

# A mutation causing wrinkled skin of Shar-Pei dogs is linked to periodic fever disorder

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An international investigation has uncovered the genetics of the Shar-Pei dog's characteristic wrinkled skin. The researchers, led by scientists at Uppsala University and the Broad Institute, have connected this mutation to a periodic fever disorder and they propose that the findings could have important human health implications. Details appear on March 17 in the open-access journal *PLoS Genetics*.

Purebred dogs are selected for defined physical features, and the inadvertent enrichment for disease-risk genes may have unexpected health consequences. The thickened and wrinkled skin of Shar-Pei dogs contains an excess of hyaluronan, most likely due to the over-activation of the hyaluronan synthase 2 (HAS2) gene. The Shar-Pei also has a high prevalence of a periodic fever disorder similar to human inherited autoinflammatory periodic fever syndromes. Hyaluronan may create a 'danger' signal to the immune system, analogous to the effects a pathogen may have. Because of the health implications, Shar-Pei breed clubs have strongly supported research into the cause of periodic fever.

To find the genetic cause for wrinkled skin, the researchers first compared the Shar-Pei genome to that of other [dog breeds](#). Simultaneously, they compared the genome of healthy and sick Shar-Pei to locate the mutation for the fever. Both studies pinpointed the same region, which contained the HAS2 gene. In this breed alone, a DNA segment located close to HAS2 was duplicated erroneously, sometimes multiple times.

"It was really exciting to realize that the two traits had the same genetic origin," says Mia Olsson, one of the authors. "Copies of the duplicated segment increase the risk for periodic fever in these dogs, and the overproduction of hyaluronan is the predisposing factor."

"With this [genetic information](#), people can avoid breeding Shar-Pei with many duplications," said study co-author Linda Tintle. "Understanding the causes will also lead to more effective treatments."

The researchers have shed light on the role of hyaluronan in inflammatory disease. The association of HAS2 dysregulation and autoinflammation is of wide interest since the genetic cause of periodic fever syndromes in approximately 60% of human cases remains unexplained. "The finding that hyaluronan is a major trigger of fever opens a new research field in canine and human inflammatory disease," said senior author Kerstin Lindblad-Toh.

**More information:** Olsson M, Meadows JRS, Truve K, Rosengren Pielberg G, Puppo F, et al. (2011) A Novel Unstable Duplication Upstream of HAS2 Predisposes to a Breed-Defining Skin Phenotype and a Periodic Fever Syndrome in Chinese Shar-Pei Dogs. *PLoS Genet* 7(3): e1001332. [doi:10.1371/journal.pgen.1001332](https://doi.org/10.1371/journal.pgen.1001332)

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