

常染色体隐性遗传小头畸形相关蛋白研究进展

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摘要: 脑发育相关疾病是一类影响大脑或中枢神经系统生长和发育的疾病。常染色体隐性遗传小头畸形 (autosomal recessive primary microcephaly, MCPH) 是一种神经系统发育障碍疾病, 病人主要表现为头围减小, 并伴随一定程度的智力衰退。迄今为止已发现至少有 25 个基因突变都会导致 MCPH, 根据它们发现的顺序分别命名为 *MCPH1*~25。MCPH 蛋白作为重要的成份参与调控大脑发育相关信号通路。本文对目前发现的 25 个 MCPH 相关蛋白的表达模式、细胞定位、分子生物学功能、表型及动物模型进行了综述, 旨在提升人们对脑发育相关疾病的致病机制的认知, 促进对神经元生成、脑尺寸大小及脑功能调控等分子机制的研究。

关键词: 小头畸形; 表达模式; 细胞组分; 表型概述; 分子生物学功能; 动物模型

Update on autosomal recessive primary microcephaly (MCPH)-associated proteins

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Abstract: Brain development diseases refer to a group of diseases that affect the development of the brain or the central nervous system. Autosomal recessive primary microcephaly (MCPH) is a typical neurodevelopmental disorder characterized by a decreased brain size, mental retardation and abnormal behaviors. To date, at least 25 genes have been discovered to cause MCPH when mutated. These genes were named *MCPH1*–25 according to the discovery order. MCPH proteins play important roles in regulating brain developmental signaling pathways. Here, we provide a timely review of the expression patterns, cellular localization, molecular functions, phenotypes, as well as animal models of these 25 MCPH proteins that will expedite our understanding of the pathogenesis of brain disorders at both molecular and cellular levels.

Keywords: microcephaly; expression pattern; cellular component; phenotype overview; molecular function; animal models

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大脑是人体最重要和最复杂的器官,拥有上万亿个神经元和彼此间相互作用形成的百万亿个连接点。大脑通过形成庞大而复杂的神经网络控制着其他器官或系统的正常功能。理解大脑的运转机制,是人类与科学届面临的最伟大的挑战之一。脑科学是 21 世纪各种前沿科学中最为引人关注的领域之一,同时也是多学科交叉的重要前沿科学领域。2013 年,美国启动“脑计划”旨在探索人类大脑工作机制,绘制脑活动全图,并最终开发出针对大脑疾病的疗法。2018 年以来,“北京脑科学中心”和“上海脑科学中心”相继成立,标志着“中国脑计划”也正式拉开了帷幕。

脑发育异常会导致其功能异常,并最终导致严重的神经疾病如自闭症、精神分裂症及小头症等^[1-7]。小头症即小头畸形(microcephaly)是一种比较罕见的大脑疾病,是由于大脑神经系统发育障碍导致的,发病率在 2~12/万^[8]。胎儿出生后的头围测量是诊断小头症最常用的方式之一^[8]。诊断小头症的临床标准是病人的头围相对于其同年龄与性别的平均值明显小 2 个标准差以上^[9]。通常在孕 28 周左右应用超声波技术和核磁共振扫描检测即可发现患儿的头围测量值及脑容量低于正常同龄胎儿。小头症的主要表现是脑的重量明显轻于正常、脑回过小或根本无脑回、大脑的发育明显迟缓,甚至在婴儿第 3~5 个月时就停止发育,最后导致患儿的头顶变得小而尖、鼻梁凹陷、耳大、下额后缩、前额狭小并且头围明显小于正常婴儿,最大的头围不足 43 cm。小头症患儿大脑发育障碍常常伴有不同程度的智力低下,有的患儿还会出现癫痫、运动障碍、语言障碍及其他行为异常^[10]。造成小头症的原因有很多,大致可分成两类:一类是由遗传因素引起,即染色体或基因突变所导致;另一类是由环境因素引起,即胎儿在妊娠早期受到各种有害因素影响包括营养不良、中毒、物理或化学影响以及子宫感染(弓形虫病,风疹,疱疹,梅毒,巨细胞病毒及艾滋病病毒)所导致。2015 年,一种虫媒病毒(寨卡病毒)在美洲和热带地区爆发导致小头症新生儿的大量产生引发了全世界的关注^[11]。通过动物模型验证,科学家已经证实寨卡病毒感染确实会导致小头症的发生^[12-14]。

常染色体隐性遗传小头畸形(autosomal recessive

primary microcephaly, MCPH)是一种比较少见的神经分裂异常引起的脑发育疾病。病人主要表现为头围减小并伴有不同程度的智力衰退^[8]。目前发现的与 MCPH 有关的 25 个基因包括: *MCPH1* (*BRIT1*)、*MCPH2* (*WDR62*)、*MCPH3* (*CDK5RAP2*)、*MCPH4* (*CASC5*)、*MCPH5* (*ASPM*)、*MCPH6* (*CENPJ*)、*MCPH7* (*STIL*)、*MCPH8* (*CEP135*)、*MCPH9* (*CEP152*)、*MCPH10* (*ZNF335*)、*MCPH11* (*PHC1*)、*MCPH12* (*CDK6*)、*MCPH13* (*CENPE*)、*MCPH14* (*SAS6*)、*MCPH15* (*MFSD2A*)、*MCPH16* (*ANKLE2*)、*MCPH17* (*CIT*)、*MCPH18* (*WDFY3*)、*MCPH19* (*COPB2*)、*MCPH20* (*KIF14*)、*MCPH21* (*NACAPD2*)、*MCPH22* (*NACAPD3*)、*MCPH23* (*NCAPH/BRRN*)、*MCPH24* (*NUP37*)和 *MCPH25* (*MAP11*)^[15]。全世界范围内,超过 50% 的 MCPH 患者是由于 *MCPH5* (*ASPM*)和 *MCPH2* (*WDR62*)基因突变造成的^[8]。本文通过查询小鼠基因组信息(Mouse Genome Informatics, MGI)和美国国立生物技术信息中心(National Center for Biotechnology Information, NCBI)数据库对已命名的 25 个 MCPH 相关蛋白的表达模式、细胞定位、分子生物学功能、表型及动物模型等进行了综述,旨在提升人们对 MCPH 发病机制的认知并加深人们对神经元生成及脑尺寸大小调控机理的理解。

1 MCPH 基因的时空特异性表达

结合 MGI 和 NCBI 网站数据分析发现, *MCPH* 相关基因存在非常明显的时空特异性表达(图 1, 图 2)。MCPH 作为一类神经发育疾病相关蛋白,大多数与细胞分裂相关,因此在细胞分裂活跃的组织表达较高。MGI 数据库(基于免疫组化和 RNA 原位杂交结果)结果显示,有 21 个 *Mcph* 基因都在神经系统表达,仅 *Mcph13* 和 *Mcph20* 未在神经系统中检测到表达。除神经系统外,大部分 *Mcph* 在视觉系统、生殖系统和消化系统中也有表达。NCBI 数据(基于正常组织 RNAseq)显示在人体组织中,已发现的 25 个 MCPH 中有 11 个基因在睾丸(相对其他组织)中表达量最高,分别是 *MCPH2* (*WDR62*)、*MCPH3* (*CDK5RAP2*)、*MCPH4* (*KNL1*)、*MCPH6* (*CENPJ*)、*MCPH7* (*STIL*)、*MCPH9* (*Cep152*)、*MCPH11* (*PHC1*)、*MCPH15*

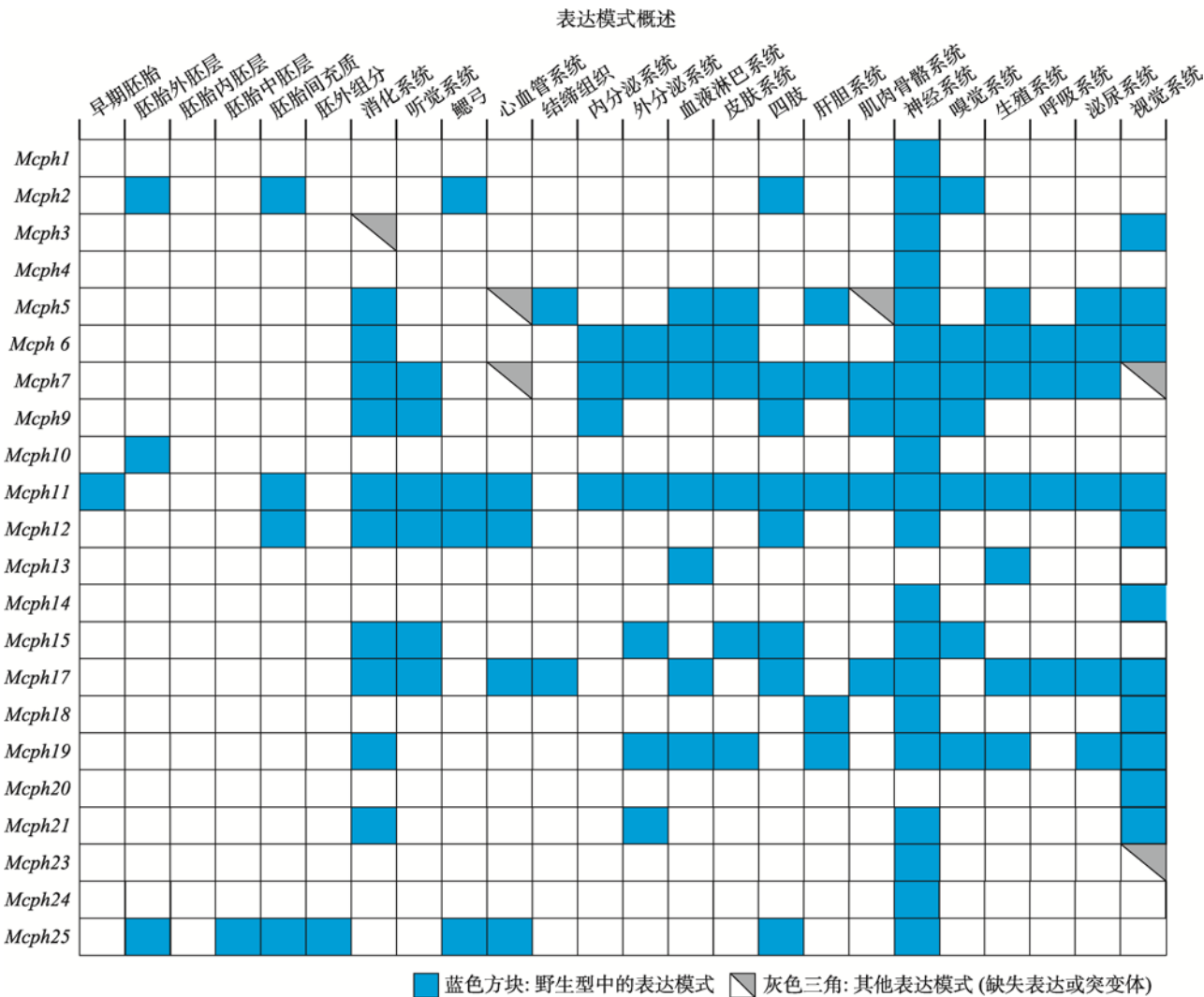


图 1 *Mcph* 在小鼠不同组织的表达模式
Fig. 1 *Mcph* expression patterns in different mouse organizations

根据小鼠基因组信息(Mouse Genome Informatics, MGI)数据库总结得到 22 个 *Mcph* 基因在不同组织的表达模式。

(MFSD2A)、*MCPH16* (ANKLE2)、*MCPH23* (*NCAPH*) 和 *MCPH25* (*MAP11*)。另外，还有 4 个基因在睾丸(相对其他组织中表达量次高，其中包括 *MCPH1* (*BRIT1*)、*MCPH14* (*SAS-6*)、*MCPH17* (*CIT*)和 *MCPH24* (*NUP37*)。主要原因可能是 *MCPH* 基因在分裂旺盛的组织表达较高，而睾丸在产生精子过程中首先会产生很多精原干细胞。

此外，通过分析 NCBI 数据库 RNA-seq 结果，将 25 个 *Mcph* 基因在小鼠脑发育不同阶段的表达情况进行汇总，结果发现大部分 *Mcph* 在脑发育早期(胚胎 11.5 天)表达量较高，随着发育的进行(胚胎 18

天)表达量逐渐下降，在成年脑皮质中表达量更低甚至几乎检测不到(图 2)。*MCPH* 基因的时空特异性表达决定其在调控脑发育和育性方面起着非常重要的作用。

2 *MCPH* 蛋白在细胞中的定位

通过蛋白序列分析或结构预测发现，大部分 *MCPH* 蛋白定位在细胞骨架和细胞核中(图 3)。中心体是微管组织中心，大部分 *MCPH* 蛋白都定位在有丝分裂装置如中心体或纺锤体上^[16]。在脑发育过程

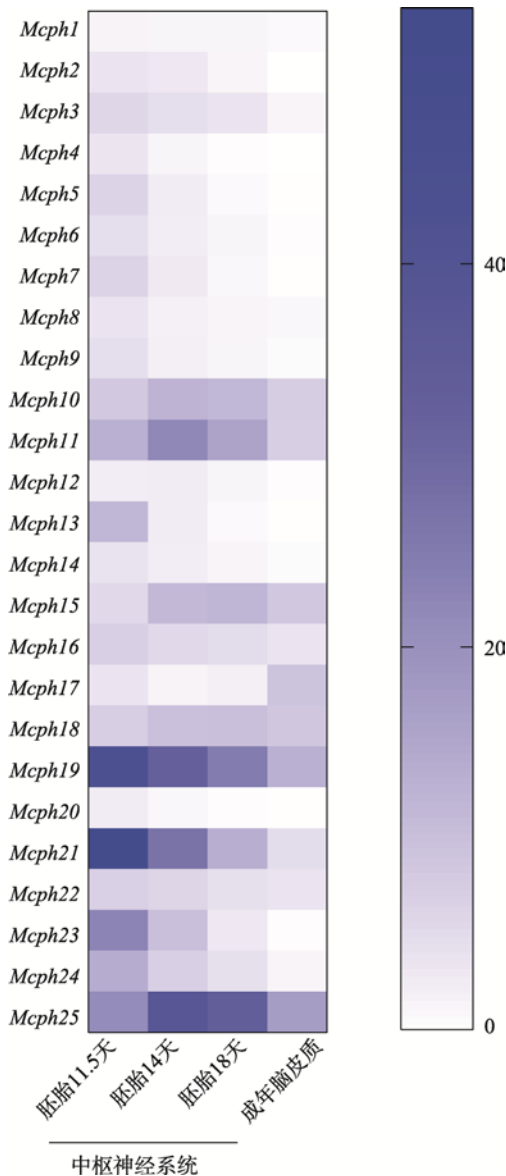


图 2 *Mcph* 基因在小鼠脑发育不同阶段的表达情况
Fig. 2 Expression of *Mcph* genes at different stages of mouse brain development

根据美国国立生物技术信息中心(National Center for Biotechnology Information, NCBI)数据库总结得到不同 *Mcph* 基因在小鼠不同发育阶段中枢神经系统的表达情况。蓝色不同强度代表表达强弱, 越接近蓝色表达越强, 越接近白色表达越弱。

中, 中心体和纺锤体的正确组装对于产生和维持正常的神经细胞的数量起着非常关键的作用。MCPH 蛋白缺失或突变会干扰中心体或纺锤体的正常形成, 影响细胞周期及 DNA 复制等过程, 进而影响神经前体细胞的增殖、分化和凋亡等过程, 最终导致神经元数量减少并形成偏小的大脑^[17-20]。MCPH2/WDR62

表现出非常明显的细胞周期依赖性表达。在有丝分裂中期或前中期, WDR62 主要集中在纺锤体极点, 而在有丝分裂间期 WDR62 则弥散地分布在细胞质中^[21]。在细胞有丝分裂间期, 高尔基体是除中心体外的另一个微管组织中心。有些 MCPH 蛋白定位在高尔基体上, 如 MCPH3 (CDK5RAP2)通过 ATP 及中心体依赖的形式定位在高尔基体上^[22]。MCPH19 (COPB2, β -辅酶亚基)以 GTP 依赖形式结合在高尔基体膜上并对高尔基体的形成及囊泡运输过程起重要作用^[23]。还有些 MCPH 蛋白(MCPH15/MFSD2A 和 MCPH16/ANKLE2)则定位在内质网上^[24,25](图 3)。

3 MCPH 蛋白参与的生物学过程

动物个体发育是一个复杂而精细的过程。大部分 MCPH 蛋白在发育过程参与细胞成分组装进而调控细胞的增殖分化及系统发育等过程(图 4)。大脑的大小是通过调节神经干细胞增殖、分化和凋亡的平衡来控制的^[26]。目前研究得比较多的一些 MCPH 蛋白(如 MCPH5/ASPM、MCPH2/WDR62 和 MCPH6/CENPJ 等)在神经干细胞的增殖或分化过程中起着重要作用^[20,27-30]。神经迁移与神经发生和大脑尺寸调控密切相关。在大脑皮层形成过程中, 正常的神经迁移是至关重要的一个环节, 是构成大脑皮层复杂的组织结构及特殊回路的前提和基础。一些 MCPH 蛋白(如 MCPH5 和 MCPH6)参与调控大脑皮层神经细胞的迁移^[27,28]。一些 MCPH 蛋白(如 MCPH1)则参与调控细胞凋亡或 DNA 损伤过程^[31]。一些 MCPH 蛋白(如 MCPH2/WDR62、MCPH3/CDK5RAP2 和 MCPH5/ASPM)参与调控微管的组装、聚合或解聚^[32-34]。MCPH7/STIL 参与小鼠胚胎体轴的特化和神经管的发育^[35]。MCPH18/WDFY3 通过调控自噬过程来影响大脑发育^[36]。

4 MCPH 突变表型

4.1 MCPH 突变病人的表型

MCPH 病人一般比较矮小, 身高和体重亦低于正常值下限。MCPH 是一种神经发育障碍疾病, 并

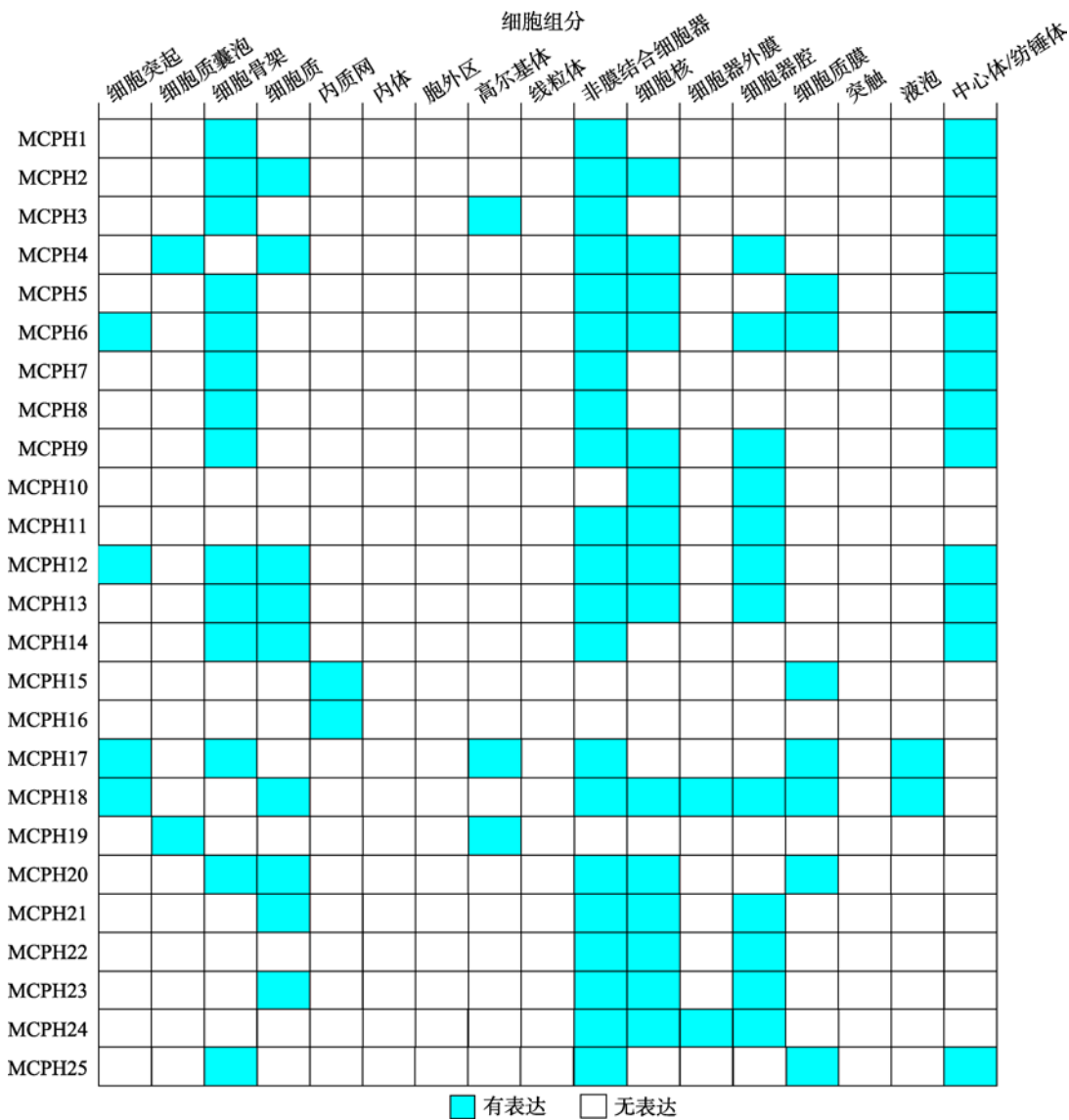


图 3 MCPH 蛋白的细胞定位

Fig. 3 Cellular localization of MCPH proteins

根据小鼠基因组信息(Mouse Genome Informatics, MGI)数据库总结得到 25 个 MCPH 蛋白在不同细胞组分中的定位。

且大部分 MCPH 基因在神经系统高表达，因此 MCPH 基因突变病人的表型主要集中在神经系统(图 5)。大脑体积减小和皮质发育不良是 MCPH 病人的主要特征。同时一些 MCPH 病人还表现出小脑、脑干及胼胝体发育不良^[15]。MCPH 病人在行为上主要表现为不同程度的智力障碍，部分表现出运动及语言障碍，也有部分病人表现出共济失调、癫痫及先天性耳聋等症状^[37-39]。

有丝分裂过程和分离缺陷、微管和纺锤体异常以及 DNA 损伤和细胞周期异常等过程在 MCPH 病

人来源或 MCPH 基因突变的细胞中被发现^[21,40-44]。也有研究表明由于神经前体细胞中 RNA 加工模式的不同是导致 MCPH 突变影响神经系统的原因^[45]。根据 MGI 数据库显示大部分 *Mcp* 突变会影响有丝分裂引起不同组织的多种表型，同时也会影响减数分裂引起生殖系统出现问题(图 5)。

4.2 MCPH 相关动物模型的构建

研究 MCPH 蛋白功能的动物模型主要有斑马鱼 (*Danio rerio*)、果蝇(*Drosophila melanogaster*)和小鼠

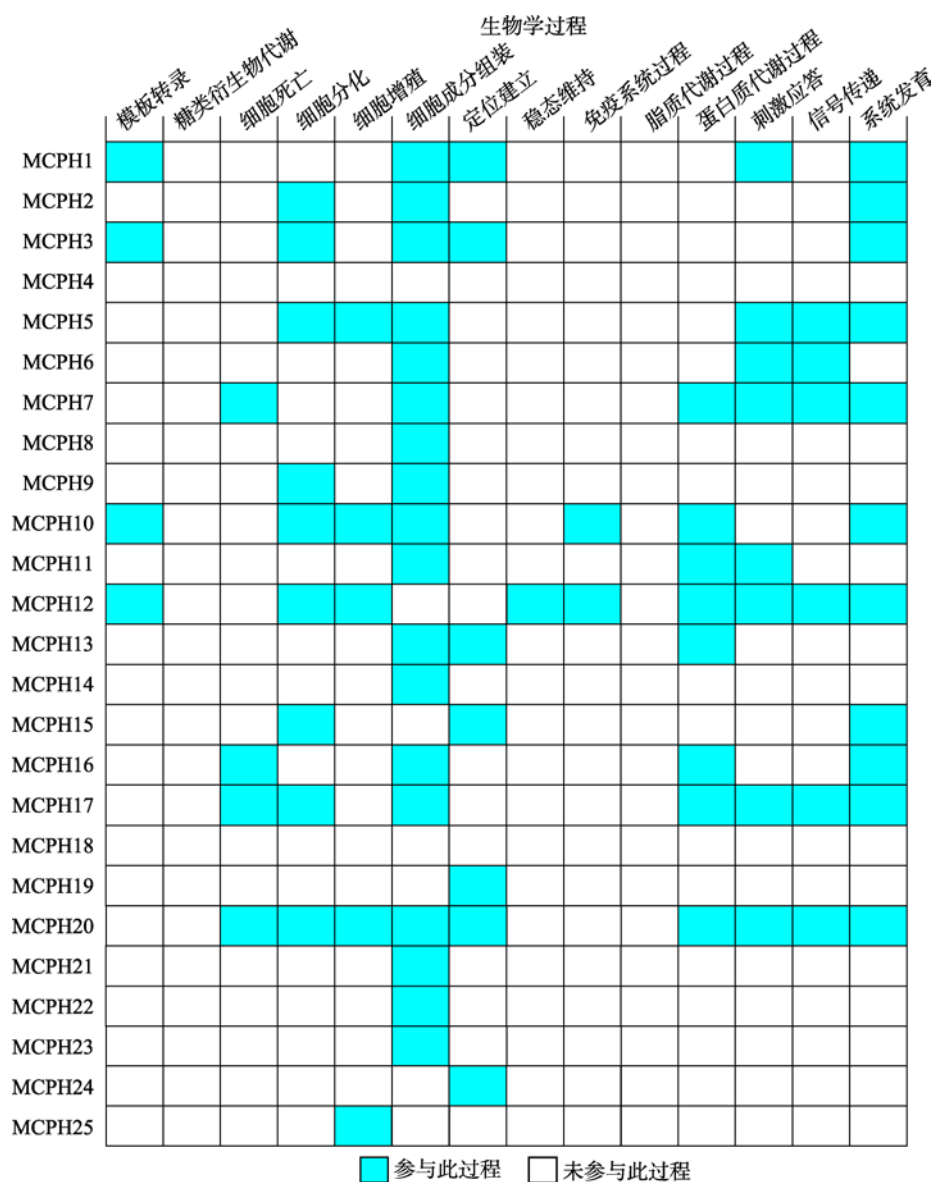


图 4 MCPH 蛋白参与的生物学过程

Fig. 4 Biological processes participated by MCPH proteins

根据小鼠基因组信息(Mouse Genome Informatics, MGI)数据库总结得到 25 个 MCPH 蛋白参与的生物学过程。

(*Mus musculus*)。MCPH 除在神经系统发育上表现出小头症的表型外，在个体生长发育过程中也起着重要作用(表 1)。另外，MCPH 蛋白在生殖系统中高表达，因此，MCPH 蛋白缺失会导致小鼠生殖细胞发育缺陷进而引起育性降低，甚至不育^[46-49]。近年来，有研究表明 *Mcp1* 缺失也会影响小鼠听力并引发中耳炎^[50]。由于 MCPH 蛋白对动物生长发育的关键作用，一些 MCPH 蛋白缺失甚至会导致动物胚胎致死或细胞凋亡。*Mcp* 基因敲除小鼠的构建为表型分析和 MCPH 致病机制的研究提供了有效的动物模型。

但由于小鼠大脑与人脑相比没有脑回结构及更多类型的神经前体细胞，*Mcp* 基因敲除小鼠有时不能很好地模拟小头症的表型。2016 年，科学家利用 TALEN 技术制备了 *MCPH1/BRIT1* 突变体食蟹猴 (*M. fascicularis*)，*MCPH1* 等位基因突变食蟹猴表现出头围减小、胼胝体发育不良以及上肢痉挛等特征模拟了大部分小头症病人的临床表型^[51]。近年来有研究在雪貂(*Mustela putorius furo*)中敲除 *Mcp5/Aspm*，敲除 *MCPH5* 雪貂表现出更为明显的小头症表型^[52]。

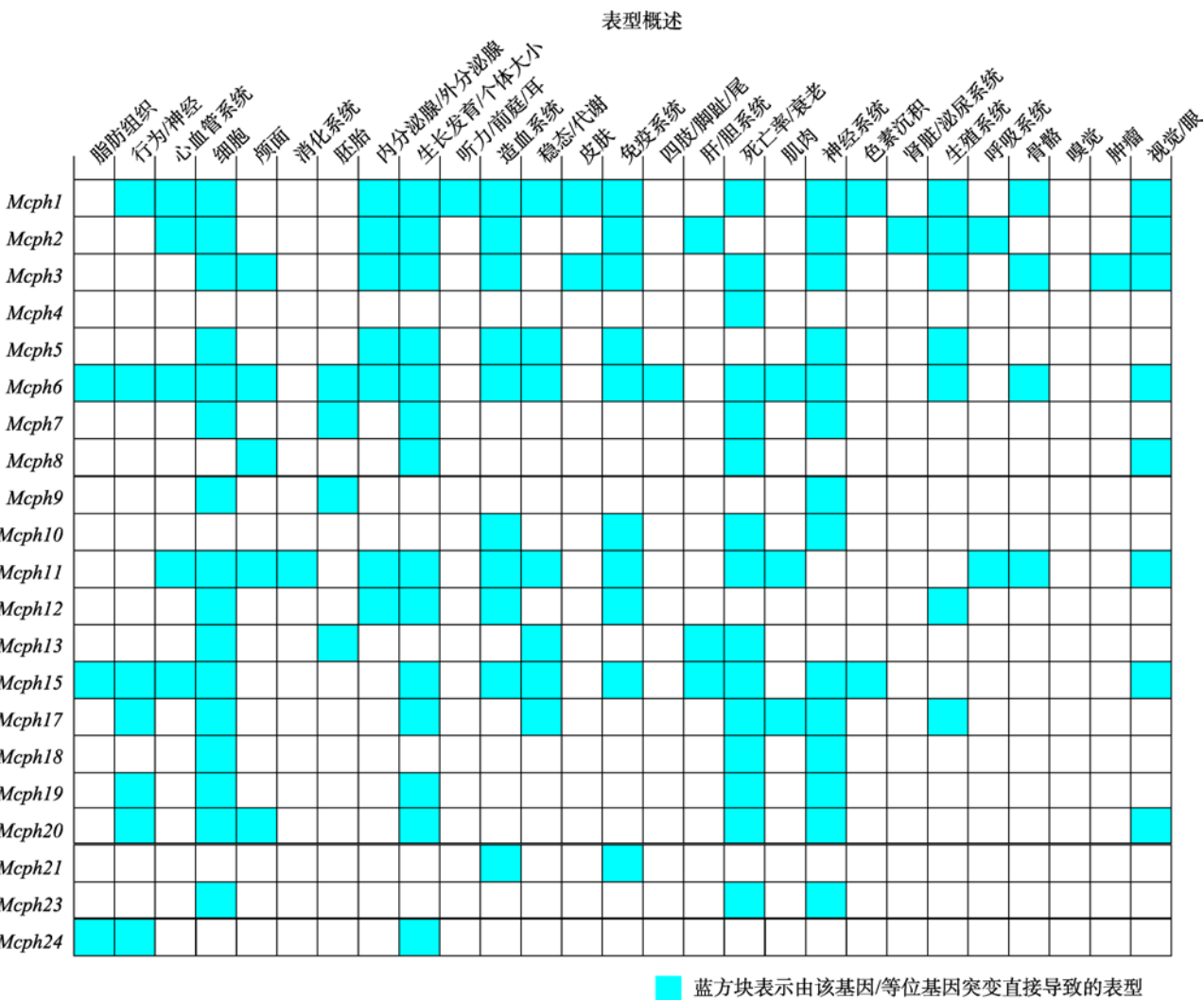


图 5 *Mcph* 基因突变相关表型

Fig. 5 Related phenotypes of *Mcph* mutation

根据小鼠基因组信息(Mouse Genome Informatics, MGI)数据库总结得到 25 个 *Mcph* 基因突变的表型。

表 1 MCPH 相关动物模型

Table 1 MCPH-related animal models

基因	别名	动物模型	表型	参考文献
MCPH1	BRIT1	<i>Mcph1^{del}</i> 小鼠	大脑皮层变薄，增殖减少，凋亡增多，不育	[53]
		<i>Mcph1^{tm1a/tm1a}</i> 小鼠	轻度或中等听力异常	[50]
		<i>MCPH1^{mt/mt}</i> 猴子	头围减少，染色体早期凝集，胼胝体发育不良和上肢痉挛	[51]
MCPH2	WDR62	<i>Wdr62^{-/-}</i> 小鼠	小头，皮层变薄，中心体复制异常	[29]
		<i>Wdr62</i> gene trap 小鼠	大脑变小，皮层变薄，神经前体细胞变少，凋亡增加	[30]
		<i>Wdr62</i> gene trap 小鼠	小头，神经前体细胞增殖和分化缺陷	[54]
		<i>wdr62^{D2a}</i> and <i>wdr62^{D3-9}</i> 果蝇	果蝇神经干细胞中心体的对称性发生变化	[55]
		胶质细胞特异性敲降 <i>Wdr62</i> 果蝇	蝇大脑变小，胶质前体细胞和神经干细胞减少	[56]
		<i>Wdr62</i> 敲降斑马鱼	脑和眼睛变小，细胞分裂异常	[57]
		<i>Wdr62^{-/-}</i> 小鼠	完全不育，减数分裂起始缺陷	[48]

续表

基因	别名	动物模型	表型	参考文献
MCPH3	CDK5RAP2/ CEP215	<i>Cdk5rap2</i> 基因突变小鼠	胚胎致死, 不孕, 生殖细胞缺失	[49]
		<i>Cdk5rap2</i> 基因突变小鼠	中心粒复制缺陷	[58]
MCPH4	CASC5	未见有动物模型表型报道		
MCPH5	ASPM	<i>Aspm</i> ^{-/-} 小鼠	神经干细胞分裂异常	[59]
		<i>Aspm</i> ^{-/-} 小鼠	小头, 睾丸显著变小, 精子发育异常	[46]
		<i>Aspm</i> ^{-/-} 小鼠	皮层变薄, 分化异常	[60]
		<i>Aspm</i> ^{-/-} 雪貂	非常明显的小头症, 体重不变, 神经前体细胞定位异常	[52]
MCPH6	CENPJ/ CPAP/ SAS4	<i>Cenpj</i> ^{tm/tm} 小鼠	原发性侏儒症, 小头, 记忆缺陷, 眼睛和骨骼发育异常	[61]
		<i>Sas4</i> ^{-/-} 小鼠	大脑神经前体细胞位置异常, 细胞凋亡, 神经元减少, 大脑变小	[62]
MCPH7	STIL/SIL	<i>Stil</i> ^{CZ65+/-} 斑马鱼	小头, 细胞阻滞在 M 期	[58]
		<i>Sil</i> ^{-/-} 小鼠	小头, 神经管发育异常, 胚胎致死	[35]
MCPH8	CEP135	<i>Bld10/Cep135</i> 突变果蝇	果蝇神经干细胞中心体对称性被破坏	[63]
MCPH9	CEP152	未见有动物模型表型报道		
MCPH10	ZNF335	<i>Znf335</i> 基因突变小鼠	胚胎致死	[64]
MCPH11	PHC1	未见有动物模型表型报道		
MCPH12	CDK6	未见有动物模型表型报道		
MCPH13	CENPE	未见有动物模型表型报道		
MCPH14	SAS-6	<i>SAS-6</i> 突变果蝇	精母细胞中心体形成缺陷	[65]
MCPH15	MFSD2A	<i>mfsd2a</i> 突变斑马鱼	血脑屏障破坏, 小头, 致死	[24]
MCPH16	ANKLE2	<i>dAnkle2</i> 突变果蝇	小头, 胸髂缺失	[66]
MCPH17	CITK	<i>CitK</i> ^{-/-} 小鼠	大脑变小, 神经前体细胞凋亡, 小脑浦肯野细胞发育异常	[67]
MCPH18	WDFY3/ALFY	转突变人源 <i>ALFY</i> 果蝇	小头	[36]
MCPH19	COPB2	<i>Copb2</i> 基因突变小鼠	小头, 神经凋亡	[68]
MCPH20	KIF14	<i>Kif14</i> 基因敲除小鼠	小头, 髓鞘形成减少	[69]
MCPH21	NCAPD2	未见有动物模型表型报道		
MCPH22	NCAPD3	未见有动物模型表型报道		
MCPH23	BRRN1	未见有动物模型表型报道		
MCPH24	NUP37	未见有动物模型表型报道		
MCPH25	MAP11	<i>Map11</i> 基因敲除斑马鱼	小头, 增殖减少	[70]

5 MCPH 分子机制研究

5.1 MCPH 蛋白功能预测

MCPH 蛋白分子的功能是多样化的。根据 MGI 网站生物信息学分析预测一些 MCPH 蛋白如 MCPH3、MCPH6、MCPH13、MCPH20 和 MCPH25 主要参与结合细胞骨架蛋白。一些 MCPH 蛋白结合 DNA (MCPH3、MCPH10 和 MCPH11)和糖类及其衍生物 (MCPH12、MCPH13、MCPH17 和 MCPH20); 还有一

些蛋白则作为各种酶如水解酶(MCPH13 和 MCPH20)、转移酶(MCPH6、MCPH12、MCPH17 和 MCPH18)催化各种生物化学反应来调控生物体内的新陈代谢和能量转换(图 6)。

5.2 MCPH 参与的信号通路

MCPH 蛋白通常调控细胞周期, 因此很多 MCPH 蛋白都参与细胞周期相关信号通路的调控。MCPH1 通过 Chk1-Cdc25-Cdk1 调控中心体及纺锤体的形成进而调控神经前体细胞的分裂^[53]。MCPH1/BRIT1 还可以与 E2F1 结合调控 CHK1 和 BRCA1 参

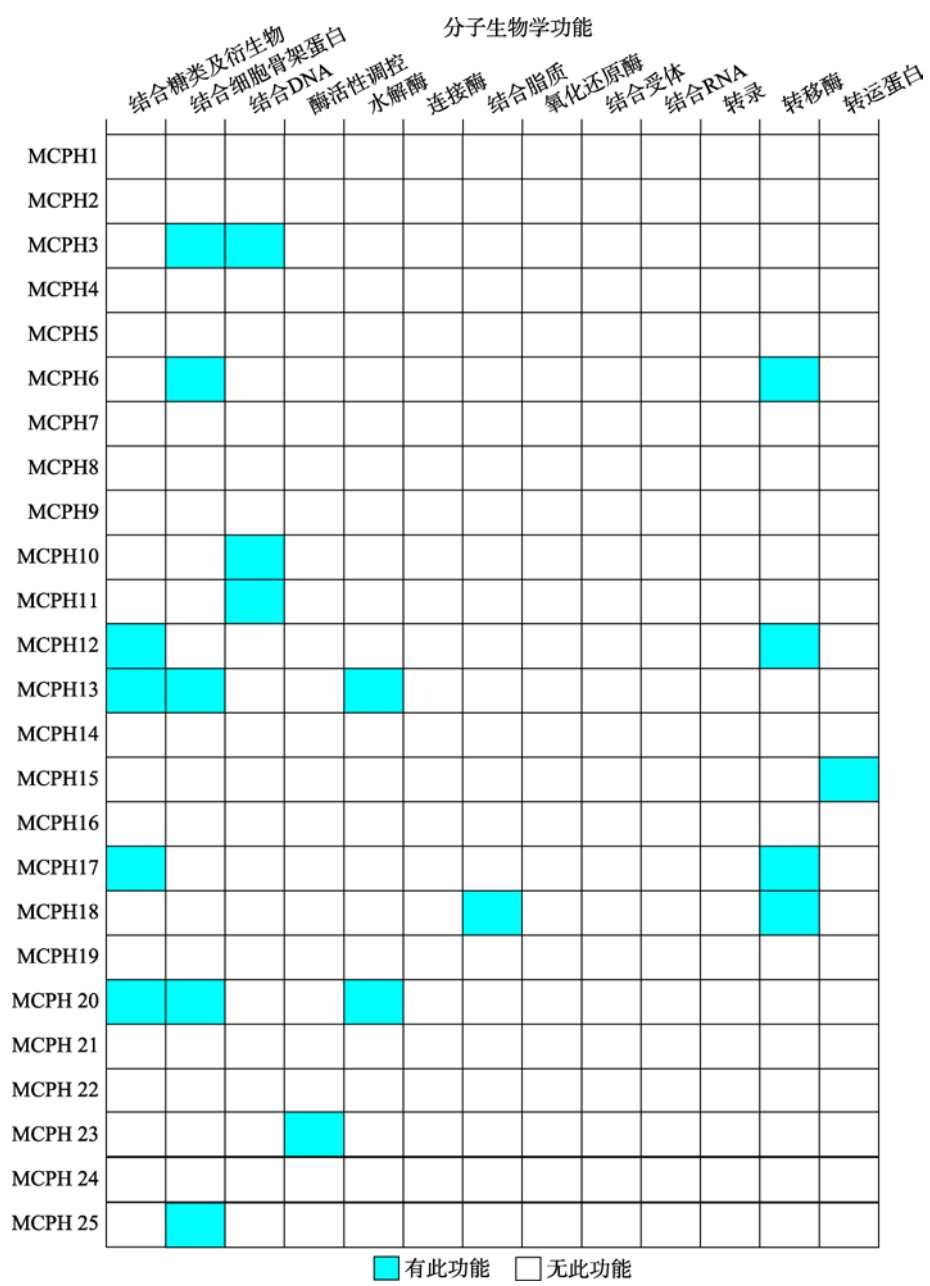


图 6 MCPH 蛋白的分子生物学功能

Fig. 6 Molecular function of MCPH proteins

根据小鼠基因组信息(Mouse Genome Informatics, MGI)数据库总结得到 25 个 MCPH 蛋白的分子生物学功能。

与 DNA 修复和细胞凋亡调控^[71]。MCPH2/WDR62 通过 JNK 信号通路调控神经前体细胞的增殖和分化^[20]。同时，MEKK3 和 FBW7 双向调控 WDR62 蛋白的稳定性进而调控大脑皮层神经干细胞稳态平衡^[72]。MCPH3/CDK5RAP2 与 EB1 结合调控微管的动态组装^[32]。MCPH5/ASPM 通过 Wnt 信号通路调控神经前体细胞的增殖和分化^[27]。MCPH6/CPAP 在

大脑发育过程中作用于 Ascl1 下游来调控神经前体细胞的分裂及神经迁移^[28]。MCPH7 通过调控 Sonic hedgehog (Shh)信号通路来调控胚胎体轴的发育^[36]。MCPH9/CEP152 与 PLK4 结合调控中心粒的复制^[52]。MCPH9/CEP152 和 MCPH17/CITK 被报道与 p53 信号通路相关^[47,67]。MCPH18/ALFY 通过调控自噬来调控经典 Wnt 信号通路^[35]。MCPH19/COPB2 通过

上调 YAP 表达来调控细胞增殖^[73]。

6 结语与展望

现代人大脑的尺寸大小约是 3 百万年前人类祖先南方古猿人大脑的 3 倍,特别是大脑皮层及脑回数量增加达 100 倍^[74]。大脑的尺寸大小及结构复杂度的增加必然伴随认知功能的增加^[75]。由于大脑的尺寸大小及脑回数量与神经元的数量密切相关,因此研究那些影响神经细胞增殖、分化及凋亡的基因有利于了解脑发育过程及人类的进化过程。MCPH 是一种常染色体隐性遗传小头畸形病症。本文对已报道的 25 个 MCPH 蛋白的表达、定位和功能进行了总结和概述,为研究大脑发育相关蛋白特别是 MCPH 蛋白的致病机制提供了理论依据和线索。在已报道的 25 个 MCPH 中, *WDR62* 和 *ASPM* 突变导致的 MCPH 病人较多,因此相关研究也较多。同时根据被发现的顺序,一些较早发现的 MCPH 蛋白(MCPH1~MCPH10)的动物模型建立较多,而较晚发现的 MCPH11~MCPH25 只有少部分蛋白的动物模型已经建立。在已建立的动物模型中,大部分 MCPH 缺失或突变模型都会导致小头症的典型特征即大脑明显变小,还有一部分动物模型影响了生殖系统。导致小头症的分子机制研究主要集中在调控中心体或纺锤体的形成进而影响神经前体细胞的增殖分化和细胞凋亡。也有一些 MCPH 突变小鼠表现出小脑发育不良或神经元轴突发育异常。近年来,大脑类器官的建立为研究大脑疾病包括小头症的发病机制提供了很好的模型^[76,77]。Gabriel 等^[77,78]利用人 iPSC 诱导的类脑模型研究 MCPH6/CPAP 的致病机制。鉴于大脑类器官模型在体外培养的限制性,构建小头症相关蛋白缺失或突变的动物模型仍是未来研究小头症发病机制的有效手段。

大脑的尺寸在一定程度上反应脑重量和脑容量的大小^[79]。但是拥有一个更大的大脑并不意味着人类或动物在认知方面就表现得更好。病人的头围相对于其同年龄与性别的平均值明显大 2 个标准差以上会导致另外一种脑发育疾病称为巨脑症(macrocephaly)^[80]。巨脑症主要是由于神经增殖和迁移异常引起,病人表现出智力低下并有部分伴有自闭症样

行为^[80-83]。因此,维持大脑尺寸的正常发育对于脑功能的正常发挥起着非常重要的作用。

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