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Brief Review: Genetics of coronary artery disease

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Coronary heart disease affects approximately 15.4 million individuals in the US[1] and is one of the main causes of mortality and morbidity.[1] A familial component contributes to cardiovascular disease (CVD) susceptibility,[2] but it was not until the emergence of genome-wide association studies (GWAS) that genetic loci have been identified that displayed consistent associations with coronary artery disease (CAD) across multiple cohorts. The present article describes recent advances in the understanding of the genetic basis of CAD.

Main results from genome-wide association studies and recent gene-centric approaches

Family[2] and twin studies[3] provided convincing evidence that CAD clusters in families and has a heritable component.[2-5] However, the delineation of the specific genetic architecture predisposing to CAD has been challenging, with initial candidate gene approaches yielding inconsistent results.[6] In contrast to candidate gene approaches which focus on genetic variation in genes whose gene products are known to play an important role in cardiovascular physiology, GWAS assess simultaneously the association with CAD of hundreds of thousands of genetic variants distributed across the whole genome. Therefore, GWAS represent an essentially unbiased approach that is not limited by the current (patho)physiological understanding of CVD, and bears the potential of discovering completely new molecular mechanisms predisposing to CAD.

In 2007, the first GWAS for CAD were published.[7-9] The main finding was a locus on chromosome 9p21, which is still the most consistently associated CAD locus to date.[10] Subsequent studies revealed that this locus is related to a broad spectrum of vascular phenotypes, including e.g., CAD and myocardial infarction,[7-9] coronary artery calcification,[11] peripheral artery disease,[12, 13] and abdominal aortic aneurysm.[14] In order to increase power for the detection of genetic variants with smaller effect sizes, large consortia have been built which combine genetic-epidemiological data from multiple cohorts and ten-thousands of participants. Examples are the CARDIoGRAM (**C**oronary **AR**tery **D**Isease **G**enome-Wide **R**eplication **A**nd **M**eta-Analysis)[15] and the Coronary Artery Disease (C4D) Genetics consortium.[16] Such consortia identified multiple additional loci associated with CAD and MI.[16-23] Complementary to the genome-wide approaches, also candidate gene-

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based and gene centric approaches are being evaluated in a coordinated fashion, for example within the CARe project (Candidate Gene Association Resource)[24] or the IBC 50k CAD Consortium.[25] Furthermore, the Metabochip,[26] a custom array with approximately 200.000 genetic variants associated with cardio-metabolic traits in prior analyses, has been assessed in the context of CAD.[20] To date, 50 genetic loci associated with CAD on a genome-wide level ($p<5\times10^{-8}$) have been reported (**Table**). In aggregate, these loci explain approximately 10% of the heritability of CAD,[17, 20] still leaving most of the CAD heritability unexplained. Interestingly, most genome-wide significant hits were not related to traditional risk factors,[16, 20, 27] underscoring the potential of GWAS to identify previously unknown genomic regions and biological pathways that contribute to disease susceptibility. The main traditional risk factors which show some evidence for association with CAD-associated SNPs are lipid and blood pressure traits.[17, 20]

Genetic predictors in patients with established CAD

Genetic analyses were not restricted to prevalent or incident CAD. Single nucleotide polymorphisms (SNPs) are increasingly evaluated as prognostic factors in patient with established CAD. Genetic variation at 1p13.3 and 1q41 (both loci have been associated with prevalent CAD in prior GWAS[7, 22]) were associated with cardiovascular outcomes in patient with established CAD (including readmission for CVD and survival)[28] and genetic variation in the *thrombomodulin* gene was associated with long-term survival in patients undergoing bypass surgery.[29] These findings underscore the concept that a common or overlapping genetic architecture might influence several stages along the atherosclerotic disease spectrum. This premise is further supported by the observation that certain genetic loci are related to several vascular traits, as has been reported e.g. for the chromosome 9p21 locus (see above). On a parallel note, genetic variants also contribute to the susceptibility for sudden cardiac death in patients with established CAD, including SNPs in the genes *CASQ2*, *GPD1L* and *NOS1AP*.[30]

Thus, the genetic predisposition is not only relevant for the development of CAD, but also emerged as potential prognostic factor in patients with established disease. It needs to be assessed, though, whether genetic information is useful to refine clinical decisions when treating patients with CAD, a premise that requires further investigations. So far, data on the efficacy of genotype-based treatment strategies vs. conventional care from randomized controlled trials are often lacking. Newer initiatives are addressing this gap in our scientific knowledge for some clinical settings.[31]

Impact of CAD phenotype definition on effect estimates in genetic association studies

Since large consortia have been built in order to detect genetic variants with smaller effect sizes, it emerged as an important question whether and how different phenotype definitions for CAD in such combined or meta analyses might affect the results. Some prior studies reported indeed slightly stronger genetic association signals in patients with angiographically confirmed CAD, as compared to CAD patients without angiographic data.[17] Furthermore, family-based analyses revealed different heritability estimates for distinct sub-phenotypes of CAD.[32] On the other hand, there is a remarkable consistency in genetic association findings across cohorts (with varying phenotype definitions), underscoring that different manifestations of CAD might have a common genetic architecture. Kitsios and colleagues reanalyzed data from 965 individual studies assessing the association of 32 genetic variants (in 22 genes) with CAD. The authors observed substantial variability in the phenotype definitions used across studies (for both, cases and controls),[33] but these differences contributed relatively little to the overall between-study

heterogeneity. Furthermore, more stringent phenotype definitions (e. g. acute coronary syndrome or angiographically documented CAD) did not lead to systematically different association measures in genetic analyses as compared to broader definitions of the disease.[33] The authors conclude that all available "evidence for CAD phenotypes should be considered" in genetic meta-analyses.[33]

Replicated and consistent association signals from genetic-epidemiological studies stimulate further research. Conceptually, this work-up can be categorized in at least 3 main areas of research. First, the identification of the causal genetic variant at a given locus and the elucidation of the precise biological mechanism by which a genetic locus leads to increased CAD susceptibility. Second, the application of genetic variants in risk prediction models to forecast more precisely the onset or the natural course of disease or to predict more accurately the response to a given treatment. Third, identifying newer therapeutic targets and conducting randomized trials focusing on these targets.

Functional work-up of GWAS results

To clarify the biological mechanisms responsible for a genetic association signal, genetic-epidemiological information is increasingly combined with data from other high-throughput OMICs technologies and with cellular or animal experiments. Several studies assessed whether significantly associated CAD-SNPs affect the expression of nearby genes in different tissues.[16, 20, 34] Additional work-up strategies include the identification of the causal variant at a given locus through fine-mapping, or through knock-down or overexpression experiments of the putative causal genetic variant in cellular and animal models, e.g. to assess potential consequences of the genetic variant on physiological traits (e.g., lipid levels).

In a landmark article, Musunuru[35] and colleagues elucidated much of the biological mechanism how a newly discovered locus on chromosome 1p13 contributes to CAD susceptibility. In prior analyses, non-coding SNPs at 1p13 were associated with an adverse lipid profile and the risk of CAD.[7, 22, 36] Through fine mapping, a close survey of genetic variation around the top SNPs in a given locus, and a series of experiments, the authors identified rs12740374 as the putative causal variant of the locus. This variant is located within a transcription factor binding site. The CAD risk allele alters this binding site and, thereby, affects the expression of the *SORT1* gene in the liver.[35] The *SORT1* gene product sortilin 1 modulates cellular LDL uptake in vitro[37] and secretion of VLDL particles in experimental settings[35], thereby influencing circulating lipid concentrations.[38] Thus, the current evidence indicates that the genetic risk variant at the 1p13 locus leads to impaired *SORT1* expression in the liver, higher hepatic VLDL secretion and reduced cellular LDL uptake, and is - as a consequence - associated with higher circulating LDL levels and, thereby, increases CAD risk.[38] This work was one of the first examples, how GWAS and subsequent functional analyses identified an entirely new molecular mechanism affecting circulating lipid levels and predisposition to CAD. The sortilin pathway could be a potential therapeutic target to prevent dyslipidemia and reduce CAD risk.

Use of genetic information for risk prediction and assessment of clinical utility

The use of genetic information to more accurately predict i) the development of diseases in asymptomatic individuals, ii) the natural course of disease, or iii) the response to therapy in patient with established disease, belonged to the key motivations for the human genome project and for the efforts to unravel the genetic architecture of diseases. In this context, it is of central interest, whether genetic variants add information to such prediction models

beyond established risk factors. Different performance measures have been established to assess the incremental contribution of biomarkers (including genetic variation).[39] Important indices include calibration (how well agree predicted and observed absolute disease risks), discrimination and reclassification.[39] Discrimination refers to the ability to distinguish individuals who develop the disease from those who will not,[39] and reclassification quantifies how many individuals (with or without the outcome of interest) will be categorized in a more accurate risk category if genetic information is added to models with established risk factors. Given the complexity of the genetic architecture of CAD with several variants conferring modest increases in relative disease risk (**Table**), genetic information is often aggregated using genetic risk scores which sum-up and weight the number of risk alleles carried by each individual. In general, genetic risk scores for CAD are independently associated with CAD, even after adjustment for classic CVD risk factors.[40-43] This is not surprising, given that many of the CAD-associated risk variants are not related to traditional risk factors.[27] However, genetic risk scores only modestly improved discrimination (if at all) and reclassification.[40-42, 44, 45]

Analyses in the Atherosclerosis Risk in Communities (ARIC) study revealed that after adding genetic information from the 9p21 locus to a prediction model based on established risk factors, 12-13% of participants in the intermediate risk category (10-years risk, 5%-20%) are reclassified.[46] The authors emphasized that this reclassification might affect treatment decisions and treatment goals, e. g. for LDL-cholesterol, in a relevant proportion of individuals.[46] However, future studies need to establish whether such reclassification and alternative treatment strategies based on genetic variation ultimately improve patient outcomes.[39, 47]

One strategy to assess the clinical utility of genetic biomarkers is to conduct a randomized trial where a treatment strategy based on genetic information is compared to usual care (where no genetic information is considered).[39, 47]

Conceptually, knowledge of genetic variation may improve patient outcome in several ways, not just via better medical decisions by the physician.[47] Knowledge of an increased genetic susceptibility to CAD (as reflected by a high genetic risk score) might also lead to higher compliance and better adherence to risk factor therapy by the patient,[47, 48] a premise that is currently being investigated in an ongoing clinical trial.[48] In patients referred to a preventive cardiology clinic with an estimated 10-year CVD-risk ≥6% or an estimated ≥20% CVD-risk over 30 years, the investigators will assess whether knowledge of the genetic risk score by the patient further improves risk factor levels (e.g. LDL levels, blood pressure) during short-term follow-up, even though patient management and treatment decisions are *not* influenced by the results of the genetic risk score; the results of the genetic risk score are disclosed after the treatment decisions have been made.[48]

Currently, the use of genetic information to modify therapeutic strategies is not broadly recommended because of the lack of efficacy data from clinical trials in most clinical settings. Emerging clinical trials in this field will provide important insights into the potential clinical utility of genetic markers.[31]

Furthermore, due to their modest effect sizes,[49] genetic markers may not be suitable as screening tools in asymptomatic individuals at present.

Conclusion

GWAS and collaborative gene-centric approaches – in conjunction with other large scale OMICs technologies – substantially improved our understanding of the molecular basis of

CAD by identifying consistently associated genetic variant and by elucidating some of the underlying patho-mechanisms. However, the effect sizes per risk allele were modest (**Table**) leaving much of the CAD heritability still unexplained. GWAS and candidate gene approaches typically focused on relatively common SNPs with a minor allele frequency >5%. More recently, new sequencing technologies enable whole exome (where all protein coding segments of the DNA are analyzed) or whole genome sequencing at declining costs and facilitate more comprehensive analyses of rare genetic variants (minor allele frequency <1%) to assess their significance for CAD.[50] Furthermore, it is increasingly recognized that cardiovascular disease processes are governed by complex biological networks.[51] Important technical advances form the basis to measure several components of such biological networks. Therefore, genetic information will increasingly be analyzed in the context of complementary gene expression, proteomic and metabolomic data. As an example, data on Protein-Protein-Interactions can be considered in the analyses of GWAS and by combining information on Protein-Protein-Interactions with GWAS data, new groups of genes can be identified that might be relevant for the pathogenesis of CAD,[52] even though the SNPs in isolation do not reach genome-wide statistical significance.[52] Additional research efforts include analyses of epigenetic modifications,[53] and of interactions between genes or between genes and environmental factors. Furthermore, modifiers of gene expression and protein processing are increasingly analyzed. Ideally, these different components are evaluated in combined analytical approaches to elucidate entire biological systems governing physiological function of the cardiovascular system.[51]

In that context, repeated (at different points in time) and comprehensive molecular phenotyping of large samples under steady state conditions as well as in the context of challenges that cause perturbations of physiological traits, are important requisites to improve our understanding of the biological networks underlying cardiovascular function and disease development.[54]

Beyond the identification of new disease-associated biomarker profiles, systematic analyses are needed to elucidate the underlying biological mechanisms; and intensified research is required to assess the potential clinical utility of genetic variants in patients with established CAD and their potential use as screening tools in asymptomatic individuals.

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Table 1

Genetic loci associated with coronary artery disease and/or myocardial infarction

Band	rs-number	Gene(s)	Risk allele	Risk allele frequency	OR (95% CI)	p-Value	Reference (examples)
1p13.3	rs599839	*SORT1*	A	0.77	1.29 (1.18-1.40)[7]	4.05×10^{-9}	7, 17, 22
1p32.2	rs17114036	*PPAP2B*	A	0.91	1.17 (1.13-1.22)[17]	3.81×10^{-19}	17
1p32.3	rs11206510	*PCSK9*	T	0.81	1.15 (1.10-1.21)[22]	9.6×10^{-9}	22
1q21.3	rs4845625	*IL6R*	T	0.47	1.04 (1.02-1.07)[20]	3.55×10^{-8}	20
1q41	rs17465637	*MIA3*	C	0.72	1.14 (1.10-1.19)[22]	1.4×10^{-9}	7, 17, 22
2p11.2	rs1561198	*VAMP5-VAMP8-GGCX*	A	0.45	1.05 (1.03-1.07)[20]	4.48×10^{-9}	20
2p21	rs6544713	*ABCG5-ABCG8*	T	0.30	1.06 (1.04-1.09)[20]	8.72×10^{-10}	20, 25, 55
2p24.1	rs2123536	*TTC32-WDR35*	T	0.39	1.12 (1.08-1.16)[19]	6.83×10^{-11}	19
2p24.1	rs515135	*APOB*	G	0.83	1.08 (1.05-1.11)[20]	4.80×10^{-10}	20
2q22.3	rs2252641	*ZEB2-AC074093.1*	G	0.46	1.04(1.02-1.06)[20]	3.66×10^{-8}	20
2q33.2	rs6725887	*WDR12*	C	0.14	1.17 (1.11-1.23)[22]	1.3×10^{-8}	17, 22
3q22.3	rs2306374	*MRAS*	C	0.18	1.12 (1.07-1.16)[17]	3.34×10^{-8}	17, 21
4q31.22	rs1878406	*EDNRA*	T	0.15	1.06 (1.02-1.11)[20]	2.54×10^{-8}	20
4q32.1	rs7692387	*GUCY1A3*	G	0.81	1.06 (1.03-1.09)[20]	4.57×10^{-9}	19, 20
5q31.1	rs273909	*SLC22A4-SLC22A5*	C	0.14	1.09 (1.05-1.12)[20]	1.43×10^{-8}	20
6p21.2	rs10947789	*KCNK5*	T	0.76	1.06 (1.03-1.08)[20]	1.63×10^{-8}	20
6p21.31	rs17609940	*ANKS1A*	G	0.75	1.07 (1.05-1.10)[17]	1.36×10^{-8}	17
6p21.32	rs9268402	*C6orf10-BTNL2*	G	0.59	1.16 (1.12-1.20)[19]	2.77×10^{-15}	19
6p21.33	rs3869109	*HLA-C, HLA-B, HCG27*	G	0.55	1 14[56]*	1.12×10^{-9}	56
6p24.1	rs12526453	*PHACTR1*	C	0.65	1.12 (1.08-1.17) [22]	1.3×10^{-9}	17, 22
6p24.1	rs6903956	*C6orf105*	A	0.07	1.65 (1.44-1.90)[57]	2.55×10^{-13}	57
6q23.2	rs12190287	*TCF21*	C	0.62	1.08 (1.06-1.10)[17]	1.07×10^{-12}	17
6q25.3	rs3798220	*LPA*	C	0.02	1.51 (1.33-1.70)[17]	3.00×10^{-11}	17, 23
6q26	rs4252120	*PLG*	T	0.73	1.06 (1.03-1.09)[20]	5.00×10^{-9}	20
7p21.1	rs2023938	*HDAC9*	G	0.10	1.07 (1.04-1.11)[20]	4.94×10^{-8}	20

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Band	rs-number	Gene(s)	Risk allele	Risk allele frequency	OR (95% CI)	p-Value	Reference (examples)
7q22.3	rs10953541	*BCAP29*	C	0.8	1.08 (1.05-1.11)[16]	3.12×10^{-8}	16
7q32.2	rs11556924	*ZC3HC1*	C	0.62	1.09 (1.07-1.12)[17]	9.18×10^{-18}	17
8p21.3	rs264	*LPL*	G	0.86	1.05 (1.02-1.08)[20]	5.06×10^{-9}	20
8q24.13	rs2954029	*TRIB1*	A	0.55	1.04 (1.02-1.06)[20]	4.53×10^{-8}	20, 25
9p21.3	rs1333049	*CDKN2A, CDKN2B*	C	0.47	1.37 (1.26-1.48)[7]	1.80×10^{-14}	7-9
9q34.2	rs579459	*ABO*	C	0.21	1.10 (1.07-1.13)[17]	4.08×10^{-14}	17, 55, 58
10p11.23	rs2505083	*KIAA1462*	C	0.38	1.07 (1.04-1.09)[16]	3.87×10^{-8}	16, 18
10q11.21	rs1746048	*CXCL12*	C	0.84	1.17 (1.11-1.24)[22]	7.4×10^{-9}	7, 17, 22
10q23.31	rs1412444	*LIPA*	T	0.42	1.09 (1.07-1.12)[16]	2.76×10^{-13}	16, 25, 59
10q24.32	rs12413409	*CYP17A1, CNNM2,NT5C2*	G	0.89	1.12 (1.08-1.16)[17]	1.03×10^{-9}	17
11q22.3	rs974819	*PDGFD*	T	0.32	1.07 (1.04-1.09)[16]	2.41×10^{-9}	16
11q23.3	rs964184	*ZNF259, APOA5-A4-C3-A1*	G	0.13	1.13 (1.10-1.16)[17]	1.02×10^{-17}	17
12q21.33	rs7136259	*ATP2B1*	T	0.39	1.11 (1.08-1.15)[19]	5.68×10^{-10}	19
12q24.12	rs3184504	*SH2B3*	T	0.38	1.13 (1.08-1.18)[60]	8.6×10^{-8}	20, 60
13q12.3	rs9319428	*FLT1*	A	0.32	1.05 (1.03-1.08)[20]	1.01×10^{-8}	20
13q34	rs4773144	*COL4A1,COL4A2*	G	0.44	1.07 (1.05-1.09)[17]	3.84×10^{-9}	17
14q32.2	rs2895811	*HHIPL1*	C	0.43	1.07 (1.05-1.10)[17]	1.14×10^{-10}	17
15q25.1	rs3825807	*ADAMTS7*	A	0.57	1.08 (1.06-1.10)[17]	1.07×10^{-12}	16, 17, 58
15q26.1	rs17514846	*FURIN-FES*	A	0.44	1.05 (1.03-1.08)[20]	4.49×10^{-10}	20
17p11.2	rs12936587	*RASD1,SMCR3,PEMT*	G	0.56	1.07 (1.05-1.09)[17]	4.45×10^{-10}	17
17p13.3	rs216172	*SMG6, SRR*	C	0.37	1.07 (1.05-1.09)[17]	1.15×10^{-9}	17
17q21.32	rs46522	*UBE2Z, GIP,ATP5G1, SNF8*	T	0.53	1.06 (1.04-1.08)[17]	1.81×10^{-8}	17
19p13.2	rs1122608	*LDLR*	G	0.75	1.15 (1.10-1.20)[22]	1.9×10^{-9}	17, 22
19q13.32	rs2075650	*APOE/TOMM40*	G	0.14	1.14 (1.09-1.19)[25]	3.2×10^{-8}	20, 25
21q22.11	rs9982601	*SLC5A3-MRPS6-KCNE2*	T	0.13	1.20 (1.14-1.27)[22]	6.4×10^{-11}	17, 22

In each row, data on rsnumber, gene(s) at the locus, risk allele, risk allele frequency and p-value, were obtained from the same reference as the odds ratio

[*] The 95% confidence interval of the odds ratio was not numerically provided.