纤毛疾病和与之相关的基因

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摘要:近年来,研究发现纤毛在生成或者形态的缺陷均能导致新生儿遗传性疾病。与其他细胞器不同的是,纤毛这一小的毛发状细胞器能在几乎所有的极性细胞表面上生成,而且功能非常多样化。纤毛在调节脊椎动物的发育和内环境的平衡起着相当重要的作用,而与纤毛相关基因的缺失则与一系列疾病相关,包括:Nephronophthisis、Joubert 综合症、Meckel-Gruber 综合症和 Bardet Biedl 综合症等。结合最近的研究,本文主要对四类主纤毛相关疾病的基因进行归类总结。

关键词:纤毛;Nephronophthisis;Joubert 综合症;Meckel-Gruber 综合症;Bardet Biedl 综合症
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Ciliary Disease and the Related Genes

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ABSTRACT: Recently, Cilia has been added to a well-known causes of human diseases. Unlike other cellular organelles, cilia are tiny hair-like organelles that attached to the cell surface, and are located on almost all polarized cell types of the human body. Cilia play a crucial role in regulating vertebrate development and tissue homeostasis. The various cellular functions of cilia explain why cilia-related disorders can affect many organ systems. Defects in ciliary genes cause lots of ciliary diseases, such as: Nephronophthisis, Joubert Syndrome, Meckel-Gruber Syndrome and Bardet Biedl Syndrome.

Key words: Cilia; Nephronophthisis; Joubert Syndrome; Meckel-Gruber Syndrome; Bardet Biedl Syndrome
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纤毛是一种在低等到高等生物中非常保守的结构。从莱茵衣藻的鞭毛到人类的几乎所有细胞中,纤毛起着非常重要的作用。从纤毛的顶端起可以分为纤毛尖端(ciliary tip)、纤毛膜(ciliary menbrane)、轴丝(axoneme)、过渡区(transition zone)和基底(basal body)这五个部分[1]。在这五个部分中,基底和过渡区处于纤毛的最低端,她们把纤毛内部组分和细胞质组分隔离开来,那么无论是在物质运输还是信号传递上,都对纤毛起着精确的调控。在早期的研究中,人们估计在纤毛基底上大概有150 种不同蛋白。最近通过比较基因组学和蛋白质组学分析,纤毛基底和轴丝上的蛋白质达到 1000 种[2](http://www.ciliaproteome.org)。小鼠眼睛光感受器的外膜和纤毛链接部位的蛋白组学结果表明,还有更多的蛋白与纤毛的功能相关。这其中的很多基因功能的异常直接导致纤毛性疾病的产生。

1 Nephronophthisis 疾病(NPHP)

NPHP 是一种常染色体隐性肾囊疾病,是一种在小孩和年轻人肾脏疾病中最常见的基因性疾病。据估计,在美国每八百三十万人当中就有九个人患有此疾病。而在加拿大,每五万个新生儿当中就有一个新生儿患有肾囊肿病。通过基因克隆,目前已经发现了 10 个与肾结核相关的基因(NPHP1-9 和 NPHP11)。不论是在人还是动物模型上,这些基因表达的蛋白都在初级纤毛和中心体上表达(表 1)。而且这些 NPHP 基因的突变都可以使 Wnt 和 Hedgehog 信号通路产生缺陷,从而使细胞极性和组织不能很好的形成[3]。在临床表现上,这些基因的功能不正常也可以导致视网膜退化、小脑发育不全、肝纤维化和智力迟钝。

2 Joubert 综合症(JBTS)

JBTS 是一种常染色体隐性疾病,由于这种疾病使小脑蚓部和脑干部分发育不良或者畸形,而表现出肌肉无力、眼睛和舌头运动异常、呼吸紊乱和认知缺陷[14](表 2)。有一些 JBTS 也表现出视网膜障碍或者肾脏畸形。目前已知这种疾病的发生几率超过了三万分之一。

3 Meckel-Gruber 综合症(MKS)

MKS 是一类常染色体隐性致死疾病,这种疾病能导致出生前或者出生早期婴儿致死。形态学上表现为神经管缺损、肾囊肿和畸形。目前已经报道有 8 个基因都与 MKS 综合征相关(表 3)。

4 Bardet Biedl 综合症(BBS)

BBS 是典型的常染色体遗传病,表现出多种症状,包括多趾症、视网膜障碍、肥胖、生殖机能不良、学习能力缺陷和肾功

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能障碍等[20]。约有小于 10%的 BBS 病人是由于多个 BBS 基因位点突变而致病。在 2005 年，Karmous-Benailly 等人观察到 13 个 BBS6 的杂合体中有 3 个表现出肾囊肿病样，并证明在 BBS 与 MKS 这两类遗传性疾病之间也有基因之间的重合（表 4）。

表 1 NPHP 相关的基因

Table 1 NPHP Related Gene

Gene	Other names	Protein localization	Percentage in NPHP
NPHP1[4]	JBTS4	Basal body and Tranzition zone	21%
NPHP 2[5]	Inversin	Basal body and Tranzition zone	1%
NPHP 3[6]		Cilia	1%
NPHP 4[7]		Basal body and Transition zone	2%
NPHP 5[8]	IQCB1	Basal body	3%
NPHP 6[9]	CEP290/ MKS4/JBTS5/BBS14	Basal body, Transition zone and Centrosome	1%
NPHP 7[10]	GLIS2	Cell membrane	0.1%
NPHP 8[11]	RPGRIP1L/MKS5/JBTS7	Centrosome and Transition zone	0.5%
NPHP 9[12]	NEK8	Basal body and Centrosome	0.1%
NPHP 11[13]	MKS3/TMEM67/JBTS6	Ciliary membrane	

JBTS: Joubert syndrome; MKS: Meckel-Gruber syndrome; NEK: Never in mitosis kinase 8.

表 2 JBTS 相关的基因

Table 2 JBTS Related Gene

Gene	Other names	Protein localization
JBTS1[15]	CORS1/INPP5E	Golgi
JBTS 2[16]	CORS2/MKS2/TMEM216	Ciliary membrane
JBTS 3[17]	AHI1	Basal body and Transition zone
JBTS 4	NPHP1	Basal body and Transition zone
JBTS 5	CEP290/MKS4/NPHP6/BBS14	Basal body, Transition zone and Centrosome
JBTS 6	TMEM67/MKS3/NPHP11	Ciliary membrane
JBTS 7	RPGRIP1L/MKS5/NPHP8	Centrosome and Transition zone

AHI1: Abelson helper integration site gene.

表 3 MKS 相关的基因

Table 3 MKS Related Gene

Gene	Other names	Protein localization
MKS1[18]	BBS13	Basal body and Transition zone
MKSR1[18]		Basal body and Transition zone
MKSR2[18]		Basal body and Transition zone
MKS2	JBTS2/CORS2/TMEM216	Ciliary membrane
MKS3[13]	TMEM67/JBTS6/NPHP11	Ciliary membrane
MKS4	CEP290/NPHP6/BBS14/JBTS5	Basal body, Transition zone and Centrosome
MKS5[11]	RPGRIP1L/JBTS7/NPHP8	Centrosome and Transition zone
MKS6[19]	CC2D2A	Cilia

我们对纤毛的认识绝大多数来自对莱茵衣藻和基因突变的老鼠的研究，随着模式生物秀丽隐杆线虫的加入，大家对纤毛疾病的研究变得越来越火热，也有越来越多的纤毛疾病相关的基因被发现。在本文中，我们讨论了四类主要的纤毛疾病，并总结了这四类疾病在基因水平上存在很大的关联。比如：NPHP8 基因，它的缺失或者突变不仅能引起 NPHP 疾病，也可

能引起 MKS、JBTS 等疾病。针对纤毛基底和过渡区的研究发现，纤毛的基底和过渡区是由许多类型蛋白聚集，共同起作用。当一个基因的功能不正常后，很可能能引起另外一个基因不能正常表达或者使表达后的蛋白不能正确定位到纤毛上，从而产生多种临床表现。这也就解释了为什么在这四种疾病临床表型上很多的相似性。

表 4 BBS 相关的基因

Table 4 BBS Related Gene

Gene	Other names	Protein localization	Percentage in BBS
BBS1[21]		Basal body	23-56%
BBS2[22]		Basal body	8-16%
BBS3[23]	ARL6	Basal body	2-4%
BBS4[24]		Basal body and Centrosome	3%
BBS5[25]		Basal body	3%
BBS6[26]	MKKS	Basal body and Centrosome	4-5%
BBS7[27]		Basal body	3.5%
BBS8[28]	TTC8	Basal body	1-2%
BBS9[29]	B1	Basal body	
BBS10[30]		Basal body	20%
BBS11[31]	TRIM32	Basal body	
BBS12[32]		Basal body	
BBS13	MKS1	Basal body and Transition zone	
BBS14	CEP290/MKS4/NPHP6/JBTS5	Basal body, Transition zone and Centrosome	

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