Journal of Genetics (2023)102:30
https://doi.org/10.1007/s12041-023-01427-9

REVIEW ARTICLE

Role of cryptic rearrangements of human chromosomes in the aetiology of schizophrenia

LIVIA JURISOVA and ROMAN SOLC*

Department of Anthropology and Human Genetics, Faculty of Science, Charles University, Vinicna 7, 128 00 Prague, Czech Republic
*For correspondence. E-mail: roman.solc@natur.cuni.cz.

Received 19 July 2022; revised 23 January 2023; accepted 23 February 2023

Abstract. Schizophrenia (SZ) is a highly inherited disease that affects ∼0.5% of the population. The genetic and environmental factors are involved in its aetiology and they interact with each other. Combination of symptoms is unique to each patient, the disease seriously interferes with the ability to function in society and affects the mental state of the patient. In most patients, the first manifestations of SZ appear during the adolescence or early adulthood. The hypothesis that SZ origin in impaired development of the nervous system is currently widely accepted. Some studies have identified several genetic and environmental factors that increase the risk of the disease manifestation, but none of them can be considered as the only cause of SZ. The genetics of the disease is complex and in last two decades it is assumed that the cryptic rearrangements could be one of its causes. Cryptic rearrangements (microdeletions and microduplications) are the chromosomal rearrangements smaller than 3–5 Mb. Their discovery was conditioned by the development of molecular genetic and molecular cytogenetic techniques. The aberrations affect one or more genes and change the gene dose. In this article, we present the rearrangements of the regions of human chromosomes more closely associated with the onset and development of SZ. Next, the candidate genes will be presented together with their inclusion in the context of theories trying to explain the origin of SZ through some important factors (e.g. action of dopamine or glutamate or GABA, formation of dendrites and neuronal synapses, etc.).

Keywords. cryptic rearrangement; schizophrenia; human chromosomes; copy number variations; aetiology of schizophrenia; genetics of schizophrenia.

Introduction

Schizophrenia (SZ) is a serious mental disorder that affects ∼24 million people or one in 300 people (0.32%) worldwide. This rate is one in 222 people (0.45%) among adults (IHME 2022). The sexes are affected in approximately the same way, with a later onset observed in women. The onset may be gradual or acute, with acute being associated with severely impaired behaviour (World Health Organization 1992, ICD-10). The inheritance of SZ is around 80% (Hilker *et al*. 2018), but both genetic and environmental factors play a role in its development.

The symptoms are divided into three categories: positive, negative and cognitive. The positive symptomes are present in schizophrenics, but not in a healthy people. Examples could be disillusions and hallucinations of various kinds, auditory e.g. they comment on the actions and thoughts of the affected person, or the voices can talk about the person among themselves. They also include disturbed thinking, which is reflected in incoherent narration and incoherence. Patients' attention is often focussed on common things and details that they consider more important than the whole object or situation (Tandon *et al.* 2013b; World Health Organization 1992). The negative symptoms indicate a lack or absence of normal mental functions including thinking, behaviour, and perception. These include, for example, impoverished speech, decreased ability to communicate, limited social relationships, decreased affective expression, and others (Tandon *et al.* 2013b). The cognitive symptoms include impaired working, long-term and episodic memory, attention, and learning. Patients have difficulty in understanding the meaning of words (Kurtz *et al.* 2001). Paranoia, irritability, loss of goals, and transition to aimless behaviour are also common. Thus, the disease significantly reduces the ability to function in social situations (Tandon *et al.* 2013b).

Published online: 09 May 2023

Table 1. Cryptic rearrangements of chromosomes analysed.

Chromosomal region	del/dup	Effect on SZ risk	Candidate genes	Involvement of genes in the aetiology of SZ
1q21.1	del	++	*GJA8*	Synapse, signalling; GABA
	dup	+	*GJA5*	Synapse, signalling; GABA
			BCL9	Development of NS; other
			PRKAB2	Other
2p16.3	del	+	*NRXN1*	Synapse, signalling
3q29	del	++	*PAK2*	Dendrites; synapse, signalling
			DLG1	Glutamate; dendrites; development of NS
			FBXO45	Synapse, signalling; development of NS
7q36.3	dup	(+)	*VIPR2*	Development of NS
7q11.23	dup	+		
15q11.2	del	(+)	*CYFIP1*	Glutamate; dendrites; synapse, signalling; development of NS
15q13.3	del	+	*CHRNA7*	Other
			OTUD7A	Dendrites
15q11-13	dup	+	*UBE3A*	Synapse, signalling
16p11.2	dup	++	*KCTD13*	Other
			MAPK3	Other
16p13.1	dup	++	*NTAN1*	Development of NS
			NDE1	Synapse, signalling; development of NS
17q12	del	(+)	*LHX1*	Synapse, signalling; development of NS
	dup	(+)		
22q11.2	del	++	*COMT*	Dopamine
			PRODH	Glutamate

+, Positive effect on the development of SZ.
++, Strong positive effect on the development of SZ.
(+), Uncertain positive effect on the development of SZ

The hypothesis that SZ origin in impaired development of the nervous system, is currently widely accepted. Studies have identified several genetic and environmental factors that increase the risk of disease manifestation, but none can be considered the sole cause of SZ.

Genetics of SZ is complex and a lot of candidate genes have been presented in association with SZ (i.e. *DISC1*, *NRG1*, *COMT*, *GRM3* and other genes) (González-Castro *et al.* 2016; Saini *et al.* 2017; Jagannath *et al.* 2018; Wang *et al.* 2018). However, the problem is inconsistent replication of study results (Harrisoñ and Weinberger 2005). Whole genome association studies were followed, which identified a number of common low-effect alleles associated with the diagnosis (Ripke *et al.* 2013; Li *et al.* 2017).

The discovery of cryptic rearrangements enriched in schizophrenics has attracted attention due to the potentially high impact—the rearrangements often involve several genes and affect the gene dose. In addition to their association with SZ as its cause, it is possible that the presence of some may have the opposite effect, e.g. 22q11 duplication is likely to protect the wearer from SZ manifestation (Marshall *et al.* 2017).

Environmental factors are likely to interact with genetic factors, increasing the risk of disease. Examples of such factors are prenatal maternal immune activation, perinatal hypoxia, adolescent marijuana use, stress, and many more (Schmidt and Mirnics 2015).

Cryptic rearrangements

The chromosomal aberrations which are lesser than 3–5 Mb are considered as cryptic rearrangements. They got their name due to their undetectability by classical cytogenetic methods (dyeing and banding). They are also referred as microdeletions, microduplications, etc. They belong to the so-called copy-number variants (CNV), which are defined as differences from the reference human genome in terms of DNA sequence losses or gains. CNVs are divided into recurrent and nonrecurrent (sporadic) which is related to how and where they originate.

Cryptic rearrangements can lead to the so-called microdeletion or microduplication syndrome, or may not have any clinical phenotype. The onset of syndromes is conditioned by a change in the copy number of a gene that is sensitive to the gene dose, and in the case of a deletion, it can lead to haploinsufficiency. The organism better tolerates duplications leading to partial trisomies than deletions causing haploinsufficiency. Thus, duplications usually have a milder or no clinical manifestation. Changes in gene dose caused by microdeletion or microduplication may also play a role in the aetiology of polygenic disorders such as SZ or autism.

Cryptic rearrangements associated with SZ (see table 1)

Chromosome 1: deletion and duplication in 1q21.1

There are several regions on chromosome 1 that are thought to be associated with SZ. From them the existence of cryptic deletions and duplications has been described in 1q21.1 region (International Schizophrenia Consortium 2008; Stefansson *et al.* 2008; Levinson *et al.* 2011; Rees *et al.* 2014; Marshall *et al.* 2017). Two types of CNV are typical for this area. The more common type I contains only the distal part of the 1q21.1 area of 1.8 Mb and type II of 2.7 Mb occurs proximally (Brunetti-Pierri *et al.* 2008). Deletion in this area represents almost seven-fold increase in SZ risk (Chang *et al.* 2016). Studies with a sufficiently large sample did not detect rearrangements in control subjects (Mefford *et al.* 2008), or they were detected in a very small number of control subjects (0.02%) (Stefansson *et al.* 2008).

In the 1q21.1 region, there are four genes associated with SZ and affected by CNV: *GJA8*, *GJA5*, *BCL9* and *PRKAB2*. Changing their gene dose (heterozygous deletion/duplication) increases the risk of SZ.

Gap junction protein alpha 8; connexin 50 (*GJA8*) is the gene encoding the alpha 8 conductive junction protein, while gap junction protein alpha 5; connexin 40 (*GJA5*) is the gene encoding the alpha 5 conductive junction protein. Connexins are the basis of a gap junctions and they serve for metabolic and electrical intercellular communication. Communication through them is affected by antipsychotic drugs. As well GABAergic interneurons (γ-aminobutyric acid, GABA) connected by electrical synapses, and the damage of these synapses can result in manifestations of SZ (Rouach *et al.* 2002; Ni *et al.* 2007).

BCL9 is a gene whose product plays a role in the Wnt signalling pathway, important for development, function and structure of the nervous system and thus it could play a role in the development of the mental diseases (Xu *et al.* 2013; Li *et al.* 2011; Kimura *et al.* 2015a).

Studies focussing on the association of the *PRKAB2* gene with SZ in humans does not exist yet. A study of its ortholog on an animal model is the only one that exists (Nagy *et al.* 2018).

Chromosome 2: deletion in 2p16.3

The first finding of *NRXN1* gene disorder associated with SZ was in 2007 (Kirov *et al.* 2007). The 0.25-Mb deletion in the 2p16.3 regions was diagnosed in two siblings with SZ and their mother without SZ. The deletion included the promoter and exon 1 of the gene. Due to the previous deletions in patients with mental retardation and autism it was considered pathogenic. The nonpathogenic maternal phenotype suggests that the deletion has an incomplete penetrance.

In the following years, other cases of deletion of different sizes were reported (0.018–0.420 Mb), but they have been discovered only in some patients (Walsh *et al.* 2008; Kirov *et al.* 2009; Need *et al.* 2009). Because the deletions are rare and the studies have been performed with small samples, Kirov *et al.* (2009) performed a meta-analysis of data from the above studies and two others (International Schizophrenia Consortium 2008; Rujescu *et al.* 2009), in order to obtain the convincing results for the association with SZ. Their analysis provided strong evidence for the association of the exon extending deletions with SZ. The affected gene encodes proteins that are involved in the release of neurotransmitters from the presynaptic vesicles (Missler *et al.* 2003) and in the formation of synapses (Craig and Kang 2007).

Chromosome 3: deletion in 3q29

Bailer *et al.* (2002) and Schosser *et al.* (2004) performed binding studies that indicated an association of the 3q29 region with SZ. The subsequent studies have found that the size of deletions occur in the area 0.8–1.6 Mb. The presence of a deletion in the 3q29 region increases the risk of SZ more than 40-fold (Mulle 2015). By comparing the deletions of patients and controls, it was found that the region deleted in patients is longer, includes more genes and was created *de novo*, making it considered pathogenic (Mulle *et al.* 2010).

PAK2, *DLG1* and *FBXO45* are considered as candidate genes. *PAK2* and *DLG1* are genes homologous to X chromosome genes (*PAK3*, *DLG3*), which are associated with mental retardation (Levinson *et al.* 2011).

The serine/threonine kinase PAK 2, encoded by *PAK2*, is highly expressed in the foetal brain. It plays a role in cytoskeletal regulation, nuclear signalling, and possibly plays a role in neuronal differentiation (Demyanenko *et al.* 2010). It also attenuates the inhibitory interaction between RhoGDI and ras-related C3 botulinum toxin substrate 1 (Rac1) (Shin *et al.* 2009), wherein Rac1 is a regulator of the dendritic spine morphology of maturing neurons (Nakayama *et al.* 2000).

The level of scaffold protein encoded by *DLG1* was reduced to half in the prefrontal cortex in patients with SZ (Toyooka *et al.* 2002). The protein affects the dendrit growth (Zhou *et al.* 2008) and plays a role in glutamate receptor transport. Its loss in mice did not avert the incorporation of glutamate receptors because other proteins from their group were expressed and compensated its absence (Howard *et al.* 2010).

The *FBXO45* gene (coding FBXO protein 45, a substrate-recognition subunit of E3 ligases) has been characterized to have pivotal roles in many human diseases, including nervous system diseases. However, it is mainly investigated in connection with carcinogenesis (Lin *et al.* 2020).

Chromosome 7

***Duplication in 7q36.3*:** The duplications in the 7q36.3 region affects a single gene for vasoactive intestinal peptide receptor 2 (*VIPR2*). Duplications of different sizes were detected in the gene, optionally they occurred 0.089 Mb upstream of the gene sequence. An area of 0.362 Mb is considered as a critical (Vacic *et al.* 2011).

In the same year, a study was also published that found the exonic duplications in patients with positive symptoms (Levinson *et al.* 2011). The study by Aleksic *et al.* (2013) suggest that for further studies of the association of duplication with SZ, it is necessary to pinpoint the begining and the end of CNV, because they examined the smaller duplication (0.035 Mb) in the critical area which was not associated with SZ. The metaanalysis does not support the association because of the increased incidence in patients which was not significant in comparation with the incidence in control subjects (Rees *et al.* 2014). Studies performed on the Chans support the association (Yuan *et al.* 2014; Li *et al.* 2016).

VIPR2 is a receptor for the vasoactive intestinal peptide (VIP) and the pituitary adenylate cyclase-activating polypeptide (PACAP), which are important for the embryonic development of the nervous system and its protection, and they were also associated with disease as well (Hashimoto *et al.* 2007; Levinson *et al.* 2011). The receptor is expressed in areas of the brain that are associated with cognition and behaviour (Sheward *et al.* 1995).

***Duplication in 7q11.23*:** *De novo* duplications in the area have been associated with autism and subsequently discovered in patients with SZ (Stewart *et al.* 2011; Kirov *et al.* 2012). The association with SZ is also supported by other studies that identified the duplications of different lengths (0.47–1.56 Mb). The duplications increase the risk of SZ 10-fold. It is considered risk mainly due to its rarity and the current association with autism, which are properties that share CNV associated with SZ (Mulle *et al.* 2014; Li *et al.* 2016). The significant support for the association was provided by Marshall *et al.* (2017).

Chromosome 15

***Deletion in 15q11.2*:** A deletion in the 15q11.2 region of 0.47 Mb in association with SZ was described by Stefansson *et al.* (2008). A support for this study is also provided by studies by Kirov *et al.* (2009), Melhem *et al.* (2011) and Rees *et al.* (2014). In contrast, the studies by Ikeda *et al.* (2010) and Saxen *et al.* (2019) did not support the association and claim that the deletions are not pathogenic.

The region includes four genes, with *CYFIP1* being considered a candidate gene. This gene encodes the protein interacting with the fragile X mental retardation protein (FMRP), from which its name is also derived—cytoplasmic FMR1 interacting protein 1 (CYFIP1). It also modulates the actin dynamics and interacts with Rac1, which is involved in the regulation of the dentrite growth (Stefansson *et al.* 2008). Reduced *CYFIP1* expression resulted in impaired expression of the *FMRP* gene and postsynaptic density genes associated with SZ (Fromer *et al.* 2014; Purcell *et al.* 2014; Nebel *et al.* 2016).

FMRP is a RNA binding protein that regulates translation and is required for neurogenesis and glutamate signalling at synapses (Callan and Zarnescu 2011). The postsynaptic density genes play a role in dendritic plasticity and in the excitatory components of neurons (Purcell *et al.* 2014).

The haploinsufficiency of *CYFIP1* in mice resulted in a decrease of its level and thus in a decrease of dendritic complexity and an increase of the incidence of immature dendritic processes (Pathania *et al.* 2014). A recent study confirms the effect of *CYFIP1* haploinsufficiency in mice on stability of the dendritic thorns, but not on the formation and the deficits in social behaviour that are in some cases the symptoms of SZ as well (Bachmann *et al.* 2019).

***Deletion in 15q13.3*:** In 2008, a two or more studies showed an association of a 1.57-Mb long deletion in the 15q13.3 regions which was also present in small portion of the control subjects (0.02%) (International Schizophrenia Consortium 2008; Stefansson *et al.* 2008). This was also supported by the study of Levison *et al.* (2011), which also pointed out that the shorter deletions in this area are not associated with SZ. The deletions in the area are up to 10 times more common in schizophrenics, but the risk of manifestation of the disease is only 10% if deletion present (Levinson *et al.* 2011; Fejgin *et al.* 2014). According to the study by Marshall *et al.* (2017), the deletion occurs almost 16 times more frequent in patients than in controls.

The deletion affects seven genes, of which *CHRNA7* and *OTUD7A* are considered candidate genes. *CHRNA7* encodes an acetylcholine receptor subunit. In a mouse model with microdeletion the defects in the processing of sound stimuli similar to patients with SZ were detected using an electroencephalogram (Fejgin *et al.* 2014; Thelin *et al.* 2016). The study of Uddin *et al.* (2018) focussed on the *OTUD7A* gene, which they consider important for brain development because it occurs in mice model participated in the formation of dendritic spines. The protein encoded by *OTUD7A* is a deubiquitinase whose role is to remove ubiquitin from proteins intended for degradation. It is located in the postsynaptic density, where it probably regulates the proteins important for synapse maturation. It is not yet known whether it cooperates with CHRNA7 in the regulation of dendritic growth, or if these proteins act in other cell types or in different time (Uddin *et al.* 2018).

***Duplication in 15q11-13*:** The finding of about 5-Mb long duplications in schizophrenics supports the claim that SZ belongs to the spectrum 15q11-13 duplication syndrome disease (Ingason *et al.* 2011b; Liao *et al.* 2012). An atypical

0.129-Mb long duplication involving only the *UBE3A* gene was also found (Noor *et al.* 2015).

Therefore, the *UBE3A* gene became a candidate gene. It plays a role in the creation of synapses based on experience (so-called experience-driven synaptic plasticity) (Greer *et al.* 2010). The new study also provides the support for the duplication of this candidate gene (Salminen *et al.* 2019).

Chromosome 16

***Duplication in 16p11.2*:** A 0.6 Mb microduplication posed up to a 14-fold increased risk of SZ (McCarthy *et al.* 2009). The support of the association of duplication with SZ is relatively large and both rare, and common gene variants and are associated with SZ risk (Vacic *et al.* 2011; Steinberg *et al.* 2014; Chang *et al.* 2017; Zhou *et al.* 2018).

The region includes 28 genes, of which at least 17 are expressed in the mammalian brain. In patients with microduplication, a microcephaly was found, but this was not statistically significant (McCarthy *et al.* 2009). In another study, there was the statistical significance between the microcephaly in humans and the microduplication (Shinawi *et al.* 2010). Because of that the *KCTD13* gene (which has an effect on changes in head size in *Danio rerio*) is considered significant candidate gene (Golzio *et al.* 2012). It is one of the genes whose expression is positively correlated with gene dose (Kusenda *et al.* 2015).

MAPK3 is another candidate gene. Its locus is associated with SZ (Schizophrenia The Working Group of the Psychiatric Genomics Consortium 2014) and it is in transcription relationship with *KCTD13*. In particular, when in *D. rerio* with overexpressing *KCTD13* (which leads to microcephaly), the *MAPK3* suppression occurs and a normal phenotype is observed.

***Duplication in 16p13.1*:** The association of the duplication in the 16p13.1 region with SZ is relatively strong (Kirov *et al.* 2009; Ikeda *et al.* 2010; Ingason *et al.* 2011a; Rees *et al.* 2014), although there are studies that do not support this association (Grozeva *et al.* 2012). The microdeletion is 1.5 Mb in size and is surrounded by LCR that destabilize this area. It is not clear whether the rearrangements are benign or pathogenic (Ingason *et al.* 2011a).

Candidate genes in this region are *NTAN1* and *NDE1*. The genes play a role in the brain development, in the neuronal proliferation and migration, and in the synapse formation. *NTAN1* encodes an N-terminal asparagine amidase that is thought to be important for social behaviour and memory (Ingason *et al.* 2011a). In the case of *NDE1*, a rare single-nucleotide variant has been discovered that is associated with SZ (Kimura *et al.* 2015b). The effect of haploinsufficiency of the genes is not known yet, and thus their susceptibility to gene dose changes is only presumptive.

Chromosome 17

***Deletion in 17q12*:** Moreno-De-Luca *et al.* (2010) identified a deletion of 1.4 Mb, which in almost all patients form *de novo* and it can therefore be considered pathogenic. In Rees *et al.* (2014), one patient with a deletion was described. The study by Grozev *et al.* (2012) decreased the association of the deletion, but it remained significant. Any deletion in this area is considered important because it is one of the 10 most common pathogenic deletions in children with unspecified neurodevelopmental disorders (Moreno-De-Luca *et al.* 2010).

LHX1 could be considered a candidate gene. It plays a role as a transcription factor in the nerve cell differentiation, in the transcriptional control, and in the axonal guidance (Avraham *et al.* 2009). In knockout mice, the gene ortholog was found to be an important regulator of the head organizer (Shawlot and Behringer 1995). So far, its role in the SZ is only at the level of speculation.

***Duplication in 17q12*:** Szatkiewicz *et al.* (2014) found in a relatively large and homogeneous sample of schizophrenics the duplication reciprocal to the deletion occuring in 17q12 . Since this discovery, a case of the treatment-resistant patient with SZ has been described with the duplication. The authors of the study assume a connection between CNV and treatment resistance (Rogdaki *et al.* 2016).

Chromosome 22: deletion in 22q11.2

The deletion syndrome of chromosome 22q11.2, also known as DiGeorge syndrome, is probably the most common microdeletion syndrome. A 3-Mb long deletion and an overlapping proximal 1.5-Mb long are the most typical ones (McDonald-McGinn *et al.* 2015). As many as 30% of people with a deletion are diagnosed with SZ in adulthood and 0.5–1% of schizophrenics carry this deletion (Schneider *et al.* 2014). The association of the deletion with SZ is well known and represents up to 20% increased risk. It is therefore considered one of the three most risk factors for manifestation of the disease. The deletion affects a large number of genes and two candidate genes in this region will be described: *COMT* and *PRODH*.

COMT encodes the protein catechol-O-methyltransferase, whose role is the degradation of catecholamines, and thus including dopamine. The gene occurs in two functional polymorphisms $COMT^{158}Val$ and $COMT^{158}Met$. $COMT^{158\text{-}Met}$ encodes an enzyme with reduced activity (McDonald-McGinn *et al.* 2015). Too low or too high dopamine levels are thought a risk for SZ, so the activity of this enzyme could be a critical factor (Cools and D'Esposito 2011). The decreased expression, enzyme activity and changes in dopamine signalling were observed in the deletion carriers (Evers *et al.* 2014; Gothelf *et al.* 2014). In the schizophrenics with deletion, neither the more frequent

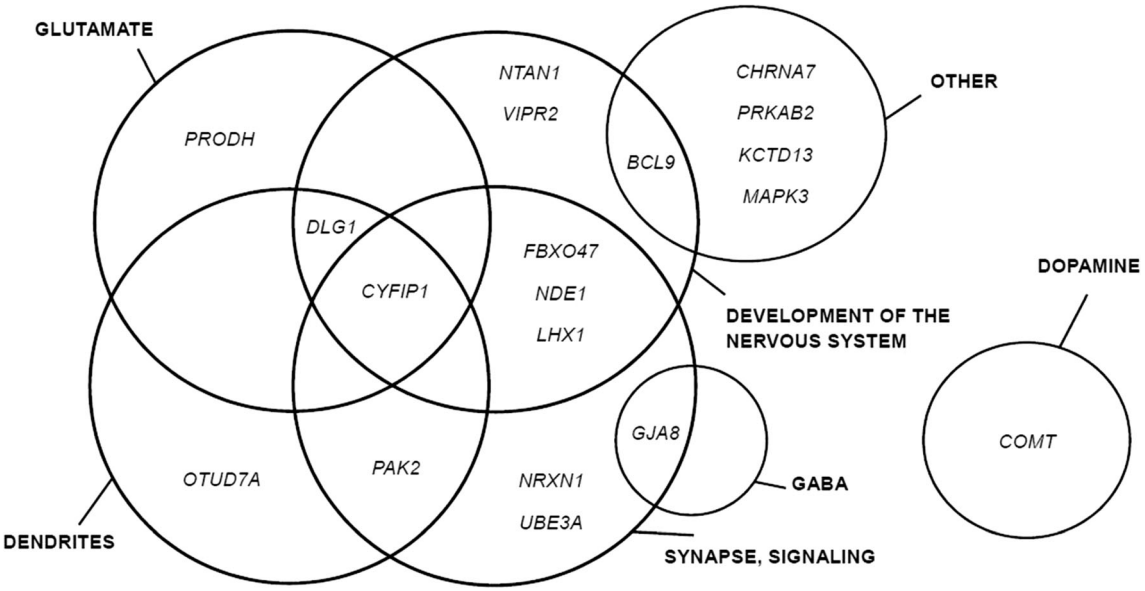

Figure 1. Various theories linking genes involved in cryptic rearrangements with SZ.

occurrence of one of the alleles nor the association between *COMT*^{158}*Met* allele and the disease was not proven (Bassett *et al.* 2007; Gothelf *et al.* 2013). The consequences of *COMT* haploinsufficiency at the neuronal level, in relation with the system of reward and with the psychotic symptoms are currently unclear.

PRODH is a gene for proline dehydrogenase that catalyzes the first reaction in the proline conversion to glutamate. Therefore, the glutamate abnormalities could occur in patients with deletion. Some studies have reported increased and some unchanged glutamate levels (Tebartz van Elst *et al.* 2005; Lutkenhoff *et al.* 2010).

Theories linking genes in cryptic rearrangements with SZ

Now, here is an overview that integrates gene into the context of SZ theories (see figure 1). One of the leading properties of a gene, that makes it a candidate gene for SZ, is the localization of its expression. For obvious reasons, these are the most common genes expressed in the brain, where they could cause the disruptions in the connectivity of neurons to each other or to individual areas of brain.

The theory that links all the following hypotheses and gene properties comprehends SZ as a disease of pathologically altered brain connectivity. For example, the severity of the positive symptoms is associated with the reduced overall structural connectivity, the increased or reduced structural and functional interconnection of areas of the brain and the reduced efficiency of the whole brain network. The severity of negative symptoms is associated with the reduced overall function connectivity, the increased structural and functional interconnection and also the reduced efficiency of the whole brain network (Skudlarski *et al.* 2010; Wang *et al.* 2012).

Many candidate genes are associated with an effect on the dendritic growth, the morphology of the dendritic spines and dendritic complexity. The studies point to the reduced dendritic complexity, which causes (together with the reduced number of synapses) the reduction of the gray matter (Glantz and Lewis 2000; Sweet *et al.* 2009). The complexity of dendritic approval determines the number of receptive synapses and its reduction could impair the healthy connectivity.

The dopamine hypothesis assumes that the psychosis can be attributed to dopamine deregulation. The dopamine deregulation could cause aberrant salience (Howes and Kapur 2009). The role of dopamine in reward processes is well known, it also plays a role in the positive reinforcement for required behaviour. The animal model studies suggest that dopamine is also involved in aversive behaviour (Barr *et al.* 2009; Fadok *et al.* 2009). The dopamine is likely to convert the neutral property to attractive or aversive feature. It therefore affects saliency, the process by which the situations and thoughts attract attention and, depending on their association with reward or aversion, a reaction arises (Berridge and Robinson 1998). In psychosis, a long-term process occurs, which starts with an increase of attention and an increase of emotionality associated with anxiety. The saliency is then abnormal, because a situation or an object is assigned a property not based on context, but based on the current mental state. This results in the disillusionment, this is the way the brain copes with the confusion that has arisen (Yung and McGorry 1996).

The glutamate hypothesis states that impaired glutamatergic signalling may be responsible for the manifestation

of the SZ. The hypothesis is based on the results of studies which found that the antagonists of the N-methyl-D-aspartate (NMDA) glutamate receptors cause SZ-like symptoms and that their administration to schizophrenics prolongs and worsens the symptoms (Krystal *et al.* 1994; Malhotra *et al.* 1997). For example, the phencyclidine in rats caused a decrease of the functional connectivity, which is also observed in the schizophrenics (Dawson *et al.* 2014).

The glutamatergic neurons predominate in the excitatory signalling, which occurs through the metabotropic and ionotropic receptors. The symptoms are probably caused by a malfunction of NMDA receptors (Pilowsky *et al.* 2006; Stone 2011). Studies suggest that the increased levels of glutamate and glutamine (an indicator of glutamate signalling generated by recycling of synaptic glutamate) (Tandon *et al.* 2013a; Bustillo *et al.* 2014). It is not known how the glutamate abnormalities cause the symptoms of SZ.

In connection with SZ, it is important to mention the γ-aminobutyric acid (GABA) signalling. The GABAergic neurons are inhibitory and they are thought that the reduction of their activity leads to the apathetic behaviour or social separation because it affects the emotional and cognitive functioning (Gur *et al.* 2000). In schizophrenics, the overall GABAergic activity is likely to be reduced, starting with the GABA synthesis and ending with the GABA receptor level compensation. The imitation of the reduced GABA synthesis in the rats resulted in the impaired working memory performance, which is one of the common SZ signs (Enomoto *et al.* 2011).

Conclusion

With the expansion of the new methods of molecular genetics and molecular cytogenetics, it was possible to discover a number of the earlier unknown (cryptic) chromosomal rearrangements, whose association with SZ is the subject of many studies for last two decades. Several cryptic rearrangements associated with SZ are presented in this article.

The chromosomal area 22q11.2 is considered to be one of the three most important risk factors for the diagnosis of SZ. The areas 1q21.1, 15q11.2 and 15q13.3 were discovered among the first and support for their association with SZ is relatively strong. The areas 7q11.23, 15q11-13 or 16p12.1 can represent a new direction in research, as they have gained the support in the association during the last five years. The 17q12 region is poorly studied and was included due to its association with the neurodevelopmental damage and the possible effect on the SZ resistance to treatment. In this area, further research is needed to determine their significance in SZ. The other mentioned rearrangements are extensively researched and despite the existence of studies which do not support the association, they remain significant still.

Many cryptic rearrangements point to the problems of their study. An example is deletion in the 2p16.3 regions where the rarity of the rearrangement may affect the estimation of the significance of the association. The cryptic rearrangements are a possible cause of the disease in only 2–4% of the patients.

A collective feature of the candidate genes is their effect on brain connectivity. The genes play roles in the development of the nervous system, the synapse formation, the signalling or the social behaviour.

The opinions on the influence of these cryptic rearrangements on the manifestation of SZ are different, but they definitely represent an interesting area of research with the potential in diagnostic or in the drug development. The heterogeneity of the disease suggests the need for further and extensive research to identify the structure of the interactom, and the causes and symptoms of the disease.

Acknowledgement

This study was supported by Charles University (PROGRES Q43).

Authors' contribution

RS: designed the study; LJ: reviewed the literature; RS and LS: analysed the information obtained and prepared the manuscript.

References

Aleksic B., Kushima I., Ohye T., Ikeda M., Kunimoto S., Nakamura Y. *et al.* 2013 Definition and refinement of the 7q36.3 duplication region associated with schizophrenia. *Sci. Rep.-UK* **3**, 2587.

Avraham O., Hadas Y., Vald L., Zisman S., Schejter A., Visel A. *et al*. 2009 Transcriptional control of axonal guidance and sorting in dorsal interneurons by the Lim-HD proteins Lhx9 and Lhx1. *Neural. Dev.* **4**, 21.

Bachmann S. O., Sledziowska M., Cross E., Kalbassi S., Waldron S., Chen F. *et al*. 2019 Behavioral training rescues motor deficits in Cyfip1 haploinsufficiency mouse model of autism spectrum disorders. *Transl. Psychiat.* **9**, 29.

Bailer U., Leisch F., Meszaros K., Lenzinger E., Willinger U., Strobl R. *et al*. 2002 Genome scan for susceptibility loci for schizophrenia and bipolar disorder. *Biol. Psychiat.* **52**, 40–52.

Barr G. A., Moriceau S., Shionoya K., Muzny K., Gao P., Wang S. *et al*. 2009 Transitions in infant learning are modulated by dopamine in the amygdala. *Nat. Neurosci.* **12**, 1367–1369.

Bassett A. S., Caluseriu O., Weksberg R., Young D. A. and Chow E. W. C. 2007 Catechol-O-methyl transferase and expression of schizophrenia in 73 adults with 22q11 deletion syndrome. *Biol. Psychiat.* **61**, 1135–1140.

Berridge K. C. and Robinson T. E. 1998 What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res. Rev.* **28**, 309–369.

Brunetti-Pierri N., Berg J. S., Scaglia F., Belmont J., Bacino C. A., Sahoo T. *et al*. 2008 Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities. *Nat. Genet.* **40**, 1466–1471.

Bustillo J. R., Chen H., Jones T., Lemke N., Abbott C., Qualls C. *et al*. 2014 Increased glutamine in patients undergoing long-term treatment for schizophrenia. *JAMA Psychiat.* **71**, 265–272.

Callan M. A. and Zarnescu D. C. 2011 Heads-up: New roles for the fragile X mental retardation protein in neural stem and progenitor cells. *Genesis* **49**, 424–440.

Chang H., Li L., Peng T., Li M., Gao L. and Xiao X. 2016 Replication analyses of four chromosomal deletions with schizophrenia via independent large-scale meta-analyses. *Am. J. Med. Genet. B* **171**, 1161–1169.

Chang H., Li L., Li M. and Xiao X. 2017 Rare and common variants at 16p11.2 are associated with schizophrenia. *Schizophr. Res.* **184**, 105–108.

Cools R. and D'Esposito M. 2011 Inverted-U–shaped dopamine actions on human working memory and cognitive control. *Biol. Psychiat.* **69**, e113–e125.

Craig A. M. and Kang Y. 2007 Neurexin–neuroligin signaling in synapse development. *Curr. Opin. Neurobiol.* **17**, 43–52.

Dawson N., Xiao X., McDonald M., Higham D. J., Morri B. J. and Pratt J. A. 2014 Sustained NMDA receptor hypofunction induces compromised neural systems integration and schizophrenia-like alterations in functional brain networks. *Cereb. Cortex.* **24**, 452–464.

Demyanenko G. P., Halberstadt A. I., Rao R. S. and Maness P. F. 2010 CHL1 cooperates with PAK1-3 to regulate morphological differentiation of embryonic cortical neurons. *Neuroscience* **165**, 107–115.

Enomoto T., Tse M. T. and Floresco S. B. 2011 Reducing prefrontal gammaaminobutyric acid activity induces cognitive, behavioral, and dopaminergic abnormalities that resemble schizophrenia. *Biol. Psychiat.* **69**, 432–441.

Evers L. J. M., Curfs L. M., Bakker J. A., Boot E., da Silva Alves F., Abeling N. *et al*. 2014 Serotonergic, noradrenergic and dopaminergic markers are related to cognitive function in adults with 22q11 deletion syndrome. *Int. J. Neuropsychoph.* **17**, 1159–1165.

Fadok J. P., Dickerson T. M. K. and Palmiter R. D. 2009 Dopamine is necessary for cue-dependent fear conditioning. *J. Neurosci.* **29**, 11089–11097.

Fejgin K., Nielsen J., Birknow M. R., Bastlund J. F., Nielsen V., Lauridsen J. B. *et al*. 2014 A mouse model that recapitulates cardinal features of the 15q13.3 microdeletion syndrome including schizophrenia- and epilepsy-related alterations. *Biol. Psychiat.* **76**, 128–137.

Fromer M., Pocklington A. J., Kavanagh D. H., Williams H. J., Dwyer S., Gormley P. *et al*. 2014 De novo mutations in schizophrenia implicate synaptic networks. *Nature* **506**, 179–184.

Glantz L. A. and Lewis D. A. 2000 Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Arch. Gen. Psychiat.* **57**, 65–73.

Golzio C., Willer J., Talkowski M. E., Oh E. C., Taniguchi Y., Jacquemont S. *et al*. 2012 KCTD13 is a major driver of mirrored neuroanatomical phenotypes of the 16p11.2 copy number variant. *Nature* **485**, 363–367.

González-Castro T. B., Hernández-Díaz Y., Juárez-Rojop I. E., López-Narváez M. L., Tovilla-Zárate C. A. and Fresan A. 2016 The role of a catechol-Omethyltransferase (COMT) Val158Met genetic polymorphism in schizophrenia: A systematic review and updated meta-analysis on 32,816 subjects. *Neuromol. Med.* **18**, 216–231.

Gothelf D., Schneider M., Green T., Debbané M., Frisch A., Glaser B. *et al*. 2013 Risk factors and the evolution of psychosis in 22q11.2 deletion syndrome: A longitudinal 2-site study. *J. Am. Acad. Child Psy.* **52**, 1192-1203.e3.

Gothelf D., Law A. J., Frisch A., Chen J., Zarchi O., Michaelovsky E. *et al*. 2014 Biological effects of COMT haplotypes and psychosis risk in 22q11.2 deletion syndrome. *Biol. Psychiat.* **75**, 406–413.

Greer P. L., Hanayama R., Bloodgood B. L., Mardinly A. R., Lipton D. M., Flavell S. W. *et al*. 2010 The Angelman Syndrome protein Ube3A regulates synapse development by ubiquitinating arc. *Cell* **140**, 704–716.

Grozeva D., Conrad D. F., Barnes C. P., Hurles M., Owen M. J., O'Donovan M. C. *et al*. 2012 Independent estimation of the frequency of rare CNVs in the UK population confirms their role in schizophrenia. *Schizophr. Res.* **135**, 1–7.

Gur R. E., Cowell P. E., Latshaw A., Turetsky B. I., Grossman R. I., Arnold S. E. *et al*. 2000 Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. *Arch. Gen. Psychiat.* **57**, 761–768.

Harrison P. J. and Weinberger D. R. 2005 Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol. Psychiatry* **10**, 40–68.

Hashimoto R., Hashimoto H., Shintani N., Chiba S., Hattori S., Okada T. *et al*. 2007 Pituitary adenylate cyclase-activating polypeptide is associated with schizophrenia. *Mol. Psychiatr.* **12**, 1026–1032.

Hilker R., Helenius D., Fagerlund B., Skytthe A., Christensen K., Werge T. M. *et al*. 2018 Heritability of schizophrenia and schizophrenia spectrum based on the nationwide Danish twin register. *Biol. Psychiat.* **83**, 492–498.

Howard M. A., Elias G. M., Elias L. A. B., Swat W. and Nicoll R. A. 2010 The role of SAP97 in synaptic glutamate receptor dynamics. *P. Natl. Acad. Sci. USA* **107**, 3805–3810.

Howes O. D. and Kapur S. 2009 The dopamine hypothesis of schizophrenia: version III–the final common pathway. *Schizophrenia Bull.* **35**, 549–562.

Ikeda M., Aleksic B., Kirov G., Kinoshita Y., Yamanouchi Y., Kitajima T. *et al*. 2010 Copy number variation in schizophrenia in the Japanese population. *Biol. Psychiat.* **67**, 283–286.

Ingason A., Rujescu D., Cichon S., Sigurdsson E., Sigmundsson T., Pietiläinen O. P. H. *et al*. 2011a Copy number variations of chromosome 16p13.1 region associated with schizophrenia. *Mol. Psychiatr.* **16**, 17–25.

Ingason A., Kirov G., Giegling I., Hansen T., Isles A. R., Jakobsen K. D. *et al*. 2011b Maternally derived microduplications at 15q11-q13: Implication of imprinted genes in psychotic illness. *Am. J. Psychiat.* **168**, 408–417.

Institute of health Metrics and Evaluation (IHME) Global Health Data Exchange (GHDx). http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/27a7644e8ad28e739382d31e77589dd7 (Accessed 02 December 2022).

International Schizophrenia Consortium 2008 Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature* **455**, 237–241.

Jagannath V., Gerstenberg M., Correll C. U., Walitza S. and Grünblatt E. 2018 A systematic meta-analysis of the association of Neuregulin 1 (NRG1), D-amino acid oxidase (DAO), and DAO activator (DAOA)/G72 polymorphisms with schizophrenia. *J. Neural. Transm.* **125**, 89–102.

Kimura H., Tanaka S., Kushima I., Koide T., Banno M., Kikuchi T. *et al*. 2015a Association study of BCL9 gene polymorphism rs583583 with schizophrenia and negative symptoms in Japanese population. *Sci. Rep.* **5**, 15705.

Kimura H., Tsuboi D., Wang C., Kushima I., Koide T., Ikeda M. *et al*. 2015b Identification of rare, single-nucleotide mutations in NDE1 and their contributions to schizophrenia susceptibility. *Schizophrenia Bull.* **41**, 744–753.

Kirov G., Gumus D., Chen W., Norton N., Georgieva L., Sari M. *et al*. 2007 Comparative genome hybridization suggests a role for NRXN1 and APBA2 in schizophrenia. *Hum. Mol. Genet.* **17**, 458–465.

Kirov G., Grozeva D., Norton N., Ivanov D., Mantripragada K. K., Holmans P. *et al*. 2009 Support for the involvement of large copy number variants in the pathogenesis of schizophrenia. *Hum. Mol. Genet.* **18**, 1497–1503.

Kirov G., Pocklington A. J., Holmans P., Ivanov D., Ikeda M., Ruderfer D. *et al*. 2012 De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. *Mol. Psychiatr.* **17**, 142–153.

Krystal J. H., Karper L. P., Seibyl J. P., Freeman G. K., Delaney R., Bremner J. D. *et al*. 1994 Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch. Gen. Psychiat.* **51**, 199–214.

Kurtz M. M., Moberg P. J., Gur R. C. and Gur R. E. 2001 Approaches to cognitive remediation of neuropsychological deficits in schizophrenia: A review and meta-analysis. *Neuropsychol. Rev.* **11**, 197–210.

Kusenda M., Vacic V., Malhotra D., Rodgers L., Pavon K., Meth J. *et al*. 2015 The influence of microdeletions and microduplications of 16p11.2 on global transcription profiles. *J. Child Neurol.* **30**, 1947–1953.

Levinson D. F., Duan J., Oh S., Wang K., Sanders A. R., Shi J. *et al*. 2011 Copy number variants in schizophrenia: Confirmation of five previous findings and new evidence for 3q29 microdeletions and VIPR2 duplications. *Am. J. Psychiat.* **168**, 302–316.

Li J., Zhou G., Ji W., Feng G., Zhao Q., Liu J. *et al*. 2011 Common variants in the BCL9 gene conferring risk of schizophrenia. *Arch. Gen. Psychiat.* **68**, 232–240.

Li Z., Chen J., Xu Y., Yi Q., Ji W., Wang P. *et al*. 2016 Genome-wide analysis of the role of copy number variation in schizophrenia risk in Chinese. *Biol. Psychiat.* **80**, 331–337.

Li Z., Chen J., Yu H., He L., Xu Y., Zhang D. *et al*. 2017 Genome-wide association analysis identifies 30 new susceptibility loci for schizophrenia. *Nat. Genet.* **49**, 1576–1583.

Liao H.-M., Chao Y.-L., Huang A.-L., Cheng M.-C., Chen Y.-J., Lee K.-F. *et al*. 2012 Identification and characterization of three inherited genomic copy number variations associated with familial schizophrenia. *Schizophr. Res.* **139**, 229–236.

Lin M., Wang Z.-W. and Zhu X. 2020 FBXO45 is a potential therapeutic target for cancer therapy. *Cell. Death Dis.* **6**, 55.

Lutkenhoff E. S., van Erp T. G., Thomas M. A., Therman S., Manninen M., Huttunen M. O. *et al*. 2010 Proton MRS in twin pairs discordant for schizophrenia. *Mol. Psychiatr.* **15**, 308–318.

Malhotra A., Pinals D. A., Adler C. M., Elman I., Clifton A., Pickar D. *et al*. 1997 Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. *Neuropsychopharmacology* **17**, 141–150.

Marshall C. R., Howrigan D. P., Merico D., Thiruvahindrapuram B., Wu W., Greer D. S. *et al*. 2017 Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. *Nat. Genet.* **49**, 27–35.

McCarthy S. E., Makarov V., Kirov G., Addington A. M., McClellan J., Yoon S. *et al*. 2009 Microduplications of 16p11.2 are associated with schizophrenia. *Nat. Genet.* **41**, 1223–1227.

McDonald-McGinn D. M., Sullivan K. E., Marino B., Philip N., Swillen A., Vorstman J. A. S. *et al*. 2015 22q11.2 deletion syndrome. *Nat. Rev. Dis. Primers* **1**, 1–19.

Mefford H. C., Sharp A. J., Baker C., Itsara A., Jiang Z., Buysse K. *et al*. 2008 Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes. *New Engl. J. Med.* **359**, 1685–1699.

Melhem N., Middleton F., McFadden K., Klei L., Faraone S. V., Vinogradov S. *et al*. 2011 Copy number variants for schizophrenia and related psychotic disorders in Oceanic Palau: risk and transmission in extended pedigrees. *Biol. Psychiat.* **70**, 1115–1121.

Missler M., Zhang W., Rohlmann A., Kattenstroth G., Hammer R. E., Gottmann K. *et al*. 2003 α-Neurexins couple Ca2+ channels to synaptic vesicle exocytosis. *Nature* **423**, 939–948.

Moreno-De-Luca D., SGENE Consortium, Mulle J. G., Simons Simplex Collection Genetics Consortium, Kaminsky E. B., Sanders S. J. *et al.* 2010 Deletion 17q12 is a recurrent copy number variant that confers high risk of autism and schizophrenia. *Am. J. Hum. Genet.* **87**, 618–630.

Mulle J. G. 2015 The 3q29 deletion confers >40-fold increase in risk for schizophrenia. *Mol. Psychiatr.* **20**, 1028–1029.

Mulle J. G., Dodd A. F., McGrath J. A., Wolyniec P. S., Mitchell A. A., Shetty A. C. *et al*. 2010 Microdeletions of 3q29 confer high risk for schizophrenia. *Am. J. Hum. Genet.* **87**, 229–236.

Mulle J. G., Pulver A. E., McGrath J. M., Wolyniec P., Dodd A. F., Cutler D. J. *et al*. 2014 Reciprocal duplication of the Williams-Beuren syndrome deletion on chromosome 7q11.23 is associated with schizophrenia. *Biol. Psychiat.* **75**, 371–377.

Nagy S., Maurer G. W., Hentze J. L., Rose M., Werge T. M. and Rewitz K. 2018 AMPK signaling linked to the schizophrenia-associated 1q21.1 deletion is required for neuronal and sleep maintenance. *PLoS Genet.* **14**, e1007623.

Nakayama A. Y., Harms M. B. and Luo L. 2000 Small GTPases Rac and Rho in the maintenance of dendritic spines and branches in hippocampal pyramidal neurons. *J. Neurosci.* **20**, 5329–5338.

Nebel R. A., Zhao D., Pedrosa E., Kirschen J., Lachman H. M., Zheng D. *et al*. 2016 Reduced CYFIP1 in human neural progenitors results in dysregulation of schizophrenia and epilepsy gene networks. *PLoS One* **11**, e0148039.

Need A. C., Ge D., Weale M. E., Maia J., Feng S., Heinzen E. L. *et al*. 2009 A genome-wide investigation of SNPs and CNVs in schizophrenia. *PLoS Genet.* **5**, e1000373.

Ni X., Valente J., Azevedo M. H., Pato M. T., Pato C. N. and Kennedy J. L. 2007 Connexin 50 gene on human chromosome 1q21 is associated with schizophrenia in matched case control and family-based studies. *J. Med. Genet.* **44**, 532–536.

Noor A., Dupuis L., Mittal K., Lionel A. C., Marshall C. R., Scherer S. W. *et al*. 2015 15q11.2 duplication encompassing only the UBE3A gene is associated with developmental delay and neuropsychiatric phenotypes. *Hum. Mutat.* **36**, 689–693.

Pathania M., Davenport E. C., Muir J., Sheehan D. F., López-Doménech G. and Kittler J. T. 2014 The autism and schizophrenia associated gene CYFIP1 is critical for the maintenance of dendritic complexity and the stabilization of mature spines. *Transl. Psychiat.* **4**, e374.

Pilowsky L. S., Bressan R. A., Stone J. M., Erlandsson K., Mulligan R. S., Krystal J. H. *et al*. 2006 First in vivo evidence of an NMDA receptor deficit in medication-free schizophrenic patients. *Mol. Psychiatr.* **11**, 118–119.

Purcell S. M., Moran J. L., Fromer M., Ruderfer D., Solovieff N., Roussos P. *et al*. 2014 A polygenic burden of rare disruptive mutations in schizophrenia. *Nature* **506**, 185–190.

Rees E., Walters J. T. R., Georgieva L., Isles A. R., Chambert K. D., Richards A. L. *et al*. 2014 Analysis of copy number variations at 15 schizophrenia-associated loci. *Brit. J. Psychiat.* **204**, 108–114.

Ripke S., O'Dushlaine C., Chambert K., Moran J. L., Kähler A. K., Akterin S. *et al*. 2013 Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat. Genet.* **45**, 1150–1159.

Rogdaki M., Jauhar S., McCutcheon R. and Howes O. 2016 Treatment-resistant schizophrenia in a patient with 17q12 duplication. *Biol. Psychiat.* **80**, e19–e20.

Rouach N., Avignone E., Même W., Koulakoff A., Venance L., Blomstrand F. *et al*. 2002 Gap junctions and connexin expression in the normal and pathological central nervous system. *Biol. Cell* **94**, 457–475.

Rujescu D., Ingason A., Cichon S., Pietiläinen O. P. H., Barnes M. R., Toulopoulou T. *et al*. 2009 Disruption of the neurexin 1 gene is associated with schizophrenia. *Hum. Mol. Genet.* **18**, 988–996.

Saini S. M., Mancuso S. G., Mostaid M. S., Liu C., Pantelis C., Everall I. P. *et al*. 2017 Meta-analysis supports GWAS-

implicated link between GRM3 and schizophrenia risk. *Transl. Psychiat.* **7**, e1196.
Salminen I., Read S., Hurd P. and Crespi B. 2019 Genetic variation of UBE3A is associated with schizotypy in a population of typical individuals. *Psychiat. Res.* **275**, 94–99.
Saxena S., Kkani P., Ramasubramanian C., Kumar S. G., Monisha R., Prasad Rao G. *et al*. 2019 Analysis of 15q11.2 CNVs in an Indian population with schizophrenia. *Ann. Hum. Genet.* **83**, 187–191.
Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014 Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421–427.
Schmidt M. J. and Mirnics K. 2015 Neurodevelopment, GABA System Dysfunction, and Schizophrenia. *Neuropsychopharmacology* **40**, 190–206.
Schneider M., Debbané M., Bassett A. S., Chow E. W., Fung W. L. A., van den Bree M. B. *et al*. 2014 Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: Results from the International Consortium on Brain and Behavior in 22q11.2 deletion syndrome. *Am. J. Psychiat.* **171**, 627–639.
Schosser A., Fuchs K., Leisch F., Bailer U., Meszaros K., Lenzinger E. *et al*. 2004 Possible linkage of schizophrenia and bipolar affective disorder to chromosome 3q29: A follow-up. *J. Psychiat. Res.* **38**, 357–364.
Shawlot W. and Behringer R. R. 1995 Requirement for LIml in head-organizer function. *Nature* **374**, 425–430.
Sheward W. J., Lutz E. M. and Harmar A. J. 1995 The distribution of vasoactive intestinal peptide2 receptor messenger RNA in the rat brain and pituitary gland as assessed by in situ hybridization. *Neuroscience* **67**, 409–418.
Shin E.-Y., Shim E.-S., Lee C.-S., Kim H. K. and Kim E.-G. 2009 Phosphorylation of RhoGDI1 by p21-activated kinase 2 mediates basic fibroblast growth factor-stimulated neurite outgrowth in PC12 cells. *Biochem. Bioph. Res.* **379**, 384–389.
Shinawi M., Liu P., Kang S.-H.L., Shen J., Belmont J. W., Scott D. A. *et al*. 2010 Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioural problems, dysmorphism, epilepsy, and abnormal head size. *J. Med. Genet.* **47**, 332–341.
Skudlarski P., Jagannathan K., Anderson K., Stevens M. C., Calhoun V. D., Skudlarska B. A. *et al*. 2010 Brain connectivity is not only lower but different in schizophrenia: A combined anatomical and functional approach. *Biol. Psychiat.* **68**, 61–69.
Stefansson H., Rujescu D., Cichon S., Pietiläinen O. P. H., Ingason A., Steinberg S. *et al*. 2008 Large recurrent microdeletions associated with schizophrenia. *Nature* **455**, 232–236.
Steinberg S., de Jong S., Mattheisen M., Costas J., Demontis D., Jamain S. *et al*. 2014 Common variant at 16p11.2 conferring risk of psychosis. *Mol. Psychiatr.* **19**, 108–114.
Stewart L. R., Hall A. L., Kang S.-H.L., Shaw C. A. and Beaudet A. L. 2011 High frequency of known copy number abnormalities and maternal duplication 15q11-q13 in patients with combined schizophrenia and epilepsy. *BMC Med. Genet.* **12**, 154.
Stone J. M. 2011 Glutamatergic antipsychotic drugs: a new dawn in the treatment of schizophrenia? *Therap. Adv. Psychopharmacol.* **1**, 5–18.
Sweet R. A., Henteleff R. A., Zhang W., Sampson A. R. and Lewis D. A. 2009 Reduced dendritic spine density in auditory cortex of subjects with schizophrenia. *Neuropsychopharmacology* **34**, 374–389.
Szatkiewicz J. P., O'Dushlaine C., Chen G., Chambert K., Moran J. L., Neale B. M. *et al*. 2014 Copy number variation in schizophrenia in Sweden. *Mol. Psychiatr.* **19**, 762–773.
Tandon N., Bolo N. R., Sanghavi K., Mathew I. T., Francis A. N., Stanley J. A. *et al*. 2013a Brain metabolite alterations in young adults at familial high risk for schizophrenia using proton magnetic resonance spectroscopy. *Schizophr. Res.* **148**, 59–66.
Tandon R., Gaebel W., Barch D. M., Bustillo J., Gur R. E., Heckers S. *et al*. 2013b Definition and description of schizophrenia in the DSM-5. *Schizophr. Res.* **150**, 3–10.
Tebartz van Elst L., Valerius G., Büchert M., Thiel T., Rüsch N., Bubl E. *et al*. 2005 Increased prefrontal and hippocampal glutamate concentration in schizophrenia: Evidence from a magnetic resonance spectroscopy study. *Biol. Psychiat.* **58**, 724–730.
Thelin J., Halje P., Nielsen J., Didriksen M., Petersson P. and Bastlund J. F. 2016 The translationally relevant mouse model of the 15q13.3 microdeletion syndrome reveals deficits in neuronal spike firing matching clinical neurophysiological biomarkers seen in schizophrenia. *Acta Physiol.* **220**, 124–136.
Toyooka K., Iritani S., Makifuchi T., Shirakawa O., Kitamura N., Maeda K. *et al*. 2002 Selective reduction of a PDZ protein, SAP-97, in the prefrontal cortex of patients with chronic schizophrenia. *J. Neurochem.* **83**, 797–806.
Uddin M., Unda B. K., Kwan V., Holzapfel N. T., White S. H., Chalil L. *et al*. 2018 OTUD7A regulates neurodevelopmental phenotypes in the 15q13.3 microdeletion syndrome. *Am. J. Hum. Genet.* **102**, 278–295.
Vacic V., McCarthy S., Malhotra D., Murray F., Chou H.-H., Peoples A. *et al*. 2011 Duplications of the neuropeptide receptor gene VIPR2 confer significant risk for schizophrenia. *Nature* **471**, 499–503.
Walsh T., McClellan J. M., McCarthy S. E., Addington A. M., Pierce S. B., Cooper G. M. *et al*. 2008 Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science* **320**, 539–543.
Wang Q., Su T.-P., Zhou Y., Chou K.-H., Chen I.-Y., Jiang T. *et al*. 2012 Anatomical insights into disrupted small-world networks in schizophrenia. *NeuroImage* **59**, 1085–1093.
Wang H.-Y., Liu Y., Yan J.-W., Hu X.-L., Zhu D.-M., Xu X.-T. *et al*. 2018 Gene polymorphisms of DISC1 is associated with schizophrenia: Evidence from a meta-analysis. *Prog. Neuro-Psychoph.* **81**, 64–73.
World Health Organization. 1992 The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/37958/9241544228_eng.pdf?sequence=8&isAllowed=y.
Xu C., Aragam N., Li X., Villla E. C., Wang L., Briones D. *et al*. 2013 BCL9 and C9orf5 are associated with negative symptoms in schizophrenia: Meta-analysis of two genome-wide association studies. *PLoS One* **8**, e51674.
Yuan J., Jin C., Sha W., Zhou Z., Zhang F., Wang M. *et al*. 2014 A competitive PCR assay confirms the association of a copy number variation in the VIPR2 gene with schizophrenia in Han Chinese. *Schizophr. Res.* **156**, 66–70.
Yung A. R. and McGorry P. D. 1996 The prodromal phase of first-episode psychosis: past and current conceptualizations. *Schizophrenia Bull.* **22**, 353–370.
Zhou W., Shi Y., Li F., Wu X., Huai C., Shen L. *et al*. 2018 Study of the association between Schizophrenia and microduplication at the 16p11.2 locus in the Han Chinese population. *Psychiat. Res.* **265**, 198–199.
Zhou W., Zhang L., Guoxiang X., Mojsilovic-Petrovic J., Takamaya K., Sattler R. *et al*. 2008 GluR1 controls dendrite growth through its binding partner, SAP97. *J. Neurosci.* **28**, 10220–10233.

Corresponding editor: Ashwin Dalal