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## The WNT2 gene polymorphism associated with speech delay inherent to autism<sup>☆</sup>

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## ABSTRACT

Previous evidence suggests that language function is modulated by genetic variants on chromosome 7q31–36. However, it is unclear whether this region harbors loci that contribute to speech delay in autism. We previously reported that the WNT2 gene located on 7q31 was associated with the risk of autism. Additionally, two other genes on 7q31–36, FOXP2 and the EN2 genes are also found to play a role in language impairment. Therefore, we hypothesize that the WNT2 gene, FOXP2 gene, and EN2 gene, may act in concert to influence language development in the same population. A total of 373 individuals diagnosed with autistic disorder were recruited in the current study. We selected 6 tag single nucleotide polymorphisms (SNPs) within the WNT2 gene, 3 tag SNPs in the FOXP2, and 3 tag SNPs in the EN2 genes, to study the effect of these genes on language development. Age of first phrase was treated as a quantitative trait. We used general linear model to assess the association between speech delay and these variants. The results show that rs2896218 in the WNT2 gene was moderately significantly associated with age of first phrase (permutation  $p = 0.0045$ ). A three-locus haplotype in the WNT2 gene was significantly associated with age of first phrase (permutation  $p = 2 \times 10^{-4}$ ). Furthermore, we detected an interaction effect on age of first phrase between a SNP rs2228946 in the WNT2 gene and another SNP rs6460013 in the EN2 gene ( $p = 0.0012$ ). Therefore, the WNT2 gene may play a suggestive role in language development in autistic disorder. Additionally, the WNT2 gene and EN2 gene may act in concert to influence the language development in autism.

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## 1. Introduction

Autism is a severe developmental disorder characterized by heterogeneous clinical features, including impairments in language, behaviors, and social communication. The role of genetic factors in etiological pathways for autism has been extensively documented. Recently, genome-wide association studies have suggested a number of common genetic variants associated with the risk of autism (Anney et al., 2010; Ma et al., 2009; Wang et al., 2009), whereas many of these findings have not been confirmed in other populations yet. The failure to replicate the original positive finding in another population (a.k.a., “winner’s curse”) may be partially attributed to genetic heterogeneity. Previous evidence indicates that the power of a meta-analysis to detect a small genetic effect decreases as between-study heterogeneity increases (Nakaoka & Inoue, 2009). Clinical heterogeneity has been found to be a norm rather than an exception in autism, and hence could lend some support to the presence of genetic heterogeneity. Several approaches to circumvent the problem of genetic heterogeneity include targeting clinically homogeneous populations and focusing on sub-phenotypes (Viding & Blakemore, 2007).

Speech delay is one of the hallmark features of autism. Previous family studies have suggested that language development is influenced by genetic factors (Lennon et al., 2007). For example, a review by Stromswold documents strong evidence for familial aggregation of disorders of speech and language (DSL); the prevalence of DSL in individuals of families of children diagnosed with DSL has been found to be 5–10 times higher than those without family history of DSL (Stromswold, 1998). DeThorne et al. (2006) reported that the heritability estimates for difficulties in expressive language and articulation were 0.54 and 0.97, respectively. Hence, these lines of evidence imply that genetic factors may play a larger role than environmental factors in the language development. Uncovering the genetic pathway associated with the language development related to autism may shed some light on the genetic basis of autism.

Previous studies have suggested that chromosome 7q may harbor genetic loci associated with language function. A genome-wide linkage study showed that age of first word in autism was linked to the 7q35–36 region (Alarcon, Cantor, Liu, Gilliam, & Geschwind, 2002). A follow-up linkage study incorporating “age of first word” by ordered subset analysis revealed that the linkage signal on 7q35–36 might be attributable to autistic individuals with an earlier onset of first word (Alarcon, Yonan, Gilliam, Cantor, & Geschwind, 2005). Another linkage study also confirmed that chromosome 7q may contain variants linked to language impairment (Villanueva et al., 2011). Meanwhile, Lai, Fisher, Hurst, Vargha-Khadem, and Monaco (2001) reported their landmark finding that mutations and translocation in the FOXP2 (forkhead box P2) gene (OMIM 605317) on chromosome 7q may cause verbal dyspraxia due to impaired motor sequences of orofacial muscles. A subsequent study showed that the mutations in the FOXP2 gene lead to impairments in not only sound production, but also written language and non-verbal cognitive functions (Watkins, Dronkers, & Vargha-Khadem, 2002). The FOXP2 gene encodes a transcription factor modulating expressions of a great many genes (Vernes et al., 2007). Among the genes regulated by the FOXP2 gene, the CNTNAP2 gene has been found to be related to nonsense-word repetition, an inheritable biomarker for specific language impairment (Vernes et al., 2008). In addition, a deletion in the WNT2 (wingless-type MMTV integration site family member 2) gene, located 2.2 Mb away from the FOXP2 gene on chromosome 7q, was found to be involved in specific language impairment (Lennon et al., 2007). Another 7q gene, the EN2 (Engrailed 2) gene, may also play a putative role in “presence of phrase speech” (Brune et al., 2008).

The associations between these candidate genes on 7q and risk of autism might be equivocal. Since these genes may play a role in language development, the inconsistent associations between loci and autism may be attributed to variation in language features. It has been proposed that incorporating speech-related endophenotypes may lead to the discovery of risk variants of heterogeneous effects of autism (Bradford et al., 2001). Hypothetically, these genes may contribute to the risk of autism by perturbing the language function. Alternatively, these loci may at best modulate language development in autism, while they play a limited role in susceptibility to autism. Hence, in the present study, we selectively investigated the role of a set of genes, FOXP2, WNT2 and EN2 on chromosome 7q, in language development in individuals with autism.

## 2. Methods

### 2.1. Subjects

The original sample consisted of totally 1164 subjects from 393 families (probands aged  $9.1 \pm 3.99$  years, male 88.6%), recruited from the outpatient clinic of Psychiatric Department of three institutes (i.e., National Taiwan University Hospital and Chang-Gung Memorial Hospital, and Taoyuan Mental Hospital in Taoyuan) in Northern Taiwan. All subjects were Han Chinese. The initial diagnoses of probands were made by senior board-certified child psychiatrists based on the DSM-IV diagnostic criteria of autistic disorder or Asperger’s disorder, and were further confirmed by the structured interviews using the Chinese version of the Autism Diagnostic Interview-Revised (ADI-R) (Gau et al., 2010). Among these 393 probands, 373 were clinically diagnosed as autistic disorder and 20 were diagnosed as Asperger’s disorder. Probands diagnosed with fragile X and Rett’s disorder based on DNA testing or clinical features were excluded. Additionally, probands with previously identified chromosomal structural abnormality associated with autism, or had any other major neurological or medical conditions were also excluded. Two primary quantitative traits, age of first word and age of first phrase, were retrieved from the ADI-R interviews of the parents. The Research Ethics Committee of three research sites approved this study. Written informed consent was obtained from majority of the

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