Impact of Individual Factors on DNA Methylation of ADME Genes: A Systematic Review

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Abstract

Individual differences in drug response have always existed in clinical treatment. Many non-genetic factors show non-negligible impacts on personalized medicine. Emerging studies have demonstrated epigenetic could connect non-genetic factors and individual difference in treatment. We used systematic retrieval methods and reviewed studies that showed individual factors' impact on DNA methylation of ADME genes. In total, 63 studies were included, and half(n=32) were cohort studies. Six aspects of individual factors were summarized from the perspective of personalized medicine: parental exposure, environmental pollutants exposure, obesity and diet, drugs, gender and others. The largest number of studies (n=11) studied methylation of ABCG1. Most studies showed these non-genetic factors could result in a significant DNA methylation alteration in ADME genes, which subsequently affect the process of drug metabolism. However, the underlying mechanisms remain unknown. Finally, we put forward some views for future research.

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Declarations

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Authorship and Confict of Interest

LH contributed to conception and design of the study. BJ, JZ and YL helped with the literature search. JB organized literatures and wrote the manuscript. JB, SH and XH contributed to data extraction and form production. All authors contributed to manuscript revision. All authors read and approved the final manuscript. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Approval, Consent to Participate, Consent to Publish, Availability of Data and Material, Code Availability

Not applicable

Abstract

Individual differences in drug response have always existed in clinical treatment. Many non-genetic factors show non-negligible impacts on personalized medicine. Emerging studies have demonstrated epigenetic could connect non-genetic factors and individual difference in treatment. We used systematic retrieval methods and reviewed studies that showed individual factors' impact on DNA methylation of ADME genes. In total, 63 studies were included, and half(n=32) were cohort studies. Six aspects of individual factors were summarized from the perspective of personalized medicine: parental exposure, environmental pollutants exposure, obesity and diet, drugs, gender and others. The largest number of studies (n=11) studied methylation of ABCG1. Most studies showed these non-genetic factors could result in a significant DNA methylation alteration in ADME genes, which subsequently affect the process of drug metabolism. However, the underlying mechanisms remain unknown. Finally, we put forward some views for future research.

Key words: DNA methylation; individual factor; ADME gene; systematic review.

Introduction

Inherent features of disease and response to therapeutics are often clustered in individuals, families, and population groups. Yet, a broad approach to diagnosis and therapy has been adopted for the most history of medicine practice. Individual difference is widely existing in clinical practice. Personalized medicine is paid increasing attention after human genome sequencing[1], and linking genomic and clinical profiles of individual patients helps to understand their disease at a deeper level to develop more targeted therapies. Patients will get maximum benefit but minimum risk because of personalized medicine. The absorption, distribution, metabolism and excretion (ADME) process of drugs in human body is an important part which induces individual differences in medicine therapy[2]. The protein activity and abundance of drug-metabolizing enzymes and transporters are very important in ADME process.

Most of the personalized medicine relevant studies focus on the genetic polymorphism of ADME genes using pharmacogenetics. SLCO1B1 gene mutation (c.521T $>$ C, p.Val174Ala) decreases the transportation of active simvastatin from portal circulation into the liver, leading to increased plasma concentration of simvastatin acid and an enhanced risk of myopathy adverse reaction[3]. A website was established to query drug pharmacokinetic data and to predict targeted ADME relevant protein, which integrates, genetic, proteomic, phenotypic and molecule interaction data[4]. However, the protein activity and abundance not only depend on the structure change caused by the change of DNA sequence, but also be regulated by the mRNA expression. Many studies explored the relationship between the expression of ADME genes and drug reaction difference from the perspective of epigenetics, especially DNA methylation[5]. Resistance to chemotherapeutics is associated with promoter hypermethylation of ABCG2[6]. Xu Hao et al. summarized the correlation between ADME gene expression and DNA methylation exact locations and explained individual differences in clinical treatment[7]. In addition, source of differences in DNA methylation levels of ADME genes between individuals is not clear. A large number of studies showed that non-genetic factors such as age, gender, race, diet, pathophysiological status, and combined drugs may affect drug efficacy and safety by regulating the PK process. Some non-genetic factors may affect the DNA methylation of genes. Dioxins and dietary factors affecting metabolic gene methylation have attracted much attention and been published[8, 9]. The cause of retinopathy in patients with hypercholesterolemia may be caused by hypermethylation of ABCA1[10]. Epigenetic can be a bridge connecting affecting factors and personalized medicine[11, 12]. This systematic review summarizes individual factors and their effects on methylation characteristics of gene related to drug metabolism, and aims to screen out the influential individual factors, to find possible signaling pathways or targets for individualized factors and to provide new insights into the causes of individualized differences in clinical treatment.

Method

Search strategy

We searched the Pubmed and Embase exhaustively about what and how individual factors influence the DNA methylation of genes related to drug metabolism. Searches used the following title, abstract, keyword and Medical Subject Headings (MeSH) terms: (1) DNA methylation; (2) genes related to drug metabolism; (3) influence, related, affect, factors. Reference lists of identified articles and reviews were also searched for additional references. The search and filtering process was done under the supervision of senior researchers.

Selection criteria

The studies were selected for inclusion if they fulfilled the following criteria: (1) published from 2000 onwards. (2) published in English. (3) experiments about people, mice or cells. (4) genes were involved in metabolism. The reason why we choose experiment about people, mice and cells was that we need findings to be used in clinical treatment. We excluded the DNA methylation related to diseases because these genes were often part of disease pathogenesis, hardly involved in metabolism, and nearly have no influence on drug metabolism. Each reviewer screened part of the publications independently with the inclusion and exclusion criteria and inter-reviewer disagreement was discussed and resolved by a senior author. More details are in Fig.1 about the selection process.

Data extraction

For the papers included, we extracted following information.

- Author.
- Year of publication.
- Research type.
- Methods for detection of methylation.
- Research object.
- Sample size.
- individual affect factor.
- Gene & CpG sites.
- Main result of the methylation.

Information was recorded by two authors independently and any disagreement were discussed and resolved by a senior author. Complete records were aggregated in appendix.

Result

In total, 63 articles were included (details in appendix). Half of all studies (n=32) were cohort study of population. The number of studies increased with years. Included studies were limited to observational studies, and exploratory experiment studies were rare. The frequency of genes studied was counted in the literature, and the genes were listed with frequencies more than once(Fig.2). ABCG1, involved in the transportation of lipid elements, was ranked first with as many as 11 studies. These 11 articles were all population cohort studies, and some researched the same CpG sites. Individual factors were classified into six categories, which were listed below.

Mother during pregnancy

There were 13 studies showed that mother's behavior would leave an epigenetic mark on offspring's DNA(Table.1). Mothers' smoking would lead to lighter baby birth weight and DNA methylation played an important role in this process. CYP1A1 CpG sites was significantly associated with birthweight ($P = 4.76\times10^{-5}$) and had significant mediation effect together with GFI1 and AHRR genes[13]. Correlation differed in gender and race. CYP1A1 was considered to detoxification of the components of tobacco smoke in phase I metabolism. CYP1A1 methylation may be one of the signal paths that how smoking affects babies. Trace metals exposure also affected fetal gene methylation levels. Cadmium (Cd), lead (Pb), total mercury

(Hg), manganese (Mn) and selenium (Se) were associated with CpG sites[14]. Especially, Pd was associated with CYP24A1(cg01243877) ($P<0.001$) and Arsenic(As) was associated with CYP2A4 and CYP7B1[15]. CYP24A1 CpG sites, involved in vitamin D3 metabolism and cellular calcium homoeostasis, provided an evidence supporting Pb as a neurotoxicant. Maternal hormone affected the fetus' ABCA1 and CYP11A1 methylation during pregnancy[16, 17]. Maternal gestational weight gain was related to offspring ABCA1 methylation (β = -1.1% per quartile; 95% CI: -2.0, -0.3)[18]. Poor nutrition or food deprivation during fetal development was related to PPARγ and ABCA1 methylation[19, 20]. ABCA1 may play a role in the efflux of intracellular cholesterol to apoliproteins and the formation of nascent high density lipoproteins (HDLs). These factors may influence baby HDL through DNA methylation. These studies suggested that parental generation affects DNA methylation in offspring, a reminder to be more careful during pregnancy to protect the fetus.

Environmental pollutants exposure

There were 11 studies exploring environment affects(Table.2). Environmental pollution has been attached great importance, and scientists are studying its impact on people. Smoking was one of well-known risk factors. Studies showed that smoking led to CYP1A1, CYP1A2, CYP2A6, CYP11B2 and PARβ methylation alteration[13, 21-26]. Polycyclic aromatic hydrocarbons (PAHs), one kind of carcinogens of cigarette, were metabolized by phase I (e.g. CYP1A1) and detoxified by phase II (e.g. GSTM1) before targeting DNA[27]. Epigenetic differences in CYP1A1 may explain individual metabolic differences and lung cancer risk in smokers. CYP2A6 was involved in 90% nicotine metabolism and its expression differed in gender and age. Men had lower nicotine clearance than women, and older people also had lower nicotine clearance than younger people[24]. DNA methylation explained some of the variation. Other common environmental pollutants, like PM2.5, dust mite and chemicals, were related to aberrant methylation. Shang Y et al. employed the mouse model to prove that the reprogramming of lung or airways by dust mite can be mediated through epigenetic[28]. Polycyclic aromatic hydrocarbons including dioxin affected CYP1A1 demethylation via aryl hydrocarbon receptor (Ahr)[29]. The change was tissue specific and may account for their carcinogenicity. These results suggested that our genes were sensitive to environmental pollutants, and we should minimize environmental pollution exposure.

Obesity and Diet

There were 18 studies showed that body mass index (BMI) and blood lipids affected the DNA methylation(Table.3). Obesity or high BMI had wide effects on gene methylation, including ABCG1,ABCC1, CYP27B1, SLC45A3,SLC1A5,and SLCO3A1. ABCG1 was an important part of lipid metabolism and also the most researched and conclusive gene. ABCG1 was believed that responsible for macrophage cholesterol and phospholipid transport[30]. Downregulation of ABCG1 led to reduce cholesterol efflux, which was associated with cardiovascular disease risk, obesity and dyslipidemia. High-risk groups of these diseases were often found hypermethylation of ABCG1[31-33]. Exactly, the results correspond to its function. However, we were not sure whether the methylation changes occur before or after the disease. Studies on ABCG1 were population cohort studies or case-control studies, while none of the studies explored specific mechanisms. These studies suggested that changes in epigenetics was one of the reasons for individual differences in obesity.

The ratio of different nutrients in the diet affected LMAO2, MnSOD, GSTM1, GSTT1, CYP1A1 and CYP2E1 methylation[34-36]. High fat diet led to CYP2R1,CYP27A1,CYP27B1,CYP24A1 and PPAR-α methylation alteration, but had no significant effect on PPAR-γ methylation[37-39]. These genes were involved in the metabolism of adipocytes, and studies shown that the body's response to the stimulation of high-fat diet. However, the specific mechanism was still unclear. Specially, lack of folic acid led to demethylation of ABCG2[40], lack of Vitamin D led to hypermethylation of CYP24A1 and CYP27B1[41, 42]. The folic acid excretion cells increased or decreased when folic acid was excessive or deficient. This process was transported by ABCG2 and the expression of ABCG2 was regulated by methylation. Finally, the total folic acid maintain stable[40]. 24-hydroxylase encoded by the CYP24A1 gene was a catabolic enzyme and both 25(OH)D and 125(OH)2D were catabolized by the 24-hydroxylase into inactive metabolites, thereby lowering the vitamin D levels[41].

Drugs

There were 7 studies showed that some drugs can also influence the DNA methylation (Table.4). Although most studies did not display the magnitude of the effect, the genes drugs affected were important metabolic genes. Berberine can lead to hypermethylation of CYP2B6 and CYP3A4[43]. Aspirin can induce hypermethylation of ABCB1[44]. Methadone can cause hypermethylation of ABCB1 and CYP2D6, and the influence can be transmitted to the fetus[45]. Therefore we need pay more attention to drug combination and may have deeper understandings of drug interactions. However, there were another results that attracted our attention. García-Calzón, S. et al. found that metformin can influence methylation degree of SLC22A1, SLC22A3 and SLC47A1[46]. At the same time, metformin was their metabolic substrate. Additionally, Wang, X. K. et al. found that afatinib can effectively resist to the multidrug resistance (MDR) by hypermethylation in promoter and downregulating the expression of ABCG2[47]. Meanwhile, afatinib was also the transporter substrate of BCRP, coded by ABCG2.These findings may help us better understand the process of drug metabolism in the human body.

Gender

There were 6 studies showed that DNA methylation alteration was different in gender groups (Table.5). Study showed that CYP1A1, CYP2E1 and CYP7B1 methylation was different among genders[48]. Moreover, the same exposure affected different genders differently. Smoking showed significant methylation alternation of CYP11B2 and ABCG1 in different gender[22, 26]. Lead exposure influenced GPX1, CYP1A1 and SOD3 methylation differently in gender groups[49]. Polycyclic aromatic hydrocarbons exposure caused different PPARγ methylation in gender groups[50]. LDL-C and TG had different association with ABCG1 DNA methylation in different gender groups[33]. These studies reminded us that gender needed to be considered in personalized medicine.

Other factors

Besides above factors, other studies reported some meaningful experiment (Table.6). Some factors that often taken into account, like race, age and inflammation, also been shown to affect gene methylation[51-53]. Nano-SiO_2, not often mentioned, led to hypomethylation of PARP and decreased expression on mRNA and protein level[54]. ABCA1 promoter methylation level was an independent risk factors for premature coronary artery disease along with traditional risk factors, like high BMI and HbA1c[55]. Worthy of attention, 2 studies explored the correlation of methylation changes with time and periodicity[56, 57]. CYP27B1 methylation was weakly association with season and CYP17A1 promoter was hypomethylated after circadian rhythm was disrupted. These findings provided evidence for the new idea to explain the relationship between the affecting factors and individualized medicine that time affected methylation periodically.

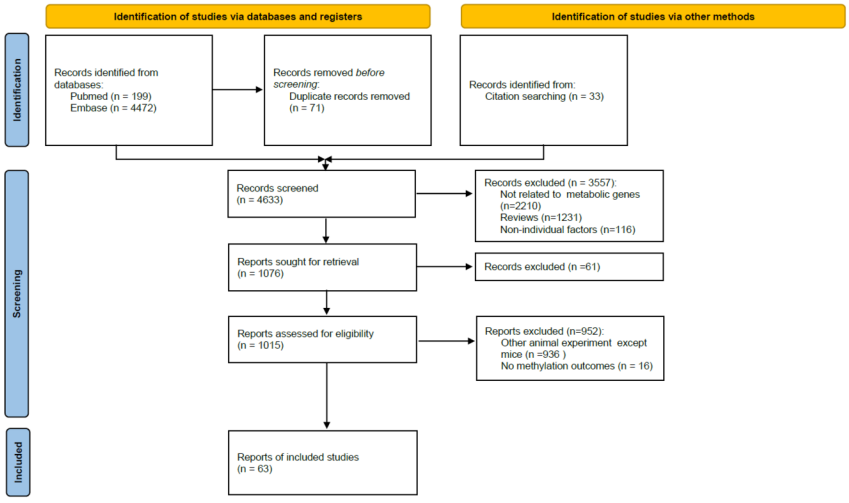

Fig.1 Systematic review flow chat

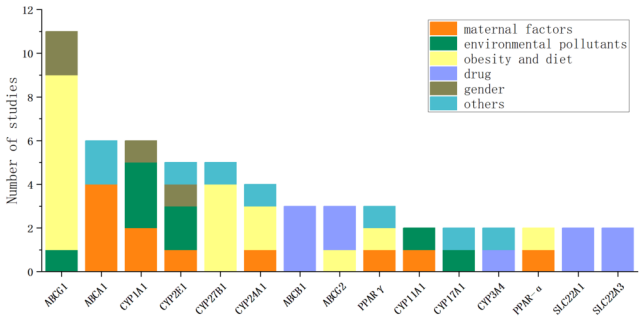

Fig.2 Frequency of reported genes in the studies

Table.1 Offspring ADME genes methylation changes induced by mother during pregnancy

Author, year (Ref.)	Research type	Object*	Sample size	Factors	Gene	CpG sites	Method	Main result** value)
Xu, R. 2021[13]	cohort study	H	954	mother smoking	CYP1A1	8 sites	850K array	significa hypome
Aung MT 2021[14]	cohort study	H	97	trace metals in blood	CYP24A1	cg02143877	450K array	β=5(8.2
Waalkes, M. P. 2004[15]	controlled experiment	H&M	7	placental arsenic	CYP2A4	13 sites	BSP followed by cloning PCR prod-ucts on plasmids	hypome
Bahl, A. 2015[16]	cohort study	H	40	placental hormone	ABCA1	/***	450K array	under-represe
Hogg, K. 2013[17]	cohort study	H	161	placental hormone	CYP11A1NR3C1 CYP19	1 sites	bisulfite pyrosequencing	in appe
Huang, J. Y. 2017[18]	cohort study	H	589	maternal gesta-tional weight gain	ABCA1	/	Epityper	hypome
Veenendaal, M. V. 2012[19]	cohort study	H	759	prenatal hunger	PPAR-α	/	methyquant	hyperm
Talens, R. P. 2012[20]	multicenter RCT Study	H	248	prenatal hunger	ABCA1	/	Epityper	non-significa (0.093)

Author, year (Ref.)	Research type	Object*	Sample size	Factors	Gene	CpG sites	Method	Main result** value)
Witt, S. H. 2018[21]	cohort study	H	282	mother smoking	CYP1A1	cg05549655	450K array	differen (4.76×1
Houde, A. A. 2013[58]	cohort study	H	100	LDL-C and TG	ABCA1	2 sites	bisulfite pyrosequencing	in append
Zhao, N. 2019[59]	controlled experiment	M	20	Maternal betaine exposure	CYP7A1	/	MeDiP*	hyperm (¡0.05)
Yan, Z. 2014[50]	controlled experiment	M	39	polycyclic aromatic hydrocarbons	PPAR-γ	3 sites	bisulfite pyrosequencing	in append
Miura, R. 2018[60]	controlled experiment	H	190	prenatal perfluoroalkyl substance exposure	SLC9A4 CYP2E1	/	450K array	in appe

*H is short for human, M is short for mice, C is short for cell; **Main result refers to the beta-value mean-differences between experiment and control groups, and the detailed results of multiple sites are in the appendix; *** "/" represents that no valid information has been extracted from the original text; BSP is short for bisulfite sequencing PCR; *MeDiP is short for Methylated DNA immunoprecipitation.

Table.2 ADME genes methylation changes induced by environmental pollutants exposure

Author, year (Ref.)	Research type	Object*	Sample size	Factors	Gene	CpG sites	Method	Main result** value)
Gu, T. 2016[22]	case control study	H	954	smoking	CYP11B2	4 sites	bisulfite pyrosequencing	in append
Peng, P. 2014[26]	case control study	H	97	smoking	ABCG1	/***	MSP	non-significa (0.132)
Jiang, W. 2021[25]	cohort study	H&M	7	smoking	CYP1A2	cg11473616	850K array	hypome (¡0.01)
Jin, Y. 2010[23]	case control study	H	40	smoking	CYP1A1	/	methyquant	hyperm
Al Koudsi, N. 2010[24]	cohort study	H	161	smoking	CYP2A6	/	BSP followed by cloning PCR products on plasmids	non-significa

Author, year (Ref.)	Research type	Object*	Sample size	Factors	Gene	CpG sites	Method	Main result** value)
Shang, Y. 2013[28]	controlled experiment	M	589	dust mite	SLC8A3	/	BSP followed by cloning PCR products on plasmids	hyperm
Liang, Y. 2021[61]	cohort study	H	248	PM2.5	CYP1B1	/	MethylTarget	hypome (¡0.05)
Amenya, H. Z. 2016[29]	controlled experiment	M	282	Dioxins	CYP1A1	2 sites	MSRE-qPCR*	hypome (¡0.05)
Li, H. 2014[62]	control study	M	100	N-hexane	CYP11A1 CYP17A1 CYP1A1	/	MeDiP	hyperm
Jiménez-Garza, O. 2020[63]	controlled experiment	H	124	toluene exposed	CYP2E1	/	bisulfite pyrosequencing	hypome (¡0.05)
Jiménez-Garza, O. 2015[64]	cohort study	H	190	benzene exposure	CYP2E1 GSTP1	10 sites	bisulfite pyrosequencing	in appe

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Table.3 ADME genes methylation changes induced by obesity and diet

Author, year (Ref.)	Research type	Object*	Sample size	Factors	Gene	CpG sites	Method	Main result** value)
Parsanathan, R. 2019[37]	controlled experiment	M&C	/	high fat diet	CYP2R1 CYP27A1 CYP27B1 CYP24A1 VDR	/	MSRE-PCR	significa (¡0.05)
Cifani, C. 2015[38]	control study	M	56	high fat diet	PPAR-γ	6 sites	Bisulfite Pyrosequencing	non-significa (¿0.05)

Author, year (Ref.)	Research type	Object*	Sample size	Factors	Gene	CpG sites	Method	Main result** value)
Ge, Z. J. 2014[39]	controlled experiment	M	36	high fat diet	PPAR-α	14 sites	BSP followed by cloning PCR products on plasmids	in append
Ács, O. 2017[65]	cohort study	H	82	obesity	CYP27B1	/	Bisulfite Pyrosequencing	non-significa (¿0.05)
Akinyemiju, T. 2018[30]	cross-sectional study	H	614	obesity	ABCG1	cg06500161	450K array	β=0.02 (1.08×1
Braun, K. V. E. 2017[66]	cohort study	H	1485	blood lipids	ABCG1	cg06500161	450K array	in append
Pfeiffer, L. 2015[32]	cohort study	H	3603	blood lipids	ABCG1	3 sites	450K array	in append
Dekkers, K. F. 2016[31]	cohort study	H	3269	blood lipids	ABCG1	2 sites	450K array	in append
Guay, S. P. 2014[33]	cohort study	H	98	blood lipids	ABCG1	1 sites	bisulfite pyrosequencing	in append
Geurts, Y. M. 2018[67]	case control study	H	5361	BMI	SLC9A1 SLC45A3 ABCC1	3 sites	450K array	in appe
Mendelson, M. M. 2017[68]	cohort study	H	3743	BMI	ABCG1 SLC1A5	5 sites	450K array	in appe
Shah, S. 2015[69]	cohort study	H	2884	BMI	ABCG1	cg06500161	450K array	significa (2.85×1
Demerath, E. W. 2015[70]	cohort study	H	2107	BMI	ABCG1 SLCO3A1	4 sites	450K array	in append
Wang, Y. 2020[41]	case control study	H	81	vitamin D	CYP24A1 CYP27B1	/	BSP followed by direct sequencing	non-significa
Anderson, C. M. 2015[42]	prospective study	H	48	vitamin D	CYP27B1	/	MeDiP, 450K array	hyperm ([?]0.05

Author, year (Ref.)	Research type	Object*	Sample size	Factors	Gene	CpG sites	Method	Main result** value)
Ahmad Najar, R. 2016[40]	controlled experiment	M	36	folic acid	ABCG2	/	methylation-sensitive high-resolution melting PCR	hypome
Colacino, J. A. 2012[34]	cohort study	H	49	nutrition intake	LMO2	cg33870264	bead array	hyperm (6.64×1
Thaler, R. 2009[35]	case control study	H	80	nutrition intake	MnSOD	/	BSP followed by direct sequencing	hyperm

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Table.4 ADME genes methylation changes induced by drugs

Author, year (Ref.)	Research type	Object*	Sample size	Factors	Gene	CpG sites	Method	Main result** value)
Lei Zhang, 2016[43]	controlled experiment	M&C	4	berberine	CYP2B6 CYP3A4	13 sites	MeDiP, Epityper	hypome
Wang, X. K. 2014[47]	controlled experiment	C	30	afatinib	ABCG2	/	BSP followed by cloning PCR prod-ucts on plasmids	hyperm
McLaughlin, P. 2017[45]	cohort study	H	21	methadone	ABCB1 CYP2D6	/	bisulfite pyrosequencing	hyperm
Martín, V. 2013[71]	controlled experiment	C	/	melatonin	ABCG2	/	MSRE-qPCR	hyperm
Lin, R. 2013[72]	controlled experiment	C	40	cisplatin	SLC22A1 SLC22A2 SLC22A3	/	MSP	hyperm
Li, X. 2017[44]	cohort study	H	438	aspirin	ABCB1	CpG21,22	bisulfite pyrosequencing	significa
García-Calzón, S. 2017[46]	cohort study	H	42	metformin/ insulin	SLC22A1 SLC22A3 SLC47A1	31 sites	450K array	in appe

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Table.5 ADME genes methylation changes induced by gender

Author, year (Ref.)	Research type	Object*	Sample size	Factors	Gene	CpG sites	Method	Main result** value)
Yan, Z. 2014[50]	controlled experiment	M	124	polycyclic aromatic hydrocarbons&gender	PPAR-γ	/	bisulfite pyrosequencing	/
Gu, T. 2016[22]	case control study	H	192	smoking& gender	CYP11B2	4 sites	bisulfite pyrosequencing	in appe
Peng, P. 2014[26]	case control study	H	139	smoking& gender	ABCG1	/	MSP	in appe
Sen, A. 2015[49]	cohort study	H	43	lead exposure& gender	GPX1	/	450K array	in appe
Guay, S. P. 2014[33]	cohort study	H	98	blood lipids& gender	ABCG1	1 sites	bisulfite pyrosequencing	in appe
Penaloza, C. G. 2014[48]	controlled experiment	H	/	gender	CYP1A1 CYP7B1 CYP2E1	/	bisulfite pyrosequencing	/

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Table.6 ADME genes methylation changes induced by other factors

Author, year (Ref.)	Research type	Object*	Sample size	Factors	Gene	CpG sites	Method	Main result** value)
Park, C. S. 2019[52]	cohort study	H	221	race	CYP21A2 SLC22A15	/	850K array	/
Kumsta, R. 2016[73]	cohort study	H	52	Severe psychosocial deprivation	CYP2E1	9 sites	bisulfite pyrosequencing	in appendi
Kacevska, M. 2012[53]	controlled experiment	H	72	age	CYP3A4	75 sites	bisulfite pyrosequencing	/
Wang ZY,2020[74]	cohort study	H	59	explosion	SOD3	/	450K array	hyperm

Author, year (Ref.)	Research type	Object*	Sample size	Factors	Gene	CpG sites	Method	Main result** value)
Huang RL,2020[75]	case control study	H	193	steroid	ABCB1	3 sites	MethylTarget	in append
An, F. 2021[51]	case control study	H	115	inflammation	ABCA1	8 sites	bisulfite pyrosequencing	/
Medina-Aguilar, R. 2016[76]	controlled experiment	C	/	resveratrol	SLC35E	3 sites	250K array	/
Guay, S. P. 2014[55]	cohort study	H	88	age	ABCA1	/	bisulfite pyrosequencing	hyperm (0.02)
Košir, R. 2012[57]	controlled experiment	H&M	/	circadian	CYP17A1	/	MSRE-PCR	hypome
Gong, C. 2012[54]	cohort study	C	1423	nano-SiO_2	PARP	/	BSP followed by cloning PCR products on plasmids	hypome
Wjst, M. 2010[56]	cohort study	H	384	season	CYP27B1 CYP24A1	/	bisulfite pyrosequencing	/

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Discussion

Personalized medicine is attached more and more importance since late 1990s. Personalized medicine can better cope with individual differences in the therapy, thus bringing better clinical outcomes to patients. Individual difference is mainly caused by the ADME process of drugs in human body, especially caused by drug-metabolizing enzymes and transporters. These protein activities are regulated by kinds of individual factors, such as genetic polymorphism, medicine combination and age. On the other hand, changes in epigenetic characteristics of genes can cause differences in mRNA expression. Epigenetic differences, especially DNA methylation, in ADME genes have attracted more and more attention, but the upstream regulatory factors and mechanism still unclear. Studies showed non-genetic factors may affect the DNA methylation level of genes. This systematic review was conducted to summarizes individual factors and their effects on methylation of ADME genes and to provide insights into the inner mechanism.

The systemic review searched all studies from 2000 till now and 63 articles were included totally. Half of all studies (n=32) were cohort study of population. We summarized six aspects of individual factors from the perspective of personalized medicine: parental exposure, environmental pollutants exposure, obesity and

diet, drugs, gender and others. Common individual factors, for example, high fat diet, obesity and smoking left marks on the DNA methylation. Most studies reported significant changes in methylation results, and fewer published no significant results. Publication bias may exist. Whether the CpG sites were reported was not related to publishing year or sample size, but may be related to detection method and experimental funds. The factor with the largest number of studies and the largest sample size was obesity. The possible reason was that obesity has become a major global concern, and over-weight people are easier to collect. Some individual factors had a central tendency on methylated ADME genes and CpG sites, for instance, BMI and ABCG1. However, several key ADME genes, such as CYP2C19, CYP2D6 and CYP3A5, were not involved. The reason might be that the initiators of these studies focused on pathogenesis, while the impact of individual factors on drug metabolism via epigenetic regulating could be paid more attention.

Although most studies included did not explore deeply into mechanism, they provided a new sight of how individual factor influence human metabolism. Yang Song et al. reported arsenic led ABCA1 hypermethylation via reactive oxygen species (ROS) pathway[77]. Arsenic-treated cells were found hypermethylation of the ABCG1 promoter and a dose-dependent decrease in ROS generation. Two conceptual models was proposed to explain the arsenic-induced methylation process, but neither model satisfactorily represented each step of the process[78]. S-adenosylmethionine (AdoMet) was the methyl group donor in both models. Dioxins induced CYP1A1 promoter demethylation via aryl hydrocarbon receptor (Ahr)[29]. Ahr is a highly conserved nuclear receptor that mediates toxic response to environmentally persistent organic pollutants, PAHs included. Using siRNA knockout method, Tet2, Tet3, and Tdg were also found play important role in the process. Besides, changes in methylation can be used as markers for cancer detection, side effects, or drug efficacy. There is evidence that resistance to chemotherapeutics is associated with promoter hypermethylation of ABCG2[6].

Various epidrugs were developed reverse epigenetic markers, for example, DNMT inhibitors, Vidaza (5-Azacytidine) and Dacogen (Decitabine), will lead to global methylation level alteration[79, 80]. However, epidrugs were unspecific and bring many concerns in clinical application because of apparent cytotoxicity during treatment[81]. At present, in addition to epidrugs, changes in our personal behavior habits could also change some epigenetic markers. Kaliman et al. found that intensive practice of mindfulness meditation could lead to alterations of H4ac and H3K4me3, as well as a decreased expression of RIPK2 and COX2 compared to control group[82]. Either epidurgs or behavior's impact on ADME genes methylation has not been reported yet.

Recommendation for the future research

The included studies had some drawback and weakness. Cohort study or clinical controlled trial are more recommended, and as many samples as possible should be included. Experiments should provide both raw and processed data to ensure rigor. It is best to use mathematical models to quantify the weights of influencing factors. The mechanisms how individual factors influence epigenetics and more individual factors should be studied.

Strengths and limitations

The strengths of the research are that research types and research objects are listed. We can figure out the current research stages. Moreover, we classify and analyze the research on individualized factors, and propose six aspects of common individualized factors for the first time. We not only describe the results of various experiments, but also search papers to make a conjecture about the possible mechanism pathway.

The limitations of the research are that most studies only published the correlation, we do not know the causal relationship between the factors and DNA methylation. Furthermore, the regulatory mechanism behind that is still unclear. There may be a complex network regulation mechanism, and DNA methylation epigenetics is only one of the pathways. Some studies did not exclude the mixed factors. Our findings are based on included studies. Positive results are more likely to be published, so our findings may be biased.

Conclusion

The individualized differences in drug response require more precise personalized strategies to achieve better clinical outcomes. Some individual factors account for these individual differences through affecting ADME gene expression. The expression of ADME gene is not only determined by the nucleotide sequence, but also affected by epigenetic. This review summarized the effects of individual factors on DNA methylation of ADME genes, and attempted to provide epigenetic insights in explaining individual differences in clinical treatment by combining DNA methylation of ADME gene and expression. There are six kinds of factors that are summarized: parental exposure, environmental pollutants exposure, obesity and diet, drugs, gender and others. Most studies reported significant methylation changes, but few mechanistic findings were reported. Many clinical studies included showed that such findings can be translated into clinical practice with clinical significance. The epigenetic mechanism underlying the effects of individual factors remained to be studied.

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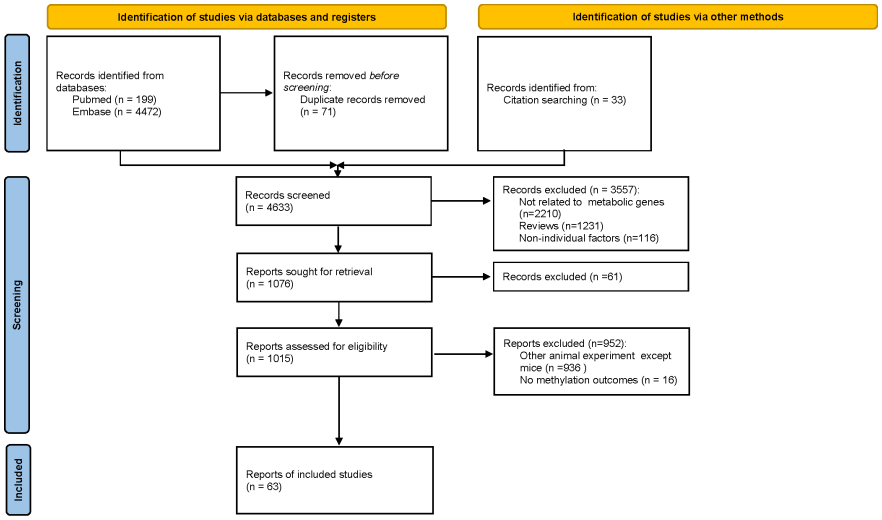

Fig.1 Systematic review flow chat

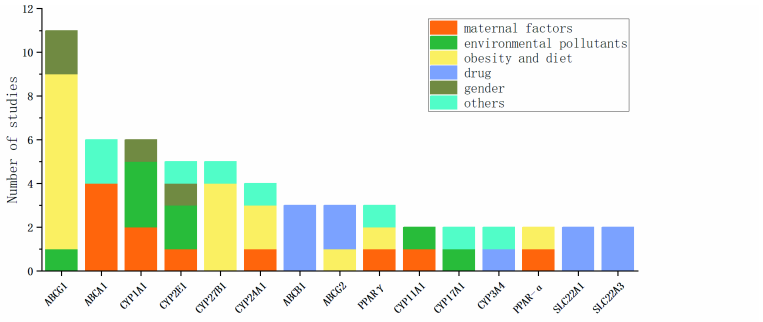

Fig.2 Frequency of reported genes in the studies