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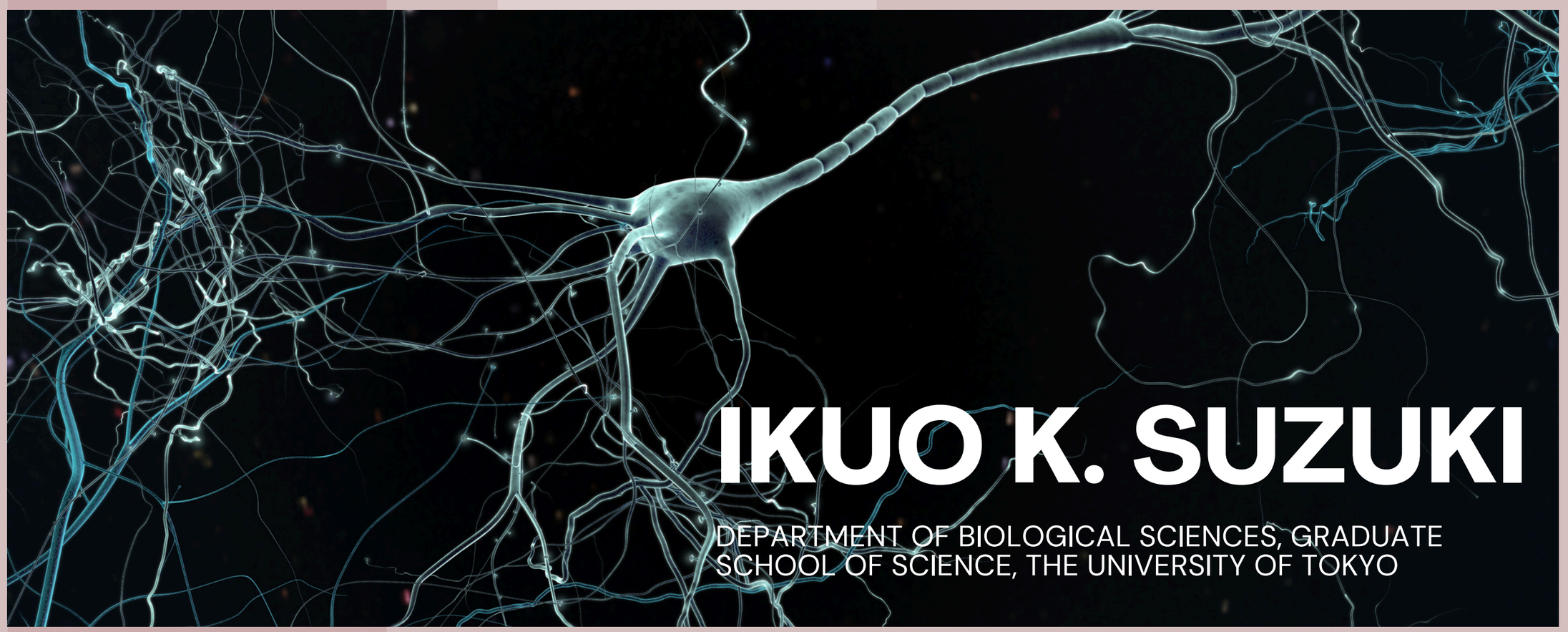

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GENOMIC AND MOLECULAR MECHANISMS OF HUMAN BRAIN EVOLUTION

Humans are characterized by their outstanding cognitive abilities, which are enabled by an enormous increase of neurons in the cerebral cortex. The molecular mechanisms leading to the construction of human-specific cortical architectures are beginning to be identified, exemplified by the human-specific genes, some of which promote neurogenesis leading to cortical expansion. Most human-specific genes originated by duplication of preexisting genes, and copy number variation of these gene families is often associated with congenital neurodevelopmental disorders. It remains to be determined whether all paralogs are equally important or only limited copies are selectively functional. Although genotyping closely related paralogs has been extremely difficult using short-read sequencing, here we identified an evolutionarily novel allele of a NOTCH2NL paralog with the signature of selective sweep in the modern human population. We comprehensively surveyed NOTCH2NL paralogs and alleles using the human pangenome references, and population genomics simulation showed that this novel allele underwent evolutionary adaptation and spread rapidly in human populations. Molecular experiments showed that this mutation cell-autonomously enhances the neurogenetic activity of cortical progenitors by fine-tuning the folding of the Notch ligand protein in the endoplasmic reticulum. In summary, we have uncovered a novel evolutionary mechanism of human brain enlargement, in which a specific allele of a specific paralog that increases cortical neurons began its rapid adaptation to the human population just before the onset of migration out of Africa. This study also provides evidence that a single nucleotide mutation in complexly duplicated genes drives human evolutionary adaptation.

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