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Genetics Research Paper: The Inheritance of Schizophrenia

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Genetics Research Paper: The Inheritance of Schizophrenia

Kolbi Holmes

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ABSTRACT

Schizophrenia is a spectrum of disorders defined by abnormalities in one or more areas including delusions, hallucinations, disorganized thinking or speech, grossly disorganized or abnormal motor behaviors including catatonia and other negative symptoms (*American Psychology Association, 2013*). Schizophrenia is inherited on autosomal chromosome 8p12. Neuregulin 1 (*NRG1*), an epithelial growth factor protein, located at 8p12, has been identified as being a nucleotide variation of the single-nucleotide polymorphism (SNP), rs833497 located on chromosome 18q21.1 that is associated with schizophrenia.

INTRODUCTION

Schizophrenia is spectrum of psychiatric and schizotypal disorders. The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), characterizes schizophrenia spectral disorders as being defined by abnormalities in one or more areas including delusions, hallucinations, disorganized thinking or speech, grossly disorganized or abnormal motor behaviors including catatonia and other negative symptoms (*American Psychology Association, 2013*). Sufferers have an altered perception of reality and experience symptoms for a significant period lasting longer than one month. Schizophrenia was first distinguished from “common madness” in 1887 by a German physician, Emile Kraepelin, who described the disorder as “dementia praecox”. According to the National Institute of Mental Health, approximately 1% of all U.S adults have schizophrenia.

There are two types of schizophrenics differentiated by the symptoms they exhibit. A person with Type I schizophrenia is said to be producing positive symptoms which are a

combination of hallucinations, delusions bizarre behavior and racing thoughts. A person with Type II would experience what are known as negative symptoms which include apathy, a lack of emotion, poor social functioning and catatonia (Comer, 2009).

GENETIC BACKGROUND

There are many debates among scientist about whether or not environmental or genetic factors play a role in the cause of schizophrenia. However, many research studies have revealed that there is in fact an inherited element of the diseases. In fact, if one identical twin is diagnosed with schizophrenia there is about a 50% change that the other twin will also be diagnosed (Gottesman, 1991). A notable association study between the dymeclin (DYM) gene and schizophrenia in the Japanese population revealed that each copy of a C at rs833497, in the DYM gene was associated with 1.16 times more likeliness of schizophrenia (Yazaki, et al., 2010). The DYM gene is associated with the Golgi apparatus, which packages proteins after they are synthesized by the rough endoplasmic reticulum of a cell, and cellular vesicle trafficking, which moves proteins packaged by the Golgi apparatus and other substances across the cell membrane to specific locations in the plasma membrane and is in chromosome 18q21.1 (Yazaki, et al., 2010) (Figure 1).

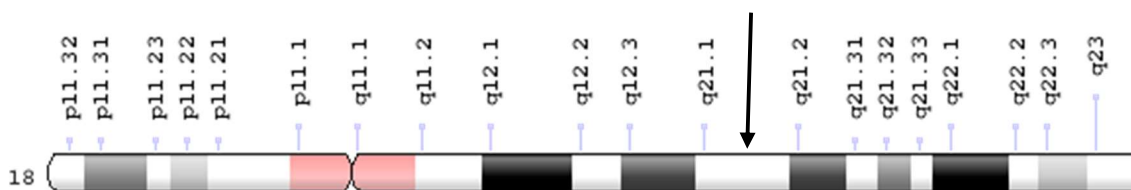


Figure 1: Chromosome Location of DYM gene 18q21.1 (Created using the National Center for Biotechnology Information's Genomic Decoration Page)

This means that schizophrenia has an autosomal inheritance and the single-nucleotide polymorphism (SNP), rs833497 is associated with schizophrenia. In the same study a meta-analysis of genetic association, on family studies was conducted which revealed Neuregulin 1 (*NRG1*) as being a nucleotide variation in Golgi apparatus genes with schizophrenia (*Yazaki, et al., 2010*). A case-control association study of 478 Icelandic schizophrenic patients mapped schizophrenia to 8p and identified *NRG1* as a schizophrenia gene (*Gulcher, et al., 2003*). *NRG1* is an epithelial growth factor protein that regulates activity-dependent synaptic plasticity, stimulates glial development, epithelial differentiation, and effects neuro-signaling. *NRG1* is involved in many aspects of brain development and is located in chromosome 8p12 (Figure 2).

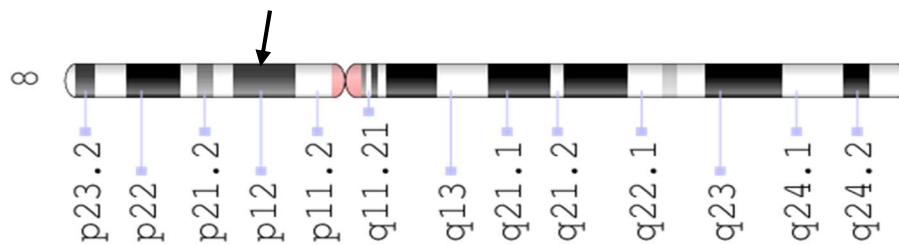
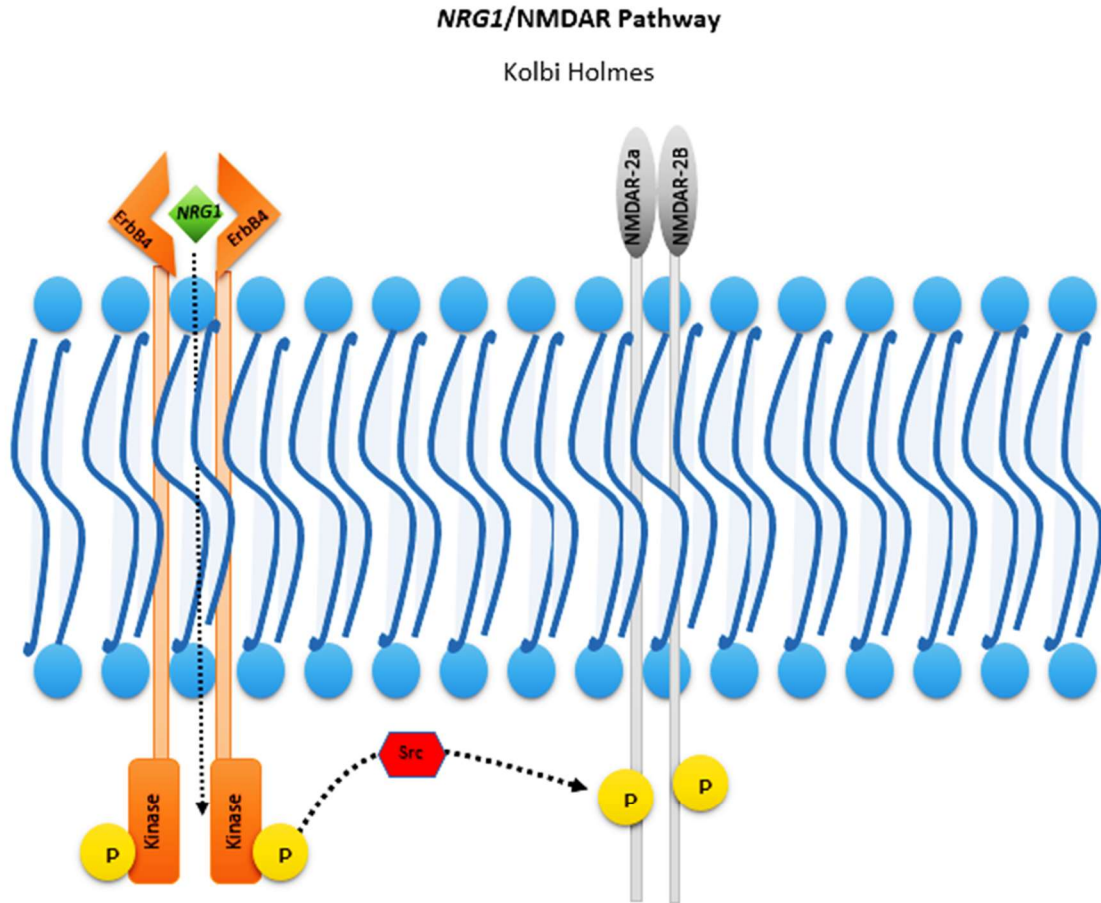


Figure 2: Chromosome Location of *NRG1* 8p12 (Created using the National Center for Biotechnology Information’s Genomic Decoration Page)

NRG1 interacts with cells through the receptor tyrosine-protein kinase erbB-4 (ErbB4) receptor, which is a part of the epidermal growth factor receptor family (*Pitcher, et al., 2010*). This family of genes consists of *NRG1*, *NRG2*, *NRG3*, and *NRG4*. They bind to and activate the ErbB family of receptor tyrosine kinases (ErbB1, ErbB2, ErbB3, ERbB4) (*Pitcher, et al., 2010*). The *NRG1*-Erb4 signal suppresses the kinase activity of proto-oncogene tyrosine-protein kinase Src (Src), which phosphorylates *N*-methyl-D-aspartate receptor (*NMDAR*) subunits 2a and 2b, which control synaptic plasticity and memory function (*Pitcher, et al., 2010*). This binding is more frequent in an individual with schizophrenia leading to overactive signaling which suppresses

and depletes NMDAR leading to low glutamate levels which are associated with low energy levels, memory loss and depression (Pitcher, et al., 2010). Test studies conducted on mice mutant for *NRG1* or ErbB4, displayed behavior abnormalities consistent with schizophrenic models (Gulcher, et al., 2003).



Neuregulin 1 (*NRG1*) binding to receptor tyrosine-protein kinase ErbB-4 (ErbB4) activating and signaling suppression of kinase activity reducing proto-oncogene tyrosine-protein kinase Src (*src*), from mediating phosphorylation of *N*-methyl-D-aspartate receptor (NMDAR) subunits.

Figure 3: *NRG1*/NMDAR pathway

TREATMENT

There are currently no available treatments for schizophrenia on a genetic level. There is also no cure of any kind for schizophrenia. Anti-psychotic medications have been used since the 1950's as a way to attempt to control symptoms associated with schizophrenia along with various types of therapies. Based on the current available research on the genetic components of schizophrenia I believe finding a cure lies in understanding why the *NGR1-ErbB-4* binds over-actively producing signals that inhibit src from phosphorylating NMDAR in an individual with schizophrenia. If scientist could figure out how to either 1. How to reduce the *NGR1-ErbB-4* binding or 2. Reactivate NMDAR, through other means of phosphorylation then a cure may not be too far away. Because *NRG1* plays such a big role in brain development, its effect on the less significant processes may lead to how schizophrenia is formulated within the brain.

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