

# The epidemiological status, environmental and genetic factors in the etiology of Keshan disease

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**Keshan disease (KD) is an endemic cardiomyopathy with myocardial lesions for which the precise etiology has not been determined. It was named after the location where it was first identified: Keshan County in China. KD is mainly distributed in a selenium-deficient zone from northeast to southwest China. In recent years, the incidence and prevalence of KD have significantly decreased. Meanwhile, more knowledge was accumulated about the etiology of KD and recent data indicated that genetic factor was involved. In this review, we will first update an overview of the epidemiological status and the environmental and genetic factors involved in this disease. *Cardiovasc Endocrinol Metab* 10: 14–21 Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.**

## Introduction

Keshan disease (KD), an endemic cardiomyopathy found only in China, Korea and Japan, is characterized by multifocal myocardial necrosis and fibrosis, which are clinical symptoms similar to those of dilated cardiomyopathy [1]. It is named after the location where it was first identified in 1935: Keshan County, Heilongjiang Province, northeast China. Although the incidence and prevalence of KD were reduced significantly in recent years, the clinical prognosis of KD is still poor [2]. In our previous study, the five-year survival rate of 92 KD patients with a mean follow-up of  $4.8 \pm 1.9$  years was only 77.1% [3]. Based on the duration of the disease, KD is clinically divided into four categories: acute, subacute, chronic and latent KD. Viral infection, selenium deficiency and malnutrition were once considered as factors in the pathogenesis of KD [1,2]. Recent studies also pointed out several genetic polymorphisms and mutations could be related to KD [4]. In this review, we will try to discuss the epidemiological status, environmental and genetic etiological factors that are related to KD.

## The current epidemiological status of Keshan disease

### Detection and incidence rates of Keshan disease in nationwide of China

The national surveillance of KD in China was conducted from 1990 to 2009. During the years, the results were reported in the annual conference of KD in China. This work was led by the Keshan Disease Research Institute, Centers for Disease Control of China. Later on, the

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national surveillance switched to a local surveillance since 2010, due to the low incidence rate of KD. In this review, we will try to have a whole picture of the epidemiology of KD from 2009 to 2018, especially focusing on the most recent updates of seven historically severe epidemic provinces in 2010–2018.

KD is classified into four categories as follows: (1) acute KD, characterized by cardiogenic shock, arrhythmia and acute heart failure, with sudden onset, rapid progression and acute circulatory dysfunction; (2) subacute KD, with a slower onset than acute KD and a more rapid one than chronic KD, with similar symptoms to acute KD, along with congestive heart failure; (3) chronic KD, characterized by cardiac dilatation, a slow onset, and a long course, with most patients having a cardiac function range of NYHA II–IV and (4) latent KD, which can develop in either previously unaffected individuals or those with the other three types of KD, featuring myocardial injury and usually arrhythmia, but with normal heart function [5]. The detection rate refers to the proportion of individuals diagnosed as KD among the total population during the survey. The incidence rate indicates the proportion of newly diagnosed individuals among the total population during the survey.

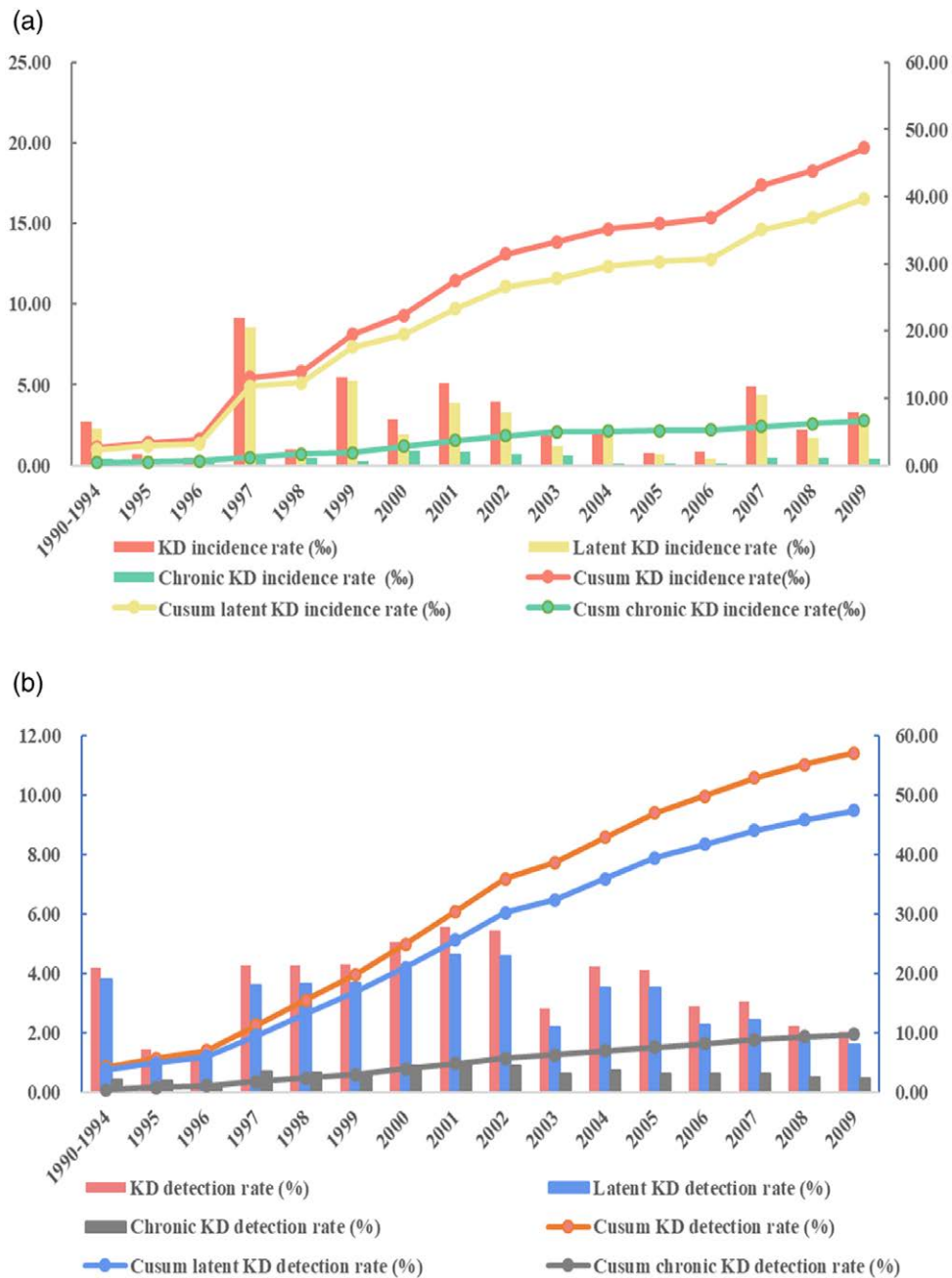
In total, 380 103 individuals were surveyed from 1990 to 2009, among whom 10 770 KD patients were identified, including 8827 latent KD patients and 1937 chronic KD patients being identified. The crude annual average detection rate of KD was 2.85%, ranging from 1.33 to 5.54%, the crude annual average detection rate of latent

KD was 2.37%, ranging from 1.04 to 4.63%, and the equivalent value for chronic KD was 0.48%, ranging from 0.24 to 0.91%. As for the crude incidence rate of KD in this period, 1004 new KD patients were identified, including 834 latent KD patients and 164 chronic ones. The crude annual average incidence rates were 2.36‰, with a range of 0.49–9.15‰, 1.99‰ with a range of 0.28–8.60‰ and

0.33‰ with a range of 0.06–0.68‰, for KD, latent KD and chronic KD, respectively [6–20]. Overall, the findings show that detection rates of KD, latent KD and chronic KD decreased in 2007–2009, and the incidence rates of KD, latent KD and chronic KD remained stable.

From Fig. 1 and Table 1, it can be seen that, from 1990 to 2009, the lowest detection rates of KD, latent KD and

Fig. 1



The national detection and incidence rate of Keshan disease (KD) in China from 1990 to 2009. (a) The plot showed the trends of the national detection rates of KD, latent KD and chronic KD during 1990–2009. (b) The plot showed the trends of the national incidence rates of KD, latent KD and chronic KD during 1990–2009.

**Table 1 The national (Cusum) detection and incidence rate of Keshan disease in China from 1990 to 2009**

Year	KD detection rate (%)	Cusum KD detection rate (%)	Latent KD detection rate (%)	Cusum latent KD detection rate (%)	Chronic KD detection rate (%)	Cusum chronic KD detection rate (%)	KD incidence rate (‰)	Cusum KD incidence rate (‰)	Latent KD incidence rate (‰)	Cusum latent KD incidence rate (‰)	Chronic KD incidence rate (‰)	Cusum chronic KD incidence rate (‰)
1990–1994	4.2	4.2	3.8	3.8	0.4	0.4	2.7	2.7	2.29	2.29	0.4	0.4
1995	1.43	5.63	1.04	4.84	0.39	0.79	0.69	3.39	0.63	2.92	0.06	0.46
1996	1.33	6.96	1.09	5.93	0.24	1.03	0.49	3.88	0.28	3.2	0.21	0.67
1997	4.26	11.22	3.58	9.51	0.68	1.71	9.15	13.03	8.6	11.8	0.55	1.22
1998	4.27	15.49	3.62	13.13	0.65	2.36	0.95	13.98	0.5	12.3	0.45	1.67
1999	4.29	19.78	3.69	16.82	0.59	2.95	5.5	19.48	5.25	17.55	0.25	1.92
2000	5.06	24.84	4.16	20.98	0.89	3.84	2.86	22.34	1.9	19.45	0.9	2.82
2001	5.54	30.38	4.63	25.61	0.91	4.75	5.13	27.47	3.87	23.32	0.87	3.69
2002	5.44	35.82	4.57	30.18	0.87	5.62	3.95	31.42	3.27	26.59	0.68	4.37
2003	2.79	38.61	2.19	32.37	0.6	6.22	1.84	33.26	1.23	27.82	0.61	4.98
2004	4.22	42.83	3.51	35.88	0.71	6.93	1.94	35.2	1.82	29.64	0.11	5.09
2005	4.11	46.94	3.51	39.39	0.6	7.53	0.76	35.96	0.67	30.31	0.09	5.18
2006	2.89	49.83	2.25	41.64	0.6	8.13	0.84	36.8	0.38	30.69	0.08	5.26
2007	3.03	52.86	2.41	44.05	0.62	8.75	4.88	41.68	4.41	35.1	0.49	5.75
2008	2.21	55.07	1.71	45.76	0.5	9.25	2.21	43.89	1.72	36.82	0.49	6.24
2009	2.02	57.09	1.58	47.34	0.44	9.69	3.33	47.22	2.89	39.71	0.44	6.68

chronic KD occurred in 1996, while the highest were in 2001. Regarding the trend of national crude KD detection rates, these were stable in 1995–1996 and 2003–2009, while there were relatively high KD detection rates in the period of 1996–2002. In addition, regarding the trend of latent KD detection rates, they were at a low level during 1995–1996, but high during the periods of 1996–2009; however, the average detection rate of latent KD in 2003–2009 was lower than those in the period of 1996–2002, and the detection rates of chronic KD had the same trend of latent KD.

Regarding the total incidence rate of KD in China during 1990–2009, the lowest incidence rates of KD and latent KD occurred in 1996, while the highest ones were in 1997. The lowest chronic KD incidence rate was in 1995 and the highest was in 2000. In addition, for the incidence rates of KD and latent KD, both of them reached high levels in 1996–1997, 1999–2002 and 2007–2009, but remained at low levels during 1994–1996, 1998 and 2003–2006, and there was a stable trend in the chronic KD incidence rate, as a basic control of chronic KD, during 1990–2009. The results of this analysis indicate that the status of KD exhibited relatively stable trends, in particular that the chronic KD detection and incidence rates were remained at lower levels.

#### The status of Keshan disease in seven historically severe epidemic provinces in 2010–2018

Although the summary for the National Keshan Disease Surveillance conference was not produced after 2009, the survey was still continued in the focal monitoring area every year. The focal monitoring area included seven regions with a relatively higher disease incidence, namely, Heilongjiang, Jilin, Inner Mongolia, Sichuan, Yunnan Shaanxi and Shandong provinces, so we selected the data from these areas for analysis.

During 2011–2016, a total of 801 hospitals participated in surveying 27 046 people in Heilongjiang Province.

Among these, there were 3051 cardiomyopathy patients and 143 patients diagnosed with KD, all of whom had chronic KD, and no new cases of KD were found, so the incidence rate was zero [21]. The annual average crude detection rate of KD, latent KD and chronic KD were 0.094%, 0 and 0.094% from 2011 to 2016, respectively.

In 2011, a total of 6746 people were surveyed in 16 villages in Jilin Province. A total of 55 KD patients were identified, giving a total crude detection rate of 0.815%. The latent and chronic KD cases numbered 46 (0.682%) and nine (0.133%) [22], respectively. In 2012, a total of 5110 residents were surveyed and there were four KD patients, whom were all diagnosed latent KD; thus, the detection rate of KD and latent KD were both 0.080% [23]. During 2014–2016, about 18 757, 15 931 and 14 936 people were surveyed in Jilin Province and 80 (0.427%), 61 (0.380%) and 60 (0.402%) KD patients were identified, respectively. The corresponding detection rates of chronic KD and latent KD were 0.064% (12/18 757) and 0.363% (68/18 757), 0.040% (6/15 931) and 0.350% (55/15 931), 0.134% (20/14 936) and 0.268% (40/14 936), respectively [24–26].

From 2006 to 2012, in Inner Mongolia Province, 31 463 residents were investigated. Among these, 1123 KD patients were detected, including 822 with latent KD and 301 with chronic KD. The detection rates of KD, latent KD and chronic KD were 3.57%, 2.61% and 0.96%, respectively [27]. The status of KD in Inner Mongolia was stable from 2006 to 2012.

During 2011–2013, we reported that the number of people surveyed in Sichuan Province was 14 295, among which 71 cases (0.50%) of KD were detected, including 40 cases of latent KD and 31 cases of chronic KD. The corresponding detection rates of chronic KD and latent KD were 0.28% and 0.22%, respectively [28,29]. During 2014–2015, a total of 62 793 people had been surveyed, and 64 (0.10%) KD patients were detected, including 14

(0.02%) chronic KD and 50 (0.08%) latent KD [30]. From the previous of our studies [28–30], it is shown that the status of KD in Sichuan Province was relatively stable from 2011 to 2013, while the detection rate dropped to a lower level during 2014–2015.

From 2010 to 2012, researchers monitored 21 300 people in Yunnan Province, among which 115 cases of KD were detected. The total detection rate was 0.54%. Overall, there were 96 cases of latent KD, with a detection rate of 0.45%, along with 19 cases of chronic KD, with a detection rate of 0.09%. No acute or subacute KD cases were identified [31–33].

In the period 2010–2018, only 2011 was the year in which KD monitoring was performed in Shaanxi Province. In that year, a total of 9145 people were surveyed, among whom 41 latent KD patients were detected, with a detection rate of 0.45% [34].

In Shandong Province, monitoring of 3031 people was carried out at seven survey sites during 2011–2015. A total of 53 KD patients were found, including 42 with latent KD and 11 with chronic KD; the detection rates were 1.75%, 1.39% and 0.36%, respectively [35].

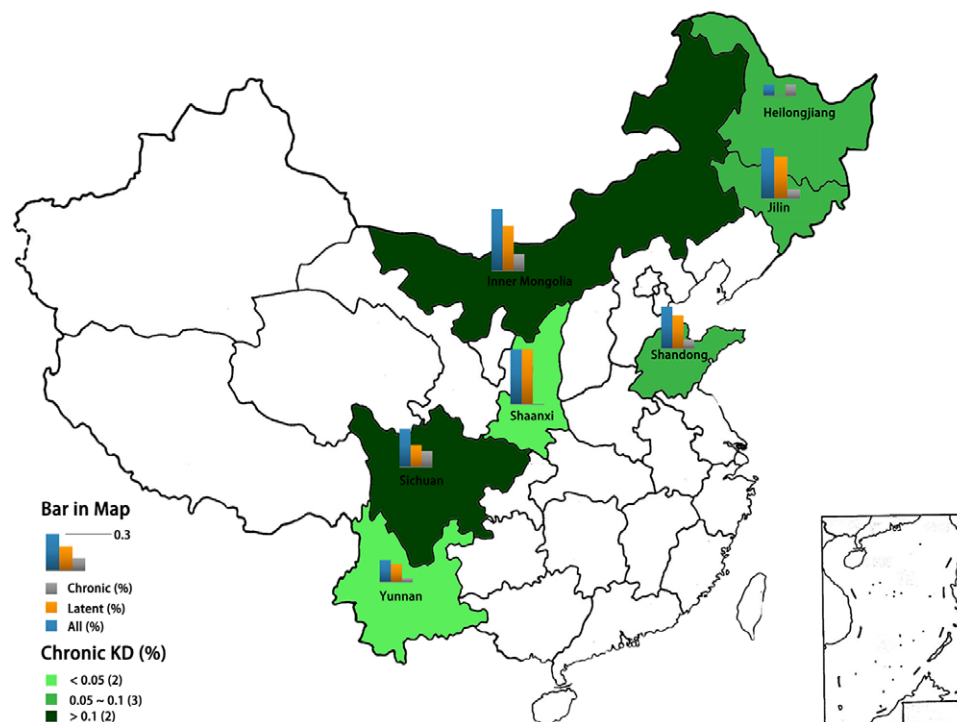
These data indicate that the prevalence of KD in the main affected provinces has been consistently at a low level in recent years. As shown in Fig. 2, Inner Mongolia had the

highest annual detection rate of chronic KD (0.137%), followed by Sichuan (0.131%), Heilongjiang (0.094%), Jilin (0.074%), Shandong (0.073%), Yunnan (0.030%) and Shaanxi (0); the annual detection rates of two provinces were lower than 0.05%, while two of them were higher than 0.1%. Most provinces had reached a control level; however, KD has not been eliminated, further research should be done at the county and province levels.

### Selenium deficiency and virus infection

Although the etiological mechanism of KD remains largely unclear, selenium and Coxsackie virus infection have been suggested to be highly involved in the pathogenesis of KD [36,37]. KD and selenium deficiency were similar in geographical distribution, both located in the same belt region from northeast to southwest in China. Previous studies found that the selenium levels in whole-blood and hair samples in the Keshan endemic area residents were lower than those in the nonendemic areas [36,37]. Selenium supplementation significantly reduced the incidence of KD in a large number of population [36]. In addition, selenium deficiency has been linked to thyroiditis, Graves' disease and goiter to low selenium status [38]. Some studies shown that the thyroid level might be different between KD patients and controls. Liu *et al.* reported that myocardial thyroxine (T4) 5'-monodeiodinase activity, endogenous triiodothyronine

Fig. 2



The detection rates of Keshan disease (KD) of the seven provinces in China during 2010–2016.

(T3) content in myocardial tissue and myocardial mitochondrial  $\alpha$ -glycerol-phosphate dehydrogenase activity decreased in the endemic grain group, while the atrial natriuretic peptide content in myocardium was increased [39]. Wu *et al.* showed that abnormal thyroid hormone metabolism existed in the KD patients [40]. Subclinical or clinical thyroid dysfunction were correlated cardiac function and dilated cardiomyopathy [41,42].

It was accepted that selenium deficiency is the key etiological factor for KD; however, it may not be the only etiological factor, the role of virus infection in the KD could not be ruled out [3,43]. Coxsackie virus was detected in the myocardium of KD patients at different stages, and it was found that Coxsackie B virus can increase the virulence through the gene mutation in the selenium-deficient mice [44,45]. Li-Qun Ren *et al.* found the Coxsackievirus B3 RNA positive rate in KD patients; moreover, the area, range and the distribution of the positive signal of Coxsackie B3 virus were associated with the development of KD [44]. What's more, the increases in serum soluble intercellular adhesion molecule-1 and soluble vascular cell adhesion molecular-1 in KD patients may be related to Coxsackie B virus infection [45]. Interestingly, the selenium could have several effects, both direct and indirect, on CV [40,46,47]. Recent studies have shown that selenium could prevent genetic adaptations in the viral genomic RNA that lead to increased virulence and cardiac pathology [46]. Moreover, selenium deficiency could lead to the increase of T4 and the decrease of T3 in the peripheral largely due to the inactivation of type I deiodinases [40]. The decreased concentration of T3 could impair the activity of innate immune cells including natural killer cells and dendritic cells (DC), which may lower the efficacy of virus clearance [47].

Although selenium supplementation therapy is proved useful [36], the dose of selenium supplementation needs to be carefully calculated, because over-dose of selenium could lead to type 2 diabetes (T2D). In a recent systematic review of 13 observational studies, eight demonstrated a statistically significant positive association of Se concentration and T2D; however, among the randomized clinical trials, this association was not observed [48]. Therefore, further investigation is required to make a clear conclusion.

### Progress in potential genetic etiology in Keshan disease

#### Family clustering of Keshan disease

KD is an endemic cardiomyopathy, which might be related to genetic factors. The tendency for KD to cluster within families has been reported in a few studies [4,49,50]. In 1983, Zhao *et al.* conducted a pedigree investigation in 130 children of Yi ethnicity with KD aged from 1 to 15 years old. These data showed that 29.23% of the patients

had a family history of KD; the prevalence rate was significantly higher in their relatives than in the general population, and the prevalence rate of KD was higher in those who had married consanguineously, strongly suggesting a genetic component to KD [49]. Moreover, in 2003, Zhang *et al.* carried out an epidemiological survey in 52 families with KD in Huangling County, Shaanxi Province. The prevalence rate of KD in relatives of these patients was significantly higher than that in the general population locally [50]. The above studies suggested that KD was an inherited disease with clear familial clustering.

#### Genetic polymorphisms of Keshan disease

Studies have shown that the pathogenesis of KD is related to immune disturbance, so immune function and genes encoding proteins related to oxidative stress have been a particular focus in KD research. Human leukocyte antigen (HLA), which plays an important role in immunomodulation, is one of the most complex and varied gene systems, which can be classified into HLA-I, II and III types. The *HLA-II* gene region includes at least the DR, DQ, DP, DOB and DM subregions. Moreover, the DR subregion contains one *DRA* gene and nine *DRB* genes, with *HLA-DRB1* being the most polymorphic of all *HLA-II* genes [51–53]. Polymorphisms in the *HLA-DRB1* gene have been found to be associated with the pathogenesis of dilated cardiomyopathy susceptibility in China and elsewhere [51–53]. Niu *et al.* were the first to report on the association between KD and genotyping of *HLA-DRB1* gene in 118 KD patients. As a result, 10 alleles at the *HLA-DRB1* locus of KD patients were identified, with DR15 (0.3438 vs. 0), DR4 (0.1563 vs. 0.139) and DR9 (0.1875 vs. 0.120) being found at higher frequencies in KD patients, suggesting that *HLA-DRB1* gene polymorphism is associated with KD [52]. Moreover, Wei *et al.* reported a further study on the relationship between *HLA-DRB1* gene polymorphism and KD. In this work, 13 related alleles were detected at the *HLA-DRB1* locus. The frequencies of the DR7 allele of *HLA-DRB1* were significantly lower in the KD group (0.0170 vs. 0.10000,  $P < 0.01$ ) and chronic KD group (0.0091 vs. 0.10000,  $P < 0.01$ ) than that in normal controls, indicating that this allele might be protective against KD. Meanwhile, the DR15 allele was found to be significantly associated with KD and linked to the susceptibility loci of KD ( $\chi^2 = 7.40$ ,  $P < 0.01$ ). Those findings indicate that KD might have a potential genetic etiology [53]. In another study, Wang *et al.* analyzed the association between *HLA-DRB1* gene polymorphism and KD. The DR15 allele frequency of *HLA-DRB1* in KD patients and their parents was 0.39 vs. 0.24. They found that KD is associated and linked with the DR15 allele of *HLA-DRB1*, ( $\chi^2 = 12.25$ ,  $P < 0.01$ ) [54]. The above studies show that DR15, DR4 and DR9 could increase the risk of KD while DR7 could reduce it. And the above analysis indicates that the up- or down-regulation of immune-related genes might increase the

susceptibility to KD, and that polymorphism of HLA-II-type genes might be related to the pathogenesis of KD.

Several studies have shown that selenium and GPX-1 enzyme activity were also related to KD [3,54]. For example, a study by Lei *et al.* [54] showed that the blood selenium level and GPx-1 enzyme activity were significantly lower in KD patients than in normal controls, and a variant at the Pro198 site of the *GPx-1* gene (Pro198Leu) was identified. The study showed that the frequency of Pro198Leu polymorphism in patients with KD (21.1%) was significantly higher than that in controls (10.7%), and the polymorphism frequency in the chronic KD group was the highest. Further study confirmed that there was a synergistic interaction between 198 allelic polymorphisms and selenium deficiency, and that overexpression of GPx-1 (198Leu) in neonatal rat cardiomyocytes decreased the activity of GPx-1 enzyme by 30%. Variation at residue 198 in *GPx-1* gene might modify the function of the GPx-1 protein regulated by selenium, with the mutant requiring more selenium to achieve the same enzyme activity as the wild type. In 2014–2015, Jiang *et al.* [55] investigated blood selenium, GPx-1 enzyme activity and *GPx* gene polymorphism in 30 patients with KD and 30 healthy individuals. They found that the decrease of GPx enzyme activity was largely related to low selenium and *GPx* gene polymorphism. The blood selenium index and the GPx-1 enzyme activity in patients with *Gpx-1* gene polymorphism were significantly lower than those in normal controls ( $t = 14.632$ ,  $P < 0.05$ ), suggesting that the interaction of *GPx* gene polymorphism and selenium deficiency could increase the risk of KD onset. Moreover, Wei *et al.* sequenced the *GPx* gene in KD patients and healthy controls. In that study, four and 24 mutated loci were detected in the promoter and exon regions of the *Gpx1* gene, respectively, and a higher mutation frequency in exon 474 was detected in the KD group (7/36 vs. 2/41). Moreover, the blood selenium level and Gpx activity were lower in KD patients than in healthy controls in this KD-endemic region [56]. The above studies indicate that the synergistic interaction of low blood selenium and *GPx* gene polymorphism results in a decrease of GPx-1

enzyme activity, which increases the susceptibility to KD, and that Pro198Leu at *GPx-1* is related to the risk of KD onset.

The human *SCN5A* gene is a member of the voltage-gated sodium channel family. It is expressed in human heart tissue, and has been shown to be mutated in many cardiomyopathy and arrhythmia cases. Jiang [57] studied the association between the H558R polymorphism of *SCN5A* and KD. For this, they recruited 71 KD patients and 80 region-matched control subjects from a KD-affected area in northeast China and found that the H558R polymorphism of exon 12 is significantly associated with KD, which might increase susceptibility to KD and QRS duration prolongation in Electrocardiograph. Moreover, Allele C carriers had a decreased risk for KSD with an odds ratio of 0.332 (95% CI, 0.160–0.692).

### Gene mutations and Keshan disease

Mutation of the *SCN5A* gene, which encodes a myocardial sodium channel, leads to cardiac electrophysiological disorders, resulting in Brugada syndrome, hereditary long QT syndrome and cardiac conduction system dysfunction. Mutations in the coding region of the *SCN5A* gene can also cause familial and hereditary cardiomyopathy, leading to sudden cardiac death. Moreover, recent studies have shown that *SCN5A* gene mutations can also damage the contractile function of the myocardium, leading to the development of dilated cardiomyopathy into heart failure [57]. In 2007, Han Shuang *et al.* reported a study of *SCN5A* gene mutations in KD patients, as determined by PCR. Specifically, they determined the sequence of exon 28 of the *SCN5A* gene in KD patients, and the results showed that an abnormal single strand was found in KD patients, and point mutations were present in exon 28 of the *SCN5A* gene, indicating that the structure of the *SCN5A* gene-encoded myocardial sodium channel in KD patients differs from that in the normal population. This suggests that *SCN5A* gene mutation might be one of the factors leading to increased susceptibility to environmental factor-induced KD [58].

**Table 2** Gene polymorphism and mutation in Keshan disease patient

Gene name	Site	Change	Gene ID	Description	Location	Author
Gene polymorphism <i>HLA-DRB1</i>			3123	Major histocompatibility complex, class II, DR beta 1	Chromosome 6, NC_000006.12	
	DR15, DR4, DR9 DR7 DR15	Up-regulated Down-regulated Exist genetic susceptibility				XiaolinNiu Jin Wei Yaping Wang
<i>GPX-1</i>	198	Pro198Leu	24 404	Glutathione peroxidase 1	Chromosome 8, NC_005107.4	Cong Lei
<i>SCN5A</i>	Exon 474 Exon 12	A higher mutation frequency H558R polymorphism	6331	Sodium voltage-gated channel alpha subunit 5	Chromosome 3, NC_000003.12	H.L. Wei Jiang S
Gene mutation <i>SCN5A</i>	Exon28	Exist genetic mutation	6331	Sodium voltage-gated channel alpha subunit 5	Chromosome 3, NC_000003.12	Shaung Han

The above studies show that KD is associated with multiple *HLA-DRB1* alleles. Meanwhile, a low selenium level and *GPx-1* gene polymorphisms showed synergistic effects on increasing the risk of KD onset. Mutation of the *SCN5A* gene might be one of the factors leading to increased susceptibility to environmental factors that induce the onset of KD. The gene polymorphism and mutation in KD patients were shown in Table 2.

### Conclusion

KD is an endemic cardiomyopathy that is exclusively found in China, Korea and Japan. According to the data on KD reported from 1990 to the present, clear progress has been made in controlling KD. The KD with detection rates had significantly decreased between 2000–2004 and 2005–2009. In terms of these historically severely affected KD provinces in 2010–2018, the crude annual detection rates of two provinces had lower than 5%. Studies shown that the DR15 allele of *HLA-DRB1*, the *GPx-1* gene (Pro198Leu), exon 474 of *GPX-1* gene and exon 28 mutation of the *SCN5A* gene were found at higher frequencies in KD patients; however, DR7 allele of *HLA-DRB1* and Allele C of H558R polymorphism of *SCN5A* were lower frequencies in KD patients.

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Data availability: data are available from the authors upon request. The data that support the findings of this study are available from the corresponding author (Xiaoping Li; e-mail: lixiaoping0119@163.com) upon request.

### Conflicts of interest

There are no conflicts of interest.

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