miR-433 polymorphic targeting at FGF20 confers risk for Parkinson’s disease

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INTRODUCTION. The major causes of Parkinson’s disease (PD) are still largely unknown. We have previously shown linkage of PD to chromosome 8p1. Subsequently, fibroblast growth factor 20 (FGF20) at 8p21.3-22 was identified as a risk factor2. To identify the risk-conferring polymorphism in FGF20 we performed genetic and functional analysis of single nucleotide polymorphisms (SNP) within the gene.

METHOD. In a sample of 729 nuclear families with 1089 affected and 1165 unaffected individuals, we have genotyped 8 SNPs by ABI Taqman assay. Pedigree disequilibrium test (PDT) and association in the presence of linkage (APL) were utilized for association analysis3. We also used dual luciferase assay to test the effects of miRNA polymorphic binding.

RESULTS. The strongest association came from the SNP rs12720208 at 3’-UTR of FGF20. rs12720208 lies within a predicted binding site for miR-433. The allele C of rs12720208 matches the predicted miR-433 binding domain, while the T allele represents a G:U wobble base pairing (Fig. 1A, B).

In transiently transfected Neuro2A cells, the translation of Renilla luciferase from constructs containing the C allele was dramatically reduced in the presence miR-433 in a concentration-dependent manner. However, no repression of Renilla luciferase translation was seen for the T allele construct when miR-433 was added (Fig. 1C, D & E).

We further showed that miR-433 (1~10 pmol) repressed FGF20 translation in fibroblasts, with greater inhibitory effects found in the fibroblasts homozygous for allele C than the heterozygous fibroblasts (data not show). As expected, human brain homozygous for allele T has the highest FGF20 level, whereas brains carrying the C allele have substantially lower levels of FGF20. Finally, we found that increased FGF20 induces α-synuclein overexpression which is a known cause for PD.
DISCUSSION. Although the exact function of α-synuclein remains to be understood, pertinent to this study is that triplication and duplication of the α-synuclein gene can also cause dominant PD4.

Our finding clearly shows that the variations of miR-433 binding at rs12720208 of FGF20 cause dramatic difference in FGF20 translation. We suggest that at later stages of life, the chronically increased level of FGF20 may indirectly contribute to dopaminergic neuron death through increased α-synuclein level. We predict that miR-433 and FGF20 will be potentially useful for PD diagnosis and treatment.

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REFERENCES