

**MARDI  
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COLLOQUE**

**HEURE:** 12H15-13H15

**LIEU:** AUDITOIRE A, GÉNOPODE, UNIL (SITE DORIGNY)

& via Lien à distance

## **Evolutionary and functional perspective on human polygenic traits**

### **SPEAKER**

■ Prof. Shamil Sunyaev, Harvard Medical School, Boston

### **ABSTRACT**

Human complex traits, including common diseases, are highly polygenic. Almost universally, the genetic component of the traits is governed by myriads of common non-coding variants of individually small effects with the minor contribution of rare coding variants of larger effect sizes. It is unclear how the balance of evolutionary forces maintains stable variation in complex traits in the human population. The mechanistic biology underlying the phenotypic variation is equally mostly unknown. We tested existing theoretical models of population genetics using massive GWAS datasets. We relied on two statistics: first, on the joint distribution of risk allele frequency and effect sizes; second, on effect size correlations between proximal variants. Surprisingly, our analysis supports the models of stabilizing selection favoring intermediate values of genetic liability even for disease phenotypes. This analysis also generates specific hypothesis regarding the density and directions of phenotypically important mutations. To bridge human genetics and mechanistic biology, we developed a network-level rare variant test that uses results of functional screens as an input. This new method called NERINE increases power of association testing and simultaneously allows selecting the most informative experimental assays. NERINE has been applied to neurological and cardiovascular phenotypes.

Recommandé par la Société Suisse des Spécialistes en prévention et santé publique (SPHD) pour la reconnaissance de la formation continue.

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