Case report of a patient with schizophrenia and a mutation in the insulin receptor substrate-4 gene

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Abstract

This report deals with a female patient with schizophrenia who was found to have a mutation in the insulin receptor substrate-4 gene that is located on chromosome Xq22.3. Since this mutation is expected to change amino acid coding from histidine to tyrosine and cause an altered insulin receptor substrate-4 protein, and the insulin receptor substrate-4 protein may be involved in neuronal growth and function in the brain, it is possible that it is this insulin receptor substrate-4 gene mutation that underlies this patient's schizophrenia development.

INTRODUCTION

The literature on the schizophrenia illness provides strong evidence for a role of genetic factor(s) in its aetiology (Craddock *et al.* 2005). However, the main genetic factor(s) associated with the disorder still remain(s) to be found (Craddock *et al.* 2005; Crow 2007). There are also clear indications that schizophrenia is a systemic disorder and not only a brain disease (Flyckt 2001). Therefore, I and my colleagues sought for a common molecular basis for schizophrenia abnormalities in brain and body and found an interesting hypothesis, described more in detail in two recent studies (Melkersson & Persson 2011; Melkersson *et al.* 2011), that impaired insulin/ insulin-like growth factor (IGF) signalling in cells might underlie known abnormalities associated with schizophrenia in both the central nervous system (i.e. structural and functional changes) and in peripheral organs (i.e. growth dysregulation, impaired glucose tolerance, lowered resting energy expenditure and neuromuscular dysfunction). This report concerns a female patient with schizophrenia, who was found to have a mutation in the insulin receptor substrate-4 (*IRS-4*) gene, which is coding for one link in the insulin/ IGF signalling pathways in cells.

CASE REPORT

This patient was one of 95 patients with schizophrenia who gave written informed consent to participate in a genetic study that was approved by the Ethics Committee of Karolinska Institutet, Stockholm, Sweden (Melkersson 2009; Melkersson *et al.* 2011). She also gave her written informed consent to participate in this case report. She was structurally interviewed by a psychiatrist (K.M.) about mental and physical health in herself and her relatives. Besides this, complementary information was obtained from her case record.

Case history

The patient, a 50-year old Caucasian woman, was diagnosed with schizophrenia for the first time at age 15. Even as a child, she was silent and retir-

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ing. Whereas her development of motor functions in the first years was only a little late and culminated in walking at age 1.5, her language development clearly was delayed and she began to talk first at 3 to 4 years of age. As a child, she was vaccinated against pertussis, but nevertheless caught this infection. In school she attended normal class, was good at drawing and painting, but otherwise she achieved low marks in her reports. Intelligence testing at age 15 showed a normal intelligence quotient (IQ) of 86 (normal ≥ 80). Her test results varied however between the sub-tests; with best, over average results in the figure classification and block sub-tests concerning logical inductive ability and visuo-spatial cognition, and worst, below average result in the synonym sub-test concerning verbal understanding. Having left school she has been working at a sheltered workshop, in the beginning full-time, then half-time in combination with half early retirement because of her psychotic illness. Then she lived alone in her own flat, but for the last 15 years she has been living with her mother.

The patient has paranoid type of schizophrenia according to DSM-IV criteria (American Psychiatric Association 1994), and has earlier been admitted several times to psychiatric clinics because of acute psychotic relapses including symptoms such as auditory hallucination, thought disorder and paranoid delusions. However, her mental status has been relatively stable over the last five years and during this period she has needed only follow-up at a psychiatric polyclinic. During these five years she has been regularly taking the antipsychotic medication tablet perphenazine (Trilafon®) 8 mg daily.

Besides her schizophrenia illness, the patient has a mild form of rheumatoid arthritis since age 36, for which she intermittently uses the anti-inflammatory agent naproxen (Naproxen®) 250 mg daily. She also has elevated body mass index (28 kg/ m^2). Otherwise, she is physically healthy. She is the oldest of four siblings, of whom one brother suffers from systemic lupus erythematosus and two sisters are healthy. Her mother has rheumatoid arthritis too, and her paternal grandmother was treated in mental hospital because of paranoid schizophrenia. Moreover, both her paternal grandmother and paternal grandfather suffered from cancer of unknown type.

Methods

Venous blood was taken in an EDTA-containing tube and stored at –20 °C until preparation of DNA. Genomic DNA was extracted from peripheral blood leukocytes, using a Genomic DNA Purification Kit (Gentra Systems, Inc., Minneapolis, MN, USA). The extracted DNA was frozen at –20 °C until sequenced.

DNA sequencing of the whole *IRS-4* gene was performed as follows. Genomic DNA was amplified by polymerase chain reaction (PCR), carried out in a Gene Amp® PCR System 2700 (Applied Biosystems, Foster City, CA, USA), followed by cleaning of the PCR products with Shrimp Alkaline Phosphatase and Exonuclease I (Fermentas International Inc., Burlington, Canada). Then, the PCR fragments were sequenced in both directions, using BigDye® Terminator v3.1. sequencing kit (Applied Biosystems, Foster City, CA, USA), and analyzed by means of capillary electrophoresis in an ABI Prism 3730 Sequencer (Applied Biosystems, Foster City, CA, USA). Post-sequencing editing and alignment of sequences were made with the program Sequencher™4.5 (Gene Codes Corporation, Ann Arbor, MI, USA).

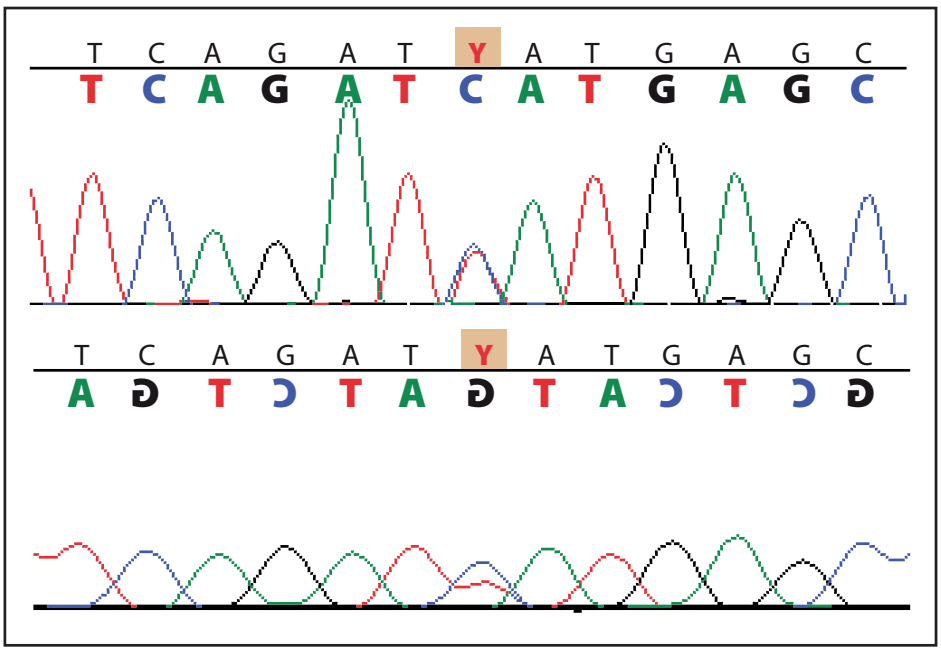

Fig. 1. Electropherograms of the analysis of the G/A mutation (rs1801164) located at position 107 863 596 in the insulin receptor substrate-4 gene. Forward and reverse directions are shown. The marked Y-letters indicate the point of change.

Genetic findings

The DNA sequence of the patient's *IRS-4* gene along with 8 base pairs upstream and 9 base pairs downstream (i.e. from position 107 866 303 to 107 862 359) was compared to the reference sequence of the gene (9,10), and it was found that the patient had what is referred to as a mutation: the G/A genotype instead of G/G, G/C or C/C at the same gene position (i.e. 107 863 596) as the previously known G/C single nucleotide polymorphism (SNP) with accession number rs1801164 (Figure 1), resulting in a change in amino acid coding from histidine to tyrosine at amino acid position 879. This novel G/A SNP was recently registered by myself and colleagues in dbSNP, where it became assigned to the same accession number as the earlier G/C SNP, i.e. rs1801164 (Melkersson *et al.* 2011). However, no other mutations or SNPs were detected in this patient's *IRS-4* gene sequence.

DISCUSSION

This report deals with a female patient with schizophrenia and a G/A mutation in the *IRS-4* gene at position 107 863 596 and with accession number rs1801164. Since this mutation is expected to change the amino acid coding from histidine to tyrosine at position 879 and cause an altered IRS-4 protein (9,10), and the IRS-4 protein may be involved in neuronal growth and function in several areas of the brain (Chiba *et al.* 2009; Goren *et al.* 2004; Numan & Russell 1999; Ye *et al.* 2002), it is possible that it is this *IRS-4* gene mutation that underlies this patient's schizophrenia development.

Although this patient completely fulfills the DSM-IV criteria for paranoid schizophrenia (American Psychiatric Association 1994), she is in several aspects an atypical schizophrenia patient. Firstly, she belongs to the smaller group of schizophrenia patients who develop their illness early in life (i.e. at age 18 or earlier), in whom gene mutations have been reported to be more common than in schizophrenia patients in general (Walsh *et al.* 2008). Secondly, she has both schizophrenia and rheumatoid arthritis, which are two diseases seldom occurring in one and the same patient (Eaton *et al.* 1992; Vinogradov *et al.* 1991). Thirdly, since a genetic predisposition to schizophrenia is suggested to entail a protection against cancer, this patient also is atypical in that she was the only one of the 95 patients with schizophrenia previously studied who had a relative (namely her paternal grandmother) suffering from both schizophrenia and cancer (Melkersson 2009). Thus, although this patient has a typical paranoid schizophrenia according to the DSM-IV criteria (American Psychiatric Association 1994), she discriminates from schizophrenia patients in general in that she developed her schizophrenia early in life and also has rheumatoid arthritis and a relative with both schizophrenia and cancer.

Interestingly, this patient's *IRS-4* gene mutation may be a so-called inherited mutation (Xu *et al.* 2008), derived from her paternal grandmother who also had a diagnosis of paranoid schizophrenia. In addition, her paternal grandmother suffered from cancer, indicating that she lacked the protection against cancer that is usually found in individuals with schizophrenia or a genetic predisposition to schizophrenia (Melkersson 2009). However, a mutation in the *IRS-4* gene would only be expected to protect against development of some forms of cancers (Karrman *et al.* 2008; Mertens *et al.* 2011; Tseng *et al.* 2002; Uchida *et al.* 2000).

The IRS-4 protein is also known to be highly expressed in the hypothalamus that plays a main role in the regulation of body weight, and in a recent study, lower body mass index in patients with schizophrenia was found to be associated with six SNPs in the *IRS-4* gene (Melkersson & Persson 2011). However, the patient in this case report, who had an elevated body mass index of 28 kg/m^2, did not carry any of these six SNPs (Melkersson & Persson 2011). Furthermore, the IRS-4 protein shows expression in T-lymphocytes and thymus (Cai *et al.* 2003; Karrman *et al.* 2008), which would seem to explain why this patient as a child, carrying a mutation in the *IRS-4* gene, failed to develop a satisfactory immune response and protection against pertussis infection by vaccination. This patient has in addition been investigated regarding SNPs in both the insulin receptor substrate-3 (*IRS-3*) gene and the serotonin receptor 2A (*HTR2A*) gene (Melkersson & Hulting 2009; Melkersson & Persson 2012). Just as 92 other schizophrenia patients studied, she lacked the A allele of the *IRS-3* SNP rs117078492 that has been suggested to protect against schizophrenia development (Melkersson & Persson 2012). On the other hand, she carried the 452Tyr variant of the *HTR2A* His452Tyr SNP rs6314 that has been shown to be associated with decreased serotonin-induced calcium mobilization in cells, family history of schizophrenia, and paranoid subtype of schizophrenia in female patients (Melkersson 2010; Melkersson & Hulting 2009).

In conclusion, it seems that this patient belongs to the group of schizophrenia patients who have multiple, individually rare mutations impacting genes in pathways of the brain important for neurodevelopment and/ or neurotransmission, thereby contributing to schizophrenia (Walsh *et al.* 2008). It is also possible that the case of this single patient with schizophrenia and an *IRS-4* gene mutation tells us that the insulin/ IGF signalling pathways in cells are of clear interest in the future search for schizophrenia genes.

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