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原发性痛风易感基因研究现状

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摘　要

痛风是一种严重影响健康和生活质量的代谢性疾病，受到遗传因素和环境因素共同作用，且近年来患病率呈上升趋势。原发性痛风是一种多基因遗传性疾病，其发病及临床特征具有明显的遗传特异性。近年来，随着分子生物学技术的发展，全基因组关联分析(Genome-wide association studies, GWAS)已经检测到了导致痛风的多个易感位点和相关候选基因。本文简要介绍了这些基因以及其基因突变位点在痛风发病机制中的作用和对痛风发病的影响，以及这些基因与环境危险因素之间的潜在相互作用，以促进人们对痛风发病机制的理解。

关键词

痛风，基因，全基因组关联分析

Research Status of Susceptibility Genes of Primary Gout

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Abstract

Gout is a metabolic disease that seriously affects health and quality of life. It is affected by both genetic and environmental factors, and its prevalence has been increasing in recent years. Primary gout is a polygenic genetic disease with significant genetic specificity in its pathogenesis and

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clinical characteristics. In recent years, with the development of molecular biology technology, genome-wide association studies (GWAS) have detected multiple susceptibility sites and related candidate genes that cause gout. This article briefly introduces the role of these genes and their mutation sites in the pathogenesis of gout and their impact on the pathogenesis of gout, as well as the potential interactions between these genes and environmental risk factors, in order to promote people's understanding of the pathogenesis of gout.

Keywords

Gout, Gene, Genome-Wide Association Studies

1. 引言

痛风是一组由嘌呤代谢紊乱引起血尿酸水平升高，单钠尿酸盐晶体沉积，从而引起组织损伤的临床综合征[1]。痛风分为原发性和继发性两类，原发性痛风由遗传因素和环境因素共同致病，具有一定的家族易感性；继发性痛风发生在肾脏病、血液病等其他疾病的病程中，或因服用某些药物，接受肿瘤放射或化学治疗等引起[2]。本综述特指原发性痛风。此外，痛风发作可导致急性关节炎、间质性肾炎、关节畸形及障碍等，且患者常伴剧烈疼痛，对健康和生活质量造成严重影响。痛风也是其他慢性疾病的重要风险因素，包括心血管疾病和慢性肾脏病，高血压、2 型糖尿病，血脂异常等疾病，成为亟需关注的公共卫生健康问题。本文主要介绍了痛风的遗传学研究现状，以及这些基因与环境危险因素之间的潜在相互作用，以促进人们对痛风发病机制的理解。

2. 痛风的发病机制

高尿酸血症与痛风的发病密切相关，是痛风发病的重要危险因素，许多研究已经证明了这种关联的存在。高尿酸血症患者中大约 20%的人会发展为痛风，而且血尿酸水平的变化幅度与痛风发作有关[3]。血尿酸水平的急剧波动可使单钠尿酸盐晶体或形状发生变化，从而在组织基质中松动，促使晶体从痛风石已形成沉积的部位释放，引发急性痛风性关节炎。但是大部分高尿酸血症患者不会进展为痛风[4]，高尿酸血症向痛风的进展可分为 4 个阶段[5] [6]。

2.1. 无症状性高尿酸血症与无单钠尿酸盐晶体沉积期

高尿酸血症是指由于尿酸生成过多和/或尿酸排泄减少导致血液尿酸水平升高(血尿酸水平 > 7 mg/dL)，大约 90%的高尿酸血症和痛风患者是由于尿酸排泄量减少和尿酸的重吸收增多引起的[7]。尿酸合成过多主要是由磷酸核糖焦磷酸合成酶(Phosphoribosyl pyrophosphate synthetase 1, PRPS1)和次黄嘌呤/鸟嘌呤磷酸核糖转移酶(Hypoxanthine phosphoribosyl transferase 1, HPRT1)等单基因突变、高嘌呤饮食、酒精和果糖的摄入引起，直接或间接影响嘌呤合成和代谢，导致尿酸生成过多[5]；而尿酸排泄阻碍型则是由于尿酸的转运过程中位于肾近端小管、肠上皮细胞和血管平滑肌细胞中特殊的转运蛋白发生改变引起血液中的尿酸排泄障碍[8]。这些因素共同导致血液尿酸水平升高，引发高尿酸血症和痛风。

2.2. 单钠尿酸盐晶体沉积，但还未出现痛风症状期

单钠尿酸盐晶体优先形成并沉积在软骨上，并且存在于多种不同蛋白质和分子的生物体液中，因此单钠尿酸盐成核在体内很可能是由外来颗粒诱导的。许多研究报告，从痛风患者身上采集的滑液在离体成核试验中增强了单钠尿酸盐晶体成核。特别是与健康人和关节炎或其他晶体性关节病患者的滑液相比，在过饱和尿酸钠溶液中加入痛风滑液导致单钠尿酸盐晶体出现的时间更快，形成的单钠尿酸盐晶体总重量更大[9] [10] [11]。且结缔组织内的不同蛋白质和因子包围在体内尿酸盐分子和尿酸钠晶体周围可能促进晶体继续形成与沉积[12]，有大量证据表明，来自软骨、滑液因子在体外和离体测定中都改变了尿酸盐溶解度[13]，健康人群的尿酸盐在血浆和滑液中的溶解度低于尿液[14] [15]。

2.3. 单钠尿酸盐晶体沉积，且既往或当前出现痛风急性关节炎发作

在大多数患者中，这个阶段表现为痛风发作或者严重的急性炎症性关节炎或腱膜炎。尿酸钠晶体激活的核苷酸结合寡聚化结构域样受体蛋白 3 (NOD-like receptor protein 3, NLRP3)炎症小体与痛风的发作密切相关，其激活依赖于双信号启动系统[16] [17]。第一个为单核细胞膜表面的 Toll 样受体(Toll-like receptor, TLR)介导，第二个为尿酸钠晶体作为刺激信号诱导 NLRP3 炎症小体[18]。最终促进血管扩张导致单核细胞的招募与大量中性粒细胞进入关节液和滑膜，引起痛风的急性发作[19]。

2.4. 晚期痛风

通常发生在痛风已经存在多年后，并与并发症相关，表现为慢性痛风性关节炎或痛风石出现。痛风石是尿酸单钠的结节性肿块。痛风石可能会被感染，引起疼痛的同时也可能引发并发症[20]。

3. 痛风的的全基因组关联分析

痛风的不同流行率表明了种族和基因上的差异[21]。既往 GWAS 研究发现 ABCG2、SLC2A9、SLC22A、SLC17A3 等基因的多态性位点与血尿酸和痛风相关[8] [22] [23] [24]。这些基因通过编码尿酸转运蛋白或相关蛋白，在调节尿酸排泄和维持血尿酸稳态中起关键作用。目前发现起主要调节作用的尿酸转运蛋白基因包括三磷酸腺苷结合转运蛋白 G 超家族成员 2 基因(ABCG2)和葡萄糖易化转运蛋白-9 (SLC2A9)等[25] [26]。由于单核苷酸多态性(single nucleotide polymorphism, SNP)作为生物标志物具有相对稳定、检测费用低、易于快速筛检和分型等特点，国内外学者开展了大量关于尿酸转运基因多态性与血尿酸/痛风关联的研究[27]。

1) ABCG2 基因

ABCG2 被认为是与血尿酸水平和痛风关系最密切的基因之一，ABCG2 位于肾近端小管细胞的刷状边界膜中，编码一种腺苷三磷酸依赖的尿酸分泌分子，在尿酸的顶浆分泌中起重要作用[28] [29]。ABCG2 功能障碍的严重程度是通过两种常见 ABCG2 变体的基因型组合来估计的，即无功能 Q126X (rs72552713) 和半功能 Q141K (rs2231142)，可使相关蛋白功能降低至 50%以下[30]。并且 rs2231142 的 A 等位基因在亚洲人中的突变频率较高，如在日本、韩国和我国汉族人群中约 30%。Kim 等人在韩国的一项病例对照研究(99%的研究对象为男性)结果显示，rs2231142A 等位基因携带者痛风风险是非携带者的 3.32 倍[21]。Chen 等人的研究发现，我国台湾地区的男性 HUA 患者，rs2231142 位点突变基因纯合子型、杂合型携带者痛风发病风险分别是非携带者的 3.37 和 1.84 倍[31]。吴蕾等人的 Meta 分析结果显示，东亚人群痛风与 rs2231142 位点的 A 等位基因多态性存在相关，突变等位基因、杂合子和纯合子基因型痛风发病风险分别是非突变基因携带者的 2.04、1.97 和 3.71 倍[32]。

2) SLC2A9 基因

SLC2A9 基因同样被认为与高尿酸血症和痛风密切相关，该位点存在很强的 GWAS 信号。rs16890979

突变等位基因频率在亚洲人群中同样较高，约 50% [33] [34]。然而与 ABCG2 不同，部分研究发现 SLC2A9 基因 rsl6890979 的突变型等位基因可能是痛风的保护因素[35] [36]，但相关研究结论并不一致。例如，Jade 的一项研究表明，相对于新西兰毛利人、太平洋岛屿的人群来说，SLC2A9 在新西兰高加索样本组中更易患痛风[37]。而 Meng 等人的 Meta 分析结果显示，携带突变型等位基因的人群痛风的患病风险比非携带者降低 56%，分层分析结果提示，该保护效应在亚洲人群中同样显著，携带突变型等位基因者痛风患病风险比非携带者降低 60% [36]；而游玉权等人针对福建人群(男性约占 80%)的研究却发现，rs16890979 突变型等位基因携带者较非携带者痛风患病风险增加 3 倍以上[38]。这些研究结论表明了 SLC2A9 基因的多态性对血液尿酸水平具有群体特异性的影响。除研究结论不一致外，也有学者认为，SLC2A9 基因多态性与痛风的关联还存在性别差异，女性中该基因变异频率更高，致病效应更强[39]。

3) SLC22A 基因

GWAS 研究表明与血液尿酸浓度相关的该家族基因也有 SLC22A11 和 SLC22A12，分别编码 OAT4 和 URAT1 [40]。SLC22A11/OAT4 是一种有机阴离子转运蛋白亚型，位于近端小管的顶膜，它作为有机阴离子与二羧酸交换剂，介导尿酸盐转运穿过肾脏的顶膜[41] [42] [43]。URAT1 是有机阴离子转运蛋白家族的成员，也是血液尿酸积累/转运候选基因[44]，URAT4 与 OAT4 一样，位于近端小管的顶膜，它们都作用于近曲小管对尿酸的重吸收[41]。在一项对欧洲大型人群研究的荟萃分析中发现 SLC22A12 基因可以解释 0.23%的血液尿酸浓度表型变异[45]，而在非裔美国人群体中可使血液尿酸浓度下降 1.21 mg/dL [46]。

4. 环境与遗传因素的相互作用

越来越多的研究证据强调，除遗传因素外，痛风的发病也是遗传和环境危险因素相互作用的结果，包括富含嘌呤的饮食[47] [48]、饮酒[49] [50]、含糖饮料和果糖[51]等环境因素。最近的研究表明，空气污染物如颗粒物，二氧化硫(SO2)和一氧化碳(CO)可能会增加痛风的风险[52] [53]，并且温度和湿度的变化也会影响尿酸水平[54] [55]。环境因素可能诱导或加速促炎介质的产生和释放，从而引起炎症[56]。

基因所起的致病作用及其风险程度需与人群特定的环境因素结合考虑，而且环境危险因素在疾病的发展中起重要作用[57]。2015 年在台湾的一项全国人口研究表明，痛风存在家族聚集性，报告中男性的遗传力为 35.1%，女性为 17.0%，证实了遗传和环境因素在痛风易感性中的重要性[58]。另一项研究报告发现居住在新西兰城市的托克劳安移民患痛风的风险增加了 9 倍，这也强调了决定痛风发生的基因和环境之间的相互作用[59]。易感基因携带者在不良环境因素刺激下的发病风险远高于处于同样环境危险因素暴露水平下的非携带者。

众所周知，高尿酸血症和痛风与饮酒，特别是食用富含嘌呤的酒精饮料有关[60] [61]。Choi 和 Curhan 调查评估了 14,809 名参与者的血清尿酸水平与酒类的摄入量之间的关系。在调整高尿酸血症的其他危险因素前后，啤酒和酒的摄入量与血清尿酸水平的升高呈正相关($P < 0.001$) [62]。除了发现酒精与痛风的相关之外，。在 Choi 的报告中，调整了其他潜在混杂因素后，还发现了饮酒与痛风风险的剂量－反应关系[49]。而在日本的研究发现 LRP2544390 rs1 基因与血清尿酸水平以及 SLC22A12、ABCG2 和 SLC2A9 的多态性有关，且男性饮酒者与 rs2544390 的相关性更强[63] [64]，证明了酒精的摄入与 LRP2 相互作用。Yamanaka 的一项分析也说明了酒精摄入是血清尿酸水平升高的主要因素之一，摄入酒精后 LRP2 可能激活肝脏嘌呤降解途径或者减小肾尿酸排泄量[65]。ALDH2 基因是人类乙醇代谢的关键酶，且证明具有多态性。ALDH2*2 的纯合子在大约 10%的日本和亚洲人群中存在，但在高加索人中极为罕见[66]。ALDH2*2 纯合子的个体对乙醇相当敏感。在酒精性肝病和慢性酒精中毒患者中，ALDH2*2 等位基因的频率显著较小[67]。等位基因 ALDH2*1 为纯合子者，乙醇摄入使血液和尿液中的次黄嘌呤含量显著增加，而 ALDH2*2 等位基因携带者没有此特点，可能为纯合 ALDH2*1 患者体内乙醇引起了大量的嘌呤核苷酸降解[65]。

糖的摄入量也被发现与发生痛风事件的风险有剂量－反应关系，参与尿酸重吸收的蛋白 SLC2A9 参与果糖与葡萄糖的转运[51]，这种关系可能与果糖诱导而发生高尿酸血症有关[68]。一项研究发现 SLC2A9 是高尿酸血症和痛风的强遗传危险因素，研究中观察到 rs11942223 变异影响对果糖负荷的急性血清尿酸反应，这表明 SLC2A9 基因型与 SLC2A9 暴露于含果糖饮料之间存在联系。同时研究的一个关键观察结果是 SLC2A9 对血清尿酸浓度的影响仅限于欧洲高加索人群，同一研究中的新西兰和澳大利亚人 C 等位基因却没有此作用，表明了高尿酸血症是由基因背景和环境因素之间复杂互作的结果[69]。

5. 结语

关于痛风的流行病学的新数据表明，痛风的流行率正在上升。导致痛风的遗传因素众多，嘌呤代谢紊乱是引起血尿酸水平升高和痛风重要的因素。目前，对影响血尿酸水平的候选基因的研究已经提供了具有痛风风险的特定基因多态性的初步证据，然而其他社会经济、饮食和个人因素与遗传因素相互作用，不仅需要考虑各遗传因素和环境因素的主效应，还需要考虑遗传和环境因素的交互作用。流行病学报告已经确定了导致该疾病的一些遗传和环境风险因素。而痛风作为一种复杂的代谢异常疾病，遗传和环境因素的综合作用复杂，对痛风流行病学的研究提出了重要的挑战。

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