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Cover: Statue of Ardhanarishvara, the half-male, half-female form of Shiva, India 11th century A.D.

SOX5 IS INVOLVED IN GERM CELL REGULATION AND SEX DETERMINATION IN MEDAKA FOLLOWING CO-OPTION OF NESTED TRANSPOSABLE ELEMENTS

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Sex determination relies on a hierarchically structured network of genes, and is one of the most plastic processes in evolution. The evolution of sex-determining genes within a network, by neo- or sub-functionalization, also requires the regulatory landscape to be rewired to accommodate these novel gene functions. We previously showed that in medaka fish, the regulatory landscape of the master male-determining gene dmrt1bY underwent a profound rearrangement, concomitantly with acquiring a dominant position within the sex-determining network. This rewiring was brought about by the exaptation of a transposable element (TE) called Izanagi, which is co-opted to act as a silencer to turn off the dmrt1bY gene after it performed its function in sex determination.

We now show that a second TE, Rex1, has been incorporated into Izanagi. The insertion of Rex1 brought in a preformed regulatory element for the transcription factor Sox5, which here functions in establishing the temporal and cell-type-specific expression pattern of dmrt1bY. Mutant analysis demonstrates the importance of Sox5 in the gonadal development of medaka, and possibly in mice, in a dmrt1bY-independent manner. Moreover, Sox5 medaka mutants have complete female-to-male sex reversal.

Our work reveals an unexpected complexity in TE-mediated transcriptional rewiring, with the exaptation of a second TE into a network already rewired by a TE. We also show a dual role for Sox5 during sex determination: first, as an evolutionarily conserved regulator of germ-cell number in medaka, and second, by *de novo* regulation of dmrt1 transcriptional activity during primary sex determination due to exaptation of the Rex1 transposable element.