This article examines the evidence of a genetic basis for cutaneous forms of lupus erythematosus (LE), namely, subacute cutaneous LE (SCLE) and discoid LE (DLE). The current theory is that multiple genes, including particular allelic polymorphisms, may confer susceptibility to these LE-specific skin diseases (Sontheimer 1996) and that perhaps some of these alleles may be shared with polymorphous light eruption (PLE), a common condition that is clinically related to lupus (Nyberg et al. 1997).

Sequeira (Sequeira 1903) described two pairs of sisters (not twins) affected by cutaneous LE (CLE), raising the possibility that it might be a familial condition. Since then, several studies have reported the occurrence of CLE, particularly DLE, in monozygotic twins (Steagall et al. 1962, Wojnarowska 1983) and first-degree relatives of lupus probands (Beckett and Lewis 1959, Leonhardt 1957). Gallo and Forde (Gallo and Forde 1966) suggested that inheritance of a “dominant gene,” with or without common environmental factors, may explain the observation of DLE across three generations of one family. A mathematical analysis of the age and sex distribution of DLE incidence in the population was also used in the 1960s by Rowell to support a genetic basis for DLE (Burch and Rowell 1968).

More recently, Lawrence et al. (Lawrence et al. 1987) investigated first-degree relatives of 37 patients with DLE in a case-control study. They found a significantly increased prevalence of DLE (3.5%) in 255 first-degree relatives of DLE probands compared with 0.5% in 664 controls. Heritability analysis suggested a polygenic inheritance, with 44% heritability. Several recent genome-wide marker scans for systemic LE (SLE) have subsequently been performed in families with multiple affected individuals to identify regions of the genome that may be linked to the disease phenotype (Gaffney et al. 1998, 2000, Gray-McGuire et al. 2000, Lindqvist et al. 2000, Moser et al. 1998, Nath et al. 2001, Shai et al. 1999). These scans confirm that susceptibility to lupus is likely to be determined by multiple genetic regions, with different susceptibility loci in different ethnic groups.

It has long been known that certain conditions predispose to CLE. For example, DLE has been described in patients and carriers of X-linked and autosomal-recessive chronic granulomatous disease (Arnett 1997, Yeaman et al. 1992) and is also associated with non-X-linked hyper-immunoglobulin M syndrome (Wolpert et al. 1998). We and others have found a higher prevalence of PLE in patients with both SCLE and DLE than in controls (Millard et al. 2001a, Nyberg et al. 1997), suggesting that they may share a common genetic background. The study of these conditions may help shed light on the genetic basis of LE in the future.
Techniques to Examine Susceptibility Genes in Cutaneous Lupus Erythematosus

There are several major approaches to the study of genetic susceptibility in any given complex (multifactorial) disease, including twin pair analysis, association analysis, family linkage studies (including “genome scans”), and transmission disequilibrium testing. Twin pair analysis is probably the best approach to investigate the relative importance of genetic and environmental factors in disease susceptibility; however, the prevalence of CLE is too low for a formal concordance study even in a large population-based twin sample. Association studies (case-control) examine the relationship between the disease and a given candidate gene in the population. They assume that the candidate gene is involved in the pathogenesis of the disease and that a specified allelic variant (polymorphism) of this gene will be overrepresented in patients compared with unaffected controls. For example, this approach has been used to support a role for corneodesmosin in psoriasis (Enerback et al. 2000). This technique requires careful phenotype selection and is vulnerable to the problem of matching the ethnic background of cases and controls (“population stratification”). Another potential problem is that the association between a candidate gene polymorphism and disease may exist only because the polymorphism is a marker for the real disease-causing allele, either at the same gene locus or at a nearby gene, with the marker and the disease alleles being in “linkage disequilibrium” (Ralston 1998).

Family linkage analysis has the advantage that it does not require a candidate locus and also avoids the problem of population stratification. However, it requires a large set of several hundred molecular markers to type polymorphisms throughout the entire genome to identify regions that are linked within the family to the disease. These genome-wide scans, used in human SLE, have identified high “logarithm of odds” (lod) scores for several regions, including FcγRIIA at band 1q23, the major histocompatibility complex (MHC) at 6p21.3, and 1q31, which includes the genes encoding interleukin (IL) 10 and Ro60 (Moser et al. 1998, Gaffney et al. 1998, Shai et al. 1999). No genome-wide searches have so far been performed in CLE, although DLE families with multiple affected individuals are probably sufficiently common for such an analysis in the future.

Transmission disequilibrium testing (TDT) assumes that a heterozygous parent should transmit the disease-associated allele to an affected child more often than the 50% expected from standard Mendelian inheritance (Lewis 2000). TDT therefore tests family linkage in the presence of association, avoiding the problem of population stratification, and may be used to narrow candidate regions identified through genome-wide searches. We are currently using TDT to investigate susceptibility genes for SCLE and DLE.

Candidate Genes in Cutaneous Lupus Erythematosus

Selection of candidate genes for analysis in complex multifactorial traits such as CLE draws on multiple sources of information. In the case of LE, these include family linkage studies in human and animal models of lupus, immunohistochemical analysis of skin samples, and studies of alleles identified as possible candidates in other (related)
autoimmune diseases. For example, at least 10 loci have been found to predispose to LE in New Zealand lupus-prone mice (Kono et al. 1994), in addition to the previously mentioned loci that are linked to human lupus. In the murine model, genetic susceptibility seems to confer different levels of pathogenesis, including separate loci for autoantibody production, specific organ destruction, and mortality. Only one locus, the MHC (H-2 in mice), is linked to all three levels of disease.

Immunohistochemical analysis may be used to localize the expression of specific proteins within the skin of patients with lupus, perhaps implying abnormal regulation of the underlying genes that encode these proteins. For example, increased keratinocyte expression of intercellular adhesion molecule-1 (ICAM-1) has been demonstrated in evolving ultraviolet (UV)-induced lesions of CLE and PLE, but not in healthy controls (Nyberg et al. 1999). Thus, ICAM-1, its ligand, and upstream regulators may be deemed possible candidates to study (Norris et al. 1992).

Association in other autoimmune disorders is reported for various loci encoding cytokines, cytokine receptors, antioxidant enzymes, and adhesion molecules in rheumatoid arthritis, dermatomyositis, and SLE. It is therefore possible that the polymorphisms at these loci may be candidates for the related autoimmune CLE.

Finally, a candidate gene may be inferred from knowing the therapeutic action of drugs used to treat the disease. For example, thalidomide, which inhibits tumor necrosis factor (TNF)-α, is particularly effective for treating SCLE and DLE (Wallace 1997). This suggests that TNF (or possibly one of its common polymorphisms) may contribute to the pathogenesis of CLE.

The Major Histocompatibility Complex

From such studies, a variety of candidate gene loci have emerged that may prove important in the pathogenesis of CLE. The most important of these loci to date are found within the MHC. The human MHC (Fig. 15.1) is a diverse genetic region that plays a crucial role in control of the immune response and that has recently been sequenced by the MHC Sequencing Consortium (1999). The human MHC genes, clustered together in a segment of chromosome 6 (6p21.3), are organized into three regions (I, II, and III) and encode three major classes of proteins: class I human leukocyte antigens (HLAs) (including the classical antigens A, B, and Cw), HLA class II antigens (DP, DQ, and DR), and class III molecules, including complement components, TNF (α and β), and heat shock proteins.

HLA Genes and Cutaneous Lupus Erythematosus

In several serologic studies of the class I and class II HLA regions in patients with SCLE (mainly Caucasian), the HLA A1, B8, DR3, DQ2, DRw52, C4null ancestral haplotype has been consistently identified as a susceptibility haplotype for SCLE, particularly in patients seropositive for anti-Ro/SSA (Bielsa et al. 1991, Herrero et al. 1988, Johansson-Stephansson et al. 1989, Provost et al. 1988, Søntfheim et al. 1981, 1982, Vazquez-Doval et al. 1992, Watson et al. 1991), confirmed by our recent analysis of HLA genes in 36 patients with SCLE (Millard et al. 2001b). This ancestral haplotype is associated with susceptibility to a variety of other autoimmune diseases, including insulin-dependent diabetes mellitus, dermatitis herpetiformis, and myasthenia gravis (Price et al. 1999).
Watson et al. (Provost and Watson 1993, Watson et al. 1991) found that this association was only present in SCLE, SLE, and Sjögren’s syndrome in the presence of anti-Ro/SSA, suggesting that the immunogenetic association is primarily with the production of antibody. There is substantial evidence to support the pathogenic role of the anti-Ro/SSA antibody in SCLE (Ben-Chetrit 1993), where circulating anti-Ro/SSA binds keratinocytes expressing surface Ro/SSA antigen, leading to the destruction of basal keratinocytes (Norris 1993) (Fig. 15.2). In addition to controlling the presence or absence of the anti-Ro/SSA response, the MHC may also determine the level of the response; Harley et al. (Harley et al. 1986) found that possession of both HLA DQ1 and DQ2 led to the highest titers of anti-Ro/SSA. This MHC specificity suggests that class II HLA antigens may determine whether the individual can present fragments of Ro/SSA antigen to their lymphocytes.

The Ro/SSA 60-kDa protein (Ro60 or SSA2) is the major component of the Ro ribonucleoprotein (RNP) complex [in stable association with a human cytoplasmic RNA (hY RNA) and the La/SSB protein, Fig. 15.3], to which an immune response is a specific feature of several autoimmune diseases, including SCLE and SLE. We recently characterized the Ro60 gene structure (Fig. 15.4) and examined whether any observed sequence alterations were associated with serum anti-Ro/SSA antibody in SCLE and could therefore be of pathogenic significance (Millard et al. 2002). Heteroduplex analysis of polymerase chain reaction (PCR) products from patients and controls spanning all Ro60 exons (1 to 8) revealed a common bandshift in the PCR products spanning exon 7. Sequencing of the corresponding PCR products demon-
strated an A>G substitution at nucleotide position 1318-7, within the consensus acceptor splice site of exon 7 (GenBank XM001901). The allele frequencies were major allele A (0.71) and minor allele G (0.29) in 72 control chromosomes, with no significant differences among patients with SCLE (anti-Ro/SSA positive), patients with DLE (anti-Ro/SSA negative), and healthy controls, suggesting no relationship between this nucleotide substitution and generation of anti-Ro/SSA.

Fig. 15.2. Probable pathogenic mechanism of photosensitive skin lesions in LE. Ultraviolet radiation (UVR) stimulates the cell surface expression of nuclear antigens, including Ro/SSA, on the surface of keratinocytes and induces E-selectin and intercellular adhesion molecule-1 (ICAM-1) expression on dermal endothelial cells, which leads to the margination and local migration of lymphocytes. Norris (Norris 1993) proposed this model of photosensitive LE, whereby circulating anti-Ro/SSA antibody binds keratinocytes that express this surface Ro/SSA antigen, leading to antibody-dependent cellular cytotoxicity by the infiltrating cytotoxic lymphocytes and the subsequent destruction of basal keratinocytes. Casciola-Rosen and Rosen (Casciola-Rosen and Rosen 1997) have added to this model by describing the expression of Ro/SSA antigen in “surface blebs” of UVB-irradiated apoptotic keratinocytes, which may contribute to induction of autoimmunity to Ro/SSA. IL-1, interleukin-1; TNF, tumor necrosis factor

Fig. 15.3. Organization of the Ro/SSA RNP complex (Gordon et al. 1994). hY RNA, human cytoplasmic RNA
A relatively small number of studies have examined HLA associations in Caucasian patients with DLE. The major associations include the A1, B8, DR3 and also the B7, DR2 haplotypes (Fowler et al. 1985, Knop et al. 1990, Millard et al. 1977), although other studies have found no HLA associations with DLE (Bielsa et al. 1991, Tongio et al. 1982). Our own data indicate a significant association with the previously mentioned haplotypes and DLE (Millard et al. 2001b). Finally, the photosensitive “butterfly rash” of lupus (acute CLE) rarely occurs outside the context of active SLE, so little effort has been made to determine any specific HLA associations (Sontheimer and Provost 1997).

Complement Genes
The MHC also includes genes for various complement components (C2, C4A, C4B, and factor B) in the class III region (Meo et al. 1977), between class I and class II, which have been implicated in the pathogenesis of CLE. Inherited deficiencies of components C2 and C4 are associated with DLE (Braathen et al. 1986, Provost et al. 1983), SCLE (Callen et al. 1987, Levy et al. 1979, Provost et al. 1983), and the presence of anti-Ro/SSA (Meyer et al. 1985, Provost et al. 1983). In addition, lupus profundus has been reported in patients with partial deficiency of both C4 allotypes (Burrows et al. 1991, Nousari et al. 1999). The proposed basis for these associations includes either a failure to clear immune complexes and apoptotic cells or linkage disequilibrium with the real disease-predisposing locus (Levy et al. 1979, Sullivan 1998).

TNF Genes
TNF is encoded by a class III gene of the MHC (Carroll et al. 1987, MHC Sequencing Consortium 1999). TNF has been implicated in the pathogenesis of CLE following UVR (Kock 1990, Norris 1993) (Fig. 15.2) since it stimulates expression of the Ro antigen on the keratinocyte surface. The rare –308A polymorphic form of TNF (TNF2)
(Abraham et al. 1999) is associated with increased UVB-induced TNF production in keratinocytes (Silverberg et al. 1999) and has demonstrated a strong association with SCLE (Werth and Sullivan 1999). TNF –308A does, however, lie on the A1, B8, DR3 extended haplotype in Caucasians (Wilson et al. 1993) and may therefore demonstrate association only because of linkage disequilibrium. However, a recent analysis in patients with SLE suggests that both TNF –308A and HLA-DR3 contribute independently to lupus susceptibility (Rood et al. 2000).

**Heat Shock Protein Genes**

The three heat shock protein 70 (Hsp70) genes are located within the class III MHC region, and linkage disequilibrium with other HLA genes has led several authors to investigate the role of Hsp70 genes in susceptibility to autoimmune and allergic disease (Aron et al. 1999). The activation of Hsp gene expression (the “stress response”) is a cellular mechanism that protects cells against stresses such as heat, UVR, cytokines, and chemicals (Muramatsu et al. 1992, Stephanou et al. 1997). Ghoreishi et al. (Ghoreishi et al. 1993) used immunohistologic analysis to demonstrate diffusely increased Hsp70 expression in the lesional skin of patients with SLE vs controls and DLE samples. Furukawa et al. (Furukawa et al. 1993) observed increased binding of anti-Ro/SSA antibodies to keratinocytes after incubation with a prostaglandin stressor that is known to induce Hsp formation, suggesting that heat shock proteins may be involved in the expression of Ro antigen at the cell surface. Various polymorphisms exist for the Hsp70 genes (Bolla et al. 1998, Esaki et al. 1999), although none have yet been examined for association in CLE.

**Candidate Loci Outside the MHC**

Several genetic regions outside the MHC seem to confer susceptibility to cutaneous forms of LE or demonstrate association or linkage with the anti-Ro/SSA response, including loci encoding cytokines, cytokine receptors, molecules involved in antigen recognition, and antioxidant enzymes, all of which are plausible candidates and are summarized in Table 15.1.

**IL-1 Gene Cluster**

The primary cytokine IL-1 is a major proinflammatory cytokine, encoded by a gene cluster at band 2q13, comprising IL-1α and IL-1β (synthesized by keratinocytes and Langerhans’ cells, respectively) and the IL-1 receptor antagonist gene (IL-1RN), which has been associated with photosensitivity in LE and with DLE by two separate teams in case-control studies (Blakemore et al. 1994, Suzuki et al. 1997). In our association analysis, we found that IL1B +3954 T was significantly less frequent in patients with SCLE (28%) compared with controls (47%; $P=0.039$), although this was lost on correction for multiple testing (Millard et al. 2001c).

**IL-10**

Linkage in human lupus has been shown for band 1q31 (Moser et al. 1998), within which lies the gene encoding IL-10 (Eskdale et al. 1997, Kim et al. 1992). IL-10 is expressed by UVB-stimulated keratinocytes and is chemotactic for CD8+ T cells. It promotes an inflammatory response through its effects on B cells in lupus, whose produc-
The expression of immunoglobulin is largely IL-10 dependent (Llorente et al. 1995). It also up-regulates the expression of ICAM-1 and E-selectin on human dermal endothelial cells (Palmetshofer et al. 1994). Three functional single nucleotide polymorphisms (SNPs) of the IL-10 gene promoter were reported by Turner et al. (Turner et al. 1997), including –1082 G/A, –819 C/T, and –592 C/A, who showed that they influenced in vitro production of IL-10 by mononuclear cells. Comparing the overall haplotype combinations at these three loci, significant distortion was demonstrated between anti-Ro/SSA-positive and anti-Ro/SSA-negative SLE cases ($P=0.005$), with overrepresentation of the GCC and ACC haplotypes in the former group (Lazarus et al. 1997). This suggests that

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>1. Cytokine genes</td>
<td></td>
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</tr>
<tr>
<td>Interleukin-1 gene cluster (IL-1A, B, and RA)</td>
<td>2q13</td>
<td>Association of an IL-1 RA allele with DLE and with photosensitivity in SLE. Linkage of 1q31 to human LE. Association of three IL-10 SNPs with anti-Ro production in SLE.</td>
</tr>
<tr>
<td>Interleukin-10 (IL-10)</td>
<td>1q31</td>
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2. Adhesion molecule/receptor genes

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<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>Intercellular adhesion molecule-1 (ICAM1)</td>
<td>19p13.3-p13.2</td>
<td>Increased keratinocyte expression of ICAM-1 in CLE.</td>
</tr>
<tr>
<td>E-selectin (SELE)</td>
<td>1q23–25</td>
<td>Up-regulated endothelial expression in the skin of patients with cutaneous LE vs controls.</td>
</tr>
<tr>
<td>Fc gamma receptor II (FCGR2A)</td>
<td>1q23</td>
<td>Linkage of 1q23 to human systemic LE. Necessary for ADCC (Fig. 15.4).</td>
</tr>
<tr>
<td>T-cell receptor (TCR) Cβ1 and Cβ2</td>
<td>7q35</td>
<td>Association of two RFLPs, for TCRs Cβ1 and Cβ2, with anti-Ro/SSA production in SLE.</td>
</tr>
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3. Antioxidant enzyme genes

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<th>Gene</th>
<th>Locus</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>Glutathione S-transferase M1 (GSTM1)</td>
<td>1p13</td>
<td>Association of GSTM1 null status and anti-Ro/SSA production in SLE.</td>
</tr>
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4. Apoptosis genes

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<tr>
<th>Gene</th>
<th>Locus</th>
<th>Evidence</th>
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</thead>
<tbody>
<tr>
<td>Fas (TNFRSF6)</td>
<td>10q24.1</td>
<td>Association of an SNP with photosensitivity in SLE</td>
</tr>
</tbody>
</table>

* Genes within the MHC are illustrated in Fig. 15.1. ADCC, antibody-dependent cellular cytotoxicity; CLE, cutaneous lupus erythematosus; DLE, discoid LE; MHC, major histocompatibility complex; RA, receptor antagonist; RFLP, restriction fragment length polymorphism; SLE, systemic LE; SNP, single nucleotide polymorphism.
IL-10 may be important in generation of the immune response to Ro and, therefore, potentially relevant to SCLE, although our initial study found no association with SCLE or DLE for either the –819 or –1082 SNPs (Millard et al. 2001c).

**T-Cell Receptor Cβ Gene**

Genes encoding the T-cell receptor (TCR) have demonstrated an association with the generation of anti-Ro/SSA. Frank et al. (Frank et al. 1990) reported an association between a set of restriction fragment length polymorphisms (RFLPs) for TCRs Cβ1 and Cβ2 (Bgl II 9.8-kb and Kpn I 1.75-kb) that was present in 76% of patients with SLE and anti-Ro/SSA but in only 41% of patients with SLE without anti-Ro/SSA ($P=0.002$). The same group found that certain HLA DQ types, in combination with the TCR Cβ RFLPs, increased the strength of this association (Scofield et al. 1994). This molecular specificity was cited as evidence that the breaking of tolerance to the Ro proteins in lupus requires the association of a class II HLA molecule with a fragment of Ro peptide and a particular TCR form.

**Glutathione S-Transferase**

The antioxidant enzymes encoded by the glutathione S-transferase (GST) genes are widely expressed in mammalian tissues. Ollier et al. (Ollier et al. 1996) examined the role of the GSTM1 null polymorphisms in the production of anti-Ro/SSA and anti-La/SSB in SLE using PCR to identify GSTM1 [chromosome band 1p13 (Pearson et al. 1993)] null homozygotes. A significant association was demonstrated between the Ro+ve/La–ve phenotype in SLE and GSTM1 null status, implicating oxidant stress in the loss of immunologic tolerance to Ro/SSA antigen.

**Adhesion Molecules**

ICAM-1 and E-selectin are potential candidate genes for CLE. ICAM-1 is usually expressed at very low levels on keratinocytes, but increased keratinocyte expression has been demonstrated in evolving lesions of CLE and PLE (Nyberg et al. 1999, Norris et al. 1992). Two functional polymorphisms of the ICAM-1 gene (ICAM1) were reported by Vora et al. (Vora et al. 1994), including G/R at codon 241 and K/E at codon 469, which therefore represent plausible candidates for CLE. The endothelial adhesion molecule E-selectin is also up-regulated in the skin of patients with CLE and patients with PLE compared with controls (Nyberg et al. 1999); elevated serum levels of soluble E-selectin have also been described in patients with DLE (Nyberg and Stephansson 1999). The E-selectin gene at band 1q23–25 (Collins et al. 1991) contains an A/C SNP at position 561, coding for serine or arginine at codon 128 (Wenzel et al. 1994a), which, so far, has demonstrated clinical association with atheromatous vascular disease (Wenzel et al. 1994b).

**Fcγ Receptor II**

The Fcγ receptor II genes, at chromosome band 1q23 (Qiu et al. 1990), lie within an area that has demonstrated strong linkage to SLE in humans, with an lod score of 3.37 (Moser et al. 1998). The Fc receptor is required by cytotoxic cells to initiate antibody-dependent cellular cytotoxicity of keratinocytes, which is up-regulated in CLE (Furukawa et al. 1999), and possibly directed against the Ro/SSA antigen (Norris 1993). The FcγRIIa gene (FCGR2A) possesses an SNP (G/A) coding for arginine or
histidine at codon 131 (R/H131) in the EC2 domain of FcγRIIa, which alters the ability of the receptor to bind immunoglobulin G (Clark et al. 1989, Warmerdam et al. 1990).

**Apoptosis Genes and Photosensitivity in Lupus**

Apoptosis is a form of programmed cell death, over 6–48 h, that is characterized by cell shrinkage and nuclear condensation in response to the activation of the enzyme caspase 3 (Elkon 1997, Salmon and Gordon 1999). On early apoptotic keratinocytes, Casciola-Rosen (1997) reported the formation of surface blebs, which are highly enriched with several lupus autoantigens, including Ro/SSA; in genetically susceptible individuals, expression of this autoantigen is proposed to initiate an autoantibody response. Multiple stimuli, including UVR, cytokines, cytotoxic T cells, and cytotoxic drugs, are capable of inducing apoptosis (Arnold et al. 1999, Danno and Horio 1982, Elkon 1997, Haake and Polakowska 1993, Stone et al. 1998). The Fas transmembrane glycoprotein receptor (Fas, encoded by TNFRSF6) has an intracellular death domain that initiates a cascade of events when Fas binds external Fas ligand, leading to death of the cell by apoptosis. In normal human skin, Fas is found mainly in the basal layer of the epidermis; expression then gradually diminishes toward the stratum granulosum. The specific role of Fas and Fas ligand in human CLE is still a matter of debate, but both molecules are expressed on infiltrating cells around blood vessels and hair follicles (Fushimi et al. 1998, Nakajima et al. 1997). Consistent with this co-expression of Fas and Fas ligand around hair follicles, apoptotic cells in this region were found (Nakajima et al. 1997).

In murine models, the Fas/Fas ligand axis may be involved in LE. Mice that are homozygous for the *lpr* (lymphoproliferation) recessive mutation accumulate large numbers of CD3+ CD4- CD8- T cells, which lead to the induction or acceleration of systemic autoimmunity (Kono and Theofilopoulos 1997, Takahashi et al. 1994). The *lpr* mutation on mouse chromosome 19 causes a point mutation in Fas that abolishes its ability to transduce the apoptotic signal. A recent study of MRL/n (control) mice found that they develop LE-like skin lesions later in life than the closely related MRL/lpr (homozygous) mice (Furukawa et al. 1996). In humans, the Fas gene is located on chromosome 19q24.1 (Inazawa et al. 1992). Huang et al. (Huang et al. 1999) examined a Fas polymorphism, the MvaI RFLP (MvaI*1/ MvaI*2, caused by an A/G SNP at the -670 nucleotide position) in 103 Caucasian patients with SLE and found that MvaI*2 homozygosity was significantly higher in patients with photosensitive SLE, but polymorphic Fas loci have not yet been examined by association or linkage in CLE.

**Summary**

The genetic architecture of LE is far from understood. The most significant immunogenetic associations to date have been found in the presence of anti-Ro/SSA and/or anti-La/SSB in CLE and SLE, where HLA, TNF, complement, IL-10, TCR, and GST genes may be involved. However, other LE-specific associations, outside the context of anti-Ro/SSA, have been less well characterized to date. For CLE, where the phenotype
can be accurately characterized, there are still numerous candidate gene loci in the wings.

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