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ORIGINAL ARTICLE

The *INS-IGF2* transcript in schizophrenia or related psychosis: tendency towards association between an *INS-IGF2* SNP and schizoaffective disorder, and one report of a patient with this SNP and diagnoses of both schizoaffective disorder and polycystic ovary syndrome

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Abstract

OBJECTIVES: We found earlier increased antibody reactivity against the insulin receptor-A and insulin-like growth factor 1 receptor and their ligands (insulin and insulin-like growth factor 1) in patients with schizophrenia or related psychosis. Hypothetically, a newly-identified insulin-insulin-like growth factor 2 (INS-IGF2) protein may be a ligand to these receptors too, and recently, significantly higher antibody reactivity was found against a part of this protein in patients with schizophrenia or related psychosis in partial than full symptom remission. The aim of this study was to map the region of the *INS-IGF2* transcript that codes this part of the protein in schizophrenia and related psychosis susceptibility.
MATERIAL AND METHODS: The present *INS-IGF2* region was DNA-sequenced by the Sanger method in a study population, consisting of 94 patients with schizophrenia, 11 patients with schizoaffective disorder and 58 controls.
RESULTS: Two novel SNPs were identified solely in patients, but not in controls. Tendencies towards overall differences in genotype- and allele frequencies between patients with schizophrenia or schizoaffective disorder and controls were found for SNP no 1 ($p = 0.067$ and $p = 0.067$, respectively), with the G/A-genotype and G-allele appearing more frequently in patients with schizoaffective disorder. The patient with SNP no 1 was diagnosed with both schizoaffective disorder and polycystic ovary syndrome, and the patient with SNP no 2 was diagnosed with schizophrenia, paranoid type with affective features.
CONCLUSION: The findings in this exploratory study suggest that SNPs in the *INS-IGF2* transcript may be associated with psychosis, specifically with schizoaffective disorder, and warrant replication in larger samples.

Abbreviations:

CNS	- central nervous system
C-peptide	- connecting-peptide
IGF1	- insulin-like growth factor 1
IGF2	- insulin-like growth factor 2
IGFBP2	- insulin-like growth factor binding protein 2
IGF1R	- insulin-like growth factor 1 receptor
IGF2R	- insulin-like growth factor 2 receptor
IMP2	- insulin-like growth factor 2 mRNA-binding protein 2
INS	- insulin
INS-IGF2	- insulin-insulin-like growth factor 2
INSR	- insulin receptor
INSR-A	- insulin receptor-A
INSR-B	- insulin receptor-B
IRS	- insulin receptor substrate
SNP	- single nucleotide polymorphism
vs	- versus

INTRODUCTION

The literature on schizophrenia provides strong evidence for a role of genetic factors in its aetiology (Craddock *et al.* 2005; Hilker *et al.* 2018; Owen *et al.* 2016; Wirgenes *et al.* 2023). A variety of genes, each with small or moderate effect, have been suggested to be involved (Gottesman & Shields, 1967), and to date around 300 such genetic loci associated with schizophrenia have been reported (Allen *et al.* 2008; Bray & O'Donovan, 2019; Chen *et al.* 2015; Cipriani *et al.* 2025; Forero *et al.* 2016; Giegling *et al.* 2017; Kang *et al.* 2016, 2018; Kanwal *et al.* 2023; Lam *et al.* 2019; Lee *et al.* 2023; Li *et al.* 2017, 2022; Liu *et al.* 2021; Loureiro *et al.* 2019; Morita *et al.* 2014; Pardiñas *et al.* 2018; Ptacek *et al.* 2011; Raabe *et al.* 2024; Rees *et al.* 2020; Ripke *et al.* 2014; Ruderfer *et al.* 2018; Rujescu, 2012; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2022; Schwab & Wildenauer, 2013; Sekar *et al.* 2016; Singh *et al.* 2022; Vacic *et al.* 2011; Wang *et al.* 2022; Yu *et al.* 2017). Of all these genetic loci reported, it is the gene region encompassing the major histocompatibility complex on chromosome 6p22.1 playing an important role in the immune system that is the most significant and consistent, followed by genes involved in calcium ion import into cells, those involved in cell membrane depolarization during action potential, and those in synaptic transmission (Hall *et al.* 2020; Pardiñas *et al.* 2018; Ripke *et al.* 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2022; Sekar *et al.* 2016). However, a substantial proportion of the heritability for schizophrenia is still unknown (Pardiñas *et al.* 2018; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2022).

Since there are also clear indications that schizophrenia is a systemic disorder and not only a brain disease (Flyckt, 2001; Kirkpatrick *et al.* 2014; Moises *et al.* 2002), I and my colleagues sought a common molecular basis for schizophrenia abnormalities in brain and body, and formulated a hypothesis (described more in detail in three previous studies: Melkersson & Persson, 2011, 2012; Melkersson *et al.* 2011) that impaired cellular signalling via the insulin receptor (INSR), and probably also via the insulin-like growth factor 1 receptor (IGF1R), may underlie known abnormalities associated with schizophrenia in both the central nervous system (CNS) and in peripheral organs. Besides this support of clinical studies for our hypothesis, there is also growing evidence from in vitro studies in neuroblastoma- and astrocyte cell lines and post-mortem brains of patients with schizophrenia that impaired cellular signalling via these two receptors may play a role in the pathogenesis of schizophrenia (Altar *et al.* 2008; Bernstein *et al.* 2009, 2017; Chu *et al.* 2009; Zhao *et al.* 2006). Moreover, two of our recently-published studies point to that an autoimmune-mediated process in the CNS, and to some extent in peripheral organs, underlies the development of a core group of schizophrenia cases and that the insulin receptor-A (INSR-A) and IGF1R and their ligands insulin (INS) and insulin-like growth factor 1 (IGF1) may constitute antigen targets (Melkersson & Bensing, 2021, 2023).

However, we did not find any differences in antibody reactivities against the insulin-like growth factor 2 (IGF2) or insulin-like growth factor 2 receptor (IGF2R) between patients with schizophrenia or related psychosis and control subjects in that recently-published study (Melkersson & Bensing, 2021). Nevertheless, IGF2 is a ligand not only to IGF2R, but also to the INSR and IGF1R (Rui & White, 2004). All these three receptors and their ligands (i.e. INS, IGF1 and IGF2) are present in both the CNS and peripheral organs in humans (Carlsson-Skwirut *et al.* 1986; Dorn *et al.* 1982, 1983; Kahn & Saltiel, 2005; McCowen & Smith, 2005; Rui & White, 2004; Sara *et al.* 1982; Werner & LeRoith, 2014), and although the IGF2R binds only IGF2, there is substantial cross-reactivity for the other two receptors; the INSR binds INS, IGF1 and IGF2, and the IGF1R binds IGF1, INS and IGF2, though there are differences in the binding affinities and functions (Dimitriadis *et al.* 2000; Pardo *et al.* 2019; Rui & White, 2004; Werner & LeRoith, 2014). Studies regarding functional differences between INSR-A and insulin receptor-B (INSR-B) have also revealed that INSR-A, in contrast to INSR-B, binds IGF2 with high affinity close to that of INS (Denley *et al.* 2004; Frasca *et al.* 1999), and that activation of INSR-A by IGF2 primarily leads to mitogenic effects, whereas activation of INSR-A by INS primarily leads to metabolic effects, utilizing different intracellular signalling pathways (Frasca *et al.* 1999).

Hypothetically, the newly-identified insulin-insulin-like growth factor 2 (INS-IGF2) protein may be a ligand to INSR-A and IGF1R too, and thereby may play a role in the pathogenesis of schizophrenia. It is 200 amino acid long and consists of the INS signal peptide (amino acid 1-24), the INS ß-chain (amino acid 25-54), and the first 8 amino acids of the connecting-peptide (C-peptide)

chain (amino acid 55-62), in addition to 138 amino acids (amino acid 63-200) coded from the intergenic DNA-sequence between the *INS*- and *IGF2* genes (Cook *et al.* 2023; Monk *et al.* 2006). Recently, antibody reactivity against the INS-IGF2 protein in cerebrospinal fluid and serum was found to be higher in patients with schizophrenia or related psychosis in partial than full symptom remission (Melkersson, 2025), and among other diseases, the involvement of this protein has been reported earlier in metabolic disorders such as diabetes mellitus type 1 and 2, in cancers such as insulinoma, nephroblastoma, non-small-cell lung cancer, phaeochromocytoma and uterine cervical cancer, and in the autoimmune disorder systemic sclerosis (Følling *et al.* 2021; Gao *et al.* 2019; Jalal *et al.* 2024; Johannessen *et al.* 2016; Kanatsuna *et al.* 2013, 2015; Masuda *et al.* 2020; Ng *et al.* 2014; Zhu & Deng, 2024).

Genetic studies on the INSR and IGF1R and their ligands have shown associations between gene variants in the *INSR* gene (located on chromosome 19p13.3 - p13.2) and heredity, body mass index, height, severe treatment-resistance, or diabetes mellitus type 1 or type 2 in patients with schizophrenia, and tendencies to associations between single nucleotide polymorphisms (SNPs) in the *INS* gene (located on chromosome 11p15.5) and schizophrenia (Kanwal *et al.* 2025; Melkersson, 2018; Melkersson & Persson, 2022, 2023), but not between SNPs or variable number tandem repeat in the *IGF1R* or *IGF1* genes (located on chromosomes 15q26.3 and 12q23.2, respectively) and schizophrenia (Bonvicini *et al.* 2010; Gunnell *et al.* 2007; Kim *et al.* 2013). Moreover, associations between SNPs in exon and intron 13 in the *INSR* gene and schizoaffective disorder have been reported (Melkersson, 2018). Regarding the *IGF2* gene (located downstream of the *INS* gene on chromosome 11p15.5; Hampton *et al.* 1989; Jansen *et al.* 1985; Rotwein, 1991), it has been found in an RNA sequencing study to be the top down-regulated gene in post-mortem brains of patients with schizophrenia (Fromer *et al.* 2016). To that, decreased mRNA expression of the insulin-like growth factor binding protein 2 (*IGFBP2*) gene (located on chromosome 2q35) in post-mortem brains of patients with schizophrenia, as well as an association between SNP rs4402960 in the insulin-like growth factor 2 mRNA-binding protein 2 (*IMP2*, also called *IGF2BP2*) gene (located on chromosome 3q27.2 and coding a protein, which binds to *IGF2* mRNA and regulates its translation) and schizophrenia have been reported (Christiansen *et al.* 2009; Nielsen *et al.* 2001; Weissleder *et al.* 2021; Zhang *et al.* 2013). As concerns the insulin receptor substrates (IRSs) 1-4, linking both the INSR and IGF1R coupled with their ligands with intracellular pathways (Choi & Sung, 2000; Kahn & Saltiel, 2005; Lavan *et al.* 1997; White, 1998; Xu *et al.* 1999), SNPs in the *IRSs 1-4* genes (located on chromosomes 2q36.3, 13q34, 7q22.1 and Xq22.3, respectively) have too been investigated in relation to schizophrenia (Gunnell *et al.* 2007; Kim *et al.* 2013; Melkersson, 2013; Melkersson & Persson, 2011, 2012; Melkersson *et al.* 2011). While no associations have been found between SNPs in the *IRS-1* gene and schizophrenia (Gunnell *et al.* 2007; Kim *et al.* 2013), an SNP in the *IRS-3* gene has been shown to be negatively associated with schizophrenia (Melkersson & Persson, 2012). Further, positive associations have been reported in patients with schizophrenia both between an *IRS-2* SNP and auditory hallucinations, and between *IRS-4* SNPs and family history or body mass index, as well as one case of a patient with schizophrenia and an *IRS-4* gene mutation (Kim *et al.* 2013; Melkersson, 2013; Melkersson & Persson, 2011; Melkersson *et al.* 2011). As regards the *INS-IGF2* transcript, coding the newly-identified INS-IGF2 protein, until now it has been little studied in schizophrenia; two SNPs (rs5505 in exon 2, 5' untranslated region and rs3842749 in intron 2-3) have shown tendencies to associations with schizophrenia (Melkersson & Persson, 2022), while two other SNPs (rs3842756 in intron 2-3 and rs2239681 in intron 4-5) have shown no associations (Li *et al.* 2022), and in schizoaffective disorder, to our best knowledge it has not been studied.

Given this background, the aim of this study was to investigate further the involvement of the *INS-IGF2* transcript in susceptibility to schizophrenia and schizoaffective disorder, by sequencing the part of this transcript encoding the amino acid sequence against which antibody reactivity recently was found to be higher in patients with schizophrenia or related psychosis in partial than full symptom remission (Melkersson, 2025).

MATERIAL AND METHODS

Ethical approval

The study was approved by The Ethics Committee of Karolinska Institutet, Stockholm, Sweden.

Patients and control subjects

Consecutive out-patients from psychiatric polyclinics in the region of Stockholm, Sweden, diagnosed with schizophrenia or schizoaffective disorder according to Diagnostic and statistical manual of mental disorders criteria (American Psychiatric Association, 2013) were invited to participate in this study. In total 94 patients with schizophrenia (46 males and 48 females) and 11 patients with schizoaffective disorder (3 males and 8 females) gave written informed consent to participate. The study population is described elsewhere in detail (Melkersson, 2009, 2018). In brief, all patients were unrelated Caucasian individuals. They were in full or partial remission regarding psychotic symptoms, and were all receiving long-term therapy with antipsychotics. Control subjects were 58 unrelated Caucasian individuals (16 males and 42 females) from the Stockholm County or the nearby Uppsala County, who gave written informed consent to participate in the

Tab. 1. Data regarding the two single nucleotide polymorphisms in the *insulin-insulin-like growth factor 2* transcript identified in this study

SNP numbering	SNP identification[a,b]	SNP position[a]	Polymorphism[c]	Location in the *INS-IGF2* transcript; known function
1.	novel	2149272	A>**G**	exon 3; synonymous coding (proline, amino acid no 87)
2.	novel	2149232	A>**G**	exon 3; synonymous coding (serine, amino acid no 101)

Abbreviations: *INS-IGF2=insulin-insulin-like growth factor 2*, SNP=single nucleotide polymorphism
[a] rs numbers and positions (according to GRCh38.p13) from the dbSNP (http://www.ncbi.nlm.nib.gov/SNP)
[b] No's 1 and 2 refer to potential novel SNPs not described in the dbSNP, and were therefore registered by us (http://www.ncbi.nlm.nib.gov/SNP)
[c] Polymorphism bases on the forward strand with the alternative base (=allele 2) written in bold text

study. They were healthy individuals with no heredity for psychotic disorder or diabetes mellitus type 1, type 2 or other types.

Collection and DNA-preparation of blood samples

Venous blood was taken in EDTA-containing tubes from all patients and control subjects and stored at -20°C until preparation of DNA. Genomic DNA was extracted from peripheral blood leukocytes by using a Genomic DNA Purification Kit (Gentra Systems Inc., Minneapolis, MN, USA). The extracted DNA was frozen at -20°C until genotyped.

Sanger sequencing of DNA

For identification of SNPs of interest, the region of the *INS-IGF2* transcript coding the sequence of amino acids no's 64-96 of the INS-IGF2 protein, against which recently antibody reactivity was found to be higher in patients with schizophrenia or related psychosis in partial than full symptom remission (Melkersson, 2025), together with one more amino acid (i.e. no's 63 and 97) and additional flanking regions (25 and 57 base-pair long respectively) in each end of this sequence (i.e. 2149158 to 2149370 on chromosome 11p15.5, according to GRCh38.p13; http://www.ensembl.org), was DNA-sequenced in both directions by the Sanger method in the whole study population.

Statistical methods

Categorial data were summarized using frequency counts and percentages. Associations between genotype or allele frequencies and disease (schizophrenia or schizoaffective disorder versus controls) were analyzed with Chi-square test or Fisher's exact test. As this was an exploratory study, the *p*-values for pairwise comparisons concerning the three groups were performed without any correction for multiple testing. The difference between the schizoaffective disorder- and schizophrenia groups and between the schizoaffective disorder- and control groups regarding the occurrence of the G/A-genotype of SNP no 1was also presented as odds ratios with 95% confidence intervals. The Haldane-Anscombe correction was used to resolve the "zero cell problem" in the tables by adding 0.5 to each cell, which prevents division by zero and yields a definite odds ratio. The correction is a tool for estimation and should not be used for hypothesis testing, where the Fisher's exact test is appropriate. A p-value < 0.05 was considered statistically significant different, whereas a p-value ≥ 0.05, but ≤ 0.10 was considered to indicate a tendency to a difference. The statistical analyses were performed using the statistical program Statistica for Windows 13.5 (TIBCO Software Inc., USA).

RESULTS

The reads of the DNA-sequenced part of the *INS-IGF2* transcript were compared to the corresponding reference sequence in all 105 patients and 58 control subjects, and totally two SNPs were identified. Data regarding these two SNPs are given in Table 1. Both SNPs refer to potential novel SNPs not described in the dbSNP, and were therefore registered by us (http://www.ncbi.nlm.nih.gov/SNP).

Genotype distributions and allele frequencies for the two SNPs, together with results of single association analyses, are given in Table 2. In comparison between patients with schizophrenia, patients with schizoaffective disorder, and control subjects, tendencies towards overall differences in genotype distribution and allele frequency were found for SNP no 1 (Table 2: $p = 0.067$ and $p = 0.067$, respectively). Pairwise analyses showed that it was the G/A-genotype and G-allele of this SNP that tended to be more common in patients with schizoaffective disorder than in patients with schizophrenia or control subjects (Table 2). When carriers of the G/A-genotype were compared with non-carriers, the odds of carrying SNP no 1 were higher in schizoaffective disorder patients than schizophrenia patients (odds ratio 27, 95% confidence interval 1-706), reflecting the single carrier in the schizoaffective disorder group and the absence of carriers in the schizophrenia group. Similar, the odds of carrying SNP no 1 were higher in schizoaffective disorder patients than control subjects (odds ratio 17, 95% confidence interval 0.6-439).

The two SNPs were found only in patients, and not in control subjects (Table 2). Single nucleotide polymorphism no 1 was present in 1 (9.1%) of 11 patients with schizoaffective disorder, and SNP no 2 was present in 1 (1.1%) of 94 patients with schizophrenia (Table 2), indicating that each variant was observed in a single patient in this cohort. The patient who carried the G/A-genotype and G-allele of SNP no 1 was a woman diagnosed with both schizoaffective disorder and polycystic ovary syndrome, and the patient who carried the G/A-genotype and G-allele of SNP no 2 was a woman diagnosed with schizophrenia, paranoid type with affective features.

DISCUSSION

In this study, we observed a tendency towards an association between SNP no 1 in the *INS-IGF2* transcript and schizoaffective disorder. In all, two *INS-IGF2* SNPs, i.e. one more SNP (no 2), were identified only in patients, and not in control subjects. Both these SNPs were novel, located in exon 3 of the *INS-IGF2* transcript, and synonymous coding; SNP no 1 for proline 87 and SNP no 2 for serine 101. The amino acid no 87 is located within the part of the INS-IGF2 protein against which higher antibody reactivity recently was found in patients with schizophrenia or related psychosis in partial than full symptom remission, and the amino acid no 101 is located near one of the borders of this part of the INS-IGF2 protein (Melkersson, 2025). The patient who carried SNP no 1 was a woman diagnosed with both schizoaffective disorder and polycystic ovary syndrome, and the patient who carried SNP no 2 was a woman diagnosed with schizophrenia, paranoid type with affective features.

The patient who carried SNP no 1 and was diagnosed with both schizoaffective disorder and polycystic ovary syndrome had also earlier been investigated genetically by us for SNPs in the *INSR*-, *INS*-, *IRS-3*-, *IRS-4*- and *5HTR2A* genes. However, no specific SNPs were identified in these five genes discriminating this patient from all other patients and control subjects, which SNP no 1 in the *INS-IGF2* transcript in this study does (Melkersson & Hulting, 2009; Melkersson & Persson, 2011, 2012, 2022, 2023; Melkersson *et al.* 2011). The polycystic ovary syndrome is a complex disorder with a genetic determinism, and a major cause of infertility and includes insulin resistance as a profound component (Ehrmann, 2005). In a number of earlier genetic studies, the polycystic ovary syndrome has also been reported to be associated with SNPs (in exons 9 and 19, and introns 8 and 11) of the *INSR* gene (Du *et al.* 2014; Feng *et al.* 2015; Hanzu *et al.* 2010; Vambergue *et al.* 2006). Previously, we have also reported association between schizoaffective disorder and two SNPs (in exon and intron 13) of the *INSR* gene (Melkersson, 2018). However, associations between the polycystic ovary syndrome

Tab. 2. Genotype distributions and allele frequencies for the two single nucleotide polymorphisms in the *insulin-insulin-like growth factor 2* transcript identified in this study, together with results of single association analyses

SNP[a]	Polymorphism[b]	Numbers of S-P/ SA-P/ C	Genotype distributions (%)									Allele frequencies (%)[c]				
			S-P			SA-P			C							
			1-1	1-2	2-2	1-1	1-2	2-2	1-1	1-2	2-2	*p*-value[d]	S-P	SA-P	C	*p*-value[d]
1.	A>**G**	94/ 11/ 58	100.0	0.0	0.0	90.9	9.1	0.0	100.0	0.0	0.0	**0.067**[e]	100.0	95.5	100.0	**0.067**[f]
2.	A>**G**	94/ 11/ 58	98.9	1.1	0.0	100.0	0.0	0.0	100.0	0.0	0.0	1.000	99.5	100.0	100.0	1.000

Abbreviations: C=control subjects, S-P=patients with schizophrenia, SA-P=patients with schizoaffective disorder, SNP=single nucleotide polymorphism, vs=versus

[a] Same SNP numbering as in Table 1

[b] Polymorphism bases on the forward strand with the alternative base (=allele 2) written in bold text

[c] Only highest allele frequency is shown

[d] A tendency towards a difference is written in bold text

[e] S-P vs SA-P: $p = \mathbf{0.105}$, S-P vs C: not applicable (no variation), SA-P vs C: $p = 0.159$

[f] S-P vs SA-P: $p = \mathbf{0.105}$, S-P vs C: not applicable (no variation), SA-P vs C: $p = 0.159$

or schizoaffective disorder and *INS-IGF2* SNPs have not been studied before.

Even though these are single observations, the findings in this study that refer specifically to schizoaffective disorder are also in line with a) our previously-described hypothesis for schizophrenia that impaired cellular signalling via the INSR-A, and probably also via the IGF1R, may underlie known schizophrenia-related abnormalities in the CNS and peripheral organs (Melkersson & Persson, 2011, 2012; Melkersson *et al.* 2011), b) results in our foregoing studies, indicating that an autoimmune-mediated process may underlie the development of a core group of schizophrenia cases and that the INSR-A and IGF1R and their ligands INS and IGF1 may constitute main antigen targets (Melkersson & Bensing, 2021, 2023), c) our earlier genetic studies showing associations between gene variants in the *INSR* gene and heredity, body mass index, height, or diabetes mellitus type 1 or type 2 in patients with schizophrenia, and tendencies to associations between SNPs in the *INS* gene and schizophrenia (Melkersson, 2018; Melkersson & Persson, 2022, 2023), and d) are also supported by several studies by others, reporting sign of a hypometabolic state in brains, INSR deficits and decreased IGF1R-, IGF1- and IGFBP2 mRNA expression in post-mortem brains, INS signalling abnormalities, altered IGF2 signalling, and associations between *INSR* gene variants and severe treatment-resistance and between an *IRS-2* SNP and auditory hallucinations, in patients with schizophrenia (de Bartolomeis *et al.* 2023; Huang *et al.* 2006; Kanwal *et al.* 2025; Kapogiannis *et al.* 2019; Kim *et al.* 2013; van Beveren *et al.* 2014; Weissleder *et al.* 2021; Wu *et al.* 2013; Yang *et al.* 2020; Zhao *et al.* 2006).

Both the INSR and IGF1R bind, besides INS and IGF1, IGF2 (Dimitriadis *et al.* 2000; Pardo *et al.* 2019; Rui & White, 2004; Werner & LeRoith, 2014). To that, INSR-A, in contrast to INSR-B, binds IGF2 with high affinity close to that of INS (Denley *et al.* 2004; Frasca *et al.* 1999). However, the newly-identified INS-IGF2 protein, that has a somewhat misleading name, is coded from a part of the *INS* gene (i.e. the INS signal peptide, INS ß-chain and first 8 amino acids of the C-peptide chain) and an intergenic DNA-sequence between the *INS*- and *IGF2* genes (i.e. the 138 amino acid sequence), and is neither coded from the *IGF2* gene, nor is it identical with the IGF2 protein. In a recent study, antibody reactivity in cerebrospinal fluid and serum against the INS-IGF2 protein was found to be associated with psychotic symptomatology in patients with schizophrenia or related psychosis, indicating that the INS-IGF2 protein may be present in the CNS and involved in the autoimmune-mediated process underlying the development of schizophrenia (Melkersson, 2025). Whether the INS-IGF2 protein is formed in the CNS as a consequence of such an autoimmune-mediated process and functions as a ligand to, by the autoimmune attack, damaged INSR-As is however not known.

To compare, serum levels of IGF2 have been reported to be a) lower in schizophrenia patients with first episode- or acute exacerbation of psychosis compared with control subjects, and inversely correlated to their negative and cognitive symptoms, and b) to increase with antipsychotic treatment and declining of psychotic symptomatology, and to be higher in patients with chronic schizophrenia, compared with control subjects (Akanji *et al.* 2007; Chao *et al.* 2020; Fernández-Pereira *et al.* 2022; Yang *et al.* 2020). The *IGF2* gene (located downstream of the *INS* gene on chromosome 11p15.5; Hampton *et al.* 1989; Jansen *et al.* 1985; Rotwein, 1991) has also been found in an RNA sequencing study to be the top down-regulated gene in post-mortem brains of patients with schizophrenia (Fromer *et al.* 2016). Thus, these previous findings regarding IGF2 seem to reflect an involvement also of IGF2 in the autoimmune-mediated process in schizophrenia, although in a contrary way to that by INS-IGF2.

The strength of this study includes its comprising of both diagnostically homogenous groups of patients diagnosed with schizophrenia or schizoaffective disorder and not with other types of psychotic disorders, and a group of healthy control subjects with no heredity for either psychotic disorder or diabetes mellitus type 1, type 2 or other types, allowing specific investigations of the involvement of the *INS-IGF2* transcript in schizophrenia or schizoaffective disorder susceptibility. The limitation of the study, on the other hand, includes its comprising of a study population with relatively limited size, especially the schizoaffective disorder sample, which means that the results in the study should be interpreted with caution and as hypothesis-generating until replicated.

In conclusion, the findings in this study indicate that SNPs in the *INS-IGF2* transcript may be linked to psychosis, specifically to schizoaffective disorder.

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