

Environmental Factors Influence the Rate of Human Herpesvirus Type 8 Infection in a Population with High Incidence of Classic Kaposi Sarcoma

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High prevalence of human herpesvirus type 8 (HHV-8) infection has been reported on the island of Sardinia. Among emigrants from Sardinia, rates of HHV-8 infection are lower than they are in Sardinia and are similar to those observed in the local population. Thus, environmental factors seem to play a relevant role in affecting the prevalence of HHV-8 infection.

Sardinia, a Mediterranean island west of Italy's mainland, is a region with one of the highest incidences of classic Kaposi sarcoma (KS) in the world [1]. For geographical and historical reasons, a very limited amount of immigration has been reported in Sardinia, thus contributing to clustering on the island of some genetic traits frequently found in the Sardinian population. Since the identification of human herpesvirus type 8 (HHV-8) as the etiologic agent of KS, many epidemiological studies have been conducted [2]. Unlike other herpesvirus infections, HHV-8 infection is not ubiquitous; the highest rates have been described in Central Africa, reaching up to 70% of the general population, whereas HHV-8 infection is quite uncommon in North America and northern Europe, with prevalences ranging from 0% to 10%. In the Mediterranean basin, an intermediate seroprevalence has been observed, ranging

from 5% to 40% in different regions in the area. So far, several surveys carried out in Sardinia have shown a high prevalence of HHV-8 infection in the healthy population (up to 40% in the northern part of the island), matching the area's high incidence of classic KS [3, 4]. Reasons for the high diffusion of HHV-8 infection are largely unknown, and environmental or genetic factors have been hypothesized to play a role.

Besides HHV-8, other cofactors are certainly involved in the pathogenesis of KS. Recently, it has been suggested that a genetic susceptibility to KS combined with HHV-8 infection may play a role in the pathogenesis of this disease [5]. Similar findings have been reported by other authors; however, the role of genetic factors in KS development and/or HHV-8 infection are far from being established [6, 7]. Furthermore, an elevated prevalence among relatives of persons with KS and high rates of intrafamilial infection have been observed [8, 9].

On the basis of reports demonstrating a correlation between classic KS incidence in Sardinia and the presence of specific HLA-DR alleles, we recently analyzed the existence of a possible correlation between the same genetic factors and susceptibility to HHV-8 infection among healthy individuals living in Sardinia [10]. This study did not reveal any significant association between the HLA-DR5 alleles that we examined and HHV-8 infection, indicating that the genetic traits that were tested are not linked to an increased risk of HHV-8 infection.

In the present survey, we further extended the research to evaluate potential genetic susceptibility to HHV-8 infection. Here, we have analyzed the prevalence of HHV-8 infection among healthy persons born in Sardinia who have immigrated stably to other regions of Italy characterized by a lower HHV-8 prevalence in the local population.

Methods. Volunteers were enrolled by contacting the Sardinian cultural clubs and associations that exist in many Italian cities to promote the gathering of Sardinian-born immigrants. Overall, we examined individuals living in the following 4 cities in north-central Italy: Florence (Tuscany), Parma (Emilia-Romagna), Piacenza (Emilia-Romagna), and Magenta (Lombardy). The majority of the Sardinian emigrants that were analyzed had been living away from Sardinia >30 years at the time of testing. A control population of healthy donors born in the same cities and matched with the study group by age and sex was also created in the above-indicated areas. Finally, we assayed a control group of healthy subjects born and living in Sardinia who were age- and sex-matched with the previous

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Table 1. Seroprevalence of human herpesvirus type 8 (HHV-8) among Sardinian emigrants and relative control subjects.

Region of residence	Sardinian subjects			Control subjects	
	<i>n</i>	Age range, years	HHV-8–infected	<i>n</i>	HHV-8–infected
Region of residence					
Magenta	46	21–78	3 (6.5)	47	4 (8.5)
Piacenza	50	21–78	4 (8.0)	50	4 (8.0)
Parma	121	14–82	7 (5.8)	48	2 (4.2)
Florence	56	18–79	2 (3.6)	60	2 (3.3)
Sardinia	254	18–83	71 (28.0)
Subtotal	273	...	16 (5.9)	205	12 (5.9)

NOTE. Data are no. (%) of subjects, unless otherwise indicated.

groups. All individuals who were analyzed had been previously informed of the study.

HHV-8 serostatus was determined by detection of antibodies to viral lytic antigens by indirect immunofluorescence, combined with the detection of specific antibodies to the K8.1 HHV-8 protein by ELISA, as reported elsewhere [4]. Serum samples were diluted 1:20 to assay the serostatus, and positivity was attributed to the sample that had positive results of both tests.

Results and discussion. As described in table 1, we analyzed 273 Sardinian-born subjects who had emigrated from the island (121 aged 20–49 years and 152 aged >50 years), 205 control subjects who were living in the examined areas, and 254 Sardinian subjects living on the island. Among Sardinian emigrants, the prevalence rates ranged from 3.6% to 8%. On the other hand, among the local control population, HHV-8 prevalence ranged from 3.3% to 8.5%. Interestingly, within each area assayed, no relevant difference in HHV-8 prevalence was found between Sardinian subjects and control subjects. Among the emigrants, as expected, age seemed to be a factor; indeed, 3 (2.5%) of 121 subjects aged 20–49 years were seropositive, compared with 13 (8.6%) of 152 subjects aged >50 years. On the other hand, sex did not seem to be relevant, because 9 (5.8%) of 155 men and 7 (5.9%) of 118 women were found to be seropositive, and quite similar rates were observed among men and women in the control group (5.9% vs. 5.8%). Finally, among control subjects born and residing in Sardinia, 71 (28.0%) of 254 were found to be seropositive for HHV-8, which is in line with previous surveys conducted on the island [3, 4, 10]; among control subjects, seroprevalence was higher in individuals >50 years old, compared with individuals aged 20–49 years (36.9% vs. 16.8%), whereas no significant difference was observed between men and women (28.1% vs. 27.7%).

The relatively low HHV-8 prevalence reported among Sardinian emigrants, compared with that observed among Sardinians living on the island, and the very similar prevalence

rates found between emigrants and the control population living in the analyzed areas of Italy's mainland seem to indicate the Sardinians' lack of a genetic predisposition to be infected by HHV-8.

Nonetheless, the uneven distribution of this viral infection throughout the world still needs to be explained, and it might be related to the way HHV-8 is transmitted. Although the routes of HHV-8 infection are not fully understood, a growing body of evidence shows that HHV-8 is frequently shed in the saliva of seropositive subjects. Therefore, living in a population with a high prevalence of HHV-8 infection, as it is the case in Sardinia, might represent a higher risk for exposure to the virus released in the saliva by a seropositive individual. Thus, it is conceivable that environmental, behavioral, or other factors play major roles in affecting HHV-8 infection, whereas a genetic predisposition might be a cofactor in causing the development of KS in HHV-8–infected persons.

Occupation has been considered as a potential factor that could affect the risk of infection with HHV-8. The data collection form used at the time of blood collection also requested information regarding the occupation of each subject who was assayed. Although our study was not specifically designed to evaluate the potential role of occupation as a risk factor for HHV-8 infection, analysis of data we collected revealed that Sardinian emigrants living in Florence, Piacenza, and Magenta are mostly employed in offices or industries (indoor occupations), whereas in Parma, they are more frequently employed as agricultural workers (outdoor occupations); in the latter case (agricultural workers), lifestyle is more similar to that of a high number of Sardinians living on the island. Nevertheless, in Parma, no significant difference could be observed between the 2 groups, and the rate observed among emigrants is significantly lower than that observed in Sardinia. Should this observation be confirmed by the analysis of a larger group, the potential role of occupation could be ruled out, which has been invoked as one of the factors involved in the high prevalence

alence of HHV-8 infection, as well as incidence of classic KS, reported on the island.

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