



**Control/Tracking Number:** 08-F-5215-ACR

**Activity:** Fellow

**Current Date/Time:** 7/15/2008 1:53:19 PM

### **Mif Gene Polymorphism In Wegener's Granulomatosis**

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*Abstract:*

#### **Statement of Purpose and Background:**

Increasing evidence supports the concept of Macrophage Migration Inhibitory Factor (*MIF*) as an inflammatory cytokine that plays a central role in the pathogenesis of vasculitis. Increased *MIF* levels have been found in the serum of patients with Wegener's granulomatosis (WG) and microscopic polyangiitis. Polymorphisms in the *MIF* gene influence its expression and may influence development and severity of vasculitis. Two specific polymorphic sites have been identified in the *MIF* promoter that correlate with MIF production *in vivo*: a -794 CATT repeat and a -173 G/C Single Nucleotide Polymorphism (SNP). We studied the association of "high expression" *MIF* alleles and haplotypes with disease severity in WG.

#### **Methods:**

The study consisted of 502 patients with WG and 576 matched controls. Because of genetic variation among races, the study focused on Caucasians (the majority of the cohort). Genotyping for the CATT site was performed by polymerase chain reaction (PCR) plus capillary electrophoresis; SNP analysis was performed by real-time PCR using ABI Prism 7900 HT. The frequencies of high expression *MIF* alleles/haplotypes were calculated and compared between patients and controls, and in the same vasculitis cohort, between patients with severe and limited disease. The results were compared using Pearson Chi-square. Haplotypes were analyzed using

HPlus 2.5 software.

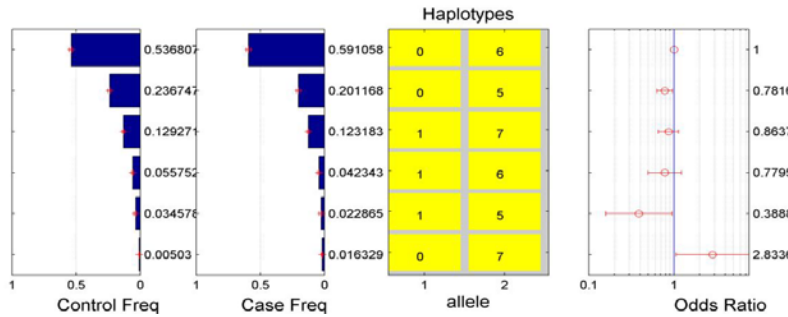
**Results:**

The percentage of individuals carrying a single 6,7, or 8-CATT repeat (high *MIF* expression) was 61% in patients with WG and 58% in controls (p=0.32), whereas the percentage increased from 54% to 64% in patients with a limited versus a severe form of WG (p=0.04). There was no statistical significance in the -173 G/C SNP between these groups. Haplotype results in cases and controls are summarized in Figure 1. Patients with haplotype 7/G had an odds ratio of 2.8 ([1.06-7.58] p=0.038) for developing WG, whereas patients with haplotype 5/G and 5/C had odds ratio of 0.78 ([0.63-0.97] p=0.02) and 0.39 ([0.16-0.95] p=0.038) respectively. There was no statistical difference in the frequencies of haplotypes between patients with limited and severe WG.

Figure 1: Haplotype frequencies in cases and controls. Allele 1=-173 SNP G/C (0=G, 1=C). Allele 2=CATT repeats (5=5-CATT repeats, 6=6-CATT repeats, 7=7-CATT repeats, 8=8-CATT repeats)

**Conclusion:**

High expression *MIF* CATT alleles (6-, 7-, 8-CATT) but not the -173 SNP is associated with increased severity of WG. Furthermore, the presence of haplotype 7/G triples the risk of the disease, whereas haplotypes 5/G and 5/C decrease the risk.



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**Author Disclosure Information:** T.G. Sreih, Yale University has applied for a patent describing the therapeutic value of MIF genotyping, 9; L. Leng, None; A.D. Mahr, None; P. Dellaripa, None; G.S. Hoffman, None; U. Specks, None; R. Spira, None; E. St. Clair, None; P. Seo, None; J.H. Stone, None; J. Edberg, None; P.A. Merkel, None; R. Bucala, Yale University has applied for a patent describing the therapeutic value of MIF genotyping, 9.

**Category (Complete):** 30. Vasculitis

**Keywords (Complete):** MIF ; Vasculitis ; Polymorphism

**Additional Keyword (Complete):**

**Eligibility (Complete):**

**\*Has the data contained in the submitted abstract been presented or accepted for presentation at another meeting prior to the ACR submission deadline of August 11?: Yes**

**If yes, please indicate the meeting at which the presentation was or will be made. :** ACR Research Workshop

**Additional Information (Complete):**

**Research Method:** Translational

**Type of Trial:** Epidemiologic or Observational

**Phase:** Not Applicable

**Presentation Preference (Complete):** &nbsp;Poster Only

**Payment (Complete):** Your credit card order has been processed on Tuesday 15 July 2008 at 1:51 PM.

**Attached Files:**

ACR justification letter from the program director (Microsoft-WORD, 28160 bytes)

**Status:** Complete