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Caspase-12 and lupus: the curious case of the dog that didn’t bark

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CASPASE-12 (CASP12) has an anti-inflammatory function during infection, and is a risk factor for sepsis in African-Americans (AA). To determine if CASP12 could be protective for systemic lupus erythematosus (SLE) in AA, we genotyped AA SLE patients and controls. We found that, at best, there was a weak association between CASP12 genotype with the absence of anti-dsDNA autoantibodies in SLE patients. No effect was seen upon serum interleukin-1 beta levels, nor was any other protective effect noted for the CASP12 genotype, whether upon association with SLE, or any of the 11 American College of Rheumatology classification criteria. We concluded that CASP12 genotype thus does not influence the phenotype of SLE in AA. This raises the issue as to why this protein would not play a more significant role in a chronic inflammatory disease process.

**Keywords:** Inflammation; Caspase-12; Autoimmunity; Lupus

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Most humans lack a functional CASP12 gene. In all Caucasians and East Asians examined, and in 80% of people of African lineage \(^1\), \(^2\), the gene exists as a pseudogene (CASP12p1), the result of a premature termination mutation \(^3\). In approximately 20% of persons of recent African lineage, an intact gene is found where a single nucleotide polymorphism (#rs497116; A->G) converts the stop codon into one encoding Arg \(^1\), \(^2\).

Intact CASP12 is a risk factor for sepsis in African-Americans in response to pro-inflammatory agents such as bacterial lipopolysaccharide. This is due to CASP12’s ability to down-regulate production of inflammatory cytokines such as interleukin (IL)-1β or tumor necrosis factor (TNF) and by interfering with the activation of the transcription factor NFκb \(^4\), \(^5\). In African-Americans with severe sepsis, the mortality rate was 54% in individuals who carried CASP12, compared with 17% in individuals with possessed only CASP12p1. Knockout mice lacking CASP12 are also more resistant to sepsis and death than wild-type mice \(^6\). These anti-inflammatory activities are proposed to result from CASP12 biding to inflammasome components such as CASP1 and CASP5 \(^6\) and/or to adaptor proteins downstream of pattern recognition molecules, such as NOD2 \(^7\) or RIG-1 \(^8\).

The intact allele of CASP12 is still found in approximately 20% of African-Americans, with higher allele frequencies in some populations in sub-Saharan Africans, and in some populations of Central and South Asians \(^1\), \(^2\), \(^9\). This implies...
that despite its selective disadvantage, it may play a protective role in inflammatory processes exploited by specific pathogens [10].

If CASP12 is a risk factor for sepsis, we posited that this allele would be protective against some inflammatory autoimmune diseases. If CASP12 causes a derangement in IL-1β or TNF production, individuals carrying the CASP12 allele, but not CASP12p1, should be less likely to develop inflammatory disease. To test this hypothesis, we sought to determine if CASP12 genotype would have an effect upon the pathologic manifestations of systemic lupus erythematosus (SLE). To do so, we genotyped CASP12 in patients and controls from the Lupus Family Registry and Repository cohort [11], and assessed >714 patients and >300 healthy controls.

Patients had at least at least four of the 11 American College of Rheumatology (ACR) SLE classification criteria for SLE [12, 13]. We found that CASP12 genotype was neither a risk factor nor protective. CASP12 polymorphisms did not affect any of the 11 ACR classification criteria. In addition, there was no association between CASP12 genotype and clinical criteria in patients in a case-only design. That is, having or lacking CASP12 did not affect a patient from being susceptible to, or protected from any particular lupus manifestation, nor from combinations of the more severe diagnostic criteria, such as lupus nephritis plus neuropsychiatric symptoms. At best, we found a weak protective effect against the development of anti-double-stranded DNA antibodies, but no other autoantibodies, such as anti-Sm, -Ro, -La, -snRNP, and -cardiolipin).

The first question arising is, what role, if any, does CASP12 play in autoimmune pathogenesis? In a previous study, we found that the presence of intact CASP12 had no overall effect upon the development of rheumatoid arthritis in AA, there was a subtle protective effect against the erosive pathologies of RA, as defined by radiographic changes of baseline joint erosion and joint space narrowing scores. Baseline joint narrowing and total disease scores were greater in CASP12p1 homozygous patients than those who were CASP12 homozygous. No significant differences could be identified for any other clinical parameters [14].

Given the reported downregulatory effects that CASP12 exerts upon IL1β production via inhibition of CASP1 and subsequent IL1β generation [4, 6], we expected to see reduced serum IL-1β levels in a genotype-dependent manner in our patient group, with the lowest levels in the CASP12 homozygous patients. These expectations were predicated on the known defects in the ability of peripheral blood mononuclear cells to produce IL-1β occur in SLE patients [15] and the decreased IL-1β levels seen in patient serum [16]. In looking at any potential role of CASP12 in SLE, it is important to bear in mind that the contribution of IL1 to the pathogenesis of SLE is murky. In the murine lupus model, the NLRP3 inflammasome mediates lupus nephritis, with CASP1 playing a key role in the pathogenic process [17], and SLE patients show transcriptional upregulation of inflammasome component genes [18]. Yet this was not the case, although our small sample size makes us view this data with caution.

The next question arising is whether CASP12 can influence the production of autoantibodies. The pathology of SLE is mediated by chronic autoantibody production (of which anti-dsDNA antibodies are the most important clinically [19, 20] and immune complex deposition, which triggers inflammation and tissue destruction [21-23]. We observed a weak but significant effect on anti-dsDNA. Yet after adjusting for multiple testing in the case-control and case-case analyses, no significant results remained, and no significant effects were seen for the other autoantibodies. Given the role of CASP1 in the generation of autoantibodies [17], it is possible that an IL1-independent pathway is involved.

How CASP12 exerts the protective effects described above is unknown. If CASP12 is downregulatory, it may fail to reduce serum concentrations of pathogenic cytokines driving autoantibody production below disease-inducing levels, but does so at the tissue or cellular level. This notion is supported by the observation that there is less macrophage infiltration into adipose tissues of obese African-American children who are CASP12-positive [24].

The above leads us to a third question: Is CASP12 actually anti-inflammatory? Saleh and colleagues extended their finding on CASP12 and IL1-β to other inflammatory cytokines with the observation that obese African-American children who are CASP12-positive have lower serum IL6 and C-reactive protein levels [24]. Unfortunately, these workers did not report on any findings concerning IL-1β or TNF. Perhaps then IL-1β is not triggered at a systemic level following metabolism-based inflammation, but instead is either activated by non-CASP1-mediated mechanisms in different disease states (reviewed in [25]) or IL-1β production is not affected by CASP12. We lean toward the latter interpretation.

CASP12 genotype does not influence susceptibility or adverse events in African-Americans or black South Africans with community-acquired pneumonia [26]. In addition, the CASP12 allele does not affect susceptibility to Candida
levels were assessed.

CASP -11 restoration of the immune function to these animals [34]. Hence, the contradictory [5, 28, 31]. Further, while hepatitis C virus is an 

Doyle’s short story The Adventure of the Silver Blaze bring us to the title of this review. In Sir Arthur Conan Doyle’s short story The Adventure of the Silver Blaze, the detective Sherlock Holmes noted that a guard dog was supposed to bark at prowlers in the night, yet didn’t do so prior to the occurrence of a crime. CASP12 is posited to downregulate inflammation mediated by cytokines, to such an extent that this activity renders a subject more susceptible to sepsis. This would explain the near extirpation of the population [1, 2]. However, it is worth noting two key effects of CASP12 on cytokine concentrations in the pathology of candidiasis [27] or in in vitro responses to Yersinia pestis [28]. While malaria would be an obvious candidate for a positive selective effect upon maintenance of CASP12, there is no association between CASP12 genotype and either the presentation of severe malaria or outcomes in individual clinical parameters in malaria patients [29].

CASP12’s effects upon TNF production, which is elevated in all lupus patients, especially African-Americans [30], is also contradictory [5, 28, 31]. Further, while hepatitis C virus is an IL-1β inducer [32], CASP12 genotype has no effect on the clearance of this pathogen [33]. Confounding the metabolic findings described above by Skeldon and co-workers, no protective effects are found in African-American adults with CASP12 when metabolic parameters or C-reactive protein levels were assessed.

Our findings with two separate rheumatologic diseases bring us to the title of this review. In Sir Arthur Conan Doyle’s short story The Adventure of the Silver Blaze, the detective Sherlock Holmes noted that a guard dog was supposed to bark at prowlers in the night, yet didn’t do so prior to the occurrence of a crime. CASP12 is posited to downregulate inflammation mediated by cytokines, to such an extent that this activity renders a subject more susceptible to sepsis. This would explain the near extirpation of the functional allele from the vast majority of the human population [1,2]. However, it is worth noting two key effects observed by Vande Walle and colleagues in CASP12-knockout mice: they also lack CASP11, and restoration of the CASP-11 gene restores inflammatory immune function to these animals [34]. Hence, the down-regulatory effects of CASP12 on the inflammasome observed by Saleh and colleagues at best, appear not to be applicable to rheumatic disease in humans, and at the worst, may be artefactual.

Conflicting interests

The authors have declared that no conflict of interests exist.

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Abbreviations

AA: African-American; ACR: American College of Rheumatology; CASP: Caspase; IL: interleukin; SLE: Systemic lupus erythematosus; TNF: Tumor necrosis factor.

References


