



**INTERNATIONAL GENETIC  
EPIDEMIOLOGY SOCIETY**

## **Save The Date: Friday, April 10, 2026**

**11 am (EDT), 8 am (PDT) and 5 pm (CEST)**

Dear IGES members,

IGES hosts regular virtual journal clubs throughout the year to increase IGES members' familiarity with emerging and classic literature in genetic epidemiology and to foster discussion and networking among members. This month's journal club discusses RAVA-FIRST, a functionally informed rare variant association framework that defines whole-genome testing units using CADD-based regions, applies region-specific filtering, and performs a burden test that incorporates genomic categories to improve rare variant discovery beyond coding regions. Validated through simulations and real datasets, the method, implemented in the Ravages R package, offers a more interpretable and computationally efficient alternative for analyzing rare variants across the entire genome. Make plans to attend our next meeting!

**Title: “Making the most of whole-genome sequencing data for rare variant association tests” (*PLoS Genet.* 2022;18(9):e1009923. Published 2022 Sep 16.)**

**Article: <https://doi.org/10.1371/journal.pgen.1009923>**

**Abstract (adapted from the original abstract):**

Rare variant association tests (RVAT) are essential for studying the contribution of rare variants to complex traits, which often lack statistical power in genome-wide association studies. While high-throughput sequencing technologies have made whole-genome data widely accessible, RVAT are typically limited to coding regions, leaving much of the genome unexplored. This limitation stems from the need to aggregate and filter rare variants into testing units, a process that is straightforward in exomes (using genes as natural units and

filtering based on consequences of variants on proteins) but challenging in non-coding regions. Existing solutions, such as the STAAR pipeline, use sliding windows and multiple annotations, but can be computationally intensive and difficult to interpret. To address these challenges, we developed RAVA-FIRST (RAre Variant Association using Functionally-InfoRmed Steps), a three-step approach based on: (1) defining whole-genome testing units based on functionally-adjusted CADD scores from gnomAD ("CADD regions"); (2) applying region-dependent filtering to retain rare variants representing functional variation tolerated in the general population; (3) implementing a functionally-informed burden test that considers genomic categories within CADD regions. We validated RAVA-FIRST using simulations and real-world datasets. The method is freely available in the R package Ravages. The RAVA-FIRST strategy, its recent update supporting build 38, and future directions and enhancements will be presented.

**Registration Link:**

[https://msm-edu.zoom.us/meeting/register/cpbTEEjaT9mzLys6Q\\_fhGw](https://msm-edu.zoom.us/meeting/register/cpbTEEjaT9mzLys6Q_fhGw)

After registering, you will receive a confirmation email containing information about joining the meeting.

**Bio:**

Ozvan Bocher is an Assistant Professor at the Université de Bretagne Occidentale (Brest, France), where she leads research at the intersection of statistical genetics and omics analyses. After earning her PhD in genetic epidemiology in 2021, she pursued post-doctoral training at the Institute of Translational Genomics (Helmholtz Munich) with Eleftheria Zeggini, focusing on large-scale genetic and omics analyses, particularly in type 2 diabetes and its comorbidities. Since late 2024, her work in Brest is centered on developing statistical methods to bridge genetics, and omics data, with a particular emphasis on characterization of the microbiome in population-based cohorts.

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Do you have any suggestions for interesting topics, papers, or presenters for further talks? Or would you like to support us in organizing the Journal Club? Please contact Dr. Silke Szymczak ([silke.szymczak@uni-luebeck.de](mailto:silke.szymczak@uni-luebeck.de))

On behalf of the organizing team of the IGES Journal Club,

Silke Szymczak

Heejong Sung

Cheryl Cropp

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