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·耳科学专栏·

中耳胆脂瘤的遗传学研究进展

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摘 要: 中耳胆脂瘤是一类位于鼓室和/或乳突内的团块,由角化的鳞状上皮细胞、上皮下的结缔组织以及角化碎片构成,伴/不伴炎症反应。临床表现主要为耳流脓和听力下降,当侵袭周围组织结构时则可产生眩晕、周围性面瘫、颅内感染等一系列颅内外并发症,甚至危及生命。手术是目前唯一有效的治疗方式。其病因及发病机制仍未完全清楚。随着全外显子测序等新一代测序技术的发展,中耳胆脂瘤的遗传学研究取得了一些突破性进展。近年来,关于胆脂瘤的家族聚集性、基因突变及其与综合征的关系的相关研究越来越多,本文将对上述内容进行综述,从而为中耳胆脂瘤的非手术治疗、药物研发提供参考。

关 键 词:中耳胆脂瘤;遗传学;基因突变;综合征

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Advances in the genetics of middle ear cholesteatoma

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Abstract: Cholesteatoma of the middle ear is a mass formed by the keratinizing squamous epithelium of the tympanic cavity and/or mastoid and subepithelial connective tissue and keratin debris, with/without a surrounding inflammatory reaction. When invading the surrounding tissue structures with mainly clinical manifestations of ear discharge and hearing loss, it can produce a series of intracranial and extracranial complications such as vertigo, peripheral facial paralysis, intracranial infections and even life-threatening. Surgery remains the only available treatment now. The etiology and pathogenesis of middle ear cholesteatoma are not entirely clear. With the development of whole exon sequencing (WES) and other new generation sequencing technology, some breakthroughs have been made in the genetics of middle ear cholesteatoma. In recent years, there are more and more studies on the family aggregation and gene mutation of cholesteatoma, and the relationship between cholesteatoma and syndrome. This article will review the above for the sake of the non-surgical treatment and drug development of middle ear cholesteatoma.

Keywords: Middle ear cholesteatoma; Genetics; Genetic mutation; Syndrome

中耳胆脂瘤是一种非肿瘤性病变,呈进行性发展。“Cholesteatoma”一词由德国生理学家 Müller 于 1838 年首创[1]。尽管后来学者们发现,胆脂瘤一词为误用,但仍沿用至今。角化的鳞状上皮异常增殖、分化并转移至中耳,侵蚀骨质,最终引起一系列颅内外并发症甚至死亡的可能。中耳胆脂瘤分为先天性胆脂瘤和后天性胆脂瘤[2]。先天性胆脂瘤为完整鼓膜后出生前即形成的白色肿块,没有中耳炎病史或耳科手术史;后天性胆脂瘤通常是出生后经过一系列病理变化形成[3-4]。关于中耳胆脂瘤的病因众说不一,迄今不明。目前大多数研究结果表明环境因素与遗传因素共同导致中耳胆脂瘤的发生,其中遗传因素在发病过程中发挥重要作用。自 2007 年第一个后天性中耳胆脂瘤家系[5]被发现后,随着 DNA 检测技术的不断进步,关于中耳胆脂瘤的遗传学研究越来越多。

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1 发病率

因为中耳胆脂瘤的术前诊断率较低,所以其发病率很难确定,特别是先天性胆脂瘤。有研究表明,成人后天性胆脂瘤的年患病率约为(9～12.6)/100 000,儿童后天性胆脂瘤的年患病率约为(3～15)/100 000[6-8]。比较经济水平、职业等环境因素,发展中国家的胆脂瘤患病率高于发达国家[9],但不同社会群体之间的中耳胆脂瘤发生率没有显著差异[7]。比较性别、种族等遗传因素,中耳胆脂瘤的男女比例约为1.4∶1[1, 10],男性患病率更高;且高加索人的胆脂瘤患病率最高,其次是非洲人,非印度裔亚洲人最低[2]。这表明,从流行病学的角度中耳胆脂瘤的发生可能是遗传和环境共同作用的结果。

2 病因及发病机制

中耳胆脂瘤的病因迄今不明。学者们普遍认为先天性胆脂瘤可能是由于胚胎时期外胚层的胚胎细胞残留在中耳腔所致。而后天性胆脂瘤的病因,学者们对此议论纷纭。炎症、病毒感染[11]、外伤[7]、咽鼓管功能障碍等都可能是后天性胆脂瘤发病的因素。近年来,有研究发现,多个基因[12-15]可能参与中耳胆脂瘤的发生。后天性胆脂瘤发生的病理机制目前尚未了解透彻,主要有4种学说:①囊袋内陷学说;②上皮迁移学说;③基底细胞增殖学说;④鳞状上皮化生学说。后天性胆脂瘤最为广泛接受的发病机制是因为中耳负压而加深的囊袋阻塞时,角质难以被清除,从而导致胆脂瘤。虽然这四种学说可以对后天性胆脂瘤发病的部分机理进行合理解释,然而没有一种学说理论能够完整的解释胆脂瘤的所有临床特征。所以,从病因学的角度,我们发现,中耳胆脂瘤不仅与环境因素有关,与遗传因素也息息相关。

3 胆脂瘤的遗传性

近年来,部分学者发现一些中耳胆脂瘤家系,这表明中耳胆脂瘤可能具有家族遗传性。如Homøe等[5]报道了一个来自格陵兰的后天性胆脂瘤家系,这个家庭由父母和7个兄弟姐妹组成,其中母亲和3个儿子均确诊患有中耳胆脂瘤;Landegger等[16]报道了1例先证者和他的哥哥均患有胆脂瘤;胆脂瘤在双胞胎中也有报道[17]。也有学者通过横断面研究,调查发现大部分中耳胆脂瘤患者具有家族史。如Podoshin等[18]通过对以色列的3个集体农场中10岁以上的人(受试者们都生活在相同的社会经济环境中,吃着相似的食物,接受相同水平的医疗和治疗,所有的受试者都在他们的集体农场生活了10年以上)行耳科检查,发现64%的胆脂瘤患者有家族史;一项国际的线上调查显示[19],报道中有较高比例的受访者有胆脂瘤家族史。随着对其遗传方式研究的逐渐深入,一些学者认为胆脂瘤是典型的单基因或少基因疾病遗传模式,具有不完全外显性[14]。鉴于此,英国已经建立了一个数据库和DNA样本库,可用于在家族中识别与胆脂瘤共分离的遗传变异。

4 胆脂瘤的基因学

4.1 *APC* 基因

APC 基因位于染色体5q22.2区域,它不仅在抑制肿瘤生长中发挥重要作用,而且可以调控正常细胞的生长和空间排列[20]。*APC* 基因功能丧失后易致癌症发生,如家族性腺瘤性息肉病。Shaoul等[12]描述了一个患有家族性腺瘤性息肉病和先天性胆脂瘤的6岁男孩。DNA分析发现该患者的 *APC* 基因的密码子1309－1311(外显子15)有一个5 bp的缺失(GAAAG)。*APC* 基因的蛋白产物含有几个功能结构域,其中一些是β-连环蛋白的结合和降解位点。β-连环蛋白是一种92 kDa的蛋白质,参与构成组织架构和维持细胞极性[21]。Peifer[22]通过回顾β-连环蛋白在果蝇中的作用,推断APC蛋白－连环蛋白复合物可能通过激活E-钙黏蛋白调节粘附。E-钙黏蛋白是一种依赖于Ca^{2+}的黏附分子,控制上皮细胞[21, 23]之间粘附连接的形成和维持。E-钙黏附素还可能通过影响细胞迁移和形态发生来控制胚胎发育过程中的细胞运动[21, 24]。先天性胆脂瘤的发病机制可能是因上皮细胞间粘附功能减弱,导致上皮细胞脱落和异常生长。

4.2 *ABCC11* 基因

ABCC11 位于染色体16q12区域,主要参与大汗腺分泌物的形成(表现为湿耳垢型或干耳垢型、腋臭以及初乳分泌物)。有研究表明,湿耳垢与外耳炎的发病有关[25-27]。因此,日本学者[13]猜测中耳胆脂瘤与耳垢基因型的相关性,通过对比胆脂瘤组,对照组和日本普通人群组,观察到胆脂瘤组为湿耳垢基因型(*538GG* 和 *GA*)的比例显著高于对照组和普通日本人。在对照组和普通日本人群中,湿性耳

垢基因型的人比例没有显著差异。胆脂瘤组 *ABCC11* 的 *538G* 等位基因频率也显著高于对照组和日本普通人群。因此推断 *ABCC11* 基因可能与日本人获得性中耳胆脂瘤的发生有关。研究者们对其致病机制提出了一种假说,外耳道耳垢中的化合物经细菌修饰后产生挥发性的有机化合物(volatile organic compounds, VOCs),湿耳垢中 VOCs 的含量比干耳垢中的多[28]。外耳道皮肤暴露于 VOCs 可导致皮肤炎症,可能是因为它们具有氧化应激毒性[29-30]。因此,湿耳垢基因型中 VOCs 的高含量可能与因外耳炎而导致的中耳胆脂瘤有关。

4.3 *EGFL8* 和 *BTNL9* 基因

EGFL8 位于染色体 6P21.32 区域,编码表皮生长因子样结构域 8 蛋白,在皮肤中高表达。*BTNL9* 作为免疫球蛋白超家族的受体蛋白,编码类嗜乳脂蛋白 9 蛋白。最近研究表明,*EGFL8* 与肝癌[31]、胃癌[32]、大肠癌[33]等疾病的预后呈正相关,*BTNL9* 与乳腺癌[34]、非小细胞肺癌[35]等疾病的生存率呈正相关。一项 10 年的前瞻性研究[36]通过收集胆脂瘤患者的家族史资料,总结并分析了 15 个中耳胆脂瘤家系后表明胆脂瘤可能有家族聚集。他们对第一个受影响的家系行全外显子测序发现[14]两个功能丧失性突变的基因:*EGFL8* 和 *BTNL9* 及一些其他错义突变。据报道,*EGFL8* 中的无义突变与银屑病显著相关[37]。有趣的是,无论是银屑病还是胆脂瘤,角质形成细胞的增殖和分化都有改变。因此,*EGFL8* 突变可能具有多效性效应和/或这两种疾病有共同的生物驱动因素。而 *BTNL9* 突变与胆脂瘤的关系目前是未知的。究竟是 *EGFL8* 和 *BTNL9* 突变,还是其他基因的错义突变对胆脂瘤发生产生影响,这仍然是个谜。

4.4 *GJB2*

GJB2 位于染色体 13q12.11 区域,负责编码缝隙连接蛋白 26,该基因突变会导致感音神经性耳聋[38]和增生性皮肤疾病[39-41]。连接蛋白是一种跨膜蛋白,可以形成细胞间通道,允许离子和小分子的快速和选择性运输[42]。连接蛋白通道(缝隙连接)介导的细胞间信号系统在维持组织内稳态、生长控制和发育以及细胞对刺激的同步反应中起着至关重要的作用[43]。有文献表明,缝隙连接蛋白 26 在胆脂瘤中表达[44]。因此,有人推测 *GJB2* 突变可能形成胆脂瘤。一项儿童胆脂瘤的研究[15]通过对 98 例胆脂瘤患儿外周血标本进行 *GJB2* 基因突变筛查,发现有 14 例患儿至少有一个 *GJB2* 序列变异(14%),其中有 3 例患儿存在两个变异。*GJB2* 基因突变虽然在患有胆脂瘤的儿童中占少数,但是可能仍比正常人群更为常见。结合连接蛋白 26 的功能,可以推测,*GJB2* 基因可能通过使上皮细胞异常增殖和改变细胞迁移中重要的细胞间通讯而参与胆脂瘤的形成。

一些研究还发现,某些基因在胆脂瘤表达中的上调和下调,可能与胆脂瘤的增殖、分化及侵袭性相关,从而促进胆脂瘤的发生[45-48]。

5 胆脂瘤与其他遗传性疾病

5.1 胆脂瘤与非综合征型唇腭裂

非综合征型唇腭裂是人类最常见的先天畸形之一,它是由遗传和环境因素相互作用引起的一种复杂的多基因、多因素遗传病[49]。在一些研究中,发现有唇腭裂的个体患胆脂瘤的风险显著增加[50-55]。一项丹麦的研究[56]将 8 593 例非综合征型唇、腭裂患者和其 6 989 名兄弟姐妹与随机样本进行对比,发现患有腭裂的人群合并胆脂瘤的风险较未患腭裂的人群增加了 20 倍,这可能与家族性的亚临床肌肉损伤有关。

5.2 胆脂瘤与腮-耳-肾综合征

腮-耳-肾综合征是一种罕见的常染色体显性遗传病,其特征是听力损失、鳃弓异常和肾畸形。Lipkin 等[57]报道了一对母女,均在 5 岁时出现右侧先天性胆脂瘤、右耳前凹陷和双侧感音神经性听力损失的三联征。推测这两个病例可能代表了一种独特的鳃-耳发育不良。1999 年报道的另一个家庭中的两个成员也证实了这两种疾病的共存可能并非偶然[58]。这表明,中耳胆脂瘤与腮-耳-肾综合征存在一定的相关性。

5.3 胆脂瘤与唐氏综合征

唐氏综合征(Down syndrome,DS),又称 21-三体综合征,常见的头颈部表现包括耳廓小、外耳道狭窄、乳突发育不全、端头过长、腭部缩短、舌头粗大、鼻咽狭窄、面中部发育不良、咽鼓管解剖异常[59-62]等,唐氏综合征的听骨畸形,包括镫骨的固定和畸形也有报道[63-64]。最近,越来越多的研究发现唐氏综合征患者[65-68]合并中耳胆脂瘤。有研究表明,患有 DS 的儿童的胆脂瘤患病率比不伴 DS 的儿童的胆脂瘤患病率高 7 倍[69]。有学者认为外耳道狭窄可能会掩盖中耳胆脂瘤,推测胆脂瘤可能是唐氏综合征的一种亚表型,其发现率低可能是因为检查相对

困难。

5.4 胆脂瘤与 Turner 综合征

特纳综合征(Turner syndrome,TS)也称为女性先天性卵巢发育不全综合征,是一种较为常见的性染色体异常疾病,由一条 X 染色体完全或部分缺失导致。TS 核型可分为单一型、嵌合型、X 染色体结构异常和含 Y 染色体核型[70]。TS 的主要表型特征是身材矮小。不同患者之间临床表型差异很大,有时尽管有相同的核型,但有些患者表现出典型特征,有些几乎没有表现任何特征。胆脂瘤在 TS 患者中的发病率及复发率显著高于正常人群[71-73]。Verver 等[74]发现 TS 患者发生胆脂瘤的主要原因可能是颅面部发育畸形或咽鼓管功能障碍。TS 患者的耳部疾病与位于 X 和 Y 染色体短臂末端的生长调节基因(*SHOX* 基因)(Xp22.33 和 Yp11.33)存在一定的相关性[75-76]。*SHOX* 基因缺乏不仅会阻碍外胚层第一鳃弓、第二鳃弓及中胚层间充质组织向耳廓分化,还会使外耳道向下倾斜以及咽鼓管走向异常[77]。此外,Lim 等[72]发现核型为 45,X 和 46,Xi(Xq)的 TS 患者比其他核型更易患胆脂瘤。

胆脂瘤在其他综合征型疾病中也有报道,如表皮发育不全[78-79]、Beckwith-Wiedemann 综合征[80]、肉芽肿性血管炎[81]、管理者综合征[82]、原发性睫状体运动障碍[83]、Tolosa-Hunt 氏综合征[84]、Treacher Collins 综合征[85]、Wolf-Hirschhorn 综合征[86]等。

6 总结

遗传因素在中耳胆脂瘤的发病过程中发挥重要作用。目前已知有 5 个基因的突变可能与胆脂瘤的发生相关,但是其致病机制目前仍不清楚。另外有数十种综合征可伴有中耳胆脂瘤。巧合的是,*EGFL8* 与 *GJB2* 基因突变均与银屑病相关,且银屑病和胆脂瘤的角质形成细胞的增殖和分化都有改变。另外,中耳胆脂瘤在黄种人和黑种人中发病率较低,找到足够大的家系进行中耳胆脂瘤的遗传学研究分析较困难。目前关于中耳胆脂瘤的遗传学研究大多以病例为重点,中耳胆脂瘤致病基因的模式动物研究还少有开展,中耳胆脂瘤具体的分子致病机制尚需要更加深入的研究。

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