·综　述·

基因、环境及其交互作用在阅读障碍发生中的研究进展*

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【摘　要】阅读障碍包括发展性阅读障碍和获得性阅读障碍，发展性阅读障碍是指部分儿童虽然拥有正常的智力、情感、平等的教育和社会文化机会，却在阅读和拼写上存在特殊困难的症状，表现为口头交际能力差，常写错字，读书加字、漏字，不理解所读内容的意思等。为了解发展性阅读障碍的研究进展，为今后进行发展性阅读障碍相关研究提供参考，本文对发展性阅读障碍的基因、环境、基因-环境交互作用的研究进展进行综述。

【关键词】发展性阅读障碍；环境因素；遗传因素；交互作用

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Progress in researches on effects of gene, environment and gene-environment interaction on developmental dyslexia

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【**Abstract**】Dyslexia includes developmental dyslexia and acquired dyslexia. Developmental dyslexia refers that although some children have normal intelligence, emotion, equal educational and socio-cultural opportunities, they have particular difficulties in reading and spelling, such as poor verbal communication skills, often typo, reading plus words, missing words, not understanding the meaning of the contents of the reading. We reviewed the progress in the researches on effects of gene, environment and gene-environment interaction on developmental dyslexia to provide references for future researches on developmental dyslexia.

【**Key words**】developmental dyslexia; environmental factor; genetic factor; interaction

发展性阅读障碍（developmental dyslexia）指的是儿童智力、情感正常，拥有平等的社会经济条件和教育水平，但是在阅读、拼写方面存在困难，发展水平明显落后于同龄儿童。这种症状不是因器质性脑病、感知觉障碍或者心理疾病所致。流行病学显示，发展性阅读障碍在学龄期儿童中的发病率为3.9%～17.5%，男性高于女性[1]，占学习障碍儿童的80%～90%[2]。经过数十年的研究，目前普遍认为，发展性阅读障碍是环境和基因共同作用的结果，现已取得一些进展。本文将从基因、环境及其交互作用对发展性阅读障碍（以下简称阅读障碍）影响因素的研究现状进行综述。

1　环境因素

环境因素研究主要集中在孕产期因素、家庭环境因素和学校环境因素三大块。

1.1　孕产期因素　关于儿童阅读相关能力，研究较多的孕产期因素主要包括早产、低出生体重、孕期的不良暴露、疾病、营养素缺乏。有关研究显示，早产、低出生体重会对儿童的言语发育[3]、阅读能力[4]和数学能力[5]造成不利影响。meta 分析[6]显示（共纳入了 74 项研究、共 64 061 位学龄期儿童），不同程度的早产儿在学龄期及学龄期之后，其工作记忆和加工速度均落后于同龄人，并且早产儿出生体重与智商存在一个梯度关系，出生体重越低，智商下降的越多[7]。另外，不同性别的早产儿学龄期阅读、认知能力也存在差异，男性早产儿学龄期发生阅读困难的风险更大，这也解释了阅读障碍患病人群中男性比例更大的现象[8－9]。

孕期可卡因、尼古丁、酒精暴露、抗抑郁药的使用可能影响儿童语言技能或阅读能力的发育[10－14]，但是认为产前超声暴露并不是发生阅读障碍的原因[15]。孕期癌症化疗药物的使用不会对儿童学业成绩产生影响，但会增加早产几率[16]。

母亲孕期患有系统性红斑狼疮会显著增加男童发生学习障碍（特别是阅读障碍）的风险[17]，即使儿童没有出现学习困难，在神经发育的各个时间点也应及时随访以便尽早发现学习、认知障碍[18]。孕期高血压、糖尿病、产前感染等会影响胎儿神经系统的发育[19－20]。母亲孕期缺碘（即使是轻度缺碘）的

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儿童，智商及阅读分值会下降，且缺碘的程度越重，表现得越明显[21]。孕前肥胖或孕期体重增加过多会影响儿童数学、阅读和拼写能力[22]，但孕期卡路里摄入过少也会使儿童数学能力降低[23]，因此孕期合理均衡的营养摄入使身体质量指数保持在正常范围内对儿童的认知发育至关重要。

在中国人群中，神经精神性疾病家族史、孕期感染性疾病、难产、早产、新生儿窒息增加了阅读障碍的患病风险[24]，原因可能在于母亲孕期感染致病菌或炎症刺激暴露使机体免疫系统激活，而这在神经发育性疾病中是一个重要的病因[25]；当难产发生时，第二产程延长会使围产期不良结局发生的几率增加[26]；早产儿童左侧上纵束（连接额骨和颞骨的语言区域）区域白质减少[27]，可能与阅读障碍的发生有关；新生儿窒息所致的缺氧降低皮质活跃性、抑制树突生长、视觉皮质可塑性受损[28]，即使有过新生儿窒息史的儿童没有出现神经系统症状，他们发生阅读障碍的风险也会大大增加。

1.2　家庭环境因素　家庭阅读环境（home literacy environment, HLE）和家庭社会经济地位（socioeconomic status, SES）是家庭环境因素中影响儿童阅读能力最显著的两个因素[29－31]。家庭阅读环境包括阅读相关行为（包括家庭阅读氛围、藏书数量、儿童自主学习习惯等）、每周使用电子设备的时间以及儿童在家使用电子设备的规定。家庭阅读环境越好，学龄期儿童汉语阅读障碍的检出率越低[1, 32]。较好的家庭阅读环境能促进儿童的阅读行为，从而提高儿童的阅读相关能力，如语音意识、韵律意识、拼写能力[33－34]。

家庭经济地位不仅包括经济收入、职业地位，也包括非物质因素如教育机会、社会关系网络[35]。低 SES 的儿童控制语言相关活动的外侧裂周区活跃性降低[36]、灰质减少[37－38]，阅读障碍儿童的大脑结构变化也表现出了相似的特点[39－40]。SES 较高的人群中，阅读障碍的检出率较低，提示 SES 可能是阅读障碍发生的影响因素[41－42]，这可能与低 SES 放大了导致阅读障碍的遗传等其他因素有关[43]。

在中国人群中，父母文化程度低[1]、低家庭收入[44]、电子设备（电脑、电视）使用时间长是阅读障碍的危险因素（可能与阅读障碍儿童的回避型行为有关[45]，通过玩电子游戏及看电视回避较高的学习压力及阅读困难问题）。较好的阅读相关行为（家庭阅读资源、阅读动力、阅读参与）是阅读障碍的保护因素，家庭阅读资源能培养儿童阅读兴趣，并且父母的阅读模范作用也能激发儿童的阅读动力[46]。

1.3　学校环境因素　学校教育在儿童阅读能力的培养过程中有着举足轻重的地位。使人愉悦的学校建筑设施能改善学业表现[47]。权威的教学方式（高要求、高响应）注重始终如一的课堂管理、学生的学习自主性和个人兴趣，在这种教学方式下成长起来的学生在学习能力和社交方面都更胜一筹[48]，另外，对于本身没有阅读困难症状而阅读能力较差的儿童，权威的教学方式能促进其阅读能力的发展，并在一定程度上弥补因父母非权威的育儿方式所造成的负面影响[49]。同伴拒绝、同伴欺辱与课堂参与率降低、辍学率升高相关[50]。老师提供的支持性班级氛围、较短的教学年龄、较小的课堂规模对于因同伴拒绝而造成的社交和学习困难风险有保护作用[51]。

从总体上来说，目前环境影响因素的研究主要针对的是阅读相关能力，直接针对发展性阅读障碍的研究还不多。但是，这些研究结果可以为我们进一步研究发展性阅读障碍的环境影响因素提供线索和思路。

2　遗传因素

阅读障碍在人群中的发病不表现为随机分布。基因遗传因素在阅读障碍的形成中占据了重要地位，能够解释 40 %～80 % 阅读障碍的产生[52]。家系研究及双生子研究发现阅读障碍具有家庭聚集性，阅读障碍患者的同胞再发率（43 %～60 %）远高于阅读障碍的人群患病率（2 %～17.5 %）[53－54]，遗传度为 0.18～0.72[55]。

已有 9 个基因座被确定与阅读障碍发病相关，人类基因命名委员会将其连续命名为 DYX1 到 DYX9，它们在染色体上的位置分别为 15q21.3、6p22、2p16-p15、6q13-16.2、3p12-q13、18p11.2、11p15.5、1p36-p34 和 Xq27.3[52, 56]。这些基因座中已报道与阅读障碍病因有关的基因包括位于 DYX1 上的 *DYX1C1* 基因[57]，位于 DYX2 上的 *DCDC2*[58]、*KIAA0319*[59]、*THEM2*、*TTRAP*[60]、*NRSN1*[61]基因，位于 DYX3 上的 *C2ORF3*、*MRPL19*[62]基因，位于 DYX5 上的 *ROBO1* 基因[63]，位于 DYX7 上的 *DRD4* 基因[64]，位于 DYX8 上的 *KIAA0319L* 基因[65]，位于 DYX9 上的 *FMR1* 基因[66]，然而在 DYX4、DYX6 基因座位上，至今还没有阅读障碍候选基因被提出。其中，*TTRAP* rs4504469、*THEM2* rs2038137、*KIAA0319* rs2143340 已被确定为阅读障碍发生的危险单倍体，能够降低上述三个基因在表达、剪切或者转录过程中 40 % 的稳定性[67]。

也有不位于这些基因座上或与其他疾病有关的基因被发现与阅读能力有关，包括 2 号染色体上的 *FAM176A* 基因[67]，3 号染色体上的 *CEP63* 基因[68]，5 号染色体上的 *CTNND2* 基因[69]，7 号染色体上的 *FOXP2*[61, 70]、*CNTNAP2*[71]、*DOCK4*[72]和 *GTF2I* 基因[73]，12 号染色体上的 *GRIN2B*[74]、*SLC2A3*[73]、*GNPTAB* 基因[75]，13 号染色体上的 *COL4A2* 基因[61]，14 号染色体的 *NOP9* 基因[76]，15 号染色体上的 *CYP19A1* 基

因[77]，16 号染色体上的 *ATP2C2*、*CMIP* 基因[78]和 *NAGPA* 基因[75]，19 号染色体上的 *NCAN*[79]基因，21 号染色体上的 *PCNT*、*PRMT2*[67]、*DIP2A*[80]、*S100B*[81]基因。

以上众多阅读障碍候选基因中，*DYX1C1*、*DCDC2*、*KIAA0319* 和 *ROBO1* 是目前被研究最多的 4 个基因，它们与阅读障碍发病风险之间的相关性已被广泛报道[59, 63, 82－83]。研究学者们通过对这些基因的功能学探讨发现，它们在早期脑发育过程中都发挥了轴突导向、信号传导功能或者参与了神经元的迁移过程，因此目前普遍认为阅读障碍是一种神经迁移性疾病[84－88]。但是，在不同的研究中，上述基因与阅读障碍发病风险之间的相关性呈现出不一样的结果[73, 89–90]。Lin, Vance, Pericak-Vance 和 Martin[91]认为，当所研究基因位点和实际致病位点之间存在交互作用或者连锁不平衡时，就会出现这种“反转现象”。

在中国人群中的研究发现，*DIP2A* rs2255526 位点的遗传突变能增加阅读障碍患病风险[92]。神经元迁移调控网络上的 *KIAA0319* rs4504469、*DOCK4* rs2074130、*KIAA0319L* rs28366021 变异与阅读障碍发病风险呈现显著相关性[93]。*DYX1C1* rs3743205[94]、*ROBO1* rs6803202[95]对阅读障碍的影响在中国儿童中也得到了重复性研究。另外，*KIAA0319* rs4504469 在亚洲人群中是危险因素，而 rs9461045 是保护因素[96]。中国语言系统与西方国家的不同导致中国儿童在阅读障碍的表现上与西方国家存在一定差异，因此西方国家的研究结果不一定完全适用于我国，对阅读障碍易感基因的进一步探索和验证性研究是很有必要的。

3 基因－基因、基因－环境的交互作用

无论是表现复杂的疾病或者是普通病症，确定遗传基因是非常困难的，因此才出现了遗传性缺失现象。阅读障碍中只有小于 5 % 的表型变异能够被目前所发现的易感基因位点所解释[97]。造成这一现象的原因有许多，其中两个原因便是基因－基因之间的交互作用和基因－环境之间的交互作用[98]。

阅读障碍是多基因复杂性疾病，其发病过程存在基因－基因之间的交互作用和累积效应。迄今为止只有几项研究同时探讨了多个基因变异对阅读障碍发生的交互效应[73, 98－102]。主要发现有：Harold[99]等发现 *DCDC2* rs793862 和 *KIAA0319* rs761100 在阅读障碍的发生上存在显著的交互作用。Poelmans[73]等发现 *ROBO1*、*KIAA0319*、*KIAA0319L*、*S100B*、*DOCK4*、*FMR1*、*DIP2A*、*GTF2I*、*DYX1C1* 和 *DCDC2* 基因符合神经发育和理论分子框架，并且这些基因所编码的蛋白均直接或间接地调控神经迁移或轴突定向生长过程。Powers[100]等发现，个体如果同时具有 *DCDC2* 和 *KIAA0319* 危险单倍体，其阅读、语言、认知能力的测试得分要比正常值低 0.4 个标准差，而且下降得分要高于仅携带 *DCDC2* 危险单倍体下降得分与仅携带 *KIAA0319* 危险单倍体下降得分之和，提示这两个危险单倍体之间存在协同交互作用。该团队的另一项研究进一步提示 *DCDC2* READ1 与 *KIAA0319* KIAHap 相互依赖，READ1 通过 KIAHap 与 *KIAA0319* 的上游序列发生交互作用，调节 *KIAA0319* 基因的表达，共同作用于语言和阅读能力的发育[101]。Mascheretti 和 Bureau 等[98]的研究结果提示 *DYX1C1* 和 *KIAA0319*/*TTRAP* 与短时记忆能力的相关性均受 *GRIN2B* 基因的调控。最新的一项基于中国人群神经元迁移调控蛋白网络的研究也提示 *DOCK4*、*KIAA0319*、*KIAA0319L*、*DCDC2* 四个基因在阅读障碍的发生上存在高阶交互作用和累积效应[102]。

基因和环境对阅读障碍的共同作用是探讨阅读障碍发病机制重要内容之一，但是目前关于二者交互作用的研究很少[43, 74, 103－105]。研究学者们发现，父母文化程度越高，阅读障碍的遗传度越高[43, 104]。*DCDC2* 中的 SNP-rs1091047 与 HLE 相互影响，使儿童 N170（反应正字法水平的神经因子指标）的水平发生变化[105]。Mascheretti 等[103]在 168 个意大利阅读障碍核心家系中分析了七个环境因素（包括出生体重、孕期吸烟、母乳喂养、父母的生育年龄、流产、家庭社会经济地位和父母文化程度）与 *DYX1C1*、*DCDC2*、*KIAA0319* 和 *ROBO1* 四个基因上的十个变异位点在记忆能力、阅读能力、拼写能力上的交互作用，发现 *DYX1C1*-1259C/G 位点与家庭社会经济地位、孕期吸烟情况、出生体重三个环境因素变量之间在记忆和阅读能力上具有交互作用。

中国人群中的研究初步证实 *DIP2A* rs2255526 与家庭月收入高低存在交互作用，低家庭收入人群中，该位点突变是阅读障碍发生的危险因素[92]。*KIAA0319L* rs28366021 位点的基因型与父母文化程度、父母阅读书籍的频率存在显著的交互作用，当父母文化程度较高或者父母每天阅读书籍时，*KIAA0319L* rs28366021 位点的变异在汉语阅读障碍的发病风险上表现为保护作用[93]。

此外，某些针对非阅读障碍的基因与环境交互作用的研究结果也可以作为我们今后研究方向的参考意见。*DCDC2* READ1 与 SES 在个体行为表现、注意力问题上存在交互作用，携带 READ1 并且低 SES 的个体注意力缺陷最严重的[106]。另外，HLE 与 6p22、15q21 区域在个体发生功能性构音障碍的危险性上存在交互作用[107]，而 6p22、15q21 区域刚好是阅读障碍的候选基因 *DCDC2*（6p22.1）、*KIAA0319*

(6p22.3 – 6p22.2)和 *DYX1C1*(15q21.3)所处的位置。

4 今后的研究方向

虽然我们在阅读障碍的病因学研究中取得了许多进展,但是至今为止,阅读障碍的确切病因仍不明确。今后的研究可以从以下几个方面探索:第一,在现有基础上继续开展阅读障碍的基因-基因及基因-环境交互作用的研究。第二,开展阅读障碍的全基因组关联研究,并探讨新生遗传机制(拷贝数变异、表观遗传等)在阅读障碍发生上的作用。第三,进一步探索环境的作用。比如,开展专门针对阅读障碍的环境影响因素研究,大样本的队列研究设计能更好的探索基因与环境对阅读障碍表型的共同影响等。第四,阅读障碍的共病现象比较常见,尤其是注意缺陷多动障碍、语音障碍等神经发育类疾病[56],因此,探索阅读障碍和共病症的共同病因也是日后研究可以深入探索的方向。

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