A mutation causing the unique thickened skin and wrinkles of Shar-Pei dogs is linked to their periodic fever disorder and chronic inflammation.

An international research group led by scientists at Uppsala University, Sweden and the Broad Institute of MIT and Harvard in collaboration with veterinarian Linda Tintle, Wurtsboro, New York, has uncovered the genetics of the Shar-Pei dog’s characteristic wrinkled skin and connected this mutation to a periodic fever disorder. Details appear on March 17 in the open-access journal *PLoS Genetics*.

Purebred dogs are selectively bred for defined physical features. Inadvertent enrichment for genes carrying an increased risk of disease may have unexpected health consequences. The thickened skin of Chinese Shar-Pei is likely due to increased activation of hyaluronan synthase 2 (*HAS2*) causing excess hyaluronan deposition.

Shar-Pei also have a high prevalence of a periodic fever disorder similar to human inherited autoinflammatory periodic fever syndromes like Familial Mediterranean Fever. Because of the health implications, Shar-Pei breed clubs have strongly supported research into the cause of Familial Shar-Pei Fever since its association with familial renal amyloidosis was first described in 1990.

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 disorder. Both studies pinpointed the same region, which contained the *HAS2* gene. Near this gene, a DNA segment was duplicated erroneously, sometimes multiple times. This duplication event was not found in other breeds. The copy number varied between individual Shar-Pei and increased copy number variant (CNV) was associated with increased *HAS2* expression and also increased susceptibility to FSF and amyloidosis, suggesting a regulatory mutation signaling *HAS2* over-expression.

"It was really exciting to realize that the two traits had the same genetic origin," says Mia Olsson, a PhD student working on the project and first author on the paper. "Copies of the duplicated piece increase the risk for periodic fever in these dogs and the overproduction of hyaluronan is the predisposing factor."

"Our study sheds light on how damaged or degraded hyaluronan in Shar-Pei can result in fever and other inflammatory disease." says Linda Tintle, Wurtsboro Veterinary Clinic, NY, who has collaborated with researchers on this problem for over twenty years. "With this genetic information, people can avoid breeding Shar-Pei with high copy number variants. Improved knowledge of the altered biology should lead to more effective treatments."

Fragmented hyaluronan is a danger signal recognized by the innate immune system and a trigger of fever and inflammation in general. By connecting hyaluronan in Shar-Pei wrinkled skin with periodic fever, 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.
A genetic test for FSF is currently undergoing validation studies at the Broad Institute/Uppsala University with a large number of samples collected in October 2010 from dogs at the Chinese Shar-Pei Club of America, Inc.'s 2010 National Specialty as well as Swedish and other international samples. Genetic test results are currently being correlated to individual health records. A commercial test that is accurate, meaningful and useful to veterinarians, Shar-Pei owners, and breeders is the goal of this on-going study.

"The finding that hyaluronan is a major trigger of fever opens a new research field in canine and human inflammatory disease," says senior author Kerstin Lindblad-Toh, Director Science for Life Laboratory, Uppsala University and Director of Vertebrate Genome Biology at the Broad Institute of MIT and Harvard. "We have now started the search for similar mutations in human patients."

Study authors include Mia Olsson1#, Jennifer R.S. Meadows1*, Katarina Truvé2*, Gerli Rosengren Pielberg1*, Francesca Puppo3*, Evan Mauceli4, Javier Quilez5, Noriko Tonomura4, Giordana Zanna6, Maria José Docampo7, Anna Bassols7, Anne Avery8, Elinor K. Karlsson4,9, Anne Thomas10, Daniel L. Kastner3, Erik Bongcam-Rudloff11, Matthew T. Webster1, Armand Sanchez5, Åke Hedhammar12, Elaine F. Remmers3, Leif Andersson1,2, Lluis Ferrer6, Linda Tintle15#, Kerstin Lindblad-Toh1,4#

1 Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Box 582, SE-751 23 Uppsala, Sweden.
2 Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences, Biomedical Centre, Box 597, SE-751 24 Uppsala, Sweden.
3 National Human Genome Research Institute, 20892 Bethesda, Maryland, USA.
4 Broad Institute of Harvard and Massachusetts Institute of Technology (MIT), 7 Cambridge Center, Cambridge, Massachusetts 02142, USA.
5 Department of Animal and Food Science, Veterinary Molecular Genetics Service, Universitat Autònoma de Barcelona, 08193 Barcelona, Spain.
6 Department of Animal Medicine and Surgery, Universitat Autònoma de Barcelona, 08193 Barcelona, Spain.
7 Department of Biochemistry and Molecular Biology, Universitat Autònoma de Barcelona, 08193 Barcelona, Spain.
8 Department of Microbiology, Immunology and Pathology, Colorado State University Fort Collins, Colorado 80523, USA.
9 FAS Center for Systems Biology, Harvard University, 7 Divinity Avenue, Cambridge, Massachusetts 02138, USA.
10ANTAGENE Laboratory, 69578 Limonest Cedex, France.
11 Linnaeus Centre for Bioinformatics, Uppsala University, SE-751 23 Uppsala, Sweden.
12 Department of Clinical Sciences, Swedish University of Agricultural Sciences, SE-750 07 Uppsala, Sweden.
13 Wurtsboro Veterinary Clinic, Wurtsboro, New York 12790, USA.
# indicates a corresponding author.

Link to the PLoS Genetics article A Novel Unstable Duplication upstream of HAS2 predisposes to a Breed-defining Skin Phenotype and a Periodic Fever Syndrome in Chinese Shar-Pei Dogs
http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1001332