

# PARP alleles and SLE: failure to confirm association with disease susceptibility

Letter  
TO THE EDITOR

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Systemic lupus erythematosus (SLE) is the prototypic systemic autoimmune disease and has a predisposition for women and certain ethnic minority populations. Genetic epidemiologic studies implicate an important role for genetic factors, with sibling relative risk ratios ( $\lambda_s$ ) of at least 20. In an issue of the *JCI*, Tsao et al. (1) presented data suggesting that PARP (poly ADP-ribose polymerase) is at, or very close to, an SLE susceptibility gene. Specifically, using a multiallelic transmission disequilibrium test (TDT), they reported preferential transmission of PARP alleles (particularly the 85-bp allele) to affected offspring among 124 multiplex and simplex SLE families. Their interest in this region stems from their own work, as well as that of others suggesting linkage of SLE to human chromosome 1q41–42 (2–5). Their choice of PARP as a candidate gene relates to: (a) its location within this region; (b) the role of PARP in processes such as DNA repair and apoptosis that are believed to be etiologically relevant to SLE; and (c) previous studies of PARP activity and mRNA in SLE patients and their families. We report here data from three independent samples of families that do not support an association of PARP alleles with SLE.

A total of 746 individuals with SLE (all of whom met American College of Rheumatology criteria for SLE) were included in these analyses. Subjects were derived from 187 sibling pairs,

126 multiplex and 433 simplex families enrolled through the University of Minnesota (UMN), the Oklahoma Medical Research Foundation (OMRF), and the University of California at San Francisco (UCSF), respectively. The ethnic distribution of these 746 families was 58% European-American, 17% African-American, 12% Hispanic-American, 10% Asian-American, and 3% other.

All 746 SLE subjects and relevant family members were genotyped for the same CA repeat PARP polymorphism examined by Tsao et al. (1), which is located 906 bp upstream of the transcription start site. Four-hundred forty-eight families were analyzed using the multiallelic TDT (6). Rows 1–3 of Table 1 summarize the results for subgroups of the families corresponding to the three enrollment sites. Results shown are for the 85-bp allele since this allele revealed the most striking deviation from the expected transmission:nontransmission ratio of 50% in the data reported by Tsao et al. (1). We found no evidence of preferential transmission of allele 85 among any of the 3 subgroups, nor among the combined group of families. Similar results were obtained for specific major ethnic groups. Furthermore, no other PARP alleles revealed evidence of skewed transmission among these families (data not shown).

Clinical or other sources of heterogeneity is always a

potential explanation for discrepancies in genetic associations with complex diseases such as SLE. We therefore sought to explore this possibility among a subgroup of our families. Specifically, we used multivariate logistic regression to examine the association of PARP alleles with two specific disease manifestations, nephritis and the antiphospholipid antibody syndrome, among the 433 SLE patients enrolled through UCSF. These analyses, which included adjustments for ethnic background, gender, age at SLE onset, and disease duration, failed to demonstrate an association of PARP alleles with either of these disease manifestations ( $P = 0.25–0.49$ ).

In summary, we were unable to confirm an association of PARP alleles with SLE among a large, multiethnic sample of SLE patients. Nevertheless, previous studies by Tsao and others (2–5) provide evidence that an SLE susceptibility gene does reside somewhere in the human chromosome 1q41–42 region. Our data suggest that further work will be required to identify this gene(s).

**Table 1**  
Transmission of PARP allele 85 among SLE families

Study group	T <sup>A</sup>	NT	% T	P value
UMN	75	68	52	0.56
OMRF	50	44	53	0.54
UCSF	43	36	54	0.43

<sup>A</sup>Data shown describe the number of transmissions (T) and non-transmissions (NT) of the 85-bp allele of PARP from heterozygous parents to affected offspring.

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*The authors reply* — We read with interest the letter by Criswell et al. about their failure to confirm our observed association of the 85-bp PARP allele with SLE susceptibility in cohorts comprising 187 sibpair families, 126 multiplex families, and 433 simplex families. This is not unexpected in the genetic analysis of complex diseases, which are subject to both heterogeneity and variations in allelic distributions at predisposing loci among the samples studied. Since the transmission disequilibrium test (TDT) detects an allelic association of a marker with disease in the presence of its linkage to this disease, the observation that our cohort shows the strongest evidence for linkage to this region may explain why we have also been able to detect an association with PARP. Of note, the reported data from all three sites each demonstrate a numerically higher transmission (T) than non-transmission (NT) of the 85-bp PARP allele among SLE families: their respective T:NT data are 75:68, 50:44, and 43:36.

Additionally, features of their reported analyses warrant further examination. Specifically, the transmission data shown in Table 1 from 433 simplex families contained a considerably smaller proportion of informative parents (43 transmitted and 36 nontransmitted) than similar data from the other cohorts of 187 sibpair and 126 multiplex families. Also, only data from these 433 simplex families were used in a multivariate logistic regression analysis conducted to test for an association of PARP alleles with subsets of disease. A question arises whether further stratifying these transmission data into smaller numbers by disease manifestation decreases the statistical power to detect allelic associations.

Our report identified an association with SLE of a particular PARP allele within the linked chromosome 1 region (1). We observed an overall skewed transmission of PARP alleles to affected offspring in 124 multiplex and simplex families using a multiallelic TDT ( $P = 0.00008$ ), preferential transmission of a particular PARP allele to affected offspring ( $P = 0.0003$ ), and lack of transmission to unaffected offspring ( $P = 0.004$ ). Our conclusion was that PARP might be the susceptibility gene within the chromosome 1q41–42 region, or might be close to it. While the lack of association of PARP alleles with SLE in two independent studies (7) does not negate the strong association we have found in our cohort, it may be that the PARP polymorphism we tested is not a contributor to the risk for SLE. The PARP allele may be in physical proximity to the SLE susceptibility gene within 1q41–42. This interpretation is supported by results from a case-control study of PARP alleles in African-Americans (8). In

that study, there was a significant difference between the PARP allele frequencies in SLE patients and controls, and a significant deviation from Hardy-Weinberg equilibrium in SLE genotypes, but not in controls. This finding along with ours and those reported by Criswell et al. suggest that the most parsimonious explanation is that there may be linkage disequilibrium between the tested PARP polymorphism and the SLE susceptibility locus within the 1q41–42 region.

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