Evidence for a Recessive Major Gene Predisposing to Human Herpesvirus 8 (HHV-8) Infection in a Population in Which HHV-8 Is Endemic

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Infection by human herpesvirus 8 (HHV-8), as measured by the presence of specific antibodies, was shown in countries in which HHV-8 infection is endemic to exhibit familial aggregation and a peculiar variation with age (rapid increase until puberty followed by a plateau in young adults). To investigate whether host genetic factors could explain these findings, a segregation analysis was performed of 81 families of African origin (1623 subjects; HHV-8 seroprevalence, 11.9%) living in a village in French Guiana in which HHV-8 infection is endemic. Results provide evidence for a recessive gene controlling susceptibility or resistance to HHV-8 infection. This gene is predicted to have a major effect during childhood, with almost all homozygous predisposed subjects (∼6% of the population) being infected by age 15. For nonpredisposed subjects, HHV-8 infection in childhood strongly depends on virus exposure (through an HHV-8–infected mother), whereas the risk of infection appears to be low in young adults, with no evidence for heterosexual transmission.

In the early 1990s, epidemiological studies suggested that Kaposi sarcoma (KS) in human immunodeficiency virus (HIV) type 1–infected persons was caused by a sexually transmitted infectious agent [1]. There is now accumulating evidence showing that human herpesvirus 8 (HHV-8), also known as KS-associated herpesvirus, is the etiologic agent of all forms of KS [2, 3]. Cohort studies have shown that, among homosexual men, HHV-8 is transmitted during sex [4–9]. However, the occurrence of pediatric KS, as well as the high seroprevalence of HHV-8 infection in children from countries in which HHV-8 infection is endemic, especially in Africa [10–18], indicate the existence of nonsexual transmission routes. In particular, mother-to-child transmission was suggested, because HHV-8–seropositive children are more likely to have a seropositive mother [16, 19]. Moreover, our previous work conducted in a large population in which HHV-8 is endemic has shown strong familial aggregation in HHV-8 infection. Present in part: 4th International Workshop on Kaposi’s Sarcoma–Associated Herpesvirus and Related Agents, Santa Cruz, California, 5–8 August 2001 (abstract 22), 11th annual meeting of the International Genetic Epidemiology Society, New Orleans, 14–16 November 2002 (abstract 110).

Informed consent was obtained from adults or from parents of minors, and human experimentation guidelines from the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale at Necker Hospital, Paris, and the Commission Nationale de l’Informatique et des Libertés were followed.

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8 seroprevalence, with high mother-child and sibling-sibling (sib-sib) correlations [20]. Together, these results raise the hypothesis of virus transmission through close contacts, mainly through saliva, where HHV-8 has been detected [18, 21–25]. However, a striking observation, reported by the few studies in countries in which HHV-8 is endemic, is that HHV-8 seroprevalence increases rapidly until puberty and then remains stable between the ages of 15 and 40–50 years [20, 26, 27]. This peculiar HHV-8 seroprevalence pattern and the observation that some highly exposed subjects are not infected suggest that a significant proportion of the population may be resistant or less susceptible to HHV-8 infection.

For several years, we have been conducting a large epidemiological study of a whole population to detect host genetic predisposition to endemic viruses. Data were collected from 2 isolated villages of French Guiana, Maripasoula and Papatun (2000 and 700 inhabitants, respectively), which are located in the Amazonian rain forest of northeastern South America between Brazil and Surinam. Most subjects of these villages (~80%) belong to an ethnic group referred to as Noir-Marron, who are descendants of Africans who escaped from Dutch plantations in the 18th century. We first investigated in this population the risk factors of infection by human T cell leukemia/lymphoma virus type I (HTLV-I), and details have been provided elsewhere [28, 29]. Recently, we were interested in the genetic epidemiology of HHV-8 infection. The first step of the present study was to determine the risk factors and the familial aggregation of HHV-8 infection in 1337 Noir-Marron subjects of this population from French Guiana among whom HHV-8 is endemic [20]. Results have shown, first, a high HHV-8 seroprevalence (13.2%) in this ethnic group, with age as the only risk factor for HHV-8 seropositivity (in particular, there was no correlation between HHV-8- and HTLV-I-seropositive status, and none of the 300 people aged 18–34 years were HHV-1-positive), and, second, a familial aggregation of HHV-8-seropositive persons with strong mother-child and sib-sib correlation. The goal of the present study was to investigate by means of segregation analysis the existence of a major gene involved in the susceptibility or resistance to HHV-8 infection.

SUBJECTS AND METHODS

Study population. The familial structure of the studied population was the same as that used to study HTLV-I infection [29] and will be summarized briefly. All consenting Noir-Marron persons >2 years old (1623 subjects; 871 females and 752 males) living in the 2 villages and with identified familial relationships were included, representing 80% of the total Noir-Marron population of these villages. Demographic (age, sex, place of birth, home location, and type and location of dwelling) and medical (parity, gravity, and histories of hospitalization and blood transfusion) data were collected by interview and/or from medical files. Information on familial relationships was obtained on the basis of several crossed interviews, and the validity of genealogical data was checked with the local medical team and the population. The 1623 Noir-Marron subjects belonged to 81 families distributed among 21 nuclear families, 33 families with <30 persons, 22 families with 30–100 persons, and 5 families with >100 persons.

Biological methods. A 10-ml blood sample was taken from 1224 of the 1623 included subjects for HHV-8 determination; for the remaining 399 persons, mainly children, drops of blood were put on filter paper. Plasma samples and filter papers were tested at a 1:20 dilution for HHV-8-specific IgG by immuno-fluorescence assay (HHV-8 IFA; ABI) [30]. This assay, which uses the KS-1 cell line as the source of HHV-8, detects antibodies directed mainly against lytic HHV-8 antigens, is well adapted to epidemiological studies [30], and does not react with any other known human herpesviruses, including Epstein-Barr virus. To assess the properties of this assay when done on filter papers, we tested a panel of 100 persons (children and adults) with high HHV-8 seroprevalence (~50%) by use of both plasma samples and filter papers. The specificity and sensitivity of the assay done on filter papers were 100% and 88%, respectively. Because there were 8 HHV-8-seropositive subjects among the 399 tested by filter papers in the present sample, this indicates that the number of false-negative subjects is not expected to exceed 2 and should not have any substantial influence in our analyses.

Statistical methods. The phenotype of interest for segregation analysis was a binary trait—that is, HHV-8–seropositive or –seronegative status. Segregation analysis was done by use of the regressive logistic model [31], which specified a regressor relationship between the probability of a person to be infected (i.e., to be HHV-8 seropositive) and a set of explanatory variables, including major genotype, phenotype of preceding relatives, and other covariates (or risk factors). The use of the regressive model allows us to analyze large families as a whole, to estimate simultaneously genetic and risk factor effects, and to consider different patterns of familial correlations for HHV-8 status. The parameters of the major gene are q (the frequency of allele D predisposing to be HHV-8-infected) and αDd, αDD, and αdd (the 3 baseline risks of being HHV-8-seropositive on the logit scale for the 3 genotypes, DD, Dd, and dd, respectively). Three additional parameters (τDDD, τDDD, and τDdD, which denote the probabilities of transmitting D for individuals DD, Dd, and dd, respectively [32]) were used to test the hypothesis of Mendelian transmission (τDDD = 1, τDDD = 0.5, and τDdD = 0) against alternative modes of transmission. Both failure to reject general transmission hypothesis (free τs) and rejection of no parent-offspring transmission (equal τs) are required to definitely conclude in favor of Mendelian transmission and, consequently, the presence of a major gene. In

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Figure 1. Age-dependent human herpesvirus 8 (HHV-8) seroprevalences among 1623 Noir-Marron of African origin from the villages of Maripasoula and Papaïchton, French Guiana. Plasma samples were tested for HHV-8–specific IgG by immunofluorescence assay with the Kaposi sarcoma–1 cell line, which detects antibodies directed mainly against lytic HHV-8 antigens. Error bars, 95% confidence intervals of seroprevalences.

the class D pattern of familial dependence [31] used in the present analysis, 4 types of phenotypic familial dependences are considered: father-mother (spouse-spouse), father-offspring, mother-offspring, and sib-sib, with corresponding regression coefficients denoted as \( \Gamma_{FM} \), \( \Gamma_{FO} \), \( \Gamma_{MO} \), and \( \Gamma_{SS} \) respectively. To account for unknown phenotypes, each \( \Gamma \) parameter is a vector of 2 coefficients [33]—that is, \( \Gamma_{FM} = (\gamma_{FM1}, \gamma_{FM2}) \), \( \Gamma_{FO} = (\gamma_{FO1}, \gamma_{FO2}) \), \( \Gamma_{MO} = (\gamma_{MO1}, \gamma_{MO2}) \), and \( \Gamma_{SS} = (\gamma_{SS1}, \gamma_{SS2}) \). For example, the logit of being HHV-8–seropositive for an individual is modified by \( \gamma_{MO1} \) or \( \gamma_{MO2} \) or remains unchanged when his or her mother is HHV-8–seronegative, HHV-8–seropositive, or unobserved, respectively. The only covariate that has a significant effect on the phenotype was age-coded as the square root of age in years, which was the best-fitting age function based on Akaike’s information criterion (AIC) [34]. Thus, results are presented with one parameter, \( \beta \), corresponding to the regression coefficient associated with square root of age, which may be genotype-dependent, denoted as \( \beta_{DD} \), \( \beta_{Dd} \), and \( \beta_{dd} \) to test gene-by-age interaction. Segregation analysis was done with the computer program REGRESS [35], which incorporates the regressive approach into the LINKAGE package [36]. No ascertainment correction was needed for likelihood computation, because all families of the villages were included in the analysis.

RESULTS

The overall HHV-8 seroprevalence was 11.9% (193/1623 subjects), slightly lower than that observed in our first sample of 1337 subjects [20], because there was a high proportion of children among the 286 subjects we added for the present study. HHV-8 seropositivity was strongly age dependent (figure 1), with this already noted peculiar pattern: at 2.9% for subjects <5 years old, HHV-8 seroprevalence increased to a plateau of ∼14% for subjects 15 and 40–50 years old, with a final increase to 32% in subjects ≥50 years old.

Results of segregation analysis are shown in table 1. As mentioned in Methods, all models include a regression coefficient associated with square root of age, accounting for the overall increase in HHV-8 seroprevalence with age. Familial dependences were first studied 1 by 1. There was strong evidence for a mother-offspring (model I vs. IIc; \( \chi^2 \) with 2 df; \( \chi^2 = 23.26; P < 10^{-5} \)) and a sib-sib dependence (I vs. IId; \( \chi^2 = 52; P < 10^{-2} \)). There was no evidence for a father-mother (I vs. IIa; \( \chi^2 = 0.71; P > 0.7 \)) or a father-offspring correlation (I vs. IIb; \( \chi^2 = 27; P > 0.8 \)), and the \( \Gamma_{FM} \) and \( \Gamma_{FO} \) parameters were fixed at (0 0) for further analyses. In the presence of mother-offspring correlation, the sib-sib dependence remained significant (IIc vs. IIe; \( \chi^2 = 12.15; P < 0.003 \)). There was no evidence for a father-mother (I vs. IIa; \( \chi^2 = 6.62; P < 0.04 \)) or a father-offspring correlation (I vs. IIb; \( \chi^2 = 8.60; P < 0.02 \)), and both \( \Gamma_{MO} \) and \( \Gamma_{SS} \) parameters were conserved for further analyses.

In analyses done with a major gene effect, the codominant model always tended towards a recessive model (\( \alpha_{DD} = \alpha_{dd} \)), and results are shown only for a recessive major gene, which was the best-fitting model with respect to AIC. In the presence of mother-offspring and sib-sib dependence, there was evidence for a recessive major gene (IIe vs. IIIa; \( \chi^2 = 23.26; P < 10^{-5} \)) and a sib-sib dependence (I vs. IId; \( \chi^2 = 12.15; P < 0.003 \)). There was no evidence for a father-mother (I vs. IIa; \( \chi^2 = 6.62; P < 0.04 \)) or a father-offspring correlation (I vs. IIb; \( \chi^2 = 8.60; P < 0.02 \)), and both \( \Gamma_{MO} \) and \( \Gamma_{SS} \) parameters were conserved for further analyses.

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Table 1. Segregation analysis of human herpesvirus 8 (HHV-8) serological status among 81 Noir-Marron families.

<table>
<thead>
<tr>
<th>Model, hypothesis</th>
<th>(q^2)</th>
<th>(\alpha_{DD}^a)</th>
<th>(\alpha_{Dd}^a)</th>
<th>(\alpha_{dd}^a)</th>
<th>(\gamma_{FM1}^c)</th>
<th>(\gamma_{FM2}^c)</th>
<th>(\gamma_{FO1}^c)</th>
<th>(\gamma_{FO2}^c)</th>
<th>(\gamma_{MO1}^c)</th>
<th>(\gamma_{MO2}^c)</th>
<th>(\gamma_{SS1}^c)</th>
<th>(\gamma_{SS2}^c)</th>
<th>(\beta_{DD}^d)</th>
<th>(\beta_{Dd}^d)</th>
<th>(\beta_{dd}^d)</th>
<th>(\tau_{DD}^e)</th>
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<th>(\tau_{dd}^e)</th>
<th>(-2\ln L + C^f)</th>
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<td>.35</td>
<td>(\beta_{DD}^d)</td>
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<td>43.66</td>
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<td>II. Familial dependences</td>
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<tr>
<td>a. FM</td>
<td>-3.68</td>
<td>(-.16)</td>
<td>(-.16)</td>
<td>.35</td>
<td>(\beta_{DD}^d)</td>
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<td>42.95</td>
<td>38.1</td>
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<td>b. FO</td>
<td>-3.67</td>
<td>.04</td>
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<td>.35</td>
<td>(\beta_{DD}^d)</td>
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<td>43.39</td>
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<td>c. MO</td>
<td>-3.64</td>
<td>.27</td>
<td>.85</td>
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<td>(\beta_{DD}^d)</td>
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<td>20.40</td>
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<td>d. SS</td>
<td>-3.65</td>
<td>.04</td>
<td>.04</td>
<td>.34</td>
<td>(\beta_{DD}^d)</td>
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<td>31.51</td>
<td>26.7</td>
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<tr>
<td>e. MO + SS</td>
<td>-3.60</td>
<td>.27</td>
<td>.73</td>
<td>.33</td>
<td>(\beta_{DD}^d)</td>
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<td>III. Mendelian recessive major gene</td>
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<tr>
<td>a. Residual MO + SS, no interaction</td>
<td>.21</td>
<td>-4.60</td>
<td>-39</td>
<td>- .36</td>
<td>.88</td>
<td>.04</td>
<td>.46</td>
<td>(\beta_{DD}^d)</td>
<td>[1]</td>
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<td>5.18</td>
<td>8.4</td>
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<td>b. Residual MO + SS, age interaction</td>
<td>.25</td>
<td>-4.99</td>
<td>-39</td>
<td>.94</td>
<td>.09</td>
<td>.09</td>
<td>1.89</td>
<td>.49</td>
<td>[1]</td>
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<td>c. Residual MO, age interaction</td>
<td>.24</td>
<td>-4.68</td>
<td>-31</td>
<td>.90</td>
<td>-1.90</td>
<td>.45</td>
<td>[1]</td>
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<td>d. No residual, age interaction</td>
<td>.27</td>
<td>-5.22</td>
<td>- .33</td>
<td>.89</td>
<td>1.84</td>
<td>.44</td>
<td>1.00</td>
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<td>IV. Major effect with age interaction and residual MO</td>
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<tr>
<td>a. No parent-offspring transmission</td>
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<td>-4.96</td>
<td>- .37</td>
<td>1.07</td>
<td>-1.91</td>
<td>.47</td>
<td>.70</td>
<td>(\tau_{DD}^e) (\tau_{DD}^e)</td>
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<td>b. General transmission</td>
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<td>- .33</td>
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</table>

**NOTE.** All parameters in brackets are fixed at value shown. A dot (•) indicates that parameter is fixed at 0; a dash (—) indicates that parameter is not relevant for model considered. FM, father-mother; FO, father-offspring; MO, mother-offspring; SS, sibling-sibling.

\(a\) Frequency of allele D predisposing to be HHV-8-infected.

\(b\) Baseline risks of being HHV-8-infected on logit scale corresponding to 3 genotypes: DD (\(\alpha_{DD}^a\)), Dd (\(\alpha_{Dd}^a\)), and dd (\(\alpha_{dd}^a\)).

\(c\) Regression coefficients associated with following familial dependences: FM (\(\gamma_{FM1}^c\), \(\gamma_{FM2}^c\)), FO (\(\gamma_{FO1}^c\), \(\gamma_{FO2}^c\)), MO (\(\gamma_{MO1}^c\), \(\gamma_{MO2}^c\)), and SS (\(\gamma_{SS1}^c\), \(\gamma_{SS2}^c\)).

\(d\) Age regression coefficients according to genotype DD (\(\beta_{DD}^d\)), Dd (\(\beta_{Dd}^d\)), or dd (\(\beta_{dd}^d\)).

\(e\) Probabilities of transmitting D for individuals DD, Dd, and dd, respectively.

\(f\) "C" represents twice log likelihood (\(2\ln L\)) of model IIIb (\(\tau_{1206.37}\)).

\(g\) Akaike's information criterion (AIC) with baseline taken as AIC value of model IIIc (\(\tau_{1219.18}\)).
and 1 df, because $\alpha_{DD}$ tends toward $\alpha_{DD} (= \alpha_{DD})$ in the gene-by-age interaction recessive model, indicating that the genetic effect is entirely accounted for by the difference between $\beta_{DD}$ and $\beta_{dd} (= \beta_{dd})$. Overall, the test for the presence of a recessive major gene with gene-by-age interaction was highly significant (IIc vs. IIIb: $\chi^2 = 13.78; P < .002$). In the presence of this recessive major gene, there was no evidence for any residual sib-sib correlation (IIc vs. IIIb: $\chi^2 = .81; P > .6$), whereas the mother-offspring dependence remained significant (IIIc vs. IIIc: $\chi^2 = 9.97; P < .01$). In the presence of mother-offspring dependence, the transmission of the recessive major effect with gene-by-age interaction was compatible with the Mendelian hypothesis (IIId vs. IVb: $\chi^2 = 11.76; P < .005$), assuming the conclusion of the presence of a recessive major gene influencing HHV-8 infection.

Under this recessive genetic model, the frequency of predisposing the allele D was estimated at .24, indicating that ~6% of subjects are DD-homozygous, predisposed to HHV-8 infection. With respect to the overall HHV-8 seroprevalence in the population (11.9%), it is clear that a substantial proportion of HHV-8-seropositive persons are predicted to have sporadic cases. The influence of age and HHV-8 maternal status on the penetrance—that is, the probability of being HHV-8-seropositive according to genotype, is shown in figure 2 for children <15 years. By age 15, the penetrance is predicted to be almost complete (>9) for DD predisposed children whatever the maternal status, whereas it reaches .03 or .11 for Dd/dd children with HHV-8-seronegative or HHV-8-seropositive mothers, respectively.

**DISCUSSION**

The investigation of human genes controlling susceptibility or resistance to infection by viral agents, as measured by serological status, is a recent research domain. Major genetic findings have been obtained in HIV infection with the demonstration that the HIV-1-seropositive or -seronegative status was strongly associated with a 32-bp deletion in the gene encoding CCR5—that is, persons homozygous for the deletion were highly protected against HIV-1 infection [36–39]. A more recent result was the detection by segregation analysis of a dominant major gene predisposing to HTLV-I infection in children in our population in French Guiana among whom HTLV-I is endemic [29]. Familial aggregation of the HHV-8-seropositive status was already found in countries in which HHV-8 infection is endemic, and we report here the first study investigating whether these familial correlations may be explained, at least in part, by genetic factors influencing HHV-8 infection. The results of our segregation analysis show clear evidence for the presence of a recessive major gene with gene-by-age interaction predisposing to HHV-8 infection, as measured by the presence of specific antibodies. Fur-

**Figure 2.** Penetrance (i.e., probability of being human herpesvirus 8 [HHV-8]–seropositive) for children <15 years old, according to age, genotype (DD, Dd, or dd), and HHV-8 status of mother, as predicted by model IIIc of table 1. D is the allele predisposing to HHV-8 infection. DD and Dd/dd genotypes are black and shaded lines, respectively. Solid line and dashed lines correspond to children with HHV-8–seropositive and –seronegative mothers, respectively.
thermore, the pattern of familial correlations observed during this analysis (i.e., the sib-sib correlation taken into account by the major gene effect and a mother-offspring dependence remaining significant with steady coefficients) strengthens the hypothesis of virus transmission from mother to child independent of a genetic effect but argues against a predominant virus transmission between siblings.

Under this recessive genetic model, ~6% of the population is DD-homozygous, predisposed to HHV-8 infection. As shown in figure 2, the HHV-8 penetrance increases with age; it is predicted to be almost complete for DD predisposed children by age 15, whatever the maternal status, and reaches 0.03 or 0.11 for Dd/dd children with HHV-8–seronegative or HHV-8–seropositive mothers, respectively. Taking into account the estimated frequency of allele D, this indicates that most HHV-8–seropositive children born of seronegative mothers (representing ~65% of HHV-8–seropositive children in our population) are predicted to have genetically determined cases (DD homozygous) whereas most HHV-8–seropositive children born of seropositive mothers are predicted to have sporadic cases. These results also suggest that the probability of being infected is much more dependent on virus exposure (through HHV-8–seropositive mothers) in genetically nonpredisposed children than in DD susceptible children who will rapidly become infected in an endemic context.

The finding that almost all DD predisposed subjects are predicted to be HHV-8–infected by age 15 years explains, at least in part, the steady level of HHV-8 seroprevalence observed between ages 15 and 49 years in our sample. In addition, the risk of HHV-8 infection for nonpredisposed young adults appears to be low, because there was no evidence for heterosexual transmission. Although cohort studies have shown transmission during sex in both homosexual men [6, 40, 41] and women at risk for HIV infection [42, 43] in industrialized countries, this transmission appears to depend on the number of sex partners and/or specific sexual practices [9, 40, 41]. This indicates that rather high and perhaps specific virus exposures could be required for adults to become infected. Furthermore, HHV-8–infected subjects in this latter context may include a substantial proportion of genetically predisposed subjects who would have had a very low risk of encountering the virus during childhood in countries in which HHV-8 is not endemic. Together, these observations support the view of a low risk of HHV-8 infection for young HHV-8–seronegative adults living in countries in which HHV-8 is endemic, leading to the steady prevalence observed between ages 15 and 49 years.

The increase in HHV-8 seroprevalence observed in the oldest age group, also described in Italian blood donors >50 years old [27], is more difficult to explain. Analysis of risk factors that may influence HHV-8 infection in these people did not provide any specific results, especially history of blood transfusion. Although a cohort effect cannot be ruled out, one can speculate that the immune response against HHV-8 infection may become less efficient in elderly adults, leading to a reactivation of a silent HHV-8 infection and/or facilitation of a new infection. Further studies focusing on this specific population are needed to investigate this hypothesis.

In conclusion, the present study provides evidence for a recessive gene controlling susceptibility or resistance to HHV-8 infection, as measured by the presence of specific anti–HHV-8 antibodies, in a population among whom HHV-8 is endemic. That gene has a major effect during childhood, and almost all homozygous predisposed subjects (~6% of the population) are infected by age 15. For nonpredisposed subjects, HHV-8 infection in childhood strongly depends on virus exposure (through an HHV-8–infected mother), whereas the risk of infection appears to be low for young adults with no evidence for HHV-8 heterosexual transmission. Linkage studies with genetic markers are ongoing to locate the major gene detected by the present analysis, as well as a new genetic epidemiology study to confirm these findings in another population in which HHV-8 is highly endemic. In addition to the dissection of the pathways involved in HHV-8 infection, the identification of such a gene may contribute to the understanding of the mechanisms leading to the development of KS.

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**References**

7. Melbye M, Cook PM, Hjärring H, et al. Risk factors for Kaposi’s...