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Singapore: Scientists at A*STAR's Institute of Medical Biology (IMB), in collaboration with doctors and scientists in Jordan, Turkey, Switzerland and the US, have identified the genetic cause of a birth defect known as Hamamy syndrome. Their groundbreaking findings were published on May 13 inÃ?Â *Nature Genetics*. The work lends new insights into common ailments such as heart disease, osteoporosis, blood disorders and possibly sterility.

Hamamy syndrome is a rare genetic disorder that is marked by abnormal facial features (Annex A) and defects in the heart, bone, blood and reproductive cells. Its exact cause was unknown until now. The international team, led by scientists at IMB, have pinpointed the genetic mistake to be a mutation in a single gene called IRX5.

This is the first time that a mutation in IRX5 (and the family of IRX genes) has ever been discovered in man. IRX5 is part of a family of transcription factors that is highly conserved in all animals, meaning that this gene is present not only in humans but also in mice, fish, frogs, flies and even worms. Using a frog model, the scientists demonstrated that IRx5 orchestrates cell movements in the developing fetus that underlie head and gonad formation.

Carine Bonnard, a final-year PhD student at IMB and the first author of the paper, said, "Because Hamamy syndrome causes a wide range of symptoms, not just in newborn babies but also in the adult, this implies that IRX5 is critical for development in the womb as well as for the function of many organs in our adult body. For example, patients with this disease cannot evacuate tears from their eyes, and they will also go on to experience repetitive bone fractures (Annex A) or progressive myopia as they age. This discovery of the causative gene is a significant finding that will catalyze research efforts into the role of the Irx gene family and greatly increase our understanding of human health, such as bone homeostasis, or gamete formation for instance."

"We believe that this discovery could open up new therapeutic solutions to common diseases like osteoporosis, heart disease, anaemia which affect millions of people worldwide," said Dr Bruno Reversade, Senior Principle Investigator at IMB. "The findings also provide a framework for understanding fascinating evolutionary questions, such as why humans of different

ethnicities have distinct facial features and how these are embedded in our genome. IRX genes have been repeatedly co-opted during evolution, and small variation in their activity could underlie fine alterations in the way we look, or perhaps even drastic ones such as the traits seen in an elephant, whale, turtle or frog body pattern."

Only a handful of people in the world have been identified with Hamamy Syndrome making it a very rare genetic disorder. Rare genetic diseases, usually caused by mutations in a single gene, provide a unique opportunity to better understand more common disease processes. These "natural" experiments are similar to carefully controlled knockout animal experiments in which the function of single genes are analyzed and often give major insights into general health issues.

Prof Birgitte Lane, executive director of IMB, said, "Understanding how various pathways in the human body function is the foundation for developing new therapeutic targets. This is an important piece of research that I believe will be of great interest to many scientists and clinicians around the world because of the clinical and genetic insights it brings to a large range of diseases."