Consistency and mechanistic implications of genomic risk prediction studies for cancer regimen-related mucosal injury: A systematic review

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Disclosure

- I disclose no conflict of interest.

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Introduction

- What is the role of genomics in assessing individual risk?
  - Early studies focused on chemotherapy drug-metabolizing enzyme deficiencies (<5% incidence)
  - Emphasis has shifted to pathogenesis-related genomic investigations

Objectives

- To search the literature for publications assessing genomic variables in mucositis risk
- To evaluate the concordance of genes which may predict oral or GI mucositis risk between candidate gene (CGS) and GWAS studies and to validate their functional relevance
- To assess the feasibility of final common pathways for shared phenotypes using IBS with diarrhea as a model

Methods: Literature Review

PubMed Search combinations of:

- Mucositis
- Enteritis
- Toxicity
- Radiation
- Chemotherapy
- Gene
- Genetics
- Genomics
- SNPs
- Genome-wide association study (GWAS)
- Head and neck cancer

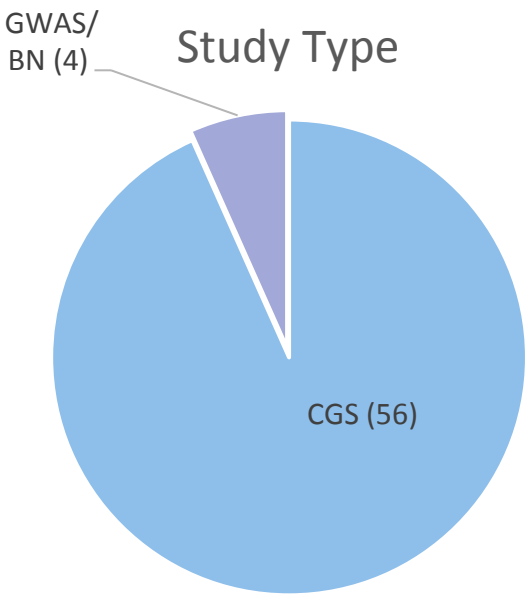
1,383 papers → **57 papers** → **60 papers**

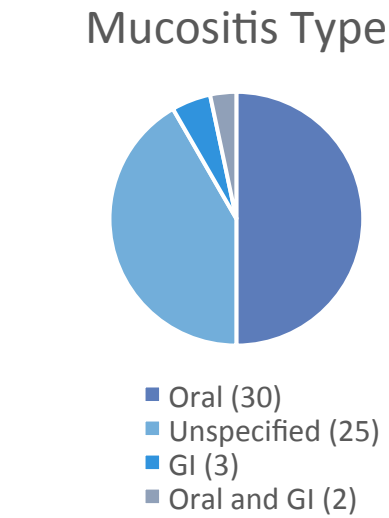
Exclude:

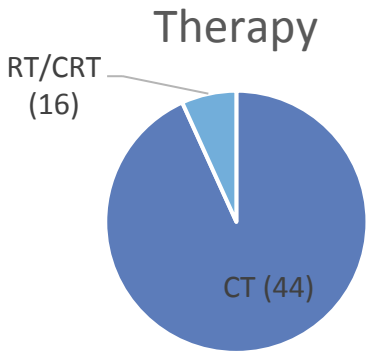
- Duplicate studies
- Non-English studies
- Non-human studies
- Case reports, meta-analyses, reviews
- Letters to the editor
- Non-genomic association studies
- Irrelevant phenotype
- Mucositis/enteritis not investigated as independent outcomes
- Allogeneic bone marrow transplant studies

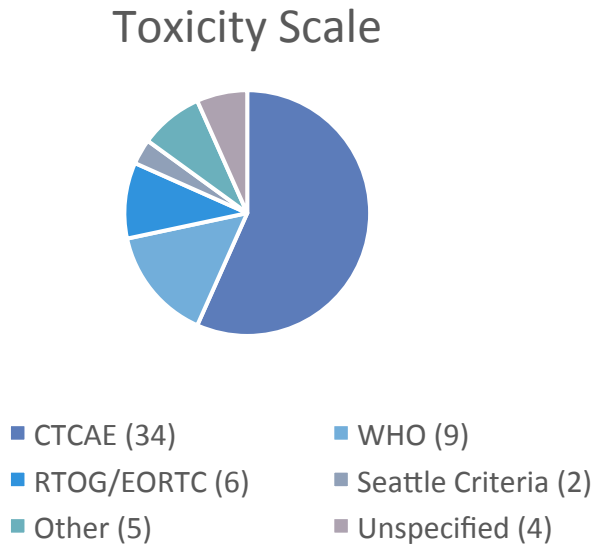
3 papers added from **review of references**

Results


Study Type
GWAS/
BN (4)
CGS (56)


Mucositis Type
Oral (30)
Unspecified (25)
GI (3)
Oral and GI (2)

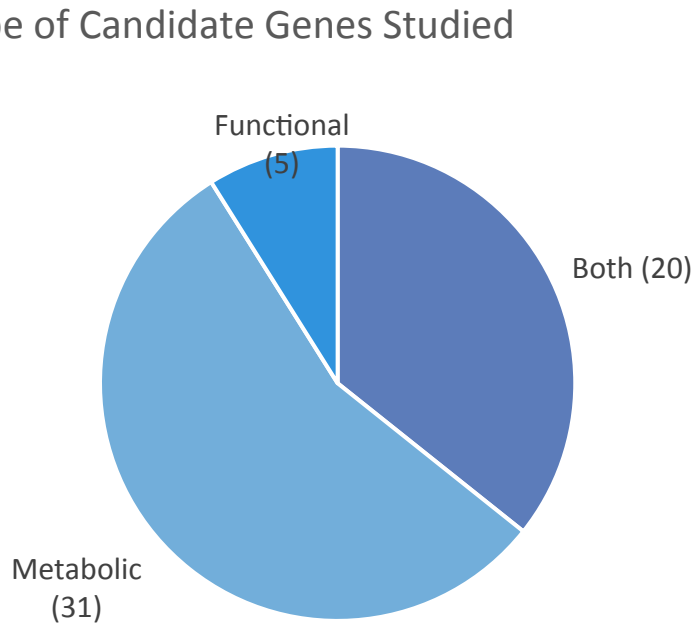

Therapy
RT/CRT
(16)
CT (44)


Toxicity Scale
CTCAE (34)
WHO (9)
RTOG/EORTC (6)
Seattle Criteria (2)
Other (5)
Unspecified (4)

Results: Candidate Gene Studies

Gene Symbol	Gene Name
ABCB1	ATP Binding Cassette Subfamily B Member 1
ABCC2	ATP Binding Cassette Subfamily C Member 2
ABCC4	ATP Binding Cassette Subfamily C Member 4
APC	APC, WNT Signaling Pathway Regulator
BRCA1	BRCA1, DNA Repair Associated
CAT	Catalase
CCND1	Cyclin D1
CDKN1A	Cyclin Dependent Kinase Inhibitor 1A
CNOT1	CCR4-NOT Transcription Complex Subunit 1
CYP1A1	Cytochrome P450 Family 1 Subfamily A Member 1
DCK	Deoxycytidine Kinase
DPYD	Dihydropyrimidine Dehydrogenase
DPYS	Dihydropyrimidinase
EDN1	Endothelin 1
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
ERCC1	ERCC Excision Repair 1, Endonuclease Non-Catalytic Subunit
GSTM1	Glutathione S-Transferase Mu 1
GSTP1	Glutathione S-Transferase Pi 1
GSTT1	Glutathione S-Transferase Theta 1
KDR	Kinase Insert Domain Receptor
MIR1206	MicroRNA 1206
MIR2053	MicroRNA 2053
MTHFR	Methylenetetrahydrofolate Reductase
NBN	Nibrin
NOD2	Nucleotide Binding Oligomerization Domain Containing 2
RAD51	RAD51 Recombinase
RB1	RB Transcriptional Corepressor 1
SLC19A1	Solute Carrier Family 19 Member 1
SLCO1B1	Solute Carrier Organic Anion Transporter Family Member 1B1
TGFB1	Transforming Growth Factor Beta 1
TNF	Tumor Necrosis Factor
TNFRSF1A	TNF Receptor Superfamily Member 1A
TYMS	Thymidylate Synthetase
UPB1	Beta-Ureidopropionase 1
XRCC1	X-Ray Repair Cross Complementing 1
XRCC3	X-Ray Repair Cross Complementing 3
XRCC6	X-Ray Repair Cross Complementing 6

38 genes found to have an association with mucositis/enteritis in candidate gene studies



Results

- CGS identified 38 genes associated with mucositis
- GWAS studies identified 400 SNPs mapped to 222 genes
  - Gene attribution methods variable
- **No overlap** between genes identified in GWAS/BN studies and CGS

Conclusion 1

- Studies investigating the genomic variables contributing to mucositis risk are largely **heterogeneous** in design, methods, and results
- Most studies are **CGS**
- There is **no concordance** between genes found to be associated with mucositis in CGS and GWAS/BN studies

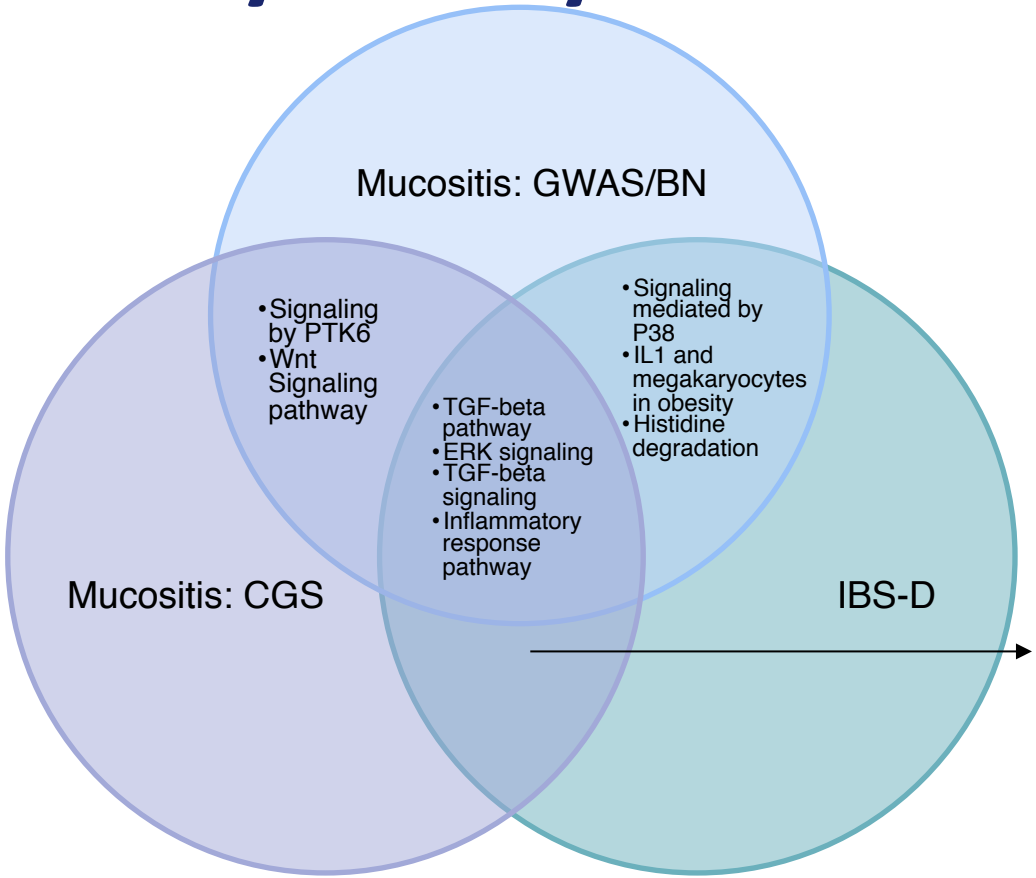
Pathways Analysis

- Although there is little concordance between genes identified among different types of mucositis studies, is there concordance in genomically-derived **biological pathways**?
- Is there overlap among pathways derived from genes associated with mucositis, and those associated with a **similar phenotype** (IBS- diarrhea)?

Pathways Analysis: Methods

- Used GeneAnalytics to identify biological pathways associated with identified gene sets:
  - Mucositis– candidate gene
  - Mucositis– GWAS/BN
  - IBS-diarrhea (Camilleri et al 2016)

Pathways Analysis: Results



- Akt signaling
- NF-kappaB family pathway
- Toll-like receptor signaling pathway
- PEDF induced signaling
- Colorectal cancer metastasis
- Cytokine signaling in immune system
- MAPK signaling/pathway
- CDK-mediated phosphorylation and removal of Cdc6
- Adhesion
- Innate immune system
- PAK pathway
- IL-2 pathway
- TNF signaling pathway
- DNA damage response (only ATM dependent)
- Hepatitis C and hepatocellular carcinoma
- IL-15 signaling pathways and their primary biological effects in different Immune cell types
- P53 signaling/pathway
- Blood-brain barrier and immune cell transmigration
- G-protein signaling: RAS regulation pathway
- Tuberculosis
- Apoptotic pathways in synovial fibroblasts
- Aryl hydrocarbon receptor pathway
- GPCR pathway/signaling
- Lung fibrosis

Conclusion 2

- Although there was no overlap among genes identified by genome-wide and candidate gene approaches in the literature, pathways analyses based on these genes revealed common underlying processes.
- The overlap in genomically-derived pathways observed in mucositis and IBS-D suggests common **pathobiology is also associated with similar clinical phenotypes.**

Thank you

- Questions?
- Contact: petra_bachour@hsdm.harvard.edu

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Future Directions

- Well-controlled, prospective studies are needed to better understand genomic variables in mucositis risk
  - Genome-wide approaches
  - Learning and validation cohorts
- Comparison of diseases with shared phenotypes or common underlying biological pathways could lead to the identification of unknown underlying genes