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P5CS mutations identified as new target for skin rejuvenation

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Led by scientists from Agency for Science, Technology and Research (A*STAR)'s Institute of Medical Biology (IMB), an international team of researchers has discovered a novel protein mutation which results in a rare premature skin ageing condition. The findings shed light on the underlying mechanisms of skin ageing, and bring us one step closer to maintaining skin youthfulness through targeting such enzymes. The study was published in the *American Journal of Human Genetics* and involved collaborations with over 16 hospitals and research centres across 11 countries.

As we age, our skin tends to become thinner, more fragile, and lacking in elasticity, leading to wrinkles. Understanding why and how our skin ages, then, is the first step to slowing down the effects.

The study examined the DNA samples of patients with suspected De Barsy Syndrome (DBS), otherwise known as 'wrinkly skin syndrome'. It belongs to a group of rare connective tissue disorders, known as cutis laxa (CL) syndromes, in which the skin hangs loosely in folds and turns inelastic.

A previous study in 2009 had found that mutation of the PYCR1 gene was an underlying cause of DBS, making PYCR1 a prime target for anti-wrinkling treatments for common disorders related to ageing. Intriguingly though, in these patients' cases, while they showed DBS-like symptoms, their PYCR1 genes did not bear any mutations, suggesting that other genes could be responsible.

It was found that a unique mutation in the enzyme P5CS affecting only the residue Arg138, was the cause for the observed symptoms and a prematurely-aged appearance. Having identified this, scientists can now develop treatments to counteract P5CS mutations, and therefore hope to recover skin elasticity.

This particular form of CL, while milder than DBS, was further found to be autosomal dominant, such that only one copy of a disease allele is necessary for one to be susceptible and there is a 50% chance the offspring will inherit the disease allele and suffer from the disorder. This is opposed to the autosomal recessive DBS, which bears only a 25% chance. This discovery will certainly ameliorate the diagnostics, treatment, and genetic counselling processes for patients.

Beyond CL patients, skin ageing and wrinkling is also a pertinent aspect of overall human ageing, and such insights can improve our management of ageing, particularly to address the global issue of an ageing population. Furthermore, this area is one of the hot focus areas for personal care companies, and this discovery identifies a novel target for the development of wrinkle-defying treatments, and improvement of the skin's self-renewal capacity and youthful appearance.

IMB and IMCB Senior Principal Investigator Dr Bruno Reversade, one of the study's corresponding authors, commented, "We are now certain that skin ageing in humans is under the control of proline metabolism, which both PYCR1 and P5CS are involved in. Our next challenge is to find out if these two enzymes are druggable to develop active compounds to slow down the effects of ageing."

Professor Birgit Lane, Executive Director of IMB, stated, "By looking at rare disorders, we have successfully identified proteins critical to normal skin ageing. This discovery has opened up new possibilities in the fields of skin and ageing research, with crucial clinical implications. We will

continue to explore rare diseases with the dual aims of changing the lives of rare disorder patients, and improving the scientific understanding of common conditions to help the general public."

More information: "Recurrent De Novo Mutations Affecting Residue Arg138 of Pyrroline-5-Carboxylate Synthase Cause a Progeroid Form of Autosomal-Dominant Cutis Laxa." *Am J Hum Genet*. 2015 Sep 3;97(3):483-92. DOI: 10.1016/j.ajhg.2015.08.001

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