# The (CTG)n polymorphism in the NOTCH4 gene is not associated with schizophrenia in Japanese individuals


## ABSTRACT

Our data suggest a lack of association between the NOTCH4 gene triplet repeat polymorphism and schizophrenia in Japanese individuals.


## INTRODUCTION

Background NOTCH activity affects the implementation of differentiation, proliferation, and apoptotic programs, influencing organ formation and morphogenesis. The formation of neuronal contacts results in activation of NOTCH receptors, leading to the restriction of neuronal growth and a subsequent arrest in differentiation. NOTCH functions as a genetic switch between neuronal and glial fates through its negative regulation of the glial cell deficient/glial cells missing (glide/gcm) gene, the gene required to induce gliogenesis in glial precursors. The human NOTCH4 gene is located on chromosome 6p21.3, and several linkage studies have suggested that a susceptibility locus for schizophrenia is present on chromosome 6p. In situ hybridization studies have determined that in embryonic and adult life, NOTCH4 transcripts are primarily restricted to endothelial cells. NOTCH4 is not necessary for embryonic development, as NOTCH4-deficient mice develop normally. However, this gene and the NOTCH1 gene have partially overlapping roles during embryogenesis in mice; both NOTCH1-mutant and NOTCH1/NOTCH4-double mutant embryos have severe defects in angiogenic vascular remodeling. Using linkage disequilibrium mapping of the human major histocompatibility complex (MHC) region in 80 British parent-offspring trios, Wei and Hemmings found that NOTCH4 was highly associated with schizophrenia. The A-to-G substitution in the promoter region (SNP2) and the (CTG)n repeat in exon 1 of NOTCH4 were considered possible candidate sites conferring susceptibility. A Japanese case-control association study reported that these polymorphisms did not show significant associations with schizoaffective disorder or schizophrenia in Japanese individuals; further, no associations were found between the polymorphisms and subcategories of schizophrenia or a positive family histry of psychoses. We conducted a case-control study using Japanese subjects to explore an association between the (CTG)n repeat polymorphism in the NOTCH4 gene and schizophrenia, and to examine subtypes, longitudinal disease course characteristics, and a positive family history of psychoses. We found no association between the NOTCH4 gene triplet repeat polymorphism and schizophrenia in this patient population.

## CONCLUSION

Conclusions Our study suggests a lack of association between the triplet repeat (CTG)n polymorphism in the NOTCH4 gene and schizophrenia in Japanese patients.