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Protein mutation alters tissue development in males before birth

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Case Western Reserve researchers have identified a protein mutation that alters specific gender-related tissue in males before birth and can contribute to the development of cancer as well as other less life-threatening challenges.

The discovery marks the latest in a series of findings related to the protein SRY (sex-determining region on the Y chromosome), which serves as a master switch for ensuring typical human male maturation. In this case, however, the mutation prevents the protein from folding properly and in turn impairs the protein's ability to direct the appropriate development of gonadal tissue. Even worse, the tissue defects in the original patient identified with this mutation also contribute to the development of gonadal cancer.

The findings appear in the November 21 edition of the *Journal of Biological Chemistry*, whose editors named the article its Paper of the Week. Case Western Reserve biochemistry doctoral student Joseph Racca is senior author of the piece, which describes the protein's infrastructure with architectural terms typically reserved for historic European churches.

"The mutation occurs in a strategic part of the SRY protein that we describe as an 'aromatic buttress'—molecular struts and girders that function in support of an angular DNA-bending surface," Racca explained. "Just as the flying buttresses of Gothic cathedrals ensure their structural stability, the aromatic buttress of SRY is responsible for

proper protein folding and stability."

Racca is a student in the laboratory of Michael Weiss, MD, PhD, the chair of biochemistry and a co-author of this paper. Weiss has led a team of scientists through the discovery of multiple unique aspects of the SRY protein mutations, each with its own signature of defects in structure and function.

"The DNA-bending module of the SRY protein is preserved among a large family of regulatory proteins that regulate key events in development, including how stem cells form the brain and other organs," said Weiss, also a Distinguished Research Professor within the medical school.

Regulatory proteins, first discovered in 1992 by Robin Lovell-Badge, PhD, and colleagues at the Medical Research Council in London, England, have attracted growing interest in terms of birth defects and cancer. SRY is considered the pivotal protein in regulating male sex determination.

Mutations in the SRY protein take place within an L-shaped protein architecture known as a high mobility group (HMG) box. The HMG box is a structure that contains chromosomal proteins that regulate DNA processes such as transcription, replication, recombination and DNA repair.

Mutations in the HMG box of the aromatic buttress essentially place a hole at a strategic point in the L shape, resulting in its collapse. The collapse leads to incomplete folding and binding with the DNA and affects all the various functions of male sex determination in humans.

"At the start of this project, we speculated that this mutation would be unfavorable," Racca said. "But we underestimated the extent and range

of impairments. A 'perfect storm' leads to the collapse of almost all the molecular functions of SRY, including cellular trafficking, stability, DNA recognition and gene regulation."

Mutations in SRY alter the dynamics of male development during fetal life. In most cases, mutations lead to XY sex reversal, a syndrome in which babies are born with a female appearance, including external genitalia, uterus and fallopian tubes. When these patients fail to menstruate at the onset of puberty, an XY chromosome may be discovered. This condition is designated 46, XY pure gonadal dysgenesis with female somatic phenotype (Swyer's syndrome, affecting one in 80,000 births). In some cases, SRY mutations cause a continuum of disorders of sex development, including pseudohermaphroditism (affecting up to 1 in 99,000 births) with partial ovarian and testicular differentiation within the intra-abdominal gonads. Impaired differentiation of the gonads confers high risk of a pediatric cancer, gonadoblastoma.

"Beyond its specific role in testicular differentiation," Racca said, "SRY illustrates general principles of protein structure and evolution."

As for next research steps, the investigators will seek to exploit the SRY database and its evolutionary linkages to other SOX transcription factors to explore applications to stem-cell biology and cancer. SOX stands for Sry-related HMG box, and SOX genes activate a family of transcription factors that bind to the minor grooves in DNA.

Racca and his fellow researchers represent the potential power of multidisciplinary collaboration as exemplified in the study of this mutation.

"Our team at Case Western Reserve is a great group of scientists and friends with complementary interests," said Racca. "My work focuses on

the molecular functions of SRY as a biophysical system, for example, while one bench away is a classmate who monitors the biological effects of mutations in a mammalian cell-culture system. Together, we related how biophysical and biochemical properties affected by the SRY mutation relate to the regulation of a gene-regulatory network in a biological system."

Provided by Case Western Reserve University