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SPOTLIGHT REVIEW

A decade of genome-wide association studies for coronary artery disease: the challenges ahead

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Abstract In this review, we summarize current knowledge on the genetics of coronary artery disease, based on 10 years of genome-wide association studies. The discoveries began with individual studies using 200K single nucleotide polymorphism arrays and progressed to large-scale collaborative efforts, involving more than a 100 000 people and up to 40 Mio genetic variants. We discuss the challenges ahead, including those involved in identifying causal genes and deciphering the links between risk variants and disease pathology. We also describe novel insights into disease biology based on the findings of genome-wide association studies. Moreover, we discuss the potential for discovery of novel treatment targets through the integration of different layers of 'omics' data and the application of systems genetics approaches. Finally, we provide a brief outlook on the potential for precision medicine to be enhanced by genome-wide association study findings in the cardiovascular field.

Keywords Coronary artery disease • Atherosclerosis • Genome-wide association studies • Genetics • Post-GWAS

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1. Introduction

Coronary artery disease (CAD) is a leading cause of death worldwide.[1] It represents the manifestation of atherosclerosis in the coronary arteries, which supply the myocardium with oxygen and other nutrients.

Atherosclerosis is an inflammatory process that is strongly driven by lipid accumulation during which the coronary artery wall thickens, forming a plaque, eventually leading to reduced blood flow and myocardial ischaemia.[2] The major sequelae of CAD include angina, myocardial infarction (MI), arrhythmias, heart failure, and sudden cardiac death. CAD has a complex aetiology, and various environmental factors, including cigarette smoking, sedentary lifestyle, unhealthy diet and obesity, and disease predisposition.[3] These lifestyle-related factors can lead to type 2 diabetes, hypercholesterolaemia and arterial hypertension, which are key risk factors for CAD. In addition, the influence of heritability on CAD susceptibility has been recognized for many years[4] and accounts for 40–50% of cases.[5] Although the inherited CAD risk is particularly evident in large families with multiple affected members,[6] decade ago only mutations in the *LDL receptor* gene were reproducibly linked to the disease. However, with the emergence of genome-wide association studies (GWAS), large number of common variants displayed strongly reproducible yet small effects and substantially broadened the spectrum of genetic factors recognized as contributing to CAD aetiology.[3,7]

2. In retrospect: 10 years of CAD GWAS

2.1 Laying the foundation for GWAS

During the period when candidate gene studies on small case–control samples often produced controversial findings, novel chip designs and decreasing costs facilitated the development of genome-wide genotyping. In parallel, statistical methods (e.g. imputation and haplotype tagging) were improving and international consortia were established to conduct large-scale GWAS on CAD.

One imperative technological breakthrough that aided the rapid success of GWAS was the completion of the International HapMap (short

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for haplotype map) Project in 2007, and the public availability of the resulting data,[8–10] which allowed the mapping of haplotype landscapes of SNPs in three continental populations. Eight years later, in 2015, the 1000 Genomes Project[11] took advantage of more affordable sequencing technologies and released freely available human genetic variation data, based on low-coverage whole-genome sequencing, reaching a pinnacle with the 1000GP3 reference panel. Recently, the Haplotype Reference Consortium (HRC)[12,13] combined all whole-genome sequencing data sets into a single haplotype reference panel to facilitate genotype imputation. Promisingly, the HRC reference panel markedly improved the concordance between assayed and imputed genotypes for low-frequency variants. This advance has permitted significant clarification of association signals, particularly for suggestive variants,[12] thereby outperforming 1000GP-based imputation concordance and final *P*-value results.

2.2 From single GWAS to large-scale collaborative research

GWAS for CAD/MI have generated numerous successful outcomes (*Figure 1*), beginning in 2007 with the discovery of the chromosome 9p21 risk locus by four independent research groups.[14–17] By 2009, twelve additional genetic risk variants had been discovered by several individual GWAS.[18–20] Subsequently, large GWAS consortia were formed and eventually merged, ultimately analysing hundreds of thousands of individuals, for example, the Coronary ARtery DIsease Genome-wide Replication and Meta-analysis (CARDIoGRAM) Consortium,[21] the MIGen Consortium,[18] the Coronary Artery Disease (C4D) Genetics Consortium,[22] and, more recently, the UK Biobank (UKBB).[23] In 2011 and 2013, the CARDIoGRAM (plus C4D) consortia reported 25 and 46 loci associated with CAD, respectively, both confirming previously published variants and identifying new associations.[24,25] Interestingly, earlier this year, three studies that analysed CAD data from the first UKBB data release, CARDIoGRAMplusC4D and other smaller studies[26–28] each found 13, 14, and 15 new loci associated with CAD, of which seven overlapped between the three studies. Subtle differences in study design (mainly phenotype definition) may explain the moderate overlap between studies. Very recently, by analysing the full UKBB data set (34 541 CAD cases and 261 984 controls) and using CARDIoGRAMplusC4D 1000 G data for replication an additional 64 novel CAD risk loci were reported.[29] Altogether, 163 loci have now been associated with CAD at a genome-wide level of significance (*Table 1*; Supplementary material online, *Table S1*; *Figure 2*). Most CAD risk variants have been discovered under an additive model of inheritance; however, for 25% of all CAD risk variants it seems that a dominant (26 SNPs) or a recessive model (12 SNPs) might offer a better fit.[29] In another analysis, only one CAD risk variant (rs11830157 tagging *KSR2* gene) showed genome-wide significance in a recessive model.[30] A more comprehensive study about the recessive component of the inheritance of CAD has been performed recently by studying runs of homozygosity (ROH). Christofidou *et al.*[31] reported an excess of homozygosity in CAD and suggested an important role of ROH in the pathogenesis of atherosclerosis.

Although most of the 163 loci represent the effects of common alleles, studies with large sample sizes also have the potential to identify low-frequency variants that are associated at the required level of significance. Nevertheless, a previous large-scale exome-wide study including more than 120 000 participants only had 80% power to detect an OR of ±2.0 for CAD-associated variants with a minor allele frequency (MAF) of 0.1%.[32] Nevertheless, it did identify two low-frequency non-synonymous genetic variants associated with CAD risk.[33]

Modern GWAS arrays and subsequent imputation cover the human autosomal genome quite well, but the X- and Y-chromosomes have been somewhat neglected due to specific analytical challenges, such as unequal gene dosage in males and females and X-chromosome inactivation.[34,35] Recommendations how to include the X-chromosome have recently been published[36] but a first GWAS for CAD for X-chromosomal variants in more than 43 000 CAD cases and 58 000 controls from 35 international study cohorts revealed no genome-wide significant association for any variant[37] which may change when larger samples are being studied.[38] Lately, a study on the human Y-chromosome has shown that genetic variation within the male-specific region of the Y-chromosome confers risk for CAD, confirming the notion that the increased risk for CAD in men cannot be fully explained through common autosomal genetic risk factors.[39]

2.3 Knowledge revealed by GWAS to date

2.3.1 Contribution of common genetic variants to CAD

As stated earlier, GWAS have identified 163 genetic loci associated with CAD risk at a genome-wide significance level after Bonferroni correction (*Table 1*; Supplementary material online, *Table S1*). Over 300 additional loci are suggestive for CAD risk, as they have false discovery rate values below 5%.[25,28] These loci may be useful for improved prediction of CAD risk and understanding of the biology underlying the disease.[28] The majority of these loci is represented by common variants with an MAF of >5% and is associated with modest increases in CAD risk.[3,7] Combined, these loci explain roughly 30–40% of CAD heritability, which is estimated to account for approximately 40% of all cases.[28] Therefore, together, common variants appear to explain a far greater proportion of CAD heritability than can be attributed to rare variants.

Loci associated with CAD at the genome-wide significance level have been assigned to several pathophysiological pathways with known functions in atherosclerosis or CAD (see Section 2.3.5 for more details, *Figure 2*); however, despite intriguing hypotheses regarding many genes and pathways at most CAD risk loci the exact mechanisms leading to the disease remain unknown. Even the assignment of these loci to genes is primarily based on proximity only. The link between genetic variants and downstream mechanisms is especially uncertain for SNPs outside protein-coding regions. In fact, the majority of common lead SNPs (approximately 75%) is located outside of coding or classical promoter regions and is rather found to cluster in regulatory elements, such as those annotated by the ENCODE project.[40] The ENCODE project also revealed that only ~27% of distal regulatory elements tend to interact with their nearest promoter, implying that the nearest gene might often not be the target of an identified GWAS variant.[41] The challenges related to gene annotation in post-GWAS analysis are discussed in more detail in Section 3.1.

2.3.2 Multiple independent signals at CAD risk loci

Traditionally, the variants with the strongest *P*-values have been reported as the lead SNPs representing a risk locus. However, fine-mapping approaches demonstrate that most of the loci show intra-locus allelic heterogeneity, i.e. a particular risk locus may contain multiple independent risk variants. For CAD, the most complete fine-mapping analysis was performed in a recent study by van de Harst and Verweij.[29] Interestingly, in their study, it was only possible to define for 28 out of the known 163 CAD risk loci a single CAD variant as the most likely causal variant.

Table 1 Summary of genome-wide significant CAD risk loci (January 2018)

No	Position	Lead SNP	EAF	OR	Gene(s) at locus	References
1	chr1: 2252205	rs36096196	T (0.15)	1.05	*MORN1*, ***SKI***	29
2	chr1: 3325912	rs2493298	A (0.14)	1.06	***PRDM16,*** *PEX10, PLCH2, RER1*	29
3	chr1: 38461319	rs61776719	A (0.53)	1.04	***FHL3***, *UTP11, SF3A3, MANEAL, INPP5B*	29
4	chr1: 55496039	rs11206510	T (0.82)	1.08	***PCSK9***	18, 90, 103, 104
5	chr1: 56962821	rs17114036	A (0.91)	1.17	***PPAP2B***	24, 90
6	chr1: 109822166	rs599839	A (0.78)	1.11	***SORT1***, *PSCR1, CELSR2*	14, 24, 90
7	chr1: 115753482	rs11806316	G (0.66)	1.04	***NGF***, ***CASQ2***	29
8	chr1: 151762308	rs11810571	G (0.79)	1.07	***TDRKH***, *RP11-98D18.9*	27, 28
9	chr1: 154422067	rs4845625	T (0.47)	1.06	***IL6R***, *AQP10, ATP8B2, CHTOP, UBAP2L*	25
10	chr1: 169094459	rs1892094	C (0.50)	1.04	***ATP1B1,*** *BLZF1, CCDC181, F5,* ***NME7***, *SELP, SLC19A2*	105
11	chr1: 200646073	rs6700559	C (0.53)	1.04	***DDX59***, ***CAMSAP2***, *KIF14*	105
12	chr1: 201872264	rs2820315	T (0.30)	1.05	***LMOD1***, *IPO9, NAV1, SHISA4, TIMM17A*	105
13	chr1: 210468999	rs60154123	T (0.15)	1.05	***HHAT, SERTAD4, DIEXF***	29
14	chr1: 222823529	rs17465637	C (0.74)	1.14	***MIA3***, *AIDA, C1orf58*	14, 24
15	chr1: 230845794	rs699	G (0.42)	1.04	***AGT,*** *CAPN9, GNPAT*	29
16	chr2: 21286057	rs515135	C (0.83)	1.07	***APOB***	25, 90
17	chr2: 44073881	rs6544713	T (0.30)	1.06	***ABCG5, ABCG8***	24, 90, 106
18	chr2: 45896437	rs582384	A (0.53)	1.03	***PRKCE***, *TMEM247*	29
19	chr2: 85809989	rs1561198	T (0.45)	1.06	***VAMP5***, ***VAMP8***, ***GGCX***	25
20	chr2: 145801461	rs2252641	C (0.46)	1.06	***ZEB2, TEX41***	25
21	chr2: 164957251	rs12999907	A (0.82)	1.06	***FIGN***	29
22	chr2: 188196469	rs840616	C (0.65)	1.04	***CALCRL***, ***TFPI***	29
23	chr2: 203745885	rs6725887	C (0.15)	1.14	***WDR12,*** *CARF, FAM117B, ICA1L,* ***NBEAL1***	18, 24
24	chr2: 216304384	rs1250229	T (0.26)	1.07	***FN1***, *ATIC, LOC102724849, ABCA12, LINC00607*	26, 28
25	chr2: 218683154	rs2571445	A (0.39)	1.04	***TNS1***, *CXCR2, RUFY4*	105
26	chr2: 227100698	rs2972146	T (0.65)	1.07	*LOC646736,* ***IRS1***, *MIR5702*	26
27	chr2: 233633460	rs1801251	A (0.35)	1.05	***KCNJ13***, *GIGYF2*	55
28	chr2: 238223955	rs11677932	G (0.68)	1.03	***COL6A3***	29
29	chr3: 14928077	rs748431	G (0.36)	1.04	***FGD5***	26
30	chr3: 46688562	rs7633770	A (0.41)	1.03	***ALS2CL, RTP3***	29
31	chr3: 48193515	rs7617773	T (0.67)	1.04	***CDC25A, SPINK8, MAP4, ZNF589***	29
32	chr3: 49448566	rs7623687	A (0.86)	1.07	***RHOA***, *AMT, TCTA, CDHRA, KLHDC8B, and others*	26–28, 105
33	chr3: 124475201	rs142695226	G (0.14)	1.08	*UMPS,* ***ITGB5***	26–28
34	chr3: 132257961	rs10512861	G (0.86)	1.04	***DNAJC13,*** *NPHP3, ACAD11, UBA5*	29
35	chr3: 136069472	rs667920	T (0.78)	1.05	***STAG1, MSL2***, ***NCK1***, ***PPP2R3A***	29
36	chr3: 138119952	rs2306374	C (0.18)	1.12	***MRAS***, *CEP70*	19, 24
37	chr3: 153839866	rs12493885	C (0.85)	1.07	***ARHGEF26***	26–28
38	chr3: 156852592	rs4266144	G (0.32)	1.03	*CCNL1,* ***TIPARP***	29
39	chr3: 172115902	rs12897	G (0.41)	1.04	***FNDC3B***	29
40	chr4: 3449652	rs16844401	A (0.07)	1.07	*HGFAC,* ***RGS12,*** *MSANTD1*	29
41	chr4: 57838583	rs17087335	T (0.21)	1.06	***REST***, ***NOA1***	30
42	chr4: 77416627	rs12500824	A (0.36)	1.04	*SHROOM3, SEPT11, FAM47E,* ***STBD1***	29
43	chr4: 81181072	rs10857147	T (0.27)	1.06	***PRDM8***, ***FGF5***	26–28
44	chr4: 82587050	rs11099493	A (0.69)	1.04	***HNRNPD***, *RASGEF1B*	29
45	chr4: 96117371	rs3775058	A (0.23)	1.04	***UNC5C***	29
46	chr4: 120901336	rs11723436	G (0.31)	1.05	***MAD2L1***, ***PDE5A***	26–28
47	chr4: 146782837	rs35879803	C (0.70)	1.05	***ZNF827***	27
48	chr4: 147472512	rs1878406	T (0.15)	1.10	***EDNRA***	25
49	chr4: 156635309	rs7692387	G (0.81)	1.08	***GUCY1A1***[a]	6, 25, 107
50	chr4: 169687725	rs7696431	T (0.51)	1.04	***PALLD***, *DDX60L*	29
51	chr5: 9556694	rs1508798	T (0.81)	1.05	***SEMA5A***, *TAS2R1*	29
52	chr5: 55860781	rs3936511	G (0.18)	1.04	***MAP3K1***, *MIER3*	29
53	chr5: 121413208	rs1800449	T (0.17)	1.09	***LOX***	26

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Table I *Continued*

No	Position	Lead SNP	EAF	OR	Gene(s) at locus	References
54	chr5: 131667353	rs273909	G (0.14)	1.07	***SLC22A4***	25
55	chr5: 131867702	rs2706399	G (0.51)	1.07	***IL5***, ***RAD50***	106
56	chr5: 142516897	rs246600	T (0.48)	1.05	***ARHGAP26***	105
57	chr6: 1617143	rs9501744	C (0.87)	1.05	***FOXC1***	29
58	chr6: 12927544	rs12526453	C (0.67)	1.10	***PHACTR1***, ***EDN1***	18, 24
59	chr6: 22583878	rs35541991	C (0.31)	1.05	***HDGFL1***	27, 28
60	chr6: 31888367	rs3130683	T (0.86)	1.09	***C2***, *C4A, and others*	55
61	chr6: 35034800	rs17609940	G (0.75)	1.07	***ANKS1A***, *UHRF1BP1*	24
62	chr6: 36638636	rs1321309	A (0.49)	1.03	*CDKN1A*, ***PI16***	29
63	chr6: 39174922	rs10947789	T (0.76)	1.07	***KCNK5***	25
64	chr6: 43758873	rs6905288	A (0.57)	1.05	***VEGFA***, *MRPL14, TMEM63B*	29
65	chr6: 57160572	rs9367716	G (0.68)	1.04	*PRIM2*, ***RAB23,*** *DST, BEND6*	29
66	chr6: 82612271	rs4613862	A (0.53)	1.03	***FAM46A***	29
67	chr6: 126717064	rs1591805	A (0.49)	1.04	***CENPW***	29
68	chr6: 134214525	rs12190287	C (0.62)	1.08	***TCF21,*** *TARID (EYA4—AS1)*	24
69	chr6: 150997401	rs17080091	C (0.92)	1.05	***PLEKHG1***, *IYD*	29
70	chr6: 160961137	rs3798220	C (0.02)	1.51	***LPA***, *SLC22A3, LPAL2*	20, 24, 90
71	chr6: 161143608	rs4252120	T (0.73)	1.07	***PLG***, *LPAL2*	25
72	chr7: 1937261	rs10267593	G (0.8)	1.04	***MAD1L1***	29
73	chr7: 6486067	rs7797644	C (0.77)	1.04	***DAGLB, RAC1***, *FAM220A*, ***KDELR2***	29
74	chr7: 12261911	rs11509880	A (0.36)	1.04	***TMEM106B***, *THSD7A*	29
75	chr7: 19036775	rs2023938	C (0.10)	1.08	***HDAC9***	25
76	chr7: 45077978	rs2107732	G (0.91)	1.06	***CCM2,*** *MYO1G*	29
77	chr7: 107244545	rs10953541	C (0.80)	1.08	***BCAP29, GPR22***	22
78	chr7: 117332914	rs975722	G (0.4)	1.03	*CTTNBP2*, ***CFTR***, *ASZ1*	29
79	chr7: 129663496	rs11556924	C (0.62)	1.09	***ZC3HC1, KLHDC10***	24
80	chr7: 139757136	rs10237377	G (0.65)	1.05	***PARP12***, ***TBXAS1***	105
81	chr7: 150690176	rs3918226	T (0.06)	1.14	***NOS3***	30
82	chr8: 18286997	rs6997340	T (0.31)	1.04	***NAT2***	29
83	chr8: 19813180	rs264	G (0.86)	1.11	***LPL***	25, 33, 90
84	chr8: 22033615	rs6984210	G (0.06)	1.08	***BMP1***, *SFTPC, DMTN, PHYHIP, DOK2, XPO7*	29
85	chr8: 106565414	rs10093110	G (0.58)	1.03	***ZFPM2***	29
86	chr8: 126490972	rs2954029	A (0.55)	1.06	***TRIB1***	25, 90, 106
87	chr9: 22125503	rs1333049	C (0.46)	1.29	***ANRIL,*** *CDKN2B-AS*	14–16, 24, 62
88	chr9: 110517794	rs944172	C (0.28)	1.04	***KLF4***	29
89	chr9: 113169775	rs111245230	C (0.04)	1.14	***SVEP1***	33
90	chr9: 124420173	rs885150	C (0.27)	1.03	***DAB2IP***	29
91	chr9: 136154168	rs579459	C (0.21)	1.10	***ABO***, *SURF6, GBGT1*	24, 90, 108
92	chr10: 12303813	rs61848342	C (0.36)	1.04	***CDC123***, *NUDT5, OPTN*	29
93	chr10: 30335122	rs2505083	C (0.38)	1.07	***KIAA1462***	22, 109
94	chr10: 44775824	rs1746048	C (0.87)	1.09	***CXCL12***	14, 24
95	chr10: 82251514	rs17680741	T (0.72)	1.05	***TSPAN14***, *MAT1A*, ***FAM213A***	29
96	chr10: 91002927	rs1412444	T (0.42)	1.09	***LIPA***	22
97	chr10: 104719096	rs12413409	G (0.89)	1.12	***CYP17A1, CNNM2, NT5C2***	24, 110, 111
98	chr10: 105693644	rs4918072	A (0.27)	1.04	*STN1*, ***SH3PXD2A***	29
99	chr10: 124237612	rs4752700	G (0.45)	1.03	***HTRA1,*** *PLEKHA1*	29
100	chr11: 5701074	rs11601507	A (0.07)	1.09	***TRIM5***, ***TRIM22***, ***TRIM6***, *OR52N1, OR52B6*	29
101	chr11: 9751196	rs10840293	A (0.55)	1.06	***SWAP70***	30
102	chr11: 10745394	rs11042937	T (0.49)	1.03	***MRVI1, CTR9***	55
103	chr11: 13301548	rs1351525	T (0.67)	1.05	***ARNTL***	27, 28
104	chr11: 43696917	rs7116641	G (0.31)	1.03	***HSD17B12***	29
105	chr11: 65391317	rs12801636	G (0.77)	1.05	*PCNX3, POLA2, RELA*, ***SIPA1***, *and others*	105
106	chr11: 75274150	rs590121	T (0.30)	1.05	***SERPINH1***	105
107	chr11: 100624599	rs7947761	G (0.28)	1.04	***ARHGAP42***	29

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Table I *Continued*

No	Position	Lead SNP	EAF	OR	Gene(s) at locus	References
108	chr11: 103660567	rs974819	T (0.32)	1.07	***PDGFD***	22
109	chr11: 116648917	rs964184	G (0.13)	1.13	***APOA1-C3-A4-A5***	24, 112
110	chr12: 7175872	rs11838267	T (0.87)	1.05	***C1S***	29
111	chr12: 20220033	rs10841443	G (0.67)	1.06	***RP11-664H17.1***	26
112	chr12: 54513915	rs11170820	G (0.08)	1.10	***HOXC4***	27
113	chr12: 57527283	rs11172113	C (0.41)	1.06	***LRP1***, *STAT6*	55
114	chr12: 95355541	rs7306455	G (0.9)	1.05	*NDUFA12*, ***FGD6***	29
115	chr12: 111884608	rs3184504	T (0.44)	1.07	***SH2B3***, *FLJ21127, ATXN2, and others*	24, 90, 110, 111, 113
116	chr12: 118265441	rs11830157	G (0.36)	1.12	***KSR2***	30
117	chr12: 121416988	rs2244608	G (0.35)	1.06	***HNF1A***, *OASL, C12orf43, and others*	26–28, 105
118	chr12: 124427306	rs11057401	T (0.69)	1.08	***CCDC92***	26
119	chr12: 125307053	rs11057830	A (0.15)	1.07	***SCARB1***	55, 105
120	chr13: 28973621	rs9319428	A (0.32)	1.06	***FLT1***	25
121	chr13: 33058333	rs9591012	G (0.66)	1.04	***N4BP2L2, PDS5B***	29
122	chr13: 110960712	rs4773144	G (0.44)	1.07	***COL4A1***, ***COL4A2***	24
123	chr13: 113631780	rs1317507	A (0.26)	1.04	***MCF2L***, *PCID2*, ***CUL4A***	29
124	chr14: 58794001	rs2145598	G (0.42)	1.03	***ARID4A, PSMA3***	29
125	chr14: 75147552	rs3832966	I (0.46)	1.05	***TMED10***, *ZC2HC1C, RPS6KL1, NEK9, EIF2B2e, ACYP1*	27
126	chr14: 94838142	rs112635299	G (0.92)	1.13	*SERPINA2*, ***SERPINA1***	29
127	chr14: 100133942	rs2895811	C (0.43)	1.07	***HHIPL1***, ***YY1***	24
128	chr15: 65024204	rs6494488	A (0.82)	1.05	*OAZ2, RBPMS2*, ***TRIP4,*** *and others*	105
129	chr15: 67455630	rs56062135	C (0.79)	1.07	***SMAD3***	30
130	chr15: 79089111	rs3825807	A (0.57)	1.08	***ADAMTS7***	22, 24, 108
131	chr15: 89574218	rs8042271	G (0.9)	1.10	***MFGE8***, *RP11-326A19.4, ABHD2*	30
132	chr15: 91416550	rs17514846	A (0.44)	1.07	***FURIN***, ***FES***	25, 107
133	chr15: 96146414	rs17581137	A (0.75)	1.04	gene desert	29
134	chr16: 56961074	rs1800775	C (0.51)	1.03	***CETP***	55
135	chr16: 72096666	rs1050362	A (0.38)	1.04	*DHX38*, ***HP***, *DHODH*	105
136	chr16: 75387533	rs3851738	C (0.60)	1.07	***CFDP1, BCAR1***	26, 27
137	chr16: 81906423	rs7199941	A (0.4)	1.04	***PLCG2***, *CENPN*	29
138	chr16: 83045790	rs7500448	A (0.77)	1.07	***CDH13***	26–28
139	chr17: 2126504	rs216172	C (0.37)	1.07	***SMG6***, *SRR*	24
140	chr17: 17543722	rs12936587	G (0.56)	1.07	***Ral1***, ***PEMT***, *RASD1, SMCR3, TOM1L2*	24
141	chr17: 27941886	rs13723	G (0.49)	1.04	***CORO6, BLMH, ANKRD13B, GIT1, SSH2, EFCAB5***	29
142	chr17: 30033514	rs76954792	T (0.22)	1.04	***COPRS, RAB11FIP4***	29
143	chr17: 40257163	rs2074158	C (0.18)	1.05	***DHX58, KAT2A, RAB5, NKIRAS2, DNAJC7, KCNH4, HCRT, GHDC***	29
144	chr17: 45013271	rs17608766	C (0.14)	1.07	***GOSR2***, *MYL4, ARL17A, and others*	105
145	chr17: 46988597	rs46522	T (0.53)	1.06	***UBE2Z***, ***GIP***, *ATP5G1*	24
146	chr17: 59013488	rs7212798	C (0.15)	1.08	***BCAS3***	30
147	chr17: 62387091	rs1867624	T (0.61)	1.04	***PECAM1***, ***DDX5***, ***TEX2***	105
148	chr18: 47229717	rs9964304	C (0.38)	1.04	***ACAA2, RPL17***	29
149	chr18: 57838401	rs663129	A (0.26)	1.06	***PMAIP1, MC4R***	30
150	chr19: 8429323	rs116843064	G (0.98)	1.14	***ANGTPL4***	33, 90
151	chr19: 11163601	rs1122608	G (0.77)	1.14	***LDLR***, ***SMARCA4***	18, 24, 90, 112
152	chr19: 17855763	rs73015714	G (0.2)	1.06	***FCHO1, COLGALT1***	29
153	chr19: 32882020	rs12976411	A (0.91)	1.33	***ZNF507***, *LOC400684*	30
154	chr19: 41854534	rs8108632[a]	T (0.48)	1.05	***HNRNPUL1,*** *CCDC97*, ***TGFB1***, *B9D2*	26–28
155	chr19: 45395619	rs2075650	G (0.14)	1.14	***APOE***, ***APOC1***, *TOMM40*, ***PVRL2***, ***COTL1***	90, 106
156	chr19: 46190268	rs1964272	G (0.51)	1.04	***SNRPD2***, *GIPR*	28
157	chr20: 33764554	rs867186	A (0.89)	1.07	***PROCR,*** *ASIP, NCOA6*, ***ITGB4BP/EIF6*** *and others*	105
158	chr20: 39924279	rs6102343	A (0.25)	1.04	***ZHX3***, ***PLCG1***, *TOP1*	29
159	chr20: 44586023	rs3827066	T (0.14)	1.04	*PCIF1, ZNF335, NEURL2*, ***PLTP, MMP9***	29, 114
160	chr20: 57714025	rs260020	T (0.13)	1.04	***ZNF831***	29

Continued

Table I *Continued*

No	Position	Lead SNP	EAF	OR	Gene(s) at locus	References
161	chr21: 30533076	rs2832227	G (0.18)	1.04	*MAP3K7CL*, ***BACH1***	29
162	chr21: 35599128	rs9982601	T (0.15)	1.18	*MRPS6, SLC5A3*, ***KCNE2***	18
163	chr22: 24262640	rs180803	G (0.97)	1.20	***ADORA2A***	30

The most likely causal gene(s) at each locus are formatted as bold text. Evidence for respective causal gene(s) is based on literature searches and/or data from the GTEx portal (V6) and SNiPA v3.2[102] (accessed January 2018).
[a]*GUCY1A3* is now designated *GUCY1A1*, according to the HUGO Gene Nomenclature Committee.

2.3.3 From rare to common variants: allelic series for CAD

For many years, it has been contended that the genetic component reflected by multiple common genetic variants identified in GWAS cannot explain the familial clustering of CAD, as indicated by a positive family history. As stated earlier, the risk variants identified in GWAS are characterized by high MAF and small effect size. In a diploid genome, every individual of Western European descent carries on average between 130 and 160 risk alleles at the 163 loci detected so far. Hence, common risk alleles appear to explain the widespread predisposition of humans to atherosclerosis, rather than the genetic signal indicated by a positive family history.[6,42] In contrast, a positive family history appears to be mediated by rare deleterious genetic variants[6] that segregate according to Mendelian inheritance or by specific interactions of more common genetic variants (epistasis).[43,44] Remarkably, a recent study by Gormley *et al.*[45] demonstrated a substantial contribution of common polygenic variation to familial aggregation in migraine, adding to the discussion of the origin of familial clustering in complex diseases. Similar results have been observed for familial dyslipidaemia.[46] Nevertheless, in a few families with multiple affected individuals, rare causal variants have been identified by exome sequencing.[6,47–49] Interestingly, there is a marked overlap between genes that exhibit co-segregation in family-based studies and those identified in GWAS. Indeed, almost all genes causing monogenic forms of CAD or MI also generate a signal in GWAS [i.e. *GUCY1A3* (now designated *GUCY1A1*, according to the HUGO Gene Nomenclature Committee), *PDE5A*, *LDLR*, *PCSK9*, *APOB*, and *LPA*], implicating the same pathways in CAD aetiology, including those regulating vascular tone, blood pressure, LDL-C, triglyceride-rich lipoproteins, inflammation, trans-endothelial migration, smooth muscle proliferation, and lipoprotein(a).[6,48–50]

2.3.4 Pleiotropy: a common characteristic of CAD risk variants

Pleiotropy describes the phenomenon whereby one gene affects more than one phenotype. It has been suspected for years that pleiotropy is a common phenomenon in the human genome;[51,52] however, it is only since the availability of comprehensive data sets, such as the GWAS catalog,[53] that a systematic analysis of pleiotropy in the human genome has been feasible.[54] Using this resource, Chesmore *et al.* discovered that the degree of pleiotropy scales positively with the average effect size of a gene variant and negatively with the variance of the effect sizes of genes with a given number of associated phenotypes. Based on this and prior data, it is becoming increasingly evident that pleiotropy is a common, if not ubiquitous, phenomenon. In general, these results have implications for the understanding of disease aetiologies, with the potential for common biological mechanisms to underlie even disparate diseases, and for the elucidation of the genotype–phenotype landscape. In the context of CAD specifically, a recent study by Webb *et al.*[55] systematically evaluated the degree of pleiotropy by testing all known CAD loci for association with cardiovascular risk factors (lipid traits, blood pressure phenotypes, body mass index, diabetes, and smoking behaviour), as well as with other diseases/traits, through interrogation of the currently available GWAS catalogue.[53] Of the 62 CAD risk loci studied by Webb and colleagues, 24 (38.7%) were significantly associated with a traditional cardiovascular risk factor, with some exhibiting multiple associations. Consistent with the findings of Chesmore *et al.*, half of CAD risk loci exhibited associations with a range of other diseases/traits (such as migraine, cancer, and height) (*Figure 3*).

2.3.5 Biological insights from GWAS

Experimental and *in silico* studies have both confirmed previous findings and revealed novel insights into the biology of atherosclerosis. In the following sections, we discuss the effects of SNPs at the chromosome 9p21 locus and in the vicinity of genes affecting nitric oxide (NO)/cGMP signalling. For a more detailed discussion of biological insights into lipid, as well as non-lipid, mechanisms underlying CAD derived from GWAS, we refer to Khera and Kathiresan.[7]

2.3.5.1 Chromosome 9p21. The strongest effects on coronary atherosclerosis risk are conferred by risk alleles at chromosomal locus 9p21, which are carried by almost 75% of the global population (excluding black Africans).[56] This locus is an archetype for the challenges that arise in attempts to unravel the precise mechanisms underlying disease.[57–60]

The 9p21 locus appears to be associated specifically with the risk of a first CHD event [hazard ratio (HR) of first event = 1.19; 95% confidence interval (CI): 1.17–1.22], rather than subsequent CHD events (HR = 1.01; 95% CI: 0.97–1.06), suggesting that the effect of the functional variant(s) at 9p21.3 may be to stimulate coronary atherosclerosis (i.e. CAD) rather than MI.[61] Recently, it was suggested that the cardiovascular disease-associated region on 9p21 is located in the last exons of a long non-coding RNA, specifically the antisense non-coding RNA in the *INK4* locus (*ANRIL*; also known as *CDKN2BAS*).[62] Interestingly, Holdt *et al.*[63] reported that a linear form of *ANRIL* confers risk, whereas its circular (circANRIL) counterpart confers atheroprotection, by controlling ribosomal RNA maturation and modulating pathways of atherogenesis. Remarkably, the observed high stability of circRNAs appears to be a common phenomenon and is therefore an appealing potential novel therapeutic target for human diseases more generally.[63] The closest protein-coding (candidate) genes include the cyclin-dependent kinase inhibitors *CDKN2A* and *CDKN2B*. As covered in a review by Hannou *et al.*,[57] several studies failed to decipher the exact mechanism through which the CDKN2A/B gene products might function in relation to CAD. Using unbiased genomic techniques based on chromosome conformation capture, Harismendy *et al.*[64] detected long-distance interactions between the enhancer interval containing the CAD locus and *CDKN2A/B*. Considering the effects of interactions across large distances, this

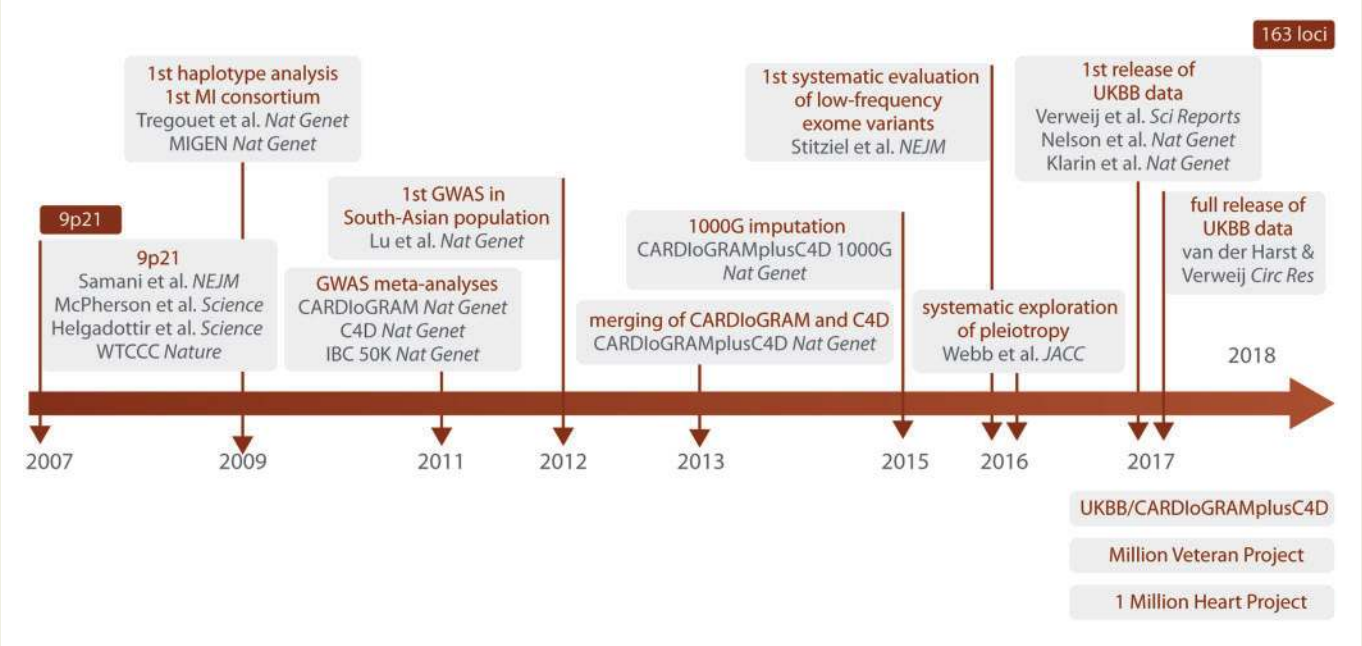

Figure 1 Milestones in cardiovascular genome research from 2007 to 2017 and beyond.

observation tentatively (and excitingly) points to the possibility that 9p21.3 disease-associated SNPs could interact with and modify other distant genes. Nevertheless, the strongest data at present time suggest that CAD risk relates to the ratio of circular to linear ANRIL which affects basic cellular mechanisms, including transcriptional activity, proliferation, and apoptosis in vascular smooth muscle cells.[63]

2.3.5.2 NO/cGMP signalling. There is strong evidence that NO/cGMP signalling has an important role in atherosclerosis, as several SNPs tagging key genes in the pathway, including *NOS3*, *GUCY1A1* (formerly *GUCY1A3*), *PDE5A*, *PDE3A*, and *MRVI1* are associated with CAD with genome-wide significance (*Figure 4*).[6,25,26,30] Moreover, a genetic risk score (GRS) using common variants in *NOS3* (rs3918226) and *GUCY1A1* (rs7692387) is associated with risk for coronary heart disease, peripheral arterial disease, and stroke.[65] Kessler *et al.*[66] elucidated the molecular link between rs7692387, which tags the *GUCY1A1* locus, and CAD risk; the SNP is located in an intronic region and modulates *GUCY1A1* promoter activity, as shown by luciferase assays. Interestingly, the transcription factor ZEB1 binds preferentially to the non-risk allele, leading to increased *GUCY1A1* expression, higher sGC levels and higher sGC activity upon stimulation with NO. In conjunction with mouse data, Kessler and colleagues subsequently linked augmented sGC expression to lower risk of CAD. Additionally, the importance of the pathway was confirmed by the fact that a loss-of-function mutation in *GUCY1A1* caused premature CAD and MI in an extended family.[6] Unlike *GUCY1A1*, the precise molecular mechanisms linking the lead SNPs at *NOS3*, *PDE5A*, *PDE3A*, and *MRVI1* with CAD risk are largely unknown.

Emdin *et al.*[65] confirmed that rare variants that inactivate the *GUCY1A1* or *NOS3* genes are associated with higher systolic blood pressure and an up to three-fold higher risk of coronary heart disease. Based on the results of these genetic studies, pharmacologic stimulation of NO signalling may prove useful in the prevention or treatment of cardiovascular disease. Indeed, Riociguate (BAY 63-2521), an sGC stimulator, is already in clinical use. In the PATENT trial, the drug had proved efficacy in patients with pulmonary hypertension.[67] Riociguate is of particular interest because it acts synergistically with NO;[68] i.e. reduced sGC activity or expression could hypothetically be compensated for by the presence of pharmacologic modulators of sGC activity. Future clinical studies are needed to define the effect of sGC stimulators on atherosclerosis phenotypes.

3. The challenges involved in moving from genetic associations to therapeutic targets and beyond

Although genetic associations provide a strong foundation for the identification of therapeutic targets, a number of challenges can arise. First, the majority of lead associated variants lies within non-coding regions, making it difficult to predict their functions and identify specific targets/genes. Secondly, almost all loci harbour multiple genes, and the likely causal gene often needs to be defined by detailed investigations. Thirdly, only few loci encompass candidate genes that unequivocally explain the association signal (e.g. *LDLR* and *PCSK9*); at all other loci, the gene(s) responsible must be determined and the underlying pathomechanisms elucidated. Finally, even where a validated gene/pathway is clear, it is necessary to demonstrate that the target is druggable. Ultimately, success in defining targets for pharmaceutical exploitation will depend not only on the identification of causal genes but also on the elucidation of the downstream pathways and biological networks, as the best druggable target may not be the causal gene, but rather some other node in the network. The following sections will discuss in more detail some of the challenges in moving from genetic association to therapeutic targets (see also *Figure 5*).

3.1 Annotation of causal genes at GWAS loci

As stated earlier, an inherent limitation of GWAS is that they do not provide information about the biological meaning of the causal variants that

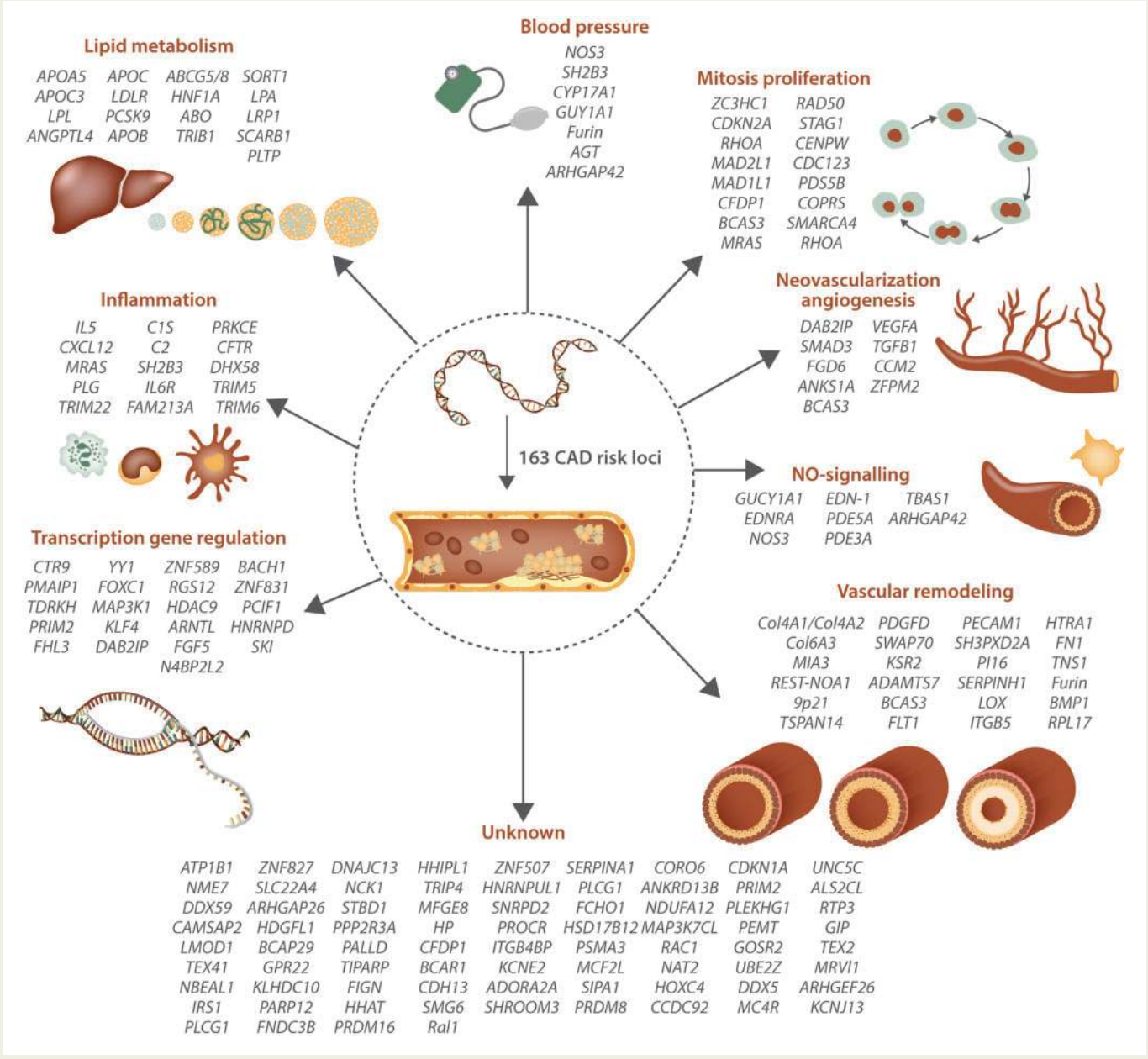

Figure 2 Genes mapped to 163 CAD risk loci and pathophysiological pathways in atherosclerosis.

are tagged by genome-wide significant SNPs (tagSNPs). To translate GWAS results to biological function, post-GWAS analysis is necessary. Usually, such analyses start with inexpensive *in silico* (bioinformatics) studies of tagSNPs. Several tools and statistical techniques are used to extract meaning from, and prioritize, association signals, which are subsequently investigated experimentally (a selection of available tools, methods, and platforms is presented in Supplementary material online, *Table S2*). In the sections below, we briefly describe some of the most strongly validated and recently developed methods.

3.1.1 Expression quantitative trait loci

Over the last decade, studies to unravel the genetics underpinning the regulation of gene expression have progressed substantially. Gene transcript levels, which are heritable and therefore amenable to GWAS, were the first expression phenotypes to be studied. SNPs that modulate transcript levels are referred to as expression quantitative trait loci (eQTL) or eSNPs, and can be associated with gene expression levels either locally (*cis*) or at a distance (*trans*, i.e. more than 5 Mb away from the associated variant).[69] Recently, the study of eSNPs has been extended to other molecular QTL that regulate gene expression at various levels, from chromatin state to cellular response. The importance of regulatory SNPs has recently been documented by a study from Nikpay *et al.*[70] showing that the heritability of CAD is mainly attributed to SNPs located in epigenetic sites associated with transcriptional activity.

Original GWAS papers reporting novel SNPs usually explore publicly available multi-tissue transcriptome data sets for differential expression levels related to the risk alleles. Such signals are used to provide additional evidence that the associated SNP has a functional effect and to

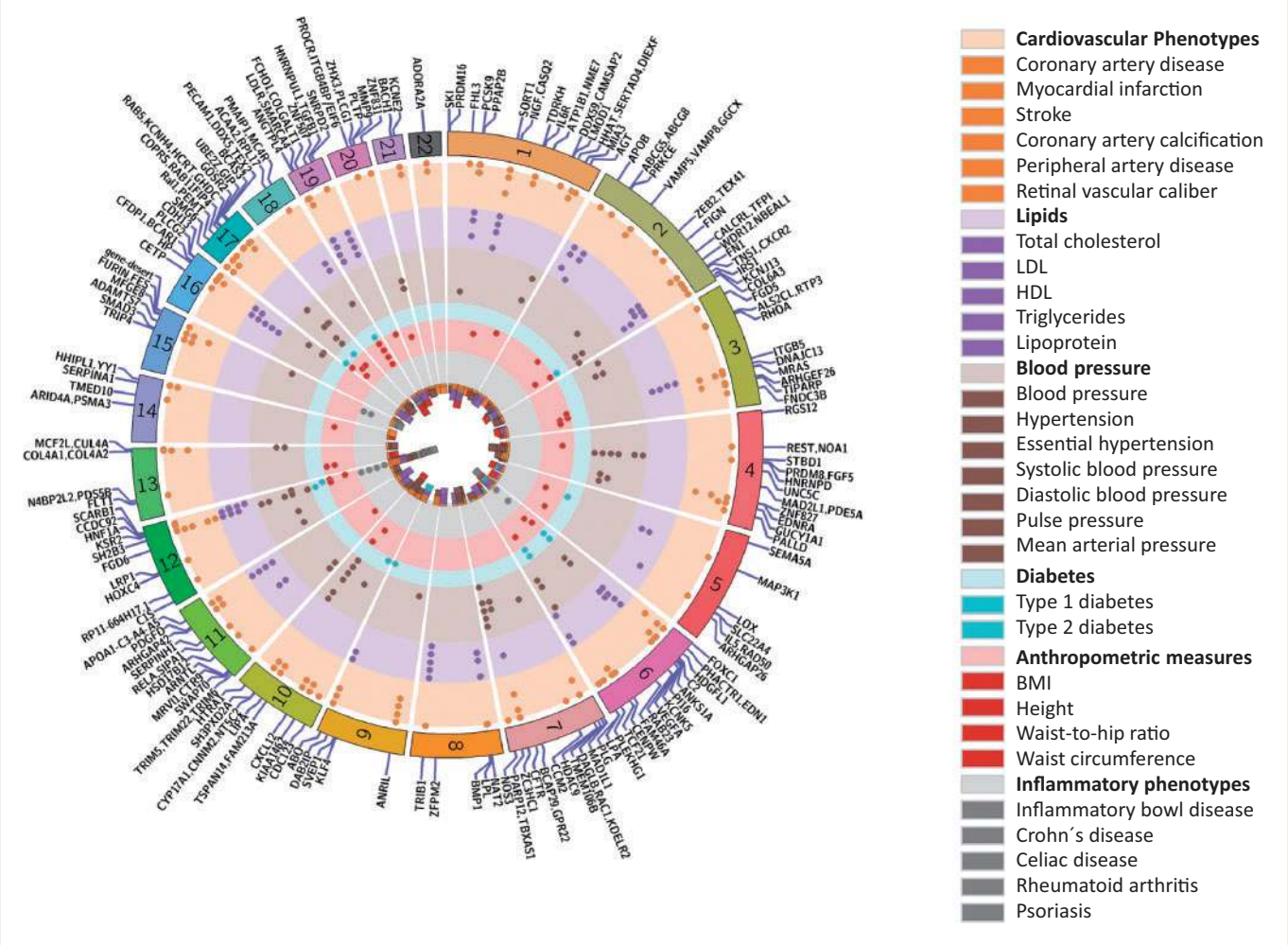

Figure 3 Circosplot showing 163 risk loci for CAD under the chromosomes, where they are located. The dots represent conditions which are likewise significantly associated with CAD risk alleles indicating pleiotropy. Some loci, e.g. the SH2B3 locus at chromosome 10, show signals for multiple diseases (January 2018).

choose candidate target genes for experimental follow-up. A variety of tissue and disease-specific databases are available, including ENCODE,[40] GTEx,[71] Epigenome RoadMap,[72] STARNET,[73] and chromatin interaction information,[74] some of which have been used to investigate CAD-relevant tissues.[75] For example, a study using STARNET data showed that *cis*- and *trans*-acting loci could contribute to a mechanism by which multiple loci affect the heritability of risk for cardio-metabolic diseases (precursors of CAD).[73] Clearly, eQTL analyses can facilitate annotation of the most likely causal gene at a locus identified by GWAS; however, prioritization of genes within a locus is sometimes difficult, because variants at a single GWAS locus are often eQTL for multiple genes, as observed by Braenne *et al.*[76]

3.2 Network analysis

There are several tools available that can either prioritize variants found during an association analysis and/or perform tissue enrichment analysis. An interesting study published recently[77] used various tissue-specific regulatory networks and protein–protein interaction networks that do not rely solely on a priori knowledge to detect genes strongly implicated in the prevalence of CAD and also identify the novel key regulators of CAD, *LUM*, *HGD*, *F2*, *ANXA3*, and *STAT3*. Recently, Vilne *et al.* demonstrated how hypercholesterolaemia can hinder mitochondrial activity during atherosclerosis progression and identified oestrogen-related receptor-α and its co-factors PGC1-α and -β as potential therapeutic targets to counteract these processes, using a network approach.[78]

3.3 Systems genetics approaches in the cardiovascular field

Reduced costs of high-throughput analyses, as well as publicly available data sets, have allowed simultaneous analysis of data generated using multiple '-omics' platforms (namely, genomics, epigenomics, transcriptomics, proteomics, metabolomics, and microbiomics); cloud[79] and/or web[80] computing are vital to this type of approach. Awareness is increasing that (i) identified CAD loci only explain part of heritability; (ii) common diseases, such as CAD, tend to occur because of gene regulation changes; and (iii) similar genetic variants contribute to different final outcomes; hence, it is logical that systems genetics has evolved to integrate data from various '-omics' studies and generate a broader view of the molecular mechanisms involved. Indeed, this approach has helped to explain the complexity of the molecular patterns associated with CAD.

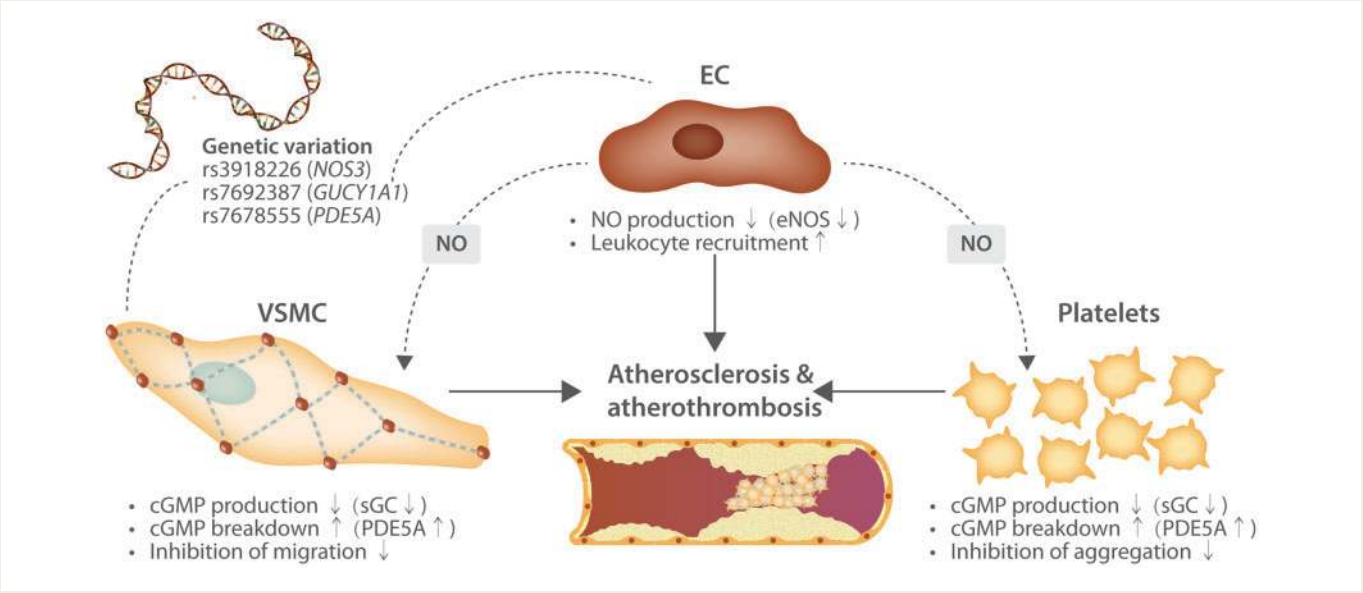

Figure 4 Role of NO-signalling in coronary artery disease.

Systems genetics, as defined by Björkegren *et al.*,[81] uses molecular mechanisms to define disease-driving molecular processes that underlie GWAS, whole-exome sequencing or whole-genome sequencing hits, and to integrate such processes with functional genomic data. One example of associated SNPs exerting tissue-dependent effects on gene expression was reported by Musunuru *et al.*[82] They integrated eQTL and protein QTL information to determine that an MI risk variant alters the expression of the *SORT1* gene in the liver (via a lipoprotein metabolism-regulated pathway). This observation supported the findings of a prior GWAS that identified a strong association between the 1p13 locus and plasma LDL-C levels in MI patients and, moreover, concluded that this locus influenced the risk of MI by conferring changes in plasma lipids. Another recent study[83] used a systems genetics approach to integrate DNA genotypes and gene expression profiles from seven CAD-relevant tissues with CAD CARDIoGRAM GWAS information. Using this method, the authors showed that RNA-processing genes are pivotal in causing CAD and, furthermore, identified several strongly inherited, evolutionarily conserved, risk-enriched CAD genes that cause regulatory gene network alterations across vascular and metabolic tissues.

Compared with individual -omics studies, the multi-omics approach provides a more comprehensive understanding of the flow of information from the disease driver to its functional consequence or interaction; however, multifactorial diseases, such as CAD, are extremely complex, which may partly account for the lack of multi-omics studies of CAD to date.

3.4 Mendelian randomization studies

Although randomized controlled trial studies are the optimal way to establish causal relationships between risk factors, exposures, and a disease of interest (in our case, CAD), sometimes they are not possible. An alternative is to use Mendelian randomization (MR) analysis of GWAS data.[84] The rationale is to use genetic variants as proxies for potentially modifiable exposures to facilitate the identification of causal effects for risk of CAD. MR analysis is resistant to confounding factors, which is an advantage over randomized controlled trials. An in-depth discussion of MR studies in the cardiovascular field can be found in this issue.[85]

3.5 Potential of precision medicine in CAD

One promise of GWAS, which has already partly been fulfilled, was that the results would facilitate the (re)identification of risk genes and disease-associated pathways useful for drug development or drug selection, as recently showcased for *GUCY1A1*,[86] *PCSK9*,[87] *ANGPTL4*,[33] and *ANGPTL3*[88] (more examples are compiled in *Table 2*). With more functional studies linking risk variants to underlying causal genes, it is likely that additional novel therapeutic targets will be identified.[7,89]

The examples depicted in *Table 2* show how the discovery of (rare) genetic variants highlighted pathways influencing both an intermediate phenotype, i.e. lipid metabolism, and coronary atherosclerosis. An important fact, however, is that the therapies which are based on genetic findings are not limited to individuals carrying such variants. The importance of *NPC1L1* in lipid metabolism and CAD risk has been clearly shown from genetic point of view.[90] The potential of treating individuals at risk with the NPC1L1 inhibitor ezetimibe, however, was successful in a large clinical trial that was not focusing on individuals with altered NPC1L1 function.[91] The same is actually true for PCSK9 inhibitors where treatment of hypercholesterolaemia and reduction of cardiovascular events was successful irrespectively of the presence or absence of PCSK9 variants.[92] Hence, in the context of precision medicine, results from GWAS might lead to two developments that have to be analysed separately: The detection of rare variants/mutations or a genetic profile associated with a distinct pathway might lead to the development and/or use of a specific treatment. An example is the *GUCY1A1* locus, which has already been discussed above. Heterozygous carriers of rare mutations in this gene might benefit from the use of a pharmacological modulator of sGC function. Indeed, *in vitro* data suggest that coding variants which are present in individuals suffering from premature CAD lead to reduced formation of the second messenger cGMP but can be compensated by the use of an sGC stimulator.[86] This is an example of precision medicine in the sense of developing individualized treatment strategies. A second

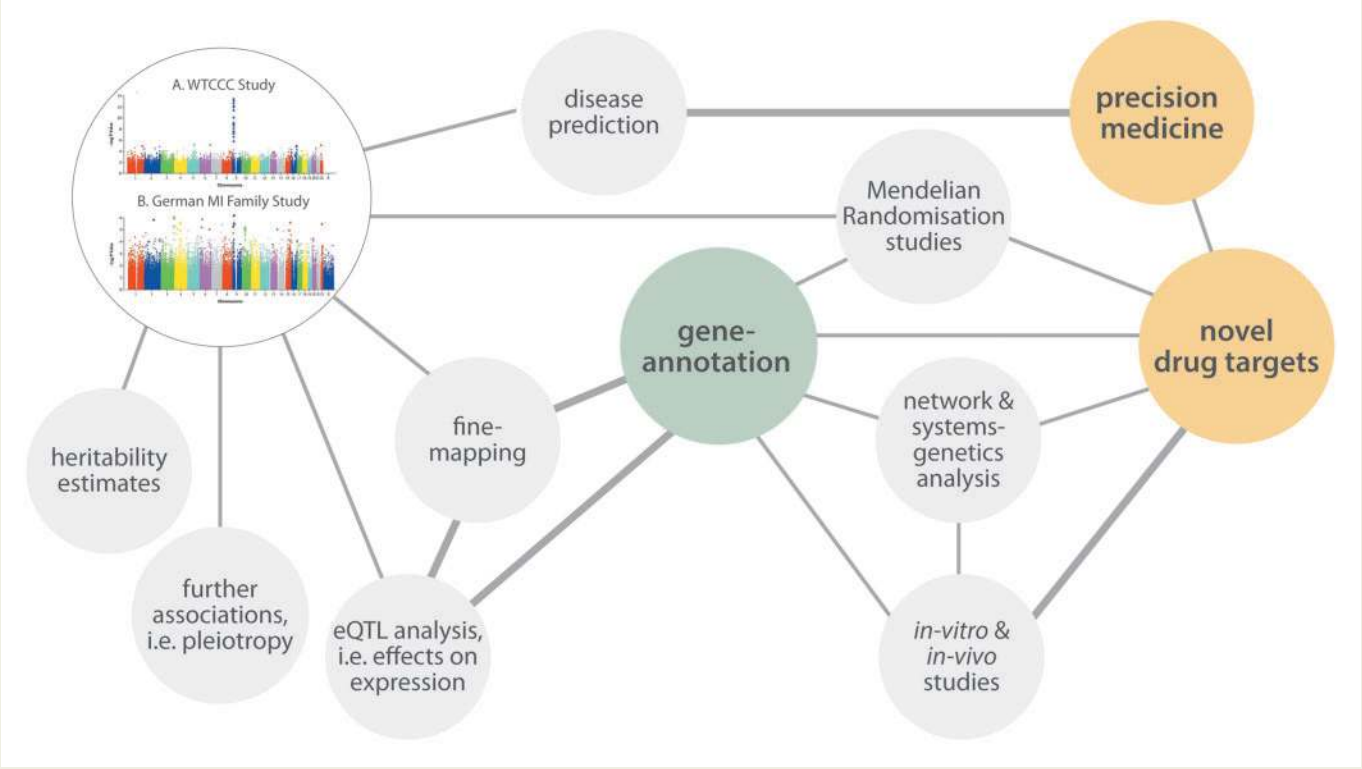

Figure 5 Complementarity of methods and analysis surveyed in yielding novel insights into disease biology. Thickness of lines reflect importance of methods/analysis to yield insights.

Table 2 Examples of genes affecting CAD and MI risk identified by large-scale array-based or deep-sequencing projects with relevance for therapeutic development

Gene	*PCSK9*	*NPC1L1*	*LPA*	*LPL*	*APOC3*	*ANGPTL4*	*ANGPTL3*
Frequency	1 in 50 blacks	1 in 150	1 in 13	1 in 10	1 in 150	1 in 500	1 in 300
Phenotype	LDL	LDL	Lp(a)	TG	TG	TG	TG, LDL
Risk	80% lower risk	53% lower risk	14% higher risk	17% lower risk	40% lower risk	57% lower risk	34% lower risk
Therapy	Evolocumab, Bococizumab, Alirocumab	Ezetimibe	Antisense in development	?	Antisense in development	Monoclonal antibodies in development	Monoclonal antibodies in development
References	115	116	117	118	119	118, 120	121–123

possible use of genetic data in precision medicine is rather linked to the development of novel therapies sharply focusing on specific molecular processes or pathways which might be useful for all patients. Again NO/cGMP signalling represents an excellent example as common non-coding variants in *GUCY1A1* gene[6,25] and four other genes[26,28,30,55] encoding important proteins in this pathway have been identified to be associated with CAD. This raises the question whether modulating NO/cGMP signalling might be a promising therapeutic strategy to prevent CAD. In fact, stimulators of the sGC and inhibitors of PDE5A are already in clinical use, e.g. pulmonary hypertension. Data regarding prevention of cardiovascular endpoints are thus far lacking. Nevertheless, enhancing NO/cGMP signalling could emerge as a strategy comparable to reducing LDL cholesterol. Taken together, GWAS laid to ground to discover novel therapies for particular individuals and for larger numbers of individuals at risk.

However, currently GWAS do not provide sufficient information necessary to stratify individuals according to severity, prognosis, and responsiveness, which is required for drug development and/or selection. To overcome these hurdles, Morita and Komuro[93] suggested stratifying large-scale prospective studies according to clinically affected sub-phenotypes in patients with similar clinical presentations, and then adding a second layer independent of the variant associated with disease onset, to search for associated variants (or driver pathways) with the disease sub-phenotype. One example of such stratification would be to discriminate between dyslipidaemia patients with and without CAD; here, a subpopulation analysis to identify genetic variants associated with

CAD susceptibility could facilitate the selection of individuals susceptible to CAD who should receive proactive, perhaps intensive, cardiometabolic abnormality management to prevent the disease.[93] On a macro level, current pharmacogenomics research is proceeding along these lines. Contrary to the sub-phenotype method, some argue that for CAD patients it would be more useful to highlight the blend of genetic and environmental causal factors (or pathways) that underlie CAD development in large population-scale cohorts.[94] Such discussion can only promote this type of research approach and be used to facilitate progression towards a future of individualized precision medicine.

3.5.1 Polygenic risk scores for CAD

One potential application of genomic research outcomes is the prediction of the risk of an individual for a complex disorder, such as CAD, and use of this information to encourage the adoption of preventive measures. Familial hypercholesterolaemia is a condition characterized by monogenic mutations in the genes encoding *LDLR*, *PCSK9*, and *APOB*. Loss-of-function variants in these genes lead to increased cholesterol, and carriers have an up to four-fold elevated risk for CAD compared with non-carriers.[95] Early diagnosis, either on the basis of clinical criteria (including LDL cholesterol and family history) or DNA sequencing, can lead to timely treatment with lipid lowering medication and consequently lower the risk of cardiovascular disease to levels equivalent to those of the general population.[96] In contrast, the value of individual common variants is very limited for risk prediction. Polygenic risk scores (PRSs), derived by summing the number of risk variant alleles in each individual weighted by the impact of each allele on disease risk, perform better than individual variants; however, the predictive power remains limited.[97,98] Nevertheless, individuals with a high GRS, i.e. those in the top quintile of the risk score distribution, appear to have a larger benefit from statin treatment than those with low scores.[99] Moreover, among participants at high genetic risk, adherence to a healthy lifestyle is associated with an almost 50% lower relative risk of CAD.[100] A novel approach, developed by Khera *et al.*,[101] which aggregated information from 6.6 million common variants to build a PRS, demonstrated convincingly that such a PRS can identify a four-fold increased risk for CAD in 2.5% of the population, comparable to familial hypercholesterolaemia mutation carriers.[101] On a cautionary note, the potential benefits of disclosing the genetic risk to patients must be weighed against possible unfavourable consequences, such as increased treatment costs, psychological distress or discrimination, and a sense of fatalism in high-risk individuals. Clearly, more work is needed to optimize the disclosure of genetic risk to patients and their healthcare providers, and to assess whether such disclosure can improve clinical outcomes.

4. Conclusion

The last decade of genomic research has led to the identification of 163 common genetic loci conferring modest risk for CAD and MI. It is foreseeable that more variants will be identified by increasing GWAS sample sizes. In addition, whole-exome and whole-genome sequencing studies have identified rare risk variants in families and large patient cohorts with stronger effects. Nevertheless, although only part of the heritable risk for CAD is yet explained, we have developed a much more comprehensive picture of the biology underlying the disease, and with increasing numbers of functional studies aiming to decipher the link between genetic variation and CAD, we will finally identify novel treatment targets, as exemplified by *PCSK9*, *ANGPTL4*, *ANGPTL3*, and *GUCY1A1*. Hence, the findings generated by CAD GWAS represent an excellent starting point for the development of individualized treatment strategies in the future.

Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

Disclosure statement

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References

1. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* **385**:117–171.
2. Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2012;**32**:2045–2051.
3. Kessler T, Vilne B, Schunkert H. The impact of genome-wide association studies on the pathophysiology and therapy of cardiovascular disease. *EMBO Mol Med* 2016;**8**:688–701.
4. Marenberg ME, Risch N, Berkman LF, Floderus B, de Faire U. Genetic susceptibility to death from coronary heart disease in a study of twins. *N Engl J Med* 1994;**330**:1041–1046.
5. Myers RH, Kiely DK, Cupples LA, Kannel WB. Parental history is an independent risk factor for coronary artery disease: the Framingham Study. *Am Heart J* 1990;**120**:963–969.
6. Erdmann J, Stark K, Esslinger UB, Rumpf PM, Koesling D, de Wit C, Kaiser FJ, Braunholz D, Medack A, Fischer M, Zimmermann ME, Tennstedt S, Graf E, Eck S, Aherrahrou Z, Nahrstaedt J, Willenborg C, Bruse P, Brænne I, Nöthen MM, Hofmann P, Braund PS, Mergia E, Reinhard W, Burgdorf C, Schreiber S, Balmforth AJ, Hall AS, Bertram L, Steinhagen-Thiessen E, Li S-C, März W, Reilly M, Kathiresan S, McPherson R, Walter U, Ott J, Samani NJ, Strom TM, Meitinger T, Hengstenberg C, Schunkert H. Dysfunctional nitric oxide signalling increases risk of myocardial infarction. *Nature* 2013;**504**:432–436.
7. Khera AV, Kathiresan S. Genetics of coronary artery disease: discovery, biology and clinical translation. *Nat Rev Genet* 2017;**18**:331–344.
8. Manolio TA, Collins FS. The HapMap and genome-wide association studies in diagnosis and therapy. *Annu Rev Med* 2009;**60**:443–456.
9. Nannya Y, Taura K, Kurokawa M, Chiba S, Ogawa S. Evaluation of genome-wide power of genetic association studies based on empirical data from the HapMap project. *Hum Mol Genet* 2007;**16**:2494–2505.
10. International HapMap Consortium. The International HapMap Project. *Nature* 2003;**426**:789–796.
11. 1000 Genomes Project Consortium, Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, Marchini JL, McCarthy S, McVean GA, Abecasis GR. A global reference for human genetic variation. *Nature* 2015;**526**:68–74.
12. Iglesias AI, van der Lee SJ, Bonnemaijer PWM, Hohn R, Nag A, Gharahkhani P, Khawaja AP, Broer L, International Glaucoma Genetics C, Foster PJ, Hammond CJ,

Hysi PG, van Leeuwen EM, MacGregor S, Mackey DA, Mazur J, Nickels S, Uitterlinden AG, Klaver CCW, Amin N, van Duijn CM. Haplotype reference consortium panel: practical implications of imputations with large reference panels. *Hum Mutat* 2017;**38**:1025–1032.

13. Loh P-R, Danecek P, Palamara PF, Fuchsberger C, A Reshef Y, K Finucane H, Schoenherr S, Forer L, McCarthy S, Abecasis GR, Durbin R, L Price A. Reference-based phasing using the Haplotype Reference Consortium panel. *Nat Genet* 2016; **48**:1443–1448.
14. Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, Dixon RJ, Meitinger T, Braund P, Wichmann HE, Barrett JH, Konig IR, Stevens SE, Szymczak S, Tregouet DA, Iles MM, Pahlke F, Pollard H, Lieb W, Cambien F, Fischer M, Ouwehand W, Blankenberg S, Balmforth AJ, Baessler A, Ball SG, Strom TM, Braenne I, Gieger C, Deloukas P, Tobin MD, Ziegler A, Thompson JR, Schunkert H. WTCCC, the Cardiogenics Consortium. Genomewide association analysis of coronary artery disease. *N Engl J Med* 2007;**357**:443–453.
15. McPherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, Hinds DA, Pennacchio LA, Tybjaerg-Hansen A, Folsom AR, Boerwinkle E, Hobbs HH, Cohen JC. A common allele on chromosome 9 associated with coronary heart disease. *Science* 2007;**316**:1488–1491.
16. Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, Jonasdottir A, Sigurdsson A, Baker A, Palsson A, Masson G, Gudbjartsson DF, Magnusson KP, Andersen K, Levey AI, Backman VM, Matthiasdottir S, Jonsdottir T, Palsson S, Einarsdottir H, Gunnarsdottir S, Gylfason A, Vaccarino V, Hooper WC, Reilly MP, Granger CB, Austin H, Rader DJ, Shah SH, Quyyumi AA, Gulcher JR, Thorgeirsson G, Thorsteinsdottir U, Kong A, Stefansson K. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science* 2007;**316**: 1491–1493.
17. Wellcome Trust Case Control Consortium. Genome-wide association study of 14, 000 cases of seven common diseases and 3, 000 shared controls. *Nature* 2007;**447**: 661–678.
18. Myocardial Infarction Genetics Consortium, Kathiresan S, Voight BF, Purcell S, Musunuru K, Ardissino D, Mannucci PM, Anand S, Engert JC, Samani NJ, Schunkert H, Erdmann J, Reilly MP, Rader DJ, Morgan T, Spertus JA, Stoll M, Girelli D, McKeown PP, Patterson CC, Siscovick DS, O'Donnell CJ, Elosua R, Peltonen L, Salomaa V, Schwartz SM, Melander O, Altshuler D, Ardissino D, Merlini PA, Berzuini C, Bernardinelli L, Peyvandi F, Tubaro M, Celli P, Ferrario M, Fetiveau R, Marziliano N, Casari G, Galli M, Ribichini F, Rossi M, Bernardi F, Zonzin P, Piazza A, Mannucci PM, Schwartz SM, Siscovick DS, Yee J, Friedlander Y, Elosua R, Marrugat J, Lucas G, Subirana I, Sala J, Ramos R, Kathiresan S, Meigs JB, Williams G, Nathan DM, MacRae CA, O'Donnell CJ, Salomaa V, Havulinna AS, Peltonen L, Melander O, Berglund G, Voight BF, Kathiresan S, Hirschhorn JN, Asselta R, Duga S, Spreafico M, Musunuru K, Daly MJ, Purcell S, Voight BF, Purcell S, Nemesh J, Korn JM, McCarroll SA, Schwartz SM, Yee J, Kathiresan S, Lucas G, Subirana I, Elosua R, Surti A, Guiducci C, Gianniny L, Mirel D, Parkin M, Burtt N, Gabriel SB, Samani NJ, Thompson JR, Braund PS, Wright BJ, Balmforth AJ, Ball SG, Hall A, Wellcome Trust Case Control C, Schunkert H, Erdmann J, Linsel-Nitschke P, Lieb W, Ziegler A, Konig I, Hengstenberg C, Fischer M, Stark K, Grosshennig A, Preuss M, Wichmann HE, Schreiber S, Schunkert H, Samani NJ, Erdmann J, Ouwehand W, Hengstenberg C, Deloukas P, Scholz M, Cambien F, Reilly MP, Li M, Chen Z, Wilensky R, Matthai W, Qasim A, Hakonarson HH, Devaney J, Burnett MS, Pichard AD, Kent KM, Satler L, Lindsay JM, Waksman R, Knouff CW, Waterworth DM, Walker MC, Mooser V, Epstein SE, Rader DJ, Scheffold T, Berger K, Stoll M, Huge A, Girelli D, Martinelli N, Olivieri O, Corrocher R, Morgan T, Spertus JA, McKeown P, Patterson CC, Schunkert H, Erdmann E, Linsel-Nitschke P, Lieb W, Ziegler A, Konig IR, Hengstenberg C, Fischer M, Stark K, Grosshennig A, Preuss M, Wichmann HE, Schreiber S, Holm H, Thorleifsson G, Thorsteinsdottir U, Stefansson K, Engert JC, Do R, Xie C, Anand S, Kathiresan S, Ardissino D, Mannucci PM, Siscovick D, O'Donnell CJ, Samani NJ, Melander O, Elosua R, Peltonen L, Salomaa V, Schwartz SM, Altshuler D. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. *Nat Genet* 2009; **41**:334–341.
19. Erdmann J, Grosshennig A, Braund PS, Konig IR, Hengstenberg C, Hall AS, Linsel-Nitschke P, Kathiresan S, Wright B, Tregouet DA, Cambien F, Bruse P, Aherrahrou Z, Wagner AK, Stark K, Schwartz SM, Salomaa V, Elosua R, Melander O, Voight BF, O'Donnell CJ, Peltonen L, Siscovick DS, Altshuler D, Merlini PA, Peyvandi F, Bernardinelli L, Ardissino D, Schillert A, Blankenberg S, Zeller T, Wild P, Schwarz DF, Tiret L, Perret C, Schreiber S, El Mokhtari NE, Schafer A, Marz W, Renner W, Bugert P, Kluter H, Schrezenmeir J, Rubin D, Ball SG, Balmforth AJ, Wichmann HE, Meitinger T, Fischer M, Meisinger C, Baumert J, Peters A, Ouwehand WH, Italian Atherosclerosis Thrombosis Vascular Biology Working Group, Myocardial Infarction Genetics Consortium, Wellcome Trust Case Control Consortium, Cardiogenics Consortium, Deloukas P, Thompson JR, Ziegler A, Samani NJ, Schunkert H. New susceptibility locus for coronary artery disease on chromosome 3q22.3. *Nat Genet* 2009;**41**:280–282.
20. Tregouet DA, Konig IR, Erdmann J, Munteanu A, Braund PS, Hall AS, Grosshennig A, Linsel-Nitschke P, Perret C, DeSuremain M, Meitinger T, Wright BJ, Preuss M, Balmforth AJ, Ball SG, Meisinger C, Germain C, Evans A, Arveiler D, Luc G, Ruidavets JB, Morrison C, van der Harst P, Schreiber S, Neureuther K, Schafer A, Bugert P, El Mokhtari NE, Schrezenmeir J, Stark K, Rubin D, Wichmann HE, Hengstenberg C, Ouwehand W, Wellcome Trust Case Control C, Cardiogenics C, Ziegler A, Tiret L, Thompson JR, Cambien F, Schunkert H, Samani NJ. Genome-wide haplotype association study identifies the SLC22A3-LPAL2-LPA gene cluster as a risk locus for coronary artery disease. *Nat Genet* 2009;**41**:283–285.
21. Preuss M, Konig IR, Thompson JR, Erdmann J, Absher D, Assimes TL, Blankenberg S, Boerwinkle E, Chen L, Cupples LA, Hall AS, Halperin E, Hengstenberg C, Holm H, Laaksonen R, Li M, Marz W, McPherson R, Musunuru K, Nelson CP, Burnett MS, Epstein SE, O'Donnell CJ, Quertermous T, Rader DJ, Roberts R, Schillert A, Stefansson K, Stewart AF, Thorleifsson G, Voight BF, Wells GA, Ziegler A, Kathiresan S, Reilly MP, Samani NJ, Schunkert H, CARDIoGRAM Consortium. Design of the Coronary ARtery DIsease Genome-Wide Replication And Meta-Analysis (CARDIoGRAM) Study: a genome-wide association meta-analysis involving more than 22 000 cases and 60 000 controls. *Circ Cardiovasc Genet* 2010;**3**:475–483.
22. Coronary Artery Disease (C4D) Genetics Consortium. A genome-wide association study in Europeans and South Asians identifies five new loci for coronary artery disease. *Nat Genet* 2011;**43**:339–344.
23. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, Liu B, Matthews P, Ong G, Pell J, Silman A, Young A, Sprosen T, Peakman T, Collins R. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015; **12**:e1001779.
24. Schunkert H, König IR, Kathiresan S, Reilly MP, Assimes TL, Holm H, Preuss M, Stewart AFR, Barbalic M, Gieger C, Absher D, Aherrahrou Z, Allayee H, Altshuler D, Anand SS, Andersen K, Anderson JL, Ardissino D, Ball SG, Balmforth AJ, Barnes TA, Becker DM, Becker LC, Berger K, Bis JC, Boekholdt SM, Boerwinkle E, Braund PS, Brown MJ, Burnett MS, Buysschaert I, Carlquist JF, Chen L, Cichon S, Codd V, Davies RW, Dedoussis G, Dehghan A, Demissie S, Devaney JM, Diemert P, Do R, Doering A, Eifert S, Mokhtari NEE, Ellis SG, Elosua R, Engert JC, Epstein SE, de Faire U, Fischer M, Folsom AR, Freyer J, Gigante B, Girelli D, Gretarsdottir S, Gudnason V, Gulcher JR, Halperin E, Hammond N, Hazen SL, Hofman A, Horne BD, Illig T, Iribarren C, Jones GT, Jukema JW, Kaiser MA, Kaplan LM, Kastelein JJP, Khaw K-T, Knowles JW, Kolovou G, Kong A, Laaksonen R, Lambrechts D, Leander K, Lettre G, Li M, Lieb W, Loley C, Lotery AJ, Mannucci PM, Maouche S, Martinelli N, McKeown PP, Meisinger C, Meitinger T, Melander O, Merlini PA, Mooser V, Morgan T, Mühleisen TW, Muhlestein JB, Münzel T, Musunuru K, Nahrstaedt J, Nelson CP, Nöthen MM, Olivieri O, Patel RS, Patterson CC, Peters A, Peyvandi F, Qu L, Quyyumi AA, Rader DJ, Rallidis LS, Rice C, Rosendaal FR, Rubin D, Salomaa V, Sampietro ML, Sandhu MS, Schadt E, Schäfer A, Schillert A, Schreiber S, Schrezenmeir J, Schwartz SM, Siscovick DS, Sivananthan M, Sivapalaratnam S, Smith A, Smith TB, Snoep JD, Soranzo N, Spertus JA, Stark K, Stirrups K, Stoll M, Tang WHW, Tennstedt S, Thorgeirsson G, Thorleifsson G, Tomaszewski M, Uitterlinden AG, van Rij AM, Voight BF, Wareham NJ, Wells GA, Wichmann H-E, Wild PS, Willenborg C, Witteman JCM, Wright BJ, Ye S, Zeller T, Ziegler A, Cambien F, Goodall AH, Cupples LA, Quertermous T, März W, Hengstenberg C, Blankenberg S, Ouwehand WH, Hall AS, Deloukas P, Thompson JR, Stefansson K, Roberts R, Thorsteinsdottir U, O'Donnell CJ, McPherson R, Erdmann J, Samani NJ. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet* 2011;**43**:333–338.
25. Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, Ingelsson E, Saleheen D, Erdmann J, Goldstein BA, Stirrups K, Konig IR, Cazier JB, Johansson A, Hall AS, Lee JY, Willer CJ, Chambers JC, Esko T, Folkersen L, Goel A, Grundberg E, Havulinna AS, Ho WK, Hopewell JC, Eriksson N, Kleber ME, Kristiansson K, Lundmark P, Lyytikainen LP, Rafelt S, Shungin D, Strawbridge RJ, Thorleifsson G, Tikkanen E, Van Zuydam N, Voight BF, Waite LL, Zhang W, Ziegler A, Absher D, Altshuler D, Balmforth AJ, Barroso I, Braund PS, Burgdorf C, Claudi-Boehm S, Cox D, Dimitriou M, Do R, Consortium D, Consortium C, Doney AS, El Mokhtari N, Eriksson P, Fischer K, Fontanillas P, Franco-Cereceda A, Gigante B, Groop L, Gustafsson S, Hager J, Hallmans G, Han BG, Hunt SE, Kang HM, Illig T, Kessler T, Knowles JW, Kolovou G, Kuusisto J, Langenberg C, Langford C, Leander K, Lokki ML, Lundmark A, McCarthy MI, Meisinger C, Melander O, Mihailov E, Maouche S, Morris AD, Muller-Nurasyid M, Mu TC, Nikus K, Peden JF, Rayner NW, Rasheed A, Rosinger S, Rubin D, Rumpf MP, Schafer A, Sivananthan M, Song C, Stewart AF, Tan ST, Thorgeirsson G, van der Schoot CE, Wagner PJ, Wellcome Trust Case Control C, Wells GA, Wild PS, Yang TP, Amouyel P, Arveiler D, Basart H, Boehnke M, Boerwinkle E, Brambilla P, Cambien F, Cupples AL, de Faire U, Dehghan A, Diemert P, Epstein SE, Evans A, Ferrario MM, Ferrieres J, Gauguier D, Go AS, Goodall AH, Gudnason V, Hazen SL, Holm H, Iribarren C, Jang Y, Kahonen M, Kee F, Kim HS, Klopp N, Koenig W, Kratzer W, Kuulasmaa K, Laakso M, Laaksonen R, Lee JY, Lind L, Ouwehand WH, Parish S, Park JE, Pedersen NL, Peters A, Quertermous T, Rader DJ, Salomaa V, Schadt E, Shah SH, Sinisalo J, Stark K, Stefansson K, Tregouet DA, Virtamo J, Wallentin L, Wareham N, Zimmermann ME, Nieminen MS, Hengstenberg C, Sandhu MS, Pastinen T, Syvanen AC, Hovingh GK, Dedoussis G, Franks PW, Lehtimaki T, Metspalu A, Zalloua PA, Siegbahn A, Schreiber S, Ripatti S, Blankenberg SS, Perola M, Clarke R, Boehm BO, O'Donnell C, Reilly MP, Marz W, Collins R, Kathiresan S, Hamsten A, Kooner JS, Thorsteinsdottir U, Danesh J, Palmer CN, Roberts R, Watkins H, Schunkert H, Samani NJ. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet* 2013;**45**:25–33.

26. Klarin D, Zhu QM, Emdin CA, Chaffin M, Horner S, McMillan BJ, Leed A, Weale ME, Spencer CCA, Aguet F, Segre AV, Ardlie KG, Khera AV, Kaushik VK, Natarajan P, Kathiresan S. Genetic analysis in UK Biobank links insulin resistance and transendothelial migration pathways to coronary artery disease. *Nat Genet* 2017;**49**:1392–1397.
27. Verweij N, Eppinga RN, Hagemeijer Y, van der Harst P. Identification of 15 novel risk loci for coronary artery disease and genetic risk of recurrent events, atrial fibrillation and heart failure. *Sci Rep* 2017;**7**:2761.
28. Nelson CP, Goel A, Butterworth AS, Kanoni S, Webb TR, Marouli E, Zeng L, Ntalla I, Lai FY, Hopewell JC, Giannakopoulou O, Jiang T, Hamby SE, Di Angelantonio E, Assimes TL, Bottinger EP, Chambers JC, Clarke R, Palmer CNA, Cubbon RM, Ellinor P, Ermel R, Evangelou E, Franks PW, Grace C, Gu D, Hingorani AD, Howson JMM, Ingelsson E, Kastrati A, Kessler T, Kyriakou T, Lehtimaki T, Lu X, Lu Y, Marz W, McPherson R, Metspalu A, Pujades-Rodriguez M, Ruusalepp A, Schadt EE, Schmidt AF, Sweeting MJ, Zalloua PA, AlGhalayini K, Keavney BD, Kooner JS, Loos RJF, Patel RS, Rutter MK, Tomaszewski M, Tzoulaki I, Zeggini E, Erdmann J, Dedoussis G, Bjorkegren JLM, Consortium E-C, CardioGramplusC4D, UKBCCC, Schunkert H, Farrall M, Danesh J, Samani NJ, Watkins H, Deloukas P. Association analyses based on false discovery rate implicate new loci for coronary artery disease. *Nat Genet* 2017;**49**:1385–1391.
29. van der Harst P, Verweij N. The identification of 64 novel genetic loci provides an expanded view on the genetic architecture of coronary artery disease. *Circ Res* 2017;**122**:433–443.
30. Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S, Saleheen D, Kyriakou T, Nelson CP, Hopewell JC, Webb TR, Zeng L, Dehghan A, Alver M, Armasu SM, Auro K, Bjonnes A, Chasman DI, Chen S, Ford I, Franceschini N, Gieger C, Grace C, Gustafsson S, Huang J, Hwang SJ, Kim YK, Kleber ME, Lau KW, Lu X, Lu Y, Lyytikainen LP, Mihailov E, Morrison AC, Pervjakova N, Qu L, Rose LM, Salfati E, Saxena R, Scholz M, Smith AV, Tikkanen E, Uitterlinden A, Yang X, Zhang W, Zhao W, de Andrade M, de Vries PS, van Zuydam NR, Anand SS, Bertram L, Beutner F, Dedoussis G, Frossard P, Gauguier D, Goodall AH, Gottesman O, Haber M, Han BG, Huang J, Jalilzadeh S, Kessler T, Konig IR, Lannfelt L, Lieb W, Lind L, Lindgren CM, Lokki ML, Magnusson PK, Mallick NH, Mehra N, Meitinger T, Memon FU, Morris AP, Nieminen MS, Pedersen NL, Peters A, Rallidis LS, Rasheed A, Samuel M, Shah SH, Sinisalo J, Stirrups KE, Trompet S, Wang L, Zaman KS, Ardissino D, Boerwinkle E, Borecki IB, Bottinger EP, Buring JE, Chambers JC, Collins R, Cupples LA, Danesh J, Demuth I, Elosua R, Epstein SE, Esko T, Feitosa MF, Franco OH, Franzosi MG, Granger CB, Gu D, Gudnason V, Hall AS, Hamsten A, Harris TB, Hazen SL, Hengstenberg C, Hofman A, Ingelsson E, Iribarren C, Jukema JW, Karhunen PJ, Kim BJ, Kooner JS, Kullo IJ, Lehtimaki T, Loos RJ, Melander O, Metspalu A, Marz W, Palmer CN, Perola M, Quertermous T, Rader DJ, Ridker PM, Ripatti S, Roberts R, Salomaa V, Sanghera DK, Schwartz SM, Seedorf U, Stewart AF, Stott DJ, Thiery J, Zalloua PA, O'Donnell CJ, Reilly MP, Assimes TL, Thompson JR, Erdmann J, Clarke R, Watkins H, Kathiresan S, McPherson R, Deloukas P, Schunkert H, Samani NJ, Farrall M. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet* 2015;**47**:1121–1130.
31. Christofidou P, Nelson Christopher P, Nikpay M, Qu L, Li M, Loley C, Debiec R, Braund Peter S, Denniff M, Charchar Fadi J, Arjo Ares R, Trégouët D-A, Goodall Alison H, Cambien F, Ouwehand Willem H, Roberts R, Schunkert H, Hengstenberg C, Reilly Muredach P, Erdmann J, McPherson R, König Inke R, Thompson John R, Samani Nilesh J, Tomaszewski M. Runs of homozygosity: association with coronary artery disease and gene expression in monocytes and macrophages. *Am J Hum Genet* **97**:228–237.
32. Stitziel NO, Stirrups KE, Masca NG, Erdmann J, Ferrario PG, Konig IR, Weeke PE, Webb TR, Auer PL, Schick UM, Lu Y, Zhang H, Dube MP, Goel A, Farrall M, Peloso GM, Won HH, Do R, van Iperen E, Kanoni S, Kruppa J, Mahajan A, Scott RA, Willenberg C, Braund PS, van Capelleveen JC, Doney AS, Donnelly LA, Asselta R, Merlini PA, Duga S, Marziliano N, Denny JC, Shaffer CM, El-Mokhtari NE, Franke A, Gottesman O, Heilmann S, Hengstenberg C, Hoffman P, Holmen OL, Hveem K, Jansson JH, Jockel KH, Kessler T, Kriebel J, Laugwitz KL, Marouli E, Martinelli N, McCarthy MI, Van Zuydam NR, Meisinger C, Esko T, Mihailov E, Escher SA, Alver M, Moebus S, Morris AD, Muller-Nurasyid M, Nikpay M, Olivieri O, Lemieux Perreault LP, AlQarawi A, Robertson NR, Akinsanya KO, Reilly DF, Vogt TF, Yin W, Asselbergs FW, Kooperberg C, Jackson RD, Stahl E, Strauch K, Varga TV, Waldenberger M, Zeng L, Kraja AT, Liu C, Ehret GB, Newton-Cheh C, Chasman DI, Chowdhury R, Ferrario M, Ford I, Jukema JW, Kee F, Kuulasmaa K, Nordestgaard BG, Perola M, Saleheen D, Sattar N, Surendran P, Tregouet D, Young R, Howson JM, Butterworth AS, Danesh J, Ardissino D, Bottinger EP, Erbel R, Franks PW, Girelli D, Hall AS, Hovingh GK, Kastrati A, Lieb W, Meitinger T, Kraus WE, Shah SH, McPherson R, Orho-Melander M, Melander O, Metspalu A, Palmer CN, Peters A, Rader D, Reilly MP, Loos RJ, Reiner AP, Roden DM, Tardif JC, Thompson JR, Wareham NJ, Watkins H, Willer CJ, Kathiresan S, Deloukas P, Samani NJ, Schunkert H. Coding variation in ANGPTL4, LPL, and SVEP1 and the risk of coronary disease. *N Engl J Med* 2016;**374**:1134–1144.
33. Stitziel NO, the Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators. Variants in ANGPTL4 and the risk of coronary artery disease. *N Engl J Med* 2016;**375**:2306.
34. Accounting for sex in the genome. *Nat Med* 2017;**23**:1243. doi:10.1038/nm.4445.
35. Molina E, Clarence EM, Ahmady F, Chew GS, Charchar FJ. Coronary artery disease: why we should consider the Y chromosome. *Heart Lung Circ* 2016;**25**:791–801.
36. Konig IR, Loley C, Erdmann J, Ziegler A. How to include chromosome X in your genome-wide association study. *Genet Epidemiol* 2014;**38**:97–103.
37. Loley C, Alver M, Assimes TL, Bjonnes A, Goel A, Gustafsson S, Hernesniemi J, Hopewell JC, Kanoni S, Kleber ME, Lau KW, Lu Y, Lyytikainen LP, Nelson CP, Nikpay M, Qu L, Salfati E, Scholz M, Tukiainen T, Willenborg C, Won HH, Zeng L, Zhang W, Anand SS, Beutner F, Bottinger EP, Clarke R, Dedoussis G, Do R, Esko T, Eskola M, Farrall M, Gauguier D, Giedraitis V, Granger CB, Hall AS, Hamsten A, Hazen SL, Huang J, Kahonen M, Kyriakou T, Laaksonen R, Lind L, Lindgren C, Magnusson PK, Marouli E, Mihailov E, Morris AP, Nikus K, Pedersen N, Rallidis L, Salomaa V, Shah SH, Stewart AF, Thompson JR, Zalloua PA, Chambers JC, Collins R, Ingelsson E, Iribarren C, Karhunen PJ, Kooner JS, Lehtimaki T, Loos RJ, Marz W, McPherson R, Metspalu A, Reilly MP, Ripatti S, Sanghera DK, Thiery J, Watkins H, Deloukas P, Kathiresan S, Samani NJ, Schunkert H, Erdmann J, Konig IR. No association of coronary artery disease with X-chromosomal variants in comprehensive international meta-analysis. *Sci Rep* 2016;**6**:35278.
38. Assimes TL, Damrauer SM, Li J, Sun Y, Lynch JA, Klarin D, Duvall SL, Huang J, Vassy JL, Lee JS, Freiberg MS, Voora D, Kathiresan S, Boden WE, Natarajan P, Miller DR, Gaziano JM, Concato J, Cho K, Wilson PW, Rader DJ, Tsao P, Donnell CJ. Abstract 16167: a GWAS of EHR-defined CAD identifies multiple novel loci including the first 3 loci on the X-chromosome: the Million Veteran Program. *Circulation* 2017;**136**:A16167.
39. Charchar FJ, Bloomer LD, Barnes TA, Cowley MJ, Nelson CP, Wang Y, Denniff M, Debiec R, Christofidou P, Nankervis S, Dominiczak AF, Bani-Mustafa A, Balmforth AJ, Hall AS, Erdmann J, Cambien F, Deloukas P, Hengstenberg C, Packard C, Schunkert H, Ouwehand WH, Ford I, Goodall AH, Jobling MA, Samani NJ, Tomaszewski M. Inheritance of coronary artery disease in men: an analysis of the role of the Y chromosome. *Lancet* 2012;**379**:915–922.
40. ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. *Nature* 2012;**489**:57–74.
41. Sanyal A, Lajoie B, Jain G, Dekker J. The long-range interaction landscape of gene promoters. *Nature* 2012;**489**:109–113.
42. Schunkert H. Family or SNPs: what counts for hereditary risk of coronary artery disease? *Eur Heart J* 2016;**37**:568–571.
43. Lin C, Chu CM, Lin J, Yang HY, Su SL. Gene-gene and gene-environment interactions in meta-analysis of genetic association studies. *PLoS One* 2015;**10**:e0124967.
44. Mascheretti S, Bureau A, Trezzi V, Giorda R, Marino C. An assessment of gene-by-gene interactions as a tool to unfold missing heritability in dyslexia. *Hum Genet* 2015;**134**:749–760.
45. Gormley P, Kurki MI, Hiekkala ME, Veerapen K, Häppölä P, Mitchell A, Lal D, Palta P, Surakka I, Kaunisto MA, Hämäläinen E, Vepsäläinen S, Havanka H, Harno H, Ilmavirta M, Nissilä M, Säkö E, Sumelahti M-L, Liukkonen J, Sillanpää M, Metsähonkala L, Jousilahti P, Anttila V, Salomaa V, Artto V, Färkkilä M, Runz H, Daly MJ, Neale BM, Ripatti S, Kallela M, Wessman M, Palotie A. Common variant burden contributes significantly to the familial aggregation of migraine in 1,589 families. *bioRxiv* 2017.
46. Ripatti P, Rämö JT, Söderlund S, Surakka I, Matikainen N, Pirinen M, Pajukanta P, Sarin A-P, Service SK, Laurila P-P, Ehnholm C, Salomaa V, Wilson RK, Palotie A, Freimer NB, Taskinen M-R, Ripatti S. The contribution of GWAS loci in familial dyslipidemias. *PLoS Genet* 2016;**12**:e1006078.
47. Braenne I, Kleinecke M, Reiz B, Graf E, Strom T, Wieland T, Fischer M, Kessler T, Hengstenberg C, Meitinger T, Erdmann J, Schunkert H. Systematic analysis of variants related to familial hypercholesterolemia in families with premature myocardial infarction. *Eur J Hum Genet* 2016;**24**:191–197.
48. Dang T, Wobst J, Kessler T, Ameln S, Lehm M, Prestel M, Braenne I, Aherrahrou R, Dichgans M, Hengstenberg C, Erdmann J, Schunkert H. Investigating the impact of a mutation in PDE5A on myocardial infarction. *BMC Pharmacol Toxicol*, 2015;**16**: A43.
49. Brænne I, Reiz B, Medack A, Kleinecke M, Fischer M, Tuna S, Hengstenberg C, Deloukas P, Erdmann J, Schunkert H. Cardiogenics Consortium. Whole-exome sequencing in an extended family with myocardial infarction unmasks familial hypercholesterolemia. *BMC Cardiovasc Disord* 2014;**14**:108.
50. Brænne I, Kleinecke M, Reiz B, Graf E, Strom T, Wieland T, Fischer M, Kessler T, Hengstenberg C, Meitinger T, Erdmann J, Schunkert H. Systematic analysis of variants related to familial hypercholesterolemia in families with premature myocardial infarction. *Eur J Hum Genet* 2016;**24**:191–197.
51. Pickrell JK, Berisa T, Liu JZ, Segurel L, Tung JY, Hinds DA. Detection and interpretation of shared genetic influences on 42 human traits. *Nat Genet* 2016;**48**:709–717.
52. Visscher PM, Yang J. A plethora of pleiotropy across complex traits. *Nat Genet* 2016;**48**:707–708.
53. Welter D, MacArthur J, Morales J, Burdett T, Hall P, Junkins H, Klemm A, Flicek P, Manolio T, Hindorff L, Parkinson H. The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. *Nucleic Acids Res* 2014;**42**:D1001–D1006.
54. Chesmore K, Bartlett J, Williams SM. The ubiquity of pleiotropy in human disease. *Hum Genet* 2018;**137**:39–44.
55. Webb TR, Erdmann J, Stirrups KE, Stitziel NO, Masca NG, Jansen H, Kanoni S, Nelson CP, Ferrario PG, Konig IR, Eicher JD, Johnson AD, Hamby SE, Betsholtz C, Ruusalepp A, Franzen O, Schadt EE, Bjorkegren JL, Weeke PE, Auer PL, Schick UM, Lu Y, Zhang H, Dube MP, Goel A, Farrall M, Peloso GM, Won HH, Do R, van

Iperen E, Kruppa J, Mahajan A, Scott RA, Willenborg C, Braund PS, van Capelleveen JC, Doney AS, Donnelly LA, Asselta R, Merlini PA, Duga S, Marziliano N, Denny JC, Shaffer C, El-Mokhtari NE, Franke A, Heilmann S, Hengstenberg C, Hoffmann P, Holmen OL, Hveem K, Jansson JH, Jockel KH, Kessler T, Kriebel J, Laugwitz KL, Marouli E, Martinelli N, McCarthy MI, Van Zuydam NR, Meisinger C, Esko T, Mihailov E, Escher SA, Alver M, Moebus S, Morris AD, Virtamo J, Nikpay M, Olivieri O, Provost S, AlQarawi A, Robertson NR, Akinsansya KO, Reilly DF, Vogt TF, Yin W, Asselbergs FW, Kooperberg C, Jackson RD, Stahl E, Muller-Nurasyid M, Strauch K, Varga TV, Waldenberger M, Wellcome Trust Case Control C, Zeng L, Chowdhury R, Salomaa V, Ford I, Jukema JW, Amouyel P, Kontto J, Investigators M, Nordestgaard BG, Ferrieres J, Saleheen D, Sattar N, Surendran P, Wagner A, Young R, Howson JM, Butterworth AS, Danesh J, Ardissino D, Bottinger EP, Erbel R, Franks PW, Girelli D, Hall AS, Hovingh GK, Kastrati A, Lieb W, Meitinger T, Kraus WE, Shah SH, McPherson R, Orho-Melander M, Melander O, Metspalu A, Palmer CN, Peters A, Rader DJ, Reilly MP, Loos RJ, Reiner AP, Roden DM, Tardif JC, Thompson JR, Wareham NJ, Watkins H, Willer CJ, Samani NJ, Schunkert H, Deloukas P, Kathiresan S. Systematic evaluation of pleiotropy identifies 6 further loci associated with coronary artery disease. *J Am Coll Cardiol* 2017;**69**:823–836.

56. Holdt LM, Teupser D. Recent studies of the human chromosome 9p21 locus, which is associated with atherosclerosis in human populations. *Arterioscler Thromb Vasc Biol* 2012;**32**:196–206.
57. Hannou SA, Wouters K, Paumelle R, Staels B. Functional genomics of the CDKN2A/B locus in cardiovascular and metabolic disease: what have we learned from GWASs? *Trends Endocrinol Metab* 2015;**26**:176–184.
58. Chen D, Gyllensten U. Lessons and implications from association studies and post-GWAS analyses of cervical cancer. *Trends Genet* 2015;**31**:41–54.
59. McPherson R. Chromosome 9p21.3 locus for coronary artery disease: how little we know. *J Am Coll Cardiol* 2013;**62**:1382–1383.
60. Musunuru K. Enduring mystery of the chromosome 9p21.3 locus. *Circ Cardiovasc Genet* 2013;**6**:224–225.
61. Dehghan A, Bis JC, White CC, Smith AV, Morrison AC, Cupples LA, Trompet S, Chasman DI, Lumley T, Volker U, Buckley BM, Ding J, Jensen MK, Folsom AR, Kritchevsky SB, Girman CJ, Ford I, Dorr M, Salomaa V, Uitterlinden AG, Eiriksdottir G, Vasan RS, Franceschini N, Carty CL, Virtamo J, Demissie S, Amouyel P, Arveiler D, Heckbert SR, Ferrieres J, Ducimetiere P, Smith NL, Wang YA, Siscovick DS, Rice KM, Wiklund PG, Taylor KD, Evans A, Kee F, Rotter JI, Karvanen J, Kuulasmaa K, Heiss G, Kraft P, Launer LJ, Hofman A, Markus MR, Rose LM, Silander K, Wagner P, Benjamin EJ, Lohman K, Stott DJ, Rivadeneira F, Harris TB, Levy D, Liu Y, Rimm EB, Jukema JW, Volzke H, Ridker PM, Blankenberg S, Franco OH, Gudnason V, Psaty BM, Boerwinkle E, O'Donnell CJ. Genome-wide association study for incident myocardial infarction and coronary heart disease in prospective cohort studies: the CHARGE Consortium. *PLoS One* 2016;**11**:e0144997.
62. Holdt LM, Beutner F, Scholz M, Gielen S, Gabel G, Bergert H, Schuler G, Thiery J, Teupser D. ANRIL expression is associated with atherosclerosis risk at chromosome 9p21. *Arterioscler Thromb Vasc Biol* 2010;**30**:620–627.
63. Holdt LM, Stahringer A, Sass K, Pichler G, Kulak NA, Wilfert W, Kohlmaier A, Herbst A, Northoff BH, Nicolaou A, Gabel G, Beutner F, Scholz M, Thiery J, Musunuru K, Krohn K, Mann M, Teupser D. Circular non-coding RNA ANRIL modulates ribosomal RNA maturation and atherosclerosis in humans. *Nat Commun* 2016;**7**:12429.
64. Harismendy O, Notani D, Song X, Rahim NG, Tanasa B, Heintzman N, Ren B, Fu XD, Topol EJ, Rosenfeld MG, Frazer KA. 9p21 DNA variants associated with coronary artery disease impair interferon-gamma signalling response. *Nature* 2011;**470**:264–268.
65. Emdin CA, Khera AV, Klarin D, Natarajan P, Zekavat SM, Nomura A, Haas ME, Aragam K, Ardissino D, Wilson JG, Schunkert H, McPherson R, Watkins H, Elosua R, Bown MJ, Samani NJ, Baber U, Erdmann J, Gormley P, Palotie A, Stitziel N, Gupta N, Danesh JN, Saleheen D, Gabriel SB, Kathiresan S. Phenotypic consequences of a genetic predisposition to enhanced nitric oxide signaling. *Circulation* 2018;**137**:222–232.
66. Kessler T, Wobst J, Wolf B, Eckhold J, Vilne B, Hollstein R, von Ameln S, Dang TA, Sager HB, Moritz Rumpf P, Aherrahrou R, Kastrati A, Bjorkegren JLM, Erdmann J, Lusis AJ, Civelek M, Kaiser FJ, Schunkert H. Functional characterization of the GUCY1A3 coronary artery disease risk locus. *Circulation* 2017;**136**:476–489.
67. Ghofrani HA, Simonneau G, Rubin LJ; Authors of CHEST-1 and PATENT-1. Riociguat for pulmonary hypertension. *N Engl J Med* 2013;**369**:2268.
68. Stasch JP, Hobbs AJ. NO-independent, haem-dependent soluble guanylate cyclase stimulators. *Handb Exp Pharmacol* 2009; 277–308.
69. Grundberg E, Small KS, Hedman AK, Nica AC, Buil A, Keildson S, Bell JT, Yang TP, Meduri E, Barrett A, Nisbett J, Sekowska M, Wilk A, Shin SY, Glass D, Travers M, Min JL, Ring S, Ho K, Thorleifsson G, Kong A, Thorsteindottir U, Ainali C, Dimas AS, Hassanali N, Ingle C, Knowles D, Krestyaninova M, Lowe CE, Di Meglio P, Montgomery SB, Parts L, Potter S, Surdulescu G, Tsaprouni L, Tsoka S, Bataille V, Durbin R, Nestle FO, O'Rahilly S, Soranzo N, Lindgren CM, Zondervan KT, Ahmadi KR, Schadt EE, Stefansson K, Smith GD, McCarthy MI, Deloukas P, Dermitzakis ET, Spector TD. Multiple Tissue Human Expression Resource C. Mapping cis- and trans-regulatory effects across multiple tissues in twins. *Nat Genet* 2012;**44**:1084–1089.
70. Nikpay M, Stewart AFR, McPherson R. Partitioning the heritability of coronary artery disease highlights the importance of immune-mediated processes and epigenetic sites associated with transcriptional activity. *Cardiovasc Res* 2017;**113**:973–983.
71. GTEx Consortium. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. *Science* 2015;**348**:648–660.
72. Roadmap Epigenomics Consortium, Kundaje A, Meuleman W, Ernst J, Bilenky M, Yen A, Heravi-Moussavi A, Kheradpour P, Zhang Z, Wang J, Ziller MJ, Amin V, Whitaker JW, Schultz MD, Ward LD, Sarkar A, Quon G, Sandstrom RS, Eaton ML, Wu YC, Pfenning AR, Wang X, Claussnitzer M, Liu Y, Coarfa C, Harris RA, Shoresh N, Epstein CB, Gjoneska E, Leung D, Xie W, Hawkins RD, Lister R, Hong C, Gascard P, Mungall AJ, Moore R, Chuah E, Tam A, Canfield TK, Hansen RS, Kaul R, Sabo PJ, Bansal MS, Carles A, Dixon JR, Farh KH, Feizi S, Karlic R, Kim AR, Kulkarni A, Li D, Lowdon R, Elliott G, Mercer TR, Neph SJ, Onuchic V, Polak P, Rajagopal N, Ray P, Sallari RC, Siebenthall KT, Sinnott-Armstrong NA, Stevens M, Thurman RE, Wu J, Zhang B, Zhou X, Beaudet AE, Boyer LA, De Jager PL, Farnham PJ, Fisher SJ, Haussler D, Jones SJ, Li W, Marra MA, McManus MT, Sunyaev S, Thomson JA, Tlsty TD, Tsai LH, Wang W, Waterland RA, Zhang MQ, Chadwick LH, Bernstein BE, Costello JF, Ecker JR, Hirst M, Meissner A, Milosavljevic A, Ren B, Stamatoyannopoulos JA, Wang T, Kellis M. Integrative analysis of 111 reference human epigenomes. *Nature* 2015;**518**:317–330.
73. Franzén O, Ermel R, Cohain A, Akers NK, Di Narzo A, Talukdar HA, Foroughi-Asl H, Giambartolomei C, Fullard JF, Sukhavasi K, Köks S, Gan L-M, Giannarelli C, Kovacic JC, Betsholtz C, Losic B, Michoel T, Hao K, Roussos P, Skogsberg J, Ruusalepp A, Schadt EE, Björkegren JLM. Cardiometabolic risk loci share downstream cis- and trans-gene regulation across tissues and diseases. *Science* 2016;**353**:827–830.
74. Schmitt AD, Hu M, Jung I, Xu Z, Qiu Y, Tan CL, Li Y, Lin S, Lin Y, Barr CL, Ren B. A compendium of chromatin contact maps reveals spatially active regions in the human genome. *Cell Rep* 2016;**17**:2042–2059.
75. Haitjema S, Meddens CA, van der Laan SW, Kofink D, Harakalova M, Tragante V, Foroughi Asl H, van Setten J, Brandt MM, Bis JC, O'donnell C, Cheng C, Hoefer IE, Waltenberger J, Biessen E, Jukema JW, Doevendans PAFM, Nieuwenhuis EES, Erdmann J, Björkegren JLM, Pasterkamp G, Asselbergs FW, den Ruijter HM, Mokry M. Additional candidate genes for human atherosclerotic disease identified through annotation based on chromatin organization. *Circ Cardiovasc Genet* 2017;**10**:e001664.
76. Brænne I, Civelek M, Vilne B, Di Narzo A, Johnson AD, Zhao Y, Reiz B, Codoni V, Webb TR, Foroughi Asl H, Hamby SE, Zeng L, Trégouët D-A, Hao K, Topol EJ, Schadt EE, Yang X, Samani NJ, Björkegren JLM, Erdmann J, Schunkert H, Lusis AJ. Leducq Consortium CADgenomics. Prediction of causal candidate genes in coronary artery disease loci. *Arterioscler Thromb Vasc Biol* 2015;**35**:2207–2217.
77. Zhao Y, Chen J, Freudenberg JM, Meng Q, Rajpal DK, Yang X. Network-based identification and prioritization of key regulators of coronary artery disease loci. *Arterioscler Thromb Vasc Biol* 2016;**36**:928–941.
78. Vilne B, Skogsberg J, Foroughi Asl H, Talukdar HA, Kessler T, Bjorkegren JLM, Schunkert H. Network analysis reveals a causal role of mitochondrial gene activity in atherosclerotic lesion formation. *Atherosclerosis* 2017;**267**:39–48.
79. Wall DP, Kudtarkar P, Fusaro VA, Pivovarov R, Patil P, Tonellato PJ. Cloud computing for comparative genomics. *BMC Bioinformatics* 2010;**11**:259.
80. Pavlovich M. Computing in biotechnology: omics and beyond. *Trends Biotechnol* 2017;**35**:479–480.
81. Bjorkegren JLM, Kovacic JC, Dudley JT, Schadt EE. Genome-wide significant loci: how important are they? Systems genetics to understand heritability of coronary artery disease and other common complex disorders. *J Am Coll Cardiol* 2015;**65**:830–845.
82. Musunuru K, Strong A, Frank-Kamenetsky M, Lee NE, Ahfeldt T, Sachs KV, Li X, Li H, Kuperwasser N, Ruda VM, Pirruccello JP, Muchmore B, Prokunina-Olsson L, Hall JL, Schadt EE, Morales CR, Lund-Katz S, Phillips MC, Wong J, Cantley W, Racie T, Ejebe KG, Orho-Melander M, Melander O, Kotelianskiy V, Fitzgerald K, Krauss RM, Cowan CA, Kathiresan S, Rader DJ. From noncoding variant to phenotype via SORT1 at the 1p13 cholesterol locus. *Nature* 2010;**466**:714–719.
83. Talukdar HA, Foroughi Asl H, Jain RK, Ermel R, Ruusalepp A, Franzén O, Kidd BA, Readhead B, Giannarelli C, Kovacic JC, Ivert T, Dudley JT, Civelek M, Lusis AJ, Schadt EE, Skogsberg J, Michoel T, Björkegren JLM. Cross-tissue regulatory gene networks in coronary artery disease. *Cell Syst* 2016;**2**:196–208.
84. Jansen H, Samani NJ, Schunkert H. Mendelian randomization studies in coronary artery disease. *Eur Heart J* 2014;**35**:1917–1924.
85. Nordestgaard BG, Palmer TM, Benn M, Zacho J, Tybjærg-Hansen A, Davey Smith G, Timspon NJ. The effect of elevated body mass index on ischemic heart disease risk: causal estimates from a Mendelian randomisation approach. *PLoS Med* 2012;**9**:e1001212. doi:10.1371/journal.pmed.1001212.
86. Wobst J, von Ameln S, Wolf B, Wierer M, Dang TA, Sager HB, Tennstedt S, Hengstenberg C, Koesling D, Friebe A, Braun SL, Erdmann J, Schunkert H, Kessler T. Stimulators of the soluble guanylyl cyclase: promising functional insights from rare coding atherosclerosis-related GUCY1A3 variants. *Basic Res Cardiol* 2016;**111**:51.
87. Durairaj A, Sabates A, Nieves J, Moraes B, Baum S. Proprotein convertase subtilisin/kexin type 9 (PCSK9) and its inhibitors: a review of physiology, biology, and clinical data. *Curr Treat Options Cardio Med* 2017;**19**:58.

88. Musunuru K, Kathiresan S. Surprises from genetic analyses of lipid risk factors for atherosclerosis. *Circ Res* 2016;**118**:579–585.
89. Stitziel NO, Kathiresan S. Leveraging human genetics to guide drug target discovery. *Trends Cardiovasc Med* 2017;**27**:352–359.
90. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee JY, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RY, Wright AF, Witteman JC, Wilson JF, Willemsen G, Wichmann HE, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJ, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BW, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PK, Lucas G, Luben R, Loos RJ, Lokki ML, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, Konig IR, Khaw KT, Kaprio J, Kaplan LM, Johansson A, Jarvelin MR, Janssens AC, Ingelsson E, Igl W, Kees Hovingh G, Hottenga JJ, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Doring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJ, de Faire U, Crawford G, Collins FS, Chen YD, Caulfield MJ, Campbell H, Burtt NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Adair LS, Taylor HA Jr, Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M, Kathiresan S. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* 2010;**466**:707–713.
91. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM. Investigators I-I. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;**372**:2387–2397.
92. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, Committee FS. Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;**376**:1713–1722.
93. Morita H, Komuro I. A strategy for genomic research on common cardiovascular diseases aiming at the realization of precision medicine: personal insights and perspectives. *Circ Res* 2016;**119**:900–903.
94. Khera AV, Kathiresan S. Is coronary atherosclerosis one disease or many? Setting realistic expectations for precision medicine. *Circulation* 2017;**135**:1005–1007.
95. Benn M, Watts GF, Tybjærg-Hansen A, Nordestgaard BG. Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. *Eur Heart J* 2016;**37**:1384–1394.
96. Louter L, Defesche J, Roeters van Lennep J. Cascade screening for familial hypercholesterolemia: practical consequences. *Atheroscler Suppl* 2017;**30**:77–85.
97. Hughes MF, Saarela O, Stritzke J, Kee F, Silander K, Klopp N, Kontto J, Karvanen J, Willenborg C, Salomaa V, Virtamo J, Amouyel P, Arveiler D, Ferrieres J, Wiklund PG, Baumert J, Thorand B, Diemert P, Tregouet DA, Hengstenberg C, Peters A, Evans A, Koenig W, Erdmann J, Samani NJ, Kuulasmaa K, Schunkert H. Genetic markers enhance coronary risk prediction in men: the MORGAM prospective cohorts. *PLoS One* 2012;**7**:e40922.
98. Bornigen D, Karakas M, Zeller T. The challenges of genetic risk scores for the prediction of coronary heart disease. *Clin Chem Lab Med* 2017;**55**:1450–1452.
99. Mega JL, Stitziel NO, Smith JG, Chasman DI, Caulfield M, Devlin JJ, Nordio F, Hyde C, Cannon CP, Sacks F, Poulter N, Sever P, Ridker PM, Braunwald E, Melander O, Kathiresan S, Sabatine MS. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy. *Lancet (London, England)* 2015;**385**:2264–2271.
100. Khera AV, Emdin CA, Kathiresan S. Genetic risk, lifestyle, and coronary artery disease. *N Engl J Med* 2017;**376**:1194–1195.
101. Khera AV, Chaffin M, Aragam K, Emdin CA, Klarin D, Haas M, Roselli C, Natarajan P, Kathiresan S. Genome-wide polygenic score to identify a monogenic risk-equivalent for coronary disease. *bioRxiv* 2017;
102. Arnold M, Raffler J, Pfeufer A, Suhre K, Kastenmuller G. SNiPA: an interactive, genetic variant-centered annotation browser. *Bioinformatics* 2015;**31**:1334–1336.
103. Abifadel M, Varret M, Rabes JP, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D, Derre A, Villeger L, Farnier M, Beucler I, Bruckert E, Chambaz J, Chanu B, Lecerf JM, Luc G, Moulin P, Weissenbach J, Prat A, Krempf M, Junien C, Seidah NG, Boileau C. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet* 2003;**34**:154–156.
104. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006;**354**:1264–1272.
105. Howson JMM, Zhao W, Barnes DR, Ho WK, Young R, Paul DS, Waite LL, Freitag DF, Fauman EB, Salfati EL, Sun BB, Eicher JD, Johnson AD, Sheu WHH, Nielsen SF, Lin WY, Surendran P, Malarstig A, Wilk JB, Tybjaerg-Hansen A, Rasmussen KL, Kamstrup PR, Deloukas P, Erdmann J, Kathiresan S, Samani NJ, Schunkert H, Watkins H, CardioGramplusC4D, Do R, Rader DJ, Johnson JA, Hazen SL, Quyyumi AA, Spertus JA, Pepine CJ, Franceschini N, Justice A, Reiner AP, Buyske S, Hindorff LA, Carty CL, North KE, Kooperberg C, Boerwinkle E, Young K, Graff M, Peters U, Absher D, Hsiung CA, Lee WJ, Taylor KD, Chen YH, Lee IT, Guo X, Chung RH, Hung YJ, Rotter JI, Juang JJ, Quertermous T, Wang TD, Rasheed A, Frossard P, Alam DS, Majumder AAS, Di Angelantonio E, Chowdhury R, Epic CVD, Chen YI, Nordestgaard BG, Assimes TL, Danesh J, Butterworth AS, Saleheen D. Fifteen new risk loci for coronary artery disease highlight arterial-wall-specific mechanisms. *Nat Genet* 2017;**49**:1113–1119.
106. Consortium IBC. Large-scale gene-centric analysis identifies novel variants for coronary artery disease. *PLoS Genet* 2011;**7**:e1002260.
107. Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, Smith AV, Tobin MD, Verwoert GC, Hwang SJ, Pihur V, Vollenweider P, O'Reilly PF, Amin N, Bragg-Gresham JL, Teumer A, Glazer NL, Launer L, Zhao JH, Aulchenko Y, Heath S, Sober S, Parsa A, Luan J, Arora P, Dehghan A, Zhang F, Lucas G, Hicks AA, Jackson AU, Peden JF, Tanaka T, Wild SH, Rudan I, Igl W, Milaneschi Y, Parker AN, Fava C, Chambers JC, Fox ER, Kumari M, Go MJ, van der Harst P, Kao WH, Sjogren M, Vinay DG, Alexander M, Tabara Y, Shaw-Hawkins S, Whincup PH, Liu Y, Shi G, Kuusisto J, Tayo B, Seielstad M, Sim X, Nguyen KD, Lehtimaki T, Matullo G, Wu Y, Gaunt TR, Onland-Moret NC, Cooper MN, Platou CG, Org E, Hardy R, Dahgam S, Palmen J, Vitart V, Braund PS, Kuznetsova T, Uiterwaal CS, Adeyemo A, Palmas W, Campbell H, Ludwig B, Tomaszewski M, Tzoulaki I, Palmer ND, Consortium CA, Consortium CK, KidneyGen C, EchoGen C, Consortium C-H, Aspelund T, Garcia M, Chang YP, O'Connell JR, Steinle NI, Grobbee DE, Arking DE, Kardia SL, Morrison AC, Hernandez D, Najjar S, McArdle WL, Hadley D, Brown MJ, Connell JM, Hingorani AD, Day IN, Lawlor DA, Beilby JP, Lawrence RW, Clarke R, Hopewell JC, Ongen H, Dreisbach AW, Li Y, Young JH, Bis JC, Kahonen M, Viikari J, Adair LS, Lee NR, Chen MH, Olden M, Pattaro C, Bolton JA, Kottgen A, Bergmann S, Mooser V, Chaturvedi N, Frayling TM, Islam M, Jafar TH, Erdmann J, Kulkarni SR, Bornstein SR, Grassler J, Groop L, Voight BF, Kettunen J, Howard P, Taylor A, Guarrera S, Ricceri F, Emilsson V, Plump A, Barroso I, Khaw KT, Weder AB, Hunt SC, Sun YV, Bergman RN, Collins FS, Bonnycastle LL, Scott LJ, Stringham HM, Peltonen L, Perola M, Vartiainen E, Brand SM, Staessen JA, Wang TJ, Burton PR, Soler Artigas M, Dong Y, Snieder H, Wang X, Zhu H, Lohman KK, Rudock ME, Heckbert SR, Smith NL, Wiggins KL, Doumatey A, Shriner D, Veldre G, Viigimaa M, Kinra S, Prabhakaran D, Tripathy V, Langefeld CD, Rosengren A, Thelle DS, Corsi AM, Singleton A, Forrester T, Hilton G, McKenzie CA, Salako T, Iwai N, Kita Y, Ogihara T, Ohkubo T, Okamura T, Ueshima H, Umemura S, Eyheramendy S, Meitinger T, Wichmann HE, Cho YS, Kim HL, Lee JY, Scott J, Sehmi JS, Zhang W, Hedblad B, Nilsson P, Smith GD, Wong A, Narisu N, Stancakova A, Raffel LJ, Yao J, Kathiresan S, O'Donnell CJ, Schwartz SM, Ikram MA, Longstreth WT Jr, Mosley TH, Seshadri S, Shrine NR, Wain LV, Morken MA, Swift AJ, Laitinen J, Prokopenko I, Zitting P, Cooper JA, Humphries SE, Danesh J, Rasheed A, Goel A, Hamsten A, Watkins H, Bakker SJ, van Gilst WH, Janipalli CS, Mani KR, Yajnik CS, Hofman A, Mattace-Raso FU, Oostra BA, Demirkan A, Isaacs A, Rivadeneira F, Lakatta EG, Orru M, Scuteri A, Ala-Korpela M, Kangas AJ, Lyytikainen LP, Soininen P, Tukiainen T, Wurtz P, Ong RT, Dorr M, Kroemer HK, Volker U, Volzke H, Galan P, Hercberg S, Lathrop M, Zelenika D, Deloukas P, Mangino M, Spector TD, Zhai G, Meschia JF, Nalls MA, Sharma P, Terzic J, Kumar MV, Denniff M, Zukowska-Szczechowska E, Wagenknecht LE, Fowkes FG, Charchar FJ, Schwarz PE, Hayward C, Guo X, Rotimi C, Bots ML, Brand E, Samani NJ, Polasek O, Talmud PJ, Nyberg F, Kuh D, Laan M, Hveem K, Palmer LJ, van der Schouw YT, Casas JP, Mohlke KL, Vineis P, Raitakari O, Ganesh SK, Wong TY, Tai ES, Cooper RS, Laakso M, Rao DC, Harris TB, Morris RW, Dominiczak AF, Kivimaki M, Marmot MG, Miki T, Saleheen D, Chandak GR, Coresh J, Navis G, Salomaa V, Han BG, Zhu X, Kooner JS, Melander O, Ridker PM, Bandinelli S, Gyllensten UB, Wright AF, Wilson JF, Ferrucci L, Farrall M, Tuomilehto J, Pramstaller PP, Elosua R, Soranzo N, Sijbrands EJ, Altshuler D, Loos RJ, Shuldiner AR, Gieger C, Meneton P, Uitterlinden AG, Wareham NJ, Gudnason V, Rotter JI, Rettig R, Uda M, Strachan DP, Witteman JC, Hartikainen AL, Beckmann JS, Boerwinkle E, Vasan RS, Boehnke M, Larson MG, Jarvelin MR, Psaty BM, Abecasis GR, Chakravarti A, Elliott P, van Duijn CM, Newton-Cheh C, Levy D, Caulfield MJ, Johnson T. International Consortium for Blood Pressure Genome-Wide Association Studies. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature* 2011;**478**:103–109.
108. Reilly MP, Li M, He J, Ferguson JF, Stylianou IM, Mehta NN, Burnett MS, Devaney JM, Knouff CW, Thompson JR, Horne BD, Stewart AF, Assimes TL, Wild PS, Allayee H, Nitschke PL, Patel RS, Myocardial Infarction Genetics C, Wellcome Trust Case Control C, Martinelli N, Girelli D, Quyyumi AA, Anderson JL, Erdmann J, Hall AS, Schunkert H, Quertermous T, Blankenberg S, Hazen SL, Roberts R, Kathiresan S, Samani NJ, Epstein SE, Rader DJ. Identification of ADAMTS7 as a

novel locus for coronary atherosclerosis and association of ABO with myocardial infarction in the presence of coronary atherosclerosis: two genome-wide association studies. *Lancet* 2011;**377**:383–392.
109. Erdmann J, Willenborg C, Nahrstaedt J, Preuss M, Konig IR, Baumert J, Linsel-Nitschke P, Gieger C, Tennstedt S, Belcredi P, Aherrahrou Z, Klopp N, Loley C, Stark K, Hengstenberg C, Bruse P, Freyer J, Wagner AK, Medack A, Lieb W, Grosshennig A, Sager HB, Reinhardt A, Schafer A, Schreiber S, El Mokhtari NE, Raaz-Schrauder D, Illig T, Garlichs CD, Ekici AB, Reis A, Schrezenmeir J, Rubin D, Ziegler A, Wichmann HE, Doering A, Meisinger C, Meitinger T, Peters A, Schunkert H. Genome-wide association study identifies a new locus for coronary artery disease on chromosome 10p11.23. *Eur Heart J* 2011;**32**:158–168.
110. Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, Glazer NL, Morrison AC, Johnson AD, Aspelund T, Aulchenko Y, Lumley T, Kottgen A, Vasan RS, Rivadeneira F, Eiriksdottir G, Guo X, Arking DE, Mitchell GF, Mattace-Raso FU, Smith AV, Taylor K, Scharpf RB, Hwang SJ, Sijbrands EJ, Bis J, Harris TB, Ganesh SK, O'Donnell CJ, Hofman A, Rotter JI, Coresh J, Benjamin EJ, Uitterlinden AG, Heiss G, Fox CS, Witteman JC, Boerwinkle E, Wang TJ, Gudnason V, Larson MG, Chakravarti A, Psaty BM, van Duijn CM. Genome-wide association study of blood pressure and hypertension. *Nat Genet* 2009;**41**:677–687.
111. Newton-Cheh C, Johnson T, Gateva V, Tobin MD, Bochud M, Coin L, Najjar SS, Zhao JH, Heath SC, Eyheramendy S, Papadakis K, Voight BF, Scott LJ, Zhang F, Farrall M, Tanaka T, Wallace C, Chambers JC, Khaw KT, Nilsson P, van der Harst P, Polidoro S, Grobbee DE, Onland-Moret NC, Bots ML, Wain LV, Elliott KS, Teumer A, Luan J, Lucas G, Kuusisto J, Burton PR, Hadley D, McArdle WL, Wellcome Trust Case Control C, Brown M, Dominiczak A, Newhouse SJ, Samani NJ, Webster J, Zeggini E, Beckmann JS, Bergmann S, Lim N, Song K, Vollenweider P, Waeber G, Waterworth DM, Yuan X, Groop L, Orho-Melander M, Allione A, Di Gregorio A, Guarrera S, Panico S, Ricceri F, Romanazzi V, Sacerdote C, Vineis P, Barroso I, Sandhu MS, Luben RN, Crawford GJ, Jousilahti P, Perola M, Boehnke M, Bonnycastle LL, Collins FS, Jackson AU, Mohlke KL, Stringham HM, Valle TT, Willer CJ, Bergman RN, Morken MA, Doring A, Gieger C, Illig T, Meitinger T, Org E, Pfeufer A, Wichmann HE, Kathiresan S, Marrugat J, O'Donnell CJ, Schwartz SM, Siscovick DS, Subirana I, Freimer NB, Hartikainen AL, McCarthy MI, O'Reilly PF, Peltonen L, Pouta A, de Jong PE, Snieder H, van Gilst WH, Clarke R, Goel A, Hamsten A, Peden JF, Seedorf U, Syvanen AC, Tognoni G, Lakatta EG, Sanna S, Scheet P, Schlessinger D, Scuteri A, Dorr M, Ernst F, Felix SB, Homuth G, Lorbeer R, Reffelmann T, Rettig R, Volker U, Galan P, Gut IG, Hercberg S, Lathrop GM, Zelenika D, Deloukas P, Soranzo N, Williams FM, Zhai G, Salomaa V, Laakso M, Elosua R, Forouhi NG, Volzke H, Uiterwaal CS, van der Schouw YT, Numans ME, Matullo G, Navis G, Berglund G, Bingham SA, Kooner JS, Connell JM, Bandinelli S, Ferrucci L, Watkins H, Spector TD, Tuomilehto J, Altshuler D, Strachan DP, Laan M, Meneton P, Wareham NJ, Uda M, Jarvelin MR, Mooser V, Melander O, Loos RJ, Elliott P, Abecasis GR, Caulfield M, Munroe PB. Genome-wide association study identifies eight loci associated with blood pressure. *Nat Genet* 2009;**41**:666–676.
112. Do R, Stitziel NO, Won HH, Jorgensen AB, Duga S, Angelica Merlini P, Kiezun A, Farrall M, Goel A, Zuk O, Guella I, Asselta R, Lange LA, Peloso GM, Auer PL, Project NES, Girelli D, Martinelli N, Farlow DN, DePristo MA, Roberts R, Stewart AF, Saleheen D, Danesh J, Epstein SE, Sivapalaratnam S, Hovingh GK, Kastelein JJ, Samani NJ, Schunkert H, Erdmann J, Shah SH, Kraus WE, Davies R, Nikpay M, Johansen CT, Wang J, Hegele RA, Hechter E, Marz W, Kleber ME, Huang J, Johnson AD, Li M, Burke GL, Gross M, Liu Y, Assimes TL, Heiss G, Lange EM, Folsom AR, Taylor HA, Olivieri O, Hamsten A, Clarke R, Reilly DF, Yin W, Rivas MA, Donnelly P, Rossouw JE, Psaty BM, Herrington DM, Wilson JG, Rich SS, Bamshad MJ, Tracy RP, Cupples LA, Rader DJ, Reilly MP, Spertus JA, Cresci S, Hartiala J, Tang WH, Hazen SL, Allayee H, Reiner AP, Carlson CS, Kooperberg C, Jackson RD, Boerwinkle E, Lander ES, Schwartz SM, Siscovick DS, McPherson R, Tybjaerg-Hansen A, Abecasis GR, Watkins H, Nickerson DA, Ardissino D, Sunyaev SR, O'Donnell CJ, Altshuler D, Gabriel S, Kathiresan S. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. *Nature* 2015;**518**:102–106.
113. Gudbjartsson DF, Bjornsdottir US, Halapi E, Helgadottir A, Sulem P, Jonsdottir GM, Thorleifsson G, Helgadottir H, Steinthorsdottir V, Stefansson H, Williams C, Hui J, Beilby J, Warrington NM, James A, Palmer LJ, Koppelman GH, Heinzmann A, Krueger M, Boezen HM, Wheatley A, Altmuller J, Shin HD, Uh ST, Cheong HS, Jonsdottir B, Gislason D, Park CS, Rasmussen LM, Porsbjerg C, Hansen JW, Backer V, Werge T, Janson C, Jonsson UB, Ng MC, Chan J, So WY, Ma R, Shah SH, Granger CB, Quyyumi AA, Levey AI, Vaccarino V, Reilly MP, Rader DJ, Williams MJ, van Rij AM, Jones GT, Trabetti E, Malerba G, Pignatti PF, Boner A, Pescollderungg L, Girelli D, Olivieri O, Martinelli N, Ludviksson BR, Ludviksdottir D, Eyjolfsson GI, Arnar D, Thorgeirsson G, Deichmann K, Thompson PJ, Wjst M, Hall IP, Postma DS, Gislason T, Gulcher J, Kong A, Jonsdottir I, Thorsteinsdottir U, Stefansson K. Sequence variants affecting eosinophil numbers associate with asthma and myocardial infarction. *Nat Genet* 2009;**41**:342–347.
114. Brænne I, Willenborg C, Tragante V, Kessler T, Zeng L, Reiz B, Kleinecke M, von Ameln S, Willer CJ, Laakso M, Wild PS, Zeller T, Wallentin L, Franks PW, Salomaa V, Dehghan A, Meitinger T, Samani NJ, Asselbergs FW, Erdmann J, Schunkert H. A genomic exploration identifies mechanisms that may explain adverse cardiovascular effects of COX-2 inhibitors. *Sci Rep* 2017;**7**:10252.
115. Kathiresan S. Myocardial Infarction Genetics Consortium. A PCSK9 missense variant associated with a reduced risk of early-onset myocardial infarction. *N Engl J Med* 2008;**358**:2299–2300.
116. Myocardial Infarction Genetics Consortium Investigators, Stitziel NO, Won HH, Morrison AC, Peloso GM, Do R, Lange LA, Fontanillas P, Gupta N, Duga S, Goel A, Farrall M, Saleheen D, Ferrario P, Konig I, Asselta R, Merlini PA, Marziliano N, Notarangelo MF, Schick U, Auer P, Assimes TL, Reilly M, Wilensky R, Rader DJ, Hovingh GK, Meitinger T, Kessler T, Kastrati A, Laugwitz KL, Siscovick D, Rotter JI, Hazen SL, Tracy R, Cresci S, Spertus J, Jackson R, Schwartz SM, Natarajan P, Crosby J, Muzny D, Ballantyne C, Rich SS, O'Donnell CJ, Abecasis G, Sunyaev S, Nickerson DA, Buring JE, Ridker PM, Chasman DI, Austin E, Ye Z, Kullo IJ, Weeke PE, Shaffer CM, Bastarache LA, Denny JC, Roden DM, Palmer C, Deloukas P, Lin DY, Tang ZZ, Erdmann J, Schunkert H, Danesh J, Marrugat J, Elosua R, Ardissino D, McPherson R, Watkins H, Reiner AP, Wilson JG, Altshuler D, Gibbs RA, Lander ES, Boerwinkle E, Gabriel S, Kathiresan S. Inactivating mutations in NPC1L1 and protection from coronary heart disease. *N Engl J Med* 2014;**371**:2072–2082.
117. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, Parish S, Barlera S, Franzosi MG, Rust S, Bennett D, Silveira A, Malarstig A, Green FR, Lathrop M, Gigante B, Leander K, de Faire U, Seedorf U, Hamsten A, Collins R, Watkins H, Farrall M, Consortium P. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 2009;**361**:2518–2528.
118. Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators. Coding variation in ANGPTL4, LPL, and SVEP1 and the risk of coronary disease. *N Engl J Med* 2016;**374**:1134–1144.
119. Working Group of the Exome Sequencing Project, Crosby J, Peloso GM, Auer PL, Crosslin DR, Stitziel NO, Lange LA, Lu Y, Tang ZZ, Zhang H, Hindy G, Masca N, Stirrups K, Kanoni S, Do R, Jun G, Hu Y, Kang HM, Xue C, Goel A, Farrall M, Duga S, Merlini PA, Asselta R, Girelli D, Olivieri O, Martinelli N, Yin W, Reilly D, Speliotes E, Fox CS, Hveem K, Holmen OL, Nikpay M, Farlow DN, Assimes TL, Franceschini N, Robinson J, North KE, Martin LW, DePristo M, Gupta N, Escher SA, Jansson JH, Van Zuydam N, Palmer CN, Wareham N, Koch W, Meitinger T, Peters A, Lieb W, Erbel R, Konig IR, Kruppa J, Degenhardt F, Gottesman O, Bottinger EP, O'Donnell CJ, Psaty BM, Ballantyne CM, Abecasis G, Ordovas JM, Melander O, Watkins H, Orho-Melander M, Ardissino D, Loos RJ, McPherson R, Willer CJ, Erdmann J, Hall AS, Samani NJ, Deloukas P, Schunkert H, Wilson JG, Kooperberg C, Rich SS, Tracy RP, Lin DY, Altshuler D, Gabriel S, Nickerson DA, Jarvik GP, Cupples LA, Reiner AP, Boerwinkle E, Kathiresan S. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med* 2014;**371**:22–31.
120. Dewey FE, Gusarova V, O'Dushlaine C, Gottesman O, Trejos J, Hunt C, Van Hout CV, Habegger L, Buckler D, Lai KV, Leader JB, Murray MF, Ritchie MD, Kirchner HL, Ledbetter DH, Penn J, Lopez A, Borecki IB, Overton JD, Reid JG, Carey DJ, Murphy AJ, Yancopoulos GD, Baras A, Gromada J, Shuldiner AR. Inactivating variants in ANGPTL4 and risk of coronary artery disease. *N Engl J Med* 2016;**374**:1123–1133.
121. Stitziel NO, Khera AV, Wang X, Bierhals AJ, Vourakis AC, Sperry AE, Natarajan P, Klarin D, Emdin CA, Zekavat SM, Nomura A, Erdmann J, Schunkert H, Samani NJ, Kraus WE, Shah SH, Yu B, Boerwinkle E, Rader DJ, Gupta N, Frossard PM, Rasheed A, Danesh J, Lander ES, Gabriel S, Saleheen D, Musunuru K, Kathiresan S. Myocardial Infarction Genetics Consortium Investigators. ANGPTL3 deficiency and protection against coronary artery disease. *J Am Coll Cardiol* 2017;**69**:2054–2063.
122. Dewey FE, Gusarova V, Dunbar RL, O'Dushlaine C, Schurmann C, Gottesman O, McCarthy S, Van Hout CV, Bruse S, Dansky HM, Leader JB, Murray MF, Ritchie MD, Kirchner HL, Habegger L, Lopez A, Penn J, Zhao A, Shao W, Stahl N, Murphy AJ, Hamon S, Bouzelmat A, Zhang R, Shumel B, Pordy R, Gipe D, Herman GA, Sheu WHH, Lee I-T, Liang K-W, Guo X, Rotter JI, Chen Y-DI, Kraus WE, Shah SH, Damrauer S, Small A, Rader DJ, Wulff AB, Nordestgaard BG, Tybjærg-Hansen A, van den Hoek AM, Princen HMG, Ledbetter DH, Carey DJ, Overton JD, Reid JG, Sasiela WJ, Banerjee P, Shuldiner AR, Borecki IB, Teslovich TM, Yancopoulos GD, Mellis SJ, Gromada J, Baras A. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *N Engl J Med* 2017;**377**:211–221.
123. Graham MJ, Lee RG, Brandt TA, Tai LJ, Fu W, Peralta R, Yu R, Hurh E, Paz E, McEvoy BW, Baker BF, Pham NC, Digenio A, Hughes SG, Geary RS, Witztum JL, Crooke RM, Tsimikas S. Cardiovascular and metabolic effects of ANGPTL3 antisense oligonucleotides. *N Engl J Med* 2017;**377**:222–232.