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Prediction of Individual Phenotypes and Polygenic Risk

Stanford researchers have developed a technology to better understand the effects of rare genetic variants on an individual's common disease risk. In particular, the researchers focus on rare variants which are highly challenging to interpret using traditional genetic methods such as GWAS, but are still predicted to have relatively large effects on disease phenotypes.

The technology ("IOGC") builds on recent findings showing that rare variants linked to molecular outliers (e.g. gene expression, splicing) are enriched for large effects on downstream disease risk. As a proof-of-concept, IOGC applied to predicting individual risk for severe obesity showed that a burden of rare variants linked to molecular outliers is associated with deviation from predicted disease risk. Individuals with extreme IOGC had a younger age of onset of clinical obesity, high blood pressure (~2.5 years), and diabetes (~4 years). These effects are independent of those captured by current polygenic risk scores (PRS), with joint modeling of PRS + IOGC resulting in more accurate disease risk classification across multiple polygenic traits.

This technology is the first to provide individual disease risk assessment by integrating the additive effects of rare, large-effect variants linked to molecular expression outliers. There are important implications of this technology in the clinical deployment of current disease PRS, gene therapies, and drug discovery.

Applications

- Clinical diagnosis of disease risk
- Direct-to-consumer genetic testing for disease risk
- Stratification of patients for treatment regimens

- Reduced search space for experimental validation of combinatorial gene targets with combined large phenotypic effects
- Identification of novel genetic targets for drug discovery, particularly gene therapies

Advantages

- Identification of rare variants with larger effects than GWAS common variants allows for powerful modeling of gene regulatory effects on disease phenotypes
- Approach can utilize multiple forms of genetic variation, e.g. SNPs, short indels, SVs
- Approach can utilize multiple molecular outlier data, e.g. gene expression, splicing, protein level

Patents

- Published Application: 20210142911
- Published Application: 20240301378

Innovators

- Stephen Montgomery
- Craig Smail

Licensing Contact

Sam Rubin

Licensing Associate, Life Science

Email