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PharmGenEd™: Bridging the Gap Between Science & Practice

Train-the-Trainer Session
for Toxicogenomics

Wednesday, May 16, 2012



UNIVERSITY of CALIFORNIA, SAN DIEGO
SKAGGS SCHOOL of PHARMACY
and PHARMACEUTICAL SCIENCES

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Train-the-Trainer Agenda

1. Introduction
 - Objective of PharmGenEd™ program
 - Shared curriculum and format
 - Introduction of author
2. Review of educational content for selected therapeutic area
3. Contact information
4. Survey to assess program materials

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Overall Objective of PharmGenEd™ Program

- The “Pharmacogenomics Education Program: Bridging the Gap between Science and Practice” (PharmGenEd™) is an evidence-based pharmacogenomics education program designed for pharmacists and physicians, pharmacy and medical students, and other healthcare professionals.
- The overall objective of the PharmGenEd™ program is to increase awareness about the validity and utility of pharmacogenomic tests and the potential implications of benefits and harms from use of the tests.

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Shared Curriculum

Educational Materials (each 1 hour)

- Asthma
- Cardiology I (warfarin & statins)
- Cardiology II (clopidogrel & beta blockers)
- Concepts and clinical applications
- Economic issues
- HIV/AIDS
- Oncology I (solid tumors)
- Oncology II (hematologic malignancies)
- Psychiatry I (depression)
- Psychiatry II (antipsychotics)

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Presentation Outline

- Introduction to toxicogenomics
- Toxicogenomics and occupational exposures
- Toxicogenomics and environmental exposures
- Toxicogenomics and medication toxicity
- Emerging areas in toxicogenomics

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Learning Objectives

Upon completion of this program, participants will be able to:

- Discuss examples of genetic variants suspected to be associated with adverse effects of **occupational** exposures
 - Discuss the ethical and social issues that arise when genotyping is considered for workers
- Discuss the current use of toxicogenomics and **environmental** exposures
- Discuss the use of genotyping to prevent **medication toxicity**

Introduction

Definitions

- **Pharmacogenomics**
 - The study of how the genome influences responses to medications
- **Toxicogenomics**
 - The study of how the genome influences responses to potentially toxic compounds
- **Pharmacogenomics and Toxicogenomics** intersect in the approaches used in both fields.

Development of Toxicogenomics

- Toxicogenomics grew out of pharmacogenomics in the 1990s as the tools of pharmacogenomics began to be applied to toxicology questions (Weber 2004).
- The first toxicogenomics application was the discovery that the severe hemolysis some patients suffered with primaquine use could be explained by glucose 6-phosphate dehydrogenase (G6PD) deficiencies (Cappellini and Fiorelli 2008).

Applications of Toxicogenomics

- Genotyping can identify workers at risk for developing adverse health effects when exposed to selected industrial compounds.
- Genotyping may identify people at risk for developing adverse health effects due to environmental exposures.
- Toxicogenomics is emerging as a tool in drug development and clinical medicine.
 - Drug development: toxicogenomics is used to investigate the mechanisms of and to predict the toxicities of medications.
 - Clinical medicine: toxicogenomics is used to identify patients at risk for adverse drug reactions because of their genotypes.

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Toxicogenomics and Occupational Exposures

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Patient Case 1

- A 68-year-old male complains of shortness of breath, cough, chest discomfort, fatigue and weight loss.
- This patient last held a job for several years machining beryllium metal parts. He has been retired for three years.
- The patient's symptoms have been worsening for quite some time.
- The patient consents to participate in a case-control study investigating the association between Chronic Beryllium Disease (CBD) and *HLA-DPβ1^{glu69}*.

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Toxicogenomics and Occupational Exposures

- Genetic variations may predispose some workers to develop disease with workplace exposures.
- The following slides provide examples of genetic polymorphisms thought to influence the risk of disease or toxicity with certain occupational exposures:
 - **Organophosphate pesticide** exposure and toxicity
 - **Trichloroethylene** exposure and risk for hypersensitivity dermatitis
 - **Aromatic amine** exposure and risk for bladder cancer
 - **Beryllium** exposure and risk of chronic beryllium disease

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Organophosphate Exposure

- Organophosphate (OP) insecticides are commonly used in the US and abroad (Wright 2005, Hofmann et al 2010).
- OPs are responsible for a large number of pesticide poisonings via their inhibition of cholinesterases. (Wright 2005, Hofmann et al 2010).
- Some OPs, especially the more toxic oxon form of some OPs, are metabolized by paraoxonase encoded by the *PON1* gene (Wright 2005, Hofmann et al 2010).

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Organophosphate Exposure

- Genetic variants in cholinesterases and OP-metabolizing enzymes are being evaluated for their association with the risk for OP toxicity (Wright 2005).
 - The rs2668207 and rs2048493 BCHE variants are associated with decreased cholinesterase activity and may contribute to OP toxicity (Howard et al 2010).
 - The Q192 variant of PON1 is less active towards oxons than the R192 variant and is currently being evaluated as a predictor of OP sensitivity in agricultural workers (Hofmann et al 2010).

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Trichloroethylene Exposure

- Trichloroethylene (TCE) is an industrial solvent and a precursor for other compounds.
- Adverse effects (ATSDR 1997)
 - Topical TCE exposure can cause dermatitis.
 - Inhalation and oral TCE exposures can cause CNS depression & adverse renal and liver effects.
 - It is a suspected human carcinogen and a possible teratogen.
- Incidence of TCE-induced hypersensitivity dermatitis is increasing with increased industrial use of TCE in Asian countries (Li et al 2007).

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Trichloroethylene Exposure

- Studies have found a significant association between the *HLA-B*1301* allele and TCE-induced hypersensitivity dermatitis in TCE-exposed workers (Li et al 2007).
- The **1301* variant has not been found in Caucasians or African Americans (Li et al 2007).
- *HLA-B*1301* has an allelic frequency of 10-13% in the Chinese population (Li et al 2007).

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Aromatic Amine Exposure

- Prior to the mid-1970's, aromatic amines were used in the production of aniline dyes (ATSDR 2001).
- Aromatic amines are known human bladder carcinogens (ATSDR 2001).

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Aromatic Amine Exposure

- The N-acetyltransferases (NATs) acetylate (detoxify) aromatic amines, competing with N-oxidation that can lead to carcinogenic metabolites (ATSDR 2001).
- Studies of aromatic amine exposures have found an association between the risk of bladder cancer and the slow acetylator phenotype (ATSDR 2001).
- The risk of developing bladder cancer has been found to be significant in the presence of the low-activity *NAT2*5* (slow acetylator) variant in several studies (Hein 2006).

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Beryllium Exposure

- Beryllium is used in many industries, including aerospace, ceramics, tool and die, nuclear defense, and prostheses manufacturing (ATSDR 2002).
- Inhalation is the primary route of exposure (ATSDR 2002).
- Beryllium exposure can result in beryllium sensitization (Samuel and Maier 2008).
- Beryllium sensitization may progress to the granulomatous pulmonary condition, chronic beryllium disease (CBD) (Samuel and Maier 2008).

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Beryllium Exposure

- CBD cases have been documented in workers exposed to allowable limits. The threshold of exposure for CBD is not clear (Samuel and Maier 2008).
- CBD susceptibility has been associated with particular alleles of the MHC Class II gene *HLA-DP*.
 - These alleles contain a glutamic acid residue at the 69th position of the β chain (*HLA-DP β 1^{glu69}*) (McCanlies et al 2003).
 - This polymorphism probably increases the risk of CBD by affecting peptide binding to the HLA receptor.

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Genetic Testing in the Workplace

- Genetic testing of employees or potential employees is possible.
- Employers may want to test workers to identify those with genetic predispositions for:
 - Developing disabling diseases
 - Increasing employer health care costs
 - Causing employees to become a public safety hazard
 - Suffering adverse responses to workplace exposures

(Council on Ethical and Judicial Affairs, 1991)

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Genetic Testing in the Workplace

There are two types of genetic testing that may be done when there is the potential for occupational exposures:

- **Genetic screening** determines the genetic make-up of individuals, identifying traits that would cause hypersensitivity to developing workplace exposure-related diseases (NHGRI 1998).
- **Genetic monitoring** determines if a person's genetic makeup has changed over time because of occupational exposures (NHGRI 1998).

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Ethical problems with Genetic Testing in the Workplace

- Potential damage or misuse of genotyping data in the workplace:
 - Genetic data could be used to change, limit, or prevent employment (Council on Ethical and Judicial Affairs 1991, NHGRI 1998).
 - Privacy may be compromised.
 - Data from genetic testing could reveal heritable conditions that are not associated with workplace exposures (NHGRI 1998).
 - Genetic data could be used by an insurance company as a rationale for not insuring such an individual.
- It is questionable whether decisions should be made regarding an employee's status based on information that may not be highly predictive (Council on Ethical and Judicial Affairs 1991).

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Restricting Use of Genetic Information in the Workplace

- Efforts have been made to prevent discrimination and damage from the misuse of genetic information gathered in the workplace.
- American Medical Association Council on Ethical and Judicial Affairs position:
 - Currently it is not appropriate to exclude workers with genetic risk of disease from workplace (BERIS 2008).
 - If genetic tests can be proven to be highly predictive, they may be used in a limited way to protect workers from disease due to occupational exposures (NHGRI 1998).

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Restricting Use of Genetic Information in the Workplace

- The Genetic Information Nondiscrimination Act (GINA) of 2008 prohibits **employers** from:
 - Discriminating on the basis of genetic tests
 - Reducing employment status on the basis of genetic tests
 - Requesting or demanding genetic tests of employees
- It prohibits **insurance companies** from:
 - Reducing coverage or increasing pricing on the basis of genetic tests
 - Requesting or demanding genetic tests
(US Department of Energy Genome Programs 2008)

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Patient Case 1 Summary

- You suspect this patient is suffering from Chronic Beryllium Disease (CBD) and will be categorized as a case subject in the study.
- You order a beryllium lymphocyte proliferation test to determine if this patient is sensitized to beryllium. This test comes back positive, indicating your patient is sensitized to beryllium.
- Further clinical testing to rule out other causes of granulomatous lung disease confirms your diagnosis of CBD.
- Genetic testing reveals this patient is heterozygous for the *HLA-DPβ^{1glu69}* allele.

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Toxicogenomics and Environmental Exposures

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Patient Case 2

- A patient is a long-time smoker.
- She has a family history of smoking, but no family history of lung cancer.
- She has heard people can get their genes tested to find out if they will develop certain diseases. She is thinking of having her genes tested to see if she has an increased risk of developing lung cancer because she smokes.
- She wants your opinion of whether she should spend the money to get her genes tested.
- How would you advise this patient?

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Toxicogenomics and Environmental Exposures

- Genetic polymorphisms influence response to environmental exposures.
- The understanding of these influences is limited because (Costa and Eaton 2006):
 - Environmental exposures are complex, usually involving multiple exposures.
 - Associations between genetic variants and adverse health effects from environmental exposures are not well understood.
 - Adverse health effects resulting from environmental exposures will most likely be influenced by multiple genes.

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Toxicogenomics and Environmental Exposures

- Efforts are ongoing to understand the influence genetic variants have on environmental exposures.
- One such effort is the Environmental Genome Project (EGP) (Costa and Eaton 2006).
 - “The long-term goal of the EGP is to characterize how specific human genetic variations, or polymorphisms, contribute to environmentally induced disease susceptibility.” (NIEHS 2011)

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Toxicogenomics & Smoking

- Efforts are underway to understand how genetic variation affects a smoker's risk of developing lung cancer.
- This is complicated by the number of carcinogens in tobacco smoke and their metabolism (Nazar-Stewart 2006).
- Some polymorphic enzymes have been identified that may affect one's genetic potential to develop lung cancer (Nazar-Stewart 2006):
 - Cytochrome P450 1A1 (CYP1A1)
 - Cytochrome P450 2E1 (CYP2E1)
 - Myeloperoxidase (MPO)
 - Glutathione S-transferase M1 (GSTM1)
- The impact of each variant on lung cancer in smokers is small, but may be important collectively (Nazar-Stewart 2006).

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Patient Case 2 Summary

- You inform your patient that scientists have identified variations in some genes that may influence the risk of developing lung cancer with smoking in some people.
- You also inform your patient that scientists have not identified all the genes involved, and that we cannot definitively measure the risk of developing lung cancer with the data available at this time.
- You emphasize that, given what is known at this time, results from genetic testing would not accurately estimate the risk she has of developing lung cancer.
- You suggest that it would be much more cost-effective for her to quit smoking rather than taking genetic tests.

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Toxicogenomics and Medication Toxicity

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Patient Case 3

- A 6-year old girl was found by her parents, barely breathing in her bed. The patient was rushed to the emergency department. A medical history was taken from the parents and a toxicology screen was ordered.
- The parents stated the child was being treated for a cold with a bad cough that was keeping her up at night. She had been prescribed cough syrup with codeine.
- A comprehensive toxicology analysis that was subsequently performed identified codeine at expected therapeutic concentrations but with morphine at substantially elevated concentrations in her serum.

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Patient Case 3

- Upon investigation, it was found the parents had been giving the cough suppressant as prescribed.
- Describe what you suspect is happening to cause this child to have respiratory depression. State what test you would request to confirm your suspicion of what is happening with this patient.

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Medication Toxicity

- Many medications on the US market have information in their drug labeling discussing the significance of genetic polymorphisms and their association with adverse effects (US FDA 2011).
- These medications include, but are not limited to
 - Abacavir
 - Azathioprine/Mercaptopurine
 - Carbamazepine
 - Irinotecan
- Polymorphisms have been identified that significantly increase the risk of severe adverse effects with the use of these medications.

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Medication Toxicity

Medication	Genetic Variant	Adverse Effect	Reference
Abacavir	<i>HLA-B*5701</i>	Hypersensitivity	GlaxoSmithKline 2008, Mallal et al 2002
Azathioprine/ mercaptopurine	TMPT-low activity variants	Myelosuppression	Prometheus Laboratories 2011, Eichelbaum et al 2006
Carbamazepine	<i>HLA-B*1502</i>	Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis	Novartis 2010
Irinotecan	<i>UGT1A1*28</i>	neutropenia	Innocenti et al 2004, Marcuello et al 2004

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- ### Medication Toxicity
- Genetic testing to determine care in a suspected overdose situation is not currently routine.
 - Forensics investigators can, in some cases, utilize patient genotype data to understand cases of **acute** toxicity (Ferreiros et al 2009, Brandolese et al 2001).
 - A few cases of **chronic** drug administration that resulted in toxicity in the presence of genetic polymorphisms have been reported (Swanson et al 1997).
 - *CYP2D6* polymorphisms are often cited in the literature as possible causes of acute and chronic toxicity.
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- ### Medication Toxicity
- Forensic investigations have revealed discrepancies between a patient’s phenotype and genotype following drug toxicity (Bailey et al 2000).
 - Postmortem drug blood concentrations may differ from antemortem blood concentrations because of postmortem drug redistribution. This explains the discrepancy between genotype and phenotype. (Kennedy 2010).
 - Drug interactions in the presence of activating mutations in drug-metabolizing enzymes may cause patients to appear to be poor metabolizers (Druid et al 1999, Zackrisson et al 2004).
 - These discrepancies may impact the conclusions made in a forensics investigation.
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- ### Patient Case 3 Summary
- You suspect this patient has multiple functional copies of the *CYP2D6* gene and is therefore an ultra-rapid metabolizer. This genotype would cause codeine to be bioactivated to morphine faster than normal, leading to an elevated level of morphine capable of causing respiratory depression.
 - You request the patient’s *CYP2D6* genotype status be determined.
 - The genotype results indicate this patient is homozygous for the *CYP2D6* ultra-rapid genotype.
 - You suggest that administration of codeine in this patient be restricted and only administered under careful supervision.
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Emerging Areas in Toxicogenomics

- Efforts are being made to apply genomics data in emergency medicine practice.
 - Providers hope to use genomics information to diagnose emergent conditions in emergency medicine. (Kaji et al 2009). This may aid in diagnosing symptoms caused by adverse exposures.
- Efforts are being made to use genomics information to improve drug safety in children.
 - A national surveillance system has been established in Canada to improve drug safety in children by gathering genomic biomarkers of drug toxicity. Investigators at the University of British Columbia have established the Genotype-specific Approaches to Therapy in Childhood (GATC) adverse drug reaction network. (Carleton et al 2009).

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**END OF CONTENT
SECTION**

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PharmGenEd™ Training for Health Professional Schools

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Post-training Survey

- For participants

<https://kuooffice.wufoo.com/forms/pharmgeneda-toxicogenomics/>

- For faculty trainers

<https://kuooffice.wufoo.com/forms/pharmgeneda-toxicogenomics-trainers/>

- Evaluate knowledge, attitudes, and self-efficacy

Question and Answer Session