Identification of a Herpes Simplex Labialis Susceptibility Region on Human Chromosome 21

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(See the editorial commentary by Koelle and Bergemann, on pages 331–4.)

Background. Most of the United States population is infected with either herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2, or both. Reactivations of HSV-1 infection cause herpes simplex labialis (HSL; cold sores or fever blisters), which is the most common recurring viral infection in humans.

Methods. To investigate the possibility of a human genetic component conferring resistance or susceptibility to cold sores (i.e., a HSL susceptibility gene), we conducted a genetic linkage analysis that included serotyping and phenotyping 421 individuals from 39 families enrolled in the Utah Genetic Reference Project.

Results. Linkage analysis identified a 2.5-Mb nonrecombinant region of interest on the long arm of human chromosome 21, with a multipoint logarithm of odds score of 3.9 noted near marker abmc65 (D21S409). Nonparametric linkage analysis of the data also provided strong evidence for linkage ($P = .0005$). This region of human chromosome 21 contains 6 candidate genes for herpes susceptibility.

Conclusions. The development of frequent cold sores is associated with a region on the long arm of human chromosome 21. This region contains several candidate genes that could influence the frequency of outbreaks of HSL.

Herpes simplex labialis (HSL) is a common and ubiquitous infection of the skin caused by herpes simplex virus (HSV). The vast majority of cases are due to HSV type 1 (HSV-1), although recurrent infections due to HSV type 2 (HSV-2) have been reported. Roughly 20%–40% of the population will experience labial or perioral outbreaks of vesicular herpetic lesions in their lifetime [1]. The frequency of these outbreaks is extremely variable, ranging, in some individuals, from rare episodes occurring every 5–10 years to outbreaks occurring monthly or on a more frequent basis among a small proportion of subjects. The severity of the illness is most often mild, although, for many persons, the illness can be uncomfortable and disfiguring. The psychological impact of having a prominent facial infection, particularly among young patients with frequent or severe recurrences, should not be underestimated. Among persons with underlying immunosuppression, lesions are of longer duration and may spread to cause major morbidity. Lastly, herpetic keratitis and herpes encephalitis are infrequent but grave complications of orofacial HSV-1 infection.

Herpes keratitis, which is due to HSV-1 infection of the corneal surface, is an important subset of HSV-1–induced diseases. Herpes keratitis is important among ocular infections in developed countries, because it is difficult to treat, recurs unexpectedly, and sometimes leads to corneal scarring and blindness [2]. Recurrences of HSV-2 infection account for the majority of cases of genital herpes. (A few cases are caused by recurrent HSV-1.) A large, recent serosurvey indicated that 17% of the US population—some 50 million persons—are infected with HSV-2 [3]. Of these HSV-2–infected persons, ~10%–20% (5–10 million persons) have recognized cases of genital herpes.

Three components are believed to account for reactivation of HSV-induced diseases in animal models and in humans. The first component is the virus itself, including the strain, the infecting inoculum, and the burden of latent virus within the ganglion. For instance, the com-
mon HSV-1 laboratory strains McKrae and 17 syn+ reactivate with reasonable frequency in mouse and rabbit models of disease [4, 5]. In contrast, the HSV-1 laboratory strain KOS does not reactivate readily in vivo, requiring explantation of the latently infected trigeminal ganglion before replicating virus appears [6]. Viral strain differences probably also occur in humans, although this has been less well studied in humans than in animals. The HSV-1 inoculum and the burden of latent virus within the ganglion also play an important role in the frequency of subsequent reactivations, at least in animal models [7, 8].

The second component contributing to expression of HSV-induced diseases is various environmental factors. Social stress, hyperthermia, hyperthermia, skin irritation, exposure to UV light, and immunosuppression are all well-established triggers for HSV reactivation in animal models [9]. In humans, fever, wind, sunburn, and surgical manipulation of the ganglion induce HSV reactivation [10].

The third component of susceptibility to HSL is host genetics. Differences among inbred strains of mice have a strong influence on the frequency of HSV-1 reactivation in animal models [11, 12]; for example, HSV-1 reactivates much more readily in BALB/c mice than in the C57Bl/6 mouse strain. Several studies have associated human HLA types with susceptibility to both HSL and genital herpes [13–17]. The HLA-A1 allele frequency is increased in patients with frequent outbreaks of genital herpes, whereas HLA-B27 appears to have a protective effect [17]. In patients with herpes simplex keratitis, an increased frequency of the HLA-B5 and Aw30 alleles was found [16]. HSV-1–induced erythema multiforme may be strongly linked to certain HLA-DQB1 alleles [15], but evidence for HLA linkage of the most common HSV-1–induced disease, HSL, is much weaker. Russell and Schlaut [18] found that HLA-A1 was significantly increased in patients with HSL, a finding not confirmed by Legendre et al. [19]. These older studies suffer from uncertainties in patient selection resulting from serological assays that could not distinguish infection with HSV-1 from infection with HSV-2. Humans that are genetically deficient in their capacity to either produce or respond to type 1 interferon are subject to severe HSV infections (reviewed in [20]), although these primary immunodeficiency states are quite rare within the population. Some new data suggest that apolipoprotein E alleles may affect the expression of HSV-1 disease, although, to date, these findings have not been confirmed in human populations [21, 22].

We performed an objective study to identify human genes that may be linked to HSL. We conducted HSL phenotyping of study subjects and correlated the findings with genotypes being determined through the Utah Genetic Reference Project (UGRP) [23–25].

**PATIENTS AND METHODS**

**Subjects.** The Utah Centre d’Etude du Polymorphisme Humain (CEPH) families consist of ~682 healthy people from 48 three-generation families whose DNA samples were included as part of the samples from 61 large families collected by the CEPH to map the human genome (Fondation Jean Dausset–CEPH Web site; available at: http://www.cephb.fr/) [26, 27]. Recently, a second set of samples was obtained from 39 of the original 48 families; this second set of samples comprises the UGRP. All of the persons studied were ≥18 years of age and were volunteers in the UGRP. Each of these individuals provided written informed consent approved by the University of Utah Institutional Review Board (IRB 6090-96).

**HSV-1 serological testing.** HSV-1 type-specific serological tests were performed on available serum samples from the subjects included in the 39 UGRP families studied. Glycoprotein-G–based type-specific ELISA was performed on serum obtained from each individual, according to the manufacturer’s instructions (HerpeSelect test; Focus Diagnostics). The IgG-based ELISA used to serotype the subjects is a qualitative test that has been developed and validated against the reference-standard herpes Western blot analysis for HSV-1 and HSV-2. An “ELISA index” is derived for each of the individuals tested, by comparing the absorbance of their serum samples against high-positive, low-positive, and negative standard serum samples supplied with the kit.

**Phenotyping of the UGRP subjects.** The subjects were asked to report information about episodes of HSL (i.e., cold sores or fever blisters) via a standardized questionnaire. The subjects were then asked to distinguish the appearance of cold sores, which normally occur on the lips, nose, or face, from that of canker sores (i.e., aphthous ulcers), which normally occur inside the mouth on the tongue, cheeks, or gums. Information about HSL triggers, HSL episodes in the subject’s lifetime (hereafter referred to as “lifetime episodes”), and prodromal symptoms was also collected, but this information was less complete than data on the annual frequency of HSL. HSV-1–seropositive subjects were classified as “frequently affected” if they experienced ≥2 HSL episodes annually, “mildly affected” if they experienced 0.1–1.9 episodes annually, and “unaffected” if they had never experienced any HSL lifetime episodes (but were still HSV-1 seropositive).

**Genotyping and linkage analysis.** Microsatellite genotyping data across the entire genome, obtained from the CEPH Ge- notype Database (version 9.0; available at: http://www.cephb.fr/ cephdb/), was used for the linkage analysis. Genotype data for ≥12 families were available at each marker across the chromosome 21 candidate region. Genetic linkage analysis was performed using the FASTLINK program (version 1.0; available at http://linkage.rockefeller.edu/soft/) to compute a logarithm of odds (LOD) score to measure the likelihood of observing linkage purely by chance between the frequently affected and unaffected phenotypes and each genetic marker. The linkage analysis was performed under the assumption of autosomal dominant and recessive modes of inheritance.
Calculation of heritability. Heritability was calculated as the proportion of phenotypic variance explained by the additive genetic effects while accounting for the age and sex covariates. The Sequential Oligogenic Linkage Analysis Routines software package (version 4.1.0; available at http://www.sfbr.org/solar) was used to fit a variance components model for estimating heritability [28].

RESULTS

HSV-1 serological testing. Of the 431 serotyped individuals from 39 separate UGRP families, 327 (76%) were seropositive, 103 (24%) were seronegative, and 1 (0%) had equivocal findings. The 327 HSV-1–seropositive subjects were selected for further study.

Phenotyping of the UGRP subjects. Of the 103 HSV-1–seronegative individuals reporting, 22 (21%) indicated that they had experienced ≥1 HSL episode. (All of the HSV-1–seronegative individuals who reported having HSL reported 0.1–1.9 episodes of HSL/year, which would categorize the subjects as having a mildly affected phenotype, a phenotype category not used in the subsequent linkage analysis.) The annual frequency of HSL was self-reported by 255 (78%) of the 327 HSV-1–seropositive individuals. Sufficient information to allow calculation of an annual HSL frequency was obtained for an additional 30 subjects, on the basis of their ages, the number of reported HSL lifetime episodes, and the age at onset of HSL. (For 30 of these 31 subjects, the annual frequencies of HSL were calculated to be 0.1–1.9 episodes/year, which would categorize them as having a mildly affected phenotype, a phenotype category not used in the subsequent linkage analysis.) Therefore, the annual frequency of HSL was available for 285 (87%) of the 327 reporting seropositive individuals. Phenotyping according to the annual frequency of HSL is shown in table 1.

Table 1. Sex distribution and reporting of herpes simplex labialis (HSL) phenotypes of herpes simplex virus type 1 (HSV-1)–seropositive individuals.

<table>
<thead>
<tr>
<th>HSL phenotype</th>
<th>Subjects, no.</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>All</td>
<td></td>
</tr>
<tr>
<td>Unaffected&lt;sup&gt;a&lt;/sup&gt;</td>
<td>48</td>
<td>37</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Mildly affected&lt;sup&gt;b&lt;/sup&gt;</td>
<td>63</td>
<td>48</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>Frequently affected&lt;sup&gt;c&lt;/sup&gt;</td>
<td>54</td>
<td>35</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>All affected</td>
<td>165</td>
<td>120</td>
<td>285</td>
<td></td>
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<tr>
<td>Unknown/no report</td>
<td>17</td>
<td>25</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Total&lt;sup&gt;d&lt;/sup&gt;</td>
<td>182</td>
<td>145</td>
<td>327</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Had never experienced any HSL lifetime episodes (but were still HSV-1 seropositive).

<sup>b</sup> Experienced 0.1–1.9 HSL episode annually.

<sup>c</sup> Experienced 0.1–1.9 HSL episodes annually.

<sup>d</sup> All HSV-1 seropositive subjects.

Thirty percent of the reporting UGRP subjects had never experienced an HSL episode (unaffected phenotype). These subjects were HSV-1 seropositive but had never had any recognized episodes of HSL, which is suggestive of protection from HSV-1–induced disease. At the other end of the spectrum were HSV-1–seropositive subjects who had been definitely and repeatedly affected by HSL episodes, some on a nearly monthly basis. A cutoff of ≥2.0 HSL episodes/year was chosen to include the most frequently affected 31% of subjects. The remaining 111 individuals had an indeterminate or mildly affected phenotype.

Using the extremes of the self-reported phenotypes (the unaffected phenotype vs. frequently affected phenotype) gave a high level of confidence in selecting patients for the subsequent genetic analysis. The main disadvantage of these phenotype rules is that 111 individuals (39%) who experienced HSL (but 0.1–1.9 HSL episodes/year) had an “uncertain” phenotype or a “mildly affected” phenotype. To keep the phenotypes as clearcut as possible for the analysis, these subjects with a “mildly affected” phenotype were excluded from the subsequent linkage analysis.

HSV-1 serological findings versus HSL episodes. To investigate the relationship between reported HSL episodes and “antibody titers” in the UGRP subjects, a regression analysis was performed on the HSL frequency and the ELISA index (figure 1). There was a weak (Spearman’s rank correlation, $r^2 = 0.048$) but significant ($P < .0001$) correlation between these 2 measurements.

HSL phenotypes are not dependent on age or sex. Among the 327 HSV-1–seropositive individuals, there was a trend toward women being more likely to self-report (or provide other data that allowed computation of) HSL frequency than were men (165 of 182 women vs. 120 of 145 men; $P = .05$, by Fisher’s exact test). However, the distribution of HSL phenotypes between the sexes was not different ($P = .57$, by $\chi^2$ test for trend).

Possible effects of age on the distribution of unaffected and frequently affected individuals were examined by categorizing the HSV-1–seropositive subjects on the basis of age quartiles and examining the mean HSL frequency for each group, as well as by

![Figure 1. Distribution of the ELISA index and the annual herpes simplex labialis (HSL) frequency.](https://academic.oup.com/jid/article-abstract/197/3/340/2908614/19734202006144/20/53/March/1999)
Linkage analysis. Two-point linkage analysis was performed using CEPH (version 9.0) genotyping data available from all 39 phenotyped families. The highest LOD score for the dominant model was 2.72 at marker D21S120 on chromosome 21, and the highest LOD score for the recessive model was 3.08 at marker abmc65 (D21S409) (table 2). The negative LOD scores at markers abmc37b (D21S1234) and above, as well as the recombination at abmc2 (D21S364) and below, further focuses the candidate region to the area between and containing these 2 markers. Thus, the “nonrecombinant” candidate region contains markers abmc37b (D21S1234), P21-4U (D21S110), abmc65 (D21S409), and abmc2 (D21S364).

Because recombination events were identified in the recessive model, multipoint analysis could be performed using this model. Multipoint analysis was performed using LINKMAP, a subroutine of the FASTLINK genetic analysis software package. We analyzed adjacent markers carrying out sequential 3-point linkage runs across the region from D21S120 to marker abmc3. This multipoint analysis revealed a maximum LOD score of 3.87 at marker abmc65 (D21S409), by use of the recessive model.

To avoid dependence on the autosomal dominant or recessive modes of inheritance, nonparametric analysis using the GENEHUNTER linkage analysis program (version 1.1; available at http://linkage.rockefeller.edu/soft/) was performed on the human chromosome 21 region for which linkage was determined by the conventional analysis. Linkage was confirmed by this

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**Table 2. Two-point logarithm of odds (LOD) scores for Centre d’Etude du Polymorphisme Humain markers on chromosome 21q.**

<table>
<thead>
<tr>
<th>Model, marker</th>
<th>0.001</th>
<th>0.01</th>
<th>0.05</th>
<th>0.10</th>
<th>0.20</th>
<th>0.30</th>
<th>0.40</th>
<th>D number</th>
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<td>Autosomal dominant</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>p26C</td>
<td>1.21a</td>
<td>1.19</td>
<td>1.08</td>
<td>0.94</td>
<td>0.62</td>
<td>0.32</td>
<td>0.09</td>
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</tr>
<tr>
<td>abmc53</td>
<td>1.87a</td>
<td>1.84</td>
<td>1.68</td>
<td>1.47</td>
<td>1.02</td>
<td>0.57</td>
<td>0.19</td>
<td>D21S408</td>
</tr>
<tr>
<td>D21S120</td>
<td>2.72a,b</td>
<td>2.67</td>
<td>2.44</td>
<td>2.12</td>
<td>1.45</td>
<td>0.80</td>
<td>0.26</td>
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</tr>
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<td>abmc37b</td>
<td>−0.14</td>
<td>−0.00</td>
<td>0.29</td>
<td>0.39a</td>
<td>0.35</td>
<td>0.20</td>
<td>0.06</td>
<td>D21S1234</td>
</tr>
<tr>
<td>p21−4U</td>
<td>−0.72</td>
<td>−0.52</td>
<td>−0.07</td>
<td>0.15</td>
<td>0.23a</td>
<td>0.15</td>
<td>0.05</td>
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<tr>
<td>abmc65</td>
<td>2.26a</td>
<td>2.22</td>
<td>2.04</td>
<td>1.78</td>
<td>1.21</td>
<td>0.65</td>
<td>0.19</td>
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<td>0.42</td>
<td>0.58a</td>
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<td>0.34</td>
<td>0.11</td>
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<td>2.00</td>
<td>1.91</td>
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<td>0.72</td>
<td>0.23</td>
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<td>1.09</td>
<td>1.05</td>
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<td>0.70</td>
<td>0.40</td>
<td>0.13</td>
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<td>VS17TB2</td>
<td>0.34</td>
<td>0.48</td>
<td>0.75</td>
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<td>0.69</td>
<td>0.43</td>
<td>0.17</td>
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<td>2.57</td>
<td>2.34</td>
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<td>0.75</td>
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<td>1.77</td>
<td>1.12</td>
<td>0.4</td>
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<td>0.01</td>
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<td>1.73</td>
<td>0.96</td>
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<td>0.63</td>
<td>1.77</td>
<td>2.08a</td>
<td>1.78</td>
<td>1.07</td>
<td>0.37</td>
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<tr>
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<td>VS17TB2</td>
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</tr>
<tr>
<td>abmc13</td>
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<td>1.53a</td>
<td>1.32</td>
<td>0.83</td>
<td>0.29</td>
<td>D21S368</td>
</tr>
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</table>

a The highest LOD score for each marker.

b Peak LOD score for the dominant model.

c Multipoint LOD score of 2.3 maximized between markers abmc65 (D21S409) and abmc52 (D21S406).

d A 2.5-Mb region of nonrecombination. Nonparametric analysis (performed using the GENEHUNTER program) of this region resulted in a P value of .0005 at marker abmc65 (D21S409).

e Multipoint LOD score of 3.9 maximized at marker abmc65 (D21S409).
nonparametric analysis at marker abmc65 (D21S409) and was found to be highly significant ($P$ = .0005).

**Heritability of the herpes phenotype.** The age- and sex-adjusted heritability of affected status (unaffected vs. frequently affected) was estimated to be 0.22 ($P$ < .00001). Age- and sex-adjusted heritabilities were also calculated for HSL lifetime episodes (0.21; $P < .001$) and the annual frequency of HSL (0.12; $P < .02$). Log transformation of the data did not appreciably affect the calculated heritabilities of these phenotypes.

**Herpes gene candidates on chromosome 21q.** The nonrecombinant region identified in the recessive model defines a 2.8-Mb HSL candidate region (University of California Santa Cruz Genome Bioinformatics; available at http://genome.cse.ucsc.edu/). This region of nonrecombination (D21S1234–D21S364) includes 4 known human genes and 2 unknown candidate genes for human HSL candidate genes. The National Center for Biotechnology Information Entrez Gene Web site (available at: http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene) was used to identify the possible function of each of these candidate genes, as presented in table 3.

**DISCUSSION**

The present study used genetic linkage analysis of members of 39 large Utah families to identify a region of herpes susceptibility on the long arm of human chromosome 21. This region of human chromosome 21 contains 6 candidate genes for herpes susceptibility. Expression of ≥1 of these candidate genes for herpes susceptibility is likely to affect the frequency of HSL recurrence in humans.

Our study found an annual frequency of HSL similar to that reported in other large surveys of HSL. For instance, Ship et al. [29] reported the occurrence of ≥2 HSL episodes/year among one-third of 1399 participants. In another cross-sectional study of blood donors in Wisconsin, of a total of 452 subjects, 71 (16%) had experienced ≥2 HSL episodes/year [30]. This finding is similar to that of our study, in which 100 (21%) of 480 total participants (including seropositive and seronegative individuals) reported ≥2 HSL episodes/year.

Two studies in the literature have addressed HSV-1 infections in twins [31, 32]. In the more recent study, that by Koelle et al. [32], approximately one-half of the twin pairs were concordant for HSV-1 serostatus (by Western blot analysis), and one-half were discordant. Unfortunately, neither study describes HSL frequency among the twin pairs. Animal studies and limited observations in humans suggest that a substantial portion of susceptibility to herpetic diseases is inherited. We calculated the heritability of human cold sores to be 0.22, a value similar to the heritabilities of fasting glucose (0.20), fasting insulin (0.23), tri-glyceride (0.20), and low-density-lipoprotein cholesterol (0.24) levels in blood [33–35].

One difficulty with the present study was in determining a valid and biologically relevant phenotype. The data set included 431 serotyped individuals from 39 families scattered across a large geographic area. This made the direct observation of HSL frequency virtually impossible, so self-reporting was employed. Some publications have based phenotyping for HSL on the annual frequency of recurrences [29, 36, 37]. Because infection with HSV-1 is generally believed to be required for episodes of HSL to develop, our analysis was limited to HSV-1–seropositive persons. The commercially available ELISA test that we selected for use, HerpeSelect HSV-1 (Focus Diagnostics), is type specific and has a sensitivity and specificity similar to those associated with HSV Western blot analysis. Although it might be possible for HSV-1–seronegative individuals to be infected with the virus and experience recurrences [38], this is not generally accepted in the field, so the exclusion of seronegative subjects appeared to be the best course for the linkage analysis. The data support the exclusion of seronegative subjects, because HSV-1–seronegative subjects were far less likely to report any HSL episodes, compared with HSV-1–seropositive subjects (21% vs. 70%; $\chi^2 = 38$; $P < .0001$). Of the seronegative subjects reporting any HSL episodes, most did not provide an annual HSL frequency, and only a single such individual reported ≥2 episodes/year. Nevertheless, the authors concede that self-reported phenotypes are far from perfect and that some individuals may over- or underreport their actual HSL frequency.

We selected ≥2 episodes/year as a somewhat arbitrary cutoff between mildly and frequently affected individuals, to allow categorization of the most severely affected one-quarter of the subjects into the frequently affected group. Only 1 subject included...
in the frequently affected group required estimation of the HSL frequency—a 61-year-old man who reported >100 HSL lifetime episodes. The other 96 subjects included in this group directly reported their annual HSL frequencies. Of course, the HSL frequencies in the unaffected group were all “0”; for the mildly affected group, the frequencies were 0.1–1.9 episodes/year. This comparison of the extreme phenotypes served to minimize the chances of including phenotyping errors in the linkage analysis.

Although women were somewhat more likely to report HSL frequency than were men, there were no differences in the frequency of HSL episodes in women versus men. We also showed that there is no correlation between age and frequency of HSL episodes. The weak yet highly significant correlation of serological findings (the ELISA index) with disease (the HSL frequency) is similar to previous findings in the literature showing higher HSV titers in persons affected by frequent reactivations [1]. This makes biological sense, because frequent HSV-1 reactivations serve as an antigenic boost leading to the stimulation of lots of antibodies and/or antibodies with a high affinity. Of course, these antibodies do not have access to the intracellular compartment (within neurons) where viral reactivation occurs, so high antibody levels cannot affect HSL frequency.

The linkage analysis data presented in this study indicate that a genetic element for herpes susceptibility lies on the long arm of chromosome 21. Surprisingly, no significant linkage was identified on chromosome 6 in the region known to include the HLA genes. These data suggest that the HLA region is not a major genetic determinant of the frequency of HSV-1 recurrences in our population. Three of the 6 genes in the chromosome 21 region that we identified are good candidates for playing a role in herpes reactivation.

Ubiquitin-specific protease 25 (USP25), a deubiquitinating enzyme, is expressed in neuroepithelial cells and postmitotic neurons. Ubiquitinating and deubiquitinating enzymes play an essential role in protein degradation via the 26S proteasome and, thus, regulate many cellular pathways, including protein trafficking, cell cycle regulation, transcription regulation, and chromatin remodeling [39]. In addition to these important pathways, ubiquitinated proteins play an essential role in viral budding from mammalian cells [40–42]. This makes USP25 an excellent candidate for playing a role in regulating HSV reactivation.

The human cellular receptor for group B coxsackieviruses and adenoviruses (CXADR) is a transmembrane glycoprotein that belongs to the immunoglobulin superfamily. Thoelen et al. [43–45] have described alternative splicing of the CXADR gene and the existence of 3 exon-skipping splice variants, in addition to the existence of the originally identified 7-exon mRNA transcript. Expression of the splice variants theoretically results in truncated proteins. These truncated CXADR proteins are predicted to lack the transmembrane region of the protein and may act as soluble receptors or perform other functions important in viral biology within the cell.

Yoshida et al. [46, 47] identified a novel member of the Tob/ BTG1 family of antiproliferative genes, termed “BTG3,” which is abundant in neuroepithelium. BTG3 expression was high in the ventricular zone of the developing central nervous system, as well as in the ovary, testis, prostate, thymus, and lung. Overexpression of BTG3 impaired serum-induced cell cycle progression from the G0/G1 phase to the S phase. In more recent work, they further showed that BTG3 interacts with the CCR4 transcription factor–associated protein Caf1. The CCR4 complex is involved in several aspects of mRNA metabolism, including transcription initiation, elongation, and mRNA degradation. Chen et al. [48] have shown that the CCR4 complex also has enzymatic properties demonstrating both RNA and single-stranded DNA 3’-5’ exonuclease activities. BTG3, which is a member of this complex, may play a role in regulating transcription of HSV genes during viral reactivation or in regulating the stability of HSV transcripts or genomes.

Of the remaining 3 genes, 2 are open-reading frames predicted to encode proteins with no currently known function (C21orf34 and C21orf91). The third gene, chondrolectin, has the characteristics of a type 1 membrane protein. It shows tissue-specific expression in the spleen, testis, prostate, and fetal liver. Expression is limited to the vascular muscle of the testis, smooth muscle of the prostate stroma, heart muscle, skeletal muscle, crypts of the small intestine, and red pulp of the spleen [49]. These characteristics suggest that chondrolectin is less likely than the other candidate genes to play a role in HSV reactivation disease.

The identification of susceptibility genes is important for gaining greater understanding of herpetic diseases and the factors that influence their frequency and severity in humans. The identification of the chromosome 21 HSL gene will provide a basis for new experiments in our research program centered on understanding herpes infection, latency, reactivation, and disease. Such insights may lead to new therapeutic strategies and interventions for HSV-induced diseases.

Acknowledgments

We thank all family members who participated in the Utah Genetic Reference Project (UGRP). We also thank Andreas P. Peiffer (UGRP Medical Director) and Melissa M. Dixon, (UGRP Study Coordinator). We also extend our thanks to Focus Diagnostics, makers of the HerpeSelect test, who provided most of the serological test kits used for the study.

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