

# 高尿酸血症和痛风的遗传学研究进展

郑敏, 麻骏武

江西农业大学, 省部共建猪遗传改良与养殖技术国家重点实验室, 南昌 330045

**摘要:** 痛风是由高尿酸血症引发的一种常见炎性关节病, 受遗传因素和环境因素共同作用。早期研究表明, *PRPS1* 和 *HPRT1* 等单基因稀有突变会引起嘌呤合成代谢紊乱, 从而引发高尿酸血症和痛风。近年来, 全基因组关联分析(Genome-wide association studies, GWAS)已检出多个导致高尿酸血症和痛风的易感位点及相关候选基因。其中 *SLC2A9*、*SLC22A11* 和 *SLC22A12* 基因功能缺失性突变可引起遗传性低尿酸血症, 而过表达则会加强尿酸的重吸收。*ABCG2*、*SLC17A1* 和 *SLC17A3* 基因功能缺陷型变异会降低肾脏和肠道对尿酸的排泄量。因此, 诱发尿酸排泄障碍(高重吸收和低排泄)的基因变异是影响高尿酸血症和痛风的主要遗传因素。另外, 抑制-激活生长因子系统、转录因子、细胞骨架以及基因和环境的互作等因素也一定程度影响血液尿酸水平。在中国汉族人群中, 两个新发现的易感基因 *RFX3* 和 *KCNQ1* 可能造成免疫应答受损和胰岛 B 细胞功能缺陷, 从而直接或间接引起高尿酸血症和痛风。本文系统综述了高尿酸血症和痛风的遗传学研究, 以促进人们对高尿酸血症和痛风发病机理的理解。

**关键词:** 痛风; 高尿酸血症; 尿酸; 嘌呤; 遗传因素; 易感位点

## Research progress in the genetics of hyperuricaemia and gout

Min Zheng, Junwu Ma

National Key Laboratory for Swine Genetics, Breeding and Production Technology, Jiangxi Agricultural University, Nanchang 330045, China

**Abstract:** Gout is one of the most common inflammatory arthritis caused by hyperuricaemia, which is affected by both genetic factors and environmental factors. Early researches show that a few of rare monogenic mutations, such as *PRPS1* and *HPRT1* mutations, lead to abnormal purine anabolism and then cause hyperuricaemia and gout. In recent years, genome-wide association studies (GWAS) have identified dozens of susceptibility loci and/or candidate genes associated with hyperuricemia and gout. Loss-of-function mutations in *SLC2A9*, *SLC22A11*, and *SLC22A12* cause hereditary hypouricaemia, while their overexpression may increase the reabsorption of uric acid. In contrast, loss-of-function mutations in *ABCG2*, *SLC17A1*, and *SLC17A3* cause urate underexcretion of renal and intestinal. These variations leading to blood uric acid excretion disorder (excess reabsorption and underexcretion) are

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作者简介: 郑敏, 硕士研究生, 专业方向: 动物遗传育种与繁殖。E-mail: wuzhizhengmin@163.com

通讯作者: 麻骏武, 博士, 副教授, 硕士生导师, 研究方向: 动物遗传育种与繁殖。E-mail: ma\_junwu@hotmail.com

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the main genetic factors affecting hyperuricemia and gout. Moreover, to some degree, inhibins-activins growth factor system, transcription factors, cytoskeleton and gene-environment interaction can also affect the level of blood uric acid. In addition, two risk genes, *RFX3* and *KCNQ1*, which might impair immune response and lead to functional deficiency of beta cell were recently discovered to influence hyperuricemia and gout in Han Chinese. This paper systematically reviews genetic studies on hyperuricaemia and gout to improve our understanding of pathogenesis of hyperuricaemia and gout.

**Keywords:** gout; hyperuricaemia; urate; purine; genetics factors; susceptibility loci

痛风是由高尿酸血症引起尿酸盐结晶沉积在关节周围而引发的最常见的炎性关节炎<sup>[1-4]</sup>。流行病学调查研究表明美国成年人发病率约为 3.9%<sup>[5]</sup>, 而中国台湾省土著成年居民发病率高达 11.7%。近 10 年, 山东沿海地区痛风发病率增加了 3 倍<sup>[6,7]</sup>。由于人类在进化过程中已丢失尿酸氧化酶(Urate oxidase, UO)基因, 导致嘌呤代谢产物尿酸不能被进一步分解, 因此人类血液尿酸浓度比哺乳动物高<sup>[8,9]</sup>。在生理 pH 值和正常体温下, 血液尿酸浓度大于 6.8 mg/dL 时会引起尿酸盐结晶<sup>[3]</sup>, 大约 10%的高尿酸血症患者最终会出现痛风临床症状<sup>[10]</sup>。对高尿酸血症和痛风患者而言, 血液尿酸水平至少要控制在 6 mg/dL 以下, 低于 5 mg/dL 水平更理想<sup>[11,12]</sup>。

高尿酸血症和痛风的遗传模式非常复杂, 由一系列主效和微效基因所控制并与环境相互作用<sup>[1,4,13]</sup>。血液尿酸水平受肝脏中尿酸的产生量及肾脏和肠的排泄与重吸收平衡状态的影响<sup>[14]</sup>, 所以对体内尿酸稳态的控制是治疗高尿酸血症和痛风的关键<sup>[15]</sup>。图 1 展示了影响高尿酸血症的各类因素, 尿酸过量合成型主要是由于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 phosphoribosyltransferase 1, HPRT1)等单基因突变、高嘌呤饮食、酒精和果糖的摄取等直接或间接地影响嘌呤合成代谢, 导致尿酸生成过量<sup>[16]</sup>; 而尿酸排泄阻碍型则是由于参与尿酸排泄和重吸收的转运蛋白发生改变引起血液中的尿酸排泄障碍。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。由此可见, 体内尿酸合成过剩和无法正常排泄是高尿酸血症和痛风的主要成因。本文主要综述了高尿酸血症和痛风的遗传学研究进展, 以促进人们对高尿酸血症和痛风发病机理的理解。

## 1 单基因稀有突变导致尿酸生成量的增加

尿酸是嘌呤物质的分解产物, 肝脏从头合成和补救途径中合成的嘌呤与消化道对嘌呤的吸收是体内嘌呤的主要来源。PRPS1 超活性和 HPRT 功能缺陷是影响尿酸合成量增加的重要遗传因素<sup>[17]</sup>。其他涉及碳水化合物代谢的基因变异也会直接或间接地影响尿酸的合成与排泄。

### 1.1 PRPS1

PRPS1 催化 5-磷酸核糖合成 5-磷酸核糖-1-焦磷酸, 是人类嘌呤和嘧啶核苷酸的从头合成和补救途径中必不可少的环节。Becker 等<sup>[18]</sup>在嘌呤过合成和痛风患者的身上发现 PRPS 酶活性是正常人的 2~3 倍, 该酶超活性导致与 X 染色体连锁的嘌呤代谢疾病, 临床表现为高尿酸血症和痛风。1972 年, Spering 等<sup>[19]</sup>在患痛风和尿酸结石的两兄弟身上首次发现, PRPS1 上第 52 位天冬氨酸被组氨酸替换, 该错义突变导致患者红细胞磷酸核糖焦磷酸含量升高, 产生高尿酸血症和痛风。该突变的蛋白质结构显示 PRPS1 稳固的交互作用结构因第 52 位组氨酸的替代而被完全摧毁, ATP 结合口袋构象也随之改变, 且对 PRPS1 抑制剂的敏感性降低<sup>[20]</sup>。另外, *PRPS1* c.424G>C(p.Val 142Leu)错义突变也会导致尿酸的过量形成和失聪等其他疾病。p.Val 142Leu 氨基酸影响 PRPS1 抑制位点和 ADP 结合位点的结构<sup>[21]</sup>。因此, PRPS1 超活性会引起高尿酸血症和痛风, 而该酶功能缺陷则会导致其他疾病, 如失聪、脑萎缩和神经性萎缩等<sup>[22, 23]</sup>。

### 1.2 HPRT1

HPRT1 是嘌呤补救途径中最重要的酶, 通过转移 5-磷酸核糖焦磷酸的 5-磷酸核糖, 催化次黄嘌呤合成次黄嘌呤核苷酸及催化鸟嘌呤转化为鸟嘌呤核

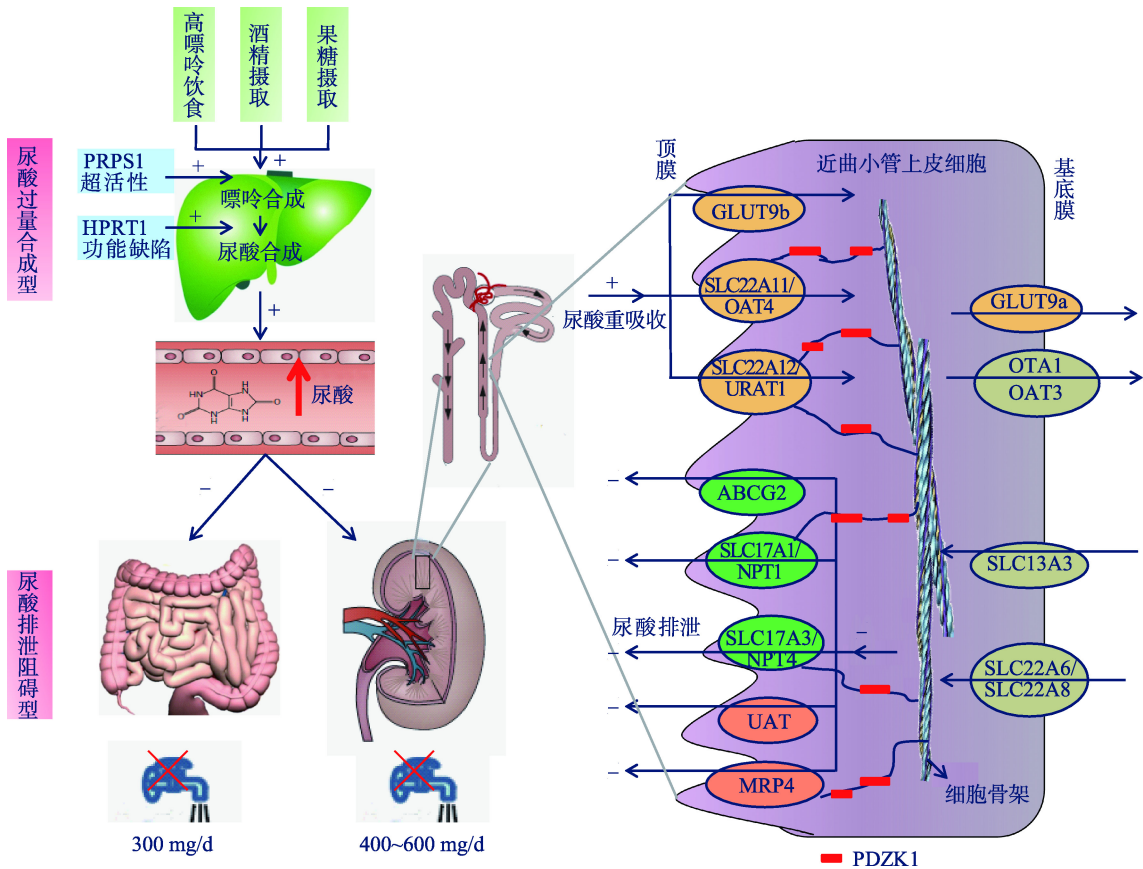


图 1 影响高尿酸血症的因素

Fig. 1 The factors influencing hyperuricaemia

苷酸。早期研究发现,该酶缺陷会引起与性别关联的 Lesch-Nyhan 综合征(自毁容貌症),引起高尿酸血症和尿酸肾结石和早期关节炎<sup>[24,25]</sup>。编码该蛋白的基因存在多个功能缺陷型的遗传变异位点<sup>[26]</sup>,日本 Lesch-Nyhan 综合征患者中,内含子 2 上的 130G>T 突变导致少量 cDNA 缺少外显子 2 和 3<sup>[27]</sup>;内含子 4 到内含子 5 的一个 4224 bp 缺失以及插入 28 bp 异常的序列,导致产生缺失外显子 5 的非正常 mRNA。欧洲和日本患者中同时发现单个碱基缺失(548delT)和点突变(532+1G>C)导致剪切错误<sup>[17]</sup>。在沙特阿拉伯患者中发现与 HPRT1 关联的高尿酸血症呈稳定的增长趋势,在这些病人中发现 13 个不同的突变,它们会不同程度地升高尿酸的含量,最显著的是一名患者 HPRT1 的第 103 位赖氨酸被甲硫氨酸替换,导致 738  $\mu\text{mol/L}$  的高水平的血液尿酸浓度<sup>[28]</sup>。在 HPRT1 功能缺陷的成纤维母细胞中,嘌呤含量正常,但是过剩的嘌呤会被代谢而排出细胞,可能过剩的

嘌呤会促进自身的分解<sup>[29]</sup>,可见 HPRT1 功能缺陷导致过剩嘌呤分解成尿酸排出细胞外是血液尿酸浓度升高的重要原因。

### 1.3 其他相关基因

除了直接参与嘌呤合成代谢途径的基因异常导致高尿酸血症和痛风之外,其他碳水化合物(如糖酵解、葡萄糖、胰岛素和脂类)代谢通路紊乱,也能间接地影响嘌呤的代谢和尿酸的转运。5,10-亚甲基四氢叶酸还原酶(5,10-methylene tetrahydrofolate reductase, 5,10-MTHFR)C677T 突变位点的突变,TT 纯合健康人群血液尿酸水平显著高于 CC 和 CT,提示 C677T 可能是导致高尿酸血症的风险因素<sup>[30]</sup>。乙酰四氢叶酸为嘌呤从头合成的原料物质,5-MTHFR 可能间接地影响嘌呤的从头合成,也可能是 C677T 引发的血管疾病影响了尿酸的排泄; $\beta_3$  肾上腺素能受体( $\beta_3$  adrenergic receptor, ADRB3)Trp64Arg 的多态性与高尿酸血症可能独立相关<sup>[31]</sup>,可能通过调节

脂类分解成脂肪酸介导产生胰岛素耐受性进而导致高尿酸血症;  $\alpha 2$  肾上腺素能受体( $\alpha 2$  adrenergic receptor, ADRA2)第 418 位赖氨酸被天冬氨酸替代会增加患高尿酸血症的风险, ADRA2 抑制去甲肾上腺素的释放, 高去甲肾上腺素使得肾脏血管流量减小, 影响尿酸的排泄<sup>[32]</sup>。与尿酸水平相关的葡萄糖激酶调控蛋白(Glucokinase regulatory protein, GCKR), 可能是通过 6-磷酸葡萄糖介导嘌呤从头合成来调控血液尿酸水平<sup>[33]</sup>。

## 2 高尿酸血症和痛风的全基因组关联分析

人血液尿酸浓度的遗传力为 0.4~0.7 左右<sup>[15]</sup>。据不完全统计(表 1), 全基因组关联分析已经成功地检出约 37 个与高尿酸血症或痛风相关的易感基因位点。不过, 这些位点总共解释不到 10% 的血液尿酸浓度表型变异<sup>[10,15,34~53]</sup>, 且它们功能各异, 其中一些位点如何发挥作用仍不清楚。多数与尿酸转运相关位点在不同的人群中得到重复验证, 但有些位点只在特定群体中被检出, 似乎存在群体特异性(图 2), *SLC2A12* 只在非裔美国人群中检出, 与痛风炎症相关的 *RFX3* 和 *KCNQ* 只在中国人群中发现<sup>[53]</sup>。这些结果极大地丰富了人们对高尿酸血症和痛风遗传基础的理解。

### 2.1 影响尿酸排泄和重吸收的常见易感位点

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。尿酸的转运需要位于肾近端小管、肠上皮细胞和血管平滑肌细胞中特殊的转运蛋白的参与, 研究发现 URAT1 (Urate transporter 1)、MRP4(Multidrug resistance-associated protein 4)、OAT1 和 OAT3(Organic anion transporter 1&3)等维持体内尿酸的稳态起到重要作用。大部分 GWAS 鉴定的候选基因能在肠和肾脏中表达与尿酸转运有关的转运蛋白, 这些蛋白质交合作用形成尿酸转运体, 维持体内尿酸的内稳态<sup>[14, 54]</sup>。尿酸转运体元件包括葡萄糖转运蛋白 9(Glucose transporter 9, GLUT9)、尿酸阴离子转运蛋白 1(URAT1)、有机阴离子转运蛋白溶质转运家族成员(*SLC22A6*、*SLC22A8*、*SLC22A11*、*SLC22A13*)、 $\text{Na}^{2+}$ 偶联单羧酸转运蛋白 1 和 2(*SLC5A8*、*SLC5A12*)和 ATP 结合盒亚家族 G 成员 2(ATP-binding cassette, subfamily G,

member 2, *ABCG2*)<sup>[4]</sup>。几乎所有的吸收和分泌的转运蛋白具有与 PDZK1(PDZ domain containing 1)蛋白结合的识别基序, 该支架蛋白把转运蛋白串联成复杂的复合物(图 1)<sup>[1]</sup>。转录因子 HNF1 $\alpha$  可以结合在 *ABCG2*、*SLC17A1*、*SLC17A3*、*SLC16A9* 和 PDZ 上游来调控而影响尿酸浓度<sup>[15]</sup>。

#### 2.1.1 GLUT9

*SLC2A9* 编码 GLUT9, 在所有与血液尿酸浓度有关的 GWAS 研究中, *SLC2A9* 解释表型变异最高, 解释男女的表型变异分别为 0.5%~2.0%和 3.4%~8.8%<sup>[4]</sup>。人类 GLUT9 有两种明显的 N 末端亚型 GLUT9a 和 GLUT9b, 通过 5'端可变性剪切产生, 分别有 540 和 511 个氨基酸残基<sup>[55]</sup>。Doring 等<sup>[37]</sup>研究发现, 在被研究群体中, 最显著关联位点的主等位基因纯合个体更倾向于产生高浓度血液尿酸, 这可能是 GLUT9b 的表达量高, 而增加尿酸的重吸收。而 *SLC2A9* 功能丧失型突变可导致低尿酸血症<sup>[56]</sup>。

与 GLUT9a 相比, GLUT9b 在 mRNA 表达水平与尿酸浓度具有更加显著的相关性, GLUT9b 可能在尿酸内稳态中起关键性作用<sup>[37]</sup>。对非洲爪蟾卵母细胞实验表明 GLUT9 是高效的尿酸转运子, 被认为是果糖转运子和果糖-尿酸交换器。它被细胞膜的去极化而激活, 其功能可能为尿酸单项传递体或电子转化器<sup>[57]</sup>。GLUT9b 负责近曲小管腔膜对尿酸重吸收的跨膜转运, 而 GLUT9a 是尿酸在基底膜往管周液转运的出口(图 1)<sup>[4]</sup>。

目前, *SLC2A9* 基因内还没鉴定出影响血液尿酸浓度的因果突变, 但该位点有很强的 GWAS 信号, *SLC2A9* 基因编码序列含有丰富的变异。在美国阿米什人群中, 进化保守的 Val253Ile 变异和血液尿酸水平强相关<sup>[58]</sup>, 而该突变对太平洋岛民没有明显的效应<sup>[58]</sup>。在日本和中国人群中, Arg265His 变异与高尿酸血症和痛风有关, 而在毛利人和波利尼西亚人中没有相关性<sup>[59,60]</sup>。提示 *SLC2A9* 的多态性影响血液尿酸水平具有群体特异性。

#### 2.1.2 SLC22A

有机阴离子转运蛋白家族(Organic anion transporter family)是一组高度同源转运有机阴离子的跨膜蛋白, 它们属于两性溶质转运蛋白家族 22A(Amphiphilic solute transporter family 22a, *SLC22A*)。GWAS

表 1 与血液尿酸水平相关的位点和候选基因

Table 1 The loci and candidate genes associated with the level of serum uric acid

基因	最显著关联位点	解释表型变异	部分作用	群体
<i>SCL2A9</i>	rs12498742	3.4%~8.8%	尿酸重吸收高亲和转运蛋白	欧洲 <sup>[35]</sup> 、亚洲 <sup>[49]</sup> 、美洲 <sup>[44]</sup>
<i>ABCG2</i>	Q141K	0.57%	尿酸排泄转运蛋白	欧洲 <sup>[36]</sup> 、亚洲 <sup>[40]</sup> 、美洲 <sup>[36]</sup>
<i>SLC17A1</i>	I269T	0.19%	有机阴离子转运蛋白, 协同转运尿酸排泄	欧洲 <sup>[39]</sup>
<i>SLC17A3</i>	V257F	0.2%~0.7%	有机阴离子转运蛋白, 协同转运尿酸排泄	欧洲 <sup>[36]</sup> 、亚洲 <sup>[50]</sup> 、美洲 <sup>[36]</sup>
<i>SLC22A11</i>	rs17300741	0.19%	尿酸重吸收转运蛋白	欧洲 <sup>[39]</sup>
<i>SLC22A12</i>	C426T	0.13%	尿酸重吸收高亲和转运蛋白	欧洲 <sup>[39]</sup> 、亚洲 <sup>[49]</sup> 、美洲 <sup>[46]</sup>
<i>GCKR</i>	rs1260326	0.13%	参与葡萄糖代谢	欧洲 <sup>[39]</sup> 、中国 <sup>[50]</sup>
<i>SLC16A9</i>	rs1171614	0.17%	肉碱转运蛋白	欧洲 <sup>[39]</sup>
<i>PDZK1</i>	rs1471633	0.19%	锚定 NAT1 和 OAT1 等转运蛋白	欧洲 <sup>[39]</sup>
<i>LRRC16A</i>	rs742132	0.12%	抑制肌动蛋白纤维加帽	欧洲 <sup>[39]</sup>
<i>RREB1</i>	rs675209	0.12%	锌指转录因子	欧洲 <sup>[39]</sup>
<i>INHBC</i>	rs1106766	0.16%	生长因子	欧洲 <sup>[39]</sup>
<i>ALDH16A1</i>	c.1580C>G	0.50%	与 HPRT1 互作, 影响嘌呤代谢	冰岛 <sup>[47]</sup>
<i>SLC2A12</i>	rs9321453		激活一些钾、钠和氯离子通道	美国 <sup>[46]</sup>
<i>MAF</i>	rs889472		转录因子, 调控胚胎发育和软骨细胞分化	欧洲 <sup>[15]</sup> 、东亚 <sup>[49]</sup>
<i>TRIM46</i>	rs11264341		含有与微管结合的结构域	欧洲 <sup>[15]</sup>
<i>INHBB</i>	rs17050272		影响性腺功能、繁殖和胚胎发育等	欧洲 <sup>[15]</sup>
<i>ORC4L</i>	rs2307394		编码复制起始复合体的一个亚基	欧洲 <sup>[15]</sup>
<i>SFMBT1</i>	rs6770152		包含 4 个恶性肿瘤结构域	欧洲 <sup>[15]</sup>
<i>TMEM171</i>	rs17632159		增加转录因子 AP1 的活性	欧洲 <sup>[15]</sup>
<i>VEGFA</i>	rs729761		血管内皮细胞生长因子	欧洲 <sup>[15]</sup>
<i>BAZ1B</i>	rs1178977		调控染色质转录	欧洲 <sup>[15]</sup>
<i>PRKAG2</i>	rs10480300		调控葡萄糖代谢、脂肪酸和胆固醇生物合成	欧洲 <sup>[15]</sup>
<i>STC1</i>	rs17786744		调节肾和肠对钙和磷酸的转运	欧洲 <sup>[15]</sup>
<i>HNF4G</i>	rs2941484		转录因子, 敲除鼠表现为低能耗肥胖	欧洲 <sup>[15]</sup>
<i>AICF</i>	rs10821905		RNA 结合亚基, 涉及 RNA 的编辑和加工	欧洲 <sup>[15]</sup>
<i>OVOL1</i>	rs642803		锌指转录抑制子	欧洲 <sup>[15]</sup>
<i>ATXN2</i>	rs653178		突变可以导致脑共济失调	欧洲 <sup>[15]</sup>
<i>UBE2Q2</i>	rs1394125		涉及细胞骨架的构造和调控	欧洲 <sup>[15]</sup>
<i>IGF1R</i>	rs6598541		生长因子, 涉及胰岛素耐受性	欧洲 <sup>[15]</sup>
<i>NFAT5</i>	rs7193778		调控渗透应力基因表达的转录因子	欧洲 <sup>[15]</sup>
<i>HLF</i>	rs7224610		肝白血病因子	欧洲 <sup>[15]</sup>
<i>LRP2</i>	rs2544390		介导配体内吞入溶酶体降解	亚洲 <sup>[43]</sup>
<i>SF1</i>	rs606458		涉及 ATP-依赖性拼接复合物的形成	中国 <sup>[50]</sup> 、美洲 <sup>[46]</sup>
<i>BCAS3</i>	rs11653176		调节 IFN- $\gamma$ , 引发炎体反应	欧洲 <sup>[15]</sup> 、中国 <sup>[53]</sup>
<i>RFX3</i>	rs12236871		转录因子, 涉及纤毛发生和 $\beta$ 细胞功能	中国 <sup>[53]</sup>
<i>KCNQ1</i>	rs179785		糖尿病易感基因, 也涉及先天免疫应答	中国 <sup>[53]</sup>

PRKAG2	STC1		
BAZ1B	RREB1	RFX3*	
VEGFA	SLC16A9	KCNQ1*	
TMEM171	R3HDM2-INHBC	LRP2	
SFMBT	ALDH16A1	SF1	
INHBB	BCAS3	BCAS3	
TRIM46	MAF	MAF	
HNF4G	SLC17A1	SLC17A1	
A1CF	SLC22A11	SLC22A11	
B3GNT4	LRRC16A	LRRC16A	
ACVR1B	PDZK1	PDZK1	
HLF	GCKR	GCKR	SLC2A12
NFAT5	SLC17A3	SLC17A3	SLC17A3
IGF1R	ABCG2	ABCG2	ABCG2
UBE2Q2	SLC22A12	SLC22A12	SLC22A12
ATXN2	SLC2A9	SLC2A9	SLC2A9

\* 中国特有

欧洲特有

亚洲特有

美洲特有

欧亚共享

三区共享

欧洲

亚洲

美洲

图 2 不同人群易感位点的比较

Fig. 2 The comparison of susceptibility loci among populations

研究表明与血液尿酸浓度相关的该家族基因有 *SLC22A11* 和 *SLC22A12*，分别编码 OAT4 和 URAT1，它们作用于近曲小管对尿酸的重吸收<sup>[39]</sup>。

在家族性低尿酸血症患者中发现 URAT1 蛋白功能缺失性突变<sup>[61]</sup>。在德国人群中启动子(−788T>A)、外显子 1(C258T)和外显子 2(C426T)的变异会引起尿酸排泄水平的降低，其中外显子 2(C426T)的效应最强<sup>[62]</sup>。在欧洲群体中 *SLC22A12* 可以解释血液尿酸浓度表型变异的 0.13%<sup>[41]</sup>，在非裔美国人群体中鉴定出非同义突变(Gly65Trp)可使血液尿酸浓度下调 1.19 mg/dL<sup>[46]</sup>。

*SLC22A11*/OAT4 在近曲小管细胞中表达并锚定于顶膜，OAT4 被证明为不对称低亲和转运蛋白，利用有机阴离子与二羧酸盐交换的形式对尿酸重吸收<sup>[63,64]</sup>。rs17300741 与血液尿酸排泄障碍型痛风显著相关，其功能暂时还不清楚，可能影响 OAT4 的表

达或与功能 SNP 强连锁<sup>[65]</sup>。

2.1.3 ABCG2

*ABCG2* 在众多群体中被鉴定与血液尿酸水平和痛风强相关。*ABCG2* 属于 ABC 超家族转运蛋白家族的多功能成员，在肾脏近曲小管刷状缘膜中表达，在尿酸的顶浆分泌中起重要作用<sup>[66]</sup>。该转运体也在小肠上皮细胞和肝脏中大量表达，可能起尿酸的肾外排泄作用<sup>[67]</sup>。

与痛风强相关的 *ABCG2* 外显子 5 上的单核苷酸多态性(Single-nucleotide polymorphism, SNP) rs2231142，导致 Glu141Lys 氨基酸置换，该 SNP 可以解释欧洲群体血液尿酸浓度表型变异的 0.57%，相对女性群体而言，该位点的多态性对男性影响大<sup>[39]</sup>。功能方面的研究表明，该变异可以引起 *ABCG2* 介导的尿酸转运减少 53%，导致尿酸的排泄吸收平衡打破，最终诱发高尿酸血症<sup>[66]</sup>。

#### 2.1.4 SLC17A

SLC17A 家族转运蛋白是  $\text{Na}^+$  依赖磷酸转运蛋白, 也会介导有机阴离子跨膜转运<sup>[68]</sup>。SLC17A1 和 SLC17A3 在多个人群的血液尿酸 GWAS 结果中得到重复验证, 二者均能在肝脏和肾脏中表达, 介导尿酸的跨膜转运<sup>[36,39]</sup>。

SLC17A1/NPT1 能够转运包括尿酸在内的多种底物, 主要在肾脏中表达。2010 年, Urano 等<sup>[69]</sup>对日本群体研究表明 SLC17A1 多态性与早期痛风有关。2015 年, Chiba 等<sup>[70]</sup>证明 NPT1 锚定于近曲小管顶膜, 第 269 位异亮氨酸被苏氨酸替换的功能获得性突变会降低患尿酸排泄型痛风的风险, NPT1 可能是肾脏中尿酸排泄的首要转运蛋白, 而 ABCG2 主要介导肠道尿酸的转运。

SLC17A3/NPT4 有 11 个外显子<sup>[68]</sup>, 在肝脏和肾脏中表达编码转运有机阴离子的钠依赖磷酸盐转运蛋白 4, 参与尿酸及多种阴离子的排泄, NPT4 的第 68 位天冬氨酸被组氨酸替换和第 304 位苯丙氨酸被丝氨酸替换显著降低尿酸转运活性<sup>[71]</sup>; 其第 257 位缬氨酸被组氨酸替换降低尿酸盐的转运水平, 进而导致尿酸排泄量减小<sup>[72]</sup>。

#### 2.1.5 NHERF3

PDZKI 基因编码钠氢交换调节因子(Sodium-hydrogen exchanger regulatory factor, NHERF3), 其 PDZ 结构域调节 URAT1、OAT4 和 NPT1 等转运蛋白的亚细胞定位, 是形成尿酸转运体的重要支架蛋白(图 1)<sup>[73]</sup>。在该基因中, rs12129861 是首先被鉴定出与血液尿酸浓度相关的多态位点<sup>[39]</sup>, 并在其他研究中得到重复验证<sup>[33]</sup>。尽管该位点的次等位基因 A 有利于降低血液尿酸浓度, 但目前未检测到与痛风相关联的信号, 暗示其可能不是强的遗传风险因子<sup>[74]</sup>。

### 2.2 中国人群特异性的易感位点

针对中国人群的 GWAS 研究相对较晚, 在其他群体中检出的一些位点在中国人群中也能检测到显著的 GWAS 信号<sup>[50,51]</sup>(图 2)。2015 年 Li 等<sup>[53]</sup>在中国人群中成功鉴定与痛风相关的 3 个新位点(BCAS3、RFX3 和 KCNQ1)。最强信号位点位于 BCAS3 内含子中, 这与在大样本的欧洲群体中检测到 BCAS3 与血液尿酸浓度相关结果相一致<sup>[15]</sup>, BCAS3 作为雌性激

素介导的转录激活剂在乳腺癌细胞中过量表达<sup>[75]</sup>。另外, 在 BCAS3 下游大约 7 kb 区域有一个 TBX 基因, 它可以调控 IFN- $\gamma$  的表达。IFN- $\gamma$  是先天适应性免疫重要的细胞因子, 尿酸盐晶体和 IFN- $\gamma$  结合, 共同调控鼠巨噬细胞中 iNOS 的表达和 NO 的产生, 因此 TBX2 可能是通过调节 IFN- $\gamma$  介导痛风的形成<sup>[60]</sup>。其他研究表明 KCNQ1 功能缺失也可导致先天性免疫应答发生改变<sup>[76]</sup>。

RFX3 和 KCNQ1 都涉及胰岛 B 细胞( $\beta$ -细胞)的功能<sup>[77,78]</sup>。RFX3 是胰岛 B 细胞功能和分化必须的, RFX3 蛋白可结合到葡萄糖激酶基因的启动子区域, 并调控其表达, 从而影响胰岛 B 细胞的功能<sup>[77]</sup>; KCNQ1 在多个群体中鉴定为糖尿病的易感基因, 其风险等位基因能够影响胰岛 B 细胞对胰岛素的分泌或应答<sup>[78,79]</sup>。胰岛 B 细胞是维持体内糖代谢的重要细胞, 糖代谢的混乱不仅直接影响嘌呤的合成代谢及尿酸的合成, 而且影响尿酸的排泄<sup>[15,33]</sup>。

近几十年来, 中国人群整体水平的饮食结构发生了极大改变, 脂类、糖类和蛋白类食物的摄入量明显提高, 代谢综合征的发病率也逐步上升, 这可能是营养和基因互作的结果, 从而使中国人群的痛风遗传呈现独有的特点。

### 2.3 基因间互作与网络的影响

2013 年 Kottgen 等<sup>[15]</sup>通过对超过 14 万样本的分析, 成功鉴定出 28 个与血液尿酸水平相关的位点。其中 B3GNT4 和 ACVR1B-ACVRL1 两个新位点是利用系统的功能网络相关性分析鉴定的, 这些位点除了涉及嘌呤的合成代谢和尿酸转运以外, 还涉及到一些其他的功能(表 1)。抑制-激活生长因子系统也被鉴定与血液尿酸浓度相关的通路有关, 该通路主要通过调控能量平衡、胰岛素释放、炎症、细胞凋亡和性激素调控等影响血液尿酸水平。另外还鉴定了转录和调控(MAF、HNF4G 和 AICF)、细胞骨架(UBE2Q2 和 LRRC16A)、脑疾病(ATXN2 和 SFMBT1)相关的基因与尿酸水平相关, 但它们准确的作用机制暂不明确。可见血液尿酸水平的遗传因素非常广泛, 为多基因间交互作用形成复杂的遗传机制。

### 3 环境和遗传互作

众所周知, 高尿酸血症和痛风与酒精的摄取有

一定关系。2010年Kamatani等<sup>[43]</sup>在日本人群中的研究发现 *LRP2* 基因与血液尿酸浓度有关。2012年Hamajima等<sup>[80]</sup>证实酒精的摄取和 *LRP2* 互作, rs254-4390 C>T 位点风险等位基因 T 纯合的人更倾向于饮酒。在摄取酒精的情况下, *LRP2* 可能激活肝脏嘌呤降解途径或者减小肾尿酸排泄量。在痛风人群中, 编码功能缺陷 *ALDH2* 的等位基因 *ALDH2\*2* 频率显著低于健康人群, 等位基因 *ALDH2\*1* 纯合患者, 酒精摄入后血液和尿液的次黄嘌呤含量显著升高, 而 *ALDH2\*2* 等位基因携带者没有此表征, 可能纯合 *ALDH2\*1* 患者体内酒精引起大量的嘌呤核苷酸降解<sup>[81]</sup>。2010年Sulem等<sup>[47]</sup>发现在 *ALDH16A1* 基因 c.1580C>G 位点的低频错义突变与痛风和尿酸浓度相关, 该基因编码蛋白参与体内酒精的代谢, 还能通过与 HPRT1 蛋白-蛋白的互作, 使 HPRT1 保持最佳酶活, 互作被破坏会导致 HPRT1 酶活降低, 而导致高尿酸血症<sup>[82]</sup>。

流行病学研究表明长期摄取果糖会显著提高痛风患病风险<sup>[83]</sup>, 参与尿酸重吸收的蛋白 GLUT9 参与果糖转运。在针对未患痛风的志愿者短期果糖摄入的研究中, 发现欧洲白种人在 *SLC2A9*(rs11942223 位点)非 C 的参与者的血液尿酸水平更可能维持在饱和水平以上。在果糖的摄入时, C 等位基因的存在会增加肾尿酸排泄比例, 同一研究中新西兰和澳大利亚人 C 等位基因却没有此效果, 提示高尿酸血症是由遗传背景和环境因素复杂互作的结果<sup>[84]</sup>。

## 4 结 语

导致高尿酸血症和痛风的遗传因素众多, 体内嘌呤代谢和能量代谢异常是引起尿酸生成过剩型高尿酸血症和痛风重要的因素。而参与尿酸重吸收的基因过量表达或参与尿酸排泄的基因发生功能缺陷型变异均会导致血液尿酸排泄障碍型高尿酸血症和痛风。全基因组关联分析还检出了其他一些易感位点及候选基因, 但仍需进行更深入的功能分析。此外, 遗传因子与环境因子互作还有待于深入研究。部分影响血液尿酸水平的多态性位点具有群体特异性, 因此可根据不同人群的遗传特点, 开发有针对性的遗传标记和药物运用于临床诊断和治疗。将遗传学和临床医学紧密结合, 实现精准医疗是未来临床实践的重要内容和方向。

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