EBioMedicine 28 (2018) 311–315

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

Disconnect Between Genes Associated With Ischemic Heart Disease and Targets of Ischemic Heart Disease Treatments

C.M. Schooling [a,b,*], J.V. Huang [b], J.V. Zhao [b], M.K. Kwok [b], S.L. Au Yeung [b], S.L. Lin [b]

[a] CUNY Graduate School of Public Health and Health Policy, New York, USA
[b] School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

ARTICLE INFO

Article history:
Received 9 December 2017
Received in revised form 15 January 2018
Accepted 16 January 2018
Available online 31 January 2018

Keywords:
Ischemic heart disease
Gene
Treatment

ABSTRACT

Background: Development of pharmacological treatments to mitigate ischemic heart disease (IHD) has encompassed disappointing results and expensive failures, which has discouraged investment in new approaches to prevention and control. New treatments are most likely to be successful if they act on genetically validated targets. We assessed whether existing pharmacological treatments for IHD reduction are acting on genetically validated targets and whether all such targets for IHD are currently being exploited.

Methods: Genes associated with IHD were obtained from the loci of single nucleotide polymorphisms reported in either of two recent genome wide association studies supplemented by a gene-based analysis (accounting for linkage disequilibrium) of CARDIoGRAMplusC4D 1000 Genomes, a large IHD case (n = 60,801)-control (n = 123,504) study. Treatments targeting the products of these IHD genes and genes with products targeted by current IHD treatments were obtained from Kyoto Encyclopedia of Genes and Genomes and Drugbank. Cohen's kappa was used to assess agreement.

Results: We identified 173 autosomal genes associated with IHD and 236 autosomal genes with products targeted by current IHD treatments, only 8 genes (*PCSK9*, *EDNRA*, *PLG*, *LPL*, *CXCL12*, *LRP1*, *CETP* and *ADORA2A*) overlapped, i.e. were both associated with IHD and had products targeted by current IHD treatments. The Cohen's kappa was 0.03. Interventions related to another 29 IHD genes exist, including dietary factors, environmental exposures and existing treatments for other indications.

Conclusions: Closer alignment of IHD treatments with genetically validated physiological targets may represent a major opportunity for combating a leading cause of global morbidity and mortality through repurposing existing interventions.

1. Introduction

Great progress has been made in the prevention and control of cardiovascular disease over the last 50 years (Ezzati et al., 2015). Nevertheless, cardiovascular disease remains the leading cause of global morbidity and mortality. Cardiovascular disease has long been acknowledged to be incompletely understood, with patterns of disease and trends that cannot be explained by existing risk factors and treatments (Ezzati et al., 2015; Marmot et al., 1975). Development of new cardiovascular disease treatments targeting risk factors, such as high density lipoprotein-cholesterol and inflammatory markers, has encompassed disappointing results and expensive late-stage failures (Jackson et al., 2016; Lincoff et al., 2017; Ridker et al., 2017; O'Donoghue et al., 2016). In some cases these failures have subsequently been explained by the treatments not acting on genetically validated targets, for example for varespladib and darapladib (Gregson et al., 2017; Talmud and Holmes, 2015). Investment in drug development for cardiovascular disease is currently not commensurate with the burden of disease (Moses et al., 2015).

Recently, genome wide association studies (GWAS) of single genetic variants have enabled significant progress to be made in unraveling the causes of ischemic heart disease (IHD) with as much as 21% of the heritability of IHD potentially explicable (Nelson et al., 2017). This development provides a new opportunity to provide an overall assessment of the extent to which existing pharmacological treatments for IHD prevention and control are exploiting genetically validated targets and conversely to identify whether any other existing treatments are targeting the products of genes strongly associated with IHD and so could potentially be repurposed. Here, we examined three complimentary questions; first whether genetically valid targets for IHD are being exploited by current pharmacological IHD treatments, second whether existing pharmacological treatments for IHD are acting on genetically valid targets, and third whether any additional pharmacological

Abbreviations: IHD, ischemic heart disease; GWAS, genome wide association study; SNP, single nucleotide polymorphism; KEGG, Kyoto Encyclopedia of Genes and Genomes.

* Corresponding author at: 55 West 125th St, New York, NY 10027, USA.
E-mail address: mary.schooling@sph.cuny.edu (C.M. Schooling).

https://doi.org/10.1016/j.ebiom.2018.01.015

treatments or nutraceuticals exist likely exploiting the products of other genes strongly associated with IHD.

2. Methods

Genes strongly associated with IHD were obtained in two ways. First, genes were identified from the loci of single nucleotide polymorphisms (SNPs) associated with IHD at genome wide significance (SNP-based GWAS) in either of two recent IHD GWAS (Nelson et al., 2017; Howson et al., 2017), largely concerning people of European descent and based on the CARDIoGRAMplusC4D consortia. Second, genes associated with IHD at genome wide significance were identified from a gene-based test applied to CARDIoGRAMplusC4D 1000 Genomes (cases = 60,801, controls = 123,504) (Nikpay et al., 2015). A gene-based test has the advantage of considering genetic variants in naturally occurring functional units, i.e., genes, whose products potentially correspond to targets of intervention, because treatments usually target specific gene products.

To identify the extent to which the genes associated with IHD are exploited by current pharmacological IHD treatments, we used two curated gene to drug cross-references, Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa et al., 2014) and Drugbank (Wishart et al., 2008), to identify whether the genes strongly associated with IHD had products targeted by existing IHD treatments. To identify whether existing pharmacological treatments for IHD are acting on genetically validated targets we used the same cross-references to identify the genes with products targeted by pharmacological IHD treatments and the gene-based test to assess their association with IHD. Finally, we identified any other existing, but not investigational, pharmacological treatments or nutraceuticals targeting products of genes strongly associated with IHD as candidate interventions for potentially repurposing as new IHD treatments.

Existing IHD treatments were defined as approved therapies for primary or secondary prevention or treatment of IHD, considered as treatments for the following conditions affecting the Cardiovascular System: “Hyperlipidaemia”, “Hypertension”, “Diuresis”, “MI, LVD”, “Thromboembolic disorders” and “Angina”, and the following categories for Diabetes: “Oral and parenteral hypoglycaemics” and “Insulins” given in MIMS UK (http://www.mims.co.uk/conditions). We did not include devices or tests. The complete list of drugs considered is given in Supplementary Table 1. We included any treatment or nutraceutical reported as relevant to a gene of interest from KEGG or Drugbank. Only autosomal genes were considered because genetic associations with the X and Y chromosomes are more complex to unravel, rarely investigated and are not available in the CARDIoGRAMplusC4D consortia. Two people conducted these searches independently in mid-January 2018.

2.1. Statistical Analysis

To obtain p-values for the association of each autosomal gene with IHD, we used a gene-based association test with an extended Simes procedure taking linkage disequilibrium into account (Li et al., 2012). To conduct this test we used a Gene-based Association Test using Extended Simes (GATES), which is a Simes test adjusted for the linkage disequilibrium of the p-values (Li et al., 2012). GATES has the advantage of not requiring simulations and provides a validated approximation to other methods (Bacanu, 2012). Linkage disequilibrium was obtained from the 1000 Genomes catalog. We used a p-value cut-off of 1.96×10^{-6} for genome wide Bonferroni corrected significance of a gene (i.e., 0.05/25463 genes). We also identified genes associated with IHD at a 5% false discovery rate on the gene-based test. Cohen's kappa was used to assess the agreement between the genes identified as associated with IHD and the genes targeted by existing IHD treatments.

This analysis of publicly available data does not require ethical approval.

2.2. Role of the Funding Source

This study was partly funded by PSC-CUNY Award # 68528-00 46. The funders had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, or approval of the manuscript.

3. Results

Table 1 shows that in total 173 autosomal genes were identified as strongly associated with IHD. Supplementary Table 2 shows that 119 genes were identified from the 109 loci recently reported as associated with IHD using SNP-based GWAS (Nelson et al., 2017; Howson et al., 2017), and 54 additionally identified from the gene-based test, 40 genes were identified by both methods. Table 1 also shows that in total 236 autosomal genes were identified as targets of existing IHD treatments. However, the overlap between the genes associated with IHD and the genes currently related to existing IHD treatments was minimal, i.e., only 8 genes. The Cohen's kappa was very low (0.03) indicating minimal agreement. If only the 119 genes associated with IHD from SNP-based GWAS were considered as associated with IHD the Cohen's kappa (0.03) was still minimal.

3.1. IHD Gene Products as Targets of Existing IHD Treatments

Of the total 173 genes associated with IHD the 8 genes related to existing IHD treatments were *PCSK9*, *LPL*, *PLG*, *EDNRA*, *CXCL12*, *LRP1*, *CETP* and *ADORA2A*. All of these 8 genes were identified from SNP-based GWAS, *PLG* was also identified by the gene-based test. Four genes *(PCSK9*, *LPL*, *EDNRA* and *ADORA2A)* were significantly associated with IHD at a 5% false discovery rate on the gene-based test, *LRP1* was nominally significant and two genes *(CXCL12* and *CETP*) were not even nominally associated with IHD on the gene-based test.

None of these 8 genes (*PCSK9*, *LPL*, *PLG*, *EDNRA*, *CXCL12*, *LRP1*, *CETP* and *ADORA2A*) are associated with widely used IHD treatments, shown in Table 2. *PCSK9* gene products are targeted by PCSK9 inhibitors. *LPL* products are targets of rarely used lipid modulators, such as Ibrolipim, elastase and Omega-3-acid ethyl esters, and anti-thrombotics, such as dextran. *PLG* products are targeted by anti-thrombotics for acute myocardial infarction. *EDNRA* products could be targeted by aspirin, and are targeted by therapies for pulmonary hypertension. *CXCL12* products may be targeted by a heparin antithrombotic. *LPR1* and *ADORA2A* products are targets of specialized anti-thrombotics. *CETP* products are currently targeted by Omega-3-acid ethyl esters. To date three cholesterylester transfer protein (CETP)-inhibitors have failed in major trials (Eyvazian and Frishman, 2017). One CETP-inhibitor (anacetrapib) met its primary endpoint, but is not going to be marketed (Merck Provides Update on Anacetrapib Development Program, 2017).

Additionally, considering the 241 genes only associated with IHD at a 5% false discovery rate on the gene-based-test yielded two additional genes, *CHRNB2* and *VEGFA*, related to IHD treatments. *CHRNB2* is related to atropine and *VEGFA* to anti-thrombotics, anti-hypertensives and sulfonylureas. For reference Supplementary Table 2 lists these 241 genes.

3.2. Existing IHD Treatments As Genetically Valid Targets

In total 236 autosomal genes were identified as related to existing pharmacological IHD treatments, but only 8 of these genes were strongly associated with IHD. Supplementary Table 3 shows all 242 genes (including 6 on the X chromosome) related to current IHD treatments, the treatment class and the p-value for their gene-based association with IHD. Genes related to widely used therapies that modulate lipids and reduce cardiovascular disease, such as statins (*HMGCR)* (Collins et al., 2016) and ezetimibe (*NPC1L1*) (Cannon et al., 2015), were nominally significant using the gene-based test (p-values of

Table 1
Comparison between the number of genes strongly associated with IHD and the number of genes related to IHD treatments.

		Genes strongly associated with IHD at genome-wide significance from SNP-based GWAS or the gene-based test		
Genes related to existing IHD treatments	Yes	Yes 8	No 228	236
	No	165	25,062	25,227
		173	25,290	25,463

0.004 and 0.0045 respectively). Genes related to less successful lipid modulators, such as niacin (*HCAR2/3*) (Landray et al., 2014), fibrates (*PPARA*) (Warren et al., 2016), and CETP-inhibitors (*CETP*) (Eyvazian and Frishman, 2017) were not significantly associated with IHD. Several genes related to anti-thrombotics (*FCGR1A*, *PROC*, *P2RY12*, *PDE5A*, *TBXAS1*, *NFKB2*, *C1R*, *C1S*, *LRP1*, *VTN*, *CALR* and *PDE4A*) were nominally significant. Genes related to aspirin (*PTGS1/2*) were not, although other genes potentially related to aspirin were, such as *EDNRA* and *NFKB2*. Genes possibly related to anti-hypertensives, such as alpha blockers (*KCNH7*), beta blockers (*VEGFA*), ACE inhibitors (*LTA4H*), calcium channel blockers (*PDE1A*), prostaglandin I2 receptor antagonists (*P2RY12*), vasodilators (*NPR1*), digitalis (*ATP1B3*) and reserpine (*SLC18A2*), were nominally significant, but not genes targeted by other anti-hypertensives. Finally, some genes potentially related to anti-diabetes therapies were nominally associated with IHD (*RAMP1*, *IGFBP7*, *ABCA1*, *IGF1R*, *RAMP2* and *VEGFA* (also significant at 5% false discovery rate)).

3.3. IHD Genes as Targets of Other Treatments, or Potential Interventions

Of the 173 genes associated with IHD, in addition to the 8 genes (*PCSK9*, *LPL*, *PLG*, *EDNRA*, *CXCL12*, *LPR1*, *CETP* and *ADORA2A*) related to existing IHD treatments, an additional 29 genes were related to other existing treatments or nutraceuticals (Table 2). Of these 29 genes, 12 genes (*IL6R*, *GGCX*, *GUCY1A3*, *LPA*, *HDAC9*, *NOS3*, *CYP17A1*, *NT5C2*, *SH2B3*,*FURIN*, *APOE* and *LDLR*) were identified by both SNP-based GWAS and the gene-based test, 14 genes from SNP-based GWAS only (*ATP1B1*, *FN1*, *ITGB5*, *SLC22A4*, *SLC22A5*, *APOA1*, *PDGFD*, *SCARB1*, *FLT1*, *OAZ2*, *MC4R*, *SNRPD2*, *TGFB1* and *PROCR*), and 3 genes from the gene-based test only (*MAT2A*, *AS3MT* and *IGF2R*).

Seven of these 29 IHD genes are related to therapies for other cardiovascular conditions (*ATP1B1*, *GGCX*, *FN1*, *GUCY1A3* and *NOS3*) and/or bleeding disorders (*LPA* and *APOE*). Another 12 of these 29 IHD genes are related to treatments for other conditions including arthritis (*IL6R*), cancer (*ITGB5*, *HDAC9*, *CYP17A1*,*PDGFD*, *SH2B3*, *FLT1* and *LDLR*), psychosis, specifically valproic acid (*HDAC9*), growth failure (*IGF2R*), adrenocortical insufficiency (*MC4R*), and infections (*NT5C2* and *SNRPD2*). *TGFB1* is related to hyaluronidase, which promotes the dispersion of injected substances. *PROCR* is related to phosphatidylethanolamine, which may play a cardiac role and is raised by testosterone (Angelova et al., 2012). Finally the remaining 8 of these 29 IHD genes (*MAT2A*, *SLC22A4*, *SLC22A5*, *AS3MT*, *APOA1*, *SCARB1*, *FURIN* and *OAZ2*) are related to dietary factors or supplements.

Several of these 29 IHD genes are also related to common modifiable interventions (Table 2). *GGCX* is related to vitamin K_1, commonly found in green leafy vegetables, and to L-glutamic acid, a common dietary amino acid. *MAT2A* and *AS3MT* are related to the derivate of the amino acid L-methionine, largely obtained from animal protein, i.e., s-denosylmethionine which plays a role in arsenic metabolism (Loenen, 2006). *SLC22A4* and *SLC22A5* are related to L-carnitine, whose major source is red meat. *NOS3* is related to the amino-acids L-citrulline and L-arginine. L-arginine is a common dietary amino acid often obtained from animal protein. *APOA1* and *APOE* are related to both zinc and copper, as are *PLG* (copper) and *FN1* (zinc). *SCARB1* is related to phosphatidyl serine, which may improve memory. Finally, *ADORA2A*, as well as being related to an existing IHD treatment, is also related to many potential interventions including cocoa derivatives, such as theobromine.

4. Discussion

This study reveals a disconnect between genes strongly associated with IHD, i.e., potentially with druggable genetic products, and genes whose products are targeted by existing IHD treatments. Only 8 of the 173 genes associated with IHD are related to the products of the 236 autosomal genes acted on by treatments for IHD and none of these treatments are widely used. However, 29 other genes associated with IHD are related to existing treatments or interventions that could perhaps be repurposed or re-developed to combat IHD.

Previous studies have validated the genetic targets of some specific IHD treatments, such as ezetimbe and PCSK9 inhibitors (Wang and Hegele, 2017; Stitziel et al., 2014). However, to our knowledge, no previous studies have comprehensively compared the genes strongly associated with IHD with the genes whose products are targeted by existing IHD treatments. Of course, not all genes associated with IHD are likely to yield easily modifiable effective targets of intervention for IHD, although lack of even a nominal association of a gene with IHD might raise questions about whether such a gene is likely to have products that are targets of effective intervention for IHD. Some of the genes associated with IHD are related to existing interventions which could perhaps be repurposed, although the direction of effect is not always obvious and needs to be deduced from other information. For example, aminocaprioc acid related to *LPA*, is usually used to prevent bleeding, and so might not be helpful in IHD.

Suggestive information about the value of some of these potential interventions for IHD already exists. Vitamin K_1 (*GGCX*) is an antagonist of the blood thinner warfarin used to treat some cardiovascular diseases. A Mendelian randomization study suggested vitamin K_1 may cause IHD (Schooling, 2016). Arsenic is thought to cause IHD (Moon et al., 2012) and methionine (*MAT2A* and *AS2MT*) restriction may increase lifespan (Ables and Johnson, 2017), consistent with the importance of removing arsenic pollution from the environment. In small trials with intermediate end-points L-carnitine (*SLC22A4*, *SLC22A5*) has shown some indications of beneficial effects (Serban et al., 2016; Anand et al., 1998). Zinc (*FN1*, *APOA1* and *APOE*) and copper (*PLG*, *APOA1* and *APOE*) have been thought to play a role in IHD for over 40 years (Klevay, 1975). Small scale trials suggest adverse effects of low copper intake on cardiac arrhythmias (Milne and Nielsen, 1996; Viestenz and Klevay, 1982), and that copper depletion may induce aneurysms (Jung et al., 2016). In vitro experiments also suggest some cardiac benefits of copper (Zhou et al., 2009). Zinc also reduces copper absorption (Van Campen and Scaife, 1967). L-arginine (*NOS3*) is a common dietary amino acid, often obtained from animal protein, which likely causes IHD (Au Yeung et al., 2016). In randomized controlled trials theobromine has beneficial effects on cardiovascular disease risk factors, such as blood pressure and lipids (Martinez-Pinilla et al., 2015), and was formerly used as a treatment for angina. Theobromine may also antagonize adenosine receptors, potentially relevant to the relation of *NT5C2* with IHD.

Despite taking an innovative approach to identify gaps and opportunities for IHD mitigation by considering genes in naturally occurring functional units, i.e., genes, this study has limitations. First, some of the genes identified as associated with IHD might not be functional. However, we specifically identified 29 genes that are related to potentially available interventions. Second, some of the genes targeted by existing treatments may represent valid physiological targets even though the genes were not clearly associated with IHD from SNP level GWAS or gene-based tests, meaning better methods of searching the human genome are required. Alternatively, discovery of new ways of treating IHD may be facilitated by use of explanatory models from other disciplines (Schooling, 2017). Third, knowledge of the relation between drugs and gene products is not definitive, and is constantly

Table 2
Pharmaceutical treatments and nutraceuticals given in KEGG (Kanehisa et al., 2014) or Drugbank (Wishart et al., 2008) as related to any of the 173 autosomal genes identified as strongly associated with IHD from SNP-based GWAS or the gene-based test.

Target	Gene	Chr	Potential therapies		
			Medicinal		Nutraceutical
			Drug	Indication	
IHD	*PCSK9*	1	PCSK9 inhibitor	Hyperlipidemia	
	EDNRA	4	Endothelin receptor antagonist	Pulmonary arterial hypertension	
			Aspirin	Myocardial infarction, cardiovascular disease risk	
	PLG	6	Plasminogen activator	Acute myocardial infarction, clotting	Copper, citric acid
	LPL	8	Dextran	Coagulation/Thrombosis	
			Elastase ES	Hyperlipidemia	
			Ibrolipim	Hyperlipidemia	
			Omega-3-acid ethyl esters	Hyperlipidemia	
	CXCL12	10	Heparin	Thromboembolism or risk thereof	
	LRP1	12	Tissue plasminogen activator	Myocardial infarction, clotting	
			Coagulation factors VIII and IX	Hemophilia	
	CETP	16	Omega-3-acid ethyl esters	Hyperlipidemia	
	ADORA2A	22	Defibrotide	occlusive venous disease of the liver	
Other diseases	*ATP1B1*	1	Digitalis	Antiarrhythmic	
	IL6R	1	Sarilumab/Tocilizumab	Arthritis and ankylosing spondylitis	
	GGCX	2	Anisindione	Prevention of thromboembolism in atrial fibrillation	Menadione
			Phylloquinone	Bleeding	L-Glutamic Acid
			Coagulation factors VIIa and IX	Hemophilia	
	MAT2A	2			S-Adenosylmethionine
	FN1	2	Ocriplasmin/Lanoteplase	Thrombosis	Zinc
	ITGB5	3	Cilengitide	Angiogenesis inhibitor	
	GUCY1A3	4	Riociguat	Pulmonary arterial hypertension	
	SLC22A4	5	L-Carnitine	Carnitine deficiency	
	SLC22A5	5	L-Carnitine	Carnitine deficiency	
	IGF2R	6	Insulin-like growth factor 1	Growth failure	
			Cerliponase alfa		
	LPA	6	Aminocaproic Acid	Bleeding	
	HDAC9	7	Histone deacetylase inhibitor	Cancer	
			Valproic Acid	Seizure disorders, mania	
	NOS3	7	Apremilast	Psoriasis	L-Arginine
			Miconazole	Fungal infections	L-Citrulline
			Sapropterin	Tetrahydrobiopterin deficiency	
			Tilarginine acetate	Cardiogenic shock	
	AS3MT	10			S-Adenosylmethionine
	CYP17A1	10	Abiraterone/Galeterone/Orteronel	Prostate cancer	Nicotinamide adenine dinucleotide + hydrogen
			Mitotane	Adrenal cortical carcinoma	
			Progesterone	Progesterone deficiency, hormonal imbalance	
	NT5C2	10	Ribavirin/Taribavirin	Hepatitis C, respiratory syncytial virus	Adenosine triphosphate
	APOA1	11			Zinc
					Copper
	PDGFD	11	Tandutinib	Cancer	
			PDGFD blocker	Kidney inflammation	
	SH2B3	12	Indazolylpyrimidine	Kidney cancer and sarcoma	
		12			
	SCARB1	12			Phosphatidyl serine
	FLT1	13	Multiple kinase inhibitor	Various cancers	
	FURIN	15	Pirfenidone	idiopathic pulmonary fibrosis	Capric acid
	OAZ2	15			Ornithine
	MC4R	18	Adrenocorticotropic hormone	Adrenocortical insufficiency	
	APOE	19	Human serum albumin	Severe blood loss	Zinc
					Copper
	LDLR	19	Hematoporphyrin derivative	Esophageal cancer	
	SNRPD2	19	Artemisinins (Artenimol)	Plasmodium falciparum infection	
	TGFB1	19	Hyaluronidase	increase the absorption and dispersion of drugs	
	PROCR	20	Phosphatidylethanolamine	phospholipid	
	ADORA2A	22	Caffeine	Drowsiness	
			Theophylline	Asthma, Chronic Obstructive Pulmonary Disease	
			Mefloquine	Malaria	
			Adenosine	Anti-arrhythmic	
			Pentoxifylline	Chronic Obstructive Pulmonary Disease	
			Theobromine	Angina (formerly)	
			Adenosine A(2A) antagonist	Parkinson's disease	

Chr: chromosome.

evolving, so we used two comprehensive cross-references from gene to treatment (Kanehisa et al., 2014; Wishart et al., 2008) and included genes and treatments found in either source. However, inexactitude and incompleteness of knowledge about gene products and how treatments operate is unlikely to explain the magnitude of the difference between the genes strongly associated with IHD and genes related to existing IHD treatments. Fourth, most genetic variation associated with IHD has been obtained from prevalent case-control studies of

people of European descent. Replication in a different study or population is unlikely to remove the disconnect between genetically valid targets and existing IHD treatments, although it may reveal some additional targets. Fifth, this study is not designed to map out full genetic functionality and etiology of IHD but instead to identify promising genetically informed targets of intervention that can be actioned now, because genetic validation is increasingly a criterion for investigation of potential interventions.

Overall, this study suggests that current IHD treatments may not be optimally targeted and genetically informed targets for IHD may be under-exploited. Closer alignment of IHD treatments with the products of genes associated with IHD represents a major opportunity for combating the leading cause of global morbidity and mortality by repurposing existing therapies identified here. Whether a similar situation exists for other major diseases might also be investigated.

Disclosures

None.

Authors' Contributions

CMS designed the study, searched databases and checked the results of the genetic analysis. SLL did the genetic analysis. JVH and SLAY independently checked the search for genes targeted by current ischemic heart disease therapies. SLAY independently checked the search for drugs acting on genes associated with ischemic heart disease. JVZ checked the extraction of known genetic loci for ischemic heart disease. JVH, SLAY, JVZ, MKK and SLL gave general advice on the study and reviewed the final version for intellectual content.

Acknowledgements

Data have been contributed by CARDIoGRAMplusC4D investigators and have been downloaded from www.CARDIOGRAMPLUSC4D.ORG.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebiom.2018.01.015.

References

Ables, G.P., Johnson, J.E., 2017. Pleiotropic responses to methionine restriction. Exp. Gerontol. 94, 83–88.
Anand, I., Chandrashekhan, Y., De Giuli, F., Pasini, E., Mazzoletti, A., Confortini, R., et al., 1998. Acute and chronic effects of propionyl-l-carnitine on the hemodynamics, exercise capacity, and hormones in patients with congestive heart failure. Cardiovasc. Drugs Ther. 12 (3), 291–299.
Angelova, P., Momchilova, A., Petkova, D., Staneva, G., Pankov, R., Kamenov, Z., 2012. Testosterone replacement therapy improves erythrocyte membrane lipid composition in hypogonadal men. Aging Male 15 (3), 173–179.
Au Yeung, S.L., Lin, S.L., Lam, H.S., Schooling, C.M., 2016. Effect of l-arginine, asymmetric dimethylarginine, and symmetric dimethylarginine on ischemic heart disease risk: a mendelian randomization study. Am. Heart J. 182, 54–61.
Bacanu, S.A., 2012. On optimal gene-based analysis of genome scans. Genet. Epidemiol. 36 (4), 333–339.
Cannon, C.P., Blazing, M.A., Giugliano, R.P., McCagg, A., White, J.A., Theroux, P., et al., 2015. Ezetimibe added to statin therapy after acute coronary syndromes. N. Engl. J. Med. 372 (25), 2387–2397.
Collins, R., Reith, C., Emberson, J., Armitage, J., Baigent, C., Blackwell, L., et al., 2016. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 388 (10059), 2532–2561.
Eyvazian, V.A., Frishman, W.H., 2017. Evacetrapib: another CETP inhibitor for dyslipidemia with no clinical benefit. Cardiol. Rev. 25 (2), 43–52.
Ezzati, M., Obermeyer, Z., Tzoulaki, I., Mayosi, B.M., Elliott, P., Leon, D.A., 2015. Contributions of risk factors and medical care to cardiovascular mortality trends. Nat. Rev. Cardiol. 12 (9), 508–530.
Gregson, J.M., Freitag, D.F., Surendran, P., Stitziel, N.O., Chowdhury, R., Burgess, S., et al., 2017. Genetic invalidation of lp-pla2 as a therapeutic target: large-scale study of five functional lp-pla2-lowering alleles. Eur. J. Prev. Cardiol. 24 (5), 492–504.
Jackson, N., Atar, D., Borentain, M., Breithardt, G., van Eickels, M., Endres, M., et al., 2016. Improving clinical trials for cardiovascular diseases: a position paper from the cardiovascular round table of the european society of cardiology. Eur. Heart J. 37 (9), 747–754.
Howson, J.M.M., Zhao, W., Barnes, D.R., Ho, W.K., Young, R., Paul, D.S., et al., 2017. Fifteen new risk loci for coronary artery disease highlight arterial-wall-specific mechanisms. Nat. Genet. 49 (7), 1113–1119.
Jung, K.H., Chu, K., Lee, S.T., Shin, Y.W., Lee, K.J., Park, D.K., et al., 2016. Experimental induction of cerebral aneurysms by developmental low copper diet. J. Neuropathol. Exp. Neurol. 75 (5), 455–463.
Kanehisa, M., Goto, S., Sato, Y., Kawashima, M., Furumichi, M., Tanabe, M., 2014. Data, information, knowledge and principle: back to metabolism in kegg. Nucleic Acids Res. 42 (Database issue), D199–D205.
Klevay, L.M., 1975. Coronary heart disease: the zinc/copper hypothesis. Am. J. Clin. Nutr. 28 (7), 764–774.
Landray, M.J., Haynes, R., Hopewell, J.C., Parish, S., Aung, T., Tomson, J., et al., 2014. Effects of extended-release niacin with laropiprant in high-risk patients. N. Engl. J. Med. 371 (3), 203–212.
Li, M.X., Kwan, J.S., Sham, P.C., 2012. Hyst: a hybrid set-based test for genome-wide association studies, with application to protein-protein interaction-based association analysis. Am. J. Hum. Genet. 91 (3), 478–488.
Lincoff, A.M., Nicholls, S.J., Riesmeyer, J.S., Barter, P.J., Brewer, H.B., Fox, K.A.A., et al., 2017. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. N. Engl. J. Med. 376 (20), 1933–1942.
Loenen, W.A., 2006. S-adenosylmethionine: Jack of all trades and master of everything? Biochem. Soc. Trans. 34 (Pt 2), 330–333.
Marmot, M.G., Syme, S.L., Kagan, A., Kato, H., Cohen, J.B., Belsky, J., 1975. Epidemiologic studies of coronary heart disease and stroke in japanese men living in japan, hawaii and california: prevalence of coronary and hypertensive heart disease and associated risk factors. Am. J. Epidemiol. 102 (6), 514–525.
Martinez-Pinilla, E., Onatibia-Astibia, A., Franco, R., 2015. The relevance of theobromine for the beneficial effects of cocoa consumption. Front. Pharmacol. 6, 30.
Merck Provides Update on Anacetrapib Development Program, 2017. http://investors.merck.com/news/press-release-details/2017/Merck-Provides-Update-on-Anacetrapib-Development-Program/default.aspx.
Milne, D.B., Nielsen, F.H., 1996. Effects of a diet low in copper on copper-status indicators in postmenopausal women. Am. J. Clin. Nutr. 63 (3), 358–364.
Moon, K., Guallar, E., Navas-Acien, A., 2012. Arsenic exposure and cardiovascular disease: an updated systematic review. Curr Atheroscler Rep 14 (6), 542–555.
Moses 3rd, H., Matheson, D.H., Cairns-Smith, S., George, B.P., Palisch, C., Dorsey, E.R., 2015. The anatomy of medical research: us and international comparisons. JAMA 313 (2), 174–189.
Nelson, C.P., Goel, A., Butterworth, A.S., Kanoni, S., Webb, T.R., Marouli, E., et al., 2017. Association analyses based on false discovery rate implicate new loci for coronary artery disease. Nat. Genet. 49, 1385–1391.
Nikpay, M., Goel, A., Won, H.H., Hall, L.M., Willenborg, C., Kanoni, S., et al., 2015. A comprehensive 1,000 genomes-based genome-wide association meta-analysis of coronary artery disease. Nat. Genet. 47 (10), 1121–1130.
O'Donoghue, M.L., Glaser, R., Cavender, M.A., Aylward, P.E., Bonaca, M.P., Budaj, A., et al., 2016. Effect of losmapimod on cardiovascular outcomes in patients hospitalized with acute myocardial infarction: a randomized clinical trial. JAMA 315 (15), 1591–1599.
Ridker, P.M., Revkin, J., Amarenco, P., Brunell, R., Curto, M., Civeira, F., et al., 2017. Cardiovascular efficacy and safety of bococizumab in high-risk patients. N. Engl. J. Med. 376 (16), 1527–1539.
Schooling, C.M., 2017. Tachykinin neurokinin 3 receptor antagonists: a new treatment for cardiovascular disease? Lancet 390 (10095), 709–711.
Schooling CM, 2016. Plasma levels of vitamin k and the risk of ischemic heart disease: a mendelian randomization study. J. Thromb. Haemost. 14 (6), 1211–1215.
Serban, M.C., Sahebkar, A., Mikhailidis, D.P., Toth, P.P., Jones, S.R., Muntner, P., et al., 2016. Impact of l-carnitine on plasma lipoprotein(a) concentrations: a systematic review and meta-analysis of randomized controlled trials. Sci. Rep. 6, 19188.
Stitziel, N.O., Won, H.H., Morrison, A.C., Peloso, G.M., Do, R., Lange, L.A., et al., 2014. Inactivating mutations in NPC1L1 and protection from coronary heart disease. N. Engl. J. Med. 371 (22), 2072–2082.
Talmud, P.J., Holmes, M.V., 2015. Deciphering the causal role of spla2s and lp-pla2 in coronary heart disease. Arterioscler. Thromb. Vasc. Biol. 35 (11), 2281–2289.
Van Campen, D.R., Scaife, P.U., 1967. Zinc interference with copper absorption in rats. J. Nutr. 91 (4), 473–476.
Viestenz, K.E., Klevay, L.M., 1982. A randomized trial of copper therapy in rats with electrocardiographic abnormalities due to copper deficiency. Am. J. Clin. Nutr. 35 (2), 258–266.
Wang, L.R., Hegele, R.A., 2017. Genetics for the identification of lipid targets beyond pcsk9. Can. J. Cardiol. 33 (3), 334–342.
Warren, J.B., Dimmitt, S.B., Stampfer, H.G., 2016. Cholesterol trials and mortality. Br. J. Clin. Pharmacol. 82 (1), 168–177.
Wishart, D.S., Knox, C., Guo, A.C., Cheng, D., Shrivastava, S., Tzur, D., et al., 2008. Drugbank: a knowledgebase for drugs, drug actions and drug targets. Nucleic Acids Res. 36 (Database issue), D901–D906.
Zhou, Y., Bourcy, K., Kang, Y.J., 2009. Copper-induced regression of cardiomyocyte hypertrophy is associated with enhanced vascular endothelial growth factor receptor-1 signalling pathway. Cardiovasc. Res. 84 (1), 54–63.