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原发性高血压全基因组关联研究进展

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摘要 原发性高血压是一种由遗传与环境因素共同导致的复杂疾病, 具有高度的遗传异质性。自2007年首个高血压全基因组关联研究(Genome-wide association studies , GWAS)报道以来, 许多GWAS相继开展。文章首先对2007年1月至2011年9月期间报道的24篇血压/高血压易感基因的GWAS按人种与染色体位置对其结果进行汇总, 经统计位点rs17249754、rs1378942和rs11191548报道频数最多。其次介绍了GWAS方法学的研究进展, 包括选择高质量的数量表型和选择多阶段研究设计来增加研究发现阳性关联的机会。统计分析方面, 除强调了已经报道过的多重比较和重复(验证)研究等问题外, 文章还介绍了通过Meta分析对GWAS数据进行深度发掘, 并应用基因型填补法对缺失数据进行填补可以提高全基因组遗传标记的覆盖率的方法。尽管GWAS发现了许多我们未知的基因与疾病表型的关联, 为了解高血压的发病机制提供了更多线索, 但是目前GWAS发现的血压/高血压相关变异多为对人群血压的影响极其微弱的常见变异。因此今后的研究中可加强深度功能学研究对易感基因精细定位和外显子组测序技术的应用, 结合GWAS的成果进行生物信息学通路分析和表观遗传学机制研究等, 逐步揭示高血压的遗传机制。

关键词: 原发性高血压 血压 全基因组关联研究 易感基因

Abstract: Since the first genome-wide association study was reported in 2007, hypertension has attracted numerous studies to identify its genetic basis. The first part of the current review summarizes the genetic loci associated with blood pressure/ hypertension identified by genome-wide association studies (GWAS) from January 2007 to September 2011, by race and chromosomal location. In the second part, we stress several important points in GWAS methodology, for example, selecting high-quality phenotypes and using multi-stage study design to increase the power studies to identify loci with minor effect. For statistical analysis, besides multiple testing correction and replication of the GWAS that have been introduced in previous reviews, computer-based genotype imputation has been described for its advantages in compensating GWAS genotyping failures. Although GWAS identifies many unknown genetic variants and improves our understanding for the pathogenesis of hypertension, the loci related to blood pressure / hypertension are common sequence variations with minor effect. The association studies are difficult to be replicated in different populations. Further studies are expected including extensive functional studies and fine mapping using advanced techniques, such as whole genome exon sequencing and pathway analysis, as well as epigenetic study to elucidate the etiology of human essential hypertension.

Keywords: essential hypertension, blood pressure, genome-wide association study, susceptibility gene

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