

Familial Occurrence of Kawasaki Syndrome in North America

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Objective: To describe families with multiple members affected with Kawasaki syndrome (KS) to increase awareness of the familial occurrence of KS among practitioners who care for these patients.

Design: Retrospective review of medical records at 2 medical centers and data collection from remote KS families who contacted the KS Research Program at the University of California, San Diego.

Results: Eighteen families with multiple affected members were identified. There were 9 families with 2 affected siblings. In San Diego, 3 (0.7%) of 424 KS fami-

lies had sibling cases. Nine families were identified with KS in 2 generations or in multiple affected members, yielding a total of 24 KS-affected children. No clear pattern of inheritance could be deduced from these pedigrees, and it is likely that multiple polymorphic alleles influence KS susceptibility.

Conclusion: Physicians should counsel affected families and make them aware of the potential increased risk of KS among family members.

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SINCE 1967, WHEN TOMISAKU Kawasaki, MD, first described Kawasaki syndrome (KS) in 50 patients,¹⁻³ researchers have attempted unsuccessfully to solve the mystery of the syndrome by finding an etiologic agent for what is the leading cause of acquired heart disease in children. Genetic influences that may modify KS susceptibility are suspected based on the following observations. Although KS has been reported in most ethnic groups, the disease is over-represented among Asian and Asian American populations.^{4,6} In Hawaii, the average annual incidence for Japanese American children is 197.7 per 100 000 children younger than 5 years, which is even higher than the incidence for Japanese children living in Japan.⁷ Asians in San Diego County, California, have a 1.5- to 3-fold increased risk compared with all other ethnic groups, even after controlling for socioeconomic status as a potential confounding factor.⁸ In Japan, siblings of an index case have a 10-fold increased relative risk of KS.⁹ In addition, the incidence of KS is 2-fold higher in Japanese parents of children with KS. The same survey in Japan showed that the incidence of recurrent KS and KS in siblings is 5 to 6 times higher in these multigenerational KS families compared with families with only

1 affected child.¹⁰ In Japan and in the United States, there is an emerging recognition of KS pedigrees with multiple affected members.¹¹⁻²⁷ We present herein further evidence of the familial occurrence of KS in North America.

METHODS

Kawasaki syndrome cases were defined according to the epidemiologic case definition of the American Heart Association for complete KS, which included children with a fever for 5 days and 4 of 5 classic criteria or 3 of 5 criteria plus either dilatation or aneurysms of the coronary arteries by echocardiogram.²⁸ We collected KS pedigrees with multiple affected members through 2 mechanisms. First, we reviewed the medical records of 424 families with at least 1 child with KS cared for at Children's Hospital of San Diego, San Diego, from January 1, 1997, through December 31, 2003. The race-specific incidence rates were calculated based on the year 2000 census data. Ascertainment of KS cases since 1997 in San Diego County has been based on active surveillance and captures 100% of diagnosed KS cases.⁸ Second, we ascertained sibling cases from the records of 341 KS cases cared for at Boston Children's Hospital during the same period. Finally, we collected information from families in the United States and Canada who spontaneously contacted and sought information from the KS Research Program at the University of Califor-

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Table 1. Families With KS With 2 Affected Siblings

Family No.	Case No.*	Age at Onset, y	Interval, y†	Ethnicity	No. of Criteria for KS Met‡	Medical Records Reviewed	Parental Interview Conducted	No. of IVIG Doses	Aneurysms
1	1	1	1.83	Filipino/Korean	4	Yes	No	1	No
	2	0.33			4	Yes	No	1	No
2	1	5	1.42	Korean	5	Yes	No	1	No
	2	3			5	Yes	No	1	No
3	1	4	2.50	Japanese	5	Yes	No	1	No
	2	6			5	Yes	No	1	No
4	1	3	0.66	White	4	No	Yes	2	Yes
	1§	3.66			4	No	Yes	1	
	2	0.67	>1		4	No	Yes	2	No
5	1	12	>1	White	5	Yes	Yes	2	No
	2	0.75			5	Yes	Yes	1	No
	2§	5	>1		5	Yes	Yes	1	No
6	1	6	0.23	White	4	Yes	Yes	2	No
	2	4			4	Yes	Yes	1	No
7	1	10	0.06	White	4	No	Yes	1	Yes
	2	2.50			4	No	Yes	0	No
8	1	4.17	4.67	White	3	Yes	No	0	No
	2	1.58			4	Yes	No	1	No
9	1	0.46	0.02	Mexican American	5	Yes	Yes	1	No
	2	0.48			5	Yes	Yes	2	No

Abbreviations: IVIG, intravenous immunoglobulin; KS, Kawasaki syndrome.

*Numbered in the order of KS occurrence.

†Time between KS episodes in the first and second child.

‡The total number possible was 5, including rash, conjunctival injection, changes in the oropharynx, changes in the extremities, or a cervical lymph node larger than 1.5 cm.

§Recurrent case.

nia, San Diego, by e-mail or telephone between January 1, 1998, and December 31, 2004. Cases were ascertained by parental interview, review of medical records, and review of death certificates or autopsy reports. After obtaining parents' informed consent, we recorded patient sex, age at KS onset, ethnicity, interval between KS in different family members, number of KS criteria met, number of intravenous immunoglobulin (IVIG) treatments, presence or absence of aneurysms, and KS-related deaths. We divided the families with more than 1 affected member into 2 groups: families with sibling cases and complex families with either more than 1 generation affected and/or extended family (eg, cousin) cases.

RESULTS

SIBLING CASES

During the 7-year period, we identified 3 (0.7%) of 424 families (families 1-3) and 1 (0.3%) of 341 families (family 8) with 2 affected siblings in San Diego and Boston, respectively. All 6 of the San Diego sibling cases were Asians younger than 5 years. Asians represented only 59 (13.9%) of the 424 total KS cases in San Diego County during that period. By using 2000 census data for San Diego County, we calculated an average race-specific incidence rate for KS in Asian children of 31 per 100 000 children younger than 5 years. Data were not available for the total number of siblings in all Asian families, so the sibling relative risk could not be calculated.

Through contacts to the KS Research Program, we collected an additional 5 remote families with 2 affected siblings each, yielding a total of 9 KS sibling pairs (**Table 1**). Only 2 (22.2%) of the 9 sibling pairs had the onset of

disease within 1 month of each other, while 6 pairs had the onset of disease separated by at least a year. Of these 6 pairs, 4 siblings were not born at the time of KS diagnosis in the first sibling. In family 9, the 2 siblings were 2 of fraternal quadruplets. The other 2 quadruplets remained well. In the San Diego families, the sibling pairs had a benign course. In the remote families (families 4-7 and 9), the high rate of complications, including recurrent KS (2 [20.0%] of 10), IVIG retreatment (5 [45.5%] of 11), and coronary artery aneurysms (2 [20.0%] of 10), likely reflects the bias that families with children with more severe manifestations of disease were more likely to seek information by contacting the KS Research Program at the University of California, San Diego.

COMPLEX FAMILIES

By reviewing medical records in San Diego and interviewing families who spontaneously contacted 1 of us (J.C.B.), 9 complex KS pedigrees were identified, yielding a total of 24 KS-affected children, 3 of whom died of coronary artery complications (**Table 2** and **Figure**).

Family 10

There were 3 affected cousins, 2 of whom were diagnosed as having KS and treated in San Diego. No clinical details were available for the first cousin who developed KS, except for the history of his diagnosis provided by the other family members. The second cousin was diagnosed as having KS in 1991 at the age of 4 months. He developed fever, rash, and conjunctival injection. An echo-

Table 2. Families With KS With Complex Pedigrees

Family No.	Case No.*	Age at Onset, y	Ethnicity	No. of Criteria for KS Met†	Medical Records Reviewed	Parental Interviews Conducted	No. of IVIG Doses	Aneurysms	Died
10	1	NA	NA	NA	No	NA	NA	NA	No
	2	0.33	Mexican American	3	Yes	No	1	No	No
	3	2	Mexican American	4	Yes	No	2	No	No
11	1	4	White	4	Yes	Yes	1	No	No
	2	9	White	1	Yes	Yes	0	Yes	Yes
	3	7	White	2	No	Yes	1	Yes	No
	4	9	White	4	No	Yes	1	No	No
12	1	4.50	White	3	No	No	0	No	No
	2	2.75	Mexican American/white	4	Yes	Yes	0	Yes	Yes
	3	2.80	Mexican American/white	4	Yes	Yes	1	No	No
13	1	1.67	White	3	Yes	Yes	1	No	No
	2	10	White	3	Yes	Yes	1	No	No
	3	13	White	4	No	Yes	1	No	No
14	1	10	White	5	No	Yes	0	No	No
	2	0.83	White	5	No	Yes	1	No	No
15	1	20s	Mixed	5	No	Yes	0	No	No
	2	13	Mixed	5	Yes	Yes	1	No	No
16	1	6	White	5	Yes	Yes	0	Yes	Yes
	2	1.50	White	5	No	Yes	1	No	No
17	1	3	Japanese	NA	NA	NA	1	No	No
	2	0.29	Japanese/white	4	Yes	Yes	1	Yes	No
18	1	6	White	5	No	Yes	0	NA	No
	2	5	White	5	No	No	0	NA	No
	3	2	White	4	Yes	Yes	1	No	No

Abbreviations: IVIG, intravenous immunoglobulin; KS, Kawasaki syndrome; NA, data not available.

*Numbered in the order of KS occurrence.

†The total number possible was 5, including rash, conjunctival injection, changes in the oropharynx, changes in the extremities, or a cervical lymph node >1.5 cm.

cardiogram revealed a dilated right coronary artery that resolved on subsequent studies. He responded to a single dose of IVIG. Characteristic peeling occurred during the subacute disease phase. The third cousin developed KS in 2000 at the age of 2 years. He presented with a 4-day history of fever, conjunctival injection, red cracked lips, and rash. During hospitalization, it was revealed that 2 cousins had been diagnosed as having KS. This cousin was treated with 2 doses of IVIG for persistent fever. The echocardiographic results were normal, and the patient recovered without sequelae.

Family 11

There were 3 affected siblings and 1 cousin. The first child was diagnosed as having KS in 1993 at the age of 4 years. She developed fever, erythema of the oropharynx, strawberry tongue, fissured lips, red eyes, lymphadenopathy, and increased irritability. She was treated with IVIG and had no complications. All of her echocardiographic results were normal. She experienced peeling of the fingers and toes during the convalescent phase. The second sibling, her older brother, developed only fever, lethargy, and conjunctival injection at the age of 9 years in 1996. The fever lasted for 3 weeks, and he was thought to have had a viral illness. One year later, this child collapsed, was rushed to the hospital, and was diagnosed as having coronary artery aneurysms by an echocardiogram. He died shortly thereafter. The autopsy report stated that he died of coronary artery

thrombosis secondary to undiagnosed and untreated KS. After the death of the second child affected with KS, the family relocated. In 2000, the third sibling, aged 7 years, developed fever, conjunctival injection, and an elevated erythrocyte sedimentation rate. An echocardiogram revealed 2 coronary artery aneurysms. In 2002, a maternal first cousin was diagnosed as having KS. She developed fever, conjunctival injection, rash, erythema of the oropharynx, and swelling of the hands. She was diagnosed as having KS on day 5 of her illness and treated with IVIG. She experienced desquamation during the convalescent phase. Her echocardiographic results were normal.

Family 12

There were 2 affected siblings and 1 uncle. The uncle was diagnosed as having KS in 1982 at the age of 4.50 years. He was treated with aspirin alone, and all of his echocardiographic results were normal. The first of the 2 siblings was hospitalized at the age of 2.75 years for what was clinically KS, with 4 of 5 clinical signs, in 1999. However, he was not diagnosed as having KS during that hospital stay. Approximately 1 year later, he died suddenly. The autopsy report stated that death was the result of coronary artery thrombosis as a complication of KS. The second sibling was diagnosed as having KS at the age of 2.80 years after 5 days of fever, with 4 of 5 criteria fulfilled. She was treated once with IVIG, and her echocardiographic results were normal.

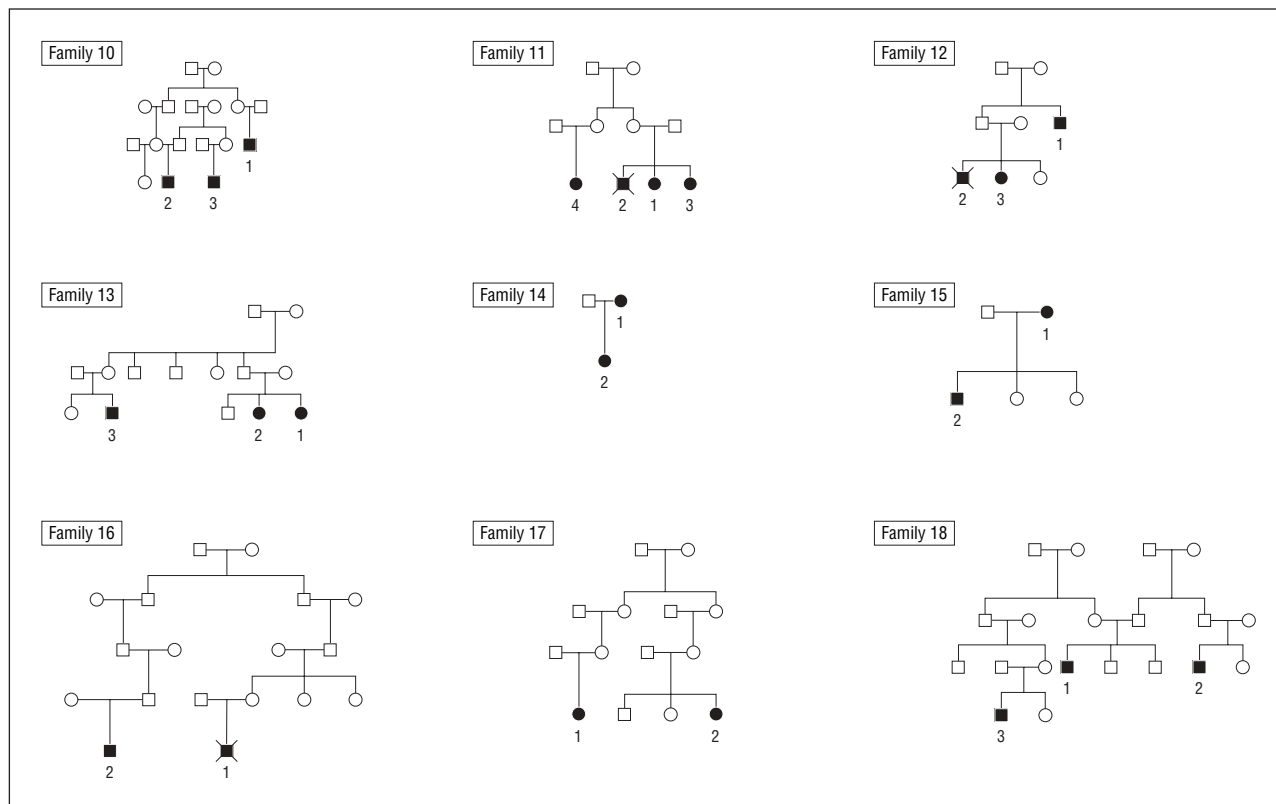


Figure. The 9 complex Kawasaki syndrome (KS) pedigrees identified (families 10-18), yielding a total of 24 KS-affected children, 3 of whom died of coronary artery complications. Circles indicate females; squares, males; unshaded symbols, unaffected individuals; shaded symbols, individuals with KS; and crossed-out symbols, deceased individuals.

Family 13

There were 2 affected siblings and 1 cousin. The first sibling was diagnosed as having KS in 1991 at the age of 20 months. She developed fevers, followed by conjunctival injection, rash, swollen hands and feet, and refusal to walk. She was diagnosed as having KS and treated with IVIG on illness day 5. All echocardiographic results were normal. The second sibling was diagnosed as having KS in 1995 at the age of 10 years. She developed fever, rash, and conjunctival injection. The mother suspected KS, but the treating physician rejected the diagnosis until illness day 11 when fever persisted and the child developed erythema, swelling, and arthralgia of the hands and feet, and an elevated platelet count. The child was treated with IVIG, and the echocardiographic results were normal. The child experienced periungual desquamation in the subacute disease phase. In 2002, a cousin was diagnosed as having KS at the age of 13 years. He developed fever, rash, cervical lymphadenopathy, pharyngeal erythema, and strawberry tongue. The result of a streptococcal culture was negative. The mother raised the possibility of KS because of the family history, but the diagnosis was initially rejected because of the patient's age. On illness day 11, the child was hospitalized and treated for KS with IVIG, with prompt defervescence. He experienced desquamation of fingers and toes in the convalescent phase. His echocardiographic results were normal.

Family 14

There was an affected mother and daughter. The mother was diagnosed as having KS in 1984 at the age of 10 years. The mother recalled that she developed fever and rash accentuated in the groin. She had conjunctival injection, strawberry tongue, arthralgias, and torticollis from unilaterally enlarged cervical lymph nodes. The diagnosis of KS was made, and she was treated with aspirin alone. She experienced periungual desquamation in the convalescent phase. Her echocardiographic results were normal. Her daughter was diagnosed as having KS at the age of 10 months after 9 days of fever associated with rash accentuated in the groin, conjunctival injection, pharyngeal erythema, red fissured lips, and enlarged cervical lymph nodes. The infant was treated with IVIG. She experienced periungual desquamation in the convalescent phase, and her echocardiographic results were normal.

Family 15

There was an affected mother and son. The mother had an illness associated with fever and all 5 clinical criteria for KS in her early 20s. The diagnosis was delayed because her physicians thought she was too old for KS. She experienced periungual desquamation during the convalescent phase, and this finding, in conjunction with all of the criteria in the clinical case definition, prompted a diagnosis of KS. Her echocardiographic results were normal. Her son was diagnosed as having the complete cri-

teria for KS at the age of 13 years. He had approximately 2 weeks of high fevers, rash, conjunctival injection, strawberry tongue, and cervical lymphadenopathy. He experienced defervescence after IVIG treatment and had perirungal desquamation. His echocardiographic results were normal.

Family 16

There were 2 affected cousins. The first cousin was diagnosed as having KS in 1984 at the age of 6 years. He was not treated with IVIG and developed aneurysms in the left main and right coronary arteries. At the age of 14 years, the patient experienced a myocardial infarction due to partial occlusion of the aneurysm in the right coronary artery. He began receiving warfarin sodium (Coumadin) therapy in addition to aspirin. At the age of 16 years, he experienced cardiopulmonary arrest and could not be resuscitated. An autopsy revealed no new thrombus, and the cause of death was presumed to be cardiac arrhythmia. In 2001, his cousin was diagnosed as having KS at the age of 1.50 years after 10 days of fever. The cousin had fever, rash, conjunctival injection, red cracked lips, strawberry tongue, enlarged cervical lymph nodes, and extremity changes. The cousin responded to IVIG and had normal echocardiographic results.

Family 17

There were 2 affected cousins. One cousin is Japanese and lives in Japan. The other cousin is half white and half Japanese and lives in the United States. The cousin in Japan was diagnosed as having KS in 1990 at the age of 3 years. She was treated with IVIG and had normal echocardiographic results. The second cousin was diagnosed as having KS in 2003 at the age of 3.50 months. She was treated once with IVIG, but continued to have a fever for a total of 21 days. She developed giant aneurysms of her right and left coronary arteries.

Family 18

There were 3 affected cousins. The first 2 affected cousins developed KS in England in 1989 and 1990 at the ages of 6 and 5 years, respectively. Both had classic KS, with 5 of 5 criteria, including unilateral lymph node enlargement. Neither was treated with IVIG and neither has had an echocardiogram. The third cousin resides in the United States and developed KS in 2004. He had 4 of 5 criteria, responded to a single dose of IVIG, and had a normal echocardiographic result.

COMMENT

We identified 9 sibling pairs and 9 additional KS families with 2-generation cases or multiple affected members. In Japan, the occurrence of KS in families is well recognized, with a 2-fold increased prevalence of a history of KS among parents of children with KS and a 10-fold increased relative risk of KS in siblings of an index

case.^{9,10} The overall rate for sibling cases in Japan was reported as 2.1% during the epidemic year of 1982.¹⁸ In the 14th nationwide epidemiologic survey on KS, which included 1995 and 1996, there were 115 (0.9%) of 12 531 families with sibling cases of KS.²⁹ Unfortunately, the trend by the Centers for Disease Control and Prevention to use insurance company and hospital discharge databases for tracking KS incidence will not allow an accurate assessment of the familial occurrence of KS in the United States.^{6,30,31} Without knowing the number of siblings in each KS family in our database, we were unable to calculate the relative risk for siblings of an index case.

In the complex families, the onset of KS in different family members was separated temporally and in many cases geographically as well. No clear pattern of inheritance could be deduced from these pedigrees, and it is likely that multiple polymorphisms are involved in KS susceptibility.³² One concern in the ascertainment of families who allegedly have multiple affected members is that families and their physicians may be biased in overdiagnosing additional cases of KS after the first affected child in a family. In interviewing these families, however, we uncovered the opposite bias, as illustrated in the case reports. Several families were specifically told by their physician that it would be "impossible" to have a second affected child in the same family, which led to a delay in diagnosis in at least 2 cases. In family 10, the second case, who was clinically incomplete (only experiencing prolonged fever and conjunctival injection), was missed and not diagnosed until autopsy. Thus, mistaken overdiagnosis of KS is unlikely to explain the occurrence of KS in multiple members of the families described herein.

To our knowledge, this is the first case series to describe multiple members affected with KS in white families. Although the incidence for Asian Americans is higher than for whites living in the same community,⁸ whites constitute the largest racial group in most published series from North America because Asians make up less than 15% of the population in most communities. Only 3 of 9 families with sibling cases and 1 of 9 complex families in our series were Asian.

The limitations of this study include the use of parental history and physician reports without independent verification by review of medical records, echocardiographic reports, and other laboratory testing results. This may have resulted in overreporting KS cases and errors in describing the results of echocardiograms. Of the 9 complex families, 3 experienced a death due to KS. Whether there is a tendency of KS to be more severe in families with multiple affected members or whether this is due to reporting bias cannot be determined from this case series. In Japan, it has been suggested that families with multiple affected members have a higher incidence of coronary artery lesions, perhaps due to a genetic predisposition.²⁷ Future prospective studies of large cohorts of KS families will be necessary to define the exact sibling relative risk and the incidence and severity of KS in extended family members of an index case.

Given the existence of sibling cases and complex multigenerational KS families, physicians should counsel affected families and make them aware of the possible increased risk of KS among first-degree family members.

Knowledge about the increased risk of KS in family members of an index case may have resulted in more timely diagnosis of several of the children in this series. Parent information is available in English, Spanish, Japanese, Chinese, Tagalog, Farsi, and Korean at the following Web site: <http://www-pediatrics.ucsd/kawasaki>. For an illness with no available diagnostic test, an extremely effective therapy, and potentially life-threatening complications if the syndrome is not recognized and treated, this type of patient education may have a significant impact.

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