Mapping a Region on Chromosome 1 That Affects Aortic Dilation in Mucopolysaccharidosis VII Mice

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Mucopolysaccharidosis VII (MPS VII) is an autosomal-recessive lysosomal storage disease that results from mutations in the gene that codes for the enzyme β-glucuronidase (GUSB). GUSB contributes to the breakdown of glycosaminoglycans (GAGs), and its deficiency causes an accumulation of GAGs throughout the body and multisystemic problems. It is believed that the accumulated GAGs bind to a cell-surface receptor that leads to signal transduction, which induces an inflammatory response that upregulates destructive proteases. This increased protease activity could be responsible for the fragmentation of elastin in the aorta, which causes aortic dilation and increases the risk of aortic aneurysms. The aortas of MPS VII mice are consistently 2 to 3 times wider than the aortas of normal mice. However, one colony of MPS VII mice from a mixed genetic background was found to have mice with dilated aortas and mice with non-dilated aortas. This observation suggests that the MPS VII mice with non-dilated aortas inherited a gene from an alternative genetic background that confers protection against aortic dilation. An initial screening showed approximately 7% genome difference between the pure MPS VII mice and the mixed genetic MPS VII mice. One hundred additional SNP markers were selected from the chromosomal regions with genetic differences, and a SNP assay was performed on 92 MSP VII mice from the mixed genetic background. We found significant associations between reduced aortic diameter and a 50 Mb chromosomal region at chromosome 1. In our search for candidate genes, we have found two IgG receptors, Fcgr2 and Fcgr4, in this gene rich region, which are upregulated in MPS VII mice with dilated aortas.