Genetics and Bioinformatics

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Individuals with common diseases but with a low polygenic risk score could be prioritized for rare variant screening

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Individuals with common diseases but with a low polygenic risk score could be prioritized for rare variant screening

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Dissect the title to know what the paper is about …

together with the abstract should give a fairly good idea about the aims and goals of the paper: **prioritization of individuals**

- **Common disease**
- **Polygenic risk score**
- **Rare variant screening of individuals**

What do you know about these dissected elements in general; Look for these terms in the paper to check whether definitions, contexts, explanations are given; When insufficient, browse the www!

A study is always carried out in a particular context …

the introduction will give clues about this and refine the aims and goals of the study; what to expect from this work

- Sometimes common diseases can be due to rare variants and may impact clinical care
- Looking for these rare variants is not common place due to several reasons
- Cost-effective method? Polygenic risk scores? → hypothesis of the paper

"individuals with a low polygenic risk for common disease

are more likely to harbor rare genetic variants than individuals without a low polygenic risk"

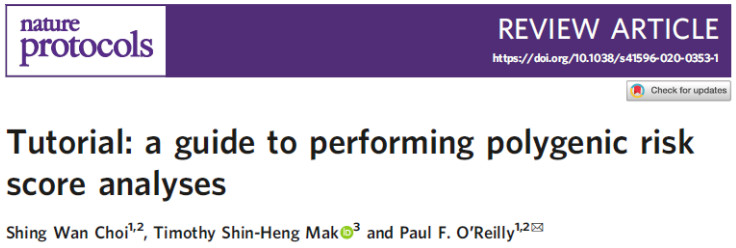
Methods

- Data & motivation (use)
  - Samples / case individuals
    - White British ancestry: focus
    - Non-white British ancestry: why? Validation? → transferrability (new addition) /generalizability
    - Which case status? Why looking at multiple diseases? multiple?
  - Panels of variants
    - Common: why needed? → PRS scoring
    - Rare: why needed? → these you want to discover with the PRS

Methods

- Where to look for rare variants?
  - When affecting the clinically actionable or disease causing genes
  - What does “affect” mean? Strong? Weak? → extra QC is needed to reduce “false positives”
- How to construct PRS?
  - Several methods were used depending on the disease? Why?

    → <u>what is common practice in the literature</u>



How to use this info to test our hypothesis?

- Relation between prevalence rare variants and disease prevalence
- Relation between higher PRS and higher risk for disease
- Relation between the distribution (and its properties) of PRS in heterozygotes of rare pathogenic variants and non-heterozygotes
- Relation between rare/common variants to augment disease risk

- Relation between low/high PRS in cases and prevalence of rare pathogenic variants → clear link with the hypothesis. What about the other analyses (previous bullet points)? → needs to be checked in the discussion

Results - Discussion

- Follow the flow of the previous bullet points
- Brief report on results
- Understand the results
  - Dig up the relevant parts in the discussion section
  - Follow up one of the results in more depth by consulting extra references or www (indicate which parts you have been digging out)
- Check in the discussion section whether the multiple results (all bullet points) are related to each other
- and jointly contribute to the preset aims/goals (here: a single hypothesis) via discussion/conclusion

Questions?