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The role of infection in Kawasaki syndrome

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Summary

Objectives: To analyse the evidence suggesting a possible infectious origin of Kawasaki syndrome (KS).

Methods: PubMed was searched for all of the studies published over the last 15 years using the key words "Kawasaki syndrome" or "mucocutaneous lymph node syndrome" and "infectious disease" or "genetics" or "vasculitis" or "pathogenesis".

Results: Various levels of evidence support the hypothesis that KS is a complex disease triggered by an infection due to one or more pathogens. Viruses or bacteria may be the primum movens, although no specific infectious agent can be considered definitely etiological. A number of genetic polymorphisms have been identified in subjects with KS, but none of them can currently be considered a real marker of susceptibility.

Conclusions: Various data suggest that KS is intimately related to infectious diseases and that its clinical expression is influenced by predisposing genetic backgrounds, but our knowledge of the infectious agent(s) involved and the genetic characteristics of susceptible children remains only partial. Further studies are needed to address the many still open questions concerning the disease.

Introduction

Kawasaki syndrome (KS), originally called "mucocutaneous lymph node syndrome" in 1967, is an acute multisystem vasculitis that causes generalised inflammatory cell tissue injury starting in the vascular endothelium and is mainly encountered in children aged less than five years regardless of their ethnicity. The injuries are particularly severe in the coronary arteries, which are frequently affected by dilatations, aneurysms or fistulae, especially in patients who do not receive prompt treatment with intravenous immunoglobulins and anti-inflammatory doses of acetylsalicylic acid. Now that rheumatic fever is largely controlled, KS has become the leading cause of acquired heart disease among children in industrialised countries.
As no specific diagnostic test is available, KS is identified on the basis of a constellation of non-specific clinical signs. According to the American Heart Association guidelines,\(^4\) which are shared by most scientific communities throughout the world, a diagnosis requires prolonged fever lasting more than five days and at least four of the following signs: 1) diffuse oral cavity inflammation (including pharyngeal infection), dry fissured lips, and a strawberry tongue; 2) bilateral non-purulent conjunctivitis; 3) heterogeneous skin rashes; 4) angioedema of the extremities (including peripheral erythema, oedema, or induration of the hands or feet); and 5) non-purulent cervical lymphadenopathy exceeding ≥1.5 cm in diameter. In what are known as “incomplete” cases, one or more of these clinical signs may be absent but a diagnosis can still be made if there is echocardiographic evidence of coronary artery abnormalities. Furthermore, a broad range of unusual clinical finding have been reported as defining the “atypical” variant of KS, including aseptic meningitis, peripheral facial nerve palsy, uveitis, gastrointestinal complaints, acalculous gallbladder hydrops, urethritis, testicular swelling, pulmonary nodules, liver impairment with jaundice, and even hemophagocytic syndrome.\(^5\) Laboratory investigations (listed in Table 1) can only support the diagnosis of KS, but they still need to be validated before they can be used in everyday clinical practice.

However, although the clinical features of KS are usually recognisable, its underlying immune mechanisms are still being investigated. Most experts consider it to be the consequence of an abnormal immunological response evoked by one or more widely distributed infectious agents in genetically susceptible individuals, but it still remains a medical enigma.

The main aim of this review is to analyse the available evidence suggesting that KS may have an infectious origin. PubMed was used to search for all of the studies published over the last 15 years using the key words: “Kawasaki syndrome” or “mucocutaneous lymph node syndrome” and “infectious disease” or “genetics” or “vasculitis” or “pathogenesis”. More than 1300 articles were found, but only those published in English or providing evidence-based data were included in the evaluation.

**What is known about Kawasaki syndrome and infections**

Various levels of evidence support the hypothesis that KS is a complex disease initiated by an infection due to one or more pathogens (Table 2). However, no strict and unmistakable correlation between specific infectious agents and the development of the disease has ever been identified.

### Microbiological data

A number of bacterial and viral infectious agents have been sporadically isolated from KS patients. The most frequently implicated bacteria are *Staphylococcus aureus*,\(^6\) *Streptococcus pyogenes*,\(^7\) and atypical pathogens,\(^8\)–\(^10\) and the viruses associated with KS over recent years are Epstein–Barr virus,\(^11\) adenovirus,\(^12\) parvovirus B19,\(^13\) herpesvirus 6,\(^14\) parainfluenza type 3,\(^15\) measles,\(^16\) rotavirus,\(^17\) dengue virus,\(^18\) and human immunodeficiency virus,\(^19\) Varicella.\(^19\) 2009 H1N1 pandemic influenza\(^20\) and Coxackie B3 virus\(^21\) have also been described in patients with KS, but they were equally found in the body fluids of both patients and healthy subjects. Moreover, no relationship was reported between KS and the circulation of the commonest respiratory viruses.\(^22\)

The most recent and numerous studies of KS-related viruses have postulated the etiological role of human coronavirus (HCoV) NL63 and bocavirus,\(^23\)–\(^25\) but this has not been confirmed by subsequent studies.

In order to evaluate the importance of HCoV-NL63 in KS, Shimizu et al. established a multi-institutional collaborative research project to test respiratory samples using real-time polymerase chain reaction (RT-PCR), and found that only one out of 48 KS patients (2%) was positive\(^26\); Domínguez et al. found exactly the same prevalence in nasopharyngeal wash samples from KS patients and healthy controls, but did not find any difference between the two groups.\(^27\) The data regarding bocavirus (a virus that has recently emerged as a possible cause of respiratory infection) are also unconvincing\(^28\); although it was identified in the serum, stool and cerebrospinal fluid of some children with KS, no definitive conclusion could be drawn concerning its etiological role.

The limited etiological importance of the pathogens so far identified seems to be supported by the studies of Benseler et al.\(^29\) and Jordan-Villegas et al.,\(^30\) who found that concomitant infections in children with KS did not alter the response to treatment with intravenous immunoglobulins, and did not influence the risk of coronary artery involvement or affect overall cardiovascular outcomes. However, the lack of any clear relationship between one or more pathogens and the development of KS does not exclude the possibility that a real infectious disease may be involved, and other factors support this hypothesis. On the other hand, the unsuccessful identification of a specific pathogen to which KS could be ascribed has led some authors to postulate that variants of normal flora in the gut, oral cavity or skin of young children with a genetic defect of proper immune maturation do not induce immune tolerance as self commensals, but rather induce an imbalance of the immune system, leading to a hyperimmune reaction and the manifesting KS.\(^32\)

| Table 1 | Laboratory findings supporting a diagnosis of Kawasaki syndrome. |
|---|---|
| 1. C-reactive protein ≥3.0 mg/dL |  |
| 2. Erythrocyte sedimentation rate ≥40 mm/h |  |
| 3. Albumin ≤3.0 g/dL |  |
| 4. Age-relative anaemia |  |
| 5. High alanine aminotransferase levels |  |
| 6. Platelet count ≥450,000/mm³ in the subacute phase of the disease |  |
| 7. White blood cell count ≥15,000/mm³ |  |
| 8. White blood cells/high-power field ≥10 in urinalysis |  |
Histopathological data

Some histological findings strongly suggest that KS has an infectious origin, although they do not identify the responsible pathogen. The most important is that persistent intracytoplasmic inclusion bodies (IIBs) showing amphophilic staining by haematoxylin-eosin and stain for RNA have been found in most of the tissues of patients who have died because of KS. As transmission electron microscopy (TEM) of bronchial epithelia has revealed virus-like particles associated with the IIBs, it was thought that these may be a "footprint" of a viral infection that may persist indefinitely: Rowley et al. speculated that the infection associated with the development of KS could be due to a new and ubiquitous RNA virus that caused only asymptomatic infection or very mild disease in the general population, but KS in genetically selected subjects. It was thought that the first site of infection was the respiratory tract, with further dissemination through macrophages to all body sites, including the medium-sized arteries (mainly the coronary arteries) that are the most crucial targets in KS.

Further findings that strongly support an infectious origin of KS are those of Orenstein et al., who used light microscopy and TEM to study tissue specimens from 32 autopsies, eight heart transplants and an excised coronary aneurysm of patients with KS and identified three different vasculopathic processes: acute self-limited necrotising arteritis (NA), subacute/chronic vasculitis, and luminal myofibroplastic proliferation. On the basis of the changes in coronary and non-coronary arteries during the different phases of KS, they considered NA the only self-limiting process of the three, and that it was consistent with an acute viral infection.

Epidemiological data

Many epidemiological findings regarding KS are consistent with an infectious origin, as they are quite similar to those of various infectious diseases. First of all, there is the occurrence of epidemics because, although cases of KS are diagnosed, there are also sometimes widespread epidemics. In Japan, where nationwide epidemiological surveys of KS have been carried out almost every two years since 1970, three large-scale epidemics were recorded in 1979, 1982, and 1986, with incidence rates that were several times higher than those reported in the previous and following year. Secondly, as in the case of a number of infectious diseases, KS is more frequent in boys, and the male to female ratio is about 1.6. Thirdly (once again as in the case of many infectious diseases), the incidence of KS seems to be closely related to weather conditions, although the predominant season varies from country to country: winter and spring in the United Kingdom, Australia and the USA, and spring and summer in China. Pitzer et al., examined seasonal changes in the age and incidence of KS hospitalisations in the USA, and found that periods of high incidence corresponded to a low average age, and vice versa. Comparison of the observed pattern with those predicted by a suite of models based on different etiological hypotheses, the age-incidence pattern of KS suggested the involvement of an imperfectly immunising infection and/or a persistently infectious agent.

The possible relationship between seasonal variations in the incidence of KS and an infectious aetiology is also supported by data showing that its incidence in the USA inversely correlates with average monthly temperature ($r = -0.47; p < 0.001$) and positively correlates with...
average monthly precipitation ($r = -0.52; p < 0.001$). Moreover, analyses of the three major KS epidemics in Japan, major non-epidemic inter-annual fluctuations of KS cases in Japan and San Diego, and seasonal variations in the incidence of KS in Japan, Hawaii and San Diego have revealed a consistent pattern linking KS cases to large-scale wind currents originating in central Asia and crossing the North Pacific. This seems to indicate that the environmental trigger of KS may be wind-borne, and this has led some experts to suggest that efforts to isolate the causative agent should concentrate on the microbiology of aerosols.

Finally, children in the first months of life only exceptionally develop KS, which supports the hypothesis that most infants are protected by passively acquired specific maternal antibodies against the possible causative agent(s). On the other hand, the very low incidence of KS beyond the fifth year suggests that most children are infected unevenly by one or more of the infectious agents associated with KS in early life and can then mount a long-lasting, strong and protective immune response. Recurrences of KS have been reported in only 1–3% of children, and are best documented in Japan.

**Clinical findings**

The clinical findings of fever, an erythematous pharynx, conjunctival injection, rash, oedema of the extremities and cervical adenitis in patients with KS, and the clear tendency of these signs to resolve spontaneously even without treatment also support an infectious aetiology. A number of viral diseases have a similar clinical picture. Moreover, some of the clinical features of KS, such as mucous membrane erythema and desquamation of the fingers and toes (usually beginning within 2–3 weeks of the onset of fever), overlap those associated with some bacterial diseases that are considered to be a consequence of the superantigen (SA)-mediated activation of T cells leading to the overproduction of cytokines, systemic inflammation and shock. The best examples in this regard are toxic shock syndrome (TSS) and scarlet fever due to *S. aureus*, and streptococcal toxic shock syndrome (STSS) due to *Streptococcus pneumoniae*. The similarity between these conditions and KS has led to the conclusion that, at least in some cases, KS may follow an infection due to an SA-producing pathogen.

A number of SAs have been identified: the most widespread bacterial pathogens are *S. aureus* and *S. pneumoniae*, but *Yersinia pseudotuberculosis*, *Mycoplasma pneumoniae* and *Mycobacterium tuberculosis* have also been associated with SA formation; among viruses, SAs have been found in Epstein Barr virus, rabies virus and mouse leukaemia virus. SAs are a family of potent immunostimulatory proteins whose particular structures and sequences lead to a shared ability to by-pass the mechanism of conventional major histocompatibility complex (MHC)-restricted antigen processing. When an SA is involved, T cell responses are quantitatively and qualitatively different from conventional T cell activation by normal antigens. In particular, SAs activate T cells in a manner that depends on the T cell receptor variable domain (Vβ), and so a large number of T cells can be simultaneously activated. The activation is extremely potent and a number of studies have found that KS is characterised by the marked activation of T cells and monocytes/macrophages, and increased production of IL-1β, TNF-α and IL-6, which are the same immunological findings as those of TSS.

Although some attempts to demonstrate the presence of SA-producing pathogens in children with KS have led to negative results, others have provided data suggesting the direct involvement of SAs. Leung et al. blindly studied bacterial SAs potentially involved in the pathogenesis of KS in cultures of patients in the acute phase and controls, and found SA-producing bacteria in 13 of the 16 patients but in only one of the 15 controls ($p < 0.0001$). Eleven of the 13 toxin-positive cultures from the patients with KS contained toxic shock syndrome toxin (TSST-1) secreting *S. aureus*, and the remaining two contained streptococci producing streptococcal pyrogenic exotoxin B (SPEB) and streptococcal pyrogenic exotoxin C (SPEC). Twelve of the culture-positive patients had toxin-producing *S. aureus* isolated from pharyngeal or rectal cultures, thus suggesting the gastrointestinal tract as the primary entry site. Similar findings of TSST-1-producing *S. aureus* and SPEC-producing streptococci in children with acute KS have been recently published. The SA theory may be supported by anecdotal reports of KS patients with guttate psoriasis because it has been suggested that this form of psoriasis is due to toxin-mediated T cell activation. Furthermore, a number of studies analysing the T lymphocyte receptor repertoire and the titres of antibodies against selected SAs have indirectly demonstrated that these proteins may be related to the development of KS.

In addition, Suemura et al. examined five SA genes in the stools of KS patients, febrile controls and healthy children, and found at least one of the genes in 42 specimens from the patients with KS (70%), in 14 from the febrile group (38.9%), and in seven from the healthy group (26.9%). The detection rate between subjects with and without KS was of at least one of the 5 SA genes ($p = 0.001$), and more than two SA genes were significantly different ($p = 0.002$), thus suggesting the direct involvement of SAs in the development of KS.

**What is known regarding Kawasaki syndrome and genetics**

Despite the direct and indirect evidence supporting the hypothesis that KS is an infectious disease, only "susceptible" subjects seem to develop it and genetics seem to play a role in selecting the patients.

KS occurs throughout the world, but is significantly more common in some Asian countries, such as Japan, Korea and Taiwan. It has been reported that the annual incidence of KS in Japan in 2009 and 2010 was respectively 206.2 and 239.6 per 100,000 children aged 0–4 years; on the contrary, a recent analysis found that the 2009 KS-related hospitalisation rate in the USA was 19 per 100,000 children aged <5 years, and even lower incidence rates have been calculated for a number of European countries. Theoretically, various factors could explain this large difference. The incidence of KS is rapidly increasing throughout the world, and so surveys carried out at
different times may lead to different results. Moreover, although KS is significantly more frequent in younger children than in older children, adolescents or adults, its frequency in younger patients also varies. A comparison of the incidence of KS in Northern European and Japan found that 86.4% of the Japanese patients were aged <5 years, but 67.8% of the cases diagnosed in Norway, Finland, Sweden and Denmark ($p < 0.001$).

The incidence of KS in different regions may be affected by differences in surveillance methods, clinical diagnostic and treatment practices, physician awareness of KS, and the occurrences of KS clusters or outbreaks. However, a global evaluation of all these factors suggests that they are unlikely to be the only reason for such a striking difference. Furthermore, American studies have clearly shown ethnicity-related variations in the incidence of KS: in comparison with white subjects, the incidence is twice as high among Asians and Pacific Islanders, and about 1.5 times higher among black subjects. Similarly, its incidence in Hawai (the state with the highest proportion of Asians and Pacific Islanders) is 2.5 times higher than that reported for the continental USA. It has also been reported that the incidence of KS is 6–10 times higher among the siblings of KS patients than in the general population, and that children with KS are more likely to have parents who have had the disease. It has been calculated that the inheritability of KS (i.e. the ratio of the incidence of KS between siblings and the general population) is only slightly less than that of type 1 diabetes and about four times more than that of allergic asthma.

All of the above findings strongly suggest that genetic factors play a substantial role in the occurrence of KS, but studies of the genetic characteristics of KS patients have not definitively identified which genetic marker(s) may favour or protect humans from developing of KS, or regulate its clinical severity.

Several candidate genes, mainly chosen among those related to innate and acquired immunity, cardiovascular function, and vascular remodelling, have been tested in patients with KS (Table 3). Results were frequently negative or conflicting, particularly when the studies enrolled a limited number of patients and were carried out in populations with significant racial differences that impact the allele frequency of some of the single nucleotide polymorphisms (SNPs) analysed in the studies. Good example at this regard are the data collected on the role of matrix metalloproteinases (MMPs), Fc gamma receptors (FCGR) and of CD40 ligand SNPs in conditioning susceptibility, evolution and outcome of KS. MMPs play an important role in processes that degrade extracellular matrices. Their activity is controlled by specific inhibitors (TIMPs) and imbalances between MMPs and TIMPs are associated with several pathological conditions, including vascular aneurysm. Association of increased MMP9/TIMP2 and MMP3/ TIMP1 ratios with risk of coronary artery lesions was found in Japanese children. On the contrary, no association was found between SNP of MMP-3 in the Korean population. Debated is also the role of CD40L, a transmembrane protein that engages with CD40 and transduces signals related to cell activation and development because a strict association between SNPs and development and severity of KS was demonstrated in the Japanese patients, but not in the Taiwanese population. However, in some studies more convincing results were found particularly when they could evidence that the same polymorphisms were present in populations with different racial characteristics. Onouchi et al. reported that multiple variants in the caspase-3 gene (CASP3) that were in linkage disequilibrium conferred susceptibility to KS in both Japanese and US subjects of European ancestry. These authors found that a G to A substitution of one commonly associated SNP located in the 5' untranslated region of CASP3 (rs7383823; $p = 4.2 \times 10^{-4}$ in the Japanese and $p = 3.7 \times 10^{-3}$ in the European Americans) abolished binding of nuclear factor of activated T cells to the DNA sequence surrounding the SNP suggesting that altered CASP3 expression in immune effector cells influences susceptibility to KS. Interesting results were also reported by Shimizu et al. that investigated genetic variation in 15 genes belonging to the TGF-B pathway in a total of 771 KD subjects of mainly European descent from the United States, the United Kingdom, Australia, and the Netherlands. Genetic variants in TGBF2, TGBF3, and SMAD3 and their haplotypes were consistently and reproducibly associated with KS susceptibility, coronary artery aneurysm formation, aortic root dilatation, and intravenous immunoglobulin treatment response in different cohorts. A SMAD3 haplotype associated with KS susceptibility replicated in 2 independent cohorts and an intronic single nucleotide polymorphism in a separate haplotype block was also strongly associated (A/G, rs1776338; $p = 0.000022$; OR, 1.50; 95% CI, 1.25–1.81). Pathway analysis using all 15 genes further confirmed the importance of the TGF-β pathway in KS pathogenesis. Because similar data regarding susceptibility were reported by Kuo et al., it was concluded that genetic polymorphisms in TGFβ signalling pathway are strictly associated with the risk of development of KS.

However, more reliable results have been obtained using genome-wide association studies (GWAS) because genome scanning without a defined hypothesis has the advantage of identifying disease genes even if the functions of these genes are not associated with previous knowledge about the disease's pathophysiology. Even in this case, the most important results were those repeatedly reported in different populations. By linkage disequilibrium mapping performed on the region of chromosome 19q13.2, it was found that an SNP within the inositol 1, 4, 5-trisphosphonate 3-kinase C (ITPKC) gene, a gene that regulates the signal transduction in T lymphocytes and the degree of inflammatory response, was associated with increased susceptibility to KS and with the development of coronary artery in both a Japanese and a USA population.

Further data confirming the relationships between genetics and KS were collected by Burgner et al. These authors conducted a GWAS with Dutch KS cases and controls and followed up associations signals with a family-based association study of KS families from Australia, USA, and UK. They reported that SNPs in intron 3 of N-acetylated α-acid dipeptidase-like 2 (NAALADL2), a protein possibly involved in immune homeostasis, were associated with KS ($p = 1.13 \times 10^{-6}$) and that mRNA expression of the same protein in erythrocytes was significantly lower in the acute phase of KS than in the convalescence period. These
findings clearly showed that immunological mechanisms (mainly unbalanced immune homeostasis) could favour the development of KS.

The presence of a predisposing genetic system favouring the development of KS and regulating its severity was confirmed by the study of Kim et al.\textsuperscript{113} who studied 186 Korean KS patients and 600 healthy controls, and found that 18 genomic regions with one or more sequence variants were associated with KS, and 26 were associated with coronary artery lesions (CALS) \((p < 1 \times 10^{-5})\). An SNP within the disabled homologue 1 (DAB1) gene locus in chromosome 1 (rs527409) was replicated in 266 children with KS and 600

| Symbol | Gene Description | Region | Clinical Findings | References |
|--------|------------------|--------|-------------------|------------|
| ACE    | Angiotensin I converting enzyme | 17q23 | KS | 69–72 |
| AGTR1  | Angiotensin II receptor, type 1 | 3q21-q25 | KS | 72 |
| CASP3  | Caspase 3 | 4q35 | KS | 73 |
| CCL3L1 | Chemokine (C-C motif) ligand 3-like 1 | 17q11.2 | KS | 74 |
| CER2, 3, 5 | Chemokine receptor 2, 3, 5 | 3p21 | KS | 74–76 |
| CD40L  | CD40 ligand | Xq26 | KS | 77,78 |
| CRP    | C-reactive protein | 1q21-q23 | KS | 79 |
| CXCR1/2 | Chemokine (C-X-C motif) receptor | 2q35 | KS | 76 |
| FCGR2A/2B/3A/3B | Fc fragment of IgG, low affinity receptors | 1q23 | Coronary Lesions | 80,81 |
| IL-4   | Interleukin 4 | 5q31.1 | KS | 82,83 |
| IL-6   | Interleukin 6 | 7p21 | KS | 84 |
| IL-10  | Interleukin 10 | 1q31-q32 | KS | 85 |
| IL-18  | Interleukin 18 | 11q22.2-q22.3 | KS | 86 |
| IL-1β  | Interleukin 1, beta | 2q11 | KS | 82 |
| IL-1Ra | Interleukin 1 receptor antagonist | 2q14.2 | KS | 82 |
| INOS   | Nitric oxide synthase 2, inducible | 17q11.2-q12 | KS | 87 |
| LTA    | Lymphotoxin alpha | 6p21.3 | KS | 88 |
| MBL    | Mannose-binding lectin | 10q11.2-q21 | KS | 89–91 |
| MCPI   | Monocyte chemoattractant protein 1 | 17q11.2-q12 | KS | 92 |
| MICA   | MHC class I polypeptide-related sequence A | 6p21.3 | Coronary Lesions | 93 |
| MMP2/3/9/12/13 | Matrix metalloproteinase | 2 = 16q13q21 | KS | 94–97 |
| MTHFR  | 5,10-methylenetetrahydrofolate reductase | 3/9/12/13 = 11q22.3 | Coronary Lesions | 98 |
| PAF AH | Platelet-activating factor acethylhydroxylase | 1p36.3 | Coronary Lesions | 99 |
| SLC11A1 | Solute carrier family 11 | 2q35 | KS | 100 |
| TGF-B  | Transforming growth factor-Beta | 19q13.1 | KS | 101,102 |
| TIMP2  | Tissue inhibitor of metalloproteinase 2 | 17q25 | KS | 103 |
| TNF-α  | Tumour necrosis factor-α | 6p21.3 | Coronary Lesions | 79,88,104–106 |
| VEGFA  | Vascular endothelial growth factor A | 6p12 | KS | 107,108 |
| VEGFR2 | Vascular endothelial growth factor receptor 2 | 4q12 | KS | 107 |

KS: Kawasaki syndrome.
normal controls (odds ratio [OR] = 2.90, 95% confidence interval [CI] = 1.85–4.54, $p = 1.46 \times 10^{-6}$), and a PEL1 locus on chromosome 2p13.3 ($rs7604693$) was replicated in 86 KS patients with CALs and 600 controls (OR = 2.70, 95% CI = 1.77–4.12, $p = 1.00 \times 10^{-5}$), thus highlighting the presence of a KS susceptibility locus in the 1p31 region and a CAL susceptibility locus in the 2p13.3 region. Unfortunately, the function of DAB1 is not known and it is not possible to establish the role of the genetic variant involving this protein. However, PEL1 seems to function as a negative regulator of Toll-like receptor (TLRs) signalling, thus confirming that genetic variants seem to be associated with variations in immune response.

Tsai et al. conducted a GWAS in 250 KD patients and 446 controls in a Han Chinese population residing in Taiwan, and further validated their findings in an independent Han Chinese cohort of 208 cases and 366 controls. The most strongly associated SNPs detected in the joint analysis corresponded to three novel loci. Among KD-associated SNPs, three were close to the COPB2 (coatomer protein complex beta-2 subunit) gene: $rs1873668$ ($p = 9.52 \times 10^{-11}$), $rs4243399$ ($p = 9.93 \times 10^{-5}$), and $rs16849083$ ($p = 9.93 \times 10^{-5}$). Moreover, an SNP in the intronic region of the ERAP1 (endoplasmic reticulum amino peptidase 1) gene ($rs149481$, $p = 4.61 \times 10^{-5}$) and six SNPs ($rs17113284$, $rs8005468$, $rs10129255$, $rs2007467$, $rs10150241$, and $rs12590667$) clustered in an area containing immunoglobulin heavy chain variable regions genes, with p-values between $2.08 \times 10^{-5}$ and $8.93 \times 10^{-6}$, were also identified. Because these KD candidates have been implicated in T cell receptor signalling, regulation of proinflammatory cytokines, as well as antibody-mediated immune responses, these findings strongly supported the relationships among genetics, alterations in immune response and development of KS.

Association of SNPs within the FCGR gene cluster on chromosome 1 with KS was identified by Khor et al. in European and Asian populations. In a large study sample (2173 individuals with KS and 9383 controls) including European and Asian populations, these authors found that two loci exceeded the formal threshold for genome-wide significance. The first was a functional polymorphism in the IgG receptor gene FCGR2A encoding an H131R substitution ($rs1801274$; $p = 7.35 \times 10^{-11}$, OR = 1.32), with the A allele (coding for histidine) leading to a high risk of disease. The second was at 19q13 ($p = 2.51 \times 10^{-9}$, OR = 1.42 for the $rs2233152$ SNP near MIA, and RAB4B; $p = 1.68 \times 10^{-12}$, OR = 1.52 for $rs28493229$ in ITPKC), thus confirming the data previously with previous studies. The involvement of the FCGR2A locus may have implications for understanding immune activation in KS pathogenesis and the mechanism of response to intravenous immunoglobulin, the only proven therapy for this disease.

More recently, Japanese and Taiwanese groups independently reported a significant association between KS and polymorphisms in the intergenic region on chromosome 8p23-p12 between B lymphoid kinase (BLK), a tyrosine kinase involved in B-cell receptor signal transduction and FAM167A, a functionally uncharacterized gene. Onouchi et al. undertook a GWAS involving 428 Japanese individuals with KS and 3379 Japanese controls genotyped at 473,803 SNPs. They validated the results in two independent replication panels of 754 cases and 947 controls, and observed significant associations in the FAM167A-BLK region ($rs2254546$, $p = 8.2 \times 10^{-21}$). Similar results were obtained by Lee et al. in 622 individuals with KS and 1107 controls in a Han Chinese population residing in Taiwan, with replication in an independent Han Chinese sample of 261 cases and 550 controls. They found that polymorphisms at BLK gene together with genetic abnormalities at CD40, were associated with KS at genomewide significance ($p < 5.5 \times 10^{-8}$) confirming the role of immune activation and inflammation in the pathogenesis of the syndrome.

However, despite these findings, the correlations between genetic markers the risk of developing and severity of KS are far from clear. At the moment the most convincing evidences of a strict correlation between genetic abnormalities and KS regards polymorphisms of ITPKC, FCGR, CASP3 and TGFB genes.

Conclusions

Although various data suggest that KS is an infection-related clinical syndrome that can only develop in children with predisposing genetic backgrounds, our knowledge of the infectious agent(s) involved and the genetic characteristics of susceptible children is still unsatisfactory. Either viruses or bacteria could act as disease, but no specific infectious agent can be considered the definite cause of KS, and so no specific anti-infective therapy can be developed. Moreover, although potential genetic determinants have been hypothesised in subjects with KS, none of them can yet be considered real markers of disease susceptibility. Consequently, the pathogenesis of KS is only partially known and measures to prevent it remain elusive. Further studies are needed to address the many still open questions concerning this still enigmatic disease.

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