REVIEW ARTICLE

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An integrative review of associations between polymorphic variants and the metabolic syndrome

Associação de variantes polimórficas com síndrome metabólica: uma revisão integrativa

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Abstract

The pathogenesis of metabolic syndrome, i.e. of each of its components, is complex and has not been entirely elucidated. As a result, it is very difficult to establish a definition of which clinical factors are the most important determinants of its development. The objective of this review is to describe Brazilian scientific research investigating associations between the metabolic syndrome and genetic factors. We selected fifteen studies that met the inclusion and exclusion criteria. Our analysis revealed that there is a modest volume of Brazilian studies investigating relationships between genes, their polymorphic variants and the metabolic syndrome and its risk factors. Therefore, more studies are needed to better understand the biological roles played by genetic polymorphisms and their relationships with metabolic syndrome or its risk factors.

Keywords: genetic polymorphism; metabolic syndrome; hypertension; obesity; insulin resistance; dyslipidemias.

Resumo

A patogênese da síndrome metabólica, ou seja, de cada um de seus componentes, é complexa e não totalmente elucidada. Por isso, há grande dificuldade em se estabelecer uma definição de quais fatores clínicos e biológicos seriam os principais determinantes no seu desenvolvimento. Esta revisão tem como objetivo caracterizar a produção científica brasileira que aborda o estudo da síndrome metabólica associada aos fatores genéticos. Foram incluídos 15 estudos, levando em consideração os critérios de inclusão e exclusão. Nossa análise revela uma razoável quantidade de trabalhos brasileiros que investigam a relação de genes e suas variantes polimórficas com a síndrome metabólica e seus fatores de risco. Dessa forma, ressalta-se a necessidade de mais trabalhos que examinem melhor o papel biológico ou a relação dos polimorfismos genéticos em pacientes com síndrome metabólica ou com seus fatores de risco.

Palavras-chave: polimorfismo genético; síndrome metabólica; hipertensão; obesidade; resistência à insulina; dislipidemia.

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INTRODUCTION

Metabolic syndrome (MS) is used as a clinical tool for identifying patients with metabolic risk of cardiovascular diseases.[1] In general, MS can be classified as a group of metabolically interrelated pathophysiologic cardiovascular risk factors that have origins in complex disorders and are subject to both environmental and genetic influences.[2,3] The pathogenesis of MS, i.e., of each of its components, is complex and has not been entirely elucidated. As a result, it is very difficult to establish a definition of which clinical factors are the most important determinants of its development. Nevertheless, there is consensus on the principal components of MS that are associated with increased cardiovascular morbidity and mortality: excess weight, elevated arterial blood pressure, and disorders of sugar and lipid metabolism.[2,4-7]

Since it is a multifactorial disorder, both the genetic factor and the environmental factor are important to understanding the interactions between all of the components of risk of development of MS. Moreover, many different gene loci are involved in expression of the components of energy metabolism, which makes it a very complex task to determine the influence of gene-environment and gene-gene interactions on each of the different cardiovascular risk factors.[8]

The most common class of markers in the human genome are small variations in DNA sequences caused by localized substitution mutations, known as single nucleotide polymorphisms (SNPs) and accounting for around 90% of sequence differences.[9] There will be 3 million differences between any two people in their roughly 10,0000 different amino acids.[10] However, the great majority of single nucleotide mutations are rare in the population, and a polymorphism must have a frequency of at least 1% of the population to be considered an SNP.

One of the principal objectives of research into SNP is to understand the genetics of human phenotypical variations and particularly the genetic bases of complex human diseases.[11,12] Genetic factors can explain part of the increase in cardiovascular risk,[13] because many different genes are involved in controlling the different metabolic pathways. The mechanisms controlled by gene alleles include inflammatory processes, platelet activity, neurohormonal activity (renin-angiotensin system), lipid metabolism, and oxidative stress.[14]

Genome studies have led to identification of many genetic markers of cardiovascular risk/protection in different populations around the world, notably the genes IL1RA, CD14, PON1, ALOX5AP, loci 9p 21.3, and PON1 (Met55Leu and Gln192Arg).[15-18] Furthermore, studies suggest that the roles played by these cardiovascular risk factors may vary between ethnic groups.[19-22] These studies indicate that genetic polymorphisms distributed differently in populations of different ethnicities play a fundamental role in the presence of the ethnic/racial differences observed in MS.

Against this background, the objective of this study is to profile Brazilian scientific output describing studies of the associations between MS and its genetic factors.

METHODOLOGY

This is an integrative review of the literature, of a descriptive and exploratory character, based on the results of electronic searches for academic publications on the subject of current genetic research into MS in Brazil.

The choice of databases to be searched took into consideration the fact that each has its own peculiarities, area of concentration, and focus. The databases chosen were those considered relevant to the subject investigated: SciELO® (Scientific Electronic Library Online), PubMed Central® (developed and maintained by the National Center for Biotechnology Information, NCBI), and the Biblioteca Virtual em Saude (BVS) Brazil. In addition to these databases, Google Scholar® was also consulted to give a wider overview of publications and provide a basis for comparison with the results from the other databases.

The electronic searches were conducted during June of 2017 and the search strategies were defined after selection of the databases. The keywords "polymorphism", "metabolic syndrome", and "Brazil" were used, combined using Boolean logical operators to refine and specify the searches. The keywords were used in Portuguese and English, depending on the requirements of each database.

Studies were selected according to the following inclusion criteria: 1) publications in magazines or journals; 2) publications that discussed the main subject (polymorphisms and MS); and 3) work published during the preceding 5 years (2013 to 2017). The criterion for exclusion was title, keywords, and abstract that did not cover the subject and did not meet the inclusion criteria.

After selection of studies, according to the inclusion and exclusion criteria, information from them was input to a form designed for recording the data collected. This instrument was created in a spreadsheet to facilitate organization, grouping, and analysis of the data, interpretation of the results, and presentation of the review. It comprises columns for insertion of

reference, category, objective, methodology, results, and conclusions.

RESULTS

Fifteen studies were selected for the review. All of them were conducted with the general objective of investigating relationships between genes and their polymorphic variations and MS and its risk factors (obesity, insulin resistance, hypertension, and lipid profile abnormalities). The genes investigated to test for associations were NOS, MMP-2, IL6R, VDR, UCP1, ADRB3, ApoE, IRS-1, PPARG, APOA5, LEP, LEPR, NR3C1, GR, IL1B, IL2, IL4, IL8, IL10, IFNγ, TNFa and ACE.

The first search was run on all four databases using just the keywords with Boolean operators: "polymorphism" AND "metabolic syndrome" AND "Brazil". The database that returned the fewest results was SciELO, with just one article, followed by BVS with 17, PubMed with 38, and Google Scholar with 4,430. In order to adapt and refine the analysis, searches were run again with a filter to restrict results to the preceding 5 years (2013-2017). It will be observed that Google Scholar® returned the highest number of studies, which is because its search metric is different to those used by the other databases. This database was therefore used to identify possible differences between the results generated by the others, since each has its own metric, which can lead to different results, as can articles contained in one database but not in another.

After filtering by availability and reading, consisting of reading the title, abstract, and keywords of each study, 15 articles were selected (Table 1).[23-37] the remainder were excluded from the analysis, because they were not aligned with the subject of the review or with the inclusion parameters.

The periodicals' fields of knowledge revealed an interesting variety of journals from different subject areas, as follows: three on nutrition, two on genetics, two on biology, and eight specifically focused on areas of medicine (hypertension, diabetes, metabolism, and endocrinology). This diversity of fields of knowledge was also observed in the qualifications of the study authors, who were qualified in the following areas: biophysics, nutrition, psychology, psychiatry, medicine, cardiovascular pharmacology, human and molecular genetics, gynecology and obstetrics, toxicogenomics and nutrigenomics, nephrology, endocrinology, cellular and molecular biology, and pharmacology.

With relation to the types of study, all publications were the result of cross-sectional, prospective studies with population samples. Eight of these were case-control studies comparing results for a given condition in carriers against "normal" subjects. The samples used in the studies varied in terms of age group: six with adults, five with adolescents, and three with children.

The majority of the studies were conducted in the state of São Paulo (10), followed by Rio Grande do Sul (4) and the Distrito Federal (1). None of the studies were conducted in states in the North or Northeast regions of Brazil (Figure 1).

REVIEW

The foci of identification of the studies selected were investigations of associations between a given genetic polymorphism of a gene involved in the process of a metabolic pathway and risk factors for MS, such as obesity, dyslipidemia, insulin resistance, and hypertension (Table 2).[23-37]

The relationship between differences in the polymorphic frequency of genes involved in obesity and MS was analyzed in five studies with samples of adults and adolescents with different population profiles. One of them found that nutritional control and exercise may be more effective at preventing risks associated with MS in individuals with the A allele for polymorphism 48867A> C (Asp358Ala) IL6R (rs2228145).[23] A study by Belo et al.[24] investigated polymorphisms of the MMP-2 gene and their relationship with metabolic risk factors in obese children and adolescents. The study showed that arterial blood pressure is related to concentrations of MMP-2 in circulation, that the CC genotype of the C polymorphism was more common in both controls and in obese subjects, and that the CT genotype and the T allele for polymorphism C (-735) T are less common in the obese. Brondani et al.[25] evaluated associations between the -3826A/G polymorphism of the UCP1 gene and the Trp64Arg polymorphism of the ADRB3 gene with type 2 Diabetes mellitus and MS characteristics. In this study these polymorphisms were not associated with diabetes, but they may have a combined effect on modulation of excess weight/obesity and on HDL-C levels in Brazilian Caucasian patients with type 2 Diabetes mellitus. Another study stressed the importance of the relationship between the C allele at locus -174 of the IL-6 gene, which was found to be involved in the inflammatory process with occurrence of MS and pathogenesis of visceral obesity.[26] Finally, another study demonstrated that genotypes of the ACE I/D gene can influence regulation of insulin resistance and reduction of cholesterol levels of low density lipoproteins in obese adolescents on long-term multidisciplinary interventions, including medical care, psychological therapy, nutritional programs, and physical exercises.[27]

Table 1. Studies selected after application of selection criteria.

Authors/data	Title	Journal	Database
Vargas et al. (2013)[23]	Influence of the 48867A>C (Asp358Ala) IL6R polymorphism on response to a lifestyle modification intervention in individuals with metabolic syndrome	Genet Mol Res	PubMed & BVS
Belo et al. (2013)[24]	Effect of metabolic syndrome risk factors and MMP-2 genetic variations on circulating MMP-2 levels in childhood obesity	Mol Biol Rep	PubMed
Brondani et al. (2014)[25]	The presence of at least three alleles of the ADRB3 Trp64Arg (C/T) and UCP1-3826A/G polymorphisms is associated with protection to overweight/obesity and with higher high-density lipoprotein cholesterol levels in Caucasian-Brazilian patients with type 2 diabetes	Metab Syndr Relat Disord	PubMed
Teixeira et al. (2015)[26]	Association of IL-6 polymorphism -174G/C and metabolic syndrome in hypertensive patients	Biomed Res Int	PubMed
Almeida et al. (2017)[27]	Different metabolic responses induced by long-term interdisciplinary therapy in obese adolescents related to ACE I/D polymorphism	J Renin Angiotensin Aldosterone Syst	PubMed
Martins et al. (2017)[28]	HPA axis dysregulation, NR3C1 polymorphisms and glucocorticoid receptor isoforms imbalance in metabolic syndrome	Diabetes Metab Res Rev	PubMed
Schuch et al. (2013)[29]	Relationship between Vitamin D Receptor gene polymorphisms and the components of metabolic syndrome	Nutr J	PubMed & BVS
Gelaleti et al. (2015)[30]	IRS-1 gene polymorphism and DNA damage in pregnant women with diabetes or mild gestational hyperglycemia	Diabetol Metab Syndr	PubMed
Franca et al. (2016)[31]	APOA5 polymorphisms associated with lipid metabolism in Brazilian children and adolescents	Genet Mol Res	PubMed
Maintinguer Norde et al. (2017)[32]	Influence of IL1B, IL6 and IL10 gene variants and plasma fatty acid interaction on metabolic syndrome risk in a cross-sectional population-based study	Clin Nutr	PubMed
Teixeira et al. (2014)[33]	Diversity of apolipoprotein E genetic polymorphism significance on cardiovascular risk is determined by the presence of metabolic syndrome among hypertensive patients	Lipids Health Dis	PubMed
Faria et al. (2017)[34]	Effects of leptin and leptin receptor SNPs on clinical- and metabolic-related traits in apparent treatment-resistant hypertension	Blood Press	PubMed
Miranda et al. (2013)[35]	eNOS polymorphism associated with metabolic syndrome in children and adolescents	Mol Cell Biochem	PubMed
Rodrigues et al. (2017)[36]	Decreased comfort food intake and allostatic load in adolescents carrying the A3669G variant of the glucocorticoid receptor gene	Appetite	PubMed
Rocha et al. (2015)[37]	Prevalence of the rs1801282 single nucleotide polymorphism of the PPARG gene in patients with metabolic syndrome	Arch Endocrinol Metab	PubMed

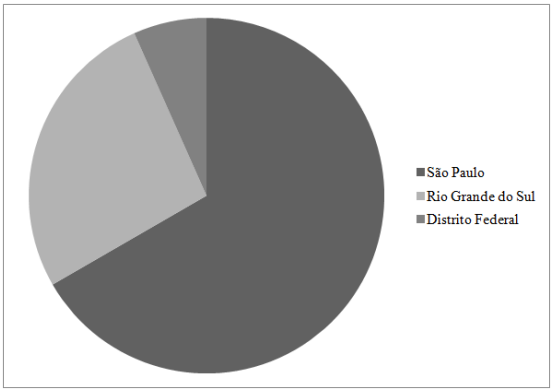

Figure 1. Distribution of articles by states.

Three studies with different populations analyzed links between insulin resistance, diabetes mellitus, and MS. One study analyzed the NR3C1 polymorphism, expression of glucocorticoid receptor (GR) isoforms and cytokines, demonstrating that patients with MS exhibited reduced hypothalamus-pituitary-adrenal axis (HPA) sensitivity to glucocorticoid feedback and that dysregulation of this axis could contribute to pathogenesis of MS.[28] An investigation of the relationships between the 2228570 C>T and 1544410 A>G polymorphisms of the VDR gene and MS in adults suggests that they could influence insulin release and insulin resistance, but was unable to determine their influence on components of MS.[29] A study by Gelaleti et al.[30] evaluated presence of the Arg972 polymorphism of the IRS-1 gene in pregnant women with diabetes or mild gestational hyperglycemia and their newborn infants. The results showed that this polymorphism was more prevalent in the newborn infants of women with diabetes and mild gestational hyperglycemia.

Table 2. Parameters investigated in the studies selected.

Authors/data	Location of research	Sample studied	Parameters associated with MS
Vargas et al. (2013)[23]	Rio Grande do Sul	Adults	Lifestyle changes and SNP 48867A> C (Asp358Ala) of the IL6R gene
Belo et al. (2013)[24]	São Paulo	Children and adolescents	Polymorphisms of the MMP-2 gene and MS
Brondani et al. (2014)[25]	Rio Grande do Sul	Adults	Polymorphism -3826A / G of the UCP1e gene, polymorphism Trp64Arg of the ADRB3 gene and type 2 Diabetes mellitus and MS
Teixeira et al. (2015)[26]	São Paulo	Adults	MS with polymorphism 174G/C of the IL-6 gene in hypertensive patients
Almeida et al. (2017)[27]	São Paulo	Adolescents	Obesity, insulin resistance and the I/D polymorphism of the ACE gene
Martins et al. (2017)[28]	Ribeirão Preto	Adults	SNPs of the GR gene, cytokines, and the hypothalamus-pituitary-adrenal axis
Schuch et al. (2013)[29]	São Paulo	Adults	VDR polymorphism, insulin release, insulin resistance, and HDL cholesterol
Gelaleti et al. (2015)[30]	São Paulo	Adults and children	Polymorphism Arg972 of the IRS-1 gene, diabetes, and hyperglycemia
Franca et al. (2016)[31]	São Paulo	Children and adolescents	Polymorphisms of the APOA5 gene and lipid metabolism
Maintinguer Norde et al. (2017)[32]	São Paulo	Adults	SNP of genes IL-6, IL-1β, and IL-10 and plasma fatty acids
Teixeira et al. (2014)[33]	São Paulo	Adults	Polymorphism of the ApoE gene and MS in hypertensive patients
Faria et al. (2017)[34]	São Paulo	Adults	SNPs rs7799039 and rs1137101 in the LEP and LEPR genes and hypertension
Miranda et al. (2013)[35]	São Paulo	Children and adolescents	Polymorphisms of the eNOS gene and MS
Rodrigues et al. (2017)[36]	Rio Grande do Sul	Adolescents	SNP A3669G of the GR gene and preferences for palatable foods and metabolic, behavioral, and neural results
Rocha et al. (2015)[37]	Brasília	Adults	Anthropometric, biochemical, and hemodynamic variables and SNP rs1801282 of the PPARG gene

Associations between genes, lipid metabolism, and MS were investigated in three studies. One of these investigated polymorphism of the APOA5 gene and lipid metabolism, demonstrating that this is a genetic risk factor for MS in children and adolescents.[31] Another investigation noted that the G allele of the IL6 SNP rs1800795 gene was associated with increased probability of MS and that the plasma fatty acid profile interacts with variants of the IL1B and IL10 genes to modulate manifestation of MS.[32] Another study with the ApoE polymorphism, involved in regulation of cholesterol and triglycerides metabolism found an association between the ApoE gene and the syndrome.[33]

De Faria et al. studied relationships between genes and hypertension,[34] but their analyses did not detect direct associations between patients with apparently treatment resistant hypertension and the leptin gene (LEP) or the leptin receptor gene (LEPR). Miranda et al.[35] examined interactions between the eNOS gene and cardiovascular risk and their results suggested that while eNOS haplotypes were not relevant, the CC genotype of the T (786) C polymorphism is associated with MS in obese children and adolescents.

A study by Rodrigues et al.[36] tested whether presence of the G variant of SNP A3669G of the GR gene would affect preference for palatable foods and alter metabolic, behavioral, and neural results. Their results showed that the GC allele is associated with reduced sensitivity which, on the cognitive and behavioral levels, results in altered ingestion of foods and response to emotional stress. Additionally, they found that this genetic variant can play an important role in reduction of risk of metabolic and psychiatric diseases.

Another study tested for interactions between the PPARG gene and anthropometric, biochemical, and hemodynamic variables in patients with MS. Their results suggested that the rs1801282 polymorphism of this gene is not correlated with predisposition to MS.[37]

DISCUSSION

Our analysis shows that despite the reasonable number of Brazilian studies investigating the relationship between genes and their polymorphic variants and MS and its risk factors, these studies are published in periodicals and written by authors from a range of areas of knowledge. This diversity is evidence of the importance of increasing knowledge of this subject in several different areas of healthcare. Additionally, the diversity of the subjects who made up the study samples demonstrates the relevance of metabolic abnormalities and cardiovascular diseases at all phases of human development and in groups with distinct populational genetic structures. Nevertheless, it can be concluded that there is a need to increase the number of studies in order to better examine the biological role played by genetic polymorphisms in patients with MS or with its risk factors.

With regard to the locations where research is conducted, our searches show that there research is highly concentrated, primarily in the state of São Paulo. This state has the majority of the country's state universities and, consequently, of the more traditional and most consolidated research centers, which are also those with better infrastructure and finance. It can be observed that Brazil needs more research of this type, considering the importance of the subject, the huge scale of the country, and its highly diverse population structure.

FINAL COMMENTS

In summary, this integrative review has demonstrated that there are insufficient studies investigating the genetic polymorphisms involved in development of MS and its risk factors in samples from the Brazilian population. As a consequence, the results are insufficient to provide an understanding of the complex genetic structure of the county's racially diverse population. Finally, it is very important that more studies be conducted to attempt to identify the roles and relationships of genetic polymorphisms in manifestations of MS and its risk factors.

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ARTIGO DE REVISÃO

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Associação de variantes polimórficas com síndrome metabólica: uma revisão integrativa

An integrative review of associations between polymorphic variants and the metabolic syndrome

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Resumo

A patogênese da síndrome metabólica, ou seja, de cada um de seus componentes, é complexa e não totalmente elucidada. Por isso, há grande dificuldade em se estabelecer uma definição de quais fatores clínicos e biológicos seriam os principais determinantes no seu desenvolvimento. Esta revisão tem como objetivo caracterizar a produção científica brasileira que aborda o estudo da síndrome metabólica associada aos fatores genéticos. Foram incluídos 15 estudos, levando em consideração os critérios de inclusão e exclusão. Nossa análise revela uma razoável quantidade de trabalhos brasileiros que investigam a relação de genes e suas variantes polimórficas com a síndrome metabólica e seus fatores de risco. Dessa forma, ressalta-se a necessidade de mais trabalhos que examinem melhor o papel biológico ou a relação dos polimorfismos genéticos em pacientes com síndrome metabólica ou com seus fatores de risco.

Palavras-chave: polimorfismo genético; síndrome metabólica; hipertensão; obesidade; resistência à insulina; dislipidemia.

Abstract

The pathogenesis of metabolic syndrome, i.e. of each of its components, is complex and has not been entirely elucidated. As a result, it is very difficult to establish a definition of which clinical factors are the most important determinants of its development. The objective of this review is to describe Brazilian scientific research investigating associations between the metabolic syndrome and genetic factors. We selected fifteen studies that met the inclusion and exclusion criteria. Our analysis revealed that there is a modest volume of Brazilian studies investigating relationships between genes, their polymorphic variants and the metabolic syndrome and its risk factors. Therefore, more studies are needed to better understand the biological roles played by genetic polymorphisms and their relationships with metabolic syndrome or its risk factors.

Keywords: genetic polymorphism; metabolic syndrome; hypertension; obesity; insulin resistance; dyslipidemias.

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INTRODUÇÃO

A síndrome metabólica (SM) tem sido utilizada como ferramenta clínica para identificar pacientes com risco metabólico de doenças cardiovasculares[1]. De forma geral, a SM pode ser classificada como um conjunto de fatores fisiopatológicos de risco cardiovascular relacionados metabolicamente com origem em desordens complexas, com influência ambiental e genética[2,3]. A patogênese da SM, ou seja, de cada um de seus componentes, é complexa e não totalmente elucidada. Por isso, há grande dificuldade em se estabelecer uma definição de quais fatores clínicos são os principais determinantes no seu desenvolvimento. Contudo, há um consenso sobre os principais componentes da SM que estão associados ao aumento da morbimortalidade cardiovascular: excesso de peso, aumento da pressão arterial, distúrbios do metabolismo dos glicídios e lipídios[2,4-7].

Por ser um distúrbio multifatorial, o fator genético, assim como o fator ambiental, é importante para o entendimento das interações entre todos os componentes de risco para o desenvolvimento da SM. Nesse contexto, vários lócus gênicos estão envolvidos na expressão dos componentes do metabolismo energético, o que torna complexo determinar a influência das interações gene-ambiente e gene-gene de cada um dos fatores de risco cardiovascular[8].

Pequenas variações na sequência de DNA causadas por mutações pontuais do tipo substituição, denominadas polimorfismos de nucleotídeo único (SNPs), representam a classe de marcadores mais comum no genoma humano, correspondendo a cerca de 90% das diferenças de sequência[9]. Logo, há 3 milhões de diferenças de uma base e cerca de 10.0000 aminoácidos diferentes entre quaisquer duas pessoas[10]. Entretanto, a maior parte das mutações de um nucleotídeo único é rara em uma população, sendo necessário que o polimorfismo apresente uma frequência de pelo menos 1% na população para ser considerado SNP.

Um dos principais objetivos de pesquisas com SNP é compreender a genética da variação fenotípica humana e, especialmente, a base genética das doenças humanas complexas[11,12]. Os fatores genéticos podem explicar parte do aumento do risco cardiovascular[13], o que se justifica pelo envolvimento de diversos genes com o controle de diferentes vias metabólicas. Os mecanismos determinados por alelos gênicos incluem processos inflamatórios, atividade das plaquetas, atividade neuro-hormonais (sistema renina-angiotensina), metabolismo de lipídeos e estresse oxidativo[14].

Estudos genômicos levaram à identificação de muitos marcadores genéticos de risco/proteção cardiovascular em diferentes populações do mundo, destacando-se os genes IL1RA, CD14, PON1, ALOX5AP, loci 9p 21.3, PON1 (Met55Leu e Gln192Arg)[15-18]. Além disso, estudos sugerem que o papel desses fatores de risco cardiovascular pode variar em função do grupo étnico[19-22]. Assim, essas pesquisas indicam que polimorfismos genéticos distribuídos distintamente entre populações de etnias diferentes exercem papel fundamental na presença das diferenças etnicorraciais observadas na SM.

Nesse contexto, este estudo tem como objetivo caracterizar a produção científica brasileira que aborda o estudo da associação entre SM e seus fatores genéticos.

METODOLOGIA

Estudo do tipo revisão integrativa de literatura, de caráter descritivo e exploratório, realizado a partir da busca de trabalhos acadêmicos que versam sobre a seguinte temática: pesquisas genéticas atuais sobre a SM no Brasil.

A triagem das bases de dados para a pesquisa foi realizada levando-se em consideração que cada base tem sua peculiaridade, área de concentração e enfoque. Dessa forma, foram escolhidas as bases consideradas relevantes ao tema de pesquisa, como SciELO® (*Scientific Electronic Library Online)*, PubMed Central®, desenvolvida e mantida pelo Centro Nacional de Informações Biotecnológicas (*National Center for Biotechnology Information,* NCBI), e Biblioteca Virtual em Saúde (BVS) Brasil. Além dessas bases de dados, o Google Acadêmico®/Google Scholar® também foi consultado para uma observação mais ampla das publicações e comparação dos resultados com as outras bases.

A busca pelos trabalhos foi realizada no mês de junho de 2017 e, uma vez escolhidas as bases, definiu-se a estratégia de busca. Assim, foram determinadas as palavras-chave polimorfismo, síndrome metabólica e Brasil a partir do tema da pesquisa, as quais foram combinadas com operadores lógicos (*booleanos*) a fim de refinar e especificar a pesquisa. Utilizaram-se as palavras-chave em português e inglês de acordo com as exigências da base.

A seleção dos trabalhos foi realizada de acordo com os seguintes critérios de inclusão: 1) publicações em revistas ou jornais; 2) publicações que versassem sobre a temática principal (polimorfismo e SM); e 3) publicações nos últimos 5 anos, entre 2013 e 2017. E, para os critérios de exclusão, foram suprimidos trabalhos que após a leitura do título, palavras-chave ou resumo não abordavam o tema e que não se enquadravam nos parâmentros de inserção.

Após a seleção dos estudos, segundo os critérios de inclusão e exclusão, as informações dos trabalhos

foram inseridas em formulário próprio para registros dos dados coletados. Tal instrumento foi criado em planilha a fim de organizar, agrupar e facilitar a análise dos dados, a interpretação dos resultados e a apresentação da revisão. Este foi constituído por colunas para inserir referência, categoria, objetivo, metodologia, resultados e conclusão do trabalho.

RESULTADO

Os 15 trabalhos incluídos na revisão apresentavam, de forma geral, o propósito de investigar a relação de genes e suas variantes polimórficas com a SM e seus fatores de risco (obesidade, resistência à insulina, hipertensão e alterações no perfil lipídico). Para verificar tal associação, os genes pesquisados foram: eNOS, MMP-2, IL6R, VDR, UCP1, ADRB3, ApoE, IRS-1, PPARG, APOA5, LEP, LEPR, NR3C1, GR, IL1B, IL2, IL4, IL8, IL10, IFNγ, TNFa e ACE.

A primeira busca gerou resultados utilizando apenas as palavras-chave combinadas com operadores *booleanos*: "polimorfismo" AND "síndrome metabólica" AND "Brasil" para as quatro bases de dados. A base que apresentou menos resultados foi o SciELO, com apenas um artigo, seguido pelo BVS com 17, PubMed com 38 e Google Acadêmico com 4.430. Para adaptar e refinar nossa análise, a segunda pesquisa foi realizada aplicando o filtro dos últimos 5 anos (2013-2017). Observa-se que o Google Acadêmico® foi a base que apresentou o maior quantitativo de trabalhos, pois possui uma métrica de busca diferente da utilizada pelas outras bases de dados. Assim, essa base foi utilizada para visualizar as possíveis diferenças entre os resultados gerados pelas outras bases, pois cada uma das bases tem sua própria métrica, o que pode gerar resultados distintos, como artigos contidos em uma base e não em outra.

Ao aplicar o filtro de disponibilidade e leitura, que consiste em ler o título, resumo e palavras-chave de cada trabalho, foram selecionados 15 artigos (Tabela 1)[23-37]. Os demais foram excluídos da análise, pois não estavam alinhados com o tema da pesquisa e com os parâmetros de inclusão.

Quanto à área de conhecimento dos periódicos, identificou-se uma variedade interessante de revistas pertencentes às seguintes áreas: três de nutrição, duas de genética, duas de biologia e oito especificamente da área médica (hipertensão, diabetes, metabolismo, endocrinologia). Essa diversidade na área de conhecimento foi verificada também na formação dos autores dos trabalhos, os quais apresentaram as seguintes formações: biofísica, nutrição, psicologia, psiquiatria, medicina, farmacologia cardiovascular, genética humana e molecular, ginecologia e obstetrícia, toxigenômica e nutrigenômica, nefrologia, endocrinologia, biologia celular e molecular, e farmacologia.

Com relação ao tipo de estudo, todos os trabalhos foram resultado de pesquisas transversais, prospectivas e com amostras populacionais. Destes, oito eram trabalhos do tipo caso-controle que comparam seus resultados entre portadores e "normais" para determinada condição. Quanto aos sujeitos que integraram as pesquisas, observa-se que os estudos aplicaram suas análises em indivíduos de faixa etária distinta: seis em adultos, cinco em adolescentes e três em crianças.

A maioria dos trabalhos encontrados na busca foi realizado no estado de São Paulo (10), seguido de Rio Grande do Sul (4) e Distrito Federal (1). Nenhum trabalho foi realizado na região Norte e Nordeste (Figura 1).

REVISÃO

Identificou-se que os trabalhos selecionados apresentaram como foco a investigação da associação de um determinado polimorfismo genético de um gene envolvido no processo da via metabólica com fatores de risco para SM, como obesidade, dislipidemia, resistência à insulina e hipertensão (Tabela 2)[23-37].

A relação entre diferenças na frequência polimórfica de genes envolvidos com a obesidade e SM foi analisada em cinco estudos com perfis populacionais distintos, compostos por adultos e adolescentes. Um deles apontou que o controle nutricional e a prática de exercícios poderiam prevenir os riscos associados à SM de forma mais eficiente em indivíduos com o alelo A para o polimorfismo 48867A> C (Asp358Ala) IL6R (rs2228145)[23]. O trabalho de Belo et al.[24] investigou polimorfismos do gene MMP-2 e sua relação com os fatores de risco metabólicos em crianças e adolescentes obesos. Esse estudo demonstrou que a pressão arterial está associada às concentrações de MMP-2 circulantes, que o genótipo CC para o polimorfismo C foi mais comum tantos nos indivíduos controles quanto nos obesos, e que o genótipo CT e o alelo T para o polimorfismo C (-735) T são menos comuns na obesidade. A associação do polimorfismo -3826A / G do gene UCP1 e do polimorfismo Trp64Arg do gene ADRB3 com diabetes melito tipo 2 e características de SM foi avaliada por Brondani et al.[25]. Nessa pesquisa, os polimorfismos não foram associados com o diabetes, mas podem ter um efeito combinado na modulação do excesso de peso/obesidade e dos níveis de HDL-C em pacientes caucasiano-brasileiros com diabetes melito tipo 2. Outro estudo enfatiza a importância da relação do alelo C no lócus -174 do gene IL-6, o qual encontra-se envolvido no processo inflamatório com a ocorrência da SM e a patogênese da obesidade visceral[26]. Por fim, outro estudo demonstra

Tabela 1. Estudos selecionados após aplicação dos critérios de seleção.

Autores/data	Título	Jornal/revista	Base de dados
Vargas et al. (2013)[23]	Influence of the 48867A>C (Asp358Ala) IL6R polymorphism on response to a lifestyle modification intervention in individuals with metabolic syndrome	Genet Mol Res	PubMed e BVS
Belo et al. (2013)[24]	Effect of metabolic syndrome risk factors and MMP-2 genetic variations on circulating MMP-2 levels in childhood obesity	Mol Biol Rep	PubMed
Brondani et al. (2014)[25]	The presence of at least three alleles of the ADRB3 Trp64Arg (C/T) and UCP1-3826A/G polymorphisms is associated with protection to overweight/obesity and with higher high-density lipoprotein cholesterol levels in Caucasian-Brazilian patients with type 2 diabetes	Metab Syndr Relat Disord	PubMed
Teixeira et al. (2015)[26]	Association of IL-6 polymorphism -174G/C and metabolic syndrome in hypertensive patients	Biomed Res Int	PubMed
Almeida et al. (2017)[27]	Different metabolic responses induced by long-term interdisciplinary therapy in obese adolescents related to ACE I/D polymorphism	J Renin Angiotensin Aldosterone Syst	PubMed
Martins et al. (2017)[28]	HPA axis dysregulation, NR3C1 polymorphisms and glucocorticoid receptor isoforms imbalance in metabolic syndrome	Diabetes Metab Res Rev	PubMed
Schuch et al. (2013)[29]	Relationship between Vitamin D Receptor gene polymorphisms and the components of metabolic syndrome	Nutr J	PubMed e BVS
Gelaleti et al. (2015)[30]	IRS-1 gene polymorphism and DNA damage in pregnant women with diabetes or mild gestational hyperglycemia	Diabetol Metab Syndr	PubMed
Franca et al. (2016)[31]	APOA5 polymorphisms associated with lipid metabolism in Brazilian children and adolescents	Genet Mol Res	PubMed
Maintinguer Norde et al. (2017)[32]	Influence of IL1B, IL6 and IL10 gene variants and plasma fatty acid interaction on metabolic syndrome risk in a cross-sectional population-based study	Clin Nutr	PubMed
Teixeira et al. (2014)[33]	Diversity of apolipoprotein E genetic polymorphism significance on cardiovascular risk is determined by the presence of metabolic syndrome among hypertensive patients	Lipids Health Dis	PubMed
Faria et al. (2017)[34]	Effects of leptin and leptin receptor SNPs on clinical- and metabolic-related traits in apparent treatment-resistant hypertension	Blood Press	PubMed
Miranda et al. (2013)[35]	eNOS polymorphism associated with metabolic syndrome in children and adolescents	Mol Cell Biochem	PubMed
Rodrigues et al. (2017)[36]	Decreased comfort food intake and allostatic load in adolescents carrying the A3669G variant of the glucocorticoid receptor gene	Appetite	PubMed
Rocha et al. (2015)[37]	Prevalence of the rs1801282 single nucleotide polymorphism of the PPARG gene in patients with metabolic syndrome	Arch Endocrinol Metab	PubMed

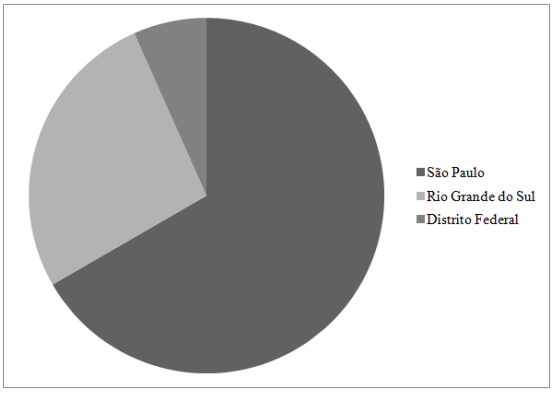

Figura 1. Distribuição dos artigos por estado.

que os genótipos do gene ACE I/D podem influenciar na regulação da resistência à insulina e na redução dos níveis de colesterol de lipoproteínas de baixa densidade em adolescentes obesos submetidos a intervenção multidisciplinar de longo prazo, como acompanhamento médico, terapia psicológica, programas nutricionais e exercícios físicos[27].

Uma ligação genética entre resistência à insulina, diabetes melito e SM foi analisada em três trabalhos de populações diferentes. O trabalho que analisou o polimorfismo NR3C1, expressão de isoformas de receptores de glucocorticóide (GR) e citocinas demonstrou que pacientes com SM apresentaram diminuição da sensibilidade do eixo hipotálamo-hipófise-adrenal (HPA) ao feedback dos glucocorticóides e que a desregulação desse eixo pode contribuir para a patogênese da SM[28]. A investigação da relação dos polimorfismos 2228570 C>T e 1544410 A>G do gene VDR com a SM em adultos sugere que eles podem influenciar a secreção de insulina e a resistência à insulina, porém não consegue determinar sua influência nos componentes da SM[29].

Tabela 2. Parâmetros pesquisados nos trabalhos selecionados.

Autores/data	Local da pesquisa	Amostra estudada	Parâmetros associados com SM
Vargas et al. (2013)[23]	Rio Grande do Sul	Adultos	Modificação do estilo de vida e o SNP 48867A> C (Asp358Ala) do gene IL6R
Belo et al. (2013)[24]	São Paulo	Crianças e adolescentes	Polimorfismos de gene MMP-2 com a SM
Brondani et al. (2014)[25]	Rio Grande do Sul	Adultos	Polimorfismo -3826A / G do gene UCP1e o polimorfismo Trp64Arg do gene ADRB3 com diabetes mellitus tipo 2 e SM
Teixeira et al. (2015)[26]	São Paulo	Adultos	SM com o polimorfismo 174G/C do gene IL-6 em hipertensos
Almeida et al. (2017)[27]	São Paulo	Adolescentes	Obesidade, resistência à insulina e o polimorfismo I/D do gene ACE
Martins et al. (2017)[28]	Ribeirão Preto	Adultos	SNPs do gene GR, citocinas com o eixo hipotálamo-hipófise-adrenal
Schuch et al. (2013)[29]	São Paulo	Adultos	Polimorfismo VDR com a secreção de insulina, resistência à insulina e colesterol HDL
Gelaleti et al. (2015)[30]	São Paulo	Adultos e crianças	Polimorfismo Arg972 no gene IRS-1 com diabetes e hiperglicemia
Franca et al. (2016)[31]	São Paulo	Crianças e adolescentes	Polimorfismos do gene APOA5 no metabolismo lipídico
Maintinguer Norde et al. (2017)[32]	São Paulo	Adultos	SNP de genes IL -6, IL-1β e IL-10 e os ácidos graxos plasmáticos
Teixeira et al. (2014)[33]	São Paulo	Adultos	Polimorfismo do gene ApoE com a SM em hipertensos
Faria et al. (2017)[34]	São Paulo	Adultos	SNPs rs7799039 e rs1137101 nos genes LEP e LEPR com hipertensão
Miranda et al. (2013)[35]	São Paulo	Crianças e adolescentes	Polimorfismos no gene eNOS com a SM
Rodrigues et al. (2017)[36]	Rio Grande do Sul	Adolescentes	SNP A3669G do gene GR com preferências por alimentos palatáveis, resultados metabólicos, comportamentais e neurais
Rocha et al. (2015)[37]	Brasília	Adultos	Variáveis antropométricas, bioquímicas e hemodinâmicas com SNP rs1801282 do gene PPARG

O trabalho de Gelaleti et al.[30] avaliou a presença do polimorfismo Arg972 do gene IRS-1 em mulheres grávidas com diabetes ou hiperglicemia gestacional leve e em seus recém-nascidos. Seus resultados verificaram que o polimorfismo foi mais prevalente em recém-nascidos de mulheres diabéticas e com hiperglicemia gestacional leve.

A associação entre genes com o metabolismo de lipídeos e a SM foi investigada em três pesquisas. O trabalho que pesquisou o polimorfismo do gene APOA5 e o metabolismo lipídico demonstrou que este é um fator de risco genético da SM em crianças e adolescentes[31]. Em outra investigação, nota-se que o gene IL6 SNP rs1800795 alelo G está associado a probabilidades aumentadas de SM e que o perfil de ácidos graxos do plasma interage com as variantes do gene IL1B e IL10 para modular a manifestação da SM[32]. Outro estudo com o polimorfismo ApoE, envolvido na regulação do metabolismo de colesterol e triglicerídeos verificou um associação entre o gene ApoE e a síndrome[33].

A relação entre genes e hipertensão foi pesquisada por Faria et al.[34], que em suas análises não encontraram associação direta entre pacientes hipertensos aparentemente resistentes ao tratamento com os genes da leptina (LEP) e do receptor de leptina (LEPR). Miranda et al.[35] examinaram a interação do gene eNOS com o risco cardiovascular e seus resultados sugerem que, embora os haplótipos de eNOS não sejam relevantes, o genótipo CC para o polimorfismo T (786) C está associado a SM em crianças e adolescentes obesos.

A pesquisa de Rodrigues et al.[36] verificou se a presença da variante G do SNP A3669G do gene GR afetaria as preferências por alimentos palatáveis e alteraria os resultados metabólicos, comportamentais e neurais. Seus resultados destacam que o alelo GC está associado com a redução de sensibilidade que, em níveis cognitivos e comportamentais, se traduz em ingestão alterada de alimentos e resposta ao estresse emocional. Além disso, constatou-se que essa variante genética pode desempenhar um papel importante na redução do risco de doenças metabólicas e psiquiátricas.

Outra pesquisa verificou a interação do gene PPARG com variáveis antropométricas, bioquímicas e

hemodinâmicas em portadores de SM. Seus resultados sugerem que o polimorfismo rs1801282 desse gene não está correlacionado com a predisposição à SM[37].

DISCUSSÃO

Nossa análise revela que, apesar da razoável quantidade de trabalhos brasileiros que investigam a relação de genes e suas variantes polimórficas com a SM e seus fatores de risco, essas pesquisas demonstram uma variedade de áreas de conhecimentos dos periódicos e dos autores. Essa diversidade reforça e evidencia a importância no aprofundamento do conhecimento desse tema em diversas áreas da saúde. Além disso, a diversificação dos sujeitos que integraram as pesquisas demonstra a relevância das alterações metabólicas e das doenças cardiovasculares em todas as fases do desenvolvimento humano e em grupos com estrutura genética populacional distinta. No entanto, observa-se que é necessário aumentar o número de pesquisas que examinem melhor o papel biológico dos polimorfismos genéticos em pacientes com SM ou com seus fatores de risco.

Quanto ao local da pesquisa, nossa busca demonstra o grande fluxo e concentração de pesquisas realizadas principalmente no estado de São Paulo. Esse estado concentra a maioria das universidades estaduais e consequentemente dos centros de pesquisas mais antigos, consolidados, estruturados e melhor financiados nacionalmente. Observa-se que mais pesquisas são imprescindíveis no país devido à relevância da temática, à grande extensão do país e à sua estrutura populacional diversificada.

CONSIDERAÇÕES FINAIS

Em suma, esta revisão integrativa demonstrou que as investigações de polimorfismos genéticos envolvidos no desenvolvimento da SM e seus fatores de risco em amostras populacionais brasileiras são insuficientes. Dessa forma, os resultados são ínfimos para compreender a complexa estrutura genética da população miscigenada do país. Finalmente, ressalta-se a importância de mais trabalhos que busquem identificar o papel ou a relação dos polimorfismos genéticos na manifestação da SM e de seus fatores de risco.

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