Report

Elevated Expression and Genetic Association Links the *SOCS3* Gene to Atopic Dermatitis

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In a systematic analysis of global gene-expression patterns, we found that *SOCS3* messenger RNA was significantly more highly expressed in skin from patients with atopic dermatitis than in skin from healthy controls, and immunohistochemical analysis confirmed a similar elevation of SOCS3 protein. Furthermore, we found a genetic association between atopic dermatitis and a haplotype in the *SOCS3* gene in two independent groups of patients ($P < .02$ and $P < .03$). These results strongly suggest that *SOCS3*, located in a chromosomal region previously linked to the disease (17q25), is a susceptibility gene for atopic dermatitis.

Atopic dermatitis (AD [MIM 603165]), also known as "eczema" according to the new World Allergy Organization nomenclature,[1] commonly begins in infancy or early childhood and is characterized by itchy and inflamed skin. AD affects 10%–20% of children in Western societies and shows a strong familial aggregation.[2] Several genetic linkage and association studies have sought the underlying genetic causes of AD, and a number of different chromosomal regions have been implicated by these studies.[2–5] In a Swedish population with AD, a previous genomewide linkage analysis[4] showed suggestive linkage ($P < 7.4 \times 10^{-4}$) to susceptibility loci on chromosomes 3, 13, 15, 17, and 18.

Yet very little is known about specific genes involved in the pathogenesis of AD. To search systematically for gene-expression patterns associated with AD, we recently adopted a genomewide approach, using human cDNA microarrays (M. Bradley, P. O. Brown, H. Y. Chang, M. Nordenskjöld, A. Scheynius, A. Sääf, and M. Tengvall-Linder, unpublished data). Nine adult patients with AD were collected at the Dermatology Unit, Department of Medicine, Karolinska University Hospital Solna, Stockholm. From each individual, two punch biopsy specimens were taken: one from lesional skin and one from noninvolved PBS-patch-tested skin on the back. AD was diagnosed using the U.K. Working Party's diagnostic criteria.[6] The patients had not received treatment for the previous 2 mo and were considered by a dermatologist to be moderately to severely affected with AD. For controls, we used four healthy individuals from the Stockholm area. Two punch biopsy specimens were taken from the back: one from normal skin and one from PBS-patch-tested skin. Each punch biopsy specimen provided 10–30 μg of total RNA. All patients with AD had allergen-specific IgE antibodies, which were not present in any of the controls.

We used human cDNA microarrays containing 41,792 elements representing ~24,500 unique genes (based on UniGene clusters) that were manufactured by the Stanford Functional Genomics Facility. Fluorescently labeled cDNA prepared from amplified RNA was hybridized to the array in a two-color comparative format, with samples from patients with AD and healthy controls labeled with Cy5 (red) and with a reference pool of human mRNAs (Stratagene) derived from 10 cell lines labeled with Cy3 (green). Data were normalized and retrieved as the $\log_2$ ratio of fluorescence intensities of the sample and the reference.

Received December 6, 2005; accepted for publication March 14, 2006; electronically published April 14, 2006.

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Am. J. Hum. Genet. 2006;78:1060–1065. 0002-9297/2006/7806-0016$15.00

In analyzing the microarray data by use of the significance-analysis-of-microarrays (SAM) algorithm,[7] we found ~5,000 genes consistently differentially expressed between skin from patients with AD and skin from control individuals, with a false-discovery rate <0.7%. The genomewide portrait of AD will be presented elsewhere (M. Bradley, P. O. Brown, H. Y. Chang, M. Nordenskjöld, A. Scheynius, A. Sääf, and M. Tengvall-Linder, unpublished data). Among all the differentially expressed genes, we focused specifically on genes located within chromosomal regions previously linked to AD. The *SOCS3* gene (Locus Link ID 9021; NCBI accession number NM_003955; UniGene cluster ID Hs.527973), located in chromosome region 17q25, was found to be significantly more highly expressed in skin from patients with AD than in skin from healthy individuals ($P < .03$, corrected for multiple testing) (table 1 and fig. 1).

SOCS3 is a member of the suppressors of cytokine signaling (SOCS) family of proteins that act as negative regulators of cytokine signaling. SOCS proteins interfere with the binding of cytokine receptors and with intracellular molecules that act downstream. Several studies have pointed to SOCS proteins as an effective block of the Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathway in the pathogenesis of various inflammatory diseases.[8] Furthermore, Seki et al.[8] have reported that patients with AD show significantly increased *SOCS3* expression ($P < .001$) in peripheral $CD3^+$ T cells. On the basis of the microarray results and the previously described role of *SOCS3* in various inflammatory diseases, we considered *SOCS3* to be a candidate gene for AD.

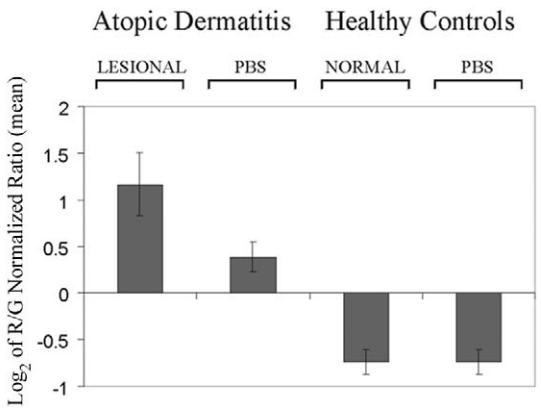

Figure 1 *SOCS3* mRNA levels in skin from patients with AD and healthy controls, measured by cDNA microarray. We analyzed lesional skin and noninvolved PBS-patch-tested skin from patients with AD and normal skin and PBS-patch-tested skin from healthy controls. The results are displayed as the mean values of all measured *SOCS3* mRNA levels for patients and controls in each group (e.g., mean values of seven lesional and six PBS-patch-tested skin samples from patients with AD and four normal skin and four PBS-patch-tested skin samples from controls). SE is indicated for each group. We found that *SOCS3* mRNA levels were significantly more highly expressed in skin from patients with AD than in skin from healthy controls. R/G = red/green.

Table 1

***SOCS3* Microarray Data**

Skin Sample	*SOCS3* Sequence GenBank Accession Number		
	AA001218	AI922872	T72915
AD lesional skin:			
ADL1	.87	.01	−.98
ADL2	2.43	2.42	2.18
ADL3	2.48	2.32	2.43
ADL4	.77	.74	.72
ADL5	.36	.42	.61
ADL6	1.16	1.36	2.13
ADL7	.47	.54	.52
AD PBS skin[a]:			
ADP1	.84	.04	−.12
ADP2	.62	.37	−.58
ADP3	NA	−.38	−.45
ADP4	.79	.33	.47
ADP5	.5	.41	−.07
ADP6	.88	.64	.69
Control normal skin:			
CN1	−.43	−.85	−.72
CN2	NA	−.95	−1.32
CN3	NA	−.95	−1.14
CN4	NA	−.41	−.78
Control PBS skin[a]:			
CP1	−.91	−1.04	−.86
CP2	−.73	−1.14	−1.16
CP3	−.21	−.72	−.77
CP4	−.42	−.75	−.62

Note.—Data are $\log_2$ of red/green normalized ratio. NA = not available.

[a] PBS-patch-tested skin.

To explore the link between mRNA levels and protein expression of SOCS3 in AD, we used immunohistochemistry. For this assessment, 15 adult patients with AD were collected at the Dermatology Unit, Department of Medicine, Karolinska University Hospital Solna, Stockholm. They were classified as having AD on the basis of the U.K. Working Party's diagnostic criteria.[6] Two punch biopsy specimen from the trunk were taken from each individual: one from lesional skin and one from noninvolved skin. Eight healthy adult controls were collected from the Stockholm area, and biopsy specimens were taken from normal skin.

Biopsy specimens were snap frozen on dry ice and were stored at −80°C. Six-micrometers-thick cryo sections were prepared and put on glass slides, fixed in acetone, and were used in the ABC-ELITE (Vector Laboratories) immunohistochemical staining method. The sections were treated with 0.3% H_2O_2 to block endogenous peroxidase activity, were incubated with normal goat serum (dilution 1/10), and were blocked with avidin

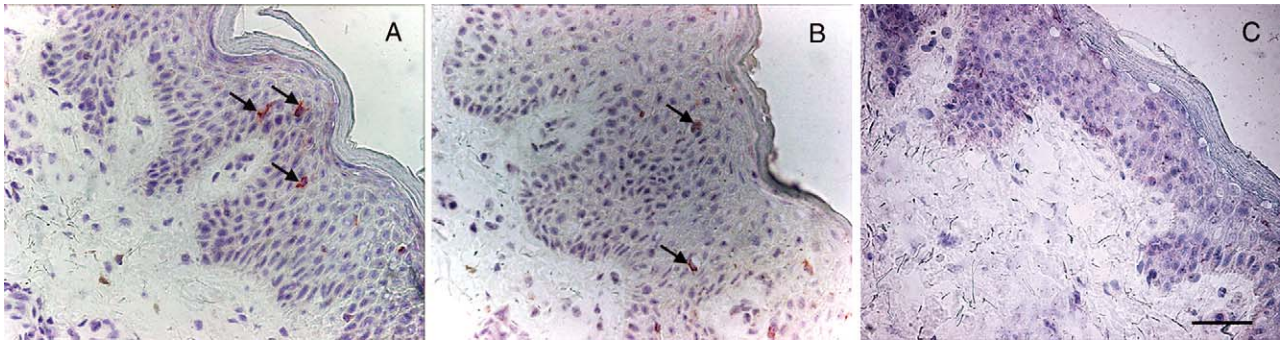

Figure 2 SOCS3 protein expression (*arrows*) in lesional skin (*A*) and nonlesional skin (*B*) from patients with AD and in normal skin from healthy controls (*C*). We found a higher expression of SOCS3 in dendritic cells and an increased number of SOCS3-positive cells in lesional AD skin (median 5.6 cells/mm; range 1.1–10.5 cells/mm) compared with nonlesional AD skin (median 1.1 cells/mm; range 0–5.6 cells/mm; $P < .043$) and normal skin (median 0.8 cells/mm; range 0–5.9 cells/mm; $P < .00079$). Frozen skin biopsy specimens were stained with antibodies to SOCS3 (dilution 1/250). Scale bar = 50 μm. Statistical tests used were the Wilcoxon matched-pairs test and Mann-Whitney *U* test.

and biotin (Vector Laboratories). A mouse monoclonal antibody against human SOCS3, dilution 1/250 (obtained from Assay Designs), was added to incubate the specimens for 30 min. A biotinylated, rabbit anti-mouse secondary antibody (dilution 1/200 [Vector Laboratories]) was also added. The specimens were allowed to react with preformed avidin-biotin-enzyme complex (ABC-ELITE reagent [Vector Laboratories]) for 30 min, followed by incubation with 3-amino-9-ethylcarbazole substrate for 15 min to develop a staining pattern. Counterstaining was done with Mayer's hematoxylin. As a control, irrelevant mouse IgG1 was used.

From the immunohistochemical staining, we found a higher expression of SOCS3 protein in dendritic cells and an increased number of SOCS3-positive cells in epidermis from lesional AD skin compared with nonlesional AD skin and normal skin from healthy controls (fig. 2). The altered SOCS3 protein expression in AD skin and the fact that *SOCS3* maps to a region that has been reported to be linked to AD supported the idea that *SOCS3* might be critically involved in AD and prompted us to investigate genetic association between *SOCS3* and AD.

We first analyzed a set of 406 Swedish families with at least one sibling affected with AD (1,334 total affected individuals). The families were recruited at the Dermatology Unit, Department of Medicine, Karolinska University Hospital Solna, Stockholm, during 1995–1997. The patients were all classified as having AD on the basis of clinical examination by dermatologists, who applied the U.K. Working Party's diagnostic criteria.[6] Mean age was 29 years. Allergen-specific serum IgE antibodies to inhalant and food allergens were measured in all siblings with AD.[9] Subjects were classified as having allergic asthma or allergic rhinoconjunctivitis on the basis of an interview. Of these 406 families, 109 were studied in the previously published genomewide linkage analysis.[4]

Ten SNPs were selected from the NCBI dbSNP Home Page from ~10 kb upstream of the *SOCS3* gene and throughout the gene. SNPs that have been been validated by several methods according to dbSNP and that had a minor-allele frequency >5% were chosen with priority. The SNPs were *rs8074003, rs12952093, rs9914196, rs4969170, rs12949584, rs11868378,* C−920→A, *rs1061489, rs2280148,* and *rs4969168*. Genotyping was performed with TaqMan SNP Genotyping Assay (Applied Biosystems [ABI]). Primers and probes were obtained from ABI. One allelic TaqMan probe was labeled with fluorescent FAM dye, and the other with VIC dye. PCRs were run in 2 × TaqMan Universal PCR Master Mix and No AmpErase UNG, with primer concentrations of 225 nM and probe concentration of 50 nM. The total reaction volume was 5 μl of 1-ng/μl genomic DNA. All SNPs were amplified using TaqMan Universal PCR protocol (95°C for 10 min, followed by 40 cycles at 92°C for 15 s, and 60°C for 1 min). The plates were then placed in the 7900HT Fast Real Time PCR System, where the fluorescence intensity in each well of the plate was read using the program SDS 2.2.1. Three of the genotyped SNPs were not found to be polymorphic when tested in 380 individuals (*rs12949584,* C-920→A, and *rs1061489*) and a fourth (*rs11868378*) failed to pass ABI's quality control.

Of 10 tested SNPs, 6 were successfully genotyped in the 3.5-kb *SOCS3* gene and in a region ~10 kb upstream of the gene (fig. 3). Population Hardy-Weinberg equilibrium was evaluated for each SNP by use of a χ^2 test as implemented in the zGenStat 1.128 software (Henric Zazzi), with a cutoff value of $P > .01$. Two of the SNPs were significantly associated with the AD phenotype

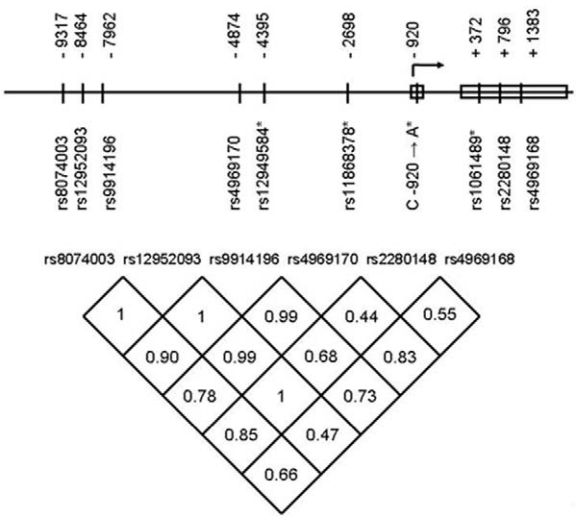

Figure 3 Schematic overview of the location and distribution of the 10 SNPs genotyped in the *SOCS3* gene and the LD structure in the region. Positions relative to the transcription start are indicated. The four SNPs marked with an asterisk (*) either were not polymorphic in the analysis (of 380 individuals) or failed to pass ABI's quality control. See main text for details on SNP selection. The number in each box in the LD plot corresponds to the pairwise LD coefficient D' between respective SNPs, calculated using Unphased.[10] Block 1 spans from *rs8074003* to *rs4969170*, and block 2 from *rs4969170* to *rs4969168*.

($P < .03$ for *rs12952093*; $P < .02$ for *rs4969170*) (table 2). When analyzing the linkage disequilibrium (LD) structure in the gene, using the program Unphased,[10] we found that all analyzed SNPs fell into two haplotype blocks. We then identified three haplotype-tagging SNPs as representative of these haplotype blocks: *rs12952093* and *rs4969170* in block 1 and *rs4969168* in block 2. Two of these were in the promoter region of the gene (*rs12952093* and *rs4969170*), and the third was in the 3′ UTR (*rs4969168*). One haplotype from the first block was positively associated with AD (A-A; $P < .02$), and one was negatively associated (C-G; $P < .04$) (table 2). In addition, the *SOCS3* gene was linked to AD in these families (LOD = 1.63; $P < .04$) in a nonparametric linkage analysis performed using the program Allegro (exponential model with power weighting of families).[13] However, the linkage did not reach the previously reported suggestive linkage level ($P < 7.4 \times 10^{-4}$) in chromosomal region 17q25, indicating that *SOCS3* is not the only gene contributing to the broad peak in the region.

To confirm the genetic association, we analyzed the three haplotype-tagging SNPs in two independent sets of patients and controls. The first was a nested case-control sample consisting of 555 children from the population-based birth cohort BAMSE, which comprises 4,089 children who were recruited in the Stockholm area between 1994 and 1996.[14–16] When the children were 1, 2, and 4 years old, questionnaires that included questions on symptoms related to wheezing and allergic diseases were completed. The children with reported symptoms of dry skin in combination with itchy rash for at least 2 wk with typical localization and/or who received a diagnosis of eczema from a doctor were classified as having AD.[14] Allergen-specific serum IgE antibodies to inhalant and food allergens were measured in all children. At 2 and/or 4 years of age, 328 children received the diagnosis of AD. Children with no reported eczema, asthma, or allergic rhinoconjunctivitis and with no allergen-specific IgE were used as healthy controls. Of the 555 total children, 328 were affected with AD and 227 were controls. Mean age was 4.3 years.

The second was a case-control study comprising 187 adult patients with AD (102 females and 85 males) and

Table 2

Genetic Association of *SOCS3* with AD in Swedish Family Material

Allele or Haplotype			Frequency	No. of Transmissions[a]	Transmission Frequency (%)	*P*
rs12952093	*rs4969170*	*rs4969168*				
A			.31	286	55	.03
	A		.37	351	54	.02
		G	.83	761	50	NS
C	G		.61	1,140	49	.04
A	A		.32	582	51	.02
C	G	G	.64	1,118	49	NS
A	A	G	.16	389	52	NS

Note.—The data shown are from 406 families, including 1,334 individuals with AD. Mean age was 29 years. Statistical analysis was performed using Unphased,[10] with the pdtphase command for multiplex families. Transmission frequencies were estimated with the program PDT[11] for alleles and with the program Transmit[12] for haplotypes. *P* values were corrected with either the number of tested SNPs ($n = 3$) or the number of tested haplotypes (haplotypes with frequency >5%; $n = 4$). NS = not significant.

[a] Transmissions to affected individuals.

Table 3

Genetic Association of *SOCS3* with AD in Two Independent Case-Control Studies

Allele or Haplotype			Swedish Nested Case-Control Study				U.K. Case-Control Study			
			Frequency (%) in				Frequency (%) in			
rs12952093	*rs4969170*	*rs4969168*	Controls	Patients	OR (95% CI)	*P*	Controls	Patients	OR (95% CI)	*P*
A			26	33	1.45 (1.10–1.92)	.03	27	26	.95 (.69–1.31)	NS
	A		31	41	1.51 (1.16–1.97)	.009	34	31	.87 (.64–1.18)	NS
		G	85	84	.90 (.62–1.31)	NS	85	90	1.53 (.99–2.36)	NS
C	G		68	58	.67 (.51–.87)	.02	66	68	1.12 (.82–1.53)	NS
A	A		33	24	1.50 (1.12–2.00)	.03	26	25	.94 (.64–1.38)	NS
C	G	G	69	58	.63 (.48–.82)	.004	66	69	1.15 (.85–1.56)	NS
A	A	G	15	23	1.72 (1.22–2.43)	.01	19	20	1.07 (.70–1.63)	NS

Note.—Shown are the association results from the Swedish nested case-control study (328 individuals with AD; 227 controls; mean age 4.3 years) and from the U.K. case-control study (187 individuals with AD; 230 controls; mean age 45 years). Statistical analysis was performed using Unphased,[10] with the cocaphase command for case-control studies. The significance of associations of individual haplotypes in the case-control studies was estimated using standard χ^2 tests. *P* values have been corrected with either the number of tested SNPs ($n = 3$) or the number of tested haplotypes (haplotypes with frequency >5%; $n = 4$). NS = not significant.

230 age- and sex-matched controls (162 females and 68 males) from the United Kingdom.[17] For all patients, AD was diagnosed by a dermatologist using the standard clinical criteria of Hanifin and Rajka.[18] The minimum age at study was 18 years, and the mean age was 45 years. Total serum IgE levels were elevated in 127 of the patients with AD, and 164 had other atopic manifestations. The controls did not have AD but were not checked for IgE levels or other atopic manifestations.

When analyzing the Swedish case-control samples, we found a highly significant genetic association between AD and both the positively associated haplotype ($P < .03$) and the negatively associated haplotype ($P < .02$) (table 3). However, we could not confirm these associations in the U.K. study (table 3). The power to detect association for the two associated haplotypes in the U.K. study was 83% for the negatively associated haplotype ($P < .05$; odds ratio [OR] 0.62) and 80% for the positively associated haplotype ($P < .05$; OR 1.72), with the assumption of the same haplotype frequencies as observed in the Swedish case-control study. Power analysis was performed using the PS software,[19] version 2.1.31.

The lack of association in the U.K. study could be because of differences between the two populations in the relative contribution of *SOCS3* as a genetic risk factor. Another potential explanation for the discrepancy is that the importance of *SOCS3* as a risk factor might be age dependent, since the most significant association of *SOCS3* was seen in children with AD. It is also possible that the selection of controls in the U.K. study influenced the results. Controls in the U.K. study were not checked for other atopic manifestations as they were in the Swedish case-control study, which is a limitation because the potential role of *SOCS3* in other atopic manifestations is unknown.[8] However, in a meta-analysis[20] of the two case-control sets, the risk haplotype was significantly associated ($P < .02$; combined OR 1.37; 95% CI 1.07–1.77) and a test of heterogeneity between the studies was not significant. The meta-analysis was performed in accordance with the method of Woolf.[20]

The consistently elevated expression of *SOCS3* in skin of patients with AD, together with evidence for genetic association in two independent patient data sets, makes *SOCS3* a strong candidate gene for AD susceptibility. This evidence is reinforced by the potential pathophysiological link between the activity of SOCS3 and the pathogenesis of AD. SOCS3 is an SH2-containing protein that binds to the activation loop of Janus kinases, inhibiting kinase activity and thereby suppressing cytokine signaling. The promoter of the *SOCS3* gene contains two STAT-responsive elements and one GC-rich element.[21] SOCS3 is expressed predominantly in T-helper type 2 (T_H2) cells and has an important role in regulating the onset and maintenance of T_H2-mediated responses.[8] Patients with AD have increased numbers of T_H2-expressing cells in peripheral blood and elevated interleukin-13 expression in the skin, which indicates a systemic T_H2 environment.[22] *Socs3* transgenic mice showed increased T_H2 responses.[8] These mice, constitutively expressing the Socs3 protein, had about two-to-three times higher expression of Myc-tagged Socs3 than of endogenous Socs3 in T_H2 cells. However, the presence or absence of AD-like features in the *Socs3* transgenic mice and the expression of Socs3 protein in cell types other than T cells were not reported. In contrast, dominant-negative mutant *Socs3* transgenic mice and mice with a heterozygous deletion of *Socs3* had decreased T_H2 development.[8] Despite the connection between *SOCS3* and AD, it is still unclear how the polymorphisms in the *SOCS3* gene might affect development of AD, but there may be a direct effect on *SOCS3* transcription, since two of the associated SNPs are located in predicted transcription-factor binding sites (RAVEN).

In conclusion, we found that *SOCS3* is consistently

more highly expressed in skin from patients with AD than in normal control skin and that specific haplotypes of the *SOCS3* gene are significantly associated with the disease. We suggest that *SOCS3* may play an important role in AD pathogenesis, at least for a Swedish population with AD. We also suggest that SOCS3 and the pathways that it regulates may be important targets for future investigations of the molecular pathogenesis of AD and for therapeutic developments.

Acknowledgments

We gratefully acknowledge financial assistance from the Swedish Asthma and Allergy Association's Research Foundation, the Edward Welander-Finsen Foundation, the Swedish Society for Medical Research, the Juvenile Diabetes Foundation International, and the U.S. National Eczema Association for Science and Education.

Web Resources

Accession numbers and URLs for data presented herein are as follows:

dbSNP, http://www.ncbi.nlm.nih.gov/projects/SNP/

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for *SOCS3* sequences [accession numbers AA001218, AI922872, and T72915])

NCBI, http://www.ncbi.nlm.nih.gov/ (for *SOCS3* [accession number NM_003955])

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for AD)

RAVEN: Regulatory Analysis of Variations in Enhancers, http://mordor.cgb.ki.se/CONSNP/

Stanford Functional Genomics Facility, http://www.microarray.org/sfgf/

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