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The Genetic Underpinnings of Anthracycline-Induced Cardiomyopathy Predisposition

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Abstract

Anthracyclines, chemotherapeutic agents that have contributed to significant improvements in cancer survival, also carry risk of both acute and chronic cardiotoxicity. This has led to significantly elevated risks of cardiac morbidity and mortality among cancer survivors treated with these agents. Certain treatment related, demographic, and medical factors increase an individual's risk of anthracycline induced cardiotoxicity; however, significant variability among those affected suggests that there is an underlying genetic predisposition to anthracycline induced cardiotoxicity. The current narrative review seeks to summarize the literature to date that has identified genetic variants associated with anthracycline induced cardiotoxicity. These include variants found in genes that encode proteins associated with anthracycline transportation and metabolism, those that encode proteins associated with the generation of reactive oxygen species, and those known to be associated with cardiac disease. While there is strong evidence that susceptibility to anthracycline induced cardiotoxicity has genetic underpinnings, the majority of work to date has been candidate gene analyses. Future work should focus on genome-wide analyses including genome-wide association and sequencing-based studies to confirm and expand these findings.

Keywords

Anthracyclines; Cancer; Cardiotoxicity; SNPs

INTRODUCTION:

Anthracyclines are a class of chemotherapeutics that have been indispensable to improvements in cancer survival, particularly for common childhood and young adult cancers such as leukemia, lymphoma, sarcoma, as well as breast cancer.[1] Mechanisms of

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their antitumor activity include DNA intercalation, production of hydroxyl free radicals, and inhibition of topoisomerase II, an enzyme that plays an important role in DNA replication and transcription.[2]

The use of anthracyclines is complicated by risk of acute and chronic cardiotoxicity, particularly cardiomyopathy and heart failure (HF). Estimates of acute and chronic cardiotoxicity attributable to anthracyclines range up to 5% and 16% of childhood cancer patients, respectively, with a much greater percentage experiencing subclinical cardiotoxicity.[3, 4] Among childhood cancer patients receiving anthracyclines, risk of HF is dose dependent with a 30-year incidence of 7% among those who received >250 mg/m2, compared with 2% among those who received lower doses.[5] This translates into an almost 8-fold increased risk of cardiac death compared with expected rates in the general population.[6]

Mechanisms of anthracycline induced cardiotoxicity (ACT) are not fully understood, but studies suggest that similar processes as those responsible for their antitumor activity contribute to cardiotoxicity, particularly generation of reactive oxygen species (ROS) and direct binding to DNA leading to inhibition of topoisomerase-II mediated DNA repair and eventually cell death.[7] While there are pharmacologic and surveillance strategies to decrease progression of cardiotoxicity as well as predictive tools that account for treatment exposure,[8] there are currently no effective tools available to assess a patient's individualized risk of ACT prior to starting therapy, knowledge that could be used to tailor anthracycline regimen, cardiac function monitoring, cardioprotective medications, and follow-up to reduce risk of cardiac morbidity and mortality. Uncovering genetic susceptibilities to ACT is key to improving up-front risk assessment and ultimately to developing targeted pharmacogenetic therapies for those at high risk. Clinical practice recommendations for genetic testing of certain variants prior to doxorubicin or daunorubicin, the two most commonly used anthracyclines, treatment in children, have been proposed and the use of such recommendations remains in discussion.[9] Expansion of the literature focused on genetic susceptibility to ACT may help move clinical genetic screening forward. The goal of this review is to provide a summary of studies that have identified genetic variation associated with ACT, with a focus on particular genes that have been implicated in innate predisposition to ACT (Table 1, Figure 1).

INNATE SUSCEPTIBILITY TO ANTHRACYCLINE-INDUCED CARDIOMYOPATHY

Anthracycline induced cardiotoxicity is assessed in different ways, with the majority of studies defining cardiotoxicity as a significant decrease in left ventricular shortening fraction (SF) or left ventricular ejection fraction (LVEF), or as clinical symptoms of cardiac disease. Temporality of onset is divided into acute, early-onset chronic, and late-onset chronic cardiotoxicity. The majority of genetic susceptibility studies focus on early-onset chronic toxicity, the most common type of ACT, that presents as asymptomatic decline in LVEF/SF and progresses to symptomatic HF over time.[10]

The risk of ACT increases with higher cumulative doses (standardized to doxorubicin equivalents),[11] shorter infusion duration, and demographic and medical factors have

been found to increase risk as well, including pre-existing cardiovascular conditions, hypertension, diabetes, receipt of additional cardiotoxic drugs and/or mediastinal radiotherapy, female sex, and age <4 years or >65 years.[10, 12–14] However, even within low and high risk populations, there is considerable variability in incidence of ACT, suggesting that there is likely an innate susceptibility that comes into play.

THE GENETIC LANDSCAPE OF ANTHRACYCLINE-INDUCED CARDIOMYOPATHY

Given the suspicion for a genetic risk factor contribution to ACT, an increasing body of literature has explored this connection. However, the variability in ACT definition, measurement of ACT and timing of ACT assessment pose variability in drawing broad conclusions. The most prevalent type of study assessing genetic risk of ACT development to date have been candidate gene analyses. Candidate genes are explored based on previously identified biological associations and with a focus on genes involved in anthracycline binding and metabolism as well as genes involved in the cardiotoxicity pathway, particularly in the generation of ROS. Unbiased, genome-wide association studies (GWAS) have also been performed, though less frequently. While the effect size of variants associated with cardiotoxicity are typically larger than those associated with cancer development, the impact on echocardiogram findings can be quite small and difficult to discern clinical significance. Here, we seek to detail these studies and to place them along a continuum of rigor ranging from biased candidate gene approaches to unbiased genome studies to independent replication in model systems.

GENES INVOLVED IN TRANSPORT AND CLEARANCE

ABC-encoded ATP Binding Cassette

The *ABC* family includes 49 genes that encode a family of transmembrane proteins found in multiple cell types, including the myocardium, that use adenosine triphosphate (ATP) to serve as active transporters.[15] ABC transporters play an important part in protecting against xenobiotics and serve to export multiple chemotherapeutics, including anthracyclines from cardiac cells.[16] The transporters encoded by *ABCC1* and *ABCB1* transport doxorubicin and play a role in tumor multidrug resistance.[17, 18] The *ABCB4* and *ABCC2* genes encode transporters primarily involved in phospholipid and bile acid transport, however have also been shown to transport doxorubicin.[19, 20] The protein encoded by the *ABCC5* gene primarily transports cyclic nucleotides, though doxorubicin transport has also been demonstrated.[21] Variants in these *ABC* genes that decrease or interfere with expression will lead to accumulation of anthracyclines in cardiomyocytes and thus increased risk of ACT. In particular, a synonymous variant in *ABCC1* (T>C, rs246221) has been associated with reduced SF among childhood acute lymphoblastic leukemia (ALL) and reduced LVEF among breast cancer survivors.[22, 23] Other *ABCC1* variants associated with ACT include a variant in the 3’ UTR (C>T, rs3743527) associated with decreased SF in childhood ALL survivors, a G>T missense variant leading to Gly671Val (rs45511401) associated with an increased risk of acute ACT in non-Hodgkin lymphoma (NHL) patients, and a G>T intron variant (rs4148350) associated with increased odds of clinically depressed SF by >2-fold in

childhood cancer survivors (CCSs).[22, 24, 25] Other polymorphisms in the *ABC* family that have been associated with increased risk of ACT in the childhood cancer survivor population include: an A>C intron variant (rs2235047) in *ABCB1* and a non-coding transcript variant (A>G, rs4148808) in *ABCB4* which were both associated with depressed SF; a C>G missense variant (rs3740066) leading to Ile1324Met in *ABCC2* was associated with reduced SF; a variant in *ABCC5* in the upstream region (A>T, rs7627754) conferred reductions in both LVEF and SF; ABCC2 Val1188Glu-Cys1515Tyr haplotype (rs8187694-rs8187710) was associated with ~2-fold increase in acute ACT; and the missense variant (rs8187710) leading to Cys1515Try increased the risk of HF by >4-fold.[24–28] In breast cancer survivors, a C>T synonymous variant (rs1045642) in *ABCB1* reduced the risk of depressed LVEF.[29]

While the studies that have assessed polymorphisms in the *ABC* gene family have primarily been candidate gene analyses, as opposed to GWAS, investigators have consistently found an association with increased risks of ACT. In fact, the *ABC* gene family has some of the most robust evidence pointing to its involvement in ACT risk thus far and the majority of studies have included large populations of survivors with adequate follow-up time. Supporting the role of SNPs in the *ABC* gene family in increasing the risk of ACT, 40% of a cohort of 15 CCSs with early onset ACT carried the *ABCC2* polymorphism (rs8187710) leading to Cys1515Tyr as described above.[30] Use of a broad range of anthracycline dosing and patient-related factors included in these relatively smaller, cohort-based, studies may hinder independent validation. Future directions to further validate these variants include larger studies with well characterized patient populations, as well as functional studies to provide supporting data.

SLC-encoded Solute Carrier Family

The *SLC* super-family of genes is classified into 65 subfamilies containing over 400 membrane bound transporters involved in the transportation of a wide variety of substances including amino acids, organic and inorganic ions, sugars, essential metals, neurotransmitters, and fatty acids.[31] Pharmaceuticals are able to bind to these transporters and cross cell membranes.[32] Doxorubicin is a known substrate of *SLC22A16* and others in the *SLC* family are thought to be important for renal anthracycline clearance as well as being expressed in the myocardium.[33, 34] Polymorphisms in *SLC* genes have been found to both increase and decrease the risk of ACT. The protein encoded by *SLC22A6* is involved in transport and excretion of organic anions and has been identified as a binding target of doxorubicin.[35] In childhood cancer patients, a T>A intron variant (rs6591722) in *SLC22A6* was associated with ~3% decrease in SF.[26] Several other polymorphisms in this family are protective against ACT in CCSs, these include a G>A synonymous variant (rs7853758) and an a G>A intron variant (rs885004), and an A>C intron variant (rs4877847) in *SLC28A3*, as well as an A>C intron variant(rs2290271) in *SLC28A1*, a C>A variant (rs4982753) in the near 3'-flanking region unknown consequence in *SLC22A17*, an *SLC22A7* A>G intron variant (rs4149178), an *SLC10A2* variant (G>A, rs7319981), and in *SLC10A* a G>A intron variant (rs9514091), all of which significantly decreased the risk of reduced SF.[25, 36] The role of the *SLC* family transporters transporters on ACT, aside from acting as direct transporters, is an emerging field of research. One mechanism is through the competition of anthracyclines with the intended substrates of *SLC* encoded transporters thus disrupting

normal cellular function.[37] To further investigate the effect of *SLC* variants on development of ACT future studies could expand to include cancer types other than childhood cancers and include larger cohorts.

GENES INVOLVED IN REGULATION AND METABOLISM

CBR3-encoded Carbonyl Reductase 3

The *CBR* gene family is involved in metabolism and clearance of anthracyclines. These genes encode proteins that catalyze many active pharmacologic and biologic carbonyl compounds into corresponding alcohols. This is important for the cardiotoxic potential of anthracyclines as the enzymes that they encode catalyze the reduction of anthracyclines to their secondary alcohol metabolites, doxorubicinol and daunorubicinol, which are thought to be major contributors to cardiotoxic effects.[1] Studies have found that *CBR1* and *CBR3* primarily contribute to the formation of these cardiotoxic metabolites, while *CBR1* is also involved in anthracycline clearance.[38] A missense variant in *CBR3* (G>A, rs1056892) leading to Val244Met was associated with reduced LVEF in breast cancer survivors and increased risk of cardiomyopathy in CCSs.[29, 30, 39] Given the function of genes in the *CBR* family, it makes sense that variation in this family could contribute to risk of ACT; however, this has not been well studied. Analysis of larger cohorts across different cancer types is needed, and focus should be placed on evaluating the strength of association for the Val244Met missense variant in *CBR3*.

CYP-encoded Cytochrome p450

The *CYP* genes encode enzymes involved in many cellular processes including metabolism of certain external medications and toxins. Variants in these genes are commonly known to affect the breakdown of pharmacotherapies.[40] Enzymes encoded by *CYP* genes are also involved in the metabolism of arachidonic acid, metabolites of which are thought to be involved in the pathophysiology of ACT.[41] A C>T intron variant (rs4646450) in *CYP3A5* has been associated with ~7-fold increase in odds of SF falling below 38% in the childhood cancer population and an intron variant (rs13249755) in *POR* (also a cytochrome p450 encoding gene) has been associated with ~3-fold increase in odds of significant LVEF reduction in acute myeloid leukemia patients.[26, 42] The protein encoded by *CYP3A5* specifically catalyzes the metabolism of steroid hormones, vitamins, and xenobiotics and variants in this gene have also been linked to hypertension.[43] *POR* encodes an oxidoreductase containing binding sites for cofactors that allow for the donation of electrons to all microsomal P450 enzymes.[43]

RARG-encoded Retinoic Acid Receptor Gamma

RARG encodes a retinoic acid receptor, proteins that act as ligand-dependent regulators of transcription in many different biological processes.[44] Expression of *RARG* is thought to be relatively high in the heart and the encoded retinoic acid receptor has been shown to bind to the *TOP2B* promotor, a gene with increased activity linked to development of ACT.[45–47] Specifically, anthracyclines stabilize the DNA double strand cuts that are mediated by the *TOP2B*-encoded topoisomerase IIB. This stabilization then leads to DNA double strand breaks, which then leads to the activation of p53, ultimately inducing cardiomyocyte cell

death.[48] In one of the few GWAS studies investigating the genetic links to ACT, a missense variant (G>A, rs2229774) in *RARG* leading to Ser427Leu was associated with nearly 5-fold increased odds of symptomatic HF or clinically significant SF depression.[49] This same polymorphism was found in 20% of a cohort of CCSs with known ACT.[30] There is strong evidence for this association as it has been replicated in several independent patient cohorts. This variant is one of the few with direct supporting functional data. Studies of human induced pluripotent stem cell derived cardiomyocyte (iPSC-CMs) cell lines with the variant had significantly increased cell death, ROS generation, and DNA double stranded breaks after treatment with doxorubicin compared with wild type cells.[50]

GENES INVOLVED IN REACTIVE OXYGEN SPECIES GENERATION

Genes encoding NAD(P)H Oxidase

NAD(P)H oxidase is an enzyme complex that plays a role in the regulation of neutrophils, essential cells in the body's inflammatory response.[51] In addition to this primary role, the NAD(P)H oxidase complex also functions as a major source of ROS in the myocardium. Overexpression and increased activity of NAD(P)H in the myocardium can lead to increases in ROS that induce a cycle of remodeling involving hypertrophy and apoptosis, that can eventually lead to congestive heart failure.[52] As generation of ROS is thought to be a key factor in the cardiotoxicity of anthracyclines, this finding may be even more meaningful in patients treated with anthracyclines. Polymorphisms in the genes that encode several of the NAD(P)H subunits have been found to be associated with ACT.

***CYBA*-encoded Cytochrome b-245 Alpha Chain—**The *CYBA* gene encodes the cytochrome b-245 alpha chain subunit of the NAD(P)H oxidase enzyme complex. It partners with a beta chain from the *CYBB* gene and both of these chains are required for NAD(P)H to function.[51] A missense variant in *CYBA* leading to His72Tyr (rs4673) has been associated with a 2-fold increased risk of chronic ACT in NHL survivors, and was found in 1/3 of CCSs with known ACT.[24, 30] While it is difficult to compare studies with different endpoint definitions, this same variant has been found to be protective against ACT in adult leukemia survivors, and in a histological autopsy study of patients treated with anthracyclines, was protective against focal myocardial necrosis.[53, 54] Future studies are needed to clarify the association of this specific SNP with ACT and also to determine whether other SNPs in this gene may also be associated with ACT predisposition.

***NCF4*-encoded Neutrophil Cytosolic Factor 4—**The *NCF4* gene encodes the neutrophil cytosolic factor 4 protein subunit in NAD(P)H.[55] *NCF4*, a G>A intron variant (rs1883112) has been associated with a 2.5-fold increase in chronic ACT in NHL survivors and ~5-fold increased risk in adult leukemia patients.[24, 54] In autopsy findings, this same polymorphism was also associated with increased odds of cardiac fibrosis.[53] These findings consistently point to the association of this G>A intron SNP in *NCF4* with ACT; however, larger studies across more cancer types are needed to confirm this finding.

RAC2*-encoded Rac Family Small GTPase 2—RAC2* encodes a small guanosine triphosphate metabolizing protein that is a regulatory subunit essential for the activation

of NAD(P)H oxidase.[56] *RAC2* has also been identified as a regulator of atherosclerotic calcification.[57] There is less evidence of the influence of polymorphisms in *RAC2* impacting risk of ACT, compared with the previously mentioned genes encoding different NAD(P)H oxidase subunits. An intron variant (T>A, rs13058338) in *RAC2* was found to increase the odds of HF by almost 3-fold in CCSs.[28]

GSTM1–encoded Glutathione S-Transferase mu 1

The protein encoded by *GSTM1* is a detoxification enzyme that catalyzes glutathione conjugation to electrophilic compounds (including anthracyclines), playing a role in protection against ROS.[43] Any variant that reduces expression or functionality of *GSTM1* should thus increase risk of ROS-mediated cardiotoxicity. A study assessing the impact of *GSTM1* null genotype both clinically among CCSs and using iPSC-CMs to quantify gene expression, found that survivors with the null genotype had ~3-fold greater odds of a clinical diagnosis of ACT compared with the *GSTM1* positive phenotype. The iPSC-CMs derived from patients with ACT showed significantly reduced expression of *GSTM1* compared with those derived from controls.[58]

HFE-encoded Homeostatic Iron Regulator

The *HFE* gene is primarily involved in maintaining the body's iron homeostasis by encoding proteins that regulate iron sensing and absorption.[59] Iron load has been found to be a risk factor for ACT, with an increased free iron load shown to potentiate ACT, as free iron can facilitate ROS formation.[60] Variation in *HFE* has been associated with increased risk of ACT in both childhood and breast cancer survivors. Specifically, a C>G missense variant (rs1799945) in *HFE* leading to His63Asp was found to increase the odds of HF by ~2.5-fold in CCSs, and in breast cancer survivors, this polymorphism was associated with ~3.5-fold increased odds of depressed LVEF.[28, 61] This same variant, along with a G>A missense variant (rs1899562) leading to Cys282Tyr, are both associated with increased cardiac iron deposition, and in survivors of childhood leukemia, were associated with depressed SF.[62, 63] While not robust, early evidence does point to the likelihood of SNPs in the *HFE* gene impacting ACT, potentially through the modulation of myocardial iron deposition.

NOS3-encoded Nitric Oxide Synthase 3

NOS3 encodes an enzyme responsible for producing nitric oxide (NO). The gene is primarily expressed in the heart endothelial tissue and plays a key role in regulation of NO, a vasodilator that has a cardioprotective role.[64] There is evidence that anthracyclines induce *NOS* expression in the heart and increase the ability of nitric oxide synthase proteins to promote anthracycline production of ROS.[65] An *NOS3* missense variant leading to a Glu298Asp replacement (rs1799983) has been found to be cardioprotective in high risk ALL patients, conferring an average of 8% increase in LVEF. In childhood cancer patients with confirmed ACT, 80% carried a variant in *NOS3* rs1799983.[27, 30] In iPSC-CMs, differential expression of *NOS3* was noted between those derived from breast cancer survivors with ACT and those without, however specific variants were not assessed in that study.[66] Given the role of NO in the heart and the association of *NOS3* with anthracycline ROS production variation in the *NOS3* gene should be a focus of future studies.

GENES INVOLVED IN THE SARCOMERIC SKELETON

TTN-encoded Titin

The *TTN* gene encodes titin which has important regulatory and structural roles in cardiac muscle. It is involved in sarcomere formation, myofilament contraction, and in structural regulation and signaling of the cardiac sarcomeres. There is strong evidence that truncating variants in *TTN* (TTNtv) are associated with familial cardiomyopathies and *TTN* has been identified as one of the most common genetic causes of dilated cardiomyopathy.[67] Emerging evidence has shown that TTNtvs may be associated with susceptibility to ACT as well based on evidence from targeted sequencing studies. In a case study of two breast cancer patients who developed severe early ACT, genetic screening found a TTNtv in both patients.[68] A larger study including both childhood and adult cancer survivors found that 7.5% of survivors with ACT hosted a TTNtv, compared with ~1% of control populations, and those adult survivors who did have a TTNtv had a significantly higher burden of HF, atrial fibrillation, and impaired myocardial recovery.[69] Despite the known association of TTNtvs with familial cardiomyopathies, this was one of the first large studies to assess whether TTNtvs may also increase the risk of ACT and the evidence of an association is compelling, though further study is needed.

OTHERS

Several other genetic variants have been associated with risk of ACT, though have not yet been found across multiple studies.[26, 36, 70–76] Similarly to genes that have been studied more frequently, other genes that have been looked at are primarily those involved in drug metabolism and excretion (*UGT1A6, SULT2B1, FMO3 and FMO3, SPG7*), propagation of ROS (*CAT, NQO1, ADH7, ETFB*), known association with cardiac conditions/hypertension (*PLCE1, ATP2B*), and genes involved in DNA regulation in the heart and in cardiac remodeling after injury (*CELF4, HAS3, PRDM2)*. The specific relationship of other genes that have been found to be associated with increased risk of ACT is still somewhat unknown and deserves further exploration in future studies. This includes *HNMT.*

CLINCICAL ACTIONABILITY AND THE PROMISE OF GENOMIC MEDICINE

In current clinical practice there are several strategies in place aimed at ACT secondary prevention and early detection, including pharmacologic intervention and screening to detect subclinical ACT. Primary prevention relies on modification of anthracycline administration and co-administration of cardioprotective agents. In adults, liposomal-encapsulated doxorubicin has promised to be less cardiotoxic than traditional doxorubicin, though this has not been studied well in the pediatric population.[77] Longer infusion times have proved effective in decreasing ACT in adults and in children, the cardioprotectant dexrazoxane is used in high-risk individuals and treatment regimens.[78] In the childhood cancer survivor population, there are risk prediction models to assess risk of treatment related cardiotoxicity.[12, 79] However, these only take into account cardiotoxic exposures and are not routinely performed prior to treatment. Thus, there is no well-established approach to determining risk before anthracycline exposure based on patient genotype and no consensus guidance on whether monitoring for cardiotoxic sequelae needs to be modified based on

genetic risk. Further, there are no consensus guidelines for implementing the outcomes of such risk-assessment testing through alterations in dosing, frequency, or introduction of cardioprotective measures. In the adult cancer survivor population, pre-treatment ACT risk assessment currently focuses on age, sex, medical history, cardiac history, cardiac biomarkers, and health behaviors.[80] Emerging data in the pediatric cancer population have shown that incorporation of genetic data into an ACT risk prediction model had higher prediction accuracy than a model including clinical factors alone.[81] Additionally, a clinical trial has recently been completed with the aim of combining genetic screening, novel biomarkers, and imaging strategies to develop a risk-prediction model to identify pediatric patients who are most susceptible to ACT prior to beginning treatment.[82] Taken together with clinical practice recommendations groups beginning to recommend genetic screening in children for certain variants prior to doxorubicin or daunorubicin treatment,[9] increased use of predictive genomic medicine in this arena is promising.

CONCLUSIONS

A growing body of data shows a link between innate genetic variation and risk of ACT. The majority of studies have focused on targeted genotyping of genes encoding products known to be involved in anthracycline metabolism or thought to be involved in the cardiotoxicity pathway. While this approach has yielded initial important data, additional functional studies are needed to confirm findings and further characterize the clinical impact of variants. Additionally, as evidence behind the genetic link to ACT continues to increase and as the cost of whole genome sequencing continues to decrease while efficiency increases,[83] this powerful tool should be harnessed to assess risk of ACT prior to treatment initiation.

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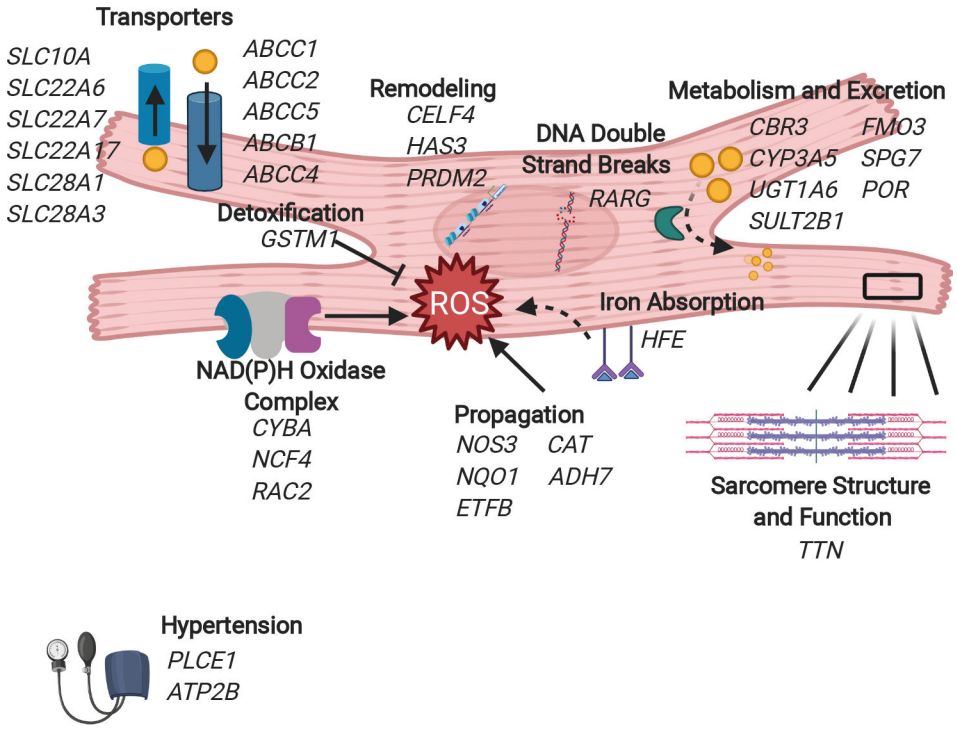

Figure 1:

Cardiomyocyte with genes associated with anthracycline induced cardiotoxicity. Created with BioRender.com

Table 1:

Gene variants associated with risk of anthracycline induced cardiotoxicity

Citation	Gene	Variant	Effect (Outcome)	Cancer Type, Age at Diagnosis, mean (SD), years	N	Follow-up Time, median(range), years	Anthracycline Type (s)
Semsei et al. *Cell Biol Int.* 2012.	*ABCC1*	rs246221	2.5%, p=0.027 (SF decline)	Childhood ALL, 5.7 (3.8)	235	6.3 (2.4–13.7)	Daunorubicin, Doxorubicin,
Vulsteke et al. *Breast Cancer Res Treat.* 2015.			OR: 1.3, 95% CI: 1.1–1.4 (LVEF decline)	Breast, 50.3 (9.5)	877	3.62 (0.4–9.6)	Epirubicin
Semsei et al. *Cell Biol Int.* 2012.		rs3743527	5.5%, p=0.001 (SF decline)	Childhood ALL, 5.7 (3.8)	235	6.3 (2.4–13.7)	Daunorubicin, Doxorubicin
Wojnowski et al. *Circulation.* 2005.		rs45511401	OR: 6.60, 95% CI: 1.60–8.40 (acute ACT)	NHL, Range: 18–75	537	Up to 5 years	Doxorubicin
Visscher et al. *Pediatr Blood Cancer.* 2013.		rs4148350	OR: 2.40, 95% CI: 1.33–4.33 (SF≤26%)	Childhood, Range 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Sagi et al. *BMC Cancer.*2018.	*ABCC2*	rs3740066	3.5%, p=0.007(SF decline)	Childhood ALL, 6.4 (4.3)	622	Range: 5–10	Not specified
Armenian et al. *Br J Haematol.* 2013.		rs8187710	OR: 5.22, 95% CI: 1.92–13.84 (heart failure)	Leukemia, Lymphoma, Range: 3–72	255	Range: 0.2–15.9	Not specified
Wojnowski et al. *Circulation.* 2005.		rs8187694-rs8187710	OR: 2.30, 95% CI: 1.0–5.4 (acute ACT)	NHL, Range: 18–75	537	Up to 5 years	Doxorubicin
Krajinovi kwt al. *Pharmacogenomics J.* 2015.	*ABCC5*	rs7627754	12%, p<0.0001 (LVEF decline), 8%, p=0.001 (SF decline)	Childhood ALL, Range: 0–18	251	Range: 0 - >5	Doxorubicin
Hertz et al. *Pharmacogenomics.* 2016.	*ABCB1*	rs1045642	OR: 0.58, 95% CI: 0.23–1.00 (LVEF <55%)	Breast, 50 (Range:24–80)	166	6.0 (1.0–20.0)	Doxorubicin
Visscher et al. *Pediatr Blood Cancer.* 2013.		rs2235047	OR: 1.79, 95% CI: 1.05–3.04 (SF≤26%)	Childhood, Range 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Visscher et al. *Pediatr Blood Cancer.* 2013.	*ABCB4*	rs4148808	OR: 1.67, 95% CI: 1.15–2.43 (SF≤26%)	Childhood, Range 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Visscher et al. *Pediatr Blood Cancer.* 2013.	*ADH7*	rs729147	OR: 1.43, 95% CI: 1.02–2.01 (SF≤26%)	Childhood, Range 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Hildebrandt et al. *Sci Rep.* 2017.	*ATP2B1*	rs17249754	OR: 0.26, 95% CI: 0.07–0.96 (clinical diagnosis ACT)	Childhood, Cases: 9.2 (4.7), Controls: 9.3 (5.7)	108	15.8	Not specified
Rajic et al. *Leuk Lymphoma.* 2009.	*CAT*	rs10836235	OR: 0.28, 95% CI: 0.09–0.87 (abnormal ECG or echocardiogram)	Childhood ALL, 6.3 (4.4)	76	19.3 (6–30)	Not specified
Blanco et al. *J Clin Oncol.* 2012.	*CBR3*	rs1056892	OR: 1.79, 95% CI: 1.08–2.96 (cardiomyopathy)	Childhood, 8.3 (6.0)	487	Range: 0.1–40.3	Doxorubicin, Daunorubicin,

Citation	Gene	Variant	Effect (Outcome)	Cancer Type, Age at Diagnosis, mean (SD), years	N	Follow-up Time, median(range), years	Anthracycline Type (s)
							Epirubicin, Idarubicin
Hertz et al. *Pharmacogenomics.* 2016.			OR: 2.5, 95% CI: 1.22–5.11, (LVEF <55%)	Breast, 50 (Range: 24–80)	166	6.0 (1.0–20.0)	Doxorubicin
Wang et al. *J Clin Oncol.* 2016.	*CELF4*	rs1786814	OR: 10.2, 95% CI: 3.8–27.2 (cardiomyopathy)	Childhood, Range: 0–21	484	Range: 0.1–41	Not specified
Wojnowski et al. *Circulation.* 2005.	*CYBA*	rs4673	OR: 2.0, 95% CI: 1.0–3.90 (chronic ACT)	NHL, Range: 18–75	537	Up to 5 years	Doxorubicin
Megias-Vericat et al. *Pharmacogenomics J.* 2017.			OR: 0.3. 95% CI: 0.1–0.9 (acute cardiac dysfunction)	AML, Median 52.5 (16–78)	225	Mean: 37 days (95% CI: 35–39 days)	Idarubicin
Sagi et al. *BMC Cancer.* 2018.	*CYP3A5*	rs4646450	OR: 6.94, 95% CI: 1.76–27.39 (SF<38%)	Childhood ALL, 6.4 (4.3)	622	Range: 0–15	Not specified
Ruiz-Pinto et al. *Breast Cancer Res Treat.* 2017.	*ETFB*	rs79338777	OR: 9.00, 95% CI: 2.83–28.60 (heart failure, or SF≤27%)	Leukemia, Sarcoma, Breast, Range: 1.2–73	144	Range: 1.0–27.5	Doxorubicin, Daunorubicin, Epirubicin
Lubieniecka et al. *Front Genet.* 2013.	*POR*	rs13240755	OR: 3.18, 95% CI: 1.22–8.27 (LVEF reduction)	AML, Mean 48.4 (19–74)	91	Not specified	Daunorubicin, Mitoxantrone
Visscher et al. *Pediatr Blood Cancer.* 2013.	*FMO2*	rs2020870	OR: 0.14, 95% CI: 0.03–0.59 (SF≤26%)	Childhood, Range: 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Visscher et al. *Pediatr Blood Cancer.* 2013.	*FMO3*	rs1736557	OR: 0.47, 95% CI: 0.25–0.87 (SF≤26%)	Childhood, Range: 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Singh et al. *Cancer.* 2020.	*GSTM1*	Null genotype	OR: 2.7, 95% CI: 1.3–5.9 (AHA criteria for cardiac compromise)	Childhood, Range: 3.3 – 14.8	167	Range: 1.3–17.2	Not specified
Wang et al. *J Clin Oncol* 2014.	*HAS3*	rs2232228	OR: 3.7, 95% CI: 1.3–10.2 (AHA criteria for cardiac compromise)	Childhood and adult, Range: 0–71	287	Range: 0.1–41.0	Not specified
Armenian et al. *Br J Haematol.* 2013.	*HFE*	rs1799945	OR: 2.58, 95% CI:1.27–5.20 (heart failure)	Leukemia, Lymphoma, Range: 3–72	255	Range: 0.2–15.9	Not specified
Vaitiekus et al. *Cardiovasc Tolxicol.* 2020.			OR: 3.44, 95% CI: 1.40–8.47 (LVEF≤55%)	Breast, Controls: 54.8 (9.0), Cases: 52.9 (10.3)	81	Not specified	Doxorubicin
Lipshultz et al. *Cancer.* 2013.		rs179945/ rs1800562	SF z-score: −0.93 (p=0.003)	Childhood ALL, Median: 6.3 (<1–17.9)	184	6.1 (1.0–16.1)	Doxorubicin
Visscher et al. *Pediatr Blood Cancer.* 2013.	*HNMT*	rs17645700	OR: 0.56, 95% CI: 0.37–0.86 (SF≤26%)	Childhood, Range: 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Visscher et al. *Pediatr Blood Cancer.* 2013.		rs17583889	OR: 1.67, 95% CI: 1.15–2.41 (SF≤26%)	Childhood, Range: 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin

Citation	Gene	Variant	Effect (Outcome)	Cancer Type, Age at Diagnosis, mean (SD), years	N	Follow-up Time, median(range), years	Anthracycline Type (s)
Wojnowski et al. *Circulation.* 2005.	*NCF4*	rs1883112	OR; 2.5, 95% CI: 1.3–5.1 (chronic ACT)	NHL, Range: 18–75	537	Up to 5 years	Doxorubicin
Megias-Vericat et al. *Pharmacogenomics J.* 2017.			OR: 5.2, 95% CI: 1.4–18.9 (acute cardiac dysfunction)	AML, Median 52.5 (16–78)	225	Mean: 37 days (95% CI: 35–39 days)	Idarubicin
Krajinovik wt al. *Pharmacogenomics J.* 2015.	*NOS3*	rs1799983	8%, p=0.02 (LVEF increase)	Childhood ALL, Range: 0–18	251	Range: 0 – >5	Doxorubicin
Sagi et al. *BMC Cancer.*2018.	*NQO1*	rs1043470	2.1%, p-0.006 (SF decline)	Childhood ALL, 6.4 (4.3)	622	Range: 5–10	Not specified
Hildebrandt et al. *Sci Rep.* 2017.	*PLCE1*	rs9327264	OR: 0.36, 95% CI: 0.18–0.76 (clinical diagnosis ACT)	Childhood, Cases: 9.2 (4.7), Controls: 9.3 (5.7)	108	15.8	Not specified
Wells et al. *Pharmacogenet Genomics.* 2017.	*PRDM2*	rs7542939	Decline in LVEF	Mixed, Range: 40–61	556	IQR: 122–755 days	Doxorubicin, Doxorubicin liposoma, Daunorubicin, Epirubicin, Idarubicin
Armenian et al. *Br J Haematol.* 2013.	*RAC2*	rs13058338	OR: 2.61, 95% CI: 1.46–4.69 (heart failure)	Leukemia, Lymphoma, Range: 3–17	255	Range: 0.2–15.9	Not specified
Wojnowski et al. *Circulation.* 2005.		rs1883112	OR: 2.5, 95% CI: 1.3–5.0 (chronic ACT)	NHL, Range 18–75	537	Up to 5 years	Doxorubicin
Megias-Vericat et al. *Pharmacogenomics J.* 2017.			OR: 5.2, 95% CI: 1.4–18.9 (cardiac dysfunction)	AML, Median 52.5 (16–78)	225	Mean: 37 days (95% CI: 35–39 days)	Idarubicin
Aminkeng et al. *Nat Genet.* 2015.	*RARG*	rs2229774	OR: 4.7, 95% CI: 2.7–8.3 (heart failure/SF≤24%)	Childhood, ≤ 18	376	Not specified	Not specified
Visscher et al. *Pediatr Blood Cancer.* 2013.	*SLC10A2*	rs7319981	OR: 0.66, 95% CI: 0.47–0.93 (SF≤26%)	Childhood, Range: 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Visscher et al. *Pediatr Blood Cancer.* 2013.		rs9514091	OR: 0.57, 95% CI: 0.38–0.87 (SF≤26%)	Childhood, Range: 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Sagi et al. *BMC Cancer.*2018.	*SLC22A6*	rs6591722	2.9%, p=0.006 (SF decline)	Childhood ALL, 6.4 (4.3)	622	Range: 5–10	Not specified
Visscher et al. *Pharmacogenomics.* 2015.	*SLC22A7*	rs4149178	OR: 0.45, 95% CI: 0.26–0.75 (SF≤26%)	Childhood, Range: 0.04–17.7	562	Range: 0.1–29.8	Doxorubicin, Daunorubicin
Visscher et al. *Pharmacogenomics.* 2015.	*SLC22A17*	rs4982753	OR: 0.50, 95% CI: 0.33–0.75 (SF≤26%)	Childhood, Range: 0.04–17.7	562	Range: 0.1–29.8	Doxorubicin, Daunorubicin
Visscher et al. *Pediatr Blood Cancer.* 2013.	*SLC28A1*	rs2290271	OR: 0.66, 95% CI: 0.48–0.91 (SF≤26%)	Childhood, Range: 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin

Citation	Gene	Variant	Effect (Outcome)	Cancer Type, Age at Diagnosis, mean (SD), years	N	Follow-up Time, median(range), years	Anthracycline Type (s)
Visscher et al. *Pediatr Blood Cancer*. 2013.	*SLC28A3*	rs7853758	OR: 0.36, 95% CI: 0.22–0.60 (SF≤26%)	Childhood, Range: 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Visscher et al. *Pediatr Blood Cancer*. 2013.		rs885004	OR: 0.34, 95% CI: 0.20–0.60 (SF≤26%)	Childhood, Range: 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Visscher et al. *Pediatr Blood Cancer*. 2013.		rs4877847	OR: 0.73, 95% CI: 0.54–0.98 (SF≤26%)	Childhood, Range: 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Visscher et al. *Pediatr Blood Cancer*. 2013.	*SPG7*	rs2019604	OR: 0.56, 95% CI: 0.35 – 0.9) (SF≤26%)	Childhood, Range: 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Visscher et al. *Pediatr Blood Cancer*. 2013.	*SULT2B1*	rs10426377	OR: 0.56, 95% CI: 0.38–0.81 (SF≤26%)	Childhood, Range: 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Garcia-Pavia et al. *Circulation*. 2019.	*TTN*	TTNtvs	Increased incidence of cardiomyopathy (LVEF<53% and ≥10% reduction from baseline);	Adult and Childhood, Three cohorts: 48.7(17.1), 49.6(10.8), 10.8(5.6)	213	Range: 0.7–7.0	Doxorubicin, Daunorubicin, Epirubicin, Mitoxantrone
Visscher et al. *Pediatr Blood Cancer*. 2013.	*UGT1A6*	rs17863783	OR: 4.30, 95% CI: 1.97–9.36 (SF≤26%)	Childhood, Range: 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Visscher et al. *Pediatr Blood Cancer*. 2013.		rs4261716	OR: 1.44, 95% CI: 1.06–1.95 (SF≤26%)	Childhood, Range: 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin
Visscher et al. *Pediatr Blood Cancer*. 2013.		rs6759892	OR: 1.43, 95% CI: 1.05–3.04 (SF≤26%)	Childhood, Range: 0–18	218	Range: 0.4–31.6	Doxorubicin, Daunorubicin, Epirubicin