Genetic Variation Associated with Tamoxifen Metabolism in Alaska Native and American Indian People

Alaska Native Health Research Conference
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65,000 voices
Vision
A Native Community that enjoys physical, mental, emotional and spiritual wellness

Mission
Working together with the Native Community to achieve wellness through health and related services
Goals
Shared Responsibility
Commitment to Quality
Family Wellness
Operational Principles

Relationships between customer-owner, family and provider must be fostered and supported

Emphasis on wellness of the whole person, family and community (physical, mental, emotional and spiritual wellness)

Locations convenient for customer-owners with minimal stops to get all their needs addressed

Access optimized and waiting times limited

Together with the customer-owner as an active partner

Intentional whole-system design to maximize coordination and minimize duplication

Outcome and process measures continuously evaluated and improved

Not complicated but simple and easy to use

Services financially sustainable and viable

Hub of the system is the family

Interests of customer-owners drive the system to determine what we do and how we do it

Population-Based systems and services

Services and systems build on the strengths of Alaska Native cultures
Core Concepts

Work together in relationship to learn and grow
Encourage understanding
Listen with an open mind
Laugh and enjoy humor throughout the day
Notice the dignity and value of ourselves and others
Engage others with compassion
Share our stories and our hearts
Strive to honor and respect ourselves and others
Leadership Principles

Operate from the strength of Alaska Native cultures and traditions of leadership.

Will stand in the gap to align and achieve the mission and vision.

Nurture an environment of trust that encourages buy-in, systematic growth and change.

Encourage ownership of responsible, calculated risk taking.

Respect and grow the skills of future generations to drive initiatives and improvements.

Share and listen to personal life stories in order to be transparent and accountable.

Encourage people in by creating a safe environment where spiritual, ethical and personal beliefs are honored.

Improve for the future by learning from the past, giving away credit and celebrating achievements.

Practice and encourage self-improvement believing there is good in every person.
Presentation Objectives

- Describe role of cytochrome P450 (CYP) enzyme
  - CYP2D6 impact on the bio-activation of tamoxifen
  - Tamoxifen pharmacogenetics study results
- Discuss how research findings can improve clinical practice
Background

- Tamoxifen is used to prevent recurrence of estrogen-positive breast cancer in pre-menopausal women
- Consistent efficacy and a favorable toxicity profile
- Endoxifen is an active metabolite of tamoxifen
  - Primary contributor to tamoxifen effectiveness
- Known CYP2D6 variants can alter hepatic enzyme activity
Study Purpose:
Identify how genetic differences in the CYP gene may alter the effectiveness of tamoxifen in AIAN women with breast cancer
To determine whether CYP2D6 gene mutations are associated with lower plasma concentrations of endoxifen among:

- Alaska Native / American Indian women
- Living in southcentral Alaska and Montana
- Being treated with tamoxifen for the prevention of breast cancer recurrence
Institutions/organizations involved (locations):

- Southcentral Foundation (Anchorage, AK)
- Alaska Native Medical Center (Anchorage, AK)
- The University of Montana (Missoula, MT)
- Confederated Salish Kootenai Tribes Tribal Health Department (Flathead Indian Reservation, MT)
- Montana Cancer Institute Foundation (Missoula, MT)
Part 1 (Identification of CYP gene variants)

- Participants: Variants in CYP2D6 were characterized in a convenience sample of 380 participants from SCF
- Gene variants studied include:
  - CYP2D6, CYP3A4, CYP3A5, and CYP2C9
Part 2 (Gene variant discovery)

- Participants: 94 healthy SCF participants
- Resequencing of CYP2D6 gene variant
  - Compared to results from Confederated Salish and Kootenai Tribes in MT
Part 3 (Genotype-phenotype associations of tamoxifen metabolism)

- Participants: 42 AIAN females, receiving tamoxifen treatment for prevention of breast cancer recurrence
- Assessed associations between CYP genotype and steady-state plasma concentrations of:
  - Tamoxifen
  - Endoxifen
  - 4-hydroxytamoxifen (4-OH-Tam)
Part 3 (Data Collection)

- **Participants:**
  - Survey of basic demographic information
    - self-reported gender, DOB, tribal affiliation/heritage
  - Medication information
    - tamoxifen dose, time of last dose, concurrent medication usage in particular selective serotonin reuptake inhibitors
  - Blood samples for DNA isolation and plasma tamoxifen and metabolite concentrations
Cohorts were tested for deviations from Hardy-Weinberg equilibrium (HWE) using a χ²-test.

Pairwise linkage disequilibrium (LD) was estimated in three cohorts and r² LD value determined between SNV and calculated using the Haploview 4.2 software.

Multivariate linear regression analyses used to assess associations between genetic variation and plasma steady-state concentrations of tamoxifen and principal metabolites.

- Metabolic ratios used to understand gene metabolite formation and elimination.

Genotype-phenotype associations were tested with linear regression analyses using RStudio, version 3.3.1.
Only CYP2D6 gene variants were significant:

- Significantly associated plasma concentration of active metabolite endoxifen (p=0.0008)
- Significantly associated with endoxifen/tamoxifen metabolic ratio
  - The MOST relevant metabolic ratio
  - Ratio was 4.3 times higher (p=4.0X10^{-7}) than poor metabolizers
- Other gene variants (CYP3A5, CYP3A4, and CYP2C9) play a minor role in tamoxifen metabolism
CYP2D6 variant is an important predictor of tamoxifen bioactivation.

Breast cancer patients who are intermediate and poor metabolizers of CYP2D6 have:

- significantly lower plasma concentrations of metabolites, endoxifen and 4-OH-Tam
- lower metabolic ratios, notably the endoxifen/tamoxifen metabolic ratio
Pharmacogenetic testing may help to guide tamoxifen therapy in AIAN people.

Patients may benefit from other prescribing strategies to decrease the incidence of breast cancer recurrence during anti-estrogenic therapy:
- Increased tamoxifen dose
- Use of aromatase inhibitors
- Direct administration of endoxifen

Identifying CYP2D6 metabolizer status prior to tamoxifen initiation may improve health outcomes.
Next Steps

- Continue to research genetic variants found in AIAN people that impact metabolism of common drug therapies
- Implementation strategies for tamoxifen pharmacogenomic testing with Southcentral Foundation and Confederated Salish and Kootenai Tribes
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