



Newsletter

Genetic Determinants of Barrett's Esophagus and
Esophageal Adenocarcinoma
2U54CA163060

Volume 1, Issue 1



Left to Right: Apoorva Chandar, MBBS; Nancy Furey, RN; Wendy Brock, RN; Guptha Baskaran, RN

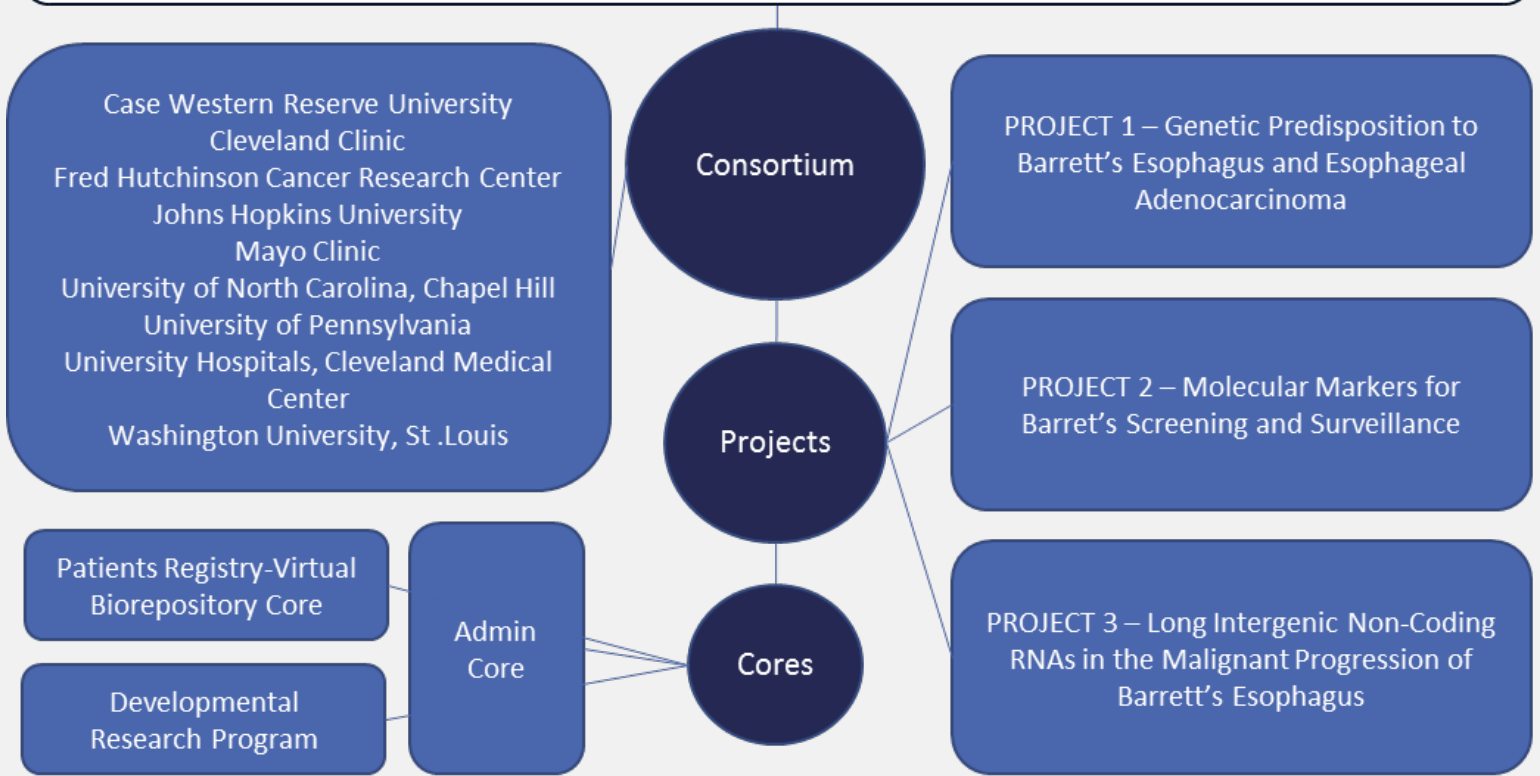
WELCOME

Welcome to Volume 1, Issue 1 of Case BETRNet Newsletter. We intend to publish this newsletter on a quarterly basis to ensure strong communication between all of our sites.

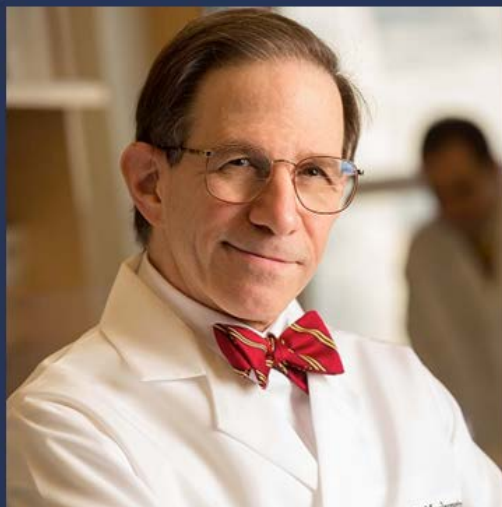
Going forward, expect to see recruitment updates for each site, updates about our site investigators and staff, new publications, progress reporting needs, etc. If you have information you wish to see published in our newsletter, please contact Alicia DePlatchett at BETRNetAdmin@case.edu or 216-368-1674.

WHO WE ARE

This BETRNet Research Center focuses on genetic, molecular, and epigenetic studies that will develop better methods of detecting BE, predicting its progression to EAC, and preventing BE from progressing to EAC.



Outstanding Investigator



Congratulations are in order for Dr. Sanford Markowitz, recipient of NIH/NCI’s prestigious R35 Outstanding Investigator Award. Dr. Sanford Markowitz’s laboratory has been recognized for making multiple landmark discoveries in the genetics of GI cancers.

Based on the R35 award, Dr. Markowitz has stepped down as Co-Principal Investigator on this U54, but will continue to function in all of his project-specific roles for our Research Center.



The BETRNet2 Retreat

October 12 – 13, 2017 // Highlights


Manuscript preparation under way in the form of a meeting report that will highlight the scientific accomplishments of BETRNet.

BETRNet has launched a new webinar series held bi-monthly on the third Monday of the month beginning at 5pm ET/4pm CT/2pm PT. The next webinar is scheduled for **Monday, November 20th** and will feature Dr. Aaron Thrift from the Baylor College of Medicine. A speaker is lined-up for January but suggestions for speakers for 2018 are needed from the RCs. The webinars are open to all centers' investigators and participation in the webinars is strongly encouraged.

PR-VB Core Working Group including Joseph Willis, MD, from our Research Center, has been formed to work with the CC to review the PR-VB and its content, current data collection practices, and data sharing processes and provide recommendations to improve the resource

Annual BETRNet Steering Committee Meeting Schedule

2018: Columbia-Penn-Mayo
2019: Michigan
2020: Cleveland



Balloon Devices should be ready for shipment by December.

The Case BETRNet Website is LIVE

<https://case.edu/medicine/dhri/betrnet/>

Recent Publications

A nonrandomized trial of vitamin D supplementation for Barrett's esophagus.

Background

Vitamin D deficiency may increase esophageal cancer risk. Vitamin D affects genes regulating proliferation, apoptosis, and differentiation and induces the tumor suppressor 15-hydroxyprostaglandin dehydrogenase (PGDH) in other cancers. This nonrandomized interventional study assessed effects of vitamin D supplementation in Barrett's esophagus (BE). We hypothesized that vitamin D supplementation may have beneficial effects on gene expression including 15-PGDH in BE.

Methods

BE subjects with low grade or no dysplasia received vitamin D3 (cholecalciferol) 50,000 international units weekly plus a proton pump inhibitor for 12 weeks. Esophageal biopsies from normal plus metaplastic BE epithelium and blood samples were obtained before and after vitamin D supplementation. Serum 25-hydroxyvitamin D was measured to characterize vitamin D status. Esophageal gene expression was assessed using microarrays.

Results

18 study subjects were evaluated. The baseline mean serum 25-hydroxyvitamin D level was 27 ng/mL (normal ≥ 30 ng/mL). After vitamin D supplementation, 25-hydroxyvitamin D levels rose significantly (median increase of 31.6 ng/mL, $p < 0.001$). There were no significant changes in gene expression from esophageal squamous or Barrett's epithelium including 15-PGDH after supplementation.

Conclusion

BE subjects were vitamin D insufficient. Despite improved vitamin D status with supplementation, no significant alterations in gene expression profiles were noted. If vitamin D supplementation benefits BE, a longer duration or higher dose of supplementation may be needed.

Cummings LC, Thota PN, Willis JE, Chen Y, Cooper GS, Furey N, Bednarchik B, Alashkar BM, Dumot J, Faulx AL, Fink SP, Kresak AM, Abusneineh B, Barnholtz-Sloan J, Leahy P, Veigl ML, Chak A, Markowitz SD. A nonrandomized trial of vitamin D supplementation for Barrett's esophagus. PLoS One. 2017 Sep 18;12(9):e0184928. doi: 10.1371/journal.pone.0184928. eCollection 2017. PubMed PMID: 28922414; PubMed Central PMCID: PMC5602627.



Genomic regions associated with susceptibility to Barrett's esophagus and esophageal adenocarcinoma in African Americans: The cross BETRNet admixture study.

Background

Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) are far more prevalent in European Americans than in African Americans. Hypothesizing that this racial disparity in prevalence might represent a genetic susceptibility, we used an admixture mapping approach to interrogate disease association with genomic differences between European and African ancestry.

Methods

Formalin fixed paraffin embedded samples were identified from 54 African Americans with BE or EAC through review of surgical pathology databases at participating Barrett's Esophagus Translational Research Network (BETRNet) institutions. DNA was extracted from normal tissue, and genotyped on the Illumina OmniQuad SNP chip. Case-only admixture mapping analysis was performed on the data from both all 54 cases and also on a subset of 28 cases with high genotyping quality. Haplotype phases were inferred with Beagle 3.3.2, and local African and European ancestries were inferred with SABER plus. Disease association was tested by estimating and testing excess European ancestry and contrasting it to excess African ancestry.

Results

Both datasets, the 54 cases and the 28 cases, identified two admixture regions. An association of excess European ancestry on chromosome 11p reached a 5% genome-wide significance threshold, corresponding to $-\log_{10}(P) = 4.28$. A second peak on chromosome 8q reached $-\log_{10}(P) = 2.73$. The converse analysis examining excess African ancestry found no genetic regions with significant excess African ancestry associated with BE and EAC. On average, the regions on chromosomes 8q and 11p showed excess European ancestry of 15% and 20%, respectively.

Conclusion

Chromosomal regions on 11p15 and 8q22-24 are associated with excess European ancestry in African Americans with BE and EAC. Because GWAS have not reported any variants in these two regions, low frequency and/or rare disease associated variants that confer susceptibility to developing BE and EAC may be driving the observed European ancestry association evidence.

Sun X, Chandar AK, Canto MI, Thota PN, Brock M, Shaheen NJ, Beer DG, Wang JS, Falk GW, Iyer PG, Abrams JA, Venkat-Ramani M, Veigl M, Miron A, Willis J, Patil DT, Nalbantoglu I, Guda K, Markowitz SD, Zhu X, Elston R, Chak A. Genomic regions associated with susceptibility to Barrett's esophagus and esophageal adenocarcinoma in African Americans: The cross BETRNet admixture study. PLoS One. 2017 Oct 26;12(10):e0184962. doi: 10.1371/journal.pone.0184962. eCollection 2017. PubMed PMID: 29073141.

NEWS FROM OUR RESEARCH CENTER SITES

Exosomal microRNAs to predict colorectal cancer recurrence

The Grady Lab, FHCRC

Podcast:

Health beyond barriers: Why should you be screened for colon cancer?

Jean S. Wang, MD, WUSTL

BI-MONTHLY SITE RECRUITMENT GOALS

4 EGD
screening



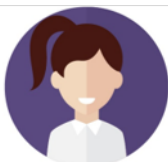
4 Colon
screening



1 Case



Share your recent publications, site news, etc., for inclusion in our next newsletter!



Questions? Comments? Have a suggestion for featured news?

Contact us

✉ BETRNetAdmin@case.edu

☎ 216-368-1674

REQUEST FOR PILOT PROJECT PROPOSALS

Barrett's Esophagus Translational Research Network (BETRNet)

DEADLINE: JANUARY 31, 2018 at 11:59 PM

All faculty members at participating institutions are invited to submit applications for Individual or Cross-BETRNet pilot projects of up to \$40,000 to be funded by NIH/NCI U54CA163060: *Genetic Determinants of Barrett's Esophagus and Esophageal Adenocarcinoma*. Deadline for submission is **January 31, 2018 at 11:59 PM**, with funding expected to begin **May 1, 2018**.

Proposals must conform to the following guidelines and must be submitted via Webgrants*:

1. Cover page listing contact information for PI and faculty collaborators
2. Proposal (5 pages) in length (excluding references) as follows:
 - Specific aims (1 page)
 - Background and Significance (1-2 pages)
 - Experimental Design (2-3 pages)
3. NIH biosketches for all faculty participants
4. Detailed Budget & Justification

Note: A BETRNet Project **must be directed toward translational research** related to Barrett's Esophagus. At least one specific aim should involve either direct patient contact or the study of patient derived tissue samples.

More information on the Case Comprehensive Cancer Center: <http://cancer.case.edu>.

More information on BETRNet available at <http://cancer.case.edu/research/initiatives/betrnet/>.

More information on grant application available at <http://webgrants.case.edu> or through emailing BETRNetAdmin@case.edu, or calling 216-368-1674.

*Applications must be submitted through Webgrants (<http://webgrants.case.edu>) by **January 31, 2018 at 11:59 PM**.

