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·综述·

LRP6基因突变导致选择性先天缺牙的研究进展

蒋彩玲[1,2]，　赵彬[1]，　吴轶群[2]
1. 山西医科大学口腔医学院，山西 太原（030012）；　2. 上海交通大学医学院附属第九人民医院口腔第二门诊部，上海（200125）

【摘要】 选择性先天缺牙是由遗传或环境因素导致的牙齿数目异常，多累及恒牙列。低密度脂蛋白受体相关蛋白6（low-density lipoprotein receptor-related protein 6，LRP6）是选择性先天缺牙的常见致病基因之一，该基因突变为常染色体显性遗传，可导致非综合征型先天缺牙或综合征型先天缺牙；非综合征型先天缺牙仅表现为牙齿数目、形态异常；综合征型先天缺牙可表现为耳部发育畸形、口面裂、毛发稀少、汗腺异常等。笔者就近年来关于LRP6基因突变导致选择性先天缺牙的表型及基因突变特点的研究现况进行综述，文献收纳24个LRP6基因突变位点和38例相关先天缺牙患者，发现LRP6基因突变导致的选择性先天缺牙好发于上颌侧切牙及上下颌第二前磨牙和第一前磨牙，极少发生于第一磨牙，尤其是下颌第一磨牙，未见上颌中切牙缺失。LRP6基因在牙发育过程中主要通过WNT/β-catenin信号通路发挥重要作用，LRP6基因突变可导致蛋白表达和功能异常、信号通路破坏从而导致选择性先天缺牙。现有文献结果显示，LRP6基因突变好发于胞外段E1、E2亚结构域，影响WNT/β-catenin信号通路的传导而致病。然而目前对于选择性先天缺牙仍缺乏成熟完善的对因治疗。

【关键词】 低密度脂蛋白受体相关蛋白6基因；　选择性先天缺牙；　综合征型先天缺牙；　非综合征型先天缺牙；　多数牙缺失；　少数牙缺失；　表型；　基因突变
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Research progress on selective tooth agenesis caused by LRP6 gene mutation

JIANG Cailing[1,2], ZHAO Bin[1], WU Yiqun[2]. 1. School of Stomatology Affiliated to Shanxi Medical University, Taiyuan 030012, China; 2. The Second Department of Stomatology, the Ninth People's Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200125, China
Corresponding author: ZHAO Bin, Email: 18636666063@163.com, Tel: 86 - 18636666063; WU Yiqun, Email: WUYQ1243@sh9hospital, Tel: 86-21-53315299

【Abstract】 Selective tooth agenesis (STA) is an abnormal number of teeth due to genetic factors or the environment and is most commonly observed for permanent teeth. LRP6 is one of the common causative genes of STA and is inherited by an autosomal dominant mechanism, leading to non-syndrome tooth agenesis (NSTA) or syndrome tooth agenesis (STA). NSTA is only involved in tooth number and appearance abnormalities, whereas STA caused by LRP6 gene mutation results abnormal ear development, oral-facial clefting, sparse hair and hypohidrosis. In this paper, we review the phenotype and gene mutation traits of selective STA caused by LRP6 gene mutation identified in recent years and describe 38 patients with tooth agenesis from 24 mutation sites of LRP6 gene. We analyzed the percentage of missing teeth and found that the lateral incisor in the maxilla and the second premolar in the maxilla and mandible were most commonly lost, whereas all central incisors in the maxilla remained. LRP6 gene plays a major role in tooth development

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【作者简介】 蒋彩玲，住院医师，硕士，Email：JiangCL0627@163.com
【通信作者】 赵彬，主任医师，硕士，Email：18636666063@163.com，Tel：86-18636666063；共同通信作者，吴轶群，主任医师，博士，Email：WUYQ1243@sh9hospital，Tel：86-21-53315299

via the WNT/β-catenin signaling pathway, and LRP6 gene mutation can lead to a series of abnormal manifestations due to the disruption of the signaling pathway. The literature showed that LRP6 gene mutations occurred mostly at the E1 or E2 subdomain, meaning that STA due to the mutants extracellularly disturbed the WNT/β-catenin signaling pathway. However, mature treatments for selective congenital tooth loss are lacking.

【Key words】 low-density lipoprotein receptor-related protein 6 gene; selected tooth agenesis; syndrome tooth agenesis; non-syndrome tooth agenesis; oligodontia; hypodontia; phenotype; gene mutation

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选择性先天缺牙(selective tooth agenesis,STA)是常见的遗传性疾病之一,根据缺牙数目可分为少数牙缺失(1～5颗牙缺失)、多数牙缺失(≥6颗牙缺失)和全口无牙,其中少数牙缺失最为常见,发病率约为4.6%～9.6%;多数牙缺失较为罕见,发病率约为0.16%[1],研究表明缺牙率与性别无明显关联[2]。根据是否伴有外胚层发育异常如毛发稀疏、汗腺异常等全身其他症状分为综合征型先天缺牙(syndrome tooth agenesis,STA)和非综合征型先天缺牙(non-syndrome tooth agenesis,NSTA)[3]。导致选择性先天缺牙的主要原因是牙发育相关基因突变使牙胚发育提前终止[4]。目前导致选择性先天缺牙常见的突变基因包括WNT10A(26.0%)、PAX9(24.7%)、MSX1(14.5%)、AXIN2(6.1%)、EDA(5.9%)、低密度脂蛋白受体相关蛋白6(low-density lipoprotein receptor-related protein 6,LRP6)(4.1%)等[5-8]。目前关于LRP6基因突变导致选择性先天缺牙的表型及基因突变特点仍需进一步研究。

因此,笔者通过PUBMED检索LRP6基因突变导致选择性先天缺牙(截至2021年10月末),共收集到突变位点24个及有详细缺牙位置描述的患者38例进行基因突变特点及表型分析,总结LRP6基因突变导致选择性先天缺牙类型、数目、位置等特点,有助于加深对LRP6基因突变导致选择性先天缺牙的认识,希望为后续研究和临床诊断及精准治疗提供一定参考。

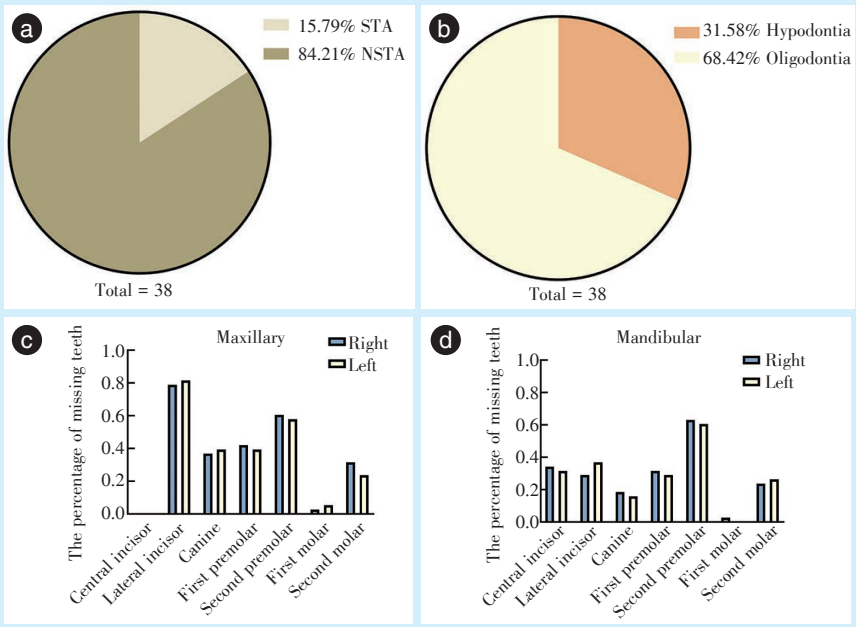
1　LRP6基因突变导致选择性先天缺牙的临床表型

LRP6基因突变通常导致非综合征型先天缺牙(84.21%),也可导致综合征型先天缺牙(15.79%)(图1a)。根据收集到的38例患者缺牙数目及缺牙位置统计,LRP6基因突变导致选择性先天缺牙常表现为多数牙缺失(68.42%),少数患者表现为少数牙缺失(31.58%),未见全口无牙的报道(图1b)。LRP6基因突变患者缺牙好发牙位为上颌侧切牙(80.25%),其次为下颌第二前磨牙(61.83%)、上颌第二前磨牙(59.21%),常呈对称性缺失,而上颌第一磨牙(3.94%)、下颌第一磨牙(1.31%)较少缺失,上颌中切牙未见缺失(图1c、1d)。患者平均缺牙数目及中位数都为9,缺失牙数最多可达18颗(1例),最少为1颗(5例)(表1)。LRP6基因突变不仅导致牙齿数目缺失,还可导致牙齿形态异常,包括上颌侧切牙或上颌中切牙表现为过小牙、上颌第一磨牙表现为牛牙症等[6,8]。

部分LRP6基因突变患者除缺牙表型外还存在全身其他症状,包括耳朵微小变异、拇指发育不全[6];唇腭裂、宽鼻底、鼻翼过大、鼻梁过宽及下颌后缩、面中部发育不良等颅颌面发育异常[7];还可表现为毛发稀疏、出汗减少等外胚层发育不良症状[8]。根据既往文献报道,LRP6基因突变主要表现为非综合征先天缺牙,主要表现为多牙缺失(≥6颗牙缺失),少数伴有牙齿形态、大小异常;极少数表现为综合征型先天缺牙,多为颅颌面发育异常。

2　LRP6基因突变导致选择性先天缺牙的基因突变特点分析

LRP6基因位于常染色体12p12.3,共编码1 613个氨基酸,分为胞外段、跨膜段和胞内段,突变好发于胞外段(表1)[9-14]。LRP6基因突变导致选择性先天缺牙的遗传方式为常染色体显性遗传,主要为杂合子突变[13]。LRP6基因突变方式主要为由单个碱基的替换而导致的错义突变(missense,45.83%)或无义突变(nonsense,12.50%)、插入或缺失单个或数个碱基而导致的移码突变(frameshift,25.00%)及在内含子区引起剪切位点改变的关键位点突变(16.67%)(图2)。根据LRP6晶体结构解析绘制LRP6氨基酸结构域示意图,关键



a: the classification of STA and NSTA about LRP6 gene mutation patients; b: the classification of hypodontia, oligodontia and anodontia about LRP6 gene mutation patients; c: the percentage of missing teeth position in maxillary from 38 patients; d: the percentage of missing teeth position in mandibular from 38 patients. STA: syndrome tooth agenesis; NSTA: non-syndrome tooth agenesis. LRP6: low-density lipoprotein receptor-related protein 6

Figure 1　An analysis of the phonetypes of tooth agenesis caused by LRP6 gene mutation

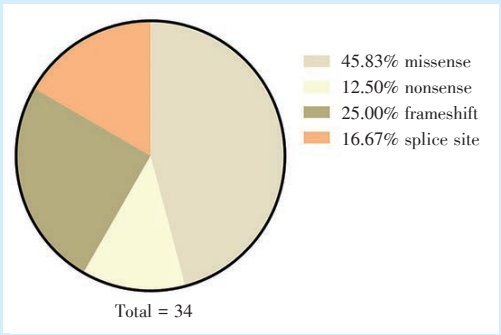
图1　LRP6基因突变导致先天缺牙表型的分析

表1　导致先天缺牙的LRP6基因突变位点总结

Table 1　A summary of the LRP6 gene mutation sites leading to tooth agenesis

cDNA mutation	Protein change	Variant type	Region	Patients	Missing teeth	Refrences
C56T	A19V	Missense	SP	4	7	[9]
c.195dup	Y66fs	Frameshift	ECD	1	16	[8]
C517G	R173G	Missense	ECD	1	9	[7]
G711T	L237F	Missense	ECD	3	6	[10]
c.1095dup	D366fs	Frameshift	ECD	2	12	[8]
c.1144_1145dupAG	A383fs	Frameshift	ECD	1	12	[6]
C1406T	P469L	Missense	ECD	1	7	[7]
A1603T	I535L	Missense	ECD	1	1	[11]
G1609A	G537R	Missense	ECD	2	6	[7]
C1681T	R561X	Nonsense	ECD	1	9	[8]
c.1779dupT	E594X	Nonsense	ECD	2	13	[6]
c.1924dup	I642fs	Frameshift	ECD	1	18	[12]
c.2224_2225dupTT	L742fs	Frameshift	ECD	3	16	[6]
G2292A	W764X	Nonsense	ECD	1	18	[8]
G2570A	R857H	Missense	ECD	4	5	[13]
c.2994+1G>A	/	Splice site	ECD	2	7	[7]
C3076T	R1026C	Missense	ECD	1	1	[11]
G3388A	D1130N	Missense	ECD	1	3	[11]
c.3398-2A>C	/	Splice site	ECD	1	9	[7]
c.3607+3_6del	/	Splice site	ECD	1	16	[13]
c.4082-2A>G	/	Splice site	/	1	6	[7]
G4136A	G1379D	Missense	/	1	4	[7]
C4298T	S1433L	Missense	/	1	2	[7]
c.4594delG	C1532fs	Frameshift	ICD	1	17	[7]

SP: signal peptide; ECD: extracellular domain; ICD: intracellular domain. LRP6: low-density lipoprotein receptor-related protein 6



LRP6: low-density lipoprotein receptor-related protein 6

Figure 2　Summary of amino acid changes caused by LRP6 gene mutation

图2　LRP6基因突变导致氨基酸变化方式总结

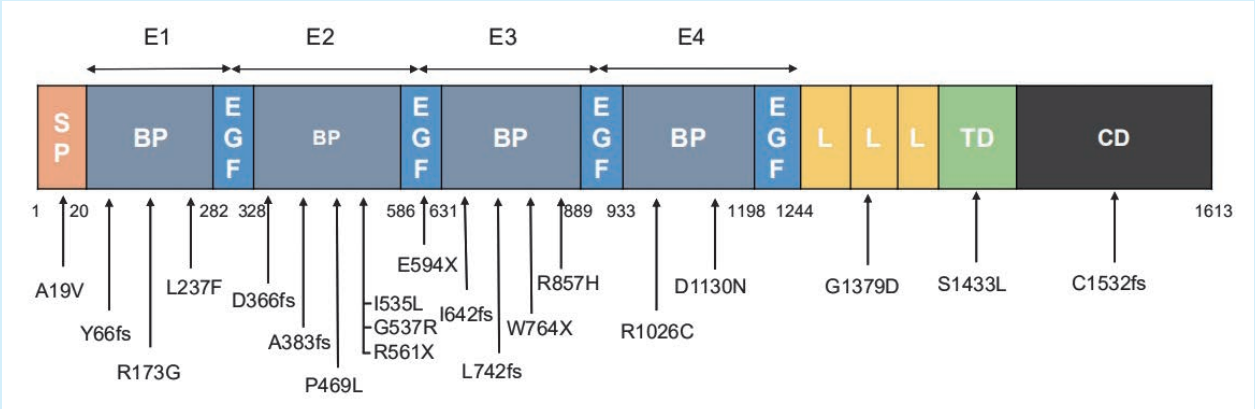
结构域为β-螺旋(beta propeller,BP)和表皮生长因子样结构域(EGF-like domain),为4个重复亚结构域的组合,标注LRP6外显子区突变导致的氨基酸序列改变位置,提示LRP6胞外段关键结构域(E1、E2、E3、E4)更易发生突变(图3)[15]。

3　LRP6基因突变导致选择性先天缺牙的分子机制探讨

LRP6基因突变导致蛋白质功能丧失或减弱是选择性先天缺牙的致病机制之一。c.C56T(A19V)、c.G711T(L237F)、c.A1603T(I535L)、c.G2570A(R857H)等错义突变可导致LRP6蛋白质三级结构构象发生改变,如脂肪族类亮氨酸(leucine,L)突变为芳香族类苯丙氨酸(phenylalanine,F),蛋白质亚细胞定位异常,与WNT结合能力受损,丧失对下游信号通路的激活能力[6,10,16]。c.1779dupT(E594X)、c.G2292A(W764X)、c.C1681T(R561X)等无义突变导致LRP6蛋白截短,功能丧失甚至产生显性负效应[6,8]。c.1095dup(D366Rfs*13)、c.4594delG(C1532fs)等移码突变导致蛋白序列错乱、翻译提前终止而引起突变蛋白发挥显性负效应、末端磷酸化异常并丧失激活下游通路的能力[7-8]。c.3607+3_6del、c.3398-2A>C等内含子区域的突变导致mRNA稳定性下降,破坏原有的剪切位点或形成新的剪切位点而使蛋白结构和功能异常[7,13]。

4　LRP6基因在牙发育中的作用

牙齿发育是由上百种基因参与调控的动态过程,根据时间发展可分为原始牙板期、蕾状期、帽状期、钟状期、牙根发育期和萌出期[17]。牙胚发育源于上皮与间充质的相互作用,参与调控细胞生长与分化的关键信号通路为WNT/β-catenin通路、FGF-BMP通路、TGF-β通路和SHH(sonic hedgehog)通路[18]。在牙发育早期,上皮细胞中FGF8驱动牙齿开始发育,此时去除β-catenin可使牙齿发育停止,说明WNT/β-catenin信号在牙胚早期开始发挥作用[19]。小鼠实验表明LRP6基因在牙发育过程中全程表达,尤其是帽状期呈现高表达状态[8]。LRP6蛋白为WNT/β-catenin信号通路中的关键跨膜蛋白,作为共受体与WNT、Frizzled形成三聚体发挥功能[20]。LRP6基因敲除实验证实WNT信号激活依赖于LRP6共受体的特定功能,在WNT通路中具有不可替代的作用[21]。近期有研究表明,



SP: signal peptide; BP: β-propeller; EGF: EGF-like domain; L: Ldl type A repeat; TD: transmembrane domain; CD: intracellular domain. LRP6: low-density lipoprotein receptor-related protein 6

Figure 3　Summary of the substructure of LRP6 and mutation sites

图3　LRP6蛋白结构域及突变总结

LRP4与LRP5/LRP6相互作用参与WNT/β-catenin信号通路的调控促进牙齿发育[9]。细胞与小鼠实验均表明LRP6基因在WNT/β-catenin信号通路中不可替代，该基因异常可导致整个通路中断，而WNT信号通路参与牙发育全程，因此LRP6基因在牙发育中至关重要，功能异常可使牙形成障碍从而表现为先天缺牙。缺牙数目及严重程度可能与突变位点导致的失功能程度有关，但由于文献证据有限未能得出确切结论，仍需进一步研究。

5　选择性先天缺牙的临床诊疗

选择性先天缺牙是牙齿发育异常的疾病之一，主要累及恒牙列，少数累及乳牙列[22]。该疾病损害患者的咀嚼、面部美观和心理健康，对生活质量造成严重影响[23-24]。目前临床上诊断先天缺牙主要通过患者主诉、家系调查、口腔专科检查和全景片等，分子诊断学主要为采集患者外周静脉血进行全外显子测序检测突变基因和位点并进行Sanger测序验证[25]。由于单基因突变导致的选择性先天缺牙的患者缺牙数目及缺失牙位存在极强的个体差异性，同一突变基因不同患者表型也不相同[26]。因此认为选择性先天缺牙的治疗需要个性化设计，因人制宜。对于少数牙缺失的患者，可通过正畸关闭间隙、种植修复等方式恢复牙列完整[27-28]。对于多颗牙缺失患者，则需要多学科联合诊疗，共同探讨进行合理方案设计，包括儿童口腔科早期发现早期维护、正畸恢复患者正常牙列关系、正颌手术矫正患者骨性错𬌗、种植修复恢复患者缺失牙位、牙周科长期维护等[29]。对于无牙颌患者，根据患者自身牙槽骨剩余骨量和经济条件可选择全口活动义齿修复、种植覆盖义齿修复、种植固定义齿修复或穿颧种植修复[30]。以上治疗手段均为对症治疗，尚缺乏基因层面的精准治疗，未来希望通过更多研究实现在胚胎时期通过采取对因治疗、剂量补足等方式促进牙胚继续发育，实现精准治疗，提高患者生活质量[31]。

6　总　结

综上，本文总结了既往报道的LRP6基因导致选择性先天缺牙的临床表型及基因突变特点，共纳入24个突变位点的38例患者，分析得出LRP6基因突变常导致多牙缺失，可表现为非综合征型或综合征型，可伴有牙齿形态异常。上颌第二侧切牙为最常见的缺失牙位，其次为第二前磨牙。LRP6基因突变多位于胞外结构域，突变导致蛋白功能减弱或丧失是选择性先天缺牙的致病原因。这些特征的总结有助于加深对LRP6基因突变导致选择性先天缺牙的理解，为该方向的深层次研究提供一定研究基础。

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