Background

Schizophrenia is a complex psychiatric disorder which affects 0.5–1% of the world wide adult population. A number of putative schizophrenia susceptibility genes have been identified recently [1,2]. Genomewide linkage analysis on large Icelandic pedigrees showed evidence for linkage with an initial LOD score of 3 on chromosome 8p13, which led to the identification of the Neuregulin-1 gene (NRG1) as a potential genetic risk factor (O.R. = 2) for schizophrenia [3]. The association was confirmed in a large Scottish case control data set [4], and both studies indicated a core haplotype (HAP_{ICE}) as the DNA variation carrying most of the risk for schizophrenia. Subsequently, 15 published studies in schizophrenia data sets of various Asian and Caucasian ethnic backgrounds have detected association in NRG1 SNPs or haplotypes, while only four studies were not able to replicate the association (see [5] and [6] for a comprehensive review). The association studies reported thus far strongly suggest a true effect of NRG1 as a susceptibility gene for schizophrenia. However, some caution should be exercised before calling NRG1 a true "schizophrenia gene" due to the lack of a known functional effect of the identified NRG1 variants, the allelic heterogeneity reported across several studies and the multiple SNPs and haplotypes analysed in different studies. Nonetheless, several recent publications report an association between schizophrenia and ErbB4, one of the receptors for NRG1 [7-9]. This provides indirect evidence supporting NRG1 association with schizophrenia and a role for aberrant neuregulin signalling in this disorder.

The Neuregulin-ErbB signalling network is involved in a multitude of processes in the developing and adult brain. Neuregulins for example promote neuronal migration and differentiation, regulate the expression of neurotransmitter receptors, influence glial proliferation, survival and differentiation and play a role in synaptic plasticity.

The neuregulins (NRG) are cell-cell signalling proteins that are ligands for receptor tyrosine kinases of the ErbB family. Whereas NRG1 is known to play essential roles in nervous system and heart development, as well as in the adult brain (see above), less is known about the other members of the NRG gene family, NRG2, -3 and -4 [10,11].

The ErbB family comprises four homologous typeI receptor tyrosine kinases (RTKs). The EGFR (epidermal growth factor receptor, HUGO name for ErbB1), ErbB3 and ErbB4 receptors can bind ligands, whereas ErbB2 lacks a ligand binding domain and functions as a preferred and very potent co-receptor. ErbB3 is devoid of an active kinase domain. ErbB4 is the only ErbB family member that binds all four neuregulins, as well as several proteins that had originally been identified as EGFR ligands (Fig. 1). Furthermore, NRG1 and NRG2 can also bind to ErbB3. In contrast, none of the neuregulins bind to EGFR which instead binds unrelated ligands such as EGF, amphiregulin and others (see Fig. 1).

Ligand binding to the extracellular domain of ErbB family members leads to receptor homo-and heterodimerisation and activation of various intracellular signalling pathways such as the Ras-Raf-MAPK and the PI-3 Kinase pathways (reviewed in [12]).

In order to investigate the involvement of neuregulin pathway genes in schizophrenia, beyond the previously published association with NRG1 and ERBB4, we have tested all eight genes from the ERBB and NRG families for association with schizophrenia. We have investigated both single genes and gene-gene interactions, using a collection of schizophrenia cases and blood bank controls from Aberdeen, Scotland.

Methods

Subjects

396 Caucasian cases were ascertained in Aberdeen, Scotland. All have a basic diagnosis of schizophrenia or schizoaffective disorder according to the Operational Cri-

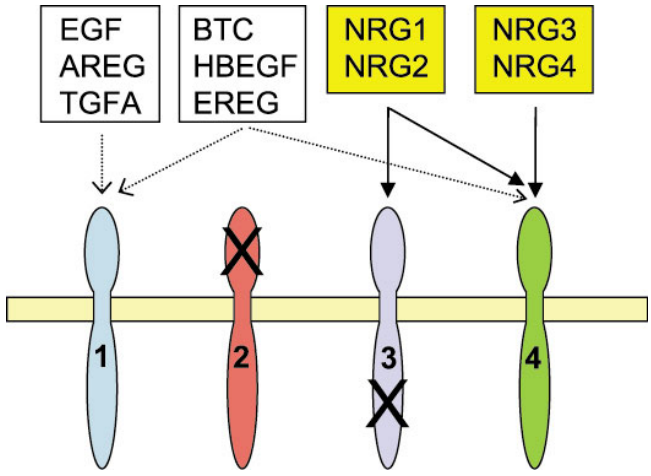

Figure 1
Binding specificities of ErbB receptor family ligands. EGF (epidermal growth factor), AREG (amphiregulin) and TGFA (transforming growth factor-α) bind EGFR (ErbB1) only. BTC (Betacellulin), HBEGF (heparin-binding EGF-like growth factor) and EREG (Epiregulin) bind EGFR and ErbB4. NRG1 and NRG2 bind ErbB3 and ErbB4. NRG3 and NRG4 are specific for ErbB4. Receptors form homo- and heterodimers after ligand-binding (not shown). As indicated (X), ErbB2 has no ligand-binding capacity and ErbB3 has no active kinase domain. Only NRG1-4 and ERBB1-4 genes were investigated in this study. (Modified from [46]).