Genetics and CVD in Cancer Patients

Saro Armenian DO, MPH
45% of cases with CHF exposed to <250 mg/m²
For a given exposure, there is marked variation in prevalence and severity of heart failure that is not explained exclusively by clinical risk factors.

Clinical risk factors:
- Age at exposure
- Female gender
- Anthracycline dose
- Comorbidities

Genetic risk factors:
- Drug metabolism and Transport
- Generation of reactive oxygen species
- Anti-oxidant defense
- DNA repair pathways
- Renin-angiotensin system

Therapy-Related Heart Failure
Anthracycline

Prescribed dose

Mitochondrial dysfunction

Aconitase/IRP1

Loss of Fe

Homeostasis

Energy/Redox Impairment

Heart Failure

Dox-semiquinone

NAD(P)H

NAD(P)+

NAD(P)H oxidase multi-enzyme complex

O2/*H2O2

Prescribed dose

Internal dose

Dox-ol

Dox-quinone

Maladaptive LV Remodeling

Asymptomatic ↓LVEF/FS

Myocyte apoptosis

Heart Failure

Mitochondrial dysfunction

Impairment

Normal Heart

Dilated ventricle

B

C

RP
Anthracycline

Prescribed dose

Internal dose

ROS

Mitochondrial dysfunction

Dox-quinone

Dox-semiquinone*

NAD(P)H oxidase multi-enzyme complex

NAD(P)H

Dox-ol

Aconitase/IRP1

Loss of Fe Homeostasis

HFE

Energy/Redox Impairment

ROS

Myocyte apoptosis

Maladaptive LV Remodeling

Asymptomatic ↓LVEF/FS

Heart Failure

OR 95% CI

Female 2.9 1.4-6.0

Chest XRT 4.7 1.0-16.5

HFE (rs1799945), GC/GG 2.5 1.0-6.3

RAC2 (rs13058338), TA/AA 2.8 1.4-5.6

ABCC2 (rs818710), GA/AA 4.3 1.5-12.5

2013 Oct;163(2):205-13
Functional genomics

- **Multidrug resistant protein (MRP2)** - rs8187710
  - MRP2 protein expression liver, kidney
  - Anthracycline clearance via biliary system
  - Inhibition of MRP2 expression, decreased anthracycline clearance
  - CHF risk – OR 2.3; 95%CI 1.0-5.4. *Circulation*, 2005, 112:3754-3762

- **NAD(P)H oxidase subunit (RAC2)** - rs13058338
  - NAD(P)H oxidase multi-enzyme complex, electron donor Dox-quinone
  - RAC2: GTPase regulator of NAD(P)H oxidase activity
  - CHF risk – OR 2.6; 95%CI 1.3-5.1 *Circulation*, 2005, 112:3754-3762

- **Hemochromatosis (HFE2)** - rs1799945
  - Iron homeostasis
  - *HFE* knock-out murine model vs. wild-type
    - *Higher myocardial iron burden*
    - *Greater anthracycline cardiotoxicity in HFE knock-out*
Receiver operating characteristic (ROC) curves

- **SNPs and Clinical**: AUC = 0.79, 95% CI = 0.75-0.83
- **SNPs only**: AUC = 0.67, 95% CI = 0.60-0.74
- **Clinical only**: AUC = 0.69, 95% CI = 0.63-0.75

*Br J Haemtol.* 2013; 163:205
Genome-wide Association Study

*rs1786814* with anthracycline, \( p = 1.14 \times 10^{-5} \)

Among non-Hispanic whites:

Evidence of gene environment (anthracycline) interaction.

SNP *rs1786814* (\( p \text{ value} = 1.14 \times 10^{-5} \)) on gene **CELF4**

Anthracycline exposure and risk of cardiomyopathy by CELF4 genotype

**CELF4 gene**

- CELF4 is a protein that in humans is encoded by the **CELF4 gene** on chromosome 18.
- CELF family of RNA-binding proteins is implicated in the **alternative splicing** of **TNNT2** gene during development.
- **TNNT2** encodes for **cardiac troponin T (cTnT)**.
- During development, splicing of **TNNT2** leads to inclusion of alternative exon 5 with insertion of 10 additional amino acids into protein.
  - **TNNT2** splicing variants carrying exon 5 are expressed in embryonic hearts, and are mostly absent from mRNAs found in adult hearts.
- Persistent expression of embryonic **TNNT2** variant in adult cardiac muscle can result in coexistence of embryonic + adult variants.
  - results in a temporally split in myofilament response to increasing Ca\(^{2+}\) concentrations
    - decreased myocardial contractility and ventricular pumping efficiency.
Genome-Wide Association Study for Anthracycline-Induced Congestive Heart Failure

Bryan P. Schneider¹, Fei Shen¹, Laura Gardner¹, Milan Radovich¹, Lang Li¹, Kathy D. Miller¹, Guanglong Jiang¹, Dongbing Lai¹, Anne O’Neill², Joseph A. Sparano³, Nancy E. Davidson⁴, David Cameron⁵, Irmina Gradus-Pizlo¹, Ronald A. Mastouri¹, Thomas M. Suter⁶, Tatiana Foroud¹, and George W. Sledge Jr⁷

- 3,431 patients from the randomized phase III adjuvant breast cancer trial E5103
- 9 SNPs P value <10⁻⁵
- 2 Validated independent data sets

• Within binding site for glucocorticoid receptor protein
• Plays important roles in the structural and functional maturation of the fetal heart and in the maintenance of proper cardiac function in animal models
Germline genomics and risk prediction
Germline genomics and heart failure risk

• Inter-individual variability in therapy-associated HF may be due to genetic modifiers of risk

• Limitations
  - Small sample sizes
  - Heterogeneous outcomes across studies
  - Lack of replication of findings across studies
  - Context relative to existing known clinical risk factors (age, CV risk factors)

• Future directions
  - Primary and secondary prevention critical to risk reduction