· 应激与心身疾病专题 ·

伴童年创伤抑郁症患者与相关候选基因多态性的研究进展

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【摘要】 童年期创伤与抑郁症的康复和预后有关,目前认为伴童年期创伤抑郁症的发生是基因和环境相互作用的结果,同时非同质的神经生物学机制也参与其中。基因多态性又称为遗传多态性,是指在某一个生物群体中,同时或经常存在两种或者多种不连续变异的基因。研究发现伴童年期创伤抑郁症可能与神经递质系统、下丘脑-垂体-肾上腺轴、脑源性神经营养因子、炎症等基因多态性相关。本文通过对抑郁症相关候选基因多态性进行综述,以期揭示伴童年期创伤抑郁症患者潜在的发病机制,为抑郁症早期诊断、治疗提供理论依据。

【关键词】 抑郁症; 童年创伤; 神经递质; 候选基因多态性; 综述
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Research progress on depressive disorder patients with childhood trauma and related candidate gene polymorphisms

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【**Abstract**】 Childhood trauma is associated with the recovery and prognosis of depressive disorder. It is believed that the occurrence of depressive disorder accompanied by childhood trauma is the result of the interaction between genes and environment, and non-homogeneous neurobiological mechanisms are also involved. Gene polymorphism, also known as genetic polymorphism, refers to the simultaneous or frequent presence of two or more discontinuous variations in a population of organisms. Research has found that childhood trauma and depressive disorder may be associated with gene polymorphisms in the neurotransmitter system, hypothalamic-pituitary-adrenal axis, brain-derived neurotrophic factor, and inflammation. This article reviews candidate gene polymorphisms related to depressive disorder, aiming to reveal the potential pathogenesis of depressive disorder patients with childhood trauma and provide theoretical basis for early diagnosis and treatment of depressive disorder.

【**Key words**】 Depressive disorder; Childhood trauma; Neurotransmitters; Candidate gene polymorphism; Review
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抑郁症是临床中常见的心境障碍,表现为持续两周以上的情绪低落、兴趣或快感缺失,伴随疲劳、焦虑、注意力不集中、体重增加或减轻、自卑及内疚感、睡眠或进食障碍,甚至出现无助、无望、绝望,从而导致自伤甚至自杀行为。童年创伤包括躯体虐待、情感虐待、性虐待、情感忽视和躯体忽视。有研究显示,童年期创伤占抑郁症相关风险的54%[1],其与抑郁症的康复和预后有关,并增加疾病复发和自杀风险[2]。儿童早期的逆境可能引发个体神经、内分泌、心理生理及行为的应激反应,进而增加其精神病理改变的长期风险[3]。目前认为,伴童年期创伤抑郁症的发生是基因和环境相互作用的结果,同时存在非同质的神经生物学机制。遗传因素占抑郁症发病风险的40%,其与童年期创伤交互作用可能导致患者脑功能及结构出现异常,从而加重抑郁情绪[4-5]。

人类遗传学的研究起初主要是针对候选基因，候选基因是指依据疾病的临床表现、生理、生化、脑影像学或某些已知的研究结果，提示某基因序列变异可能与表型变异有关，以此确定需要研究的基因，即候选基因[6]。研究中一般先假定候选基因是表型变异主基因，借助基因扩增等实验手段，应用病例对照的实验方法，研究病例组和对照组候选基因组间的差异，进而探索候选基因同表型变异的关系，以探究复杂疾病中各种可能的致病基因。

基因多态性指在某一个生物群体中，同时或经常存在两种或者多种不连续变异的基因。伴童年期创伤的抑郁症患者发病可能与多种基因多态性相关，如下丘脑－垂体－肾上腺(hypothalamic-pituitary-adrenal，HPA)轴、神经递质、BDNF、免疫炎症等，基因多态性可能通过诱导个体对环境的敏感性以及脑功能或结构的变化等导致情绪、认知功能的改变。本文通过对抑郁症相关候选基因多态性研究，探讨伴童年期创伤的抑郁症患者的潜在发病机制，旨在为抑郁症早期诊疗提供思路。

一、与神经递质系统相关的候选基因多态性

1. 5－羟色胺转运蛋白(5-hydroxytryptamine transporter，*5-HTT*)基因多态性：5-HTT也被称为可溶性载体家族6–4号(solute carrier family 6，member 4，SLC6A4)，其相对分子质量是70 320。目前，已知5-HTT不但参与5-HT的摄取，也是药物作用的靶点，可以回收突触间隙里的5-HT到突触前神经元，其中SSRIs如盐酸舍曲林片、马来酸氟伏沙明片、帕罗西汀片、氟西汀胶囊及氢溴酸西酞普兰片、草酸艾司西酞普兰片等均通过抑制5-HT再摄取发挥抗抑郁作用，由此推测*5-HTT*基因多态性与抑郁症相关[7]。目前，已知编码5-HTT的基因在染色体17q11.1～12区域，该基因大小为31 kb，由14个外显子组成，其编码的5-HTT蛋白是一种对5-HT高亲和的跨膜转运蛋白，有两个常见的多态性位点，能够影响*5-HTT*基因的表达[8]。(1)第1个多态性位点为*5-HTT*启动子区多态性位点。血清素转运体连接的多态性位点(5-hydroxytryptamine-transporter-linked polymorphic region，*5-HTTLPR*)在5-HTT编码序列的转录调控区，在5-HTT基因5′端转录起始点的上游约1 kp的启动子区插入44个碱基对或整倍数碱基对就会产生长(L)或者超长(XL)等位基因，如果缺少这种序列则会产生短(S)等位基因。这些基因多态性参与调控*5-HTT*基因表达。2003年Caspi等[9]对847名平均年龄为26岁的青年人进行研究，发现携带S等位基因者对负性生活事件的敏感性增加，更容易产生抑郁情绪。一项针对13～19岁青少年的神经影像学研究显示，携带*5-HTTLPR*的S等位基因与较小的左侧海马体积及较小的眶额叶皮层体积有关，导致成年后抑郁症发病风险的增加[10]。*5-HTTLPR*还能够增加对环境的应激作用，使无效环境对情绪的影响增加，从而导致抑郁情绪[11-12]。综上所述，携带*5-HTTLPR*的S等位基因可能是抑郁症发生的危险因素，其机制可能与增加环境敏感性和影响大脑结构和功能有关[13-14]。(2)第2个多态性位点在5-HTT第二内含子上的可变数量的重复序列(variable number of tandem repeats，VNTR)，位于*5-HTT*基因非编码区，常见等位基因包括17bp的9倍体(Stin2.9)、10倍体(Stin2.10)、11倍体(Stin2.11)、12倍体(Stin2.12)，最常见的等位基因是Stin2.10和Stin2.12。Ogilvie等[15]通过对*5-HTT*基因中的第二内含子VNTR多态性与心境障碍之间的关系进行研究，证明了*5-HTT*基因与重性抑郁障碍存在一定关联。此外，有研究发现*5-HTTVNTR*等位基因12与创伤后应激障碍相关[16]。Perea等[17]研究发现，*5HTTVNTR*等位基因与消极情绪高表达有关，在无效环境因素的刺激下(如童年期创伤)可预测抑郁症和焦虑症等疾病的易感性。但目前相关研究较少，还需进一步研究相关基因与具体环境的交互作用。

2. 儿茶酚胺氧位甲基转移酶(catechol-O-methyltransferase，*COMT*)基因多态性：COMT可以将S–腺苷蛋氨酸提供的甲基转移到儿茶酚胺苯环的第3位氧上，是具有生物活性或者具有毒性的儿茶酚胺主要代谢酶，同时还是中枢神经系统外多巴胺的主要降解酶[18]。人类大脑COMT能够代谢经过突触传导而没有重吸收的儿茶酚胺，其中1.5 kb膜结合型COMT(membrane binding-COMT，MB-COMT)的数量约占COMT总数的70%，其广泛存在于人体的前脑、基底神经节、神经胶质细胞和大脑边缘系统，且MB-COMT在突触间隙，尤其是在突触后膜的活性较高[18]。*COMT*基因Val158Met的多态性包括*Met/Met*基因型、*Val/Val*基因型以及*Val/Met*基因型3种，这些基因型的改变最终导致不同基因型编码的酶活性出现不同，*Val/Val*基因型编码的酶活性较*Met/Met*基因型编码的酶活性高3～4倍[19]。目前，研究预测*COMT*基因*Val158Met*基因多态性可以作为抑郁症发生的重要候选基因之一[20]，其中*COMT Met*等位基因携带者在接收到负性情绪时，情绪相关脑区活动和功能连接会加强，表明其对负性情绪

的刺激更加敏感[21]。研究表明，在高社会心理压力及早年逆境的影响下，与*Val*纯合子相比，*Met*携带者会表现更大的损伤。Abraham等[22]的研究提示，存在*Met*等位基因的儿童更容易受到早年逆境的影响。一项针对青少年的社区样本研究发现，携带*Val/Val*纯合子基因型的青少年较携带*Met*等位基因更容易感知到家庭教育的积极性和自主性，从而降低抑郁症的发生风险[23]。van Rooij等[24]对伴童年期创伤的73名成年女性进行研究，发现*COMT*基因与童年创伤相互作用，且与海马激活程度相关。然而Drury等[25]的一项对欧洲孤儿的追踪研究发现，在普通抚养机构成长环境下，携带*COMT Val/Val*基因型的孤儿较*Met*基因型的抑郁情绪程度更严重，但在寄养家庭环境下并未发现基因多态性对抑郁程度的影响。综上所述，基因型与环境对抑郁情绪的不同影响可能与受试者的年龄、种族或受试群体的差异相关，*COMT*基因多态性与伴童年期创伤抑郁症患者的关联尚需深入探究以阐明。

二、与HPA轴相关的候选基因多态性

HPA轴是控制应激反应的重要神经内分泌系统，其功能障碍与应激有关精神障碍的发生密切相关。目前已知应激与HPA轴过度激活有关，在应激状态下，丘脑室旁核分泌的促肾上腺皮质激素释放激素可引起促肾上腺皮质激素和糖皮质激素(glucocorticoids，GC)大量分泌[26]。GC的受体主要包括盐皮质激素受体和糖皮质激素受体(glucocorticoid receptor，GR)，其中GR在海马和下丘脑中高度表达，对调节海马的可塑性及对HPA轴的负反馈调节起关键作用[27]。抑郁症患者常存在HPA轴功能紊乱及免疫功能异常[28-29]。

1. FK506结合蛋白5(FK506-binding protein 5，FKBP5)基因多态性：*FKBP5*基因位于人类染色体6p21.3～p21.2，通过对GR的抑制作用为皮质醇介导应激反应系统提供负反馈[30]。*FKBP5 rs1360780*等位基因被认为与GR激活后FKBP5的过度表达以及HPA轴对压力反应的负反馈失调有关。机体中FKBP5过度表达导致皮质醇水平的长期升高，从而导致抑郁的发生、发展[31]。*FKBP5*基因*rs 1360780*位点T风险等位基因与抑郁障碍相关[32]。*rs 1360780*的T携带者在应激情况下更容易导致GR负反馈调节受损，因为其诱导的*FKBP5* mRNA及蛋白表达是CC纯合子的两倍[33]。影像学研究显示，与其他基因型相比，*rs 1360780*等位基因型为*TT/CT*基因型抑郁症患者各脑区的活性较低，海马及杏仁核体积更小，提示T等位基因可能是抑郁症发病的风险基因[34-35]。此外，有研究表明，*FKBP5*基因编码FK506结合蛋白51(FKBP51)的表达增加，与基线时应激反应调节受损有关，尤其是携带FKBP5变体*rs 1360780*风险等位基因患者，经过抗抑郁剂成功治疗后*FKBP5*基因和FKBP51蛋白表达均减少[36]。对于抑郁症患者，*FKBP5*基因与童年逆境已被证明存在交互作用，并与杏仁核、海马体和眶额皮质的异常活动相关[37]。

2. *GR*基因多态性：GR是可溶性单链多肽组成的磷蛋白，公认的GR结构是由激素结合亚单位和两个90 kd热休克蛋白90(heat shock protein 90，HSP90)组成的复合体，分子量为300 kd，这种复合物在HPA轴调节中起关键作用，GR信号转导受损会导致HPA轴的负反馈抑制减弱，最终导致GC水平长期持续升高[37]。人类*GR*基因(*NR3C1*)可生成GRα和GRβ两种蛋白亚型，GRα是GC配体结合蛋白，GRβ通过与GRα形成二聚体从而抑制GRα功能[38]。脑GC高水平与慢性应激状态及抑郁情绪有关，编码GC受体的基因定位于人类染色体5q31-32，被命名为*NR3C1*。目前的研究常围绕该基因的两种多态性进行，包括*Bcl I*突变位点和*ER22/23EK*多态位点[39]。这两种多态性位点能够改变受体的表达，进而影响抑郁症的易感性及临床症状的复杂多样性。一项对高加索人的研究表明，*Bcl I GG*和*ER22/23EK*携带者抑郁症患者的发病率显著高于健康对照受试者[40]。目前，关于以上两种多态性对伴有童年期创伤抑郁症患者的研究较少，研究的热点多围绕于*GR*基因的甲基化，结果显示童年期遭受性虐待、躯体虐待、情感虐待、忽视和亲密伴侣的暴力行为与位于*GR*基因*NR3C1*外显子1F的*CpG*位点甲基化之间存在显著相关[41]。

三、BDNF基因多态性

除以上基因多态性与抑郁症发生相关外，*BDNF*基因也是抑郁症遗传研究中的重要候选基因。BDNF是人脑中最丰富的神经营养因子之一，特别是在前额叶皮层和海马体中，与神经元存活、分化和凋亡、突触发生以及神经可塑性密切相关[42-43]。探究*BDNF*基因与童年期创伤的关系对抑郁症的病理机制研究非常重要。BDNF水平主要受*BDNF*基因*Val66Met*多态性的影响，*BDNF Met*等位基因与BDNF的分泌减少和活性降低有关。在应激状态下，BDNF活性降低。研究显示，暴露于更多童年期创伤的*BDNF Met*基因携带者的海马和杏仁核体积较小、心率升

高且工作记忆下降，表明*BDNF*基因在童年创伤的影响下对情绪处理和认知相关的脑区及自主神经功能产生一定影响，久而久之增加了抑郁症的发病风险[44]。Bîlc等[45]研究发现，*BDNF Met*等位基因携带者童年期创伤易感性增加，情绪调节能力降低，从而更容易发生抑郁症。

四、细胞因子的相关基因多态性

目前关于抑郁症的细胞因子假说逐渐引起关注，其中细胞因子如IL-1β的异常可能对抑郁症发生有一定影响。IL-1β通过活化p38促分裂原活化蛋白激酶增加5-HT再摄取[46]。以上研究结果表明，IL-1β与抑郁症的发生有一定相关性。目前，研究较多的是*IL-l*β基因启动子区*rsl6944*(*A*/*G*)位点多态性。Baune等[47]对256例抑郁症患者进行研究，发现携带*IL-l*β基因*rsl6944*(*A*/*G*)位点的*AA*基因型的治疗效果较差。IL-1家族基因形成的细胞因子基因簇可能影响*IL-1*基因的转录和下游蛋白的合成。Lu等[48]报道，具有童年期创伤的抑郁症患者与正常对照者相比，其面对急性应激事件时的IL-1β水平迅速增加，这与急性应激反应刺激*IL-1β*基因的表达有关。

五、总结与展望

目前对于抑郁症相关基因多态性的研究较多，但针对伴童年期创伤抑郁症的基因多态性研究相对较少。童年期是大脑发育的关键时期，如果在这个时期遭受精神创伤可能会导致大脑结构和功能的损伤，从而增加早年患病和难治性抑郁障碍的发生[49-50]。此外，个体的遗传特性叠加无效环境的交互影响可能会增加个体对精神创伤的易感性，导致抑郁症发生。因此，探讨基因与创伤的交互作用尤为重要。目前，评估患者童年期创伤的问卷一般是自我报告问卷，可能存在回忆性偏倚。未来可借助脑影像学技术和生物学研究构建抑郁症发病、疗效、转归与创伤、基因、生物学以及大脑关联的模型，为抑郁障碍的早发现、早诊断、早干预提供理论依据。

利益冲突 文章所有作者共同认可文章无相关利益冲突

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·应激与心身疾病专题·

童年期创伤与静息态血压、心率及心血管疾病的相关性研究进展

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【摘要】 童年期创伤与静息态血压及心率存在着一定的关联性,是预测心血管疾病的重要风险因素。本文通过总结童年期创伤与静息态血压、心率和心血管疾病之间的相关性以及童年期创伤影响静息态血压、心率及心血管疾病的潜在机制,包括表观遗传学、神经内分泌、氧化应激、炎性反应、不良生活方式、心理应激等,明确童年期创伤对心血管系统的潜在影响,旨在为早期防治心血管疾病提供理论依据。

【关键词】 心血管疾病; 童年期创伤; 静息态血压; 静息心率; 心率变异性; 综述
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Research progress in the correlation between childhood trauma and resting blood pressure, resting heart rate, and cardiovascular disease

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【Abstract】 Childhood trauma has a certain correlation with resting blood pressure and resting heart rate, which is an important risk factor for predicting cardiovascular disease. This review summarizes the correlation between childhood trauma and resting blood pressure and resting heart rate and cardiovascular disease, as well as the potential mechanisms of childhood trauma affecting resting blood pressure, resting

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