Progress related in genetic research on Kawasaki disease

Abstract

Kawasaki disease, It is a systemic vasioinflammatory disease in children of Asian descent, Coronary artery injury is its major complication, The disease has now become a major cause of acquired heart disease in children. The etiology of Kawasaki disease is not fully clear, and its pathogenesis is related to infection, immune damage and genetic susceptibility. Genetic research has made new progress in recent years, with the aim of trying to better discover the intrinsic link of pathogenesis and treatment, in order to better understand the pathogenesis and obtain better treatment. The exact etiology of KD is still unknown. However, increasing evidence supports that genetic factors play a key role in their occurrence and development. Studying the changes in related genes in children with Kawasaki disease will help to understand the relationship between the changes in this gene and the onset of Kawasaki disease and its coronary damage and the sensitivity of various treatments, and will contribute to the better treatment of Kawasaki disease.

keyword

Kawasaki disease gene polymorphism Coronary vein injury

Introduction

Kawasaki disease (KD), also known as the cutaneous and mucosal lymphoid syndrome (MCLS), it is a kind of acute, self-limiting vasculitis, often found in infants under 5 years old, and it is also one of the main causes of acquired heart disease in children。It was first reported by the Japanese doctor Kawasaki (Dr. Tomisaku Kawasaki) in 1967。About 20 - 30% of untreated Kawasaki cases develop coronary artery lesions, so early detection and early treatment are particularly important. The genetic background of Kawasaki disease is still unclear, and immune activation and cytokine secretion are involved in the pathogenesis of Kawasaki disease. Genetic variation often affects cytokine expression, and changes in single-nucleotide polymorphisms in genes may lead to functional changes of the corresponding cytokines. Current candidate gene studies and genome-wide association studies explored the relationship between gene effects and Kawasaki disease and found that it is associated with polymorphisms in multiple genes with susceptibility to Kawasaki disease, vascular damage, IVIG treatment resistance, incomplete Kawasaki disease, etc. It is speculated that Kawasaki disease is also a disease mediated together by multiple gene interactions. Current Kawasaki disease susceptibility genes at home and abroad, such as the MPO、ITPKC、ACE、CASP3、TGFs、BLK、CD40、 FCGR2A、KCNN2、PECAM1、NMNAT2、HCP5, more research[1], This review summarizes new advances in investigating related susceptibility genes in patients with Kawasaki disease.

一. MPO (myeloperoxidase, MPO), Pediatric myeloperoxidase。Is a member of the peroxidase subfamily, A hemoglobin that can regulate autoimmune and inflammatory responses, It plays a close role in the early warning of cardiovascular disease,

It is one of the important biological markers of vascular inflammation, Presed in Tianqing granules where the cytosol binds to the membrane, Secreted by inflammatory and immune cells, such as monocytes and neutrophils, When the body is stimulated, Activated inflammatory, immune cells rapidly release MPO, However, the granules in the MPO are secreted into the extracellular space in either degranulation form or exocytosis, Catalyze hydrogen peroxide and chloride ion to generate hypochlorite acid, Producduce a range of reactive oxygen species with broad biological effects, And leads to excessive oxidation, Lead to immune dysfunction, Damaged endothelial cells, Among them, the coronary artery damage is more common[2]。Therefore, any abnormal expression and release of MPO may exacerbate inflammation and tissue damage [3~5]。Studies have found that there is excess oxide in the body of children with KD, and it can lead to oxidative stress in the body, and then speculated that there may be an association between MPO gene and the occurrence of KD[6]。Therefore, the MPO gene may be a potential key factor in the pathogenesis of KD.

1. ACE Angiotensin converting e11. zy / ne, ACE,The total length of the human angiotensin-converting enzyme gene is 21 1 (b, with 26 exons and 25 introns, and a 287-b p insertion / deletion (I / D) polymorphism in intron 16 is associated with multiple cardiovascular diseases.[7]The renin-angiotensin system is important in the pathogenesis and pathological development of hypertension and coronary heart disease (c dishes), while angiotensin converting ase (ACE) plays an important role in this system。ACE can transform AngI into An911, stimulate the release of aldosterone (aldosterone) in adrenal globoid band cells, resulting in water and sodium retention, activation of blood plasminogen suppressor worker (PA1-I), and hypertrophy of vascular smooth muscle cells.At the same time, ACE can also promote the degradation of bradykinin, and bradykinin can act on the endothelial and monokinin receptor to produce NO, promote vascular smooth muscle cell hyperplasia, the formation of excessive cell stroma and acute and chronic vasospasm, and accelerate the formation of coronary arteriosclerosis[8]。ACE is mainly controlled by the ACE gene, which has three genotypes: insertion (I) / insertion (I), insertion (I), deletion (D) / deletion (D), heterozygous deletion (D) / insertion (I), and its insert is equivalent to a can u repeat sequence, approximately 287 bp.After the PcR reaction, the insert fragment was obtained at 490 bp and about 190 bp was deleted[9]。The study showed that nearly 50% of the difference in individual ACE levels is determined by the ACE genes, and the ACE I / D polymorphism in the ACE gene significantly affects the serum A C E levels[10]。The serum ACE levels of the KD group showed the highest type DD and the lowest type II.This study indicates that the ACE gene I / D polymorphism is closely related to the differences in serum ACE levels between unrelated individuals, which is consistent with that reported by RIGAT et al.[11]

2. BLK. Genome-wide association analysis studies showed a correlation between BLK genes and KD[12]。The BLK gene is located in the 8 p 23 to p 22 region and encodes the tyrosine kinase BLK protein.The BLK protein is one of the members of the Src tyrosine kinase family.The BLK gene expression is tightly controlled by the B cells[13]。The function of BLK in the human body is not well understood, but studies

have inferred that BLK acts as a tyrosine kinase to transduce signals downstream to the B cell receptor to activate nuclear transcription factors, and that BLK gene expression levels may influence the tolerance mechanism of B cells, leading to autoimmune disorders[14,15]。The BLK gene SNP locus (rs2736340) T allele was associated with KD susceptibility, while the SNP locus (rs2618476) polymorphism was associated with KD susceptibility, with the C allele as a risk factor.The BLK gene is associated with KD, suggesting that autoimmunity or antibody-mediated immune response may be one of the mechanisms leading to the pathogenesis of KD, and the results provide some help to better understand the pathogenesis of KD[16]。

3. cAsP3 Cypon protease 3, the rsll3420705 gene polymorphism has some correlation with the onset of Kawasaki disease in children and its occurrence of coronary artery damage。The rsl 13420705 site is located in the non-coding region of the CASP3 gene 57, with a GGAA sequence similar to the binding site of the transcription factor one-activated T cell nuclear factor (NFAT), which opens up the transcription of IL-2 and other cytokines.When the rsll3420705 site of CAsP3 gene is G allele, it can bind to NFAT and activate T cells as an enhancer factor of T cell receptor signal. CASP3 expression is up-regulated, while in children with Kawasaki disease, this site G becomes A, weakening its enhancement effect, affecting NFAT binding, significantly decreasing cAsP3 gene expression, limiting the apoptosis of T cells and activated T cells, initiating the onset of Kawasaki disease[17]。When cAsP3 expression decreases, NFATc2 cleavage reduces [18], resulting in increased multiple inflammatory factors and also promoting Kawasaki disease.These genetic variants also led to increased T cell proliferation and decreased apoptosis during the inflammatory response. In the acute and subacute stages of Kawasaki disease, peripheral blood activated T cells abnormally increased [19], which also provided the conditions for the occurrence of Kawasaki CASP3Gene polymorphism is associated with susceptibility to Kawasaki disease in Chinese Han children and is not associated with coronary artery damage is obvious. It still needs to be carried out a one-step comprehensive analysis in terms of sample size and population[20]。

4. CD40 It is a member of the TNF receptor superfamily 5, which is located in the 20q12-q13.2 region in the plasma membrane, participates in protein complex assembly, inflammatory response, immune response signaling and other processes, and studies show that the CD40-CD40L signaling pathway is involved in the pathological process of inflammatory response [21]; Increased expression of CD40 leads in increased content of inflammatory cytokines [22]。Increased expression of CD40 leads in increased content of inflammatory cytokines.Therefore, mutations or altered expression of the CD40 gene may affect the various response processes of the pathway, leading to disease development.Using genome-wide association analysis studies, Lee et al [22] showed a correlation between the CD40 gene and KD, but the SNP loci studied were different from those presented in this paper;Kuo et al [23] The association of CD40 with KD was studied in the Taiwanese population。Studies have been shown that the SNP locus rs1535045 is associated with susceptibility to KD, that TT is a risk genotype, and that children with this genotype are more likely to develop KD than Taiwanese children, possibly due to regional and ethnic differences. The SNP locus rs4810485, which is located above the intron of the CD40 gene, is not correlated with the susceptibility to KD, possibly because the SNP does not affect the function and expression of the protein.The speculation

that the SNP site rs1535045 is associated with KD susceptibility that presumably affects the expression of CD40, and then inflammatory signaling pathways such as CD40-CD40L requires further experiments to demonstrate.The main critical complication of crisis life in KD is coronary artery injury, which can lead to thrombosis, CAD, CAA rupture and even sudden death [24], Therefore, we should early observe whether KD children are vulnerable to coronary artery injury.However, no polymorphisms at two SNP sites in CD40 gene could be associated with coronary artery injury; there was no correlation between SNP site rs4810485 of CD40 gene and KD susceptibility in Han population in central Chinese mainland。While the TT genotype of rs1535045 is [25] associated with susceptibility to Kawasaki disease. Most children with KD have been characterized by conjunctival congestion, rash, lymph node enlargement, hand and foot edema and oral mucosal lesions. Some studies have found that the SNP site (rs1569723) has no correlation with conjunctival congestion, hand and foot edema and oral mucosal lesions;However, there is a correlation with rash and lymph node enlargement, children with KD with AA genotype are more likely to develop rash and lymph node enlargement. The possible cause is that CD40 participates in inflammatory signaling, and the balance of signaling pathway leads to rash and lymph node enlargement.No SNP polymorphism in the CD40 gene was associated with CAL, the SNP in CD40 (rs1569723) was associated with KD susceptibility in Han population, and this polymorphism was associated with rash and lymph nodes[26].

5. FGF23 Fibroblast growth factor 23 (FGF) It is an active substance found in the growth of the brain and the pituitary gland in the 20th century. It was named for its role after purification in the 1970s。The FGF family is involved in a range of physiological functions such as embryonic development, cell differentiation, organogenesis, tissue repair, tumor growth and invasion [27]。FGF23 is a member of the FGF19 subgroup in the fibroblast growth factor family, localizes to chromosome 12p13 and, like most members of the FGF, contains two large intron sequences that divide the functional region into three exon regions.FGF23 is mainly derived from bone tissue, produced and secreted by osteoblasts and expressed in other tissues and organs, including liver, heart, parathyroid gland, and bone marrow, FGF23 plays an important

role in maintaining renal phosphorus and VitD homeostatic balance by forming a complex with FGF receptor or αKlotho co-receptors.It have found that FGF23 is related in addition to calcium and phosphorus regulation, but also to cardiac damage. It has been shown to cause increased mortality in patients with end-stage renal disease (ESRD), and is closely related to the high incidence of cardiovascular events in ESRD [28-30]，Moreover, FGF23 is closely related to left ventricular hypertrophy, left ventricular dysfunction, atrial fibrillation, coronary artery vascular lesions, and heart failure severity and prognosis [31-34]。Studies have pointed out that FGF23 is an independent risk factor for cardiac damage and may be a predictor of changes in cardiovascular pathology [34]，this makes the study of polymorphisms at FGF23 loci important。

6．GRIN3A GRIN3A gene polymorphism associated with Kawasaki disease The GRIN3A gene is located in the 9p34 region and contains nine exons encoding the N-methyl-D-aspartate (NMDA) receptor subunit 3A, which plays an important role in ion transmembrane transport in the glutamate metabolic pathway [35]。Activation of NMDA receptors can further activate the inflammatory response in endothelial cells, play a role in systemic vascular inflammation and injury[36]。Activation of NMDA receptors can further activate the inflammatory response in endothelial cells, play a role in systemic vascular inflammation and injury[37]。It indicates that NMDA receptors may be involved in the progression of KD.GRIN3A is a subunit of the NMDA receptor, so alterations in this gene may affect the function of the NMDA receptor, thus leading to the occurrence of related diseases。RNA interference experiments have also demonstrated that the GRIN3A gene can regulate

the inflammatory response in endothelial cells by affecting the expression levels of IL-6 and IL-8[38] , it shows that this gene plays an important role in vasculitis disease。

7 .HLA—E It is a ligand for CD94 / NKG2A and CD94 / NKG2C。CD94 / NKG2A is a class of inhibitory receptors that are selectively expressed on the surface of NK cells, vascular endothelial cells, and some subsets of T cells, belonging to the type C lectin superfamily.It transduced inhibitory signals into the inner cell by binding to a specific ligand, thus negatively regulating the killing of NK cells and T cells[39,40]。KD is a multisystem involvement disease based on immune-mediated vascular inflammation.It is speculated that HLA-E, upregulated in KD during KD activation, can attenuate the killing effect of NK cells and T cells, and thus exert its immunosuppressive regulator.Plasma HLA-E levels in children with Kawasaki disease are significantly higher than that of A2, and although the effect of this mononucleate polymorphism (SNP) on the secretion of soluble HLA-E in endothelial cells is unknown, itlogically follows that allelic GG and GA types may affect the formation of plasma soluble HLA-E levels in children with KD.[41]

8. .PLCB4 The PLCB4 gene is located in the p12 region of chromosome 20 and encodes the phospholipase C beta4 protein that catalyzes the formation of 4,5 diphosphatidylinositol 1,4,5 triphosphoinositol, which plays an important role in various physiological functions such as cell morphology, metabolic regulation and signaling[42]。The PLcBl gene encodes proteins in the same family as the PLcB4 gene and performs a similar function.In addition, both genes are involved in regulating the signaling pathways of the inflammatory response, and the gene expression change affects the levels of inflammatory factors such as IL-1 and IL-6, as well as IL-18[43]。The SNP locus (rs6140791) is located

between the PLCBl and the PLCB4 gene, upstream of PLCB4. Our results found that the polymorphism at this locus is associated with CAL formation in children with KD. The C allele is a risk factor for CAL formation (OR=1.838); this result is similar to the study of Lin et al [43] in Taiwan population, indicating that the risk of CAL may be regional or population independent.The molecular mechanism associated at this locus with susceptibility to cAL may be because different alleles affect the transcriptional regulation of PLCBl and (or) PLCB4 genes, which in turn affect the levels of downstream inflammatory factors. It has been found to use siRNA technology to silence the expression of PLCBl and PLCB4 genes, and the levels of downstream inflammatory cytokines are increased[43] , Thus further activating the specific immune response system, causing damage to vascular endothelial cells and other cells[44]。It may eventually lead to CAL occurrence, and the specific molecular mechanisms require further analysis in the future.The polymorphism of the SNP locus (rs6140791) of the PLCBl / PLCB4 gene was associated with CAL susceptibility in children with KD. The C allele is a risk factor; the study also found differences in some immunological indicators between children with KD and children with KD alone, and the specific molecular mechanism requires further investigation[45].

9. **TARC/CCL17** The TARC / CCL17 gene, located in the q13 region of chromosome 16, contains four exons encoding chemokine proteins and plays an important role in the developmental maturation of T cells.TARC / CCL17 is one of the important components of the CC chemokine group, and is a ligand group of the CC chemokine 4 (CCR4) receptor [46] , While CCR4 is selectively expressed in Th2 cells; TARC / CCL17 can function on CCR4 and CCR8 receptors [47]。While CCR4 is selectively expressed in Th2 cells; TARC / CCL17 can function

on CCR4 and CCR8 receptors [48]。Studies show the presence of abnormal Th1 / Th2 proportions in KD patients [49]；In the Taiwanese population, both SNP loci (rs223895 and rs223899) were associated with susceptibility to KD, with the C and A alleles being risk factors, respectively [50]。

Disscussion and Conclusion

Many genes are involved in the development of Kawasaki disease and concurrent CAL.Studies on genetic predisposition can guide the use of genetic diagnostic techniques to identify vulnerable genes, assist in the early detection of high-risk groups in patients with Kawasaki disease, and help clinicians to select specific drugs for individualized treatment.Make the treatment of Kawasaki disease more accurate and individualized.Moreover, patients with Kawasaki disease can obtain new prevention and treatment strategies to improve the prognosis of patients with Kawasaki disease.

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