What an Amish Mutation Can Tell Us About Long Life

A new study found that people with a relatively rare mutation live longer than those without it. The mutation was found among the Amish people in Indiana, and what this mutation does says a lot about what makes for longer life, and what we can do about it. Here's what an Amish mutation can tell us about longer life.

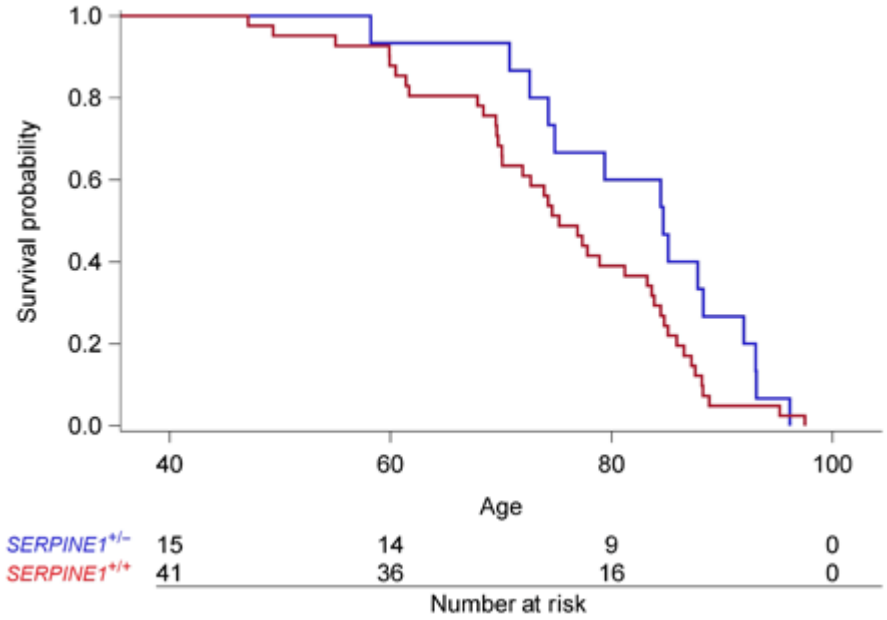
The mutation

The mutation in question is for a gene called SERPINE1, which encodes for a protein called plasminogen activator inhibitor 1. A null mutation in *SERPINE1* protects against biological aging in humans. (Thanks to commenter anonymous human for bringing this to my attention. Josh Mitteldorf wrote about what these results mean for a theory of programmed aging.) From the abstract:

> Plasminogen activator inhibitor–1 (PAI-1) has been shown to be a key component of the senescence-related secretome and a direct mediator of cellular senescence. In murine models of accelerated aging, genetic deficiency and targeted inhibition of PAI-1 protect against aging-like pathology and prolong life span. However, the role of PAI-1 in human longevity remains unclear. … We studied 177 members of the Berne Amish community, which included 43 carriers of the null *SERPINE1* mutation. **Heterozygosity was associated with significantly longer leukocyte telomere length, lower fasting insulin levels, and lower prevalence of diabetes mellitus. In the extended Amish kindred, carriers of the null SERPINE1 allele had a longer life span.** Our study indicates a causal effect of PAI-1 on human longevity, which may be mediated by alterations in

metabolism. [emphasis added]

Those Amish who were heterozygous for this mutation lived about 10 years longer on average than others. See chart below:



Just eyeballing the chart, median survival of carriers was about 85, for others about 75. That's a huge increase in lifespan, arguably much greater than almost any single factor we know in humans.

The carriers of the gene mutation produce less PAI-1, which results in a greater tendency for blood clots to break down. Those who are homozygous (-/-) for the mutation have an even greater tendency to break down blood clots, which results in a bleeding disorder. That's the immediate consequence of less PAI-1.

However, the heterozygous (+/-) carriers had longer telomeres, which is a sign of slower aging. They also had less diabetes risk, a 0% diabetes rate compared to 7% in non-carriers, even though body mass index was the same. And they had better cardiovascular risk markers, including lower blood pressure and lower carotid artery thickness, a measure of atherosclerosis.

Clearly, PAI-1 does a lot to promote aging, and having less of it appears to result in longer life.

What does this mutation tell us about the conditions necessary for longer life, and can we do anything about it?

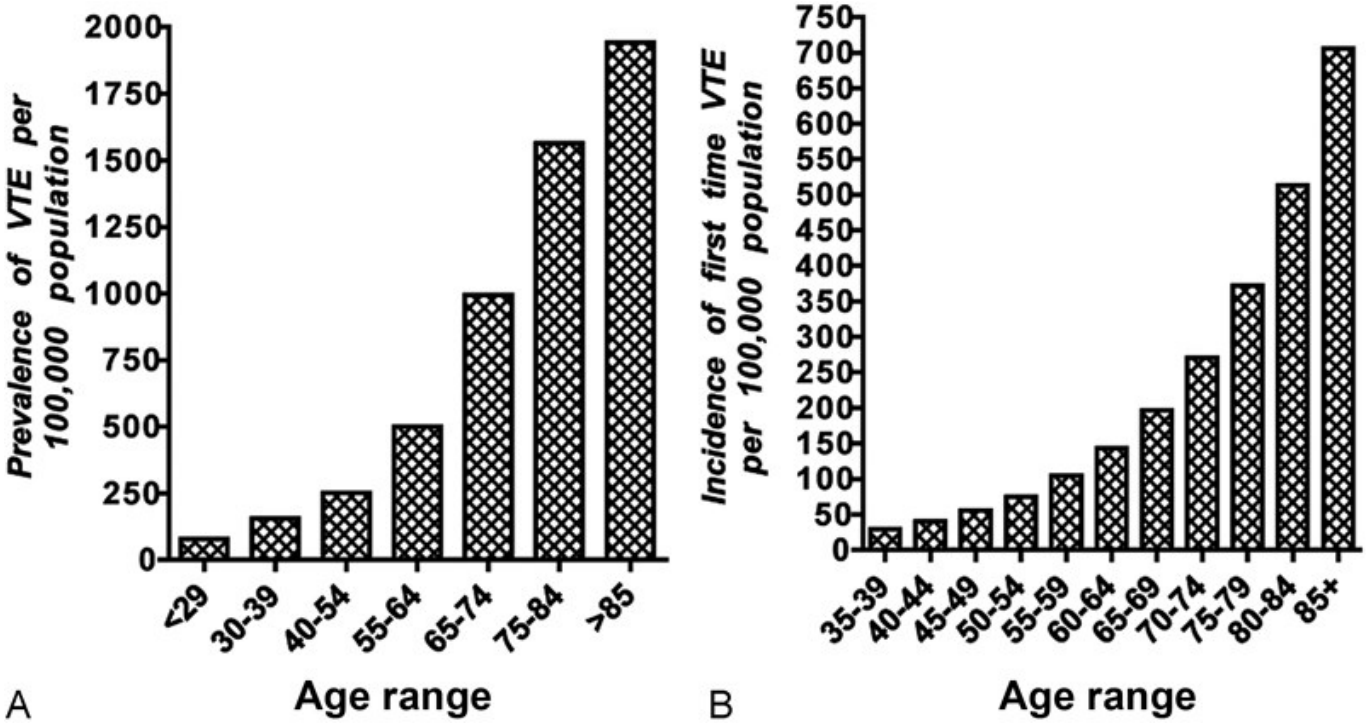
Hypercoagulability

Blood coagulation is a necessary function that protects animals from excessive bleeding, which obviously can be fatal. When a cut or injury appears, whether internal or external, many different proteins are activated to form a blood clot; regulation of the coagulation cascade is complex, and the organism must balance all these factors to have an optimal coagulation

system.

If the coagulation system becomes out of balance, either bleeding or hypercoagulability result, both of which are deleterious.

Aging promotes hypercoagulability, which generally arises from a decreasing ability to break down fibrin blood clots. This can result in thrombophilia, in which blood clots spontaneously form when not wanted and cause serious problems. The incidence of venous thromboembolism, or a blood clot in a vein, rises sharply with age. See chart below.



Several factors can promote hypercoagulability, among them bacterial lipopolysaccharides (LPS) and iron.

Iron causes irregular fibrin clots which resist breaking down.

Iron also promotes the growth of bacteria, and gram negative bacteria shed LPS, tiny amounts of which promote blood clotting.

So the first thing we can learn from the relation between less PAI-1 and longer life is that hypercoagulability can and should be avoided.

Aspirin may play a role in this, and in fact preventing blood clots is one way in which it prevents heart attacks – and also promotes bleeding.

Keeping iron in the low normal range and cultivating good gut integrity and oral hygiene to prevent incursion of gram negative bacteria can help prevent hypercoagulability in aging.

Insulin resistance

Why having less PAI-1 leads to less diabetes seems mysterious, but it does.

Type 2 diabetes is characterized by insulin resistance, which also rises with aging and obesity. Having low insulin resistance, or conversely, high insulin sensitivity, is one of the most important health risk factors.

Young, lean, fit people who eat few refined carbohydrates or sugar have the best insulin sensitivity.

Old, overweight, sedentary people who eat high carbohydrate and high sugar diets have poor insulin sensitivity.

The Amish mutation that resulted in less PAI-1 also shifted their metabolic type closer to that of the young, lean, etc. Adipose tissue is one of the main producers of PAI-1.

If you're not so lucky as to have the mutation, you can still avoid sugar and refined carbohydrates, you can exercise, and you can stay lean. Same effect.

Cellular senescence

Increased gene expression for PAI-1 is increased in senescent cells.

Senescent cells as contributory to aging is an exciting field of research that has made a lot of advances in recent years. Ridding mice of senescent cells greatly improves their health, giving them higher exercise capacity and better cardiac function.

Currently, trials in humans are contemplated to try to eliminate senescent cells, and will probably in a few years result in senescent cell therapy, which would probably only need to be done periodically, say every few years.

The Amish mutation study shows the importance of cellular senescence in aging.

Heart disease

The Amish who had this mutation had better cardiovascular risk markers.

PAI-1 has a causal effect on coronary heart disease. It also increase fasting blood glucose.

The fact that less PAI-1 means less heart disease and longer life shows its importance.

It also seems to show that cholesterol isn't a great risk factor for heart disease, if indeed it is at all.

Conclusion

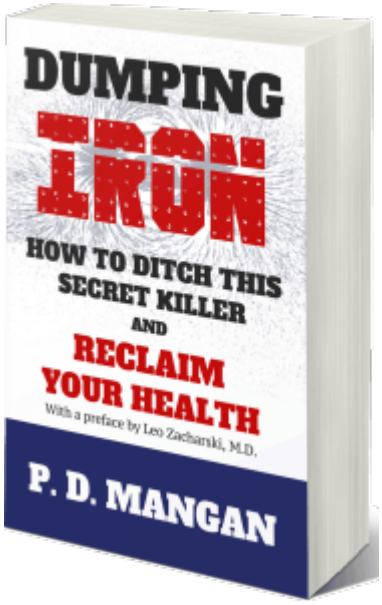
The degree of life extension conferred by the SERPENTINE1 mutation was large, 10 years or so.

As we've seen above, the result confirms the importance of

hypercoagulability, insulin resistance, and cellular senescence to aging.

It's likely possible to get the same results through the lifestyle and other factors outlined in this article.

PS: For more on the importance of iron and aging, see my book, Dumping Iron.



PPS: Check out my Supplements Buying Guide for Men.