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研究报告

端粒长度与 2 型糖尿病: 孟德尔随机化研究与多基因风险评分分析

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摘要: 多项观察性研究表明，端粒长度缩短与 2 型糖尿病(type 2 diabetes, T2D)之间存在关联。然而，传统观察性研究结果常受到混杂因素和反向因果关联的影响，端粒长度与 T2D 是否存在因果关联尚不明确。本研究在中国汉族人群中利用孟德尔随机化(Mendelian randomization, MR)和多基因风险评分(polygenic risk score, PRS)方法探索端粒长度与 T2D 的因果关系。MR 研究选取 8 个与端粒长度相关的独立遗传变异作为工具变量，利用 2632 例中国汉族人群 T2D 全基因组关联研究(genome-wide association study, GWAS)数据，检验遗传预测的端粒长度与 T2D 的关系。利用中国汉族人群 GWAS 数据，采用 PRS 分析评价端粒长度 PRS 与 T2D 的关系。MR 研究共纳入 1318 例 T2D 患者和 1314 例正常对照，逆方差加权、MR-Egger 回归、简单中位数和加权中位数法估计的 OR 值分别为 0.78 (95% *CI*: 0.36~1.68, *P* = 0.522)、0.23 (95% *CI*: 0.01~7.64, *P* = 0.412)、0.60 (95% *CI*: 0.28~1.28, *P* = 0.185)和 0.64 (95% *CI*: 0.31~1.33, *P* = 0.233)，遗传预测的较长端粒长度与 T2D 之间不存在关联。PRS 分析未发现端粒长度 PRS 与 T2D 显著关联的一致结果。本研究采用 MR 和 PRS 方法未发现端粒长度与 T2D 具有因果关联，后续研究中增大样本量有助于得出更可靠的结论。

关键词: 孟德尔随机化；多基因风险评分；端粒长度；2 型糖尿病

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Telomere length and type 2 diabetes: Mendelian randomization study and polygenic risk score analysis

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Abstract: Recent epidemiological studies suggest an association between shorter telomere length and higher risk for type 2 diabetes (T2D). However, results from observational studies are susceptible to confounding and reverse causation, and it is not clear whether there is a causal association between telomere length and T2D. Using Mendelian randomization (MR) and polygenic risk score (PRS) approaches, we had evaluated the causal effect of telomere length on T2D in the Chinese Han population. Using 8 telomere-length associated genetic variants as instrumental variables, an analysis of genetically predicted telomere length and T2D risk was performed in the MR study based on data from a T2D genome-wide association study (GWAS) in 2632 individuals (1318 cases and 1314 controls). We also applied a PRS approach to investigate the causal relationship using Chinese GWAS data. The inverse-variance weighted, MR-Egger regression, simple median, and weighted median methods yielded no evidence of association between genetically predicted longer telomere length and risk of T2D (OR = 0.78, 95% *CI*: 0.36 ~ 1.68, *P* = 0.522; OR = 0.23, 95% *CI*: 0.01 ~ 7.64, *P* = 0.412; OR = 0.60, 95% *CI*: 0.28 ~ 1.28, *P* = 0.185; OR = 0.64, 95% *CI*: 0.31 ~ 1.33，*P* = 0.233; respectively). Further, PRS analysis did not produce consistent genetic overlap between telomere length and T2D. Accordingly, this study found no evidence supporting a causal association between telomere length and T2D. Further studies with larger cohorts could yield more reliable results and conclusions.

Keywords: Mendelian randomization; polygenic risk score; telomere length; type 2 diabetes

过去几十年中，糖尿病患病率和病例数在全球范围内持续升高[1]。2017 年，全球有约 4.51 亿成人患有糖尿病[2]，而中国估计有超过 1 亿成人患糖尿病[3]。2 型糖尿病(type 2 diabetes, T2D)是一种由遗传和环境因素相互作用导致的复杂疾病[4~6]。T2D 的患病率随年龄增加而上升[7]。糖尿病及其并发症给患者家庭和国家造成了巨大的卫生经济负担。

端粒是真核细胞染色体末端的 DNA-蛋白质复合体，其功能是维持染色体的完整性[8]。由于 DNA 末端不能完全复制，正常体细胞端粒会随着细胞分裂逐渐缩短，导致细胞老化[9]。细胞老化是生物老化的重要方面，而端粒长度是细胞老化的重要标志物。端粒长度经常在白细胞中进行测量。白细胞端粒长度(leukocyte telomere length, LTL)具有遗传性，遗传度在 36%~84%之间[10]。

多项观察性研究表明，LTL 缩短与 T2D 之间存在关联[11,12]。最近，关于 LTL 与 T2D 的 meta 分析显示缩短的端粒长度与 T2D 显著相关[13,14]。然而，端粒长度缩短可能是受到疾病或治疗影响并发生在疾病诊断之后，共同的环境因素也可能既影响端粒长度又影响糖尿病风险，导致偏倚的效应估计。

近年，随着全基因组关联研究(genome-wide association study, GWAS)的大量应用，孟德尔随机化(Mendelian randomization, MR)和多基因风险评分(polygenic risk score, PRS)等方法被日益广泛用于发现疾病病因以及因果推断[15~19]。相比传统的观察性流行病学研究，MR 研究和 PRS 分析不会受到常见混杂因素的影响，且因果时序合理。本研究旨在通

过 MR 和 PRS 方法在中国汉族人群中检验端粒长度与 T2D 的因果关系。

1 材料与方法

1.1 研究对象

研究对象来自中国汉族人群 T2D GWAS 的 2632 名上海居民，包括 1318 例 T2D 患者和 1314 例正常对照。T2D 患者均符合 WHO 糖尿病诊断标准，选取同一地区空腹血糖(fasting plasma glucose, FPG)< 6.1 mmol/L 人群作为正常对照[20]。所有 2632 名研究对象均应用定量 PCR 测量外周血 LTL 并进行中国汉族人群 LTL GWAS[21]。以上研究已获中国科学院上海生命科学研究院伦理委员会批准(批准号：ER-SIBS-250701)，研究对象均已签署知情同意书。

1.2 孟德尔随机化研究

采用 MR 方法评估遗传预测的端粒长度与 T2D 的关系。MR 是将与暴露相关联的遗传变异作为工具变量以推断暴露与结局因果关联的一种方法[22]。本研究采用以下标准筛选与端粒长度相关的遗传变异：(1)在已发表的端粒长度 GWAS 研究中达到全基因组显著性水平($P<5\times10^{-8}$)；(2)在中国人群中的最小等位基因频率(minor allele frequency, MAF)>1%；(3)被选择的遗传变异间不存在明显的连锁不平衡($r^2<0.01$)。符合标准(1)的遗传变异共 16 个。同时符合标准(1)和标准(2)的遗传变异共 12 个。本研究最终筛选到 8 个遗传变异作为工具变量，并获取相关的信息，包括与较长端粒长度相关的等位基因、MAF、效应估计值(β)、标准误和 P 值。使用已发表端粒长度 GWAS 中工具变量与端粒长度的效应估计值(β)和标准误以及 2632 名中国汉族人群 T2D GWAS 中工具变量与 T2D 的效应估计值(β)和标准误计算因果效应。本研究采用 4 种 MR 方法：逆方差加权(inverse-variance weighted, IVW)、MR-Egger 回归、简单中位数(simple median estimator, SME)和加权中位数(weighted median estimator, WME)法。此外，通过 MR-Egger 的截距项评估工具变量是否存在多效性。所有的分析均采用 R (version 3.4.0, R Foundation)的软件包‘MendelianRandomization’进行。

1.3 多基因风险评分分析

采用 PRS 分析检验遗传预测的端粒长度与 T2D 的关系。PRS 分析利用 GWAS 汇总数据在人群中构建个体遗传评分[23,24]。本研究将 2632 名研究对象随机分为两组，1316 名 T2D 患者或者正常对照进行 T2D GWAS，1316 名研究对象进行 LTL GWAS。LTL GWAS 的研究对象与 T2D GWAS 的研究对象没有重叠。本研究中端粒长度 PRS 的构建基于 1316 名中国人群 LTL GWAS 的汇总数据。采用 PRSice 软件[25](http://prsice.info/)进行数据处理和分析，在 T2D GWAS 研究的 1316 个个体中计算多个 P 值阈值(P_T = 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5)的端粒长度 PRS。PRS 分析采用 Bonferroni 法进行多重检验校正，校正后显著性阈值设为 0.05/7 = 0.007。

2 结果与分析

2.1 端粒长度与 T2D 的孟德尔随机化研究

2.1.1 工具变量信息

根据本研究工具变量筛选标准，最终筛选到 8 个独立的遗传变异作为工具变量[26~28]。表 1 列出了 8 个遗传变异的相关信息，包括所在染色体、临近基因、效应等位基因、MAF、与端粒长度关联的 β 系数、与 T2D 关联的 β 系数等。其中，6 个遗传变异与端粒长度和 T2D 具有相反的效应方向，1 个遗传变异与 T2D 关联的 P 值小于 0.05。

2.1.2 孟德尔随机化研究结果

IVW、MR-Egger 回归、SME 和 WME 法的 OR 值分别为 0.78 (95% *CI*: 0.36~1.68, P = 0.522)、0.23 (95% *CI*: 0.01~7.64, P = 0.412)、0.60 (95% *CI*: 0.28~1.28, P = 0.185)、0.64 (95% *CI*: 0.31~1.33, P = 0.233)，表明遗传预测的较长端粒长度与 T2D 之间不存在关联。此外，MR-Egger 回归的截距为 0.110 (95% *CI*: –0.198~0.417, P = 0.485)，表明工具变量不存在多效性(图 1)。

进一步根据年龄将研究对象分为≤60 岁和>60 岁两层。在≤60 岁的研究对象中，IVW 法的 OR 值为 0.60 (95% *CI*: 0.27~1.33, P = 0.211)。在>60 岁的

表 1　与端粒长度相关的遗传变异

Table 1　Previously published variants associated with telomere length

SNP	Chr.	临近基因	效应等位基因	MAF	端粒长度		T2D	
					β^*	*P* 值	β	*P* 值
rs10936599	3	*TERC*	C	0.252	0.117	2.54×10^{-31}	–0.038	0.53
rs2736100	5	*TERT*	C	0.486	0.094	4.38×10^{-19}	–0.053	0.37
rs7675998	4	*NAF1*	G	0.217	0.090	4.35×10^{-16}	–0.077	0.32
rs4387287	10	*OBFC1*	A	NA	0.100	2.33×10^{-11}	–0.114	0.17
rs8105767	19	*ZNF208*	G	0.291	0.058	1.11×10^{-09}	–0.027	0.69
rs755017	20	*RTEL1*	G	0.131	0.074	6.71×10^{-09}	0.095	0.12
rs3027234	17	*CTC1*	C	0.179	0.057	2.29×10^{-08}	–0.323	0.04
rs11125529	2	*ACYP2*	A	0.142	0.067	4.48×10^{-08}	0.135	0.08

SNP：single-nucleotide polymorphism，单核苷酸多态性；Chr：染色体；效应等位基因：与较长端粒长度相关的等位基因；MAF：最小等位基因频率，来自既往 GWAS 研究；T2D：2 型糖尿病；β：效应估计值；“*”表示增加一个效应等位基因时端粒长度的增加量(kb)。

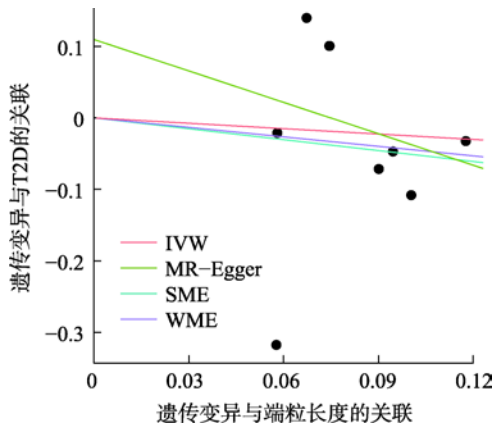

图 1　不同孟德尔随机化方法分析结果

Fig. 1　Mendelian randomization results

T2D：2 型糖尿病；IVW：逆方差加权法；SME：简单中位数法；WME：加权中位数法。

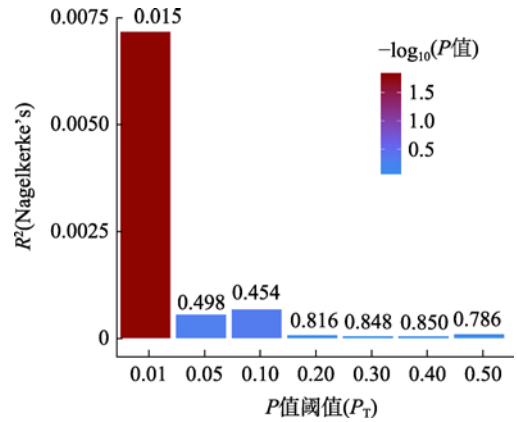

图 2　端粒长度 PRS 与 T2D 的关联

Fig. 2　Association between LTL PRS and T2D

研究对象中，IVW 法的 OR 值为 1.22 (95% *CI*: 0.36~4.08, *P* = 0.751)。在各层均未发现遗传预测的较长端粒长度与 T2D 具有关联。

2.2　端粒长度与 T2D 的多基因风险评分分析

在 1316 名 T2D 或健康对照人群中构建端粒长度 PRS 以检验端粒长度 PRS 与 T2D 的关系。仅有一个 *P* 值阈值的端粒长度 PRS 与 T2D 存在关联(*P*= 0.015)，但经过 Bonferroni 校正后，此关联无统计学意义(图 2)。

3　讨论

到目前为止，多项观察性研究表明端粒长度缩短与 T2D 之间存在关联。本课题组前期在 4016 例中国汉族人群中进行的一项病例对照研究也发现较短的 LTL 与 T2D 相关(OR = 1.52, 95% *CI*: 1.23~1.88, *P* = 0.0001)[29]。最近，一项关于端粒长度与 T2D 的 meta 分析显示缩短的端粒长度与 T2D 的关联有统计学意义(OR = 1.117, 95% *CI*: 1.002~1.246, *P* = 0.045)[13]。D'Mello 等[14]进行的 meta 分析也显示缩短的 LTL 与 T2D 有关联关系(OR = 1.37, 95% *CI*: 1.10~1.72)。端粒孟德尔随机化合作组织[30]于 2017 年发表的 MR 研究未发现遗传预测的较长端粒长度与 T2D 存在关联，但却发现遗传预测的较长端粒长度降低 1 型糖尿病的风险(OR = 0.71, 95% *CI*: 0.51~0.98, *P* = 0.04)。本研究采用 MR 和 PRS 方法，在中国汉族人群中评估端粒长度和 T2D 的因果关系，没有发现遗传预测的较长端粒长度和 T2D 存在任何显著关联。

本研究中 MR 分析选取的工具变量均为欧洲人

群发现的与端粒长度相关的遗传变异。本课题组在前期的研究中验证了欧洲人群发现的 *TERC* 附近位点 rs12696304 和 rs16847897 在中国汉族人群中与 LTL 相关(P = 4.5×10^{-3} 和 9.5×10^{-5})[31]。此外，在中国汉族人群 GWAS 研究中发现 *TERT* 上的位点 rs2736100 与端粒长度相关(P = 1.93×10^{-5})[21]，该发现与欧洲人群研究结果一致[26]。一项在亚洲人群进行的 MR 研究也表明欧洲人群发现的端粒长度相关遗传变异可以有效应用于亚洲人群[32]。

在传统的病例对照研究中，端粒长度缩短可能发生在疾病诊断之后并由疾病或治疗导致，故其结果常受反向因果关联的干扰，影响其论证因果关系的能力。本研究中遗传预测的端粒长度与抽血、疾病诊断时间无关，遗传变异先于疾病的发生，符合因果推断中“先因后果”的时序性要求。此外，本研究运用遗传预测的端粒长度，有利于将影响端粒长度的遗传因素与非遗传因素进行区分。常见影响端粒长度的非遗传因素包括衰老、氧化损伤等。

与其他研究相比，本研究具有以下优势：(1)选取与端粒长度相关的 8 个独立的遗传变异作为工具变量，避免连锁不平衡对因果估计结果的影响；(2)采用了多种 MR 方法。本研究也存在局限性：LTL GWAS 和 T2D GWAS 的样本量较小，PRS 分析的把握度较低。

综上所述，本研究在中国汉族人群中采用 MR 和 PRS 方法未发现端粒长度与 T2D 具有因果关联。后续研究中发现更多新的端粒长度相关遗传变异并增大样本量有助于得出更可靠的结论。

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