

人类身高的遗传学研究进展

陈开旭¹, 王为兰¹, 张富春¹, 郑秀芬^{1,2,3}

1. 新疆大学生命科学与技术学院, 新疆生物资源基因工程重点实验室, 乌鲁木齐 830046;
2. 加拿大西安大略大学病理科, 伦敦, N6A5A5;
3. 加拿大劳森健康研究所, 伦敦, N6A5A5

摘要: 人类身高是由环境和遗传因素共同决定的, 遗传学研究发现遗传因素对身高差异的影响更大。身高是典型的多基因遗传性状, 科研人员试图运用传统的连锁分析和关联分析寻找和发现对人类身高具有显著影响的常见 DNA 序列变异, 但进展缓慢。近年来, 随着基因分型和 DNA 测序技术的发展, 人类身高的遗传学研究取得了许多突破性进展。全基因组关联分析(GWAS)的应用, 发现和证实了上百个与人类身高相关的单核苷酸多态性位点(SNPs), 拓展了人们对人类生长和发育的相关遗传学认识, 同时也为研究人类其他复杂性状提供了理论依据和借鉴。本文综述了人类身高的遗传学研究进展, 探讨了目前该研究领域所存在的问题和未来发展方向, 以期在今后人类身高相关的遗传学研究提供参考和借鉴。

关键词: 人类身高; 连锁分析; 关联分析; 全基因组关联研究

Progress in genetic research of human height

Kaixu Chen¹, Weilan Wang¹, Fuchun Zhang¹, Xiufen Zheng^{1,2,3}

1. Key Laboratory of Biological Resources and Genetic Engineering, College of Life Science and Technology, Xinjiang University, Urumqi 830046, China;
2. Department of Pathology, Western University, London, N6A5A5, Canada;
3. Lawson Health Research Institute, London, N6A5A5, Canada

Abstract: It is well known that both environmental and genetic factors contribute to adult height variation in general population. However, heritability studies have shown that the variation in height is more affected by genetic factors. Height is a typical polygenic trait which has been studied by traditional linkage analysis and association analysis to identify common DNA sequence variation associated with height, but progress has been slow. More recently, with the development of genotyping and DNA sequencing technologies, tremendous achievements have been made in genetic research of human height. Hundreds of single nucleotide polymorphisms (SNPs) associated with human height have been identified and validated with the application of genome-wide association studies (GWAS) methodology, which deepens our understanding of the genetics of human growth and development and also provides theoretic basis and reference for studying other complex human traits. In this review, we summarize recent progress in genetic re-

收稿日期: 2015-02-13; 修回日期: 2015-04-20

基金项目: 国家自然科学基金项目(编号: 31260267), 新疆大学天山学者特聘教授科研项目(编号: 0306407)和新疆生物资源基因工程重点实验室开放课题(编号: XJDX020-2012-040080)资助

作者简介: 陈开旭, 在读博士研究生, 研究方向: 群体遗传学。E-mail: chenkaixu@126.com

通讯作者: 张富春, 教授, 博士, 研究方向: 分子生物学。E-mail: zfcxj@sina.com

郑秀芬, 教授, 博士, 研究方向: 群体遗传学。E-mail: zhengxf007@gmail.com

DOI: 10.16288/j.ycz.15-082

网络出版时间: 2015-6-4 9:25:47

URL: <http://www.cnki.net/kcms/detail/11.1913.R.20150604.0925.001.html>

search of human height and discuss problems and prospects in this research area which may provide some insights into future genetic studies of human height.

Keywords: human height; linkage analysis; association analysis; genome-wide association study

个体身高是人类最为明显的外部基本特征之一, 是一旦成年后就相对稳定并且可以准确量化的表型, 也是描述和识别个体特征的常用标记。自人类遗传学研究伊始, 遗传学家便对人类身高的遗传学机制进行了研究, 至今已有 100 多年的历史^[1]。身高是由遗传和环境因素共同决定的, 诸多遗传学研究发现, 遗传因素对身高的影响较环境因素更大。Galton^[1]和 Pearson 等^[2]研究表明, 排除环境因素, 后代的身高与父母的身高具有显著相关性, 并提出可通过父母身高来预测其后代的身高。Karlberg 等^[3]对 3650 名瑞典婴儿的身高从出生跟踪分析至 18 岁, 发现父母的身高很大程度上影响婴儿成年后的身高。许多大家系和双生子研究结果表明, 人类身高受遗传因素的影响较大, 约占 80% 以上^[4~7]。因此, 研究身高相关的遗传基因具有重大意义, 例如: 通过遗传基因分型来预测儿童将来的身高, 可帮助选育运动员; 通过对身高关联基因的基因分型推测个体的身高, 可提供现场物证 DNA 遗留者的身高等个体特征信息, 有助于司法和公共安全部门侦破案件, 打击犯罪活动, 维护社会安定; 此外, 还有助于分析治疗身高发育相关的疾病。1918 年, 在孟德尔遗传学和遗传统计学的基础上, 英国著名的遗传统计学家 Ronald A. Fisher 提出: 在某一特定人群中, 身高等数量性状在遗传表型上的差异是由许多遗传因子共同作用而产生的遗传效应, 单一遗传因子的遗传效应是十分微小的^[8]。因此, 人类身高是由多基因控制的复杂数量性状, 传统的连锁分析研究和关联分析研究具有一定的局限性, 无法从浩瀚的人类基因当中精确寻找和发现对身高具有影响的基因。近年来, 随着基因分型和 DNA 测序技术的发展, 尤其是全基因组关联分析(Genome-wide association study, GWAS)的应用, 使得人类身高的遗传学研究取得了许多突破性的成就, 但仍存在一些亟待解决的问题。因此, 本文对人类身高的遗传学研究进展进行了综述, 以期今后的相关研究提供参考和借鉴。

1 身高的遗传学特征

人类身高是由多基因控制的复杂数量性状, 其

最终发育水平取决于环境因素与遗传因素的综合作用; 而在特定的历史时期和特定的人群当中, 遗传因素则是影响身高差异的决定性因素。人类身高的遗传率(遗传因素对身高的影响程度)存在民族和地域的差异, 不同人群中身高的遗传率约为 55%~90%^[5,7], 中国汉族人群的遗传率为 64.7%^[9]。

身高是个体生命活动进程中身体生长和发育的综合结果, 身材的增高表现为骨骼长度的增加, 同时也伴随着机体组织和器官体积的相应增加。研究与人类身高相关的基因会使人们对人类的生长和发育产生新的认识及更深入地了解。调控机体生长发育关键基因的突变会导致许多生长、发育异常的疾病, 患者通常表现为生长激素缺乏、过度生长或骨骼发育不良^[10]。这类关键基因包括: 生长激素及其受体基因^[11~13], 脑垂体转录因子基因, 生长激素信号途径相关基因^[14~16], 生长板、软骨、骨骼生长和发育的相关基因^[17,18]等。但在正常健康人群中, 这类基因对个体身高差异的影响并不明显。此外研究发现, 正常范围内的身高差异与肿瘤、糖尿病、心血管疾病等多种疾病密切相关。例如: 身高较高的人患某些肿瘤的风险相对较高^[19,20]; 身高较矮的人患 2 型糖尿病和冠状动脉粥样硬化性心脏病的风险相对较高^[21,22]。因此, 人类身高差异相关基因的研究有可能为某些相关疾病的研究提供新的理论基础和研究思路。

2 人类身高的遗传学研究

2.1 连锁分析研究

最初采用连锁分析法对人类身高的相关基因进行鉴别和定位。连锁分析法的基本原理和策略是在所研究的家系中, 位于同一条染色体的两个位点在减数分裂的过程中会发生交换与重组, 重组率越低, 两个位点同时遗传给后代的机会就越多。利用分布在基因组中的遗传标记对研究家系进行基因分型, 再将遗传标记的基因分型数据与其身高数据相关联, 通过相应的数学方法计算并判断遗传标记是否与控制身高表型的基因相连锁, 从而实现对身体相

关基因的鉴别和定位。该方法是将基因定位于特定位置的一种重要手段,运用该方法发现了多个与身高表型基因紧密连锁的染色体区域^[23~27],但 Perola 等^[5]在总结大量身高位点连锁研究的结果后却发现各研究所发现的染色体区域不尽相同,且无法对与身高表型性状相连锁的基因或变异位点进行定位。在肥胖(与身高类似的多基因复杂数量性状)相关遗传位点的诸多研究中,采用全基因组连锁分析研究,确定了 300 多个与肥胖有一定相关性的染色体区域;但是在这些染色体区域内均未能成功定位出与肥胖性状连锁的基因或变异位点^[28]。这也与 Fisher^[8]的假设相一致,即在某一特定人群中,对身高、体重等数量表型性状来说,并不存在对其具有主要遗传效应的单一基因座,这些性状在遗传表型上的差异是由许多微效突变所决定的。连锁分析对于致病性高、数量少的遗传变异具有较好的适用性,但并不适合分析中效及微效突变;且连锁分析在染色体上的定位范围为 cM 级别,即百万个碱基对,其中包含成百上千个基因,因此无法对突变位点或目的基因进行精确定位^[29~31]。

2.2 关联分析研究

由于身高是由多基因控制的复杂表型数量性状,具有明显的遗传异质性。基于家系的基因组连锁分析研究在复杂性状的遗传相关性研究和复杂疾病的易感性研究中具有明显的局限性^[32~34]。另一种用于研究人类身高相关基因的方法是关联分析法,该方法能够克服连锁分析法在研究数量性状遗传模型中的缺陷,是研究人类身高相关遗传位点较为理想的一种方法^[30]。该方法研究人类身高相关遗传基因的策略是将个体的某一遗传突变和其身高数据进行关联分析,检测该遗传突变是否对身高差异具有显著性影响;如果某一突变的基因型或等位基因对身高差异具有显著的统计学相关性,则认为该遗传突变或该遗传突变附近与之相关的某一基因对身高具有一定的影响。例如对于某个 A/G 双等位基因 SNP 位点来说,在某一人群中,若携带 A 等位基因人群的平均身高与携带 G 等位基因人群的平均身高相比具有显著的统计学差异,那么则认为该位点与该人群的身高具有相关性;反之,则认为该位点与该人群的身高不具有相关性。按照关联基因检测的技术方法和检测范围的不同又可将关联分析研究分为候选

基因关联分析研究和全基因组关联研究。

2.2.1 候选基因关联分析研究

候选基因关联分析研究是根据某些基于假设、推测或有部分理论、实验依据的已知基因序列或突变位点可能与表型变异有关(如连锁分析结果或基因表达产物的功能信息等)来选定候选基因,再通过一定的检测技术比较研究对象候选基因的序列差异来确定候选基因与患病状态或数量性状间是否存在关联。由于早期测序、基因分型等技术条件的限制,加之该法能够检测的基因数量和范围十分有限,因此,即便是通过完善的实验设计及大量样本进行候选基因的关联分析,所获得的结果并不完全精确,难以确定基因与身高真实的相关性^[35~37]。近年来,随着测序和基因分型技术的快速发展,运用 SNaPshot、GoldenGate 芯片、Sequenome MassArray、SNPlex 等高效、经济的高通量测序技术以及基因分型技术,对候选基因或位点进行基因分型,在基因组制图、疾病关联分析、药物设计和应用、个体识别和亲权鉴定等诸多研究领域中都取得了良好的研究成果^[38~49]。但由于人类基因数量巨大且功能复杂,候选基因关联分析法并不适用于寻找那些生物学功能未知的数量性状基因座(Quantitative trait locus, QTL),因此需要一种更为有力的研究手段去探索和发现与身高等多基因控制的数量性状或复杂疾病相关的未知遗传基因。

2.2.2 全基因组关联分析

人类基因组中存在着数量巨大的多种遗传变异,其中绝大多数都是遗传信息和功能未知的变异。例如:单核苷酸多态性(Single nucleotide polymorphism, SNP)是最常见的人类可遗传变异,占有已知多态性的 90%以上,在人类基因组中广泛存在,平均每隔 100~300 bp 中就存在一个 SNP,其总数可达 300 万个或更多。这样数量巨大的遗传变异无法用候选基因法逐一进行检测和分析。1996 年, Risch 等^[30]首先提出了全基因组关联分析(GWAS)的概念。他认为未来人类复杂疾病的研究不再需要候选基因的预测,能够在全基因组水平检测每一个基因的变异,进行更大规模的基因检测。人类基因组计划(Human Genome Project)和基因组单倍体图谱计划(HapMap project)的完成为研究者提供了遗传多态位点(高密

度的遗传变异图谱)与特定疾病、性状风险联系的相关信息,从根本上改变了基因研究的“蓝图”,为疾病的预防、诊断和治疗提供了新的方法,为 GWAS 的应用提供了理论基础^[50]。近年来飞速发展的基因分型技术和相关统计学方法、统计分析软件的产生则为 GWAS 的应用提供了技术支持。基于 HapMap 的人类全基因组 SNPs 检测芯片问世后,研究者能够同时对每一个体的数十万到 100 万个 SNPs 进行检测^[51~53]。高效统计分析软件的出现使得海量分型数据的处理难题也迎刃而解^[54]。全基因组关联分析是在全基因组范围内利用筛选出的高密度分子遗传标记对所研究的群体进行扫描,分析扫描所得的分子遗传标记数据与表型性状之间关联关系的方法^[55]。此方法基于分子遗传标记水平,需要对高密度遗传标记进行基因分型,如 SNP、CNV 等。与以往的候选基因关联分析法策略明显不同的是:GWAS 不再需要在研究之前构建任何假设(Hypothesis free),即不需要预先依据那些尚未充分阐明的生物学基础来假设某些特定的基因或位点与疾病或表型性状之间的关联^[56]。其特点是针对全基因组范围内的遗传变异,而不再是选择候选基因或者染色体区域。全基因组关联分析可以同时检测同一座位内的多个等位基因,能够达到单基因水平,在研究广度和精度上均超过了连锁分析和候选基因分析,同时其研究结果具有较高的真实性和可靠性,可重复性强。

3 个体身高的全基因组关联研究

2005 年 *Science* 首次报道了人类年龄相关性(视网膜)黄斑变性的全基因组关联研究^[57],为复杂性状/疾病的研究开辟了全新的思路和方向,从此拉开了复杂性状/疾病全基因组关联分析研究的序幕。2007 年,哈佛大学 Broad 研究所、瑞典隆德大学(Lund)以及瑞士诺华公司(Novartis)联合开展的“糖尿病遗传学计划”(Diabetes Genetics Initiative, DGI)首次报道了约 3000 例样本的人类身高相关遗传基因的全基因组关联研究成果^[58]。但该研究结果并未发现与身高相关的 SNP 位点(全基因组显著水平 $P < 5 \times 10^{-8}$)。与此同时,英国威康信托基金病例控制协会(Wellcome Trust Case Control Consortium, WTCCC)对约 2000 例样本进行了身高的全基因组关联研究^[59,60],同样未发现与身高相关的 SNP 位点。然而将二者的研究数据合并后进行分析,在 12 号染色体高迁移率族蛋白

A2(High mobility group protein A2, *HMGA2*)基因的 3' 非翻译区发现了一个与身高显著相关的 SNP 位点(rs1042725),其相关性显著水平为 $P = 4 \times 10^{-8}$;随后扩大样本量(29 098 例样本)的验证分析结果也表明 *HMGA2* 基因的这一位点与身高具有显著的相关性^[61]。但该位点对身高的影响效应非常微小,每个 C 等位基因使平均身高增加约 0.4 cm,该位点对人群身高差异的影响为 0.3%。之后其他研究单位也通过全基因组关联研究进一步证实了 *HMGA2* 基因与身高的相关性^[62~64]。研究显示,敲除 *HMGA2* 基因的小鼠会表现出侏儒症状^[65],在染色体中 *HMGA2* 基因的易位会导致身高的过度生长^[66],包含 *HMGA2* 基因的染色体微缺失会产生多种病症,其中包括身材矮小症^[67]。因此,*HMGA2* 基因的功能可能与生长发育密切相关。2008 年,Sanna 等^[68]通过对来自芬兰和撒丁岛(意大利在地中海的一个岛)的 6669 份样本进行的全基因组关联研究和 28 801 份样本的结果验证分析,发现在生长分化因子 5(Growth/differentiation factor 5, *GDF5*)基因附近发现了 2 个与身高相关的位点(rs6060369、rs143383)。相关研究显示,*GDF5* 基因的突变会导致短指症和骨骼发育不良^[69],位点 rs143383 也与骨关节炎密切相关^[70]。因此,*GDF5* 基因的功能可能与骨骼生长相关。

受到基因 *HMGA2* 和 *GDF5* 与人类身高具有相关性这一发现的鼓舞,越来越多的研究机构致力于人类身高相关遗传基因的全基因组关联研究,并取得了丰硕的研究成果。截止到 2008 年底,共有 52 个与成人身高相关的遗传位点被相继报道^[62,71,72],但这些位点对欧洲人群身高差异的影响仅为 5%,且大多以欧洲人群为研究对象^[73]。因此,需要在更多人群和更大样本量中开展人类身高相关遗传基因的全基因组关联研究,才能发现更多与人类身高相关的遗传基因。韩国人群的全基因组关联研究以 8842 例韩国人为样本,发现了 15 个与身高相关的位点,其中发现了 8 个新位点^[74,75]。研究还表明:身高高度与高个子基因数量成正相关性,高个基因数量越多,身高越高^[75]。在日本人群的全基因组关联研究中,发现了 2 个与日本人群身高相关的新遗传位点,而其余的身高相关位点在欧洲人群中均有报道^[64,76,77]。Lei 等^[78]在中国汉族人群和欧洲人群中进行的全基因组关联研究中,首次发现了包含 *BSF2*(Set-binding factor 2)基因和 *FLNB*(Filamin B)基因的两个区域与身高具

有相关性^[78]。*ZNF510*(Zinc finger protein)和 *ZNF782* 基因的遗传区域与中国汉族人群身高相关且具有种族特异性^[79]。研究还发现除序列差异造成身高差异外, 基因拷贝数变异也与身高相关, 染色体 8p23.3-23.2 拷贝数增加(多于 2 个拷贝)越多, 个体身高越矮^[80]。

2010 年 9 月, 美国最大的人体性状遗传研究 (Genetic Investigation of ANthropometric Traits, GIANT) 协会对 183 727 例样本进行了全基因组关联研究, 发现了 180 个与身高相关的遗传位点, 这些位点对人群身高差异的影响为 10%^[81]。同时, 该研究指出: 这些与身高相关的遗传位点并不是孤立、随机的, 而是共同参与并靶向影响人类身高的某些重要功能信号途径, 从而为进一步揭示相关基因共同作用于生物信号途径来影响人类生长发育的机制指明了方向。2014 年 10 月, GIANT 研究组在之前的研究基础上, 联合超过 300 个科研机构, 对 253 288 例样本进行全基因组关联研究, 分析了约 200 万个常见基因变异, 从中筛选出了 697 个与身高相关的遗传位点(分布在 424 个基因区域), 这些位点对人群身高差异的影响为 20%^[82], 这是迄今为止在性状特征和疾病相关研究中发现的最大数目的基因。研究指出: 这 697 个与身高相关的遗传位点大多定位在生长发育相关基因和信号途径中; 同时也发现了一些新的与身高相关的基因和信号通路, 如硫酸软骨素关联基因(Chondroitin sulfate-related genes)和 *WNT/β* 连环蛋白基因。

在全基因组关联分析的推动下, 身高的遗传学研究取得了丰硕的研究成果, 相信未来随着更多研究机构的加入和研究人群的扩大及样本量的增加, 身高的全基因组关联研究会逐步深入并取得更多研究成果。

4 身高的全基因组关联研究存在的问题及未来发展方向

4.1 身高的全基因组关联研究存在的问题

虽然身高的遗传学研究在全基因组关联研究的推动下取得了丰硕的成果, 发现了许多与身高相关的 SNP, 但全基因组关联研究也存在一定的局限性。

首先, 通过统计分析遗传因素和身高的关系, 确定与身高相关联的功能性位点存在一定难度。通

过全基因组关联研究发现的许多 SNP 位点并不影响蛋白质中的氨基酸序列, 甚至许多 SNP 位点也不在蛋白编码开放阅读框(Open reading frame, ORF)内, 这对解释 SNP 位点与身高的相关性造成了一定的困难。由于身高是由多基因控制的复杂数量性状, 某些 SNP 位点可能通过影响 RNA 的转录或翻译效率, 调节相关基因的转录表达或其 RNA 剪接方式来影响身高相关基因的表达量, 从而对身高产生轻微的作用。因此, 在身高等复杂性状的遗传相关性研究中, 应同时注意到编码区和调控区位点变异的重要性^[83]。

其次, 目前通过对 253 288 例样本进行全基因组关联研究, 发现了 697 个与身高相关的遗传位点(分布在 424 个基因区域), 但这些位点仅能够解释约 20% 的身高表型变异^[82]。因此, 今后仍需要继续扩大样本量, 以便发现更多与身高相关的遗传变异位点。另外, 由于人类不同群体中可能具有不同的等位基因频率, 以及不同人群可能有着不同的连锁不平衡区域^[84], 全基因组关联研究在一个群体中发现的与身高显著相关的 SNP 位点在另外的群体中有时并不具有相关性。例如, Lei 等^[79]通过全基因组关联分析发现了 13 个与中国汉族人群身高具有显著相关性的 SNP 位点, 但在欧洲人群中这 13 个 SNP 位点与身高的相关性却不显著。而目前身高的全基因组关联研究主要集中在欧洲人群中, 因此今后有必要在其他人群中进行此类研究。

再次, 全基因组关联研究难以检测最小等位基因频率(Minor allele frequency, MAF)介于 0.5%~5% 之间的少见变异, 或者 MAF<0.5% 的罕见变异, 因为现有的基因分型芯片较难有效地发现这些遗传变异^[85,86]。发现罕见变异最为有效的方法是进行测序, 例如 Nejentsev 等^[87]通过第二代测序技术(Next-generation sequencing, NGS)发现了一个位于 *IFIH1* 基因中的罕见突变, 该突变会降低 1 型糖尿病的患病风险。高通量测序技术和第二代测序技术的发展为将来进行少见或罕见遗传变异关联分析奠定基础。

最后, 大多数的全基因组关联研究都是集中分析具有显著关联信号的 SNPs 及其邻近基因, 忽视了那些统计学关系不显著或者边缘显著的 SNP 及邻近基因。而其中有些基因可能与身高或者疾病相关, 但由于其对身高或者疾病的效应十分微弱, 在任何全基因组关联研究中都不可能达到规定的统计学显著水平, 在多重检验校正或者 SNP 初筛过程中便被

忽视或遗漏。

4.2 身高的全基因组关联研究的未来发展方向

4.2.1 基于通路的全基因组关联分析

近年来研究者们通过多种方式对传统全基因组关联分析进行完善,如多个 SNP 位点的关联分析^[88-90]、推断基因型的关联分析^[91-93]、合并连锁信息的关联分析^[94,95]以及基于通路的全基因组关联分析方法^[96,97]。其中,基于通路的全基因组关联分析法更具有代表性,该方法能在全基因组范围内检测一组相关基因与性状/疾病间的关系,分析该相关基因的统计值是否在正常偏移范围之内,以此判断这组基因与性状/疾病之间的关系。众所周知,基因并不是单独发挥功能作用的,而是相互作用、联系,构成复杂的基因联系网络或相关生物学通路,在生命活动的各个进程中共同发挥作用。因此,将目前已知功能的通路或基因集合综合考虑,检测分析它们与性状/疾病之间的关系,可帮助人们发现更多的与某些性状/疾病相关联的基因,并有利于深入研究这些基因的作用和功能^[98]。

目前,全基因组通路分析主要采取基因表达芯片的方式进行。基因功能与基因表达情况密切相关,因此检测一组基因的表达水平是否正常就能发现它们是否与某些性状或疾病相关。2005 年,Subramanian 等^[99]提出了目前在基因表达研究中使用最为广泛的通路分析方法——基因集合富集分析法(Gene set enrichment analysis, GSEA)。2007 年, Wang 等^[96]将 GSEA 法进行改进后应用于全基因组关联分析,产生了基于通路的全基因组关联分析法,并成功鉴定了与帕金森疾病相关联的通路。2010 年, Pan 等^[100]运用基于通路的全基因组关联分析法首次在中国老年人群中鉴定了与身高变异有关联的自我吞噬调节通路(Regulation-of-autophagy pathway, ROA pathway)。该方法是对传统的全基因组关联研究强有力的补充。

4.2.2 拷贝数变异的全基因组关联分析

拷贝数变异(Copy number variations, CNVs)是 2004 年由 Iafrate 和 Sebat 各自所在的研究小组首次在人类基因组中证实并描述其存在的^[101,102],是指与参考序列相比,基因组中 1 kb 的 DNA 片段插入、

缺失和/或扩增,及其互相组合衍生出的复杂染色体结构变异。随后,2006 年 Redon 等^[103]在 HapMap 计划的 270 名正常健康供者中鉴定到 1447 个 CNV 区域(CNV region, CNVR),覆盖了 12%(300 Mb)的人类基因组,而且与基因组变异和疾病致病/易感基因位点相关。因此 CNVs 可能也像 SNPs 一样影响着基因的表达、表型的变异和适应,也是一种重要的疾病易感变异,能引起疾病或增加复杂疾病的发病几率^[101,103]。

Li 等^[180]将拷贝数变异的全基因组关联分析应用于身高的遗传学研究,对 618 例中国汉族无关个体进行拷贝数变异与身高表型的全基因组关联分析,发现在 8p23.3-23.2 区域和 6p21.3 区域增加 2 个以上的拷贝均与较矮的身高相关;但上述 CNVs 区域内均没有影响身高的重要基因存在,因此推测可能是 CNVs 区域内拷贝数的变化导致与之邻近的身高相关基因发生结构重排。此外, van Duyvenvoorde 等^[104]和 Dauber 等^[105]的研究还发现拷贝数变异与身材矮小症相关。

4.2.3 基于第二代测序技术的全基因组关联分析

基于基因芯片的全基因组关联分析用于研究发现与常见疾病相关的那些已知的变异或位点,可以确定相关位点但不能直接确定基因本身,且不能有效地发现新的突变^[106]。Yang 等^[107]通过 295K 基因芯片对约 4000 个无关个体进行了基因型数据和身高表型数据的关联分析,认为目前基因芯片可捕获的 SNP 能够解释高达 45%的身高表型变异。根据该研究结果,仍有 25%的身高表型变异无法用芯片上已有的 SNP 解释,这可能是由常见变异和稀有变异(Rare variation)间的连锁不平衡、结构突变、表观遗传效应以及基因-基因、基因-环境间的交互作用所导致。研究显示:常见变异和罕见变异都对表型/致病效应有所贡献^[81,107,108],效应大小可能与频率成反比^[86,109],这也符合进化和自然选择的观点。因此,随着研究的深入,人们越发认识到罕见突变的重要性。

第二代测序技术采用高通量的平行测序方式,可以快速地获取高密度的 SNP,随着该技术的不断发展和完善,使得对人类整个外显子区域或基因组进行高效、经济的测序成为了可能。研究者可采用外显子组测序、低覆盖度测序结合基因型填充、目

标区域捕获测序、混池测序等第二代测序技术的策略,进行基于第二代测序技术的全基因组关联研究,寻找和发现与人类身高相关的罕见突变,找回那些“缺失的遗传力”。

随着目前被发现的身高相关位点(697个)和身高边缘相关位点数量的增加,运用基于通路的全基因组关联分析、拷贝数变异的全基因组关联分析、基于第二代测序技术的全基因组关联分析等方法对传统的全基因组关联研究进行完善和补充,将使身高的遗传学研究进程发展到一个新的历史高度,获得更多更可靠且具有实际意义的研究结果,有助于加深和拓展人们对人类生长发育机制和相关疾病致病机理的认识。

5 结 语

身高是遗传学研究中典型的多基因遗传性状,受遗传和环境因素共同影响,但受遗传因素的影响更大。全基因组关联研究使身高的遗传学研究取得了丰硕的研究成果,上百个与身高相关的SNP位点得以发现和鉴定。然而目前许多已发现的SNP的作用或功能仍不十分清楚,现有的研究方法可能忽略了罕见遗传变异,限制了对身高关联基因的研究与应用。基于通路或拷贝数变异的全基因组关联分析以及第二代测序技术的应用,可有助于发现与身高关联更为密切的遗传标记,加深对人类生长发育机制和相关疾病致病机理的认识,准确地根据基因分型预测与推断个体身高,发挥身高关联基因在实际工作中的应用。

参考文献

- [1] Galton F. Regression towards mediocrity in hereditary stature. *J Anthropol Inst Great Brit Ireland*, 1886, 15: 246–263. [DOI]
- [2] Pearson K, Lee A. On the laws of inheritance in man: I. Inheritance of physical characters. *Biometrika*, 1903, 2(4): 357–462. [DOI]
- [3] Karlberg J, Luo ZC. Foetal size to final height. *Acta Paediatr*, 2000, 89(6): 632–636. [DOI]
- [4] Vrieze SI, McGue M, Miller MB, LeGrand LN, Schork NJ, Iacono WG. An assessment of the individual and collective effects of variants on height using twins and a developmentally informative study design. *PLoS Genet*, 2011, 7(12): e1002413. [DOI]
- [5] Perola M, Sammalisto S, Hiekkalinna T, Martin NG, Visscher PM, Montgomery GW, Benyamin B, Harris JR, Boomsma D, Willemsen G, Hottenga J-J, Christensen K, Kyvik KO, Sørensen TIA, Pedersen NL, Magnusson PK, Spector TD, Widen E, Silventoinen K, Kaprio J, Palotie A, Peltonen L. Combined genome scans for body stature in 6, 602 European twins: evidence for common Caucasian loci. *PLoS Genet*, 2007, 3(6): e97. [DOI]
- [6] Widén E, Ripatti S, Cousminer DL, Surakka I, Lappalainen T, Järvelin M-R, Eriksson JG, Raitakari O, Salomaa V, Sovio U, Hartikainen A-L, Pouta A, McCarthy MI, Osmond C, Kajantie E, Lehtimäki T, Viikari J, Kähönen M, Tyler-Smith C, Freimer N, Hirschhorn JN, Peltonen L, Palotie A. Distinct variants at *LIN28B* influence growth in height from birth to adulthood. *Am J Hum Genet*, 2010, 86(5): 773–782. [DOI]
- [7] Silventoinen K, Sammalisto S, Perola M, Boomsma DI, Cornes BK, Davis C, Dunkel L, de Lange M, Harris JR, Hjelmborg JVB, Luciano M, Martin NG, Mortensen J, Nisticò L, Pedersen NL, Skytthe A, Spector TD, Stazi MA, Willemsen G, Kaprio J. Heritability of adult body height: A comparative study of twin cohorts in eight countries. *Twin Res*, 2003, 6(5): 399–408. [DOI]
- [8] Fisher RA. The correlation between relatives on the supposition of Mendelian inheritance. *Trans Roy Soc Edin*, 1918, 52(2): 399–433. [DOI]
- [9] Li MX, Liu PY, Li YM, Qin YJ, Liu YZ, Deng HW. A major gene model of adult height is suggested in Chinese. *J Hum Genet*, 2004, 49(3): 148–153. [DOI]
- [10] Palmert MR, Hirschhorn JN. Genetic approaches to stature, pubertal timing, and other complex traits. *Mol Genet Metab*, 2003, 80(1–2): 1–10. [DOI]
- [11] Godowski PJ, Leung DW, Meacham LR, Galgani JP, Hellmiss R, Keret R, Rotwein PS, Parks JS, Laron Z, Wood WI. Characterization of the human growth hormone receptor gene and demonstration of a partial gene deletion in two patients with Laron-type dwarfism. *Proc Natl Acad Sci USA*, 1989, 86(20): 8083–8087. [DOI]
- [12] Amselem S, Duquesnoy P, Attree O, Novelli G, Bousnina S, Postel-Vinay M-C, Goossens M. Laron dwarfism and mutations of the growth hormone-receptor gene. *N Engl J Med*, 1989, 321(15): 989–995. [DOI]
- [13] Phillips JA, Hjelle BL, Seeburg PH, Zachmann M. Molecular basis for familial isolated growth hormone deficiency. *Proc Natl Acad Sci USA*, 1981, 78(10): 6372–6375. [DOI]
- [14] Domené HM, Bengolea SV, Martínez AS, Ropelato MG,

- Pennisi P, Scaglia P, Heinrich JJ, Jasper HG. Deficiency of the circulating insulin-like growth factor system associated with inactivation of the acid-labile subunit gene. *N Engl J Med*, 2004, 350(6): 570–577. [DOI]
- [15] Wajnrajch MP. Genetic disorders of human growth. *J Pediatr Endocrinol Metab*, 2002, 15(S 2): 701–714. [DOI]
- [16] Kofoed EM, Hwa V, Little B, Woods KA, Buckway CK, Tsubaki J, Pratt KL, Bezrodnik L, Jasper H, Tepper A, Heinrich JJ, Rosenfeld RG. Growth hormone insensitivity associated with a *STAT5b* mutation. *N Engl J Med*, 2003, 349(12): 1139–1147. [DOI]
- [17] Superti-Furga A, Unger S. Nosology and classification of genetic skeletal disorders: 2006 revision. *Am J Med Genet Part A*, 2007, 143A(1): 1–18. [DOI]
- [18] Rimoin DL, Cohn D, Krakow D, Wilcox W, Lachman RS, Alanay Y. The skeletal dysplasias: clinical-molecular correlations. *Ann N Y Acad Sci*, 2007, 1117: 302–309. [DOI]
- [19] Smith GD, Hart C, Upton M, Hole D, Gillis C, Watt G, Hawthorne V. Height and risk of death among men and women: aetiological implications of associations with cardiorespiratory disease and cancer mortality. *J Epidemiol Comm Health*, 2000, 54(2): 97–103. [DOI]
- [20] Gunnell D, Okasha M, Smith GD, Oliver SE, Sandhu J, Holly JMP. Height, leg length, and cancer risk: A systematic review. *Epidemiol Rev*, 2001, 23(2): 313–342. [DOI]
- [21] Lawlor D, Ebrahim S, Smith GD. The association between components of adult height and Type II diabetes and insulin resistance: British Women's Heart and Health Study. *Diabetologia*, 2002, 45(8): 1097–1106. [DOI]
- [22] Lawlor DA, Taylor M, Smith GD, Gunnell D, Ebrahim S. Associations of components of adult height with coronary heart disease in postmenopausal women: the British women's heart and health study. *Heart*, 2004, 90(7): 745–749. [DOI]
- [23] Hirschhorn JN, Lindgren CM, Daly MJ, Kirby A, Schaffner SF, Burt NP, Altshuler D, Parker A, Rioux JD, Platko J, Gaudet D, Hudson TJ, Groop LC, Lander ES. Genomewide linkage analysis of stature in multiple populations reveals several regions with evidence of linkage to adult height. *Am J Hum Genet*, 2001, 69(1): 106–116. [DOI]
- [24] Perola M, Öhman M, Hiekkalinna T, Leppävuori J, Pakujanta P, Wessman M, Koskenvuo M, Palotie A, Lange K, Kaprio J, Peltonen L. Quantitative-trait-locus analysis of body-mass index and of stature, by combined analysis of genome scans of five Finnish study groups. *Am J Hum Genet*, 2001, 69(1): 117–123. [DOI]
- [25] Deng HW, Xu FH, Liu YZ, Shen H, Deng HY, Huang QY, Liu YJ, Conway T, Li JL, Davies KM, Recker RR. A whole-genome linkage scan suggests several genomic regions potentially containing QTLs underlying the variation of stature. *Am J Med Genet*, 2002, 113(1): 29–39. [DOI]
- [26] Wiltshire S, Frayling TM, Hattersley AT, Hitman GA, Walker M, Levy JC, O'Rahilly S, Groves CJ, Menzel S, Cardon LR, McCarthy MI. Evidence for linkage of stature to chromosome 3p26 in a large U.K. family data set ascertained for type 2 diabetes. *Am J Hum Genet*, 2002, 70(2): 543–546. [DOI]
- [27] Liu YZ, Xu FH, Shen H, Deng H, Liu YJ, Zhao LJ, Dvornyk V, Conway T, Li JL, Huang QY, Davies KM, Recker RR, Deng HW. Confirmation linkage study in support of the X chromosome harbouring a QTL underlying human height variation. *J Med Genet*, 2003, 40(11): 825–831. [DOI]
- [28] Loos RJF. Genetic determinants of common obesity and their value in prediction. *Best Pract Res Clin Endocrinol Metab*, 2012, 26(2): 211–226. [DOI]
- [29] Merikangas KR, Risch N. Genomic priorities and public health. *Science*, 2003, 302(5645): 599–601. [DOI]
- [30] Risch N, Merikangas K. The future of genetic studies of complex human diseases. *Science*, 1996, 273(5281): 1516–1517. [DOI]
- [31] Risch NJ. Searching for genetic determinants in the new millennium. *Nature*, 2000, 405(6788): 847–856. [DOI]
- [32] Sabatti C, Service S, Freimer N. False discovery rate in linkage and association genome screens for complex disorders. *Genetics*, 2003, 164(2): 829–833. [DOI]
- [33] Lander E, Kruglyak L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat Genet*, 1995, 11(3): 241–247. [DOI]
- [34] Göring HH, Terwilliger JD, Blangero J. Large ward bias in estimation of locus-specific effects from genomewide scans. *Am J Hum Genet*, 2001, 69(6): 1357–1369. [DOI]
- [35] Lettre G, Butler JL, Ardlie KG, Hirschhorn JN. Common genetic variation in eight genes of the *GH/IGF1* axis does not contribute to adult height variation. *Hum Genet*, 2007, 122(2): 129–139. [DOI]
- [36] Frayling TM, Hattersley AT, McCarthy A, Holly J, Mitchell SMS, Gloyn AL, Owen K, Davies D, Smith GD, Ben-Shlomo Y. A putative functional polymor-

- phism in the IGF-I gene: Association studies with type 2 diabetes, adult height, glucose tolerance, and fetal growth in U.K. populations. *Diabetes*, 2002, 51(7): 2313–2316. [DOI]
- [37] Jorge AAL, Marchisotti FG, Montenegro LR, Carvalho LR, Mendonca BB, Arnhold IJP. Growth hormone (GH) pharmacogenetics: Influence of GH receptor exon 3 retention or deletion on first-year growth response and final height in patients with severe GH deficiency. *J Clin Endocrinol Metab*, 2006, 91(3): 1076–1080. [DOI]
- [38] Daniel R, Santos C, Phillips C, Fondevila M, van Oorschot RAH, Carracedo Á, Lareu MV, McNevin D. A SNaPshot of next generation sequencing for forensic SNP analysis. *Forensic Sci Int Genet*, 2015, 14: 50–60. [DOI]
- [39] Ong M, Carreira S, Goodall J, Mateo J, Figueiredo I, Rodrigues DN, Perkins G, Seed G, Yap TA, Attard G, de Bono JS. Validation and utilisation of high-coverage next-generation sequencing to deliver the pharmacological audit trail. *Brit J Cancer*, 2014, 111(5): 828–836. [DOI]
- [40] Zhang ZY, Fye S, Borecki IB, Rader JS. Polymorphisms in immune mediators associate with risk of cervical cancer. *Gynecol Oncol*, 2014, 135(1): 69–73. [DOI]
- [41] Mollinari M, Serang O. Quantitative SNP genotyping of polyploids with MassARRAY and other platforms. *Methods Mol Biol*, 2015, 1245: 215–241. [DOI]
- [42] Pineda-Tenor D, Berenguer J, Jiménez-Sousa MA, Guzmán-Fulgencio M, Aldámiz-Echevarria T, Carrero A, García-Álvarez M, Díez C, Tejerina F, Briz V, Resino S. *CXCL9*, *CXCL10* and *CXCL11* polymorphisms are associated with sustained virologic response in HIV/HCV-coinfected patients. *J Clinical Virology*, 2014, 61(3): 423–429. [DOI]
- [43] Wang Y, Wang ZM, Teng YC, Shi JX, Wang HF, Yuan WT, Chu X, Wang DF, Wang W, Huang W. An SNP of the ZBTB38 gene is associated with idiopathic short stature in the Chinese Han population. *Clin Endocrinol*, 2013, 79(3): 402–408. [DOI]
- [44] Chang S-C, Chang P-Y, Butler B, Goldstein BY, Mu LN, Cai L, You N-CY, Baecker A, Yu SZ, Heber D, Lu QY, Li LM, Greenland S, Zhang ZF. Single nucleotide polymorphisms of one-carbon metabolism and cancers of the esophagus, stomach, and liver in a Chinese population. *PLoS One*, 2014, 9(10): e109235. [DOI]
- [45] Fanis P, Kousiappa I, Phylactides M, Kleanthous M. Genotyping of *BCL11A* and *HBS1L-MYB* SNPs associated with fetal haemoglobin levels: a SNaPshot mini-sequencing approach. *BMC Genom*, 2014, 15: 108. [DOI]
- [46] Cajanus K, Kaunisto MA, Tallgren M, Jokela R, Kalso E. How much oxycodone is needed for adequate analgesia after breast cancer surgery: Effect of the *OPRM1* 118A>G polymorphism. *J Pain*, 2014, 15(12): 1248–1256. [DOI]
- [47] Rodrigues P, de Marco G, Furriol J, Mansego ML, Pineda-Alonso M, Gonzalez-Neira A, Martin-Escudero JC, Benitez J, Lluch A, Chaves FJ, Eroles P. Oxidative stress in susceptibility to breast cancer: study in Spanish population. *BMC Cancer*, 2014, 14: 861. [DOI]
- [48] Fernández-Cadenas I, Del Río-Espínola A, Giralt D, Domingues-Montanari S, Quiroga A, Mendióroz M, Ruíz A, Ribó M, Serena J, Obach V, Freijo MM, Martí-Fàbregas J, Delgado P, Montaner J. IL1B and VWF variants are associated with fibrinolytic early recanalization in patients with ischemic stroke. *Stroke*, 2012, 43(10): 2659–2665. [DOI]
- [49] Alcalde M, Campuzano O, Allegue C, Torres M, Arbelo E, Partemi S, Iglesias A, Brugada J, Oliva A, Carracedo A, Brugada R. Sequenom MassARRAY approach in the arrhythmogenic right ventricular cardiomyopathy post-mortem setting: clinical and forensic implications. *Int J Legal Med*, 2015, 129(1): 1–10. [DOI]
- [50] International HapMap Consortium, Frazer KA, Ballinger DG, Cox DR, Hinds DA, Stuve LL, Gibbs RA, Belmont JW, Boudreau A, Hardenbol P, Leal SM, Pasternak S, Wheeler DA, Willis TD, Yu F, Yang H, Zeng C, Gao Y, Hu H, Hu W, Li C, Lin W, Liu S, Pan H, Tang X, Wang J, Wang W, Yu J, Zhang B, Zhang Q, Zhao H, Zhao H, Zhou J, Gabriel SB, Barry R, Blumenstiel B, Camargo A, Defelice M, Faggart M, Goyette M, Gupta S, Moore J, Nguyen H, Onofrio RC, Parkin M, Roy J, Stahl E, Winchester E, Ziaugra L, Altshuler D, Shen Y, Yao Z, Huang W, Chu X, He Y, Jin L, Liu Y, Shen Y, Sun W, Wang H, Wang Y, Wang Y, Xiong X, Xu L, Wayne MM, Tsui SK, Xue H, Wong JT, Galver LM, Fan JB, Gunderson K, Murray SS, Oliphant AR, Chee MS, Montpetit A, Chagnon F, Ferretti V, Leboeuf M, Olivier JF, Phillips MS, Roumy S, Sallée C, Verner A, Hudson TJ, Kwok PY, Cai D, Koboldt DC, Miller RD, Pawlikowska L, Taillon-Miller P, Xiao M, Tsui LC, Mak W, Song YQ, Tam PK, Nakamura Y, Kawaguchi T, Kitamoto T, Morizono T, Nagashima A, Ohnishi Y, Sekine A, Tanaka T, Tsunoda T, Deloukas P, Bird CP, Delgado M, Dermitzakis ET, Gwilliam R, Hunt S, Morrison J, Powell D, Stranger BE, Whittaker P, Bentley DR, Daly MJ,

- de Bakker PI, Barrett J, Chretien YR, Maller J, McCarroll S, Patterson N, Pe'er I, Price A, Purcell S, Richter DJ, Sabeti P, Saxena R, Schaffner SF, Sham PC, Varilly P, Altshuler D, Stein LD, Krishnan L, Smith AV, Tello-Ruiz MK, Thorisson GA, Chakravarti A, Chen PE, Cutler DJ, Kashuk CS, Lin S, Abecasis GR, Guan W, Li Y, Munro HM, Qin ZS, Thomas DJ, McVean G, Auton A, Bottolo L, Cardin N, Eyheramendy S, Freeman C, Marchini J, Myers S, Spencer C, Stephens M, Donnelly P, Cardon LR, Clarke G, Evans DM, Morris AP, Weir BS, Tsunoda T, Mullikin JC, Sherry ST, Feolo M, Skol A, Zhang H, Zeng C, Zhao H, Matsuda I, Fukushima Y, Macer DR, Suda E, Rotimi CN, Adebamowo CA, Ajayi I, Aniagwu T, Marshall PA, Nkwojima C, Royal CD, Leppert MF, Dixon M, Peiffer A, Qiu R, Kent A, Kato K, Niikawa N, Adewole IF, Knoppers BM, Foster MW, Clayton EW, Watkin J, Gibbs RA, Belmont JW, Muzny D, Nazareth L, Sodergren E, Weinstock GM, Wheeler DA, Yakub I, Gabriel SB, Onofrio RC, Richter DJ, Ziaugra L, Birren BW, Daly MJ, Altshuler D, Wilson RK, Fulton LL, Rogers J, Burton J, Carter NP, Clee CM, Griffiths M, Jones MC, McLay K, Plumb RW, Ross MT, Sims SK, Willey DL, Chen Z, Han H, Kang L, Godbout M, Wallenburg JC, L'Archevêque P, Bellemare G, Saeki K, Wang H, An D, Fu H, Li Q, Wang Z, Wang R, Holden AL, Brooks LD, McEwen JE, Guyer MS, Wang VO, Peterson JL, Shi M, Spiegel J, Sung LM, Zacharia LF, Collins FS, Kennedy K, Jamieson R, Stewart J. A second generation human haplotype map of over 3.1 million SNPs. *Nature*, 2007, 449(7164): 851–861. [DOI]
- [51] Gunderson KL, Steemers FJ, Lee G, Mendoza LG, Chee MS. A genome-wide scalable SNP genotyping assay using microarray technology. *Nat Genet*, 2005, 37(5): 549–554. [DOI]
- [52] Kennedy GC, Matsuzaki H, Dong S, Liu WM, Huang J, Liu G, Su X, Cao M, Chen W, Zhang J, Liu W, Yang G, Di X, Ryder T, He Z, Surti U, Phillips MS, Boyce-Jacino MT, Fodor SPA, Jones KW. Large-scale genotyping of complex DNA. *Nat Biotechnol*, 2003, 21(10): 1233–1237. [DOI]
- [53] Steemers FJ, Gunderson KL. Whole genome genotyping technologies on the BeadArray™ platform. *Biotechnol J*, 2007, 2(1): 41–49. [DOI]
- [54] Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, Maller J, Sklar P, de Bakker PIW, Daly MJ, Sham PC. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*, 2007, 81(3): 559–575. [DOI]
- [55] Aranzana MJ, Kim S, Zhao KY, Bakker E, Horton M, Jakob K, Lister C, Molitor J, Shindo C, Tang CL, Toomajian C, Traw B, Zheng HG, Bergelson J, Dean C, Marjoram P, Nordborg M. Genome-wide association mapping in *Arabidopsis* identifies previously known flowering time and pathogen resistance genes. *PLoS Genet*, 2005, 1(5): e60. [DOI]
- [56] Todd JA. Statistical false positive or true disease pathway? *Nat Genet*, 2006, 38(7): 731–733. [DOI]
- [57] Klein RJ, Zeiss C, Chew EY, Tsai J-Y, Sackler RS, Haynes C, Henning AK, SanGiovanni JP, Mane SM, Mayne ST, Bracken MB, Ferris FL, Ott J, Barnstable C, Hoh J. Complement factor H polymorphism in age-related macular degeneration. *Science*, 2005, 308(5720): 385–389. [DOI]
- [58] Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research, Saxena R, Voight BF, Lyssenko V, Burtt NP, de Bakker PIW, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Boström KB, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Råstam L, Speliotes EK, Taskinen M-R, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjögren M, Sterner M, Surti A, Svensson M, Svensson M, Tewhey R, Blumenstiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarata J, Chia N, Fava M, Gibbons J, Handsaker B, Healy C, Nguyen K, Gates C, Sougnez C, Gage D, Nizzari M, Gabriel SB, Chirn G-W, Ma QC, Parikh H, Richardson D, Ricke D, Purcell S. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science*, 2007, 316(5829): 1331–1336. [DOI]
- [59] Zeggini E, Weedon MN, Lindgren CM, Frayling TM, Elliott KS, Lango H, Timpson NJ, Perry JRB, Rayner NW, Freathy RM, Barrett JC, Shields B, Morris AP, Ellard S, Groves CJ, Harries LW, Marchini JL, Owen KR, Knight B, Cardon LR, Walker M, Hitman GA, Morris AD, Doney ASF, The Wellcome Trust Case Control Consortium, McCarthy MI, Hattersley AT. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science*, 2007, 316(5829): 1336–1341. [DOI]
- [60] The Wellcome Trust Case Control Consortium. Genome-wide association study of 14, 000 cases of sev-

- en common diseases and 3, 000 shared controls. *Nature*, 2007, 447(7145): 661–678. [DOI]
- [61] Weedon MN, Lettre G, Freathy RM, Lindgren CM, Voight BF, Perry JRB, Elliott KS, Hackett R, Guiducci C, Shields B, Zeggini E, Lango H, Lyssenko V, Timpson NJ, Burt NP, Rayner NW, Saxena R, Ardlie K, Tobias JH, Ness AR, Ring SM, Palmer CNA, Morris AD, Peltonen L, Salomaa V, The Diabetes Genetics Initiative, The Wellcome Trust Case Control Consortium, Smith GD, Groop LC, Hattersley AT, McCarthy MI, Hirschhorn JN, Frayling TM. A common variant of *HMGA2* is associated with adult and childhood height in the general population. *Nat Genet*, 2007, 39(10): 1245–1250. [DOI]
- [62] Weedon MN, Lango H, Lindgren CM, Wallace C, Evans DM, Mangino M, Freathy RM, Perry JRB, Stevens S, Hall AS, Samani NJ, Shields B, Prokopenko I, Farrall M, Dominiczak A, Diabetes Genetics Initiative, The Wellcome Trust Case Control Consortium, Johnson T, Bergmann S, Beckmann JS, Vollenweider P, Waterworth DM, Mooser V, Palmer CNA, Morris AD, Ouwehand WH, Cambridge GEM Consortium, Caulfield M, Munroe PB, Hattersley AT, McCarthy MI, Frayling TM. Genome-wide association analysis identifies 20 loci that influence adult height. *Nat Genet*, 2008, 40(5): 575–583. [DOI]
- [63] Yang TL, Guo Y, Zhang LS, Tian Q, Yan H, Guo YF, Deng HW. *HMGA2* is confirmed to be associated with human adult height. *Ann Hum Genet*, 2010, 74(1): 11–16. [DOI]
- [64] Takeshita H, Fujihara J, Soejima M, Koda Y, Kimura-Kataoka K, Ono R-I, Yuasa I, Iida R, Ueki M, Nagao M, Yasuda T. Confirmation that SNPs in the high mobility group-A2 gene (*HMGA2*) are associated with adult height in the Japanese population; wide-ranging population survey of height-related SNPs in *HMGA2*. *Electrophoresis*, 2011, 32(14): 1844–1851. [DOI]
- [65] Zhou XJ, Benson KF, Ashar HR, Chada K. Mutation responsible for the mouse pygmy phenotype in the developmentally regulated factor HMGI-C. *Nature*, 1995, 376(6543): 771–774. [DOI]
- [66] Ligon AH, Moore SDP, Parisi MA, Mealiffe ME, Harris DJ, Ferguson HL, Quade BJ, Morton CC. Constitutional rearrangement of the architectural factor *HMGA2*: a novel human phenotype including overgrowth and lipomas. *Am J Hum Genet*, 2005, 76(2): 340–348. [DOI]
- [67] Menten B, Buysse K, Zahir F, Hellemans J, Hamilton SJ, Costa T, Fagerstrom C, Anadiotis G, Kingsbury D, McGillivray BC, Marra MA, Friedman JM, Speleman F, Mortier G. Osteopoikilosis, short stature and mental retardation as key features of a new microdeletion syndrome on 12q14. *J Med Genet*, 2007, 44(4): 264–268. [DOI]
- [68] Sanna S, Jackson AU, Nagaraja R, Willer CJ, Chen WM, Bonnycastle LL, Shen HQ, Timpson N, Lettre G, Usala G, Chines PS, Stringham HM, Scott LJ, Dei M, Lai S, Albai G, Crisponi L, Naitza S, Doheny KF, Pugh EW, Ben-Shlomo Y, Ebrahim S, Lawlor DA, Bergman RN, Watanabe RM, Uda M, Tuomilehto J, Coresh J, Hirschhorn JN, Shuldiner AR, Schlessinger D, Collins FS, Smith GD, Boerwinkle E, Cao A, Boehnke M, Abecasis GR, Mohlke KL. Common variants in the *GDF5-UQCC* region are associated with variation in human height. *Nat Genet*, 2008, 40(2): 198–203. [DOI]
- [69] Polinkovsky A, Robin NH, Thomas JT, Irons M, Lynn A, Goodman FR, Reardon W, Kant SG, Brunner HG, van der Burgt I, Chitayat D, McGaughan J, Donnai D, Luyten FP, Warman ML. Mutations in *CDMP1* cause autosomal dominant brachydactyly type C. *Nat Genet*, 1997, 17(1): 18–19. [DOI]
- [70] Miyamoto Y, Mabuchi A, Shi DQ, Kubo T, Takatori Y, Saito S, Fujioka M, Sudo A, Uchida A, Yamamoto S, Ozaki K, Takigawa M, Tanaka T, Nakamura Y, Jiang Q, Ikegawa S. A functional polymorphism in the 5'UTR of *GDF5* is associated with susceptibility to osteoarthritis. *Nat Genet*, 2007, 39(4): 529–533. [DOI]
- [71] Gudbjartsson DF, Walters GB, Thorleifsson G, Stefansson H, Halldorsson BV, Zusmanovich P, Sulem P, Thorlacius S, Gylfason A, Steinberg S, Helgadóttir A, Ingason A, Steinthorsdóttir V, Olafsdóttir EJ, Olafsdóttir GH, Jonsson T, Borch-Johnsen K, Hansen T, Andersen G, Jorgensen T, Pedersen O, Aben KK, Witjes JA, Swinkels DW, den Heijer M, Franke B, Verbeek AL, Becker DM, Yanek LR, Becker LC, Tryggvadóttir L, Rafnar T, Gulcher J, Kiemeneý LA, Kong A, Thorsteinsdóttir U, Stefansson K. Many sequence variants affecting diversity of adult human height. *Nat Genet*, 2008, 40(5): 609–615. [DOI]
- [72] Lettre G, Jackson AU, Gieger C, Schumacher FR, Berndt SI, Sanna S, Eyheramendy S, Voight BF, Butler JL, Guiducci C, Illig T, Hackett R, Heid IM, Jacobs KB, Lyssenko V, Uda M, The Diabetes Genetics Initiative, FUSION, KORA, The Prostate, Lung Colorectal and Ovarian Cancer Screening Trial, The Nurses' Health Study, SardiNIA, Boehnke M, Chanock SJ, Groop LC, Hu FB, Isomaa B, Kraft P, Peltonen L, Salomaa V,

- Schlessinger D, Hunter DJ, Hayes RB, Abecasis GR, Wichmann H-E, Mohlke KL, Hirschhorn JN. Identification of ten loci associated with height highlights new biological pathways in human growth. *Nat Genet*, 2008, 40(5): 584–591. [DOI]
- [73] Weedon MN. Genome-wide association studies of human growth traits. *Nestle Nutr Inst Workshop Ser*, 2013, 71: 29–38. [DOI]
- [74] Cho YS, Go MJ, Kim YJ, Heo JY, Oh JH, Ban H-J, Yoon D, Lee MH, Kim D-J, Park M, Cha S-H, Kim J-W, Han B-G, Min H, Ahn Y, Park MS, Han HR, Jang H-Y, Cho EY, Lee J-E, Cho NH, Shin C, Park T, Park JW, Lee J-K, Cardon L, Clarke G, McCarthy MI, Lee J-Y, Lee J-K, Oh B, Kim H-L. A large-scale genome-wide association study of Asian populations uncovers genetic factors influencing eight quantitative traits. *Nat Genet*, 2009, 41(5): 527–534. [DOI]
- [75] Kim J-J, Lee H-I, Park T, Kim K, Lee J-E, Cho NH, Shin C, Cho YS, Lee J-Y, Han B-G, Yoo H-W, Lee J-K. Identification of 15 loci influencing height in a Korean population. *J Hum Genet*, 2010, 55(1): 27–31. [DOI]
- [76] Takeuchi F, Nabika T, Isono M, Katsuya T, Sugiyama T, Yamaguchi S, Kobayashi S, Yamori Y, Ogihara T, Kato N. Evaluation of genetic loci influencing adult height in the Japanese population. *J Hum Genet*, 2009, 54(12): 749–752. [DOI]
- [77] Okada Y, Kamatani Y, Takahashi A, Matsuda K, Hosono N, Ohmiya H, Daigo Y, Yamamoto K, Kubo M, Nakamura Y, Kamatani N. A genome-wide association study in 19 633 Japanese subjects identified *LHX3-QSOX2* and *IGF1* as adult height loci. *Hum Mol Genet*, 2010, 19(11): 2303–2312. [DOI]
- [78] Lei SF, Tan LJ, Liu XG, Wang L, Yan H, Guo YF, Liu YZ, Xiong DH, Li J, Yang TL, Chen XD, Guo Y, Deng FY, Zhang YP, Zhu XZ, Levy S, Papasian CJ, Hamilton JJ, Recker RR, Deng HW. Genome-wide association study identifies two novel loci containing *FLNB* and *SBF2* genes underlying stature variation. *Hum Mol Genet*, 2009, 18(9): 1661–1669. [DOI]
- [79] Lei SF, Yang TL, Tan LJ, Chen XD, Guo Y, Guo YF, Zhang L, Liu XG, Yan H, Pan F, Zhang ZX, Peng YM, Zhou Q, He LN, Zhu XZ, Cheng J, Liu YZ, Papasian CJ, Deng HW. Genome-wide association scan for stature in Chinese: evidence for ethnic specific loci. *Hum Genet*, 2009, 125(1): 1–9. [DOI]
- [80] Li X, Tan LJ, Liu XG, Lei SF, Yang TL, Chen XD, Zhang F, Fang Y, Guo Y, Zhang L, Yan H, Pan F, Zhang ZX, Peng YM, Zhou Q, He LN, Zhu XZ, Cheng J, Zhang LS, Liu YZ, Tian Q, Deng HW. A genome wide association study between copy number variation (CNV) and human height in Chinese population. *J Genet Genomics*, 2010, 37(12): 779–785. [DOI]
- [81] Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F, Willer CJ, Jackson AU, Vedantam S, Raychaudhuri S, Ferreira T, Wood AR, Weyant RJ, Segrè AV, Speliotes EK, Wheeler E, Soranzo N, Park JH, Yang J, Gudbjartsson D, Heard-Costa NL, Randall JC, Qi L, Vernon Smith A, Mägi R, Pastinen T, Liang L, Heid IM, Luan J, Thorleifsson G, Winkler TW, Goddard ME, Sin Lo K, Palmer C, Workalemahu T, Aulchenko YS, Johansson A, Zillikens MC, Feitosa MF, Esko T, Johnson T, Ketkar S, Kraft P, Mangino M, Prokopenko I, Absher D, Albrecht E, Ernst F, Glazer NL, Hayward C, Hottenga JJ, Jacobs KB, Knowles JW, Kutalik Z, Monda KL, Polasek O, Preuss M, Rayner NW, Robertson NR, Steinthorsdottir V, Tyrer JP, Voight BF, Wiklund F, Xu J, Zhao JH, Nyholt DR, Pellikka N, Perola M, Perry JR, Surakka I, Tammesoo ML, Altmaier EL, Amin N, Aspelund T, Bhangale T, Boucher G, Chasman DI, Chen C, Coin L, Cooper MN, Dixon AL, Gibson Q, Grundberg E, Hao K, Juhani Juntila M, Kaplan LM, Kettunen J, König IR, Kwan T, Lawrence RW, Levinson DF, Lorentzon M, McKnight B, Morris AP, Müller M, Suh Ngwa J, Purcell S, Rafelt S, Salem RM, Salvi E, Sanna S, Shi J, Sovio U, Thompson JR, Turchin MC, Vandenput L, Verlaan DJ, Vitart V, White CC, Ziegler A, Almgren P, Balmforth AJ, Campbell H, Citterio L, De Grandi A, Dominiczak A, Duan J, Elliott P, Elosua R, Eriksson JG, Freimer NB, Geus EJ, Glorioso N, Haiqing S, Hartikainen AL, Havulinna AS, Hicks AA, Hui J, Igl W, Illig T, Julia A, Kajantie E, Kilpeläinen TO, Koivari M, Kolcic I, Kosken S, Kovacs P, Laitinen J, Liu J, Lokki ML, Marusic A, Maschio A, Meitinger T, Mulas A, Paré G, Parker AN, Peden JF, Petersmann A, Pichler I, Pietiläinen KH, Pouta A, Ridderstråle M, Rotter JJ, Sambrook JG, Sanders AR, Schmidt CO, Sinisalo J, Smit JH, Stringham HM, Bragi Walters G, Widen E, Wild SH, Willemsen G, Zagato L, Zgaga L, Zitting P, Alavere H, Farrall M, McArdle WL, Nelis M, Peters MJ, Ripatti S, van Meurs JB, Aben KK, Ardlie KG, Beckmann JS, Beilby JP, Bergman RN, Bergmann S, Collins FS, Cusi D, den Heijer M, Eiriksdottir G, Gejman PV, Hall AS, Hamsten A, Huikuri HV, Iribarren C, Kähönen M, Kaprio J, Kathiresan S, Kiemeny L, Kocher T, Launer LJ, Lehtimäki T, Melander O, Mosley TH, Jr., Musk AW, Nieminen MS, O'Donnell CJ, Ohlsson C,

- Oostra B, Palmer LJ, Raitakari O, Ridker PM, Rioux JD, Rissanen A, Rivolta C, Schunkert H, Shuldiner AR, Siscovick DS, Stumvoll M, Tönjes A, Tuomilehto J, van Ommen GJ, Viikari J, Heath AC, Martin NG, Montgomery GW, Province MA, Kayser M, Arnold AM, Atwood LD, Boerwinkle E, Chanock SJ, Deloukas P, Gieger C, Grönberg H, Hall P, Hattersley AT, Hengstenberg C, Hoffman W, Lathrop GM, Salomaa V, Schreiber S, Uda M, Waterworth D, Wright AF, Assimes TL, Barroso I, Hofman A, Mohlke KL, Boomsma DI, Caulfield MJ, Cupples LA, Erdmann J, Fox CS, Gudnason V, Gyllensten U, Harris TB, Hayes RB, Jarvelin MR, Mooser V, Munroe PB, Ouwehand WH, Penninx BW, Pramstaller PP, Quertermous T, Rudan I, Samani NJ, Spector TD, Völzke H, Watkins H, Wilson JF, Groop LC, Haritunians T, Hu FB, Kaplan RC, Metspalu A, North KE, Schlessinger D, Wareham NJ, Hunter DJ, O'Connell JR, Strachan DP, Wichmann HE, Borecki IB, van Duijn CM, Schadt EE, Thorsteinsdottir U, Peltonen L, Uitterlinden AG, Visscher PM, Chatterjee N, Loos RJ, Boehnke M, McCarthy MI, Ingelsson E, Lindgren CM, Abecasis GR, Stefansson K, Frayling TM, Hirschhorn JN. Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature*, 2010, 467(7317): 832–838. [\[DOI\]](#)
- [82] Wood AR, Esko T, Yang J, Vedantam S, Pers TH, Gustafsson S, Chu AY, Estrada K, Luan J, Kutalik Z, Amin N, Buchkovich ML, Croteau-Chonka DC, Day FR, Duan Y, Fall T, Fehrmann R, Ferreira T, Jackson AU, Karjalainen J, Lo KS, Locke AE, Mägi R, Mihailov E, Porcu E, Randall JC, Scherag A, Vinkhuyzen AA, Westra HJ, Winkler TW, Workalemahu T, Zhao JH, Absher D, Albrecht E, Anderson D, Baron J, Beekman M, Demirkan A, Ehret GB, Feenstra B, Feitosa MF, Fischer K, Fraser RM, Goel A, Gong J, Justice AE, Kanoni S, Kleber ME, Kristiansson K, Lim U, Lotay V, Lui JC, Mangino M, Mateo Leach I, Medina-Gomez C, Nalls MA, Nyholt DR, Palmer CD, Pasko D, Pechlivanis S, Prokopenko I, Ried JS, Ripke S, Shungin D, Stancáková A, Strawbridge RJ, Sung YJ, Tanaka T, Teumer A, Trompet S, van der Laan SW, van Setten J, Van Vliet-Ostaptchouk JV, Wang Z, Yengo L, Zhang W, Afzal U, Arnlöv J, Arscott GM, Bandinelli S, Barrett A, Bellis C, Bennett AJ, Berne C, Blüher M, Bolton JL, Böttcher Y, Boyd HA, Bruinenberg M, Buckley BM, Buyske S, Caspersen IH, Chines PS, Clarke R, Claudi-Boehm S, Cooper M, Daw EW, De Jong PA, Deelen J, Delgado G, Denny JC, Dhonukshe-Rutten R, Dimitriou M, Doney AS, Dörr M, Eklund N, Eury E, Folkersen L, Garcia ME, Geller F, Giedraitis V, Go AS, Grallert H, Grammer TB, Gräßler J, Grönberg H, de Groot LC, Groves CJ, Haessler J, Hall P, Haller T, Hallmans G, Hannemann A, Hartman CA, Hassinen M, Hayward C, Heard-Costa NL, Helmer Q, Hemani G, Henders AK, Hillege HL, Hlatky MA, Hoffmann W, Hoffmann P, Holmen O, Houwing-Duistermaat JJ, Illig T, Isaacs A, James AL, Jeff J, Johansen B, Johansson Å, Jolley J, Juliusdottir T, Junttila J, Kho AN, Kinnunen L, Klopp N, Kocher T, Kratzer W, Lichtner P, Lind L, Lindström J, Lobbens S, Lorentzon M, Lu Y, Lyssenko V, Magnusson PK, Mahajan A, Maillard M, McArdle WL, McKenzie CA, McLachlan S, McLaren PJ, Menni C, Merger S, Milani L, Moayyeri A, Monda KL, Morken MA, Muller G, Muller-Nurasyid M, Musk AW, Narisu N, Nauck M, Nolte IM, Nöthen MM, Oozageer L, Pilz S, Rayner NW, Renstrom F, Robertson NR, Rose LM, Roussel R, Sanna S, Scharnagl H, Scholtens S, Schumacher FR, Schunkert H, Scott RA, Sehmi J, Seufferlein T, Shi J, Silventoinen K, Smit JH, Smith AV, Smolonska J, Stanton AV, Stirrups K, Stott DJ, Stringham HM, Sundström J, Swertz MA, Syvänen AC, Tayo BO, Thorleifsson G, Tyrer JP, van Dijk S, van Schoor NM, van der Velde N, van Heemst D, van Oort FV, Vermeulen SH, Verweij N, Vonk JM, Waite LL, Waldenberger M, Wennauer R, Wilkens LR, Willenborg C, Wilsgaard T, Wojczynski MK, Wong A, Wright AF, Zhang Q, Arveiler D, Bakker SJ, Beilby J, Bergman RN, Bergmann S, Biffar R, Blangero J, Boomsma DI, Bornstein SR, Bovet P, Brambilla P, Brown MJ, Campbell H, Caulfield MJ, Chakravarti A, Collins R, Collins FS, Crawford DC, Cupples LA, Danesh J, de Faire U, den Ruijter HM, Erbel R, Erdmann J, Eriksson JG, Farrall M, Ferrannini E, Ferri è res J, Ford I, Forouhi NG, Forrester T, Gansevoort RT, Gejman PV, Gieger C, Golay A, Gottesman O, Gudnason V, Gyllensten U, Haas DW, Hall AS, Harris TB, Hattersley AT, Heath AC, Hengstenberg C, Hicks AA, Hindorf LA, Hingorani AD, Hofman A, Hovingh GK, Humphries SE, Hunt SC, Hyponen E, Jacobs KB, Jarvelin MR, Jousilahti P, Jula AM, Kaprio J, Kastelein JJ, Kayser M, Kee F, Keinanen-Kiukkaanniemi SM, Kiemeny LA, Kooner JS, Kooperberg C, Koskinen S, Kovacs P, Kraja AT, Kumari M, Kuusisto J, Lakka TA, Langenberg C, Le Marchand L, Lehtimäki T, Lupoli S, Madden PA, Männistö S, Manunta P, Marette A, Matise TC, McKnight B, Meitinger T, Moll FL, Montgomery GW, Morris AD, Morris AP, Murray JC,

- Nelis M, Ohlsson C, Oldehinkel AJ, Ong KK, Ouwehand WH, Pasterkamp G, Peters A, Pramstaller PP, Price JF, Qi L, Raitakari OT, Rankinen T, Rao DC, Rice TK, Ritchie M, Rudan I, Salomaa V, Samani NJ, Saranimes J, Sarzynski MA, Schwarz PE, Sebert S, Sever P, Shuldiner AR, Sinisalo J, Steinthorsdottir V, Stolk RP, Tardif JC, Tönjes A, Tremblay A, Tremoli E, Virtamo J, Vohl MC, Electronic Medical Records and Genomics (eMERGE) Consortium, Consortium M, Consortium P, LifeLines Cohort Study, Amouyel P, Asselbergs FW, Assimes TL, Bochud M, Boehm BO, Boerwinkle E, Bottinger EP, Bouchard C, Cauchi S, Chambers JC, Chanock SJ, Cooper RS, de Bakker PI, Dedoussis G, Ferrucci L, Franks PW, Froguel P, Groop LC, Haiman CA, Hamsten A, Hayes MG, Hui J, Hunter DJ, Hveem K, Jukema JW, Kaplan RC, Kivimaki M, Kuh D, Laakso M, Liu Y, Martin NG, März W, Melbye M, Moebus S, Munroe PB, Njølstad I, Oostra BA, Palmer CN, Pedersen NL, Perola M, Pérusse L, Peters U, Powell JE, Power C, Quertermous T, Rauramaa R, Reinmaa E, Ridker PM, Rivadeneira F, Rotter JI, Saaristo TE, Saleheen D, Schlessinger D, Slagboom PE, Snieder H, Spector TD, Strauch K, Stumvoll M, Tuomilehto J, Uusitupa M, van der Harst P, Völzke H, Walker M, Wareham NJ, Watkins H, Wichmann HE, Wilson JF, Zanen P, Deloukas P, Heid IM, Lindgren CM, Mohlke KL, Speliotes EK, Thorsteinsdottir U, Barroso I, Fox CS, North KE, Strachan DP, Beckmann JS, Berndt SI, Boehnke M, Borecki IB, McCarthy MI, Metspalu A, Stefansson K, Uitterlinden AG, van Duijn CM, Franke L, Willer CJ, Price AL, Lettre G, Loos RJ, Weedon MN, Ingelsson E, O'Connell JR, Abecasis GR, Chasman DI, Goddard ME, Visscher PM, Hirschhorn JN, Frayling TM. Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat Genet*, 2014, 46(11): 1173–1186. [DOI]
- [83] Hindorff LA, Sethupathy P, Junkins HA, Ramos EM, Mehta JP, Collins FS, Manolio TA. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. *Proc Natl Acad Sci USA*, 2009, 106(23): 9362–9367. [DOI]
- [84] Myles S, Davison D, Barrett J, Stoneking M, Timpson N. Worldwide population differentiation at disease-associated SNPs. *BMC Med Genom*, 2008, 1: 22. [DOI]
- [85] McCarthy MI, Hirschhorn JN. Genome-wide association studies: potential next steps on a genetic journey. *Hum Mol Genet*, 2008, 17(R2): R156–R165. [DOI]
- [86] McCarthy MI, Abecasis GR, Cardon LR, Goldstein DB, Little J, Ioannidis JP, Hirschhorn JN. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet*, 2008, 9(5): 356–369. [DOI]
- [87] Nejentsev S, Walker N, Riches D, Egholm M, Todd JA. Rare variants of *IFIH1*, a gene implicated in antiviral responses, protect against type 1 diabetes. *Science*, 2009, 324(5925): 387–389. [DOI]
- [88] Liu JZ, McRae AF, Nyholt DR, Medland SE, Wray NR, Brown KM, Investigators A, Hayward NK, Montgomery GW, Visscher PM, Martin NG, Macgregor S. A versatile gene-based test for genome-wide association studies. *Am J Hum Genet*, 2010, 87(1): 139–145. [DOI]
- [89] Wu MC, Kraft P, Epstein MP, Taylor DM, Chanock SJ, Hunter DJ, Lin XH. Powerful SNP-set analysis for case-control genome-wide association studies. *Am J Hum Genet*, 2010, 86(6): 929–942. [DOI]
- [90] Li MY, Wang K, Grant SF, Hakonarson H, Li C. ATOM: a powerful gene-based association test by combining optimally weighted markers. *Bioinformatics*, 2009, 25(4): 497–503. [DOI]
- [91] Sargolzaei M, Chesnais JP, Schenkel FS. A new approach for efficient genotype imputation using information from relatives. *Bmc Genom*, 2014, 15: 478. [DOI]
- [92] Porcu E, Sanna S, Fuchsberger C, Fritsche LG. Genotype imputation in genome-wide association studies. *Curr Protoc Hum Genet*, 2013, Chapter 1: Unit 1. 25. [DOI]
- [93] Howie B, Fuchsberger C, Stephens M, Marchini J, Abecasis GR. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nat Genet*, 2012, 44(8): 955–959. [DOI]
- [94] Roeder K, Bacanu S-A, Wasserman L, Devlin B. Using linkage genome scans to improve power of association in genome scans. *Am J Hum Genet*, 2006, 78(2): 243–252. [DOI]
- [95] Choi S-H, Liu CY, Dupuis J, Logue MW, Jun G. Using linkage analysis of large pedigrees to guide association analyses. *BMC Proc*, 2011, 5(S 9): S79. [DOI]
- [96] Wang K, Li MY, Bucan M. Pathway-based approaches for analysis of genomewide association studies. *Am J Hum Genet*, 2007, 81(6): 1278–1283. [DOI]
- [97] Evangelou M, Smyth DJ, Fortune MD, Burren OS, Walker NM, Guo H, Onengut-Gumuscu S, Chen WM, Concannon P, Rich SS, Todd JA, Wallace C. A method for gene-based pathway analysis using genomewide association study summary statistics reveals nine new type 1 diabetes associations. *Genet Epidemiol*, 2014, 38(8): 500–510. [DOI]

- 661–670. [DOI]
- [98] Wang K, Li MY, Hakonarson H. Analysing biological pathways in genome-wide association studies. *Nat Rev Genet*, 2010, 11(12): 843–854. [DOI]
- [99] Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA, Paulovich A, Pomeroy SL, Golub TR, Lander ES, Mesirov JP. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci USA*, 2005, 102(43): 15545–15550. [DOI]
- [100] Pan F, Liu XG, Guo YF, Chen Y, Dong SS, Qiu C, Zhang ZX, Zhou Q, Yang TL, Guo Y, Zhu XZ, Deng HW. The regulation-of-autophagy pathway may influence Chinese stature variation: evidence from elder adults. *J Hum Genet*, 2010, 55(7): 441–447. [DOI]
- [101] Sebat J, Lakshmi B, Troge J, Alexander J, Young J, Lundin P, Månér S, Massa H, Walker M, Chi M, Navin N, Lucito R, Healy J, Hicks J, Ye K, Reiner A, Gilliam TC, Trask B, Patterson N, Zetterberg A, Wigler M. Large-scale copy number polymorphism in the human genome. *Science*, 2004, 305(5683): 525–528. [DOI]
- [102] Iafrate AJ, Feuk L, Rivera MN, Listewnik ML, Donahoe PK, Qi Y, Scherer SW, Lee C. Detection of large-scale variation in the human genome. *Nat Genet*, 2004, 36(9): 949–951. [DOI]
- [103] Redon R, Ishikawa S, Fitch KR, Feuk L, Perry GH, Andrews TD, Fiegler H, Shapero MH, Carson AR, Chen W, Cho EK, Dallaire S, Freeman JL, González JR, Gratacòs M, Huang J, Kalaitzopoulos D, Komura D, MacDonald JR, Marshall CR, Mei R, Montgomery L, Nishimura K, Okamura K, Shen F, Somerville MJ, Tchinda J, Valsesia A, Woodwark C, Yang FT, Zhang JJ, Zerjal T, Zhang J, Armengol L, Conrad DF, Estivill X, Tyler-Smith C, Carter NP, Aburatani H, Lee C, Jones KW, Scherer SW, Hurles ME. Global variation in copy number in the human genome. *Nature*, 2006, 444(7118): 444–454. [DOI]
- [104] van Duyvenvoorde HA, Lui JC, Kant SG, Oostdijk W, Gijsbers ACJ, Hoffer MJV, Karperien M, Walenkamp MJE, Noordam C, Voorhoeve PG, Mericq V, Pereira AM, Claahsen-van de Grinten HL, van Gool SA, Breuning MH, Losekoot M, Baron J, Ruivenkamp CAL, Wit JM. Copy number variants in patients with short stature. *Eur J Hum Genet*, 2014, 22(5): 602–609. [DOI]
- [105] Dauber A, Yu YG, Turchin MC, Chiang CW, Meng YA, Demerath EW, Patel SR, Rich SS, Rotter JI, Schreiner PJ, Wilson JG, Shen YP, Wu BL, Hirschhorn JN. Genome-wide association of copy-number variation reveals an association between short stature and the presence of low-frequency genomic deletions. *Am J Hum Genet*, 2011, 89(6): 751–759. [DOI]
- [106] Terwilliger JD, Hiekkalinna T. An utter refutation of the "fundamental theorem of the HapMap". *Eur J Hum Genet*, 2006, 14(4): 426–437. [DOI]
- [107] Yang J, Benyamin B, McEvoy BP, Gordon S, Henders AK, Nyholt DR, Madden PA, Heath AC, Martin NG, Montgomery GW, Goddard ME, Visscher PM. Common SNPs explain a large proportion of the heritability for human height. *Nat Genet*, 2010, 42(7): 565–569. [DOI]
- [108] Wray NR, Purcell SM, Visscher PM. Synthetic associations created by rare variants do not explain most GWAS results. *PLoS Biol*, 2011, 9(1): e1000579. [DOI]
- [109] Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorf LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, Cho JH, Guttmacher AE, Kong A, Kruglyak L, Mardis E, Rotimi CN, Slatkin M, Valle D, Whittemore AS, Boehnke M, Clark AG, Eichler EE, Gibson G, Haines JL, Mackay TFC, McCarroll SA, Visscher PM. Finding the missing heritability of complex diseases. *Nature*, 2009, 461(7265): 747–753. [DOI]

(责任编辑: 谢小冬)