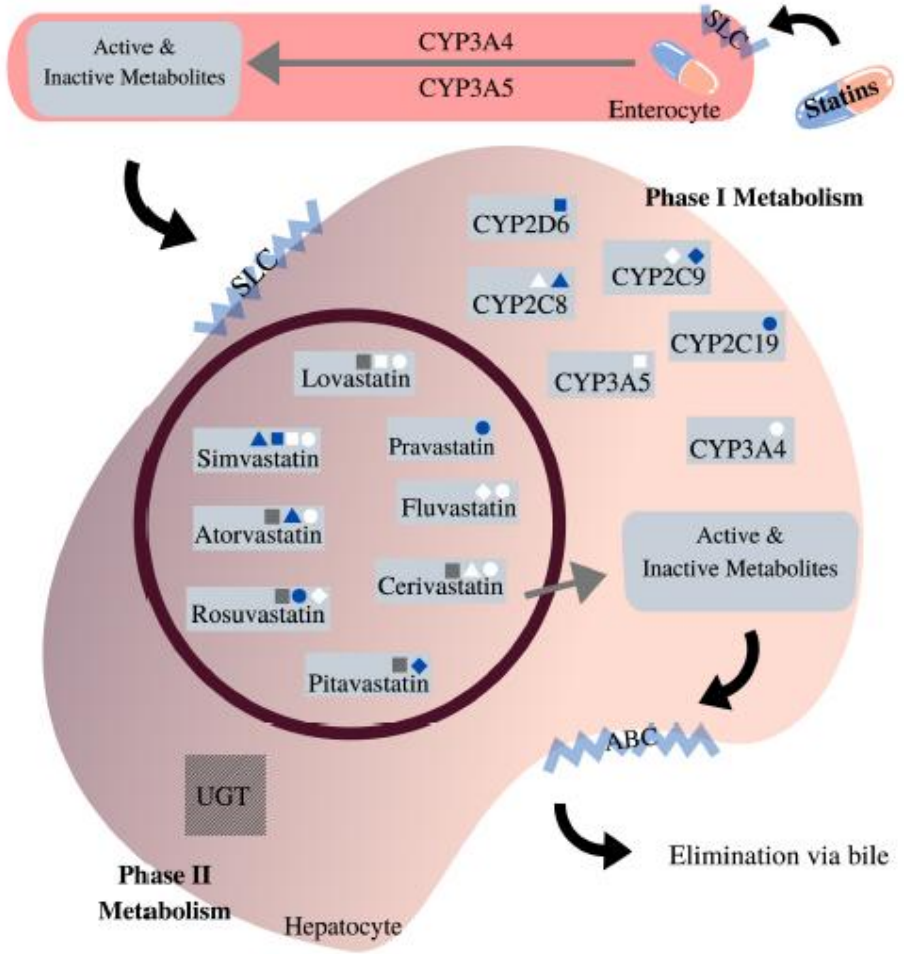

Kee SP et al. Pharmacogenetics of statin-induced myotoxicity, Frontiers in genetics. October 2020 | Volume 11 | Article 575678

Je mi 55 let, nic mi není, mám vysoký cholesterol a nebudu užívat statin, ale...

Máte vysoké geneticky podmíněné riziko = ↑ expozice

Užíváním léků pravidelně lze riziko snížit

Nemáte genetické faktory zvyšující riziko NÚ

...a máme spoustu nestatinových možností ☺

Děkuji za pozornost