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疼痛与共情专辑 论 文
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基于全基因组关联分析探究痛觉诱发脑岛神经响应的遗传基础

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摘要 通过全基因组关联分析(genome-wide association study, GWAS)探索中国汉族人群疼痛诱发脑岛神经响应个体差异背后的遗传影响因素. 研究共纳入333名经质控合格且同时采集了基因和脑影像数据的中国汉族健康被试, 基因型数据经质控插补后包含5270947个单核苷酸多态性(single nucleotide polymorphism, SNP)位点, 脑影像数据为痛觉刺激任务态功能磁共振成像(functional magnetic resonance imaging, fMRI)数据. 首先基于fMRI数据利用一般线性模型(general linear model, GLM)获得痛觉刺激条件下每位被试左侧和右侧脑岛区域各自的平均激活值以及双侧脑岛的平均激活值, 并将其作为GWAS表型数据分别对5270947个SNP逐一计算脑岛激活与SNP之间的关联. 结果显示, 在$P<5\times10^{-6}$阈值下, 10个独立SNP位点与左侧脑岛的激活水平存在显著关联, 7个独立SNP位点与右侧脑岛的激活水平存在显著关联, 12个独立SNP位点与双侧脑岛的平均激活水平存在显著关联. 所有显著位点可注释到9个基因上, 其中*BACE1*基因已被报道与疼痛相关, 其他基因与脑影像表型或常见神经精神疾病相关. 这些发现为深入理解疼痛诱发脑岛神经响应个体差异背后的遗传机制提供了有力证据.

关键词 疼痛, 脑激活, 脑岛, 全基因组关联研究, 功能磁共振成像

疼痛是一种主观体验, 具有明显的个体间差异[1]. 近年来神经影像技术发展迅速, 功能性磁共振成像(functional magnetic resonance imaging, fMRI)技术因其具有安全无创、高空间分辨率等特点, 成为探索疼痛神经机制的重要工具. 疼痛感知由大脑皮层的神经活动产生, 在既往研究中, 疼痛刺激诱发fMRI脑响应的个体差异常被视为噪声而被忽略, 但本团队[2]前期的研究表明, 基于个体脑激活图可从群体中准确识别该个体, 表明疼痛脑响应同样存在个体间差异. 遗传可能是疼痛脑响应个体差异背后的重要影响因素. 脑岛是人脑内疼痛信息处理的重要区域[3], 已有全基因组关联分析(genome-wide association study, GWAS)研究

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从脑结构的角度报道了右侧脑岛灰质密度与多个遗传位点之间的关联可能在疼痛敏感性个体差异中发挥重要作用[4], 但目前尚无研究从脑功能的角度报道疼痛刺激条件下, 脑岛激活水平的个体差异是否具有相应的遗传基础. 为此, 本研究使用GWAS方法, 以疼痛诱发的脑岛激活作为表型, 识别与其具有显著关联的遗传位点, 从而为深入理解疼痛脑响应个体差异的遗传机制提供证据.

1 资料与方法

1.1 研究对象

本研究所使用的数据集中有511名被试采集了任务态fMRI数据, 484名被试采集了外周血, 并进行DNA提取和测序. 所有被试均为中国健康被试, 经遗传和影像数据质控, 取既包含质控合格的遗传数据又包含痛觉任务态fMRI数据的汉族被试, 本研究最终纳入中国汉族健康被试333人(具体质控流程见图1), 其中女性195人, 男性138人, 平均年龄为(21.5±4.4)岁. 所有被试无急性和慢性疼痛问题, 无神经系统疾病、脑血管疾病, 以及精神障碍, 在实验开始的前一个星期内无任何镇痛药物服用记录. 在实验开始前每名被试均签署了知情同意书. 本研究获得了中国科学院心理研究所伦理委员会的批准.

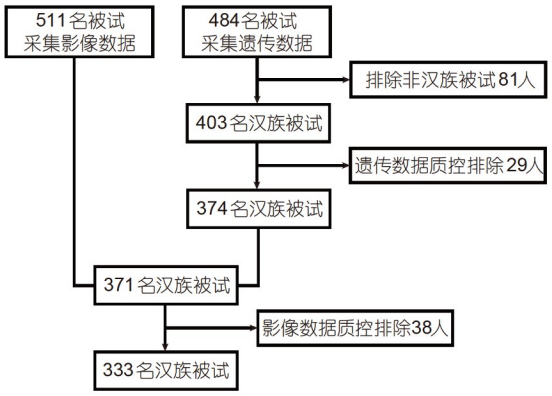

图 1 被试质控流程图
Figure 1 Flowchart of the subject quality control

1.2 实验设计

任务态fMRI实验涉及多种感觉模态的刺激. 401名被试的实验任务包括痛觉、触觉、视觉、听觉4种感觉模态刺激, 52名被试的实验任务包括痛觉、视觉、听觉3种模态刺激, 58名被试的实验任务包括触觉、视觉、听觉3种模态的刺激. 每名被试的fMRI实验均包含2个组块(block), 每一组块包含30(仅含有3种模态刺激的实验范式)或40(含有4种模态刺激的实验范式)个刺激(每种模态刺激有2个强度, 每个强度有5个刺激), 每种刺激随机呈现. 痛觉刺激由红外线激光器(Nd:YAP, Electronical Engineering, Italy)产生的激光束引起, 激光脉冲持续时间为4 ms, 施加于被试左手背的正方形区域(5 cm×5 cm). 265名被试低痛和高痛刺激强度分别为3和3.5 J, 188名被试低痛和高痛刺激强度分别为3.5和4 J. 触觉刺激由电刺激器(DS7A, Digitimer, UK)产生的恒流方波电脉冲引起, 脉冲持续时间为1 ms, 施加于被试左手手腕上, 由电极间距离1 cm的圆形电极施加, 所有被试低和高两种强度的刺激均分别设定为2和4 mA. 视觉刺激为计算机屏幕黑色背景下的灰色圆盘, 使用圆盘上2种不同的RGB数值(100, 100, 100)和(200, 200, 200)作为低和高两种刺激强度. 听觉刺激为头戴式耳机的双耳单声道纯音刺激(800 Hz, 持续时间为50 ms, 上升和下降时间均为5 ms), 低和高两种强度的刺激分别设定为76和88 dB SPL. 每个刺激呈现前屏幕中心会出现6 s的白色“十”字, 持续至刺激后10 s, 然后屏幕上出现0~10的数字评分量表(numerical rating scale, NRS; 0表示未感受到刺激, 10表示在该种模态刺激条件下所能想象到的最强烈的感觉), NRS共呈现5 s, 被试需要在此期间通过右手按键对刺激强度进行评分, 然后随机间隔1或2 s, 再重复下一个刺激的上述过程. 由于本文仅关注痛觉激活的遗传基础, 因此实验中的触觉、视觉和听觉刺激在本研究中未做分析.

1.3 MRI数据采集

本研究使用3T的MRI系统(GE Healthcare Systems, Milwaukee, WI, USA)收集MRI数据. 任务态fMRI数据通过T2加权梯度回波序列(gradient echo sequence, GRE)采集, 扫描参数为: 重复时间(repetition time, TR)=2000 ms; 回波时间(echo time, TE)=29 ms; 视野(field of view, FOV)=192 mm×192 mm; 采集矩阵(acquisition matrix)=64×64; 翻转角度(flip angle)=90°; 层厚(slice thickness, ST)=3 mm, 连续扫描43层. 高分辨率3D T1加权图像通过扰相梯度回波序列(spoiled gradient-recalled echo, SPGR)采集, 采集参数为: TR=6.896 ms; TE=2.992 ms; FOV=256 mm×256 mm; acquisition matrix=256×256; ST=1 mm.

1.4 影像数据处理

使用SPM12(Statistical Parametric Mapping, https://www.fil.ion.ucl.ac.uk/spm/)对fMRI数据进行预处理. 首先删除每个被试任务态图像的前3个时间点, 以保证图像信号稳定, 随后进行: (1) 时间层校正, 将中间层作为参考把全脑43层图像校正至同一时间点; (2) 头动校正, 使用刚体变换对所有时间点的全脑图像进行对齐, 生成7列头动参数(3列平移参数, 3列旋转参数以及1列逐帧位移参数FD(frame-wise displacement)[5]); (3) 空间标准化, 使用T1联合分割配准将功能像配准到MNI(Montreal Neurological Institute)标准空间并重采样为3 mm×3 mm×3 mm体素大小; (4) 使用6 mm半高全宽(full width at half maximum, FWHM)的高斯核进行空间平滑.

使用SPM12软件进行脑激活分析. 首先基于AAL模板[6]提取左侧及右侧脑岛区域, 再利用一般线性模型(general linear model, GLM)对每名被试脑岛区域进行逐体素的脑激活分析. GLM模型纳入的实验刺激条件包括每种模态感觉刺激时间序列及其时间导数序列, 以及刺激强度评分期. 模型还纳入了7列头动参数作为协变量. 基于该模型获得个体水平痛觉刺激条件下的脑岛激活图. 然后利用单样本t检验对个体水平脑岛痛觉激活图进行组水平分析, 获得组水平脑岛痛觉激活图, 统计显著性阈值设定为基于团块水平的FWE(family-wise error)校正后P<0.05(团块定义阈值为P<0.001). 基于所得到的组水平脑岛痛觉激活图定义左侧脑岛激活区和右侧脑岛激活区, 再从个体水平脑岛痛觉脑激活图上提取每个被试左侧和右侧脑岛激活区各自的平均激活值(β值)以及双侧脑岛总体平均激活值, 剔除激活值偏离中位绝对偏差(median absolute deviation, MAD)±6倍的被试, 然后对左侧、右侧及双侧脑岛的激活值进行正态分数转换, 作为后续GWAS分析中的3个脑影像表型.

1.5 遗传数据

484名被试的遗传数据通过Affymetrix 平台的Capital Biotechnology Precision Medicine Research Array (CBT-PMRA)Kit进行基因分型(基于人类参考基因组GRCh38版本), 后续主成分分析和数据插补时的参考模板选用千人基因组计划阶段3(1000 Genomes Project Phase 3)[7,8]的数据, 使用PLINK[9]软件将484名被试中的81名非汉族被试排除, 对剩下的403名汉族被试进行进一步质量控制. 在位点水平: 排除了583个重复位点, 检出率(call rate)低于95%的101955个位点, 次等位基因频率(minor allele frequency, MAF)小于0.01的164861个位点, 偏离哈迪-温伯格(Hardy-Weinberg)平衡点(P<1×10^{-6})的942个位点. 在个体水平: 排除了29名被试(性别不匹配的3个, 位点缺失率大于5%的12个, 杂合率在距离均值5个标准差以外的3个, 血缘同源数值大于0.1875的10个, 主成分分析中偏离参考模板亚洲人群的1个), 剩余374名质控合格的汉族被试. 质控后进行连锁不平衡(linkage disequilibrium, LD)修剪, 然后生成前20个主成分(principal component, PC), 使用Tracy-Widom测试[10]检验出前4个成分P<0.05, 将前4个PC作为GWAS分析的协变量. 对质控后的位点我们使用Snpflip(https://github.com/biocore-ntnu/snpflip)将位于负链上的位点翻转到正链上, 并删除歧义位点, 然后使用SHAPEIT2[11]和IMPUTE2[12]分别进行定相和插补, 最后将MAF≥0.05且Info值(information score)≥0.9的5270947位点纳入GWAS分析.

1.6 GWAS分析和位点注释

使用PLINK软件的线性加性模型, 在模型中加入年龄、性别和4个遗传PC作为协变量, 对5270947个SNP位点和左侧、右侧、双侧脑岛的3个痛觉激活值表型进行GWAS分析, 确定与脑岛痛觉激活值相关的遗传位点, 显著性阈值定义为P<5×10^{-6}, 基于所得到的与3个表型显著关联的SNP位点确定独立显著SNP位点(满足LD r^2<0.1且物理距离大于250 kb), 并使用SNPnexus[13]注释工具对所有显著位点进行基因及功能注释, 使用GWAS Catalog[14]查询位点匹配基因的相关研究.

2 结果

2.1 脑激活分析结果

组水平脑岛痛觉激活结果如图2所示, 左侧和右侧脑岛激活体素数分别占各自总体素数的92.23%和92.58%.

2.2 GWAS和注释结果

左侧、右侧、双侧脑岛痛觉激活表型的GWAS曼哈顿图如图3所示. 与这3个表型存在显著关联

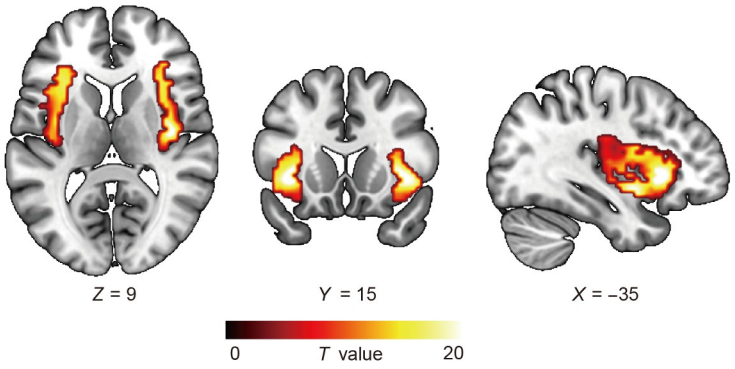

图 2 (网络版彩色)脑岛的组水平痛觉激活图(团块水平的FWE校正)
Figure 2 (Color online) Group-level insular activation map induced by nociceptive stimuli (statistical threshold corrected using cluster-level FWE)

(P<5×10^{-6})的SNP位点共有110个, 其中独立SNP位点有29个(表1). 与左侧脑岛痛觉激活表型存在显著关联的SNP位点有30个, 其中独立SNP位点有10个, 与右侧脑岛痛觉激活表型存在显著关联的SNP位点有42个, 其中独立SNP位点有7个, 与双侧脑岛痛觉激活表型存在显著关联的SNP位点有38个, 其中独立SNP位点有12个. 3个表型重叠的显著关联SNP有4个(rs2087706, rs6573058, rs2066399, rs35431736), 其中前3个均为独立位点. 110个显著SNP位点共注释到9个基因上, 基因及功能注释结果如表S1所示. 9个基因中, *BACE1*基因曾被报道与疼痛相关[15], 已被纳入疼痛基因数据库[16], 其他基因均与脑表型或者神经精神疾病相关. 其中, 位点rs2087706与3个脑岛痛觉激活表型均存在显著相关, 且相关性最为显著(P<1×10^{-6}), 距离该位点最近的上游基因是*SAMMSON*, 与双相情感障碍[17]和精神分裂症有关[18], 距离最近的下游基因是*COX6CP6*, 曾被报道和精神分裂症有关[18].

3 讨论

脑岛是人脑内疼痛信息处理的核心区域之一, 以脑岛为感兴趣区探究疼痛诱发脑激活个体差异背后的遗传影响因素具有重要意义. 由于前人文献提示左侧和右侧脑岛的功能并不完全相同[19], 且左右侧脑岛的灰质密度存在遗传差异[4], 所以本研究以疼痛诱发的左侧、右侧、双侧脑岛的激活作为3个表型, 分别进行GWAS分析, 共识别出与左侧、右侧、双侧脑岛的痛觉脑响应显著关联的SNP位点共110个, 这些SNP可被注释到9个基因上, 主要与疼痛、脑表型或神经精神疾病有关. 此外, GWAS结果显示, 与左侧、右侧、双侧脑岛显著关联的SNP并不完全相同, 提示脑岛不同区域的疼痛诱发神经响应的遗传基础也可能存在差异.

本研究发现, *BACE1*、*BCL2*、*MSI2*、*SLC29A1*、*SGPP2*、*FANCC*、*KDM2B*、*RPL13AP3*、*ZSWIM6*共9个基因与疼痛诱发的脑岛激活表型存在显著关联. *BACE1*是一种I型跨膜天冬氨酸蛋白酶, 能裂解淀粉样前体蛋白, 前人研究通过小鼠实验显示*BACE1*调节中枢神经和周围神经的髓鞘化过程和髓鞘厚度, 并表明*BACE1*的缺失会导致小鼠疼痛敏感性升高[20]. *BCL2*是抑制细胞凋亡的原癌基因蛋白, 在中枢神经系统中过表达可以防止对神经生长因子有反应的神经元的凋亡[21]. *MSI2*基因编码神经RNA结合蛋白, 在室管膜下区的神经细胞中强烈表达[22]. *BCL2*、*MSI2*、*SLC29A1*、*SGPP2*、*ZSWIM6*都曾被报道和精神分裂症有关[23~27]. *FANCC*在DNA损伤和氧化应激等细胞应激后的信号转导过程中发挥作用, 有研究发现*FANCC*促进神经元生长[28], 并有研究发现其和大脑皮层厚度有关[29]. *KDM2B*和*ZSWIM6*曾被报道和阿尔茨海默病[30,31]、双相情感障碍有关[32,33], *RPL13AP3*和认知功能有关[34]. 虽然上述基因中除*BACE1*外, 鲜有研究报道其与疼痛之间的直接关联, 但有证据提示目前已报道的与这些基因存在关联的脑表型(如皮层厚度)与疼痛感知有关, 并且精神分裂症、双相情感障碍、阿尔茨海默病等神经精神疾病患者存在疼痛感知异常及较高的疼痛症状易感性. 例如, 有研究发现, 患有精神分裂症和双相情感障碍的退伍军人相对于没有这些精神疾病的退伍军人更有可能患有慢性疼痛[35], 精神分裂症患者对痛觉刺激的感知强度明显小于健康对照组[36], 以及疼痛对日常活动的干扰可能会增加阿尔茨海默病的风险[37]. 这些结果提示, 识别与疼痛诱发脑影像表型存在显著关联的遗传位点可为发现与疼痛感知相关联

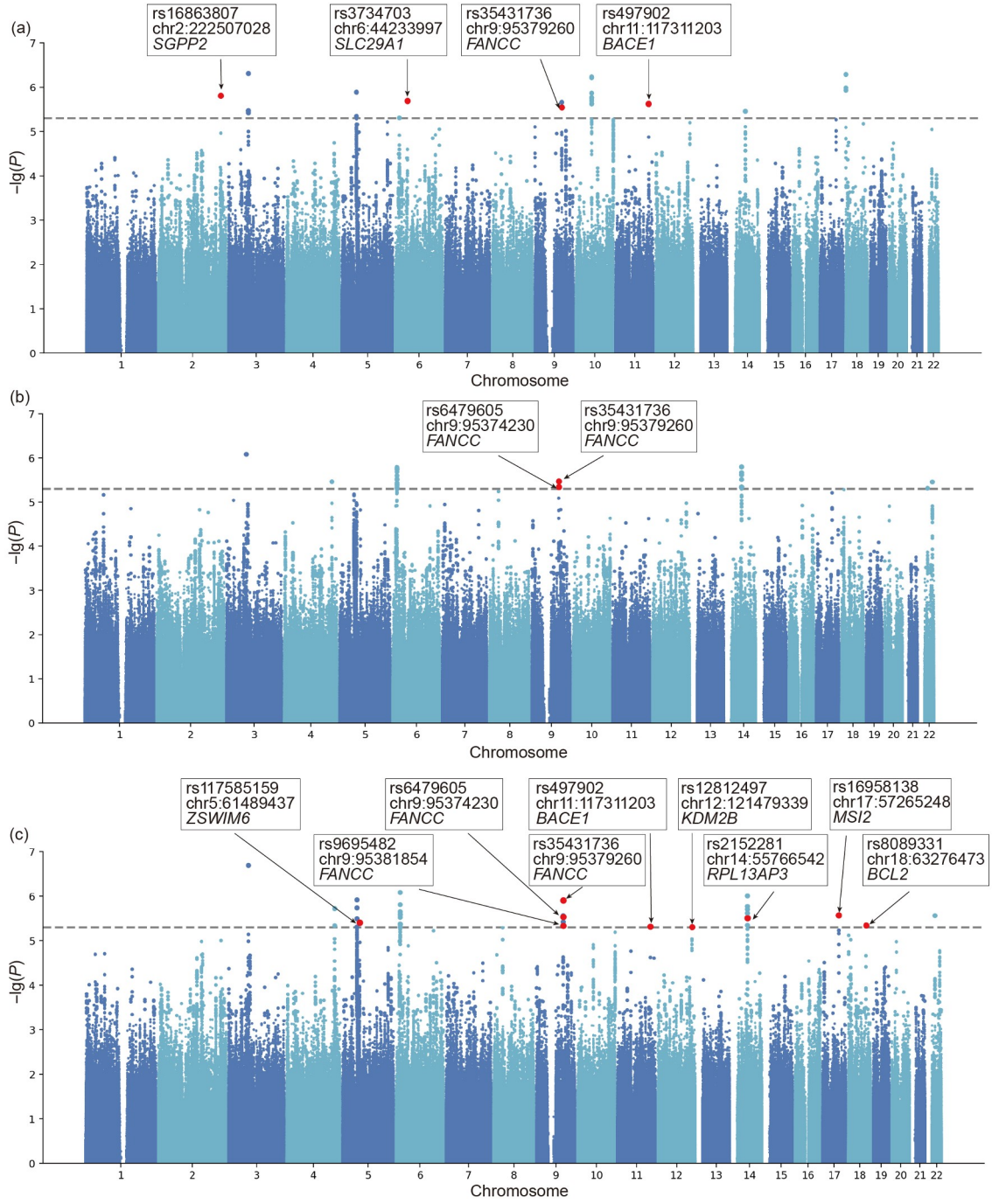

图 3 (网络版彩色)脑岛痛觉激活表型的GWAS曼哈顿图. (a)~(c)分别为左侧脑岛痛觉激活、右侧脑岛痛觉激活以及双侧脑岛痛觉平均激活的GWAS结果. 图中灰色虚线代表阈值$P=5\times10^{-6}$, 红色点代表注释到基因上的位点

Figure 3 (Color online) GWAS Manhattan plot of nociceptive-elicited insular activation phenotypes. (a)–(c) show the GWAS results of the nociceptive-elicited activations in the left insula, in the right insula and the average activation in the bilateral insula, respectively. The gray dashed lines represent the threshold of $P=5\times10^{-6}$, and the red dots represent the loci annotated to the gene

的新遗传位点提供重要线索, 并有助于深入理解疼痛脑响应个体差异的遗传机制以及神经精神疾病和疼痛感知异常之间的关系.

本研究的局限之处在于样本量对GWAS研究来说相对较小, 并且缺乏独立样本集对结果进行验证. 此外, 本研究结果均是基于统计分析所得, 未来可通过基因

表 1 脑岛痛觉激活表型GWAS显著关联的独立位点

Table 1 Independent loci significantly associated with the insular nociceptive activation phenotypes

脑岛位置	染色体号	位置	SNP ID	样本量	回归系数	*T*值	*P*值	MAF	INFO
左侧	3	70651917	rs2087706	297	0.45	5.15	4.91×10^{-7}	0.32	0.94
	18	1463031	rs72867512	278	−0.45	−5.14	5.16×10^{-6}	0.32	0.92
	10	55974993	rs12244828	321	0.71	5.10	5.82×10^{-6}	0.09	0.96
	5	51807639	rs11959832	313	−0.43	−4.94	1.30×10^{-6}	0.29	0.97
	2	222507028	rs16863807	293	−0.41	−4.91	1.55×10^{-6}	0.45	0.95
	6	44233997	rs3734703	323	−0.48	−4.84	2.04×10^{-6}	0.20	0.98
	9	95427176	rs357522	283	0.40	4.84	2.20×10^{-6}	0.46	0.93
	11	117311203	rs497902	308	−0.67	−4.81	2.37×10^{-6}	0.10	0.91
	14	55766157	rs6573058	304	0.52	4.73	3.51×10^{-6}	0.19	0.93
	6	15880309	rs2066399	302	−0.40	−4.65	4.92×10^{-6}	0.27	0.95
右侧	3	70651917	rs2087706	297	0.43	5.04	8.29×10^{-7}	0.32	0.94
	14	55766157	rs6573058	304	0.53	4.90	1.60×10^{-6}	0.19	0.93
	6	15880309	rs2066399	302	−0.41	−4.89	1.65×10^{-6}	0.27	0.95
	9	95379260	rs35431736	269	0.42	4.75	3.39×10^{-6}	0.43	0.91
	4	170236953	4:170236953-_GC_G	298	−0.40	−4.73	3.46×10^{-6}	0.40	0.96
	22	44224713	rs74731396	314	−0.53	−4.73	3.51×10^{-6}	0.15	0.95
	22	27265989	rs134792	267	−0.42	−4.67	4.87×10^{-6}	0.38	0.91
双侧	3	70651917	rs2087706	297	0.46	5.32	2.04×10^{-7}	0.32	0.94
	6	15880309	rs2066399	302	−0.43	−5.04	8.28×10^{-7}	0.27	0.95
	14	55766157	rs6573058	304	0.55	5.00	9.89×10^{-7}	0.19	0.93
	5	51807639	rs11959832	313	−0.43	−4.95	1.21×10^{-6}	0.29	0.97
	9	95379260	rs35431736	269	0.44	4.97	1.24×10^{-6}	0.43	0.91
	4	170236953	4:170236953-_GC_G	298	−0.41	−4.86	1.90×10^{-6}	0.40	0.96
	17	57265248	rs16958138	333	−0.64	−4.78	2.70×10^{-6}	0.08	1.00
	22	27265989	rs134792	267	−0.43	−4.80	2.74×10^{-6}	0.38	0.91
	5	61489437	rs117585159	333	−0.55	−4.70	3.93×10^{-6}	0.11	1.00
	18	63276473	rs8089331	294	0.47	4.68	4.49×10^{-6}	0.22	0.91
	11	117311203	rs497902	308	−0.65	−4.66	4.77×10^{-6}	0.10	0.91
	12	121479339	rs12812497	303	−0.39	−4.66	4.90×10^{-6}	0.42	0.96

调控实验对本研究结果进行生物学验证.

4 结论

本研究以痛觉诱发脑岛神经响应为表型进行了GWAS分析, 发现了与脑岛疼痛响应显著关联的SNP位点及相关基因, 这些基因大多与疼痛或神经精神疾病有关, 为理解疼痛个体差异的遗传机制以及疼痛与神经精神疾病的关联机制提供了新线索.

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补充材料

表S1 脑岛痛觉脑响应GWAS显著位点注释结果

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Summary for “基于全基因组关联分析探究痛觉诱发脑岛神经响应的遗传基础”

A genome-wide association study of insular activation by nociceptive stimuli in humans

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The insula serves as one of the central hubs for the processing of pain. This cortical structure has been shown to be robustly activated by nociceptive stimuli but exhibits large inter-individual variability. One reason behind such inter-individual variability of pain-elicited insular activation may be attributed to genetic factors. Therefore, understanding its genetic underpinnings is essential to understanding the origin of the inter-individual variability of the insular activations and consequently the inter-individual differences in pain sensitivity and behaviors. Genome-wide association study (GWAS) has emerged as a powerful tool for uncovering the genetic basis of complex traits and diseases, providing a comprehensive analysis of single nucleotide polymorphisms (SNPs) across the entire genome. The objective of the present study is to uncover possible genetic factors underlying the inter-individual differences in pain-elicited neural responses within the insula using a GWAS approach in a cohort of healthy Chinese Han subjects. A total of 333 healthy Chinese Han participants with both genetic and brain imaging data after quality control were included in the present study. The genotype data contained 5270947 SNP loci after quality control and imputation. Brain imaging data were functional magnetic resonance imaging (fMRI) data of a nociceptive stimulation task. Based on these fMRI data, a voxel-wise general linear model (GLM) was used to obtain a group-level activation by nociceptive stimulation within a pre-defined bilateral insular area; then a mean activation value (i.e., the average β value across voxels within the group-level insular activation area) was obtained for each of the left, the right and the bilateral insular regions for each participant. After outliers removal and normal score transformation, the three mean insular activations were used as the phenotypes in the subsequent GWAS analyses. In the GWAS analyses, associations were tested between each of the three insular activation phenotypes and each of the 5270947 SNPs. The results demonstrated that, at the threshold of $P<5\times10^{-6}$, the activation amplitudes of the left insula, the right insula and the overall activation of the bilateral insula were significantly associated with 10, 7 and 12 independent SNP loci, respectively. All significant SNP loci were annotated to 9 specific genes, among which *BACE1* has previously been reported to be associated with pain, and the remaining genes have been linked to brain imaging phenotypes or common neuropsychiatric disorders. In summary, the present study discovered 29 associations between pain-elicited insular activations and SNP loci in humans using fMRI and GWAS. These findings provide important evidence for the genetic underpinnings of the interindividual variability in pain-elicited neural responses within the human insula.

pain, brain activation, insula, genome-wide association analysis, functional magnetic resonance imaging

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