doi: 10.13241/j.cnki.pmb.2020.09.028

ABCA1 基因多态性 R219K 与帕金森症和阿尔兹海默症发病率的相关性研究 *

亚拉盖[1] 梁 琨[1] 锡林塔娜[2] 陶娜拉[3] 刘 燕[4△]

（1 内蒙古自治区人民医院老年医学中心 内蒙古 呼和浩特 010020；
2 内蒙古锡林郭勒盟蒙医医院心身医学科 内蒙古 锡林浩特 026000；
3 内蒙古农业大学遗传育种实验室 内蒙古 呼和浩特 010010；4 内蒙古自治区人民医院内分泌科 内蒙古 呼和浩特 010020）

摘要 目的：探讨与研究三磷酸腺苷结合盒转运体 A1 (Adenosine triphosphate (ATP)-binding cassette transporter A1) 基因多态性 R219K 与帕金森症(Parkinson disease，PD)和阿尔兹海默症(Alzheimer disease，AD)发病率的相关性。**方法：**选择 2016 年 2 月到 2019 年 8 月在本院门诊与住院的帕金森症患者 42 例作为 PD 组，同期选择本院门诊与住院的阿尔兹海默症患者 42 例作为 AD 组，同期选择本院门诊健康体检者 84 例作为对照组。调查入选者的一般资料，检测三组血液样本的 ABCA1 基因多态性 R219K 情况并进行相关性分析。**结果：**AD 组低密度脂蛋白（low-density lipoprotein，LDL-C）、总胆固醇（total cholesterol，TC）、甘油三酯（triglyceride，TG）与尿酸 (Uric acid，UA) 均低于对照组，而高密度脂蛋白（high-density lipoprotein，HDL-C）、同型半胱氨酸 (homocysteine，Hcy) 值高于对照组 (P<0.05)；AD 组 TC 均低于 PD 组，而 HDL 高于 PD 组。PD 患者 HDL-C 均低于对照组，而 LDL、TC 和 TG 与对照组无差异(P>0.05)，三组空腹血糖(Fasting blood glucose，FBG)值对比差异无统计学意义(P>0.05)。PD 组与 AD 组的 ABCA1 R219K GA 基因型、A 等位基因频率都显著高于对照组 (P<0.05)，PD 组与 AD 组对比差异无统计学意义(P>0.05)。在 168 例入选者中，直线相关分析显示 ABCA1 R219K GA 基因型与 A 等位基因与帕金森症或阿尔兹海默症发生有显著相关性(P<0.05)。**结论：**ABCA1 基因多态性 R219K 在帕金森症和阿尔兹海默症患者中比较常见，ABCA1 R219K GA 基因型与 A 等位基因可诱发帕金森症和阿尔兹海默症的发生。

关键词：三磷酸腺苷结合盒转运体 A1；基因多态性；帕金森症；阿尔兹海默症

中图分类号：R749.1；R742.5 **文献标识码：**A **文章编号：**1673-6273(2020)09-1733-04

Correlation between ABCA1 Gene Polymorphism R219K and the Incidence of Parkinson's Disease and Alzheimer's Disease*

YA La-gai[1], LIANG Kun[1], XI LIN Ta-na[2], TAO Na-la[3], LIU Yan[4△]

(1 Inner Mongolia Autonomous Region People's Hospital Geriatrics Center, Hohhot, Inner Mongolia, 010020, China; 2 Department of Psychosomatic Medicine, Inner Mongolia Xilin Gol League Hospital of Inner Mongolia, Xilinhot, Inner Mongolia, 026000, China; 3 Inner Mongolia Agricultural University Genetic Breeding Laboratory, Hohhot, Inner Mongolia, 010010, China; 4 Department of Endocrinology, Inner Mongolia Autonomous Region People's Hospital, Hohhot, Inner Mongolia, 010020, China)

ABSTRACT Objective: To investigate and study the relation of Adenosine triphosphate (ATP)-binding cassette transporter A1 gene polymorphism R219K and the incidence of Parkinson disease (PD), Alzheimer disease (AD). **Methods:** From February 2016 to August 2019, A total of 42 patients with Parkinson's disease who were admitted to our hospital were enrolled in the PD group, 42 patients with Alzheimer's disease who were admitted to the hospital and hospitalized in the same period as the AD group, and the other 84 healthy subjects in our outpatient clinic were selected as the control group. The general information of the selected subjects were investigated, and the ABCA1 gene polymorphism R219K of the three groups of blood samples were examined and correlated. **Results:** The LDL-C, TC, TG and UA in the AD group were lower than those in the control group, while the HDL-C and Hcy values were higher than those in the control group (P<0.05). The TC in the AD group was lower than that in the PD group, and the HDL was higher than the PD group. The HDL-C level of PD patients was lower than that of the control group, but LDL, TC and TG were not different from the control group (P>0.05). There was no significant difference in the FBG values between the three groups (P>0.05). The ABCA1 R219K GA genotype, AA genotype and A allele frequency of PD group and AD group were significantly higher than that of the control group (P<0.05), and there were no significant difference compared between PD group and AD group (P>0.05). In the 168 case, linear correlation analysis

* 基金项目：内蒙古自治区自然科学基金项目(2016BS0315)；内蒙古自治区人民医院院内基金项目(201718)

作者简介：亚拉盖(1984-)，女，博士，主治医师，研究方向：帕金森及痴呆方向，电话：13804713367，E-mail：yalagai101@163.com

△ 通讯作者：刘燕(1984-)，女，医学硕士，主治医师，研究方向：糖尿病、高血压、脑垂体疾病、老年性疾病、骨代谢等代谢性疾病诊治，电话：18004712706，E-mail：376650095@qq.com

（收稿日期：2019-11-12 接受日期：2019-11-30）

showed that ABCA1 R219K GA genotype, AA genotype and A allele were significantly associated with Parkinson's disease or Alzheimer's disease (P<0.05). **Conclusion:** The ABCA1 gene polymorphism R219K are more common in patients with Parkinson's disease and Alzheimer's disease. ABCA1 R219K GA genotype, AA genotype and A allele can induce the occurrence of Parkinson's disease and Alzheimer's disease.

Key words: Adenosine triphosphate binding cassette transporter A1; Gene polymorphism; Parkinson's disease; Alzheimer's disease
Chinese Library Classification(CLC): R749.1; R742.5 Document code: A
Article ID:1673-6273(2020)09-1733-04

前言

阿尔兹海默症(Alzheimer disease,AD)是一种神经退行性疾病,帕金森症(Parkinson disease,PD)也是神经退行性疾病[1]。二者在临床症状上存在一定的重叠性,某些帕金森症患者可能出现认知功能的损伤，甚至发展为痴呆，称为帕金森症痴呆(Parkinson disease with dementia,PDD)[2,3]。同时某些阿尔兹海默症患者也常伴有椎体外系统病变,表现各种各样的行动失调等[4]。ABCA1 全名为三磷酸腺苷结合盒转运体 A1(Adenosine triphosphate (ATP)-binding cassette transporter A1),是由 ABCA1 基因翻译而成的蛋白[5]。该转运蛋白在细胞内参与胆固醇的逆向运输,同时能够清除组织中多余的血脂,从而维持细胞内磷脂的稳态平衡[6,7]。研究结果表明,在脑损伤修复的早期,ABCA1 参与载脂蛋白 E(apolipoprotein E,ApoE)以及胶质细胞内胆固醇的调节[8,9]。并且当前研究显示 ABCA1 基因伴随有基因多态性 (Single Nucleotide Polymorphisms,SNPs),ABCA1 基因多态性和突变型在多个族群与神经功能性的发病显著相关[10,11]。其中 ABCA1 基因 R219K 多态性是指 ABCA1 基因其 7 号外显子第 1051 位核苷酸由 G 变成 A,对应的由精氨酸(R)转变成赖氨酸(K)[12,13]。本文具体探讨与研究了 ABCA1 基因多态性 R219K 与帕金森症和阿尔兹海默症发病率的相关性,希望为明确两者的发病机制提供一定的理论支持。现总结报道如下。为临床科学治疗提供基因导向的理论支持。

1 资料与方法

1.1 研究对象

PD 组：选择 2016 年 2 月至 2019 年 8 月在本院门诊与住院的帕金森症患者 42 例，根据英国帕金森症协会脑库标准确诊为帕金森症。AD 组:同期选择本院门诊与住院的阿尔兹海默症患者 42 例,符合最新的阿尔兹海默症的诊断标准。对照组:同期选择本院门诊健康体检者 84 例。

三组纳入标准:年龄 20-75 岁;都为汉族;知情同意本研究;彼此间无血缘关系;本院伦理委员会批准了此次研究;依从性好。排除标准:农药中毒导致类帕金森症或阿尔兹海默症患者;有反复的脑损伤史者;妊娠与哺乳期妇女;有服用抗精神病类药物或多巴胺耗竭类药物历史者。

三组一般资料对比无差异(P>0.05),PD 组与 AD 组的病程对比差异也无统计学意义(P>0.05)。见表 1。

表 1 三组一般资料对比

Table 1 Comparison of three groups of general data

Groups	n	Gender (Male Female)	Age (old)	BMI (kg/m^2)	Course of disease (year)
PD group	42	22/20	56.98±4.10	22.81±2.11	5.72±0.43
AD group	42	21/21	57.09±3.19	22.76±1.89	5.78±0.51
Control group	84	44/40	56.77±2.19	23.00±2.01	-

1.2 基因多态性分析

要求入选患者采血前 1 d 至少禁食 8 h 以上，于第 2 d 上午 8:00 空腹从肘部抽取静脉全血 3-5 mL,一部分用于分离血清用于检测常规生化指标。其余静脉血置于 EDTA 抗凝真空采血器中,采用德国 QIAGEN 公司生产的 Blood Kit 全血基因组 DNA 提取试剂盒提取人全血基因组 DNA,各步骤严格按照试剂盒说明操作。采用 PCR-RFLP 方法进行 ABCA1 基因多态性 R219K 分析,R219K G>A 扩增引物(扩增产物共 259bp)序列:上游引物 5'-TCCACACAGGACTGCCAGA-3'，下游引物 5'-TGCTCGCAGTAGGTGTCAAT-3'，采用 20 μL PCR 反应体系,PCR 扩增产物经 2%的琼脂糖凝胶进行电泳分离后，测序结果与 NCBI 在线进行序列比对,判断基因型。

1.3 调查资料

调查所有入选者的一般资料,包括性别、年龄、体重指数、种族，记录全自动生化仪检测的指标，包括空腹血糖(Fasting blood glucose,FBG)、血脂 (TG、TC、LDL-C 和 HDL-C)、尿酸(Uric acid,UA)、同型半胱氨酸(homocysteine,Hcy)等。同时记录患者的病程等资料。

1.4 统计方法

采用 SPSS 软件包(Version 18.00)对数据进行统计分析,计量数据与计数数据以($\bar{x}\pm s$)与%表示,对比采用卡方 χ^2 分析、t 检验,相关性分析采用直线相关分析,P<0.05 为差异显著。

2 结果

2.1 常规生化指标对比

AD 组 LDL-C、TC、TG 与 UA 均低于对照组，而 HDL-C、Hcy 值高于对照组(P<0.05);AD 组 TC 均低于 PD 组,而 HDL 高于 PD 组。PD 患者 HDL-C 均低于对照组,而 LDL、TC 和 TG 与对照组无差异(P>0.05),三组 FBG 值对比差异无统计学意义(P>0.05)。

表 2 三组常规生化指标对比($\bar{x}\pm s$)

Table 2 Comparison of three groups of conventional biochemical indicators($\bar{x}\pm s$)

Index	PD group (n=42)	AD group (n=42)	Control group (n=84)
TG (mmol/L)	1.23±0.16	1.20±0.16*	1.26±0.16
LDL-C (mmol/L)	2.56±0.27	2.48±0.30*	2.59±0.34
UA (μmol/L)	328.77±20.10*	329.76±19.87*	361.98±45.10
Hcy (μmol/L)	13.78±1.33*	14.09±1.7*	8.89±1.44
FBG (mmol/L)	5.89±0.34	5.90±0.24	5.87±0.32
TC (mmol/L)	4.51±0.24	4.33±0.16*#	4.52±0.24
HDL-C (mmol/L)	0.95±0.22*	2.10±0.23*#	1.35±0.12

Note: *Compared with NC group, $P<0.05$; # compared with PD group, $P<0.05$.

2.2 ABCA1 R219K 基因型频率和等位基因频率对比

PD 组与 AD 组的 ABCA1 R219K GA 基因型、A 等位基因频率都显著高于对照组($P<0.05$)，PD 组与 AD 组对比差异无统计学意义($P>0.05$)。见表 3。

表 3 三组 ABCA1 R219K 基因型频率和等位基因频率对比(例,%)

Table 3 Comparison of frequency and allele frequency of three groups of ABCA1 R219K genotypes (n, %)

Group	n	基因型频率			等位基因频率	
		GG	GA	AA	G	A
PD group	42	31(73.8)	8(19.0)	3(7.1)	35(83.3)	7(16.7)
AD group	42	31(73.8)	7(16.7)	4(9.5)	34(81.0)	8(19.0)
Control group	84	83(98.8)	1(1.2)	0(0.0)	83(98.8)	1(1.2)
F		22.215	13.678	7.602	13.678	
P		0.000	0.001	0.022	0.001	

表 4 ABCA1 基因多态性 R219K 与帕金森症阿尔兹海默症发病的相关性(n=168)

Table 4 Association of ABCA1 gene polymorphism R219K with Parkinson's disease Alzheimer's disease (n=168)

Index		GA genotype	AA genotype	A allel
PD	r	0.566	0.671	0.644
	P	0.007	0.000	0.004
AD	r	0.613	0.701	0.672
	P	0.005	0.000	0.002

2.3 相关性分析

在 168 例入选者中，直线相关分析显示 ABCA1 R219K GA 基因型与 A 等位基因与帕金森症或阿尔兹海默症发生有显著相关性($P<0.05$)。见表 4。

3 讨论

帕金森症和阿尔兹海默症都为比较常见的神经系统疾病，主要病理表现大脑黑质多巴胺能神经元的逐渐丧失，导致在临床上出现抑郁、焦虑、幻觉、运动迟缓、姿势不稳、肌肉僵直、静止性震颤等，可严重影响患者的生活质量[14,15]。并且上述两种疾病的诊治费用也比较高，也增加了当地的医疗卫生经济压力。帕金森症和阿尔兹海默症的具体发病机制还不明确，目前认为遗传、氧化应激、种族、环境、年龄等与该病的发病有关，其中遗传因素已经受到学者高度的重视[16,17]。

即使是相同的人种，随着时间的改变，生活在不同的环境中，帕金森症和阿尔兹海默症的发病率及患病率也存在一定的差异性[18,19]。本研究显示 AD 组 LDL-C、TC、TG 与 UA 均低于对照组，而 HDL-C、Hcy 值高于对照组；AD 组 TC 均低于 PD 组，而 HDL 高于 PD 组。PD 患者 HDL-C 均低于对照组，而 LDL、TC 和 TG 与对照组无差异。从机制上分析，血脂、尿酸、同型半胱氨酸的异常可引发机体产生一系列防御性应激反应事件，可故而加速帕金森症和阿尔兹海默症的发病[20]。

大约 10 %-20 %的帕金森症和阿尔兹海默症患者具有家族史，在家族史的中也有 10 %左右的是由单个基因的显性或隐性遗传而导致的[21,22]。ABCA1 基因多态性和突变型在多个族群与神经退化性疾病的发病相关，ABCA1 基因的突变在家族性帕金森综合症检出的突变中频率最高，同时其变异在散发性帕金森综合症中最为常见[23,24]。人类的 ABCA1 基因与一些脂质转运有显著相关性，R219K 基因多态性或者基因突变可通过一系列信号传导途径，最终导致神经元的变性死亡[25]。本研究

显示 PD 组与 AD 组的 ABCA1 R219K GA 基因型、A 等位基因频率都显著高于对照组，PD 组与 AD 组对比差异无统计学意义，表明帕金森症和阿尔兹海默症患者多伴随有 ABCA1 基因 R219K 多态性。当前有研究显示 ABCA1 基因 R219K 多态性能够使 mRNA 形成局部稳定的颈环结构，导致翻译的蛋白数量减少和活性改变，使得多巴胺通路的代谢发生了改变，从而对帕金森症和阿尔兹海默症的易感性产生了一定的影响[26,27]。

人类的 ABCA1 基因定位于 9q31，全长 149kb，ABCA1 蛋白在胆固醇、高密度脂蛋白胆固醇的合成和转运中起重要作用，也以介导胰岛内胆固醇流出，并对胰岛细胞分泌功能产生影响[28,29]。但是 ABCA1 SNPs 与脂代谢相关分子水平的关系的报道比较少，尤其是与帕金森症和阿尔兹海默症的关系还无相关报道。本研究直线相关分析显示 ABCA1 R219K GA 基因型与 A 等位基因与帕金森症或阿尔兹海默症发生有显著相关性。从机制上分析，ABCA1 基因编码蛋白质存在大量的精氨酸残基，有一个较高的净正电荷。由于 R219K 的替换，可能影响蛋白的构象及其表面净正电荷，从而影响和其他蛋白质的相互作用，最终影响 ABCA1 蛋白的正常功能，诱发帕金森症或阿尔兹海默症的发生[30,31]。不过本研究的样本量较少，还需要尽可能的控制或排除混杂因素的影响，从而得到更加准确的结论。

综上所述，ABCA1 基因多态性 R219K 在帕金森症和阿尔兹海默症患者中比较常见，ABCA1 R219K GA 基因型与 A 等位基因可诱发帕金森症和阿尔兹海默症的发生。

参 考 文 献(References)

[1] Aruoma OI, Hausman-Cohen S, Pizano J, et al. Personalized Nutrition: Translating the Science of NutriGenomics Into Practice: Proceedings From the 2018 American College of Nutrition Meeting[J]. J Am Coll Nutr, 2019, 38(4): 287-301

[2] Baker E, Sims R, Leonenko G, et al. Gene-based analysis in HRC imputed genome wide association data identifies three novel genes for Alzheimer's disease[J]. PLoS One, 2019, 14(7): e0218111

[3] Dincer Y, Akkaya C, Mutlu T, et al. DNA repair gene OGG1 polymorphism and its relation with oxidative DNA damage in patients with Alzheimer's disease [J]. Neurosci Lett, 2019, 709: e134362

[4] Durmaz A, Kumral E, Durmaz B, et al. Genetic factors associated with the predisposition to late onset Alzheimer's disease [J]. Gene, 2019, 707: 212-215

[5] Ehnert S, Linnemann C, Braun B, et al. One-Step ARMS-PCR for the Detection of SNPs-Using the Example of the PADI4 Gene [J]. Methods Protoc, 2019, 2(3): e63

[6] Fang X, Tang W, Yang F, et al. A Comprehensive Analysis of the CaMK2A Gene and Susceptibility to Alzheimer's Disease in the Han Chinese Population[J]. Front Aging Neurosci, 2019, 11: 84-91

[7] Franzmeier N, Rubinski A, Neitzel J, et al. The BIN1 rs744373 SNP is associated with increased tau-PET levels and impaired memory [J]. Nat Commun, 2019, 10(1): 1766-1799

[8] Huentelman M, De Both M, Jepsen W, et al. Common BACE2 Polymorphisms are Associated with Altered Risk for Alzheimer's Disease and CSF Amyloid Biomarkers in APOE epsilon4 Non-Carriers[J]. Sci Rep, 2019, 9(1): 9640-96556

[9] Li W, Qiu Q, Sun L, et al. Short-term adverse effects of the apolipoprotein E epsilon4 allele over language function and executive function in healthy older adults [J]. Neuropsychiatr Dis Treat, 2019, 15: 1855-1861

[10] Mazzeo S, Bessi V, Padiglioni S, et al. KIBRA T allele influences memory performance and progression of cognitive decline: a 7-year follow-up study in subjective cognitive decline and mild cognitive impairment[J]. Neurol Sci, 2019, 40(8): 1559-1566

[11] Miles LA, Hermans SJ, Crespi GN, et al. Small Molecule Binding to Alzheimer Risk Factor CD33 Promotes Abeta Phagocytosis [J]. iScience, 2019, 19: 110-118

[12] Miron J, Picard C, Labonte A, et al. Association of PPP2R1A with Alzheimer's disease and specific cognitive domains [J]. Neurobiol Aging, 2019, 81: 234-243

[13] Miron J, Picard C, Lafaille-Magnan ME, et al. Association of TLR4 with Alzheimer's disease risk and presymptomatic biomarkers of inflammation[J]. Alzheimers Dement, 2019, 15(7): 951-960

[14] Stamati P, Siokas V, Aloizou AM, et al. Does SCFD1 rs10139154 Polymorphism Decrease Alzheimer's Disease Risk? [J]. J Mol Neurosci, 2019, 69(2): 343-350

[15] Sumirtanurdin R, Thalib AY, Cantona K, et al. Effect of genetic polymorphisms on Alzheimer's disease treatment outcomes: an update [J]. Clin Interv Aging, 2019, 14: 631-642

[16] Wu NN, Ren J. Aldehyde Dehydrogenase 2 (ALDH2) and Aging: Is There a Sensible Link?[J]. Adv Exp Med Biol, 2019, 1193: 237-253

[17] Yao X, Risacher SL, Nho K, et al. Targeted genetic analysis of cerebral blood flow imaging phenotypes implicates the INPP5D gene [J]. Neurobiol Aging, 2019, 81: 213-221

[18] Lu Z, Luo Z, Jia A, et al. Associations of the ABCA1 gene polymorphisms with plasma lipid levels: A meta-analysis [J]. Medicine (Baltimore), 2018, 97(50): e13521

[19] Mahmoodi K, Kamali K, Ghaznavi H, et al. The C-565T Polymorphism (rs2422493) of the ATP-binding Cassette Transporter A1 Gene Contributes to the Development and Severity of Coronary Artery Disease in an Iranian Population[J]. Oman Med J, 2018, 33(4): 309-315

[20] Piko P, Fiatal S, Kosa Z, et al. Generalizability and applicability of results obtained from populations of European descent regarding the effect direction and size of HDL-C level-associated genetic variants to the Hungarian general and Roma populations [J]. Gene, 2019, 686: 187-193

[21] Smirnov GP, Malyshev PP, Rozhkova TA, et al. The effect of ABCA1 rs2230806 common gene variant on plasma lipid levels in patients with dyslipidemia[J]. Klin Lab Diagn, 2018, 63(7): 410-413

[22] Wang F, Ji Y, Chen X, et al. ABCA1 variants rs2230806 (R219K), rs4149313 (M8831I), and rs9282541 (R230C) are associated with susceptibility to coronary heart disease [J]. J Clin Lab Anal, 2019, 33 (6): e22896

[23] Wang X, Guo H, Li Y, et al. Interactions among genes involved in reverse cholesterol transport and in the response to environmental factors in dyslipidemia in subjects from the Xinjiang rural area [J]. PLoS One, 2018, 13(5): e0196042

(下转第 1744 页)

心绞痛[J]. 中国中医药现代远程教育, 2011, 09(18): 143-145

[8] 谈晓东. 中西药合用治疗冠心病心绞痛疗效观察[J]. 实用中医药杂志, 2019, 35(1): 47-48

[9] 杨建军. 冠心病心绞痛的临床治疗及疗效初步评定与报告[J]. 临床医学研究与实践, 2017, 2(6): 27-28

[10] Li XL, Wang J, Wang W. Correlation of TCM Syndrome Types, Blood Lipid and Serum Uric Acid in Coronary Heart Disease with Unstable Angina Pectoris [J]. Journal of the American College of Cardiology, 2017, 70(16): C80-C80

[11] Rupert PW, Guus AW, Kalpa DS, et al. Doppler Versus Thermodilution-Derived Coronary Microvascular Resistance to Predict Coronary Microvascular Dysfunction in Patients With Acute Myocardial Infarction or Stable Angina Pectoris [J]. The American Journal of Cardiology, 2018, 121(1): 1-8

[12] Borer JS, Swedberg K, Komajda M, et al. Efficacy Profile of Ivabradine in Patients with Heart Failure plus Angina Pectoris [J]. Cardiology, 2017, 136(2): 138-144

[13] Yesenia C, Jinwi G. Management of Coronary Artery Disease and Chronic Stable Angina[J]. U. S. pharmacist, 2017, 42(2): 27-31

[14] Weinstein G, Goldbourt U, Tanne D. Angina Pectoris Severity Among Coronary Heart Disease Patients is Associated With Subsequent Cognitive Impairment [J]. Alzheimer disease and associated disorders, 2015, 29(1): 6-11

[15] Weinstein G, Goldbourt U, David T. Angina Pectoris Severity Among Coronary Heart Disease Patients is Associated With Subsequent Cognitive Impairment [J]. Alzheimer Disease & Associated Disorders, 2015, 29(1): 6-11

[16] Kallistratos MS, Poulimenos LE. Trimetazidine in the Prevention of Tissue Ischemic Conditions[J]. Angiology, 2019, 70(4): 291-298

[17] Jiang YW, Han C, Hua Y, et al. Effect of atorvastatin and trimetazidine combination treatment in patients with NSTE-ACS undergoing PCI[J]. Cardiology Plus, 2018, 3(2): 41-46

[18] Saeed J, Shohreh K, Ali EF, et al. Anti-inflammatory effects of human embryonic stem cell-derived mesenchymal stem cells secretome preconditioned with diazoxide, trimetazidine and MG-132 on LPS-induced systemic inflammation mouse model [J]. Artificial Cells, Nanomedicine, and Biotechnology, 2018, 46(sup2): 1178-1187

[19] Ozcan MF, Hekimoglu ER, Ener K, et al. Trimetazidine has protective effects on spermatogenesis in a streptozotocin-induced diabetic rat model[J]. Andrologia, 2017, 49(10): 1085-1092

[20] 梅雪靖, 于森, 王妍, 等. 胸痹心痛贴治疗气虚血瘀型不稳定心绞痛的临床观察[J]. 养生保健指南, 2019, (23): 37

[21] 李杨, 王井飞. 论气药治胸痹心痛 [J]. 成都中医药大学学报, 2019, 42(1): 17-18, 50

[22] 庄贺, 庄慧魁, 陈泽涛, 等. 邵念方教授治疗胸痹心痛用药规律分析[J]. 中医学报, 2019, 34(3): 675-678

[23] 张如升, 张羽, 周士公. 心元胶囊联合振源胶囊对慢性充血性心力衰竭患者心功能和运动耐量的影响 [J]. 中国保健营养, 2018, 28 (32): 86

[24] 客蕊, 王明利, 佟蕊, 等. 中药复方治疗气虚血瘀型冠心病心绞痛的研究进展[J]. 广州中医药大学学报, 2019, 36(3): 435-439

[25] 高长春, 林淑梅, 徐国良, 等. 心元胶囊治疗冠心病心绞痛有效性及安全性的 Meta 分析[J]. 中国中医急症, 2015, 24(1): 52-55

[26] Konigstein M, Verheye S, Jolicoeur EM, et al. Narrowing of the Coronary Sinus A Device-Based Therapy for Persistent Angina Pectoris[J]. Cardiology in review, 2016, 24(5): 238-243

[27] Maayan K, Stefan V, Marc J. Narrowing of the Coronary Sinus: A Device-Based Therapy for Persistent Angina Pectoris [J]. Cardiology in Review, 2016, 24(5): 238-243

[28] Linde JJ, Sorgaard M, Kuhl JT, et al. Prediction of clinical outcome by myocardial CT perfusion in patients with low-risk unstable angina pectoris[J]. The international journal of cardiovascular imaging, 2017, 33(2): 261-270

[29] 陈向明, 李洁嫦, 梁鉴文. 血栓通治疗老年冠心病心绞痛疗效观察及其对血脂水平的影响[J]. 北方药学, 2019, 16(4): 69-70

[30] 范怀周, 程映雪. 不同类型冠心病患者血清炎性标志物的检测水平及意义[J].热带医学杂志, 2010, 10(7): 861-863

(上接第 1736 页)

[24] Wittkowski KM, Dadurian C, Seybold MP, et al. Complex polymorphisms in endocytosis genes suggest alpha-cyclodextrin as a treatment for breast cancer[J]. PLoS One, 2018, 13(7): e0199012

[25] Xu Y, Li Z. Relationship between ABCA1 gene polymorphism and lacunar infarction combined with arteriosclerosis in patients [J]. Exp Ther Med, 2018, 16(2): 1323-1327

[26] Yan H, Cheng L, Jia R, et al. ATP-binding cassette sub-family a member1 gene mutation improves lipid metabolic abnormalities in diabetes mellitus[J]. Lipids Health Dis, 2019, 18(1): 103-118

[27] Yang H, Chen G, Song C, et al. A novel index including SNPs for the screening of nonalcoholic fatty liver disease among elder Chinese: A population-based study[J]. Medicine (Baltimore), 2018, 97(13): e0272

[28] Yuan MZ, Han RA, Zhang CX, et al. Association of Genes in the High-Density Lipoprotein Metabolic Pathway with Polypoidal Choroidal Vasculopathy in Asian Population: A Systematic Review and Meta-Analysis[J]. J Ophthalmol, 2018, 2018: e9538671

[29] Akbulut UE, Emeksiz HC, Citli S, et al. IL-17A, MCP-1, CCR-2, and ABCA1 polymorphisms in children with non-alcoholic fatty liver disease[J]. J Pediatr (Rio J), 2019, 95(3): 350-357

[30] Dizier MH, Margaritte-Jeannin P, Pain L, et al. Interactive effect between ATPase-related genes and early-life tobacco smoke exposure on bronchial hyper-responsiveness detected in asthma-ascertained families[J]. Thorax, 2019, 74(3): 254-260

[31] Dron JS, Wang J, Berberich A J, et al. Large-scale deletions of the ABCA1 gene in patients with hypoalphalipoproteinemia [J]. J Lipid Res, 2018, 59(8): 1529-1535