

News Release

Title:

Identification of Rare, Single-Nucleotide Mutations in NDE1 and Their Contributions to Schizophrenia Susceptibility

Key points:

- Nuclear Distribution E Homolog 1 (NDE1), located within chromosome 16p13.11, plays an essential role in to microtubule organization, mitosis, and neuronal migration, and has been suggested by several studies of rare copy number variants (CNVs), that NDE1 variants may be a promising associated with schizophrenia (SCZ) candidate gene.
- Functional assays showed that S214F affected axonal outgrowth and the interaction between NDE1 and YWHAE (a neurodevelopmental regulator).
- This study strengthens evidence for an association between rare variants of NDE1 and schizophrenia, and may shed light into the molecular mechanisms underlying this severe psychiatric disorder.

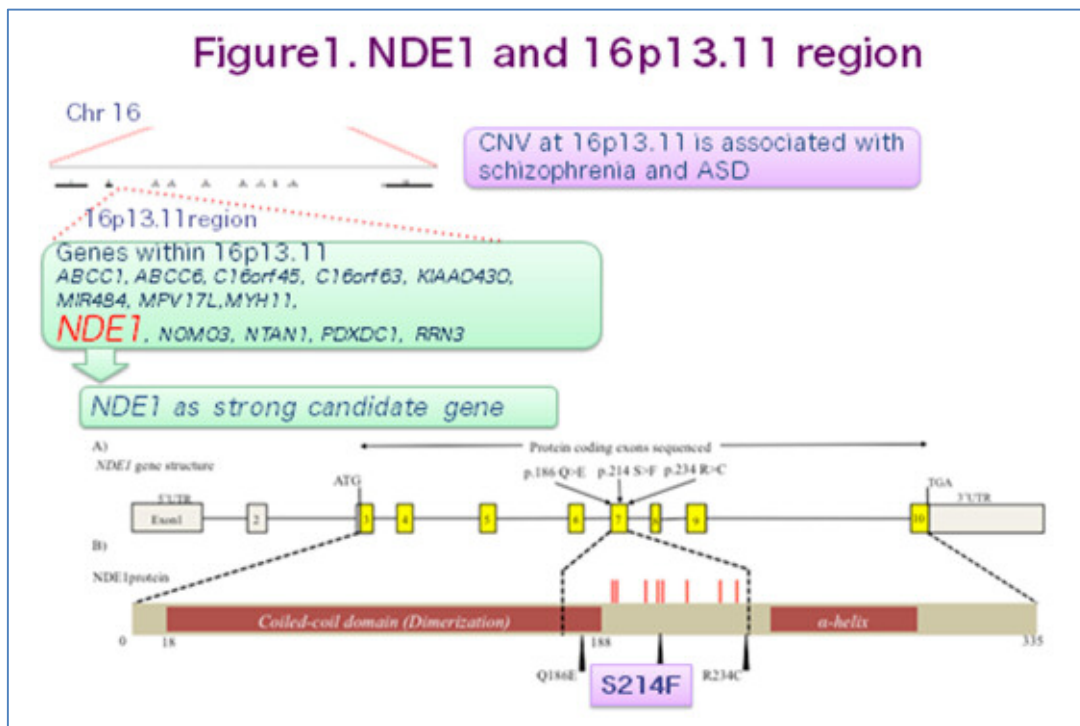
Summary

Nuclear Distribution E Homolog 1 (NDE1), located within chromosome 16p13.11, plays an is essential role in to microtubule organization, mitosis, and neuronal migration, and has been suggested by several studies of rare copy number variants (CNVs) indicated that NDE1 variants may be a promising associated with schizophrenia (SCZ) candidate gene.). Professor Norio Ozaki (Department of Psychiatry, Nagoya University Graduate School of Medicine) , and his collaborators from Nagoya University Professor Kozo Kaibuchi conducted mutational screening of NDE1 coding exons using 433 SCZ and 145 pervasive developmental disorders (PDD) samples to identify rare SNVs with a minor allele frequency (MAF) $\leq 5\%$. We then performed genetic association analysis using a large number of unrelated individuals (3554 SCZ, 1041 bipolar disorder (BD), and 4746 controls). Among the novel rare variants, we detected significant associations between SCZ and S214F ($P=0.039$) and between BD and R234C ($P=0.032$). Furthermore, functional assays showed that S214F affected axonal outgrowth and the interaction between NDE1 and YWHAE (a neurodevelopmental regulator). This study strengthens evidence for an association between rare variants of NDE1 and schizophrenia, and may shed light into the molecular mechanisms underlying this severe psychiatric disorder. This work was published online in the Schizophrenia Bulletin.

Research background

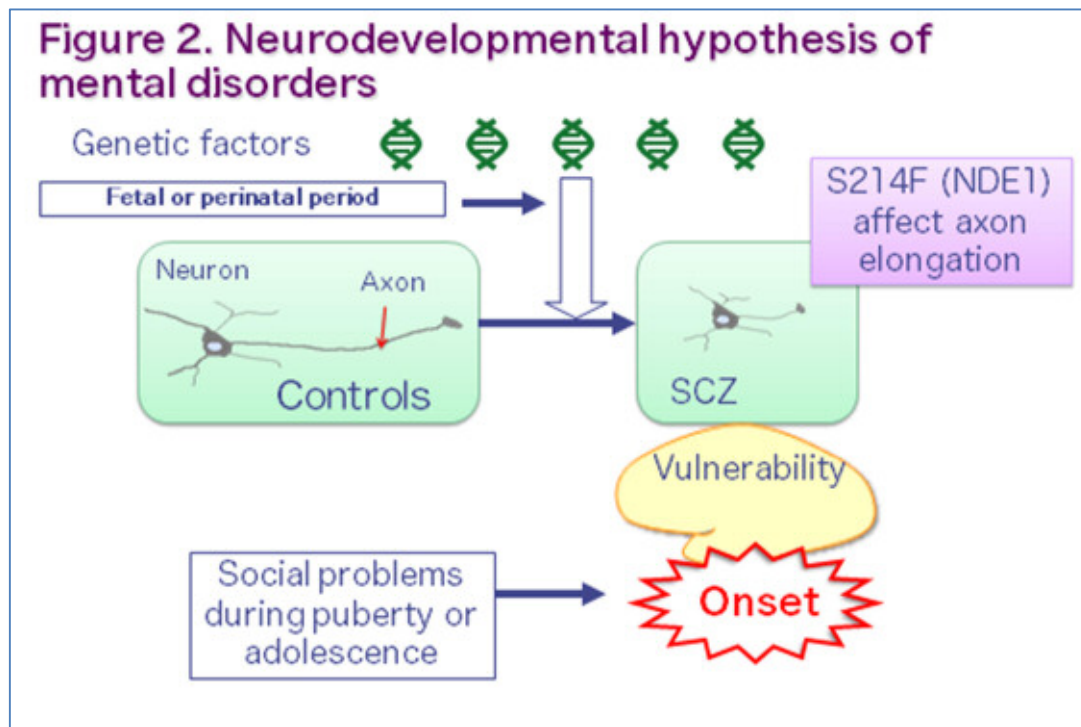
Clinical features of SCZ are characterized by hallucinations, delusions, and cognitive deficits; SCZ causes enormous personal and societal burdens, and is a severe psychiatric disorder with a lifetime risk of about 1%. The heritability of SCZ is as high as 80% making this condition a target for human genetics research. Recent

studies into the genetic architecture of SCZ have identified both common and rare variants. Accumulating evidence indicates that rare SNVs discovered from deep sequencing of candidate genes may 1) have large effect sizes, 2) account for some of the missing heritability, and 3) be useful in conjunction with functional analysis for the study of the pathogenesis of neuropsychiatric disease. Multiple lines of evidence indicate that deletions or reciprocal duplications at chromosome 16p13.11 are associated with disorders involving abnormal neurodevelopment, such as ASD, epilepsies, and SCZ. CNVs at 16p13.11 regions contain nuclear distribution E homolog 1 (*NDE1*), which are closely associated with neurodevelopmental phenotypes; *NDE1* is a strong candidate gene. Furthermore, linkage analyses indicate that *NDE1* is associated with risk of SCZ or ASD. In this study we aimed to discover rare variants with large effect size and explore the role in pathogenesis of the discovered rare variants by performing mutational screening of *NDE1* coding exons with samples from cases of SCZ or pervasive developmental disorder (PDD)



Research results

We identified four rare missense heterozygous mutations within *NDE1* coding exons (figure 1). One variant (S214) was located at a putative phosphorylation site according to the HPRD and was predicted to be deleterious by each of the three algorithms. Furthermore, detected a significant association (odds ratio=7.1, $p=0.039$) between SCZ and S214F in the sample comprising 8734 unrelated individuals. Biological assays suggested S214F mutations impaired the interaction between *NDE1* and *YWHAE*, and affected axon elongation (Figure 2).



Research summary and future perspective

Screening for mutations in *NDE1*, a candidate risk gene for SCZ and ASD based on CNV analysis, revealed novel rare missense mutations that might increase susceptibility to SCZ and BD. Importantly, we detected a significant association between SCZ and S214F, which was found to have the biological effects of changing the interaction between NDE1 and YWHAE and the axonal outgrowth. This study therefore strengthens the evidence for the role of rare variants in *NDE1* in the etiopathological role of SCZ, ASD, and BD. The present results also indicated that deep sequencing of candidate genes is a promising method, especially using current and developing NGS technology, for elucidating the missing heritability and pathogenesis of neuropsychiatric disorders. In addition, examining effects of rare single nucleotide variants using novel techniques such as iPS cells may be promising approach in future genetic studies.

The authors and title of the paper

Kimura H, Tsuboi D, Wang C, Kushima I, Koide T, Ikeda M, Iwayama Y, Toyota T, Yamamoto N, Kunimoto S, Nakamura Y, Yoshimi A, Banno M, Xing J, Takasaki Y, Yoshida M, Aleksic B, Uno Y, Okada T, Iidaka T, Inada T, Suzuki M, Ujike H, Kunugi H, Kato T, Yoshikawa T, Iwata N, Kaibuchi K, Ozaki N. Identification of Rare, Single-nucleotide Mutations in *NDE1* and Their Contributions to Schizophrenia Susceptibility. *Schizophrenia Bulletin*, October 20, 2014

Japanese ver.

http://www.med.nagoya-u.ac.jp/medical/dbps_data/material/nu_medical/res/topix/2014/NDE1_20141027jp.pdf