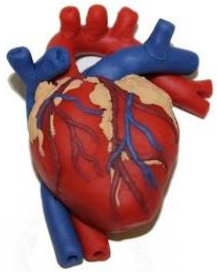
Genómica y medicina de precisión en pacientes con cardiotoxicidad secundaria al tratamiento del cáncer



María Brion

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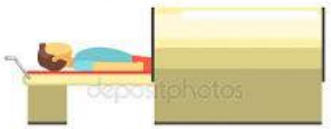
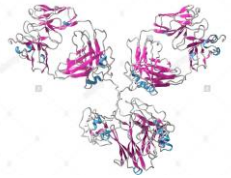
La terapia actual contra el cáncer se basa en varias modalidades:



Radioterapia

Quimioterapia

Anticuerpos monoclonales

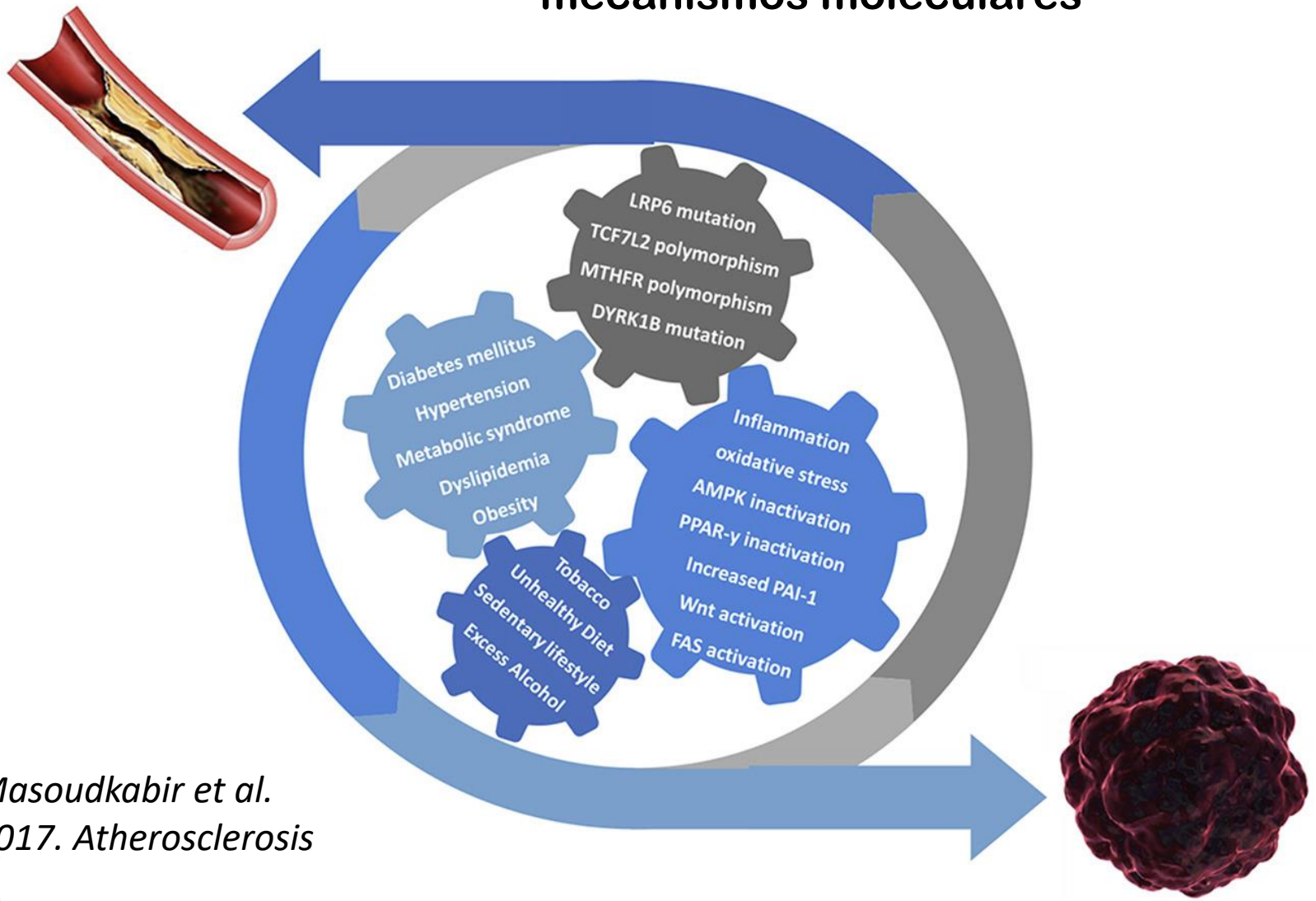


inhibidores molecularmente dirigidos

Todas estas modalidades pueden tener un impacto negativo en el sistema cardiovascular, y existe una experiencia considerable en relación con la **radioterapia y la quimioterapia.**

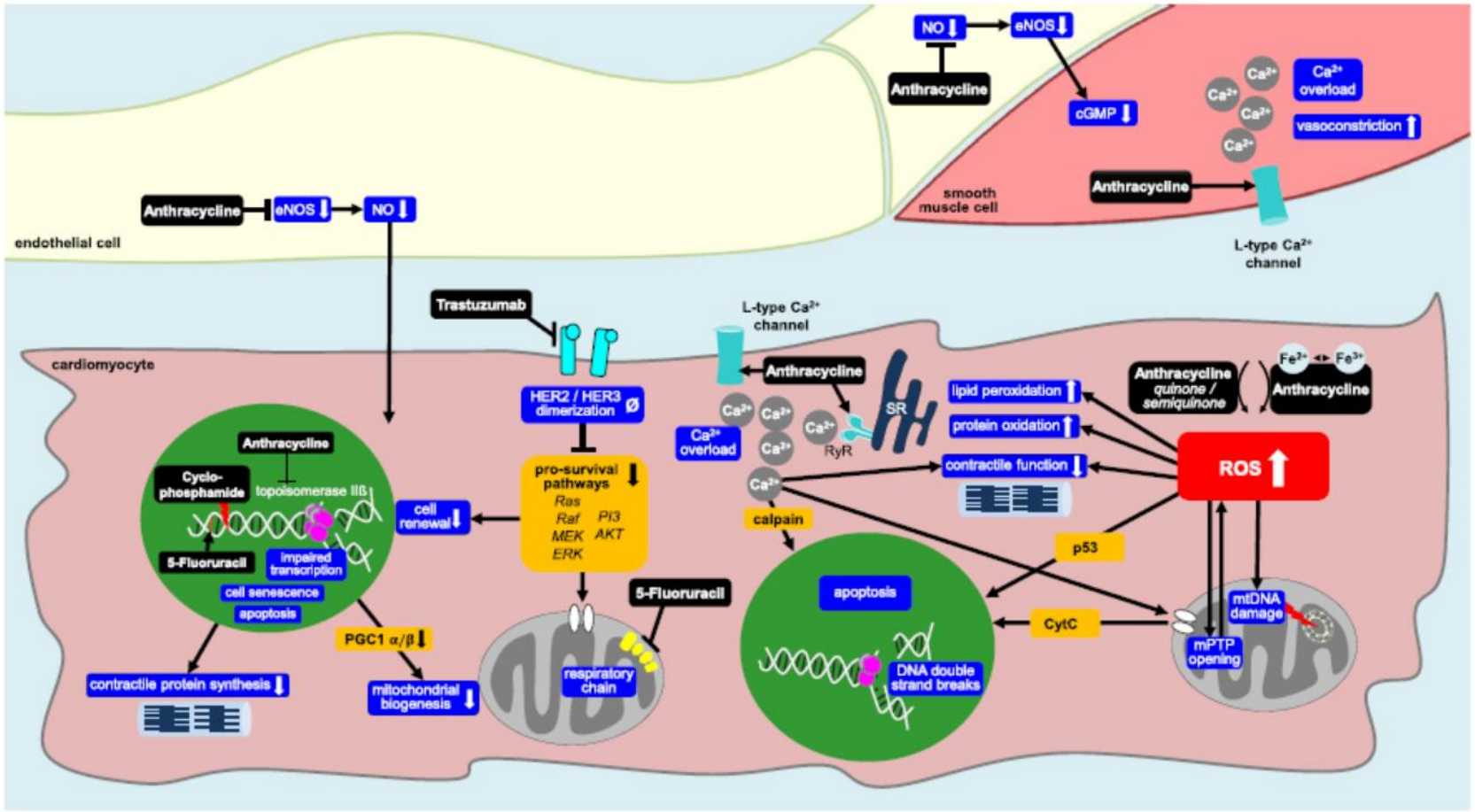
Cardiotoxicidad

El cácer y la enfermedad cardiovascular comparten factores de riesgo, genética y mecanismos moleculares



Masoudkabir et al. 2017. Atherosclerosis

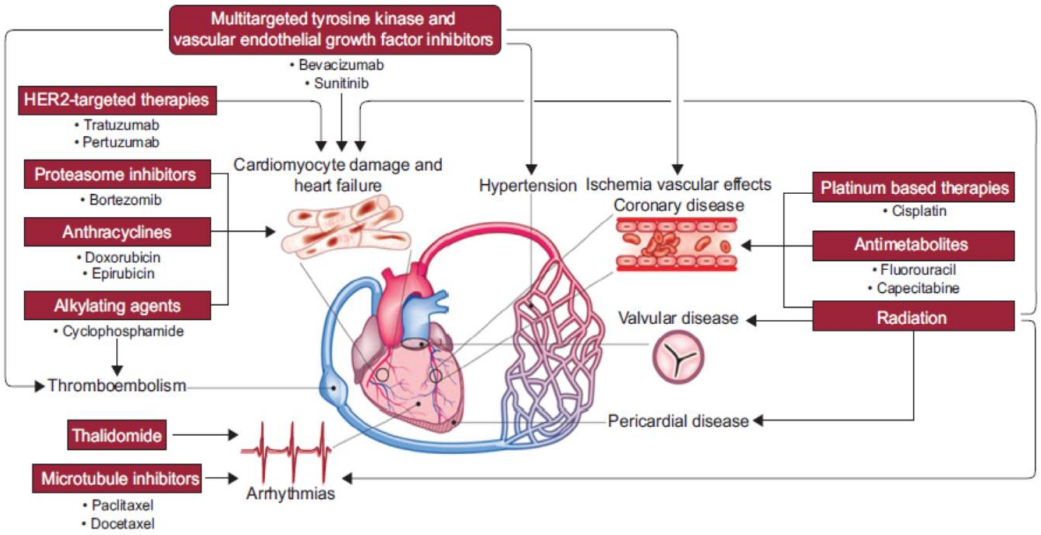
Dianas moleculares/celulares de la terapia del cáncer en los cardiomiocitos



Cardiotoxicidad y Quiomioterapia

Los efectos adversos reconocidos son diversos e incluyen disfunción ventricular, hipertensión, efectos vasculares adversos, enfermedad cerebrovascular….

Una de las complicaciones más frecuentes pero controvertidas es la disfunción ventricular (DV), definida como una reducción de la fracción de eyección del ventrículo izquierdo (FEVI) > 10% en comparación con el valor inicial, con una FEVI inferior al límite normal.



Tipos de Cardiotoxicidad

Tipo I
caracterizada por un daño directo irreversible y está relacionada con la dosis.
Ej: Antraciclinas

Tipo II
generalmente más favorable, e a menudo reversible e independiente de la dosis.
Ej: Trastuzumab

De acuerdo a la relación temporal con el tratamiento:

Aguda/Subaguda
Desarrollo en una semana, es rara y generalmente cesa tras la interrupción del tratamiento

Progresiva crónica temprana
Desarrollo en un año tras la finalización de la terapia.

Progresiva crónica tardía
Desarrollo después de un año tras la finalización de la terapia.

Farmacogenómica

→ Farmacogenética

Factores genéticos

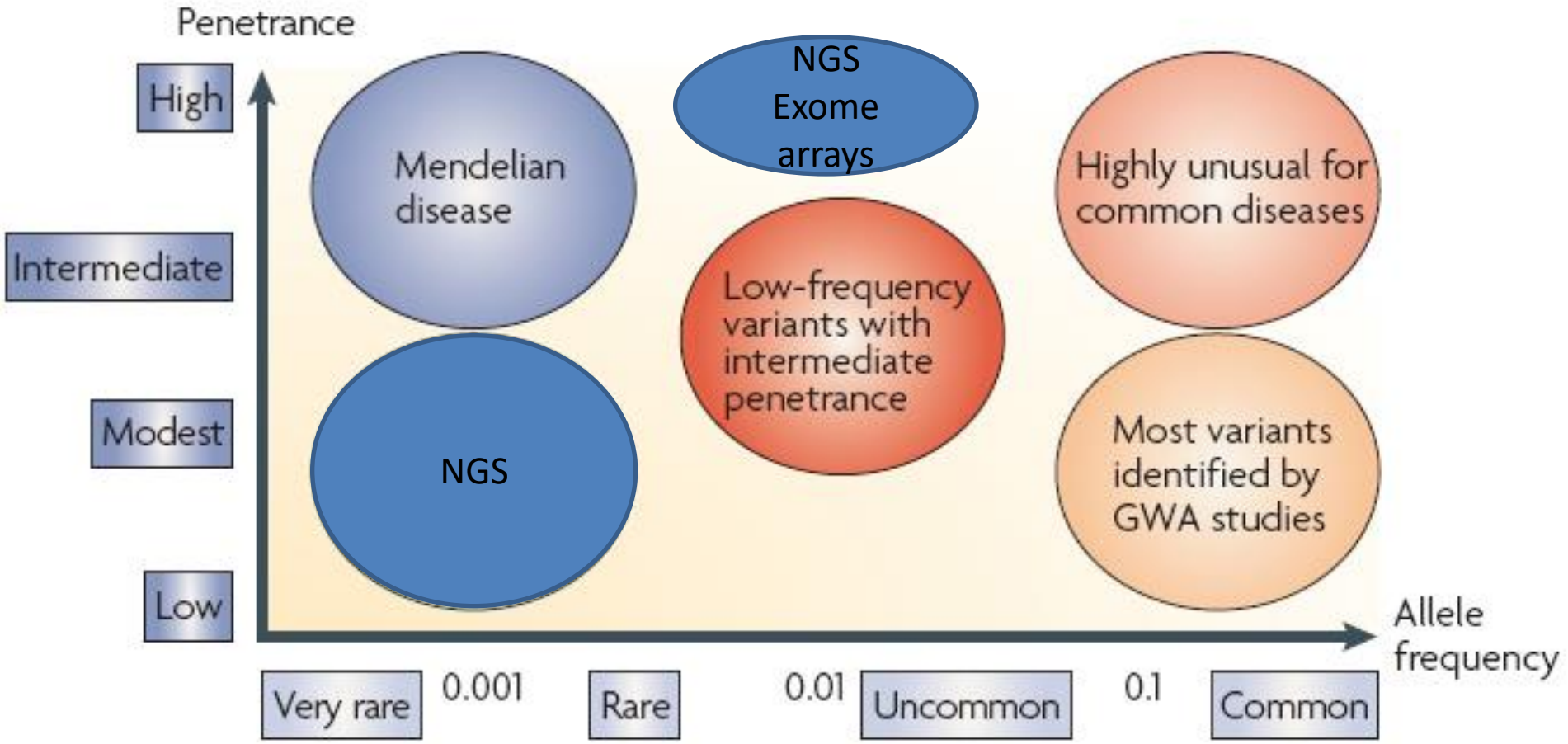
Definicion: es el estudio de factores genéticos implicados en la respuesta a fármacos.
Objetivo: Individualizar y mejorar el pronóstico del paciente mediante el uso de información genómica.

Marcadores genéticos capaces de predecir el desarrollo de **cardiotoxicidad** puede permitir:

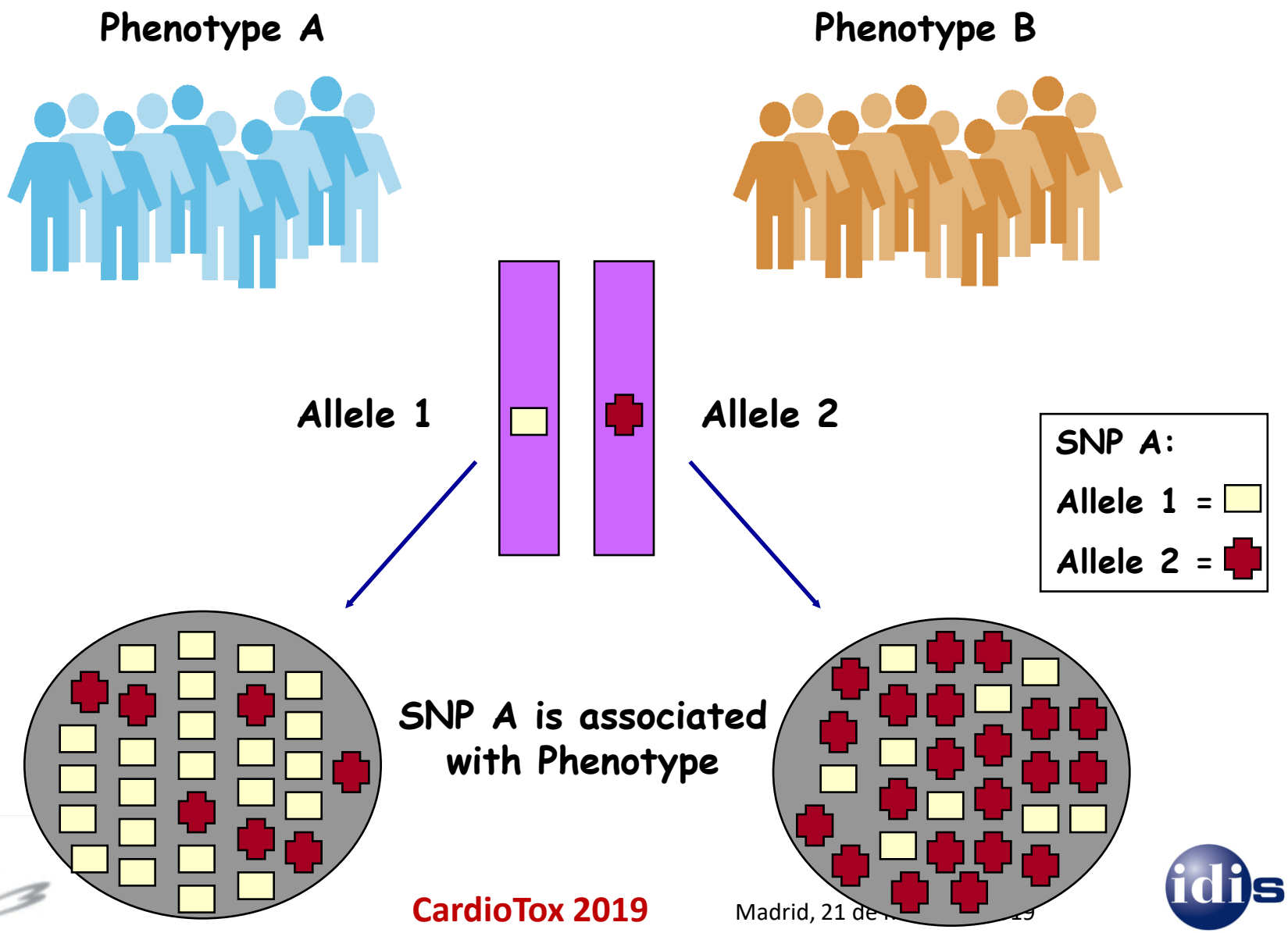
- Identificar pacientes que precisan de seguimiento especifico
- Identificar pacientes que precisar cardioprotectores
- Iniciar tratamiento de forma precoz cuando se inicie la cardiotoxicidad

Las reacciones adversas a fármacos son rasgos complejos

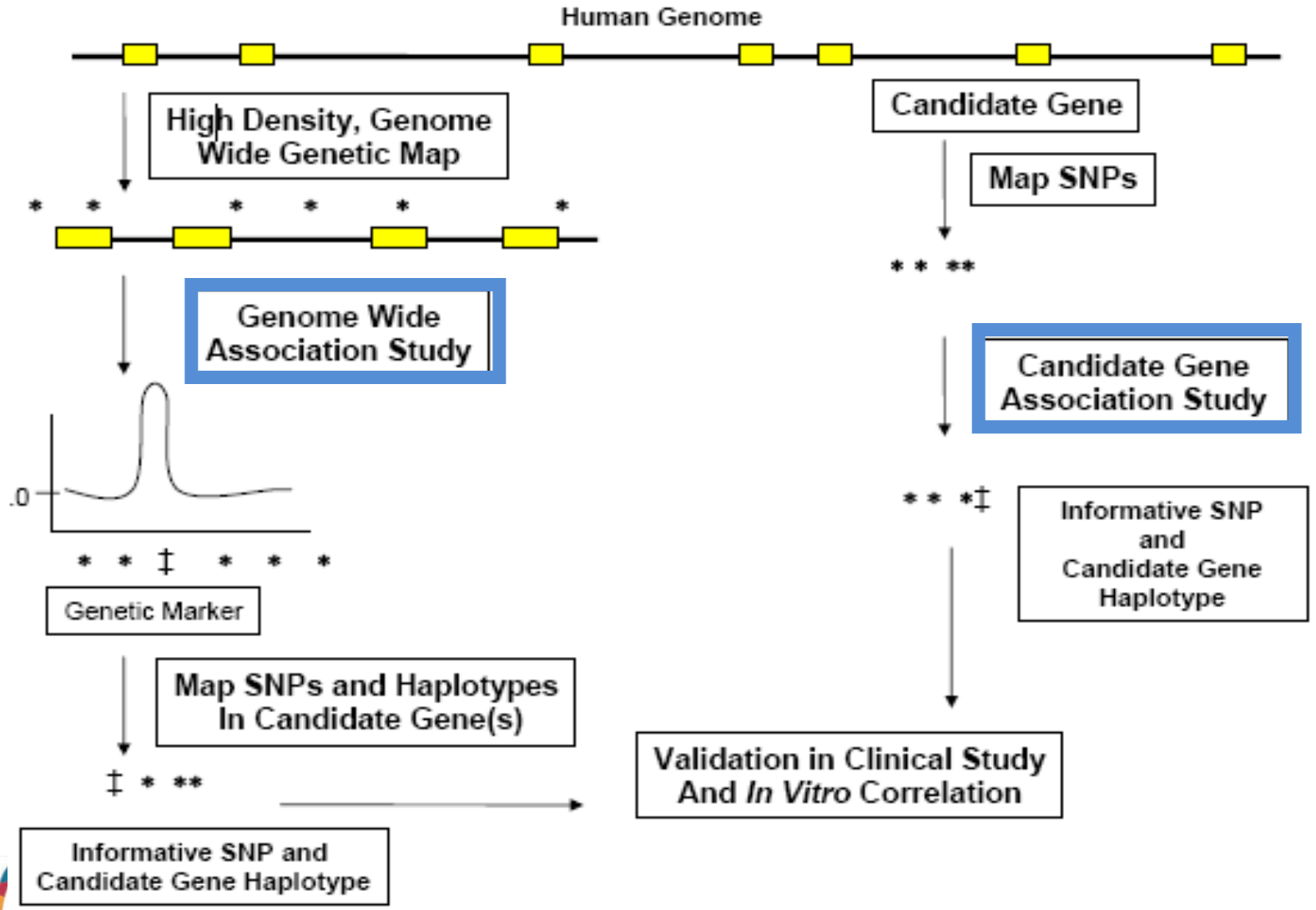
Cómo buscar marcadores geneticos asociados con un rasgo complejo

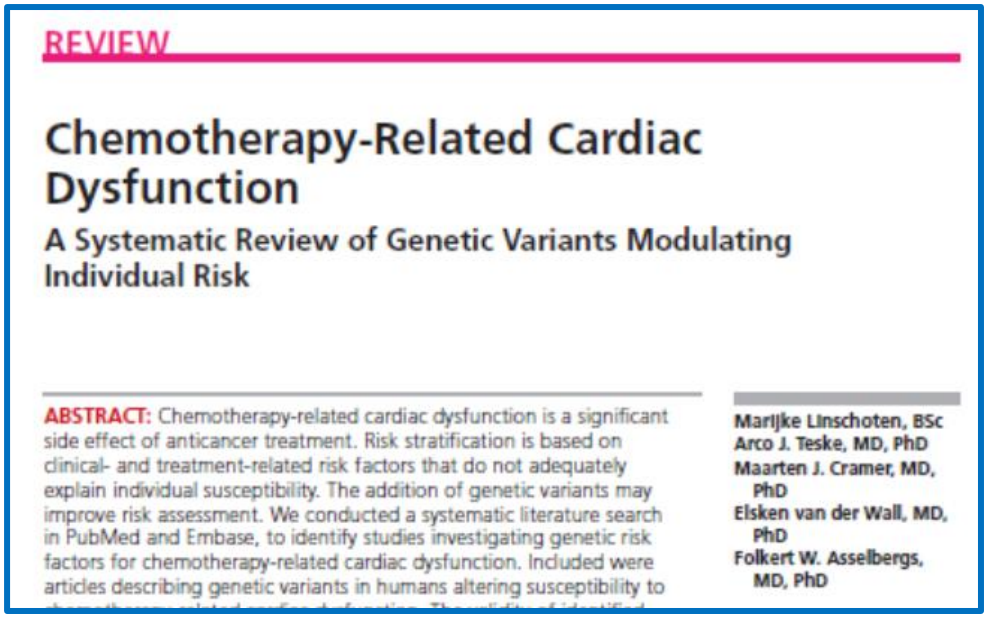


Human Genetic Association Study Design



Possible genetic approaches:





REVIEW

Chemotherapy-Related Cardiac Dysfunction

A Systematic Review of Genetic Variants Modulating Individual Risk

ABSTRACT: Chemotherapy-related cardiac dysfunction is a significant side effect of anticancer treatment. Risk stratification is based on clinical- and treatment-related risk factors that do not adequately explain individual susceptibility. The addition of genetic variants may improve risk assessment. We conducted a systematic literature search in PubMed and Embase, to identify studies investigating genetic risk factors for chemotherapy-related cardiac dysfunction. Included were articles describing genetic variants in humans altering susceptibility to

Marijke Linschoten, BSc
Arco J. Teske, MD, PhD
Maarten J. Cramer, MD, PhD
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Folkert W. Asselbergs, MD, PhD

Linschoten et al. Circ Genom Precis Med. 2018;11:e001753.

- ✓ Revisión sistemática de la literatura
- ✓ Identificar estudios que investigaran los factores de riesgo genéticos para la disfunción ventricular secundaria a cardiotóxicos
  - 40 publicaciones
- ✓ 35/40 estudios genes candidatos
- ✓ 5/40 estudios GWAS

Table. Identified Genetic Variants Associated With CTRCD

Gene	SNP ID/Location Pathogenic Mutation	Allele	Effect Of Allele on CTRCD Risk	Reference Significant	*P* Value	OR or β	Reference Nonsignificant
Anthracyclines							
Drug transport							
ABCC1	rs246221	T	Increased	12	0.027	NA	13–15
				16	0.021	1.3 (1.07–2.35)	
	rs2163627	T	Increased	12	0.001	NA	13–16
	rs45511401	T	Increased	17	0.016	2.5 (NA)	12,16,18
ABCC2	rs8187710	A	Increased	19	<0.01	4.3 (1.5–12.5)	15–18,20–23
				12	0.021*	4.3 (1.8–13.8)	
ABCC5	rs7627754	T	Increased	26†	<0.001	NA	
				26‡	<0.04	NA	
SLC28A2	rs7853758	A	Decreased	14†	0.0071	0.29 (0.11–0.81)	15,16,18,22,25,26
				14‡	0.0072	0.33 (0.13–0.80)	
				14§	1.4×10^{-4}	0.31 (0.16–0.60)	
				14,25	1.6×10^{-4}	0.36 (0.22–0.60)	
Antioxidants							
CAT	rs10836235	C	Increased	27	0.02	0.284 (0.093–0.87)	12,15,22
GSTP1	rs1695	G	Increased	28	0.008	9.6 (1.8–69)	13,14,21,29,30
HAS3	rs2232228	A	Increased	23†	0.0038	8.9 (2.1–37.5)	12,15
				23‡	0.048	4.5 (1.1–18.7)	
				23§	5.3×10^{-6}	NA	
				31	<0.0018	NA	
				22	0.028	21.8 (1.2–386.4)	
Drug metabolism							
CBR3	rs1056892	G	Increased	32	0.02	1.79 (1.08–2.96)	13–15,19,22,26, 28,29,33–35
				31	0.03*	8.8 (NA)	
NOS3	rs1799983	T	Decreased	26	<0.02	NA	13
POR	rs13240755	G	Increased	36	0.01376	3.18 (1.22–8.27)	14,15
				13	0.032*	2.0 (1.0–3.7)	
UGT1A6	rs17863783	T	Increased	14†	0.038	4.1 (1.03–16.17)	15,26
				14‡	NS	NS	
				25	0.0062	7.98 (1.85–34.4)	
				14,25	2.4×10^{-4}	4.30 (1.97–9.36)	
				22	<0.001	19.5 (3.5–110.5)	
NADPH oxidase multienzyme complex							
NCF4	rs1883112	A	Increased	17	0.016	2.0 (NA)	14–16,18–20,22,28
		G	Decreased	21	0.023	0.37 (0.16–0.87)	
RAC2	rs13058338	A	Increased	17	0.025	1.7 (NA)	13–16,18,20–22
				19	<0.01	2.83 (1.42–5.64)	
CYBA	rs4673	T	Increased	17	0.010	1.9 (NA)	13–16,18–21,28
DNA repair							
ERCC2	rs13181	C	Increased	27	<0.001	NA	14,17,28
Iron metabolism							
HFE	rs1799945	G	Increased	19	0.05¶	2.53 (1.02–6.31)	13,38,39
	rs1800562	A	Increased	39	0.015	6.79 (1.67–27.67)	19,22,38

(Continued)

Table. Continued

Gene	SNP ID/Location Pathogenic Mutation	Allele	Effect Of Allele on CTRCD Risk	Reference Significant	*P* Value	OR or β	Reference Nonsignificant
Sarcomere structure and function							
CELA1	rs17862814	G	Increased	37†	<0.001*	10.16 (2.8–27.2)	
				37‡	0.046	5.09 (1.03–25.23)	
				22	0.02	22.2 (1.5–339.2)	
MYH7	c.1633G>A (p.Asp545Asn)		Increased	10			
	c.2863G>A (p.Asp955Asn)		Increased	10			
Topoisomerase-2β expression							
RARG	rs2229774	A	Increased	13†,‖	5.0×10^{-6}	7 (2.9–17)	
				13‡,‖	0.0043	4.1 (1.5–11.5)	
				13‡,**	1.2×10^{-1}	NA	
				13§	5.9×10^{-6}	4.7 (2.7–8.2)	
		A	Decreased	15	4.1×10^{-6}	0.11 (NA)	
Intergenic region							
Unknown	rs10443221	T	Decreased	40†	2.7×10^{-6}	4.11 (SE 0.74)	
				40‡	NS	NS	
Unknown	rs28714259	A	Increased	15	9.25×10^{-6}	2.1 (NA)	
				15	0.04	1.9 (NA)	
				15	0.02	4.2 (NA)	
Trastuzumab							
ERBB2	rs1136201	G	Increased	41	0.004	NA	42,43
				44	0.021	3.80 (1.13–13.63)	
				45	0.014	5.80 (1.21–25.33)	
				46	0.026	4.27 (1.22–15.85)	
	rs1058808	C	Increased	42	0.046	2.60 (1.02–6.62)	45
		G	Decreased	43	0.003	0.09 (0.02–0.45)	

CTRCD indicates chemotherapy-related cardiac dysfunction; NA, not available; and NS, not significant.
*Not reaching genome-wide significance.
†Discovery cohort.
‡Replication cohort.
§Combined cohort.
‖Gene-environment interaction, dose-dependent relationship.
¶Significant in univariate analysis.
#European patients.
**Non-European patients.

Linschoten et al. Circ Genom Precis Med. 2018;11:e001753.

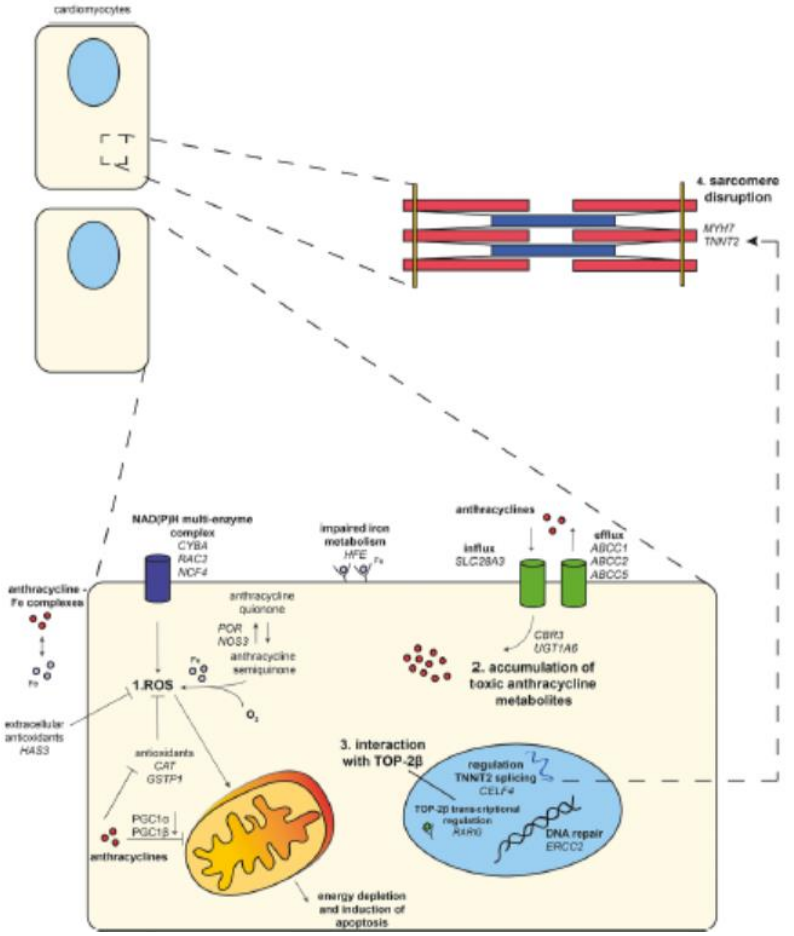
++ Evidencia Antraciclinas

Los genes apoyan 4 mecanismos fisiopatológicos implicados en la **cardiotoxicidad por antraciclinas**:

1. generación de especies de oxígeno reactivas en exceso (ROS)
2. acumulación de metabolitos cardiotóxicos
3. interacción de antraciclinas con topoisomerase-2β
4. alteración de la estructura y función del sarcómero

La cardiotoxicidad se ve además agravada por el hierro en múltiples niveles:

- interrupción del metabolismo del hierro que causa la acumulación de hierro
- aumento del estrés oxidativo
- generación de complejos de hierro y antraciclina que causan la peroxidación de la membrana lipídica



Linschoten et al. Circ Genom Precis Med. 2018;11:e001753.

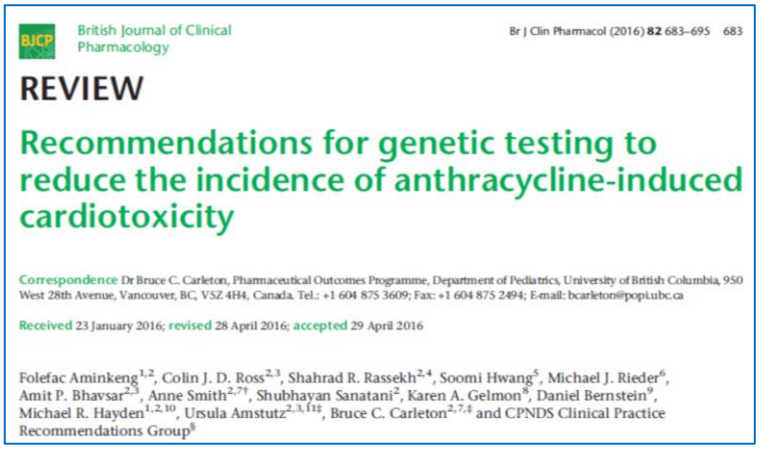
NO HAY EVIDENCIA CLARA

La variantes encontradas carecen de una réplica sólida y, por lo tanto, todavía no tienen el potencial para mejorar la estratificación del riesgo clínico en un ajuste de diagnóstico

Posibles motivos:

- ✓ La definición de cardiotoxicidad es muy variable según los estudios
  - ✓ Diferente definición de disfunción ventricular
  - ✓ Consideración d… …guda y crónica
- ✓ No hay corre… …ios de genes candidat…
- ✓ Población… …variable)
- ✓ No hay correcci… …la mayoría (población de origen europeo)
- ✓ Los cánceres tratados son muy diferentes
- ✓ Los tratamientos son variables y sus dosis también (diversas antraciclinas, tratuzumab, etc)

Población infantil



British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) 82 683–695 683

REVIEW

Recommendations for genetic testing to reduce the incidence of anthracycline-induced cardiotoxicity

Correspondence Dr Bruce C. Carleton, Pharmaceutical Outcomes Programme, Department of Pediatrics, University of British Columbia, 950 West 28th Avenue, Vancouver, BC, V5Z 4H4, Canada. Tel.: +1 604 875 3609; Fax: +1 604 875 2494; E-mail: bcarleton@popi.ubc.ca

Received 23 January 2016; revised 28 April 2016; accepted 29 April 2016

Folefac Aminkeng[1,2], Colin J. D. Ross[2,3], Shahrad R. Rassekh[2,4], Soomi Hwang[5], Michael J. Rieder[6], Amit P. Bhavsar[2,3], Anne Smith[2,7†], Shubhayan Sanatani[2], Karen A. Gelmon[8], Daniel Bernstein[9], Michael R. Hayden[1,2,10], Ursula Amstutz[2,3,11‡], Bruce C. Carleton[2,7,‡] and CPNDS Clinical Practice Recommendations Group[§]

F. Aminkeng et al.

METHODS

We followed a standard guideline development process, including a systematic literature search, evidence synthesis and critical appraisal, and the development of clinical practice recommendations with an international expert group.

RESULTS

RARG rs2229774, *SLC28A3* rs7853758 and *UGT1A6* rs17863783 variants currently have the strongest and the most consistent evidence for association with ACT. Genetic variants in *ABCC1*, *ABCC2*, *ABCC5*, *ABCB1*, *ABCB4*, *CBR3*, *RAC2*, *NCF4*, *CYBA*, *GSTP1*, *CAT*, *SULT2B1*, *POR*, *HAS3*, *SLC22A7*, *SCL22A17*, *HFE* and *NOS3* have also been associated with ACT, but require additional validation. We recommend pharmacogenomic testing for the *RARG* rs2229774 (S427L), *SLC28A3* rs7853758 (L461L) and *UGT1A6*4* rs17863783 (V209V) variants in childhood cancer patients with an indication for doxorubicin or daunorubicin therapy (Level B – moderate). Based on an overall risk stratification, taking into account genetic and clinical risk factors, we recommend a number of management options including increased frequency of echocardiogram monitoring, follow-up, as well as therapeutic options within the current standard of clinical practice.

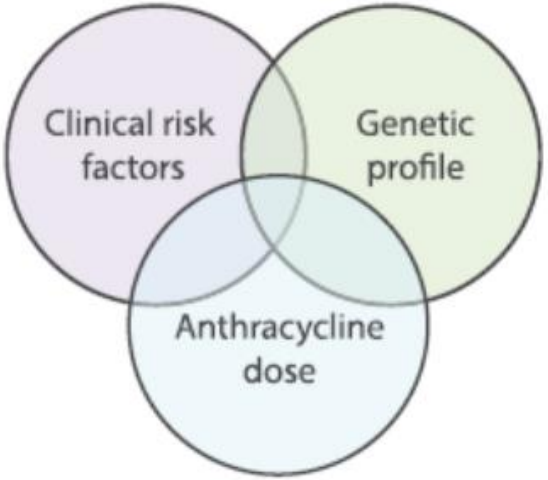
CONCLUSIONS

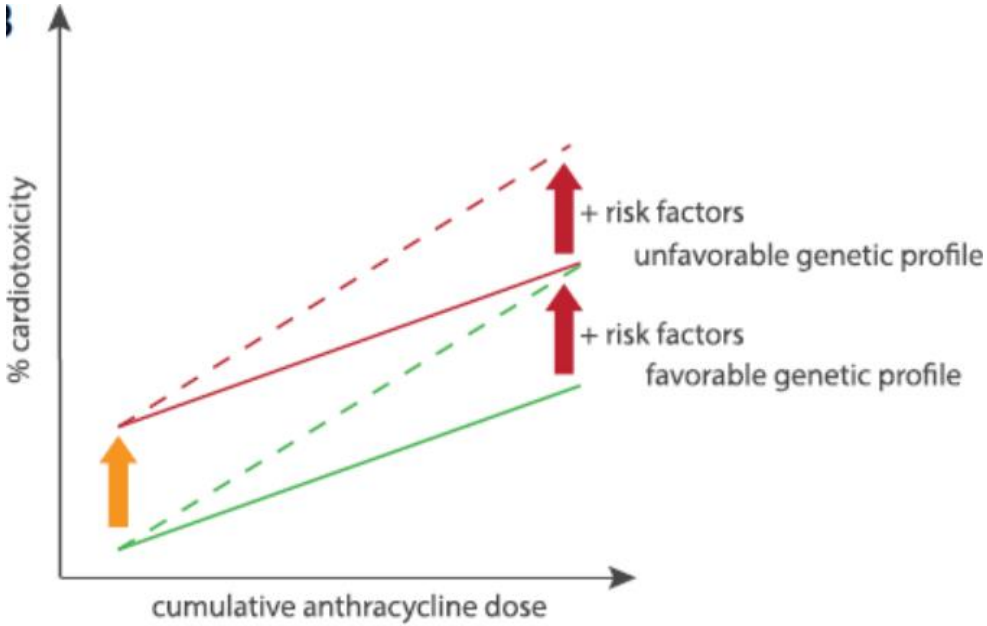
Existing evidence demonstrates that genetic factors have the potential to improve the discrimination between individuals at higher and lower risk of ACT. Genetic testing may therefore support both patient care decisions and evidence development for an improved prevention of ACT.

Genetic testing is currently not recommended in adult patients and in children receiving other types of anthracyclines

Los **principales factores** que influyen en el riesgo a desarrollar cardiotoxicidad son:

1. factores de riesgo clínicos relacionados con el paciente
2. factores de riesgo relacionados con el tratamiento (dosis)
3. perfil genético individual.



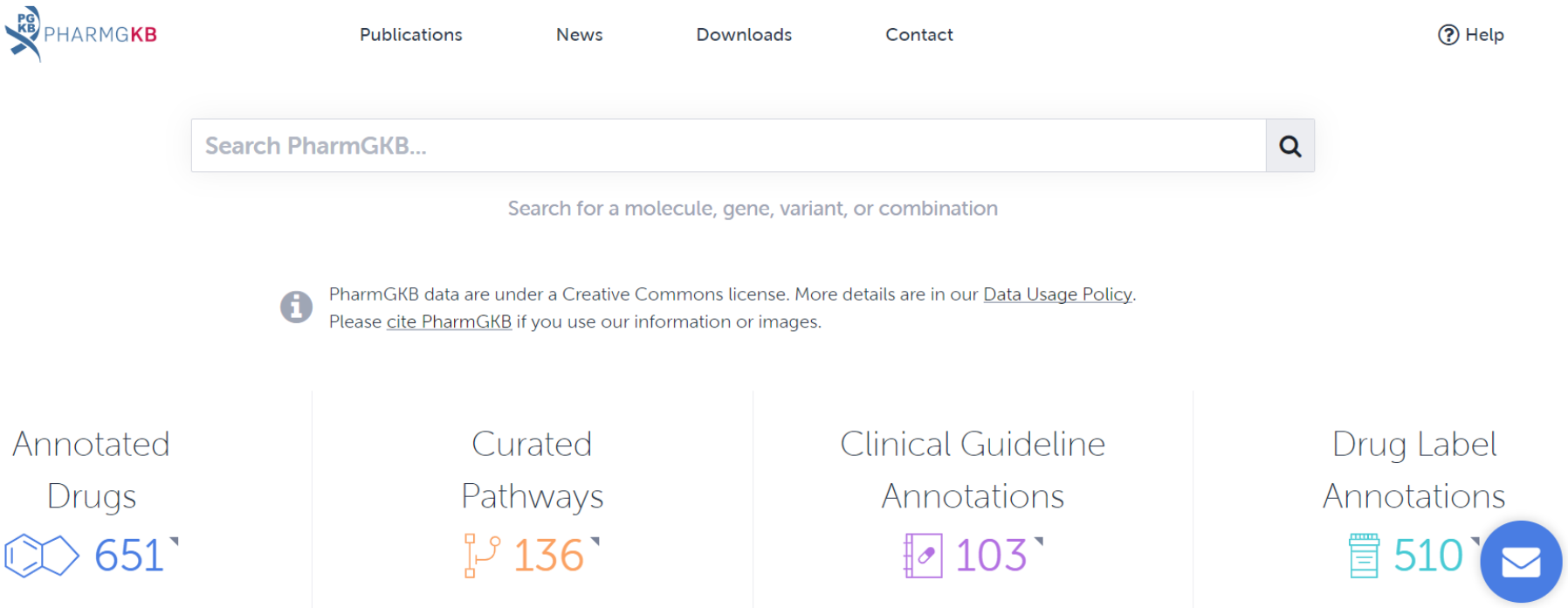


Modelo de interacción de tres factores

Linschoten et al. Circ Genom Precis Med. 2018;11:e001753.

Estudios farmacogenéticos

https://www.pharmgkb.org/



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anthracyclines an... × Add a term to make a combination...

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- Drug Label Annotations
- Clinical Annotations
- Variant Annotations
- Literature
- Pathways
- Related To
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PRESCRIBING INFO	DRUG LABEL ANNOTATIONS	CLINICAL ANNOTATIONS	PATHWAYS
1	0	156	3

Type : Drug Class

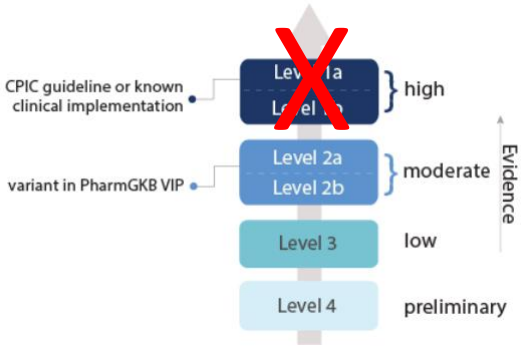
PharmGKB ID : PA130620651

Alternate Names

Generic Names

None

Category Members



What are Clinical Annotations?

PharmGKB clinical annotations provide information about variant-drug pairs based on variant annotations. PharmGKB Scientific Curators manually review variant annotations and create genotype-based summaries describing the phenotypic impact of the variant. A clinical annotation can represent information from a single paper or multiple papers. Annotations are assigned a rating based on "Strength of Evidence". Levels range from 1-4, with level 1 meeting the highest criteria.

In a clinical annotation, the phenotype for any given genotype is reported relative to the other genotypes. For example, the AA genotype for a variant may be associated with an increased risk of side effects as compared with the AG and GG genotypes, but not necessarily at an increased risk of side effects for patients on the drug in general, as this would depend on a detailed examination of the target population allele frequencies and the populations on which the original US Food and Drug Administration approval is based.

PHARMGKB

anthracyclines an... × Add a term to make a combination...

Menu Help

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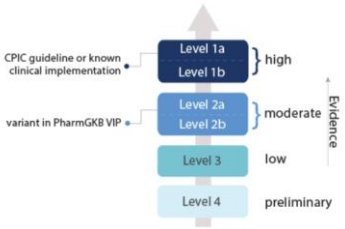
	LEVEL	VARIANT	GENE	MOLECULE	TYPE	PHENOTYPE
Read Now	Level 2A	rs1800566	NQO1	Alkylating Agents, anthracyclines and related substances, fluorouracil, Platinum compounds	Efficacy	Breast Neoplasms, Carcinoma, Non-Small-Cell Lung, Neoplasms, Ovarian Neoplasms, Stomach Neoplasms
Read Now	Level 2A	rs1695	GSTP1	cyclophosphamide, epirubicin	Efficacy/Toxicity/ADR	Breast Neoplasms
Read Now	Level 2B	rs738409	PNPLA3	asparaginase, cyclophosphamide, daunorubicin, prednisolone, vincristine	Toxicity/ADR	Precursor Cell Lymphoblastic Leukemia-Lymphoma
Read Now	Level 2B	rs7853758	SLC28A3	anthracyclines and related substances	Toxicity/ADR	Neoplasms
Read Now	Level 2B	rs2232228	HAS3	anthracyclines and related substances	Toxicity/ADR	Cardiomyopathies
Read Now	Level 2B	rs885004	SLC28A3	anthracyclines and related substances	Toxicity/ADR	Neoplasms
Read Now	Level 2B	rs1056892	CBR3	anthracyclines and related substances	Toxicity/ADR	Heart Failure, Neoplasms
Read Now	Level 2B	rs4646	CYP19A1	anastrozole, cyclophosphamide, docetaxel, doxorubicin, epirubicin, exemestane, fluorouracil, paclitaxel, radiotherapy, tamoxifen	Efficacy	Breast Neoplasms, Menopause
Read Now	Level 3	rs9024	CBR1	anthracyclines and related substances	Toxicity/ADR	Cardiomyopathies, Neoplasms
Read Now	Level 3	rs299313	HMMR	cyclophosphamide, epirubicin, fluorouracil	Toxicity/ADR	Breast Neoplasms, Neutropenia
Read Now	Level 3	rs141084494	RBX1	cyclophosphamide, epirubicin, fluorouracil	Toxicity/ADR	Breast Neoplasms, Neutropenia

2 variantes con nivel 2A
6 variantes con nivel 2B

→ 2 variantes con fenotipo cardiaco

145 variantes con nivel 3
3 variantes con nivel 4

→ 4 variantes con fenotipo cardiaco



idis

← Back to all Clinical Annotations

Clinical Annotation for rs2232228 (HAS3); anthracyclines and related substances; Cardiomyopathies (level 2B Toxicity/ADR)

Level of Evidence

Level 2B

Type

Toxicity/ADR

Genes

HAS3

Variants

rs2232228

Drugs

anthracyclines and related substances

Phenotypes

Cardiomyopathies

Biogeographical Group

Mixed Population

PharmGKB ID

1183703760

ALLELE	PHENOTYPE
AA	Patients with genotype AA may have increased cardiomyopathy risk when exposed to high-dose (> 250 mg/m2) anthracyclines in children with Neoplasms as compared to patients with genotype GG. Other genetic or clinical factors may also influence a patient's risk of toxicity to anthracyclines.
AG	Patients with genotype AG may have increased cardiomyopathy risk when exposed to high-dose (> 250 mg/m2) anthracyclines in children with Neoplasms as compared to patients with genotype GG. Other genetic or clinical factors may also influence a patient's risk of toxicity to anthracyclines.
GG	Patients with genotype GG may have decreased cardiomyopathy risk when exposed to high-dose (> 250 mg/m2) anthracyclines in children with Neoplasms as compared to patients with genotype AA or AG. Other genetic or clinical factors may also influence a patient's risk of toxicity to anthracyclines.

Evidence

Annotation of rs2232228 in HAS3

1. Genotype AA is associated with increased risk of Cardiomyopathies when exposed to anthracyclines and related substances in children with Neoplasms as compared to genotype GG.

when exposed to high-dose (> 250 mg/m2) anthracyclines. At low-to-moderate-dose anthracycline exposure, the risk of cardiomyopathy did not differ significantly by rs2232228 genotype.
PharmGKB ID
1183703753

from publication:

Hyaluronan synthase 3 variant and anthracycline-related cardiomyopathy: a report from the children's oncology group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2014. Wang Xuexia et al.

PMID: 24470002 PMCID: PMC3927733 DOI: 10.1200/JCO.2013.50.3557

Paper discusses: toxicity

Study Parameters

	SIZE	ALLELE	FREQUENCY
CASE	65	-	-
CONTROL	64	-	-

P-value : = 0.003
Ratio Stat : OR: 8.9
Confidence Interval : 2.1 - 37.5
Type : cohort, case/control
Biogeographical Group : European
Population Characteristics : Study Cohort: Discovery stage

	SIZE	ALLELE	FREQUENCY
CASE	76	-	-
CONTROL	-	-	-

P-value : = 0.04
Ratio Stat : OR: 4.5
Confidence Interval : 1.1 - 18.7
Type : cohort
Biogeographical Group : Mixed population
Population Characteristics : Study Cohort: replication stage

Clinical Annotation for rs1056892 (CBR3); anthracyclines and related substances; Heart Failure and Neoplasms (level 2B Toxicity/ADR)

Level of Evidence

Level 2B

Type

Toxicity/ADR

Genes

CBR3

Variants

rs1056892

Drugs

anthracyclines and related substances

Phenotypes

Heart Failure, Neoplasms

Biogeographical Group

Mixed Population

PharmGKB ID

652779372

ALLELE	PHENOTYPE
AA	Patients with the AA genotype may have decreased risk of cardiac damage after anthracycline exposure as compared to patients with the GG genotype. Patients with the AA genotype may still be at risk for adverse events when exposed to anthracyclines based on their genotype. Other genetic and clinical factors may also influence a patient's risk for adverse events.
AG	Patients with the AG genotype may have increased risk of cardiac damage after anthracycline exposure as compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patient's risk for adverse events.
GG	Patients with the GG genotype may have increased risk of cardiac damage after anthracycline exposure as compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patient's risk for adverse events.

Evidence

Annotation of rs1056892 in CBR3

Annotation of rs1056892 in CBR3

Annotation of rs1056892 in CBR3

3. Allele G is associated with increased risk of Heart Failure when treated with anthracyclines and related substances as compared to allele A.

PharmGKB ID
655387546

from publication:

Genetic polymorphisms in the carbonyl reductase 3 gene CBR3 and the NAD(P)H:quinone oxidoreductase 1 gene NQO1 in patients who developed anthracycline-related congestive heart failure after childhood cancer. *Cancer.* 2008. Blanco Javier G et al.
PMID: 18457324 DOI: 10.1002/cncr.23534

Paper discusses: toxicity

Study Parameters

	SIZE	ALLELE	FREQUENCY
CASE	145	-	-
CONTROL	-	-	-

P-value : = 0.092
Ratio Stat : OR: 5.44
Biogeographical Group : Mixed population
Population Characteristics : Study Cohort: Childhood Cancer Survivor Study

anthracyclines and related substances

- Overview
- Prescribing Info
- Drug Label Annotations
- Clinical Annotations
- Variant Annotations
- Literature
- Pathways
- Related To
- Links & Downloads

Prescribing Info

Clinical Guideline Annotations

These clinical guidelines provide drug prescribing recommendations that take patient genotype into consideration, and are manually curated at PharmGKB. Guidelines have been published by the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group (DPWG), the Canadian Pharmacogenomic Network for Drug Safety (CPNDS) or other professional society.

	SOURCE	GENES	TITLE
Read Now	Canadian Pharmacogenomics Network for Drug Safety	RARG, SLC28A3, UGT1A6	Annotation of CPNDS Guideline for daunorubicin,doxorubicin and RARG,SLC28A3,UGT1A6

Annotation of CPNDS Guideline for daunorubicin,doxorubicin and RARG,SLC28A3,UGT1A6

PharmGKB ID : PA166159180

Summary

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) clinical recommendation group has published guidelines for the use of *RARG* , *SLC28A3* , and *UGT1A6* when prescribing anthracyclines for pediatric cancer patients. They recommend that pharmacogenomic testing of *RARG* rs2229774, *SLC28A3* rs7853758, and *UGT1A6 *4* (rs17863783) should be performed in all pediatric cancer patients who are treated with daunorubicin or doxorubicin because the association of those genetic variants with anthracycline associated cardiotoxicity (ACT).

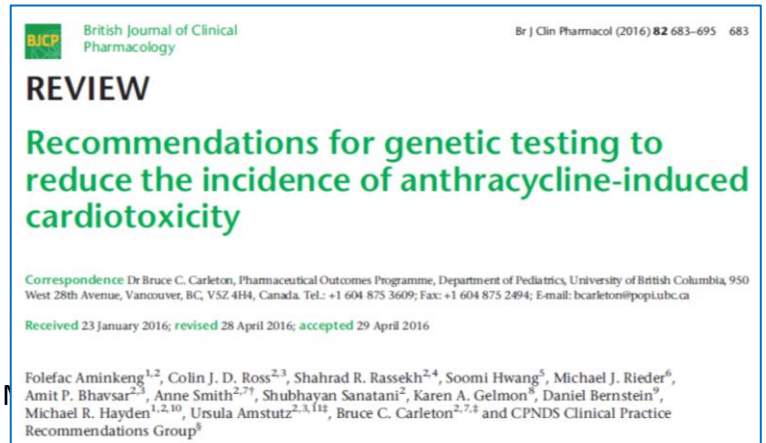
Annotation

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) clinical recommendation group has published genotype-based drug dosing guidelines for anthracyclines in the British Journal of Clinical Pharmacology. Excerpts from "Recommendations for Genetic Testing to Reduce the Incidence of Anthracycline-Induced Cardiotoxicity:" [Article:27197003] follow:

- All other patients should be considered at moderate genetic risk. Pharmacogenomic testing should be performed in all pediatric cancer patients who are treated with doxorubicin or daunorubicin for the following genetic variants *RARG* rs2229774, *SLC28A3* rs7853758, *UGT1A6*4* rs17863783. The rs2229774 A allele and the UGT1A6*4 s17863783 T allele are the high risk variants, whereas the rs7853758 A allele is a low-risk allele. For patients who carry the reduced risk allele without the high-risk alleles, classification into a lower cardiotoxicity risk should be considered ___(Level B - moderate recommendation)___.
- Genetic testing is not recommended for adults and pediatric patients receiving alternate anthracyclines ___(Level C - optional recommendation)___.

Management options based on ACT risk

- *Low risk patients - normal follow up* ***(Level A recommendation)***
- *Moderate risk patients - increase frequency of monitoring* ***(Level A recommendation)***
- *High risk patients - the following management options should be considered:*
  - Increase frequency of monitoring with serial yearly echocardiographic monitoring an follow-up as recommended by COG guidelines ***(Level A recommendation)***
  - Aggressive screening and management of cardiovascular risk factors including obesity, diabetes, hypertension, coronary artery idea, lipid disorders and peripheral vascular disease ***(Level A recommendation)***
  - Prescribe dexrazoxane ***(Level B recommendation)***
  - Use liposomal encapsulated anthracycline preparations ***(Level C recommendation)***
  - Use of continuous inclusion or slower inclusion rates ***(Level C recommendation)***
  - Use of less cardiotoxic types of anthracyclines ***(Level C recommendation)***
  - Use of other cardioprotective agents ***(Level C recommendation)***
  - Prescribe alternative chemotherapy regiments for certain tumor types where alternative regiments have been shown to be equally effective ***(Level C recommendation)***


British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) 82 683–695 683

REVIEW

Recommendations for genetic testing to reduce the incidence of anthracycline-induced cardiotoxicity

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CardioTox 2019

Conclusiones

- La cardiotoxicidad es un problema de salud muy importante que afecta a muchas personas en el que interviene factores externos y genéticos
- Las variantes genéticas junto con las variables clínicas pueden identificar a las personas en riesgo de desarrollar cardiotoxicidad.
- Los estudios realizados hasta la fecha son muy heterogéneos y no han sido correctamente replicados
- Todavía no existen biomarcadores genéticos válidos para la cardiotoxicidad.
- Existe la necesidad de desarrollar un estudio de asociación genética con un número significativo de individuos, con corrección para pruebas múltiples y replicación de los resultados positivos putativos.

Estudio de GWAS:

- Tamaño muestral elevado
- Pacientes con un mismo tipo de cáncer
- Pacientes recibiendo un mismo tratamiento y una misma dosis
- Definición de cardiotoxicidad clara y homogénea en todos los casos (DV con criterios claros, aguda, crónica, ….)
- Casos y controles de la misma localización geográfica
- Correcciones para estratificación poblacional
- Correcciones para test múltiples
- Réplica de resultados positivos

Homogeneidad

Corrección estadística


IF THE DRUGS DO CAUSE A PROBLEM THEN WE'VE GOT SOME PILLS THAT MIGHT HELP...
AND SOME OTHER PILLS FOR THE SIDE EFFECTS OF THE PILLS YOU TAKE FOR THE PROBLEMS THE DRUGS CAUSE...

THANKS