Borrelia burgdorferi complement regulator-acquiring surface protein 1 (CRASP-1), the dominant factor H and FHL-1-binding protein of the Lyme disease spirochete B. burgdorferi, is implicated in pathogen persistence and was recently reported to be nonimmunogenic in humans. Here we show that serum samples from Lyme disease patients contain antibodies with exclusive specificity for nondenatured structural determinants of CRASP-1.