论著·神经科学

妊娠期肝内胆汁淤积症与子代神经发育障碍的因果关联及脂蛋白与ATP酶的中介作用:一项孟德尔随机化研究

陈正东*,冉清琦*,肖明辉,余沁怡,彭文杰,胡章雪 陆军军医大学大坪医院儿科,重庆

[摘要] **目的** 探究妊娠期肝内胆汁淤积症(intrahepatic cholestasis of pregnancy, ICP)和子代注意缺陷多动障碍(attention-deficit hyperactivity disorder, ADHD)和妥瑞氏综合征(Tourette's Syndrome, TS)之间的因果关联以及潜在机制。**方法** 数据均来源于公共数据库全基因组关联研究(genome wide association study,GWAS)。其中暴露为ICP(*n*=123 579),来源于芬兰数据库;结局为ADHD与TS及其他抽动障碍(*n*=23 918),来源于GWAS Catalog数据库。中介分子中,高密度脂蛋白里的总胆固醇含量(*n*=21 558)来源于人类血浆蛋白质组的基因图谱,Obg样ATP酶1来源于循环代谢物全基因组研究(*n*=3 301)。本研究选择满足MR假设的工具变量。双样本MR分析主要方法为逆方差加权(inverse variance weighted, IVW),MR-Egger回归、加权中位数法、加权众数法、简单模式也被采用进行稳健性分析。Cochran's Q检验、MR-Egger截距检验和留一法等敏感性分析用来验证结果的可靠性,统计显著性设定为$P<0.05$。使用中介MR时,从暴露到中介的第一步采用双样本MR,第二步采用多变量MR,此时条件F值被采用检测工具变量的强度。最后使用乘积分布检验验证中介效应的显著性。**结果** ICP与ADHD和TS及其他抽动障碍显著相关(IVW:*OR*=1.003, 95%*CI*:1.000~1.006, *P*=0.035),敏感性分析证实了结果的稳健性。可能的中介分子包括高密度脂蛋白中总胆固醇含量[总效应(total effect, TE)=2.855×10^{-3};中介效应(mediated effect, ME)=8.628×10^{-4};中介效应占比(mediated proportion, MP)=30.217%, 95%*CI*: 0.878%~73.954%)]和Obg样ATP酶1(TE=2.855×10^{-3}; ME=1.216×10^{-3}; MP=42.572%,95%*CI*: 6.356%~90.195%)。**结论** ICP可能通过高密度脂蛋白中总胆固醇含量和Obg样ATP酶1的减少来增加子代ADHD和TS及其他抽动障碍的发病率。

[关键词] 注意缺陷多动障碍;妥瑞氏综合征;妊娠期肝内胆汁淤积症;孟德尔随机化研究;中介因素

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Causal association between intrahepatic cholestasis of pregnancy and offspring neurodevelopmental disorders and mediating roles of lipoproteins and ATPase: A Mendelian randomization study

CHEN Zhengdong*, RAN Qingqi*, XIAO Minghui, YU Qinyi, PENG Wenjie, HU Zhangxue Department of Pediatrics, Daping Hospital, Army Medical University, Chongqing, China

[**Abstract**] Objective To explore the callsal association between intrahepatic cholestasis of pregnancy (ICP) and offspring attention-deficit hyperactivity disorder (ADHD) and Tourette's syndrome (TS)

* 同等贡献者

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[通信作者] 胡章雪,Email: huzhangxue@tmmu.edu.cn
彭文杰,Email: pengwenjie@tmmu.edu.cn

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and its potential mechanisms. **Methods** Genome wide association study (GWAS) in public datasets was used to extract data. Among them, exposure was ICP (n=123 579), which stems from FinnGen dataset. Outcome was defined as ADHD, TS and other tic disorders (n=23 918), which is extracted from GWAS Catalog. Among mediators, total cholesterol in high-density lipoprotein (TC in HDL) were from the genetic map of the human plasma proteinome (n=21 558), and Obg-like ATPase 1 was from whole-genome study of circulating metabolites (n=3 301). In this study, we chose instrumental variables (IVs) that meets the Mendelian randomization (MR) hypothesis. When using two-sample MR, inverse variance weighted (IVW) was adopted as the primary method, and MR-Egger regression, weighted median, weighted mode, and simple mode were also utilized to analyse the robustness. Cochran's Q test, MR-Egger intercept test and leave-one-out sensitivity analysis were performed to verify the reliability. Significant threshold was set up as P<0.05. When using two-step MR, the first step is two-sample MR from exposure to mediator, and the second step is multivariable MR (MVMR), which is from mediator to outcome. At this time, conditional F-statistic was adopted to test the strength of IVs. At last, product distribution test was applied to determine the significance of mediation effects. **Results** ICP was significantly related to ADHD and TS as well as other tic disorders in offspring (IVW: OR=1.003, 95%CI: 1.000~1.006, P=0.035), and sensitivity analysis verified the robustness of the results. The potential positive mediators included TC in HDL [total effect (TE) =2.855×10^{-3}; mediated effect (ME) =8.628×10^{-4}; mediated proportion (MP) =30.217%, 95%CI: 0.878%~73.954%], and Obg-like ATPase 1 (TE=2.855×10^{-3}; ME=1.216×10^{-3}; MP=42.572%, 95%CI: 6.356%~90.195%). **Conclusion** ICP is possible to elevate the incidence rate of ADHD and TS and other tic disorders *via* reducing TC in HDL and Obg-like ATPase 1.

[**Key words**] attention-deficit disorder with hyperactivity; Tourette's syndrome; intrahepatic cholestasis of pregnancy; Mendelian randomization analysis; mediating factor

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注意力缺陷多动障碍(attention-deficit hyperactivity disorder, ADHD)是以注意力不集中、多动和冲动为特征的儿童神经发育障碍性疾病[1],发病率约为5.3%。在青少年中,该疾病会导致教育和职业失败、同伴冲突和社会排斥、家庭冲突和意外伤害等[2]。妥瑞氏综合征(Tourette's Syndrome, TS)和其他抽动障碍也属于一类神经发育障碍,以不自主的重复动作(运动性抽动)和发声(发声性抽动)为主要特征,影响着大约1%的儿童[3]。患有ADHD的患儿常常合并其他精神类疾病,比如重度抑郁、焦虑障碍、双相情感障碍等,同时ADHD也会增加其他器质性疾病的患病概率,如肥胖、哮喘[2],这些特征导致了该疾病对于家庭和社会的沉重负担。然而,它们的发病机制仍然不明。Meta分析和全基因组关联研究(genome-wide association studies, GWAS)分别表明ADHD和TS和其他抽动障碍的遗传倾向非常明显[2,4]。妊娠期胆汁淤积症(Intrahepatic cholestasis of pregnancy, ICP)是以瘙痒和血清胆汁酸(Bile acid, BA)水平升高为主的常见产科肝脏疾病[5]。近年来,ICP的发病率显著增加,在我国长江流域尤其是川渝地区发病率达到了6%[6]。该疾病可能导致子代多种不良结局,如胎儿窘迫、早产、不可预测的宫内死亡等[5]。而ICP引起的胆汁酸水平升高可能通过脐带血[7],穿过胎儿不完整的血脑屏障影响胎儿神经系统的发育,从而导致精神疾病。最近的一项观察性队列研究显示,143 746名(6.05%)暴露于ICP的儿童被发现患有神经发育障碍性疾病,如ADHD、孤独症谱系障碍和智力障碍,且胎儿期暴露于ICP环境中的儿童比正常对照组罹患这些疾病的概率大17%[8]。但是,该队列研究仅表明ICP和神经发育障碍性疾病相关,没有阐明ICP导致神经发育障碍性疾病的机制。

孟德尔随机化(mendelian randomization, MR)分析利用来自不同GWAS的单核苷酸多态性(single-nucleotide polymorphisms, SNPs),评估2个性状之间的关系。与传统的观察性临床研究相比,MR可以避免混杂因素的干扰,并评估危险因素的终身影响;此

外,多变量MR(multivariable mendelian randomization,MVMR)和中介MR可用于探索暴露因素如何影响结局的机制[9]。因此,本研究通过双样本MR、MVMR和中介MR的方法,探讨了ICP与子代ADHD和TS和其他抽动障碍的因果关系,以及探讨潜在的中介机制。

1 材料和方法

1.1 数据提取

本研究数据来源于IEU open GWAS(https://gwas.mrcieu.ac.uk/)。由于使用公共公开数据库,伦理审查被豁免。本研究遵循了《流行病学观察性研究报告加强指南(STROBE指南)》[10]。此外,仅欧洲人群被纳入,以避免人群异质性的偏差[11]。ICP作为暴露,ADHD和TS以及其他抽动障碍作为结局,且结局数据库为儿童队列数据。队列和GWAS数据库相关信息见表1。本研究采用两样本MR探究其因果关系,MVMR和两步MR探索潜在的中介途径。

1.2 工具变量筛选

工具变量从2个不重叠的GWAS数据库中筛选。MR分析的关键假设如下:① 相关性假设:工具变量(Instrumental variables,IVs)与暴露因素有强烈关联;② 独立性假设:混杂变量与MR推断过程的任何步骤无关;③排除限制假设:所选工具变量仅通过暴露因素影响结局(图1)。为确保工具变量的强度,并同时保证SNP的数量足够,本研究参考全基因组显著性选择SNPs,使用的P值为5E-08、7E-08或者5E-06,详细信息见表2[11]。为避免连锁不平衡造成混杂,本研究对存在该问题的SNPs进行了剔除(区域宽度=10 000 kb,r^2=0.001),与此同时回文SNP也被排除在外。随后,本研究采用F值评估工具变量的强度,公式如下:

$$F=\frac{R^2}{1-R^2}\times\frac{N-K-1}{K} \quad (1)$$

其中R^2是由该SNP解释的性状变异的比例,N是GWAS数据纳入人群的样本量,K是该研究纳入的SNP的数量。R^2使用以下公式评估:

$$R^2=2\times EAF\times(1-EAF)\times\beta^2 \quad (2)$$

EAF是SNP的效应等位基因频率,β是SNP对性状的估计效应[16]。F<10表示弱工具变量,需要排除在外。此外,本研究还使用了PhenoScannerV2(http://www.phenoscanner.medschl.cam.ac.uk/)对潜在的混杂因素进行了排查[17],任何与混杂因素有关的SNPs将会被排除。

1.3 异质性检验和水平多效性检验

若SNPs存在异质性,可能导致研究结果存在偏差。因此本研究使用了Cochrane's Q检验来评估SNPs中的异质性。若有SNPs存在异质性,使用随机

表1 MR研究GWAS数据的信息

Table 1 Information of GWAS data for MR analysis

Traits	GWAS ID	NSNP	Sample size	Ancestry	Reference
ICP	finn-b-O15_ICP_WIDE	16 379 784	123 579	European	[12]
ADHD *vs* TS and other tic disorders	ebi-a-GCST90016598	5 604 390	23 918	European	[13]
Obg-like ATPase 1	prot-a-2143	10 534 735	3 301	European	[14]
TC in HDL	met-c-898	11 864 118	21 558	European	[15]

GWAS: Genome wide association study; MR: Mendelian randomization; ICP: Intrahepatic cholestasis of pregnancy; ADHD: Attention -deficit hyperactivity disorder; TS: Tourette's syndrome; TC in HDL: Total cholesterol in high-density lipoprotein

表2 ICP与子代ADHD和TS及其他抽动障碍之间的中介效应采纳条件

Table 2 Conditions applied for mediation analysis of ICP with ADHD and TS as well as other tic disorders

Mediators	GWAS ID	Parameters	Methods	Outcome
TC in HDL	met-c-898	P_1=5E-08 P_2 threshold =7E-08 P_3=5E-06	MVMR	ADHD vs TS and other tic disorders
Obg-like ATPase 1	prot-a-2143	P_1=5E-08 P_2=5E-06 P_3=5E-06	MVMR	

P_1, P_2 and P_3 present the inclusion criteria of instrumental variables of Step 1, Step 2, and total effect, respectively. ICP: Intrahepatic cholestasis of pregnancy; ADHD: Attention-deficit hyperactivity disorder; TS: Tourette's syndrome; GWAS: Genome wide association study; TC in HDL: Total cholesterol in high-density lipoprotein; MVMR: Multivariable Mendelian randomization

效应模型的逆方差加权法（inverse variance-weighted，IVW）结果；若SNPs间异质性不显著，则使用固定效应模型的IVW结果。本研究使用留一法敏感性检验来判断MR结果的稳定性，即通过逐一排除SNP[11]，观察剔除前后的MR分析结果有无统计学差异。此外，本研究还使用MR多效性残差总和以及异常值R包（MR pleiotropy residual sum and outlier，MR-PRESSO）来获得每一个SNP的异质性P值，P<0.05的SNP被剔除[18]。MR-Egger截距回归被采纳进行多效性检测，它不受SNPs有效性的影响，并检验了回归方程的截距与0的差异性，P<0.05的结果视为存在多效性，将不被采纳[11]。

1.4 统计学分析

使用R 4.3.1软件的TwoSample MR包（版本0.5.8）分析。本研究的主要方法是经典的IVW法[19]。此外，本研究还补充了MR的加权中位数法、加权众数法、MR-Egger回归和简单模式[20]，以评估MR研究的可靠性。比值比（odds ratio，OR）表示结果的风险；标准误（standard error，SE）和95%置信区间（confidence interval，CI）表示估计值的不确定性[9]。

MVMR被用来寻找可能的中介。MVMR方法中，第一步考察ICP与中介因素（β_1）之间的关联。第二步采用MVMR，其中IVW方法被采用评估中介与ADHD和TS及其他抽动障碍的关联（β_2），采用双样本法得出的关联性定义为总效应（$\beta_{总}$），条件F统计量用于评估工具变量强度[9]。使用delta方法（即乘积分布检验，使用RMediation包版本1.2.2）评估中介效应[21]，公式如下：

$$\beta_{中介效应占比}=\frac{\beta_1\times\beta_2}{\beta_{总}} \quad (3)$$

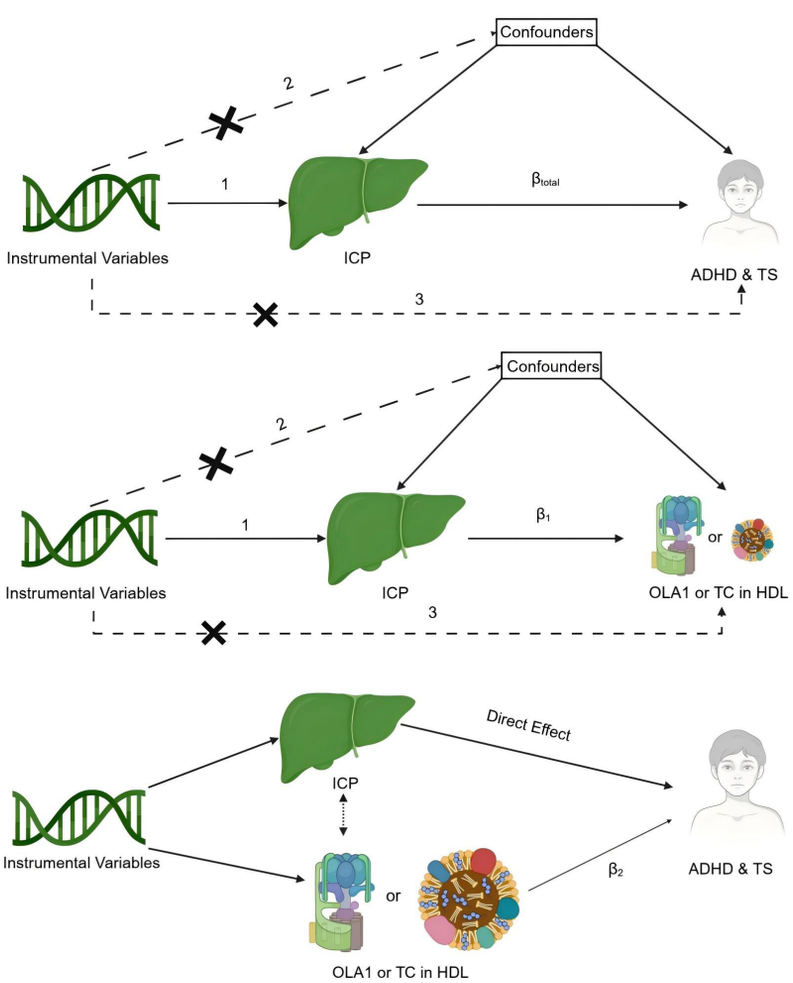


图1 研究流程图

Figure 1 Workflow of this study

2 结果

2.1 工具变量SNPs的筛选结果

经过关联性假设的筛选,该研究双样本MR纳入了17个SNPs,MVMR纳入了26个SNPs。双样本分析中F值均大于10,表明工具变量的强度是可信的,双样本MR的SNPs详细信息见表3。独立性假设筛选中,本研究逐一筛查了所有的SNP的可能混杂因素,包括单纯疱疹病毒2、母体感染、缺氧、羊水过多、早产、贫血等,发现这些SNPs和前述混杂因素相关:rs13071166、rs10008637、rs2742676、rs7660554、rs939678,并且进行了排除。因此独立性假设成立。

2.2 ICP与子代多动和抽动障碍具有关联

ICP与子代ADHD与TS和其他抽动障碍的双样本MR结果在排除混杂因素之后主要检验方法IVW结果显著(*OR*=1.003, 95%*CI*:1.000~1.006, *P*=0.035),*OR*值大于1,表明ICP是子代多动与抽动障碍的危险因素,在图2A散点图的斜线方向也佐证了这一点。异质性检验、多效性检验不具有显著性,具体的检验数据见表4。留一法发现了SNPs具有潜在显著性。但是所有结果的平均值仍然在0右侧,仍然视为有效,见图2B。MR-Egger法(*OR*=1.004, 95%*CI*:0.999~1.009, *P*=0.154)、加权中位数法(*OR*=1.003, 95%*CI*:0.999~1.007, P_{IVW}=0.123)、加权众数法(*OR*=1.003, 95%*CI*:0.999~1.007, P_{IVW}=0.190)、简单模式(*OR*=0.999, 95%*CI*:0.996~1.006, P_{IVW}=0.879)均不显著,见图3。

2.3 Obg样ATP酶1和中等大小的高密度脂蛋白中的总胆固醇为ICP和多动抽动障碍疾病之间的潜在中介

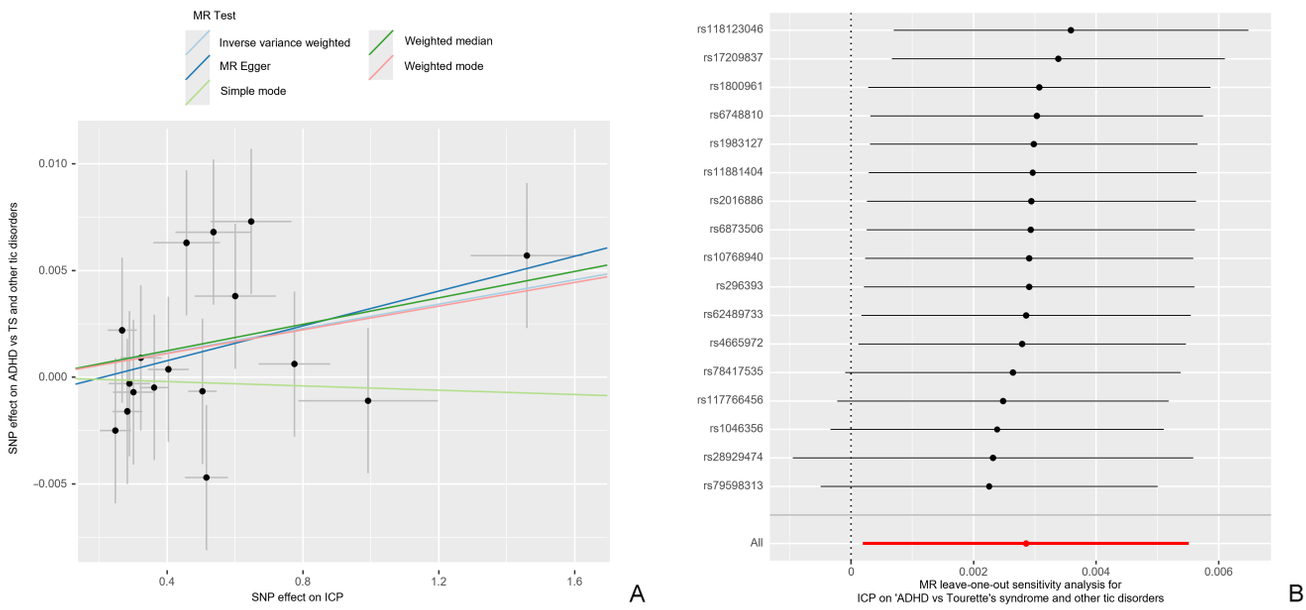
由于神经发育与能量代谢密切相关,且神经系统含有丰富的脂类物质,因此本研究选择能量代谢和脂类物质进行中介分析,并发现了2个潜在的中介变量(图4):①中等大小的高密度脂蛋白(High-density lipoprotein,HDL)中的总胆固醇(Total cholesterol, TC)[总效应(Total effect, TE)=2.855×10^{-3};中介效应(Mediated effect, ME)=8.628×10^{-4};中介效应占比(Mediated proportion, MP)=30.217%,95%*CI*:0.878%~73.954%];②Obg样ATP酶1(TE=2.855×10^{-3};ME=1.216×10^{-3};MP=42.572%,95%*CI*:6.356%~90.195%)。所有双样本MR分析中的F值和MVMR分析中的条件F值均大于10(中介为中等大小的HDL中的TC时:ICP的F=26.430,中等大小的HDL中的TC的F=22.220;中介为Obg样ATP酶1时:ICP的F=25.979,Obg样ATP酶1的F=12.254),表明不存在弱工具变量。但

表3 ICP与ADHD和TS及其他抽动障碍双样本MR分析纳入SNPs的详细信息

Table 3 Detailed information of SNPs enrolled in two-sample MR from ICP and ADHD and TS as well as other tic disorders

SNPs	Effect Allele	Other Allele	Effect Allele Frequency	Exposure			Outcome			r^2	*F*
				β	*SE*	*P*	β	*SE*	*P*		
rs1046356	T	C	0.037	0.536	0.111	1.47E-06	0.007	0.003	0.045	0.020	151.427
rs10768940	G	A	0.865	−0.289	0.061	2.55E-06	3.00E-04	0.003	0.930	0.019	144.312
rs117766456	T	C	0.050	0.457	0.098	3.11E-06	0.006	0.003	0.061	0.020	146.347
rs118123046	A	G	0.013	0.992	0.206	1.38E-06	−0.001	0.003	0.740	0.025	185.185
rs11881404	G	A	0.678	−0.283	0.044	1.55E-10	0.002	0.003	0.630	0.035	262.607
rs17209837	C	T	0.135	−0.516	0.063	4.26E-16	0.005	0.003	0.160	0.062	481.864
rs1800961	T	C	0.045	0.775	0.106	2.40E-13	0.001	0.003	0.850	0.052	397.584
rs1983127	T	G	0.284	−0.248	0.046	8.14E-08	0.003	0.003	0.460	0.025	186.044
rs2016886	C	T	0.616	−0.362	0.043	2.42E-17	4.80E-04	0.003	0.890	0.062	480.349
rs28929474	T	C	0.020	1.459	0.165	1.04E-18	0.006	0.003	0.092	0.082	645.570
rs296393	C	T	0.848	0.404	0.060	1.39E-11	3.70E-04	0.003	0.910	0.042	318.772
rs4665972	C	T	0.624	0.268	0.043	3.71E-10	0.002	0.003	0.510	0.034	253.090
rs62489733	A	G	0.138	−0.323	0.061	1.20E-07	−0.001	0.003	0.790	0.025	184.070
rs6748810	G	A	0.444	−0.504	0.042	5.72E-33	0.001	0.003	0.840	0.125	1 040.578
rs6873506	T	C	0.133	0.301	0.061	7.73E-07	−0.001	0.003	0.830	0.021	154.915
rs78417535	T	C	0.036	0.601	0.119	4.38E-07	0.004	0.003	0.260	0.025	185.393
rs79598313	T	C	0.035	0.647	0.119	5.35E-08	0.007	0.003	0.032	0.028	209.909

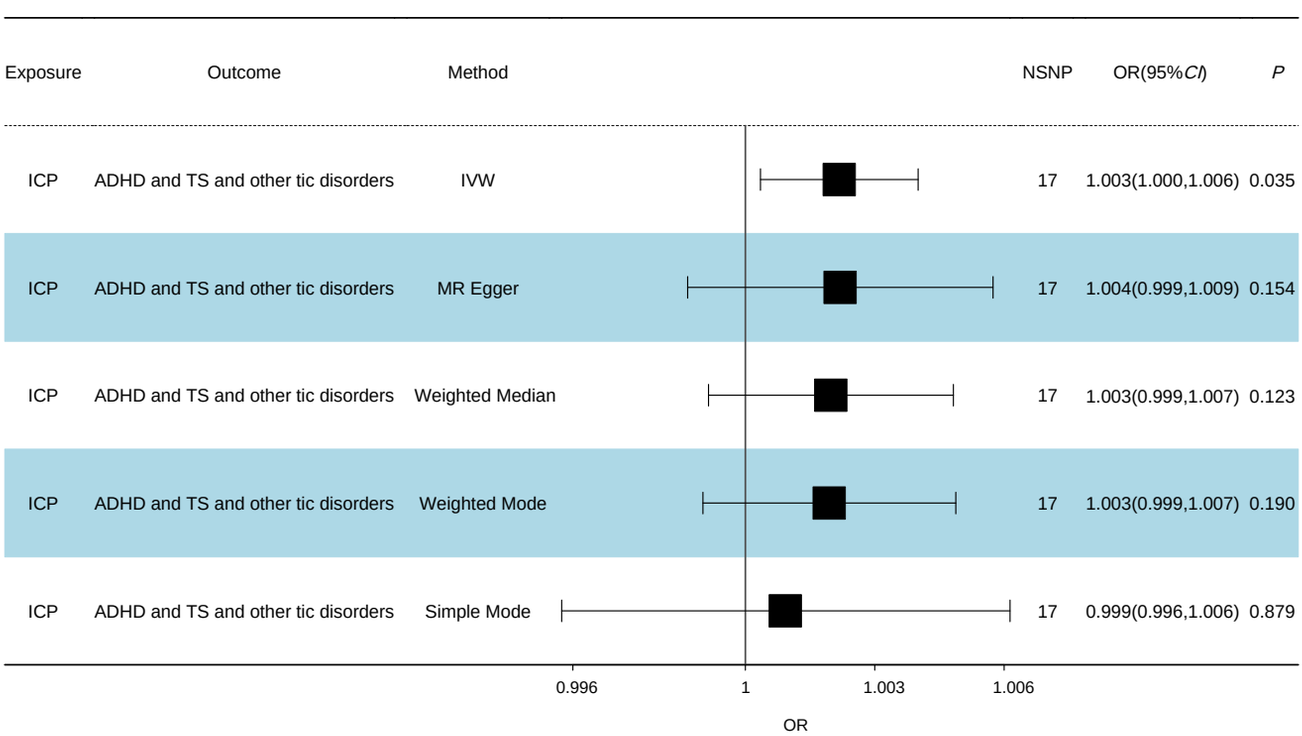
SNPs: Single nucleotide polymorphisms; MR: Mendelian randomization; ICP: Intrahepatic cholestasis of pregnancy; ADHD: Attention deficit hyperactivity disorder; TS: Tourette's syndrome



A: Scatter plot of MR analysis from ICP to ADHD and TS and other tic disorders; B: Leave-one-out analysis of MR analysis from ICP to ADHD and TS and other tic disorders. ICP: Intrahepatic cholestasis of pregnancy; ADHD: Attention-deficit hyperactivity disorder; TS: Tourette's syndrome; MR: Mendelian randomization

图2 ICP与子代ADHD和TS及其他抽动障碍双样本MR的散点图和留一法分析

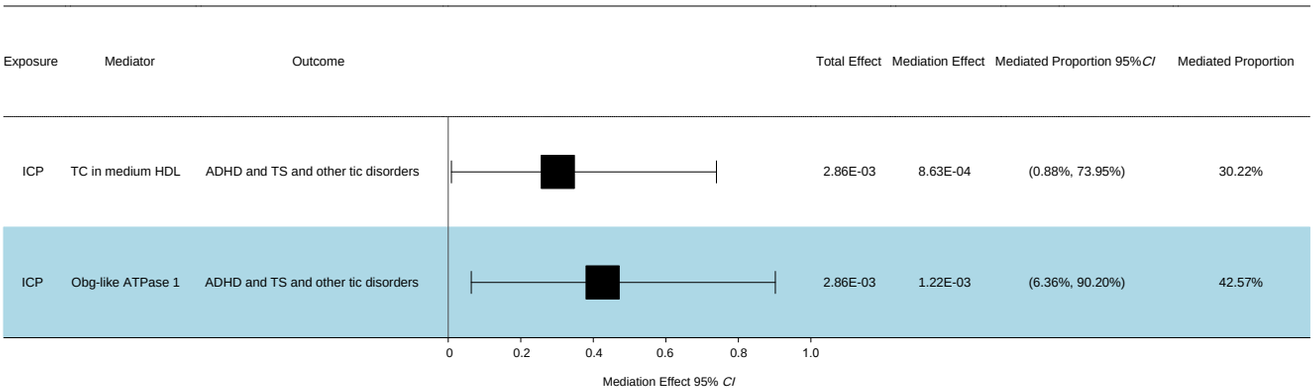
Figure 2 Scatter plot and leave-one-out analysis of the MR analysis from ICP to ADHD and TS and other tic disorders



MR: Mendelian randomization; ICP: Intrahepatic cholestasis of pregnancy; ADHD: Attention-deficit hyperactivity disorder; TS: Tourette's syndrome

图3 ICP与ADHD和TS及其他抽动障碍双样本MR分析的森林图

Figure 3 Forest plot of analysis describing the two-sample MR analysis of ICP with ADHD and TS as well as other tic disorders



ICP: Intrahepatic cholestasis of pregnancy; ADHD: Attention-deficit hyperactivity disorder; TS: Tourette's syndrome

图4 ICP与ADHD和TS和其他抽动障碍之间的中介及其中介效应占比森林图

Figure 4 Forest plot of the mediators and its mediated proportions of ICP with ADHD and TS as well as other tic disorders

表4 ICP与子代ADHD和TS及其他抽动障碍双样本MR异质性和多效性检验

Table 4 Heterogeneity test and pleiotropy test of the two-sample MR from ICP to ADHD and TS as well as other tic disorders

Methods	Heterogeneity			Pleiotropy test		
	Q	*Q_df*	*Q_P*	*egger_intercept*	*SE*	*P*
MR Egger	14.815	15	0.465	−8.576E-04	0.002	0.611
IVW	15.084	16	0.518			

MR: Mendelian randomization; ICP: Intrahepatic cholestasis of pregnancy; ADHD: Attention-deficit hyperactivity disorder; TS: Tourette's syndrome

表5 剔除离群SNP后的中介分析分步结果

Table 5 Results of each step of mediation analysis (without outliers)

Mediators	Step 1 (Without outliers)			Step 2		
	β	*SE*	*P*	β	*SE*	*P*
TC in HDL	−0.025	0.010	0.009	−0.034	0.016	0.031
Obg	−0.094	0.024	<0.001	−0.013	0.005	0.018

When analyzing HDL in TC, SNP rs1800961 was deleted; When analyzing Obg, SNP rs2161037 was deleted. SNPs: Single nucleotide polymorphisms; TC in HDL: Total cholesterol in high-density lipoprotein

在第一步分析过程中,即ICP作为暴露,中介作为结局进行双样本MR分析时,出现了异质性显著的情况(中介为中等大小的HDL中的TC时,*P*(IVW)=0.010 9,*P*(MR-Egger)=0.011 1;中介为Obg样ATP酶1时,*P*(IVW)=0.020 0,*P*(MR-Egger)=0.012 7),故使用MR-PRESSO剔除PRESSO检验显著的SNPs(数据库met-c-898中的rs1800961和prot-a-2143中的rs2161037)之后,异质性消失(中介为中等大小的HDL中的TC时,*P*(IVW)=0.452,*P*(MR-Egger)=0.352;中介为Obg样ATP酶1时,*P*(IVW)=0.504,*P*(MR-Egger)=0.416)且IVW结果仍然显著。中介每一步分析的结果见表5。

3 讨论

本研究发现,遗传预测的ICP易感性可能与子代ADHD和TS及其他抽动障碍的风险升高存在因果关联。此外,本研究探讨了ICP和子代ADHD和TS相关的潜在病理机制,且发现中等大小的HDL中的TC和Obg样ATP酶1 2个中介分子,这些为子代多动和抽动障碍性疾病的发病机制提供了新的理论依据。

3.1 ICP和子代多动抽动障碍性疾病之间的因果关联

多动和抽动障碍性疾病作为常见的儿童神经发育障碍性疾病,遗传因素是其发病机制中的重要环节,然而由于其异质性强,现有的研究无法解释其家族聚集性[22],且遗传因素导致的神经发育障碍的病理机制至今不完全明确[23]。ICP的病因亦不清楚,但同样有较强的遗传倾向,它与多种基因突变密切相关,比如*ABCB4*、*FIC1*、*ABCB11*等[24]。既往的报道显示ICP会增加氧化应激反应,影响胎儿发育[25],但是其如何影响胎儿的脑发育尚不明确。迄今为止,仅一项队列研究表明了ICP与ADHD之间存在联系,但由于其仅为观察性研究,潜在偏倚仍然无法消除[8]。本研究首次从遗传流行病学角度探讨ICP与子代多动和抽动

障碍疾病之间的关联,并揭示其因果关系,大大降低了偏倚。强调了ICP对胎儿神经系统造成了持久的不良影响,从遗传角度强有力地支持了上述队列研究。并且本研究采用了MR研究方法,通过等位基因的随机分配,避免了非差异测量误差和环境中的混杂因素的影响,具有较强的因果推断能力,异质性分析和多效性分析也支持了这一点。虽然结果仅有IVW方法是显著的,但是除了简单模式之外的方法方向均与IVW相同,也表明了较好的稳健性。然而ICP孕妇与后代ADHD发生的*OR*值为1.003,意味着患有ICP的孕妇比不患ICP的子代发生ADHD概率仅大0.3%。尽管风险效应非常微弱,但ADHD是一类不能完全治愈的神经发育障碍性疾病,只能通过临床的尽早发现与干预尽可能地缓解病情,减轻社会负担,因此其仍具有临床意义。

3.2 HDL中的TC可能穿过胎儿不完整的血脑屏障起到保护作用

在探索ICP与多动抽动障碍疾病之间的潜在中介时,本研究发现中等大小的HDL中的TC含量是其中之一,并且是起保护作用的中介因子,表明ICP会导致HDL水平下降,并且孕期HDL的下降会增加子代ADHD的发生率。这条路径的2步结果的方向分别与ZHAN等[25]的meta分析和XU等[26]的研究是一致的。JI等[27]的波士顿出生队列研究表明,孕期的HDL和TC降低会增加子代罹患多动症的风险。上述研究都是该中介在ICP和多动抽动之间作为起保护作用的中介因子的有力证据。从机制的角度,脂蛋白在妊娠期间可以透过胎盘屏障进入胎儿的血液循环[28],而胎儿期血脑屏障尚未发育完全,且HDL颗粒可以通过胞吞作用或选择性摄取进入大脑[29],这些表明孕期的HDL下降可能会导致转运至胎儿的HDL减少,干扰胎儿的脂蛋白代谢进而导致子代ADHD的发生。该中介的效应占比为30.217%,表明该类物质在减少ICP导致的多动抽动患儿中起到了一定的作用。虽然本研究通过大样本的GWAS数据降低了时间和混杂因素的影响,但是ADHD患儿的HDL来源于母体还是子代自身、HDL如何导致儿童的ADHD发病率增高、自然状态下TS患儿的胆固醇水平等一系列问题,需要更多的基础和临床研究证实。综上所述,该结果为多动和抽动障碍的发病机制指明了新的研究方向。

3.3 Obg样ATP酶1可能保护ICP孕妇胚胎免受氧化应激的损伤

与此同时,本研究发现Obg样ATP酶1也是ICP和多动抽动之间的起保护作用的中介因子之一。Obg样ATP酶1在人体多种器官中表达,通过调节*P53*和*P21*的表达调控细胞增殖。该基因的缺失会导致严重的肺发育不良和不完全致死[30]。因此,Obg样ATP酶1在胚胎发育中具有至关重要的作用。虽然并没有研究证实Obg样ATP酶1与ICP或ADHD、TS之间的关系,但有文献指出Obg样ATP酶1可以整合秀丽隐杆线虫的感觉神经元的温度和饥饿信号[31],并且在人类和动物之间该基因高度保守,因此该分子作为保护性中介是符合逻辑的。ICP与炎症细胞因子和氧化应激密切相关[32]。虽然现阶段缺乏ICP母亲体内Obg样ATP酶1的表达情况,但是现有研究认为Obg样ATP酶1能够稳定热休克蛋白70使细胞稳定,而热休克蛋白70同时可以参与发育过程[33]。因此,结合本研究的两步MR研究,本研究推测Obg样ATP酶1可能在胎儿期因ICP引起的氧化应激反应而降低,干扰热休克蛋白70介导的发育过程,进而导致多动和抽动障碍,这表明Obg样ATP酶1在神经发育中可能具有潜在的正向调控作用。但是这一假设亟需后续实验研究,如动物模型、细胞实验进行验证。

3.4 本研究的局限性

然而,本研究仍然存在一些局限性:①ICP数据集病例组人数很低(1 249人),导致识别出来的工具变量的效果欠佳。OR值与观察性研究不完全符合,需要从多个角度谨慎解读该结果;②选择SNPs的标准部分低于常规全基因组显著阈值($P<5\times10^{-8}$),虽然在多效性不显著的情况下,只要SNPs的选择标准不低于1E-04,弱工具变量效应影响较小[11],但是由于选择标准在所有分析中不完全一致,仍然可能导致假阳性的发生;③结局的2个数据库是混合数据库,不能完全区分ICP导致的是ADHD和TS中的一种还是二种;④中介效应的占比的95%*CI*偏大,不论是从生物学遗传学还是临床上均需要谨慎解读该结果。因此,仍需大量的基础研究来验证本研究的发现。

利益冲突 本文所有作者声明不存在利益冲突

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