Novel loci discovery for Blood Pressure and Heart Rate using the Exome Chip

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Abstract

Introduction

Genome-wide association studies for many cardiovascular traits have primarily identified common variants with small effects, explaining only a small percentage of the total trait variance. The missing heritability may in part be explained by rare variants.

Methods

The Exome chip includes ~250,000 rare, low-frequency and common variants, thus enables the investigation of rare variant associations.

Within large international consortia, we have led Exome chip analyses for blood pressure (BP) and heart rate (HR) in a total of ~350,000 and ~240,000 individuals, respectively.

Results

We identified 31 novel genetic regions associated with BP or hypertension, including rare missense variants in *RMB47*, *COL21A1* and *RRAS* with larger effects on BP than reported common variants, and *A2ML1*, a gene containing multiple rare variant associations. A novel low-frequency nonsense variant was identified in ENPEP, which encodes the APA enzyme of the renin-angiotensin-aldosterone system. ENPEP is a therapeutic target, and an ENPEP inhibitor is currently being tested in Phase IIa clinical trials for hypertension.

For HR we identified nine novel loci, and new independent associations at some of the 21 published loci.

Conclusions

We have discovered 40 new loci for BP or HR. Of potential interest is an overlap between genetic associations for BP and HR. One novel BP locus, MYH6, is a published association for HR. Furthermore, analyses of BP and HR each identified RNF207 as a novel locus, which is a published association for QT interval. This suggests there may be some similarities in underlying biological mechanisms, and may inform therapeutic strategies.

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