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ORIGINAL ARTICLE

Association between single nucleotide polymorphisms in non-coding regions of the insulin *(INS)* gene and schizophrenia

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Abstract

OBJECTIVES: Schizophrenia is a psychotic disorder with high heritability. There are also indications that impaired cellular signalling via the insulin receptor-A and the insulin-like growth factor 1 receptor may play a role in its pathogenesis. Insulin, and possibly also C-peptide, are ligands to these receptors. The insulin gene, coding both insulin and C-peptide, has however not been genetically studied in schizophrenia. Therefore, this study was undertaken to investigate the involvement of this gene in schizophrenia susceptibility.

MATERIAL AND METHODS: For identification of single nucleotide polymorphisms (SNPs) of interest, the whole insulin gene and parts of its promoter region were first DNA sequenced in two subgroups of the study population (37 schizophrenia patients with heredity for schizophrenia or related psychosis, and 25 controls), and mapped to the reference sequence. Then, 7 identified SNPs of potential interest were typed by TaqMan® SNP Genotyping Assays in the whole study population, consisting of 94 patients with schizophrenia and 60 controls.

RESULTS: Allele frequencies tended to differ between patients and controls for two of the 7 SNPs, rs5505 and rs3842749 (p=0.077 and p=0.078, respectively), whereas subgroup analyses of diabetes mellitus (type 1 or 2) and/ or heredity for diabetes mellitus (type 1 or 2) in patients and controls showed overall significant differences in genotype/ allele frequencies solely for rs5505 (p=0.021/ 0.023).

CONCLUSION: These findings are of interest, as the two SNPs – rs5505 and rs3842749 – may have regulatory function on the coding of insulin and C-peptide, against which increased antibody reactivity has been previously reported in schizophrenia.

INTRODUCTION

The literature on schizophrenia provides strong evidence for a role of genetic factors in its aetiology (Craddock *et al.* 2005). A variety of genes, each with small or moderate effect, have been suggested to be involved (Gottesman & Shields, 1967), and to date 270 such genetic loci associated with schizophrenia have been reported (Allen *et al.* 2008; Bray & O'Donovan, 2019; Chen *et al.* 2015; Forero *et al.* 2016; Giegling *et al.* 2017; Kang *et al.* 2016, 2018; Lam *et al.* 2019; Li *et al.* 2017; Liu *et al.* 2021; Loureiro *et al.* 2019; Pardiňas *et al.* 2018; Ptacek *et al.* 2011; Rees *et al.* 2020; Ripke *et al.* 2014; Ruderfer *et al.* 2018; Rujescu, 2012; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2020; Schwab & Wildenauer, 2013; Sekar *et al.* 2016; Vacic *et al.* 2011; Wang *et al.* 2021; Yu *et al.* 2017). Of all these genetic loci reported, it is the gene region encompassing the major histocompatibility complex (MHC) 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; Pardiňas *et al.* 2018; Ripke *et al.* 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2020; Sekar *et al.* 2016). However, a substantial proportion of the heritability for schizophrenia is still unknown; the current single nucleotide polymorphism (SNP)-based heritability, attributable to all measured SNPs, is estimated to be only 24% (Pardiňas *et al.* 2018; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2020).

Since there also are 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 for 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, our most recently-published study points 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 INSR-A and IGF1R and their ligands insulin (INS), connecting peptide (C-peptide) and insulin-like growth factor 1 (IGF1) may constitute antigen targets (Melkersson & Bensing, 2021).

The INSR-A and IGF1R and their ligands INS, C-peptide, 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). Until now, no associations have been found between SNPs or variable number tandem repeat in the *INSR*, *IGF1R* or *IGF1* genes (located on chromosomes 19p13.2, 15q26.3 and 12q23.2, respectively) and schizophrenia (Bonvicini *et al.* 2010; Gunnell *et al.* 2007; Kim *et al.* 2013), and no studies have been published regarding the *IGF2* gene (located on chromosome 11p15.5) and schizophrenia. However, associations have been reported between two *INSR* SNPs and diabetes mellitus (DM) and/ or heredity for DM in patients with schizophrenia (Melkersson, 2018). As regards the insulin receptor substrates (IRSs) 1-4, linking both the INSR-A and IGF1R coupled together 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 also 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).

The *INS* gene that is located on chromosome 11p15.5 codes proinsulin that is cleaved into equivalent amounts of INS and C-peptide before being released from the pancreatic ß-cells to the portal circulation (Bell *et al.* 1980; German, 2003; Harper *et al.* 1981; Owerbach *et al.* 1980; Rhodes, 2003; Steiner, 2004). Worthy of note, the *INS* gene has – as yet – not been studied in schizophrenia. Therefore, this study was undertaken to investigate the involvement of the *INS* gene in schizophrenia susceptibility.

MATERIAL AND METHODS

Consecutive out-patients from psychiatric polyclinics in the region of Stockholm, Sweden and with the diagnosis of schizophrenia according to DSM-5 criteria

Tab. 1. Data regarding the 15 single nucleotide polymorphisms in the insulin gene and parts of its promoter region identified in two subgroups of the study population in the first part of the study

SNP numbering	SNP identification[a,b]	SNP position[a]	Polymorphism[c]	Gene location; known function
1.	novel	2184338; 2163108	G>**T**	5′ near gene; promoter
2.	rs3842729	2184336; 2163106	G>**A**	5′ near gene; promoter
3.	novel	2184270; 2163040	T>**A**	5′ near gene; promoter
4.	rs781257482	2183916; 2162686	C>**T**	5′ near gene; promoter
5.	novel	2182505; 2161275	G>**A**	exon 1; 5′ untranslated region
6.	rs3842738	2182495; 2161265	C>**G**	exon 1; 5′ untranslated region
7.	rs3842741	2182360; 2161130	T>**C**	intron 1
8.	rs689	2182224; 2160994	A>**T**	intron 1
9.	rs5505	2182210; 2160980	G>**A**	exon 2; 5′ untranslated region
10.	rs5506	2182004; 2166774	A>**G**	intron 2
11.	rs556749542	2181624; 2160394	G>**A**	intron 2
12.	rs3842748	2181395; 2160165	C>**G**	intron 2
13.	rs3842749	2181338; 2160108	G>**A**	intron 2
14.	rs3842752	2181073; 2159843	G>**A**	exon 3; 3′ untranslated region
15.	rs3842753	2181060; 2159830	T>**G**	exon 3; 3′ untranslated region

Abbreviation: SNP=single nucleotide polymorphism
[a] rs numbers and positions (according to GRCh37.p13; GRCh38.p13) from the dbSNP (http://www.ncbi.nlm.nih.gov/SNP)
[b] No's 1, 3 and 5 refer to potential novel SNPs not described and are registered by us in the dbSNP (http://www.ncbi.nlm.nih.gov/SNP)
[c] Polymorphism bases on the forward strand with the alternative base (=allele 2) written in bold text

(American Psychiatric Association, 2013) were invited to participate in this study. In total 94 patients (47 males and 47 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 60 unrelated Caucasian individuals (17 males and 43 females) from the Stockholm County or the nearby Uppsala County, who gave written informed consent to participate in the study. They were healthy individuals with no heredity for psychotic disorder or DM type 1, type 2 or other types. The study was approved by the Ethics Committee of Karolinska Institutet, Stockholm, Sweden.

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.

For identification of SNPs of interest, the whole *INS* gene and parts of its promoter region were DNA sequenced in the first part of the study by the Sanger method in two subgroups of the study population: 1) 37 patients with schizophrenia who had heredity for schizophrenia or related psychosis (i.e. they had one or more first-, second-, third- or fourth-degree relatives, siblings excluded, with such a disorder; Melkersson, 2009), and 2) 25 control subjects. The reads were mapped to the reference sequence of the *INS* gene and parts of its promoter region (i.e. 2181009 to 2182727 and 2183256 to 2184463, respectively on chromosome 11p15.5, according to GRCh37.p13; http://www.ensembl.org), and 15 SNPs were identified. In the second part of the study, 7 of these 15 SNPs, which were present in more than one patient or control subject and considered to be of potential interest, were typed in the whole study population by TaqMan® SNP Genotyping Assays (ThermoFisher Scientific Inc., Waltham, MA, USA).

Haplotypes were calculated as previously described (Stephens & Scheet, 2005; Stephens *et al.* 2001). Categorial data were summarized using frequency counts and percentages. Associations between genotype, allele or haplotype frequencies and disease (schizophrenia versus controls) were analyzed with Chi-square test or Fisher's exact test. The same statistical methods were used to investigate associations between the variable DM (type 1 or 2) and/ or heredity for DM (type 1 or 2) in combination with schizophrenia or controls on one hand, and the groups of genotype, allele or haplotype on the other. A p-value of less than 0.05 was considered statistically significant. The statistical analyses were performed using the statistical programs Statistica for Windows 13.5 (TIBCO Software

Tab. 2. Genotype distributions and allele frequencies for the 7 single nucleotide polymorphisms typed in the whole study population, together with results of single association analyses

SNP[a]	Polymorphism[b]	Numbers of P/ C	Genotype distributions (%)							Allele frequencies (%)[c]			
			P			vs	C		*p*-value[d]	*P*	vs	C	*p*-value[d]
			1-1	1-2	2-2	1-1	1-2	2-2					
2.	G>**A**	93/ 58	58.1	37.6	4.3	51.7	46.6	1.7	0.452	76.9		75.0	0.709
8.	A>**T**	93/ 58	8.6	37.6	53.8	10.3	43.1	46.6	0.687	72.6		68.1	0.405
9.	G>**A**	94/ 58	94.7	5.3	0.0	100.0	0.0	0.0	0.157	97.3		100.0	**0.077**
12.	C>**G**	94/ 58	6.4	35.1	58.5	1.7	46.6	51.7	0.237	76.1		75.0	0.834
13.	G>**A**	93/ 58	93.5	6.5	0.0	86.2	12.1	1.7	0.175	96.8		92.2	**0.078**
14.	G>**A**	92/ 57	58.7	34.8	6.5	54.4	43.9	1.8	0.292	76.1		76.3	0.964
15.	T>**G**	93/ 58	8.6	38.7	52.7	10.3	43.1	46.6	0.758	72.0		68.1	0.465

Abbreviations: C=control subjects, *P*=patients with schizophrenia, 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 significant difference is written in bold text

Inc., USA) and R version 4.0.0 (The R Foundation for Statistical Computing).

RESULTS

Data regarding the 15 (12 registered and three potential novel) SNPs in the *INS* gene and parts of its promoter region identified in two subgroups of the study population are given in Table 1. Twelve of the 15 SNPs were polymorphic-distributed (Table 1: no´s 1-5, 8-9 and 11-15), whereas three were monomorphic-distributed, showing solely the alternative allele (Table 1: no´s 6-7 and 10). Seven of the 12 polymorphic-distributed SNPs were present in more than one patient or control subject, and were considered to be of potential interest and were typed in the whole study population (Table 1: no´s 2, 8-9 and 12-15).

Genotype distributions and allele frequencies for these 7 SNPs, together with results of single association analyses, are given in Table 2. Tendencies towards significant differences in allele frequencies between patients and control subjects were found for rs5505 and rs3842749 (Table 2: SNP no 9; p=0.077 and SNP no 13; p=0.078). A tendency towards a significant difference between patients and control subjects was also found in frequency for the haplotype no 2: G A, based on rs5505 and rs3842749 (Tables 3A and 3B: p=0.078).

Subgroup association analyses for the 7 SNPs in patients with or without DM (type 1 or 2) and/ or heredity for DM (type 1 or 2) and control subjects showed overall significant differences in genotype distributions and allele frequencies for rs5505 (Table 4: SNP no 9; p=0.021 and p=0.023, respectively), but not for rs3842749 (Table 4: SNP no 13), or the other five SNPs (data not shown). It was the A/G genotype and A allele of rs5505 that tended to be more common in patients without DM and heredity for DM than in control subjects (Table 4: p=0.077 and p=0.079, respectively), and also tended to be more common in patients with DM type 1 and/ or heredity for DM type 1 than in control subjects (Table 4: p=0.065 and p=0.065, respectively). Similar results were seen for the haplotype no 3: A G, but not for the other haplotypes (Table 4). However, subgroup association analyses for the 7 SNPs in patients with (n=36-37) or without (n=53-55) heredity for schizophrenia or related psychosis showed no differences in genotype distributions and allele frequencies (data not shown).

Tab. 3A. Estimated haplotypes, based on rs5505 and rs3842749, and their frequencies in the whole study population[a]

Haplotype[b]	Frequency (%)
1. G G	93.5
2. G A	4.6
3. A G	1.9
4. A A	0.0

[a] n=162
[b] Alleles are numbered 9 and 13 as in Table 1

DISCUSSION

In this study, we show that the *INS* SNPs rs5505 and rs3842749 tend to associate with schizophrenia. We also show that the A/G genotype and A allele of rs5505 alone, or the A G haplotype of rs5505 combined with rs3842749, tend to be more common in subgroups of schizophrenia patients with either no DM and heredity for DM, or DM type 1 and/ or heredity for DM type 1, than in healthy control subjects, who neither had heredity for psychotic disorder, nor for DM type 1, 2 or

Tab. 3B. Distributions and frequencies for the haplotypes, based on rs5505 and rs3842749, in the whole study population, together with results of haplotype association analyses

Haplotype[a,b]	Numbers of P/ C	Haplotype distributions (%)							Haplotype frequencies (%)			
		P			vs C			*p*-value[c]	*P*	vs	C	*p*-value[c]
		-/-	-/H	H/H	-/-	-/H	H/H					
1. G G	93/ 58	0.0	11.8	88.2	1.7	12.1	86.2	0.576	94.1		92.2	0.531
2. G A	93/ 58	93.5	6.5	0.0	86.2	12.1	1.7	0.175	3.2		7.8	**0.078**
3. A G	93/ 58	94.6	5.4	0.0	100.0	0.0	0.0	0.157	2.7		0.0	0.161

Abbreviations: C=control subjects, H=haplotype, *P*=patients with schizophrenia, vs=versus
[a] Same haplotype numbering as in Table 3A
[b] Alleles are numbered 9 and 13 as in Table 1
[c] A tendency towards a significant difference is written in bold text

other types. The finding for the subgroup of patients with DM type 1 and/ or heredity for DM type 1 may be explained by the fact that this subgroup consisted solely of schizophrenia patients with heredity for DM type 1 and not with DM type 1, as the α-chain of INS has been indicated to constitute an antigen link between the two autoimmune diseases DM type 1 and schizophrenia (Kent *et al.* 2005; Melkersson & Bensing, 2021), and register studies have reported that schizophrenia is associated with an increased risk for developing subsequent DM type 1, but in contrast that DM type 1 is associated with a decreased risk of developing subsequent schizophrenia (Eaton *et al.* 2006; Finney, 1989; Juvonen *et al.* 2007; Melkersson, 2020; Melkersson & Wernroth, 2019). On the other hand, the finding for the subgroup of schizophrenia patients with no DM and heredity for DM may be explained by the notion that rs5505 regulates only the coding of the ß-chain of INS and C-peptide, which not are antigen-linked to DM type 1 (Kent *et al.* 2005; Melkersson & Bensing, 2021).

The rs5505 is located in the 5' untranslated region of exon 2 in the *INS* gene, which precedes the part of exon 2 that codes the ß-chain of INS and the first part of the C-peptide chain. The rs3842749, on the other hand, is located in intron 2 of the *INS* gene which precedes exon 3 that codes the second part of the C-peptide chain and the α-chain of INS. The two SNPs are however relatively tightly linked with each other, thereby forming haplotypes. Insulin is a ligand to INSR-A in the CNS and peripheral organs, and possibly also C-peptide is too which has been suggested to exert biological effects by binding its pentapeptide: glutamic acid–glycine–serine–leucine–glutamine (EGSLQ) located in the end of its second part to cell membranes (Landreh *et al.* 2014; Melkersson & Bensing, 2021; Pramanik *et al.* 2001; Schäffer, 1994; Sima *et al.* 2009; Vejrazkova *et al.* 2020; Wahren *et al.* 2004; Yip & Jack, 1992; Yosten *et al.* 2014). Interestingly, increased antibody reactivity in serum against both the α- and ß-chains of INS and the second part of the C-peptide chain, including its pentapeptide EGSLQ, has been reported recently in patients with schizophrenia (Melkersson & Bensing, 2021). Thus, the *INS* SNPs rs5505 and rs3842749, showing association with schizophrenia in this study, may have regulatory function on the coding (Eddy, 2001) of the α- and ß-chains of INS and C-peptide, against which increased antibody reactivity in serum has been found in schizophrenia (Melkersson & Bensing, 2021).

To compare, our findings are supported by earlier genetic studies in schizophrenia on the IRSs 2, 3 and 4 that link the INSR-A and IGF1R coupled together with their ligands with intracellular pathways (Choi & Sung, 2000; Lavan *et al.* 1997; White, 1998; Xu *et al.* 1999), showing both a negative association between an SNP in the *IRS-3* gene and schizophrenia, and positive associations between an *IRS-2* SNP and auditory hallucinations, and between *IRS-4* SNPs and family history or body mass index in patients with schizophrenia (Kim *et al.* 2013; Melkersson & Persson, 2011, 2012; Melkersson *et al.* 2011). Two SNPs located in exon and intron 13 of the *INSR* gene have also been reported earlier to confer risk for psychosis, but specifically for schizoaffective disorder (Melkersson, 2018).

The strength of this study includes its comprising of both a diagnostically homogenous group of patients diagnosed with solely schizophrenia and not with other types of psychotic disorders, and a group of healthy control subjects with no heredity for either psychotic disorder, or DM type 1, type 2 or other types, allowing specific investigations of the involvement of the *INS* gene in schizophrenia susceptibility. The limitation of the study, on the other hand, includes the comprising of a study population not large enough to achieve sufficient power in some of the statistical analyses.

In conclusion, we show association between SNPs in non-coding regions of the *INS* gene and schizophrenia. The findings are in line with our previously-described hypothesis that impaired cellular signalling via the INSR, and probably also via the IGF1R, may underlie known abnormalities in the CNS and peripheral organs in schizophrenia (Melkersson & Persson, 2011, 2012; Melkersson *et al.* 2011), and also with our most recently-published study, pointing 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

Tab. 4. Subgroup association analyses for the single nucleotide polymorphisms no 9 (rs5505) and no 13 (rs3842749) and the haplotypes no's 1-3, based on rs5505 and rs3842749, in schizophrenia patients with or without diabetes mellitus (type 1 or 2) and/ or heredity for diabetes mellitus (type 1 or 2)[a] and control subjects

SNP[b]	Polymorphism[c]	Numbers of P-DM1/ P-DM2/ P-noDM/ C	*P*-value (genotype; allele, and haplotype distribution; frequency)[d]						
			P-DM1 vs P-DM2 vs P-noDM vs C	P-DM1 vs P-DM2	P-DM1 vs P-noDM	P-DM1 vs C	P-DM2 vs P-noDM	P-DM2 vs C	P-noDM vs C
9.	G>**A**	4/ 42/ 44/ 58	**0.021[e]; 0.023[f]**	0.168; 0.167	0.302; 0.298	**0.065; 0.065**	0.616; 0.621	0.420: 0.420	**0.077; 0.079**
13.	G>**A**	4/ 42/ 43/ 58	0.834; 0.492	---	---	---	---	---	---
Haplotype[g]									
1. G G		4/ 42/ 43/ 58	0.763; 0.595	---	---	---	---	---	---
2. G A		4/ 42/ 43/ 58	0.834; 0.492	---	---	---	---	---	---
3. A G		4/ 42/ 43/ 58	**0.021[h]; 0.023[i]**	0.168; 0.167	0.308; 0.304	**0.065; 0.065**	0.616; 0.621	0.420; 0.420	**0.074; 0.076**

Abbreviations: C=control subjects, H=haplotype, P-DM1=schizophrenia patients with diabetes mellitus type 1 and/ or heredity for diabetes mellitus type 1, P-DM2=schizophrenia patients with diabetes mellitus type 2 and/ or heredity for diabetes mellitus type 2, P-noDM=schizophrenia patients without diabetes mellitus and heredity for diabetes mellitus, SNP=single nucleotide polymorphism, vs=versus

[a] Two patients with diabetes mellitus other types and/ or heredity for diabetes mellitus other types were excluded

[b] Same SNP numbering as in Table 1

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

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

[e] A/G genotype: P-DM1; 25.0%, P-DM2; 2.4%, P-noDM; 6.8%, C; 0.0%

[f] A allele: P-DM1; 12.5%, P-DM2; 1.2%, P-noDM; 3.4%, C; 0.0%

[g] Same haplotype numbering as in Table 3A

[h] -/H3 distribution: P-DM1; 25.0%, P-DM2; 2.4%, P-noDM; 7.0%, C; 0.0%

[i] H3 frequency: P-DM1; 12.5%, P-DM2; 1.2%, P-noDM; 3.5%, C; 0.0%

INSR-A and IGF1R and their ligands INS, C-peptide and IGF1 may constitute antigen targets (Melkersson & Bensing, 2021). Further, our findings are supported by several studies by others, reporting INSR deficits in postmortem brains, insulin-signalling abnormalities, and altered IGF2 signalling in patients with schizophrenia (Kapogiannis *et al.* 2019; van Beveren *et al.* 2014; Wu *et al.* 2013; Yang *et al.* 2020; Zhao *et al.* 2006). Last, but not least, these present findings may bring one more important piece into the schizophrenia-aetiology puzzle.

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