

# Genetic variability in scaffolding proteins and risk for schizophrenia and autism-spectrum disorders: a systematic review

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Scaffolding proteins represent an evolutionary solution to controlling the specificity of information transfer in intracellular networks. They are highly concentrated in complexes located in specific subcellular locations. One of these complexes is the postsynaptic density of the excitatory synapses. There, scaffolding proteins regulate various processes related to synaptic plasticity, such as glutamate receptor trafficking and signalling, and dendritic structure and function. Most scaffolding proteins can be grouped into 4 main families: discs large (DLG), discs-large-associated protein (DLGAP), Shank and Homer. Owing to the importance of scaffolding proteins in postsynaptic density architecture, it is not surprising that variants in the genes that code for these proteins have been associated with neuropsychiatric diagnoses, including schizophrenia and autism-spectrum disorders. Such evidence, together with the clinical, neurobiological and genetic overlap described between schizophrenia and autism-spectrum disorders, suggest that alteration of scaffolding protein dynamics could be part of the pathophysiology of both. However, despite the potential importance of scaffolding proteins in these psychiatric conditions, no systematic review has integrated the genetic and molecular data from studies conducted in the last decade. This review has the following goals: to systematically analyze the literature in which common and/or rare genetic variants (single nucleotide polymorphisms, single nucleotide variants and copy number variants) in the scaffolding family genes are associated with the risk for either schizophrenia or autism-spectrum disorders; to explore the implications of the reported genetic variants for gene expression and/or protein function; and to discuss the relationship of these genetic variants to the shared genetic, clinical and cognitive traits of schizophrenia and autism-spectrum disorders.

## Introduction

Schizophrenia and autism-spectrum disorders are neurodevelopmental psychiatric disorders that have a prevalence of approximately 1% and 2.5% worldwide, respectively,<sup>1,2</sup> and have profound human and economic consequences.

Schizophrenia and autism-spectrum disorders were nosologically separated in the *Diagnostic and Statistical Manual Mental Disorders*, third edition (1980).<sup>3</sup> However, evidence has been accumulating to suggest that they may partially overlap in their clinical, neurobiological, behavioural and cognitive features, and that they may have some common etiological roots.<sup>4</sup> Regarding their clinical expression, some authors have proposed that the negative symptoms of schizophrenia can be construed more broadly as deficits in social communication and motivation, which are also found in people with autism-spectrum disorders.<sup>5</sup> Similarly, the grossly disorgan-

ized or abnormal motor behaviour described in schizophrenia includes a number of signs and symptoms consistent with those of autism-spectrum disorders, such as repeated stereotyped movements, echolalia, unpredictable agitation and decreased interaction with or interest in one's environment.<sup>5,6</sup> The disorders also share some cognitive deficits<sup>7-9</sup>; in particular, deficits in social cognition have received much attention.<sup>10-15</sup> As well, there are brain structural similarities between these disorders. For instance, lower grey matter volume in the limbic-striato-thalamic circuitry is common to schizophrenia and autism-spectrum disorders,<sup>16</sup> and reduced volume and thickness of the insula have been found in patients with first-episode psychosis and in high-functioning patients with autism-spectrum disorders.<sup>17</sup> Similar alterations to the white matter integrity of the left fronto-occipital fasciculus have recently been found in patients with schizophrenia and in patients with autism-spectrum disorders.<sup>18</sup>

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In recent years, the field of molecular genetics has been uncovering evidence of an overlapping and complex polygenic architecture for these disorders. Evidence suggests that studying pathways common to both may shed light on their pathophysiology and clinical heterogeneity.

Robust longitudinal and epidemiological studies have shown that 25% of people with childhood-onset schizophrenia have a history of a premorbid autism-spectrum disorder<sup>19</sup>; that the adult outcomes of children with atypical autism include psychotic disorders<sup>20</sup>; that autistic traits in infancy increase the risk for psychotic experiences later in life<sup>21</sup>; and that there is some co-occurrence of autism-spectrum disorders and psychotic disorders.<sup>22,23</sup> This overlap is further supported by family studies, which have reported that the presence of one of these diagnoses in a first-degree relative increases the risk of the other.<sup>24–27</sup> Similarly, schizophrenia is more common in parents of patients with autism than in parents of healthy controls.<sup>24</sup>

Twin studies have also recognized the important contribution of genetic factors to both schizophrenia and autism-spectrum disorders, with heritability estimates of  $h^2 = 64\%$ – $80\%$ <sup>28,29</sup> and  $h^2 = 64\%$ – $91\%$ ,<sup>30</sup> respectively.

Over the last decade, molecular studies have contributed to our initial understanding of the complex genetic architecture of schizophrenia and autism-spectrum disorders, and later to identifying genes that are involved in both disorders. In this sense, it is currently accepted that an individual's genetic risk of schizophrenia or an autism-spectrum disorder can be attributed to either many common variants with a frequency of  $> 1\%$  (single nucleotide polymorphisms [SNPs]), each conferring a modest level of risk (odds ratio = 1.1–1.5); or rare mutations with a frequency of  $< 1\%$  (single nucleotide variants [SNVs] and copy number variants [CNVs]) that are usually associated with a larger penetrance on the phenotype (odds ratio  $> 2$ ).<sup>31,32</sup>

The most recent studies to examine genome-wide SNPs contributing to these disorders have estimated that genetic variation from SNPs accounts for 23% and 17% of the variance in risk of schizophrenia and autism-spectrum disorders, respectively.<sup>33</sup> Based on the significant but small correlation between SNP heritability estimates in both disorders, the co-heritability between them has been quantified at around 4%.<sup>33</sup> In this regard, genome-wide association studies have identified several SNPs associated with schizophrenia and/or autism-spectrum disorders.<sup>34–37</sup>

Meanwhile, genome-wide and microarray-based comparative genomic hybridizations have found that the CNV burden is also increased in patients with schizophrenia or autism-spectrum disorders compared with healthy controls.<sup>38–41</sup> For example, microduplications of 1q21.1 or 16p11.2 and deletions at 2p16.3, 15q11.2 or 22q11.21 have been reported in patients with schizophrenia and autism-spectrum disorders.<sup>42</sup> De novo gene-disrupting SNVs have also been found to occur at higher rates in patients with autism-spectrum disorders than in controls.<sup>43–46</sup> In schizophrenia, the initially reported increased rates of putatively functional mutations<sup>47,48</sup> have not been replicated in 2 larger studies,<sup>49,50</sup> but those later studies found that the enrichment of loss-of-

function de novo mutations was relatively concentrated in genes that overlapped with those affected by de novo mutations in autism-spectrum disorders. In addition, an excess of de novo mutation was confirmed in an independent sample of patients with schizophrenia.<sup>51</sup>

With regard to the identification of specific genes involved in both schizophrenia and autism-spectrum disorders, findings from CNV and SNV studies have shown a notable consistency in some functionally enriched sets of genes. Genetic studies assessing common or rare variants show a certain convergence on reporting genes involved in glutamatergic synapse plasticity.<sup>49,52–55</sup> A structure located in glutamatergic synapses that has been associated with both disorders is the postsynaptic density (PSD).<sup>50,56–61</sup> For example, Bayés and colleagues found that mutations in 199 human PSD genes were involved in more than 200 diseases, half being nervous-system disorders.<sup>61</sup> That study suggested that impairments in PSD proteins might underlie psychiatric disorders and their associated cognitive, behavioural and clinical phenotypes, but no systematic review based on this hypothesis has integrated the molecular data generated across studies in the last decade. Another example has been provided by Purcell and colleagues, who, after analyzing the exome sequences of 2536 patients with schizophrenia and 2543 controls, reported that SNVs were significantly more frequent in cases than controls, and that these SNVs were especially enriched in the activity-regulated cytoskeleton-associated (ARC) complex of PSD.<sup>50</sup>

#### *PSD proteins and pathophysiological hypotheses*

The PSD is a specialized matrix located at the excitatory postsynaptic terminals with a dish-shaped aspect, a surface area of  $0.07 \mu\text{m}^2$  and a thickness of 30 to 40 nm on electron microscopy (Fig. 1A).<sup>62</sup> The PSD can also be described as a highly organized and dynamic macromolecular complex consisting of several hundred proteins that process, integrate and converge the excitatory glutamatergic synaptic signals on the nucleus. As a point of convergence for the glutamatergic signalling pathways with other neurotransmitter systems, the composition and regulation of the PSD is essential for ensuring normal synaptic neurotransmission and plasticity.<sup>63,64</sup>

The PSD is enriched with different membrane components, such as glutamate receptors, tyrosine kinases, G protein-coupled receptors, ion channels or cell adhesion molecules, which are assembled by cytoplasmatic scaffolding proteins.<sup>65</sup> Among the proteins that make up the PSD, studies have reported associations between genes coding for scaffolding proteins and both schizophrenia and autism-spectrum disorders, suggesting that variants in these genes might increase the risk of these disorders. For instance, recent studies have found that SNPs and CNVs in autism-spectrum disorders and schizophrenia are particularly concentrated in scaffolding genes and other PSD-related genes.<sup>66,67</sup> Other studies have indicated changes in the expression of scaffolding genes in schizophrenia and autism-spectrum disorders compared with healthy controls.<sup>68,69</sup> A recent study reported that gene-disrupting ultra-rare variants were more abundant in schizophrenia cases than in controls, and that these mutations were

particularly enriched in scaffolding genes and other PSD genes.<sup>70</sup>

Scaffolding proteins can be defined as molecular circuit boards that can organize a wide variety of circuit relationships between signalling proteins. More specifically, the main function of scaffolding proteins is to bring together 2 or more proteins to facilitate their interaction and functions, linked to critical roles in cellular signalling. This is possible because scaffolding proteins are composed of several protein–protein interaction modules, most notably the PSD-95/discs large/zona occludens-1 (PDZ) and Src homology 3 (SH3) domains.<sup>71</sup> Since scaffolding protein complexes are dynamic, they have the ability to change specific protein interactions to rapidly adapt to changing environmental requirements or diverse signalling cues.<sup>72</sup> This versatility is related to their modularity, which allows for recombination of protein interaction domains to generate variability in signalling pathways. Such properties are seen as a simple evolutionary solution to controlling the specificity of information flow in intracellular networks, generating precise signalling behaviours.<sup>73</sup>

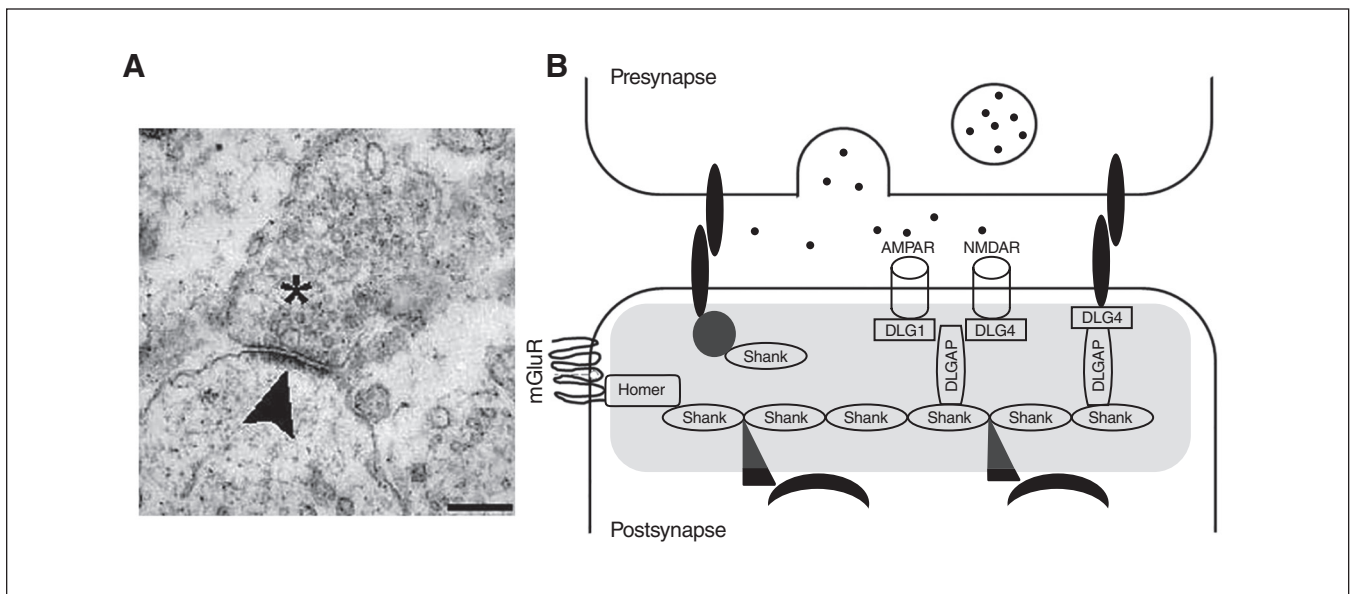
Owing to their dynamic configuration, postsynaptic scaffolding molecules not only establish the internal organization of the PSD, allowing neurons to respond efficiently to stimuli, but they also regulate processes related to synaptic plasticity, such as glutamate receptor trafficking and signalling, and dendritic structure and function,<sup>74,75</sup> which critically determine the characteristics of excitatory synaptic transmission (Fig. 1B).

Disruption of scaffolding genes might alter the homeostasis of the PSD and contribute to the synaptic dysfunctions associated with schizophrenia and autism-spectrum disorders.<sup>76</sup> However, despite the potential importance of scaffolding proteins in these psychiatric conditions, no systematic review has addressed the integration of genetic and molecular data generated across studies.

The nature and function of the different families of scaffolding proteins included in this review, and the characteristics of the genes encoding them, are shown in Figure 1 and briefly summarized below.

### The discs large protein subfamily

The discs large (DLG) subfamily is a group of proteins in the membrane-associated guanylate kinase (MAGUK) family, and consists of DLG1, DLG2, DLG3 and DLG4. These proteins have 3 PDZ domains in their N-terminus, which allow them to interact with a variety of binding partners in the PSD, such as glutamatergic receptors, as well as other cytoplasmic scaffolding proteins. The DLG proteins control the transmission of extracellular signals to downstream signalling molecules of the PSD and regulate the localization of glutamatergic receptors *N*-methyl-D-aspartate (NMDA) and  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) at neuronal synapses and dendrites.<sup>77</sup> Moreover, they regulate the trafficking and clustering of ionic channels and the excitability of the presynaptic terminals, affecting the amount of neurotransmitter released.<sup>78</sup> Since their temporal



**Fig. 1:** Image of the postsynaptic density (PSD) and scheme of the scaffolding proteins at the PSD that have been analyzed in the present review. **(A)** An electron microscope image of a synapse; vesicles can be observed in the presynaptic neuron (asterisk). The electron-dense structure observed in the postsynaptic element is the PSD (arrowhead). Scale bar, 250 nm. Image retrieved under the Creative Commons Attribution License from Heupel et al. *Neural Devel* 2008, <https://doi.org/10.1186/1749-8104-3-25>. **(B)** A scheme of the PSD (grey shading). Multimerization of Shank1 to 3 proteins generate a network that links numerous proteins to the postsynaptic receptors. Homer proteins, including Homer1b/c, Homer2 and Homer3, also act as adaptors and interact with several PSD proteins, such as type I-mGluRs. The DLGAP1 to 4 proteins interact with DLG proteins, including the DLG1/SAP-97, DLG2/PSD-93, DLG3/SAP-102 and DLG4/PSD-95, to coregulate different ion channels, such as the NMDAR and AMPAR. AMPAR =  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; DLG = discs large; DLGAP = discs-large-associated protein; mGluR = metabotropic glutamate receptor; NMDAR = *N*-methyl-D-aspartate receptor; SAP = synapse-associated protein.

and spatial expression differ, it is believed that DLG members complement each other in performing these functions from embryonic to adult stages.<sup>79</sup>

The *DLG1* gene (also known as SAP-97) maps on chromosome 3q29 and encodes the synapse-associated protein 97 (SAP-97 or DLG1), which is thought to play a role in synaptogenesis<sup>80</sup> and glutamatergic receptor trafficking during development.<sup>77</sup>

The *DLG2* gene (also known as PSD-93) is located on chromosome 11q14.1. Different studies have suggested that the protein it encodes (PSD-93, DLG2) plays a role in the regulation of synaptic plasticity. The DLG2 protein interacts with the tyrosine kinase Fyn, which is involved in the phosphorylation-based regulation of NMDA receptors that is required for the induction of NMDA-receptor-dependent long-term potentiation.<sup>81</sup>

The *DLG3* gene (also known as SAP-102) is located on Xq13.1, and the protein it encodes (DLG3) is the first protein related to intellectual disability that has been directly linked to glutamate receptor signalling and trafficking.<sup>82</sup> Later studies have replicated the association of this gene with intellectual disability,<sup>83,84</sup> suggesting that DLG3 somehow modulates cognition. This is consistent with the observed embryonic expression of this protein and its role in the regulation of synaptic formation and plasticity during brain development.<sup>85</sup>

The *DLG4* gene is located on chromosome 17p13.1, and the protein it encodes (PSD-95, DLG4) is involved in the maturation of synapse formation and the NMDA receptor signalling pathway. It participates in the clustering and trafficking of NMDA and AMPA receptors in the PSD.<sup>63,79</sup> Moreover, DLG4 interacts with the dopamine receptor D1 (DRD1) and the NMDA receptor, and regulates positive feedback between them.<sup>86</sup> The degradation of DLG4 is regulated by other proteins that have also been associated with autism-spectrum disorders.<sup>87</sup>

### The discs-large-associated protein family

The discs-large-associated protein (DLGAP) family is made up of 4 proteins encoded by different homonymous genes: *DLGAP1* (18p11), *DLGAP2* (8p23), *DLGAP3* (1p34), and *DLGAP4* (20q11). All proteins have 5 repeats of 14 amino acids in the middle region, followed by a proline-rich sequence and a C-terminal PDZ-binding motif that mediate interactions with other PSD proteins.<sup>88</sup>

Although the differential roles of each family member are unknown, all DLGAP proteins play an important role in organizing the postsynaptic signalling complex in glutamatergic synapses,<sup>89</sup> and are especially involved in the stabilization of synaptic junctions and regulation of neurotransmission.<sup>90</sup> In addition, DLGAP proteins clearly have a central role in the regulation of synaptic ion channels, including both NMDA and AMPA receptors.<sup>91</sup>

DLGAP2 (also known as SAPAP2 or GKAP) is the most studied of the proteins in this family. It interacts directly with DLG4 and Shank proteins to form a complex that plays critical roles in synaptic morphogenesis and function.<sup>90,92</sup>

It has been proposed that SAPAP proteins provide a link between the PSD-95 family of proteins and the actin-cytoskeleton

through interactions with the Shank/ProSAP proteins, which in turn bind the actin-binding protein cortactin.<sup>93–97</sup> Additionally, Shank/ProSAP binds to Homer, which interacts with metabotropic glutamate receptors.<sup>98</sup> Therefore, in the current scaffolding model, PSD-95/SAPAP/Shank interactions play an important role in organizing the large postsynaptic signalling complex at glutamatergic synapses.<sup>96,97,99,100</sup>

### The Shank protein family

Another PSD scaffolding protein group is the SH3 and multiple ankyrin repeat domains (Shank) family, which consists of 3 proteins encoded by different genes that are differentially expressed in the brain<sup>97,101</sup>: *SHANK1* (19q13.33), *SHANK2* (11q13.3) and *SHANK3* (22q13.3). So far, it is unclear whether individual Shank family proteins fulfill unique physiologic functions, but the structural similarity between Shank forms has led to the observation that many interaction partners of Shank proteins in the synapse are recognized equally by all 3 family members.<sup>93</sup>

In this regard, Shank proteins crosslink Homer, DLGAP2 and DLG4 proteins in the PSD and participate in glutamatergic downstream signalling by assembling glutamate receptors with other scaffolding proteins, cytoskeleton factors and intracellular effectors.<sup>102</sup> Multimerization of Shank1–3 proteins can generate a network in the PSD that links numerous proteins to the postsynaptic receptors. In addition, Shank proteins promote the formation, maturation and enlargement of dendritic spines.<sup>103</sup>

### The Homer protein family

Homer proteins include 3 different members that are encoded by 3 different homonymous genes: *HOMER1* (5q14), *HOMER2* (15q25) and *HOMER3* (19p13). Homer proteins can also be classified into constitutively expressed isoforms (i.e., Homer1b/c, Homer2 and Homer3), which are bimodal proteins with an N-terminal domain that mediates the interaction with other PSD proteins, and a C-terminal coiled-coil domain that enables self-assembly, as well as short splice variants (Homer1a and Ania-3) that lack the C-terminal domain and cannot self-assemble.<sup>104</sup> The various protein forms are differentially expressed over time and place.<sup>105</sup>

Homer proteins act as multimodal adaptors by interacting with several PSD proteins, such as type I metabotropic glutamate receptors (mGluR1–5), Shank proteins or synaptic signalling molecules such as inositol 1,4,5-triphosphate receptors (IP3Rs), and binding them to the cytoskeleton.<sup>102</sup> Homer proteins are also involved in glutamatergic synapses by regulating glutamatergic receptor trafficking, the function of plasma membrane ion channels and intracellular messenger systems.<sup>106</sup> For these reasons, Homer proteins are important for cell signalling, cell excitability, synaptic neurotransmission and neuronal plasticity.<sup>107,108</sup>

### Objectives

The objectives of this review were as follows: to conduct a systematic review of the literature in which variations within the above-mentioned scaffolding genes are associated

with either schizophrenia or autism-spectrum disorders, and to describe the degree of overlap between both diagnoses; to explore whether the reported genetic variants putatively associated with schizophrenia or autism-spectrum disorders are involved in changes of gene expression or protein functionality according to basic research data; and to consider the implications of the reported associations for the development of these disorders and their associated phenotypes.

## Methods

We conducted a systematic search of the PubMed, PsycINFO and Web of Science databases. The search terms were “Schizophrenia or autism” and “postsynaptic density proteins or PSD or scaffold\* proteins” without date restrictions. Inclusion criteria were original articles that reported i) the association of genetic variants (SNPs, SNVs and CNVs) of the genes in the DLG protein subfamily or the DLGAP, Shank or Homer protein families with schizophrenia or autism-spectrum disorders; and ii) genetic variations in these genes and their functional consequences, based on animal-model or in vitro studies.

This search initially retrieved 366 articles. After evaluating whether they fulfilled the inclusion criteria, we excluded 261 articles. Another 25 studies and reviews that were relevant for the topic were found from cross-referencing and

included in this review. The final pool of articles comprised 130 papers (Fig. 2).

## Results

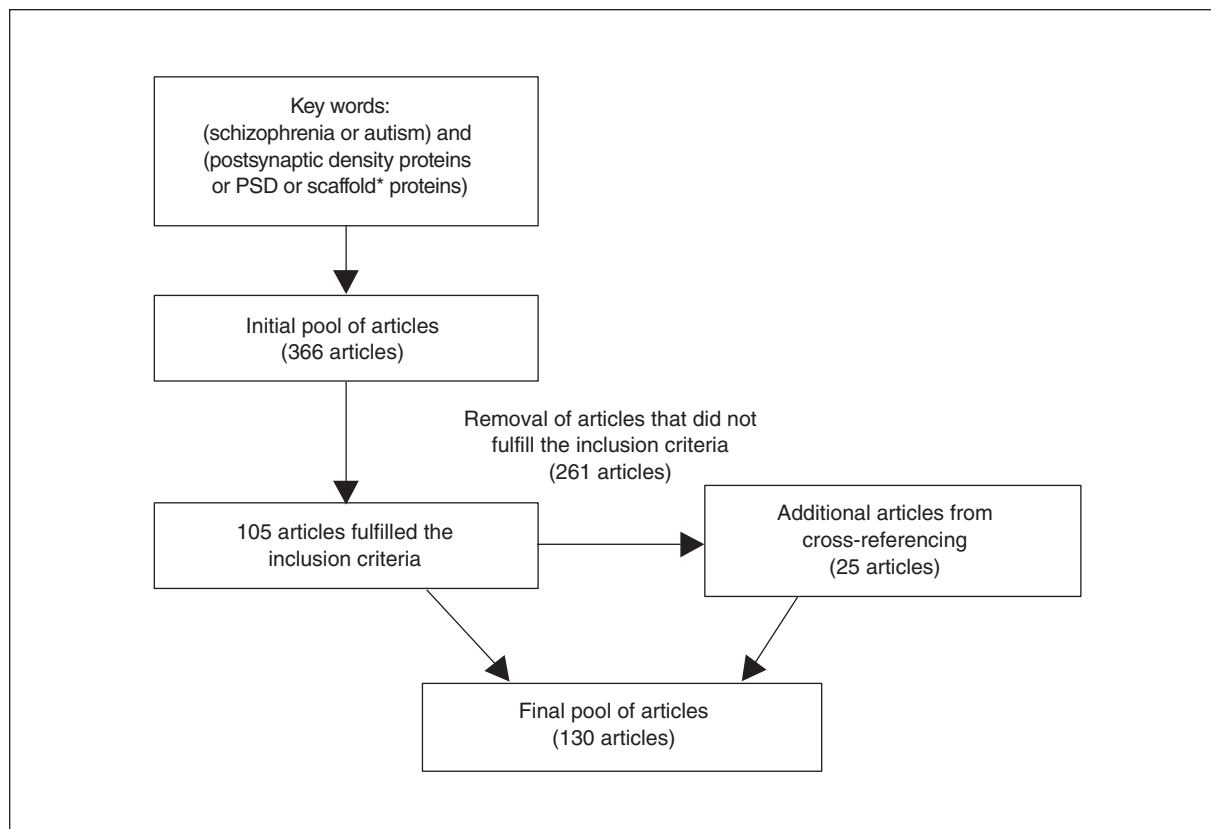
Table 1 describes SNPs in scaffolding genes that have been associated with schizophrenia or autism-spectrum disorders. Table 2 describes SNVs, and Table 3 describes CNVs. Table 4 describes expression and functional information on scaffolding genes obtained from basic studies. Table 5 describes the SNPs, SNVs and CNVs of risk that are shared by both schizophrenia and autism-spectrum disorders.

### *DLG protein subfamily*

#### **Protein DLG1**

Both SNPs in *DLG1* have been associated with schizophrenia (Table 1). An SNV has been associated with autism-spectrum disorders (Table 2). Furthermore, deletions of the chromosomal region 3q29 have been related to schizophrenia and autism-spectrum disorders (Table 3) and have been associated with impaired cognition and social dysfunction (Table 3).

Two studies reported reduced expression of *DLG1* in the prefrontal cortex of postmortem brain samples of patients with schizophrenia (Table 4). To the best of our knowledge, there are no expression studies in autism-spectrum disorders samples.



**Fig. 2:** Flow diagram of the literature search. PSD = postsynaptic density.

An animal-model study reported that glutamate-receptor NMDA antagonists upregulate *DLG1* mRNA expression in the cerebral cortex of mice (Table 4).

### Protein DLG2

Different studies have identified rare mutations in the *DLG2* gene in schizophrenia and autism-spectrum disorders. While SNVs have been detected only in schizophrenia (Table 2), CNVs have been identified in both disorders (Table 3). Interestingly, a deletion identified in intron 6 of the gene in patients with autism-spectrum disorders<sup>157</sup> partially overlaps with another deletion spanning from intron 2 to intron 6 in patients with schizophrenia.<sup>57</sup>

Although still not tested in patients with autism-spectrum disorders, alterations in mRNA and protein expression have been reported in the prefrontal cortex of postmortem brain samples of patients with schizophrenia (Table 4).

Animal-model studies seem to support the function of DLG2 as a regulator of synaptic plasticity; they have shown

that *DLG2* mutant mice display cognitive abnormalities and long-term potentiation deficits (Table 4).

### Protein DLG3

To our knowledge, only 1 genetic study has associated 6 intronic SNPs in *DLG3* with autism-spectrum disorders (Table 1), although their consequences for protein function or expression are unknown.

Despite conflicting results in postmortem brain expression studies, it seems that alterations in *DLG3* could underlie the neurobiology of schizophrenia. In this regard, both increased and decreased *DLG3* mRNA and protein expression have been reported in the thalamus of schizophrenia patients (Table 4).

Animal-model studies support a role for this gene in cognition; mice lacking *DLG3* exhibit impaired learning (Table 4).

### Protein DLG4

For the *DLG4* gene, SNPs (Table 1) and CNVs (Table 3) have been identified only in patients with schizophrenia and with

**Table 1: Single nucleotide polymorphisms in scaffolding genes associated with schizophrenia, autism-spectrum disorders and other clinical phenotypes of interest**

Gene	Single nucleotide polymorphisms				Sources
	Schizophrenia	Autism-spectrum disorders	Schizophrenia and autism-spectrum disorders	Other associated phenotypes	
<i>DLG1</i>	rs382579, rs2122824, rs7616588, rs7638423, rs6805929, rs2044862, rs4916461, rs338187, rs10489880 <sup>109</sup> , rs9843659 <sup>109,110</sup>	—	—	—	Sato et al. <sup>109</sup> Uezato et al. <sup>110</sup>
<i>DLG3</i>	—	ss104807047, rs28391150, rs1886890, rs3215810, rs41303736, ss104807048 <sup>111</sup>	—	rs28391150 (associated with intellectual disability) <sup>83</sup> ss104807047 (associated with intellectual disability) <sup>84</sup>	Zanni et al. <sup>83</sup> Philips et al. <sup>84</sup> Kantofjärvi et al. <sup>111</sup>
<i>DLG4</i>	rs2230178, rs6145976, rs2017365, rs739669, rs13333 <sup>112</sup> , rs222837 <sup>113</sup> , rs390200, rs222853, rs17203281 <sup>112,113</sup>	—	—	—	Cheng et al. <sup>112</sup> Balan et al. <sup>113</sup>
<i>DLGAP1</i>	rs145691437, rs3786431, rs201567254, rs3745051, rs11662259 <sup>114</sup>	—	—	—	Li et al. <sup>114</sup>
<i>DLGAP2</i>	rs2906568, rs2293909 <sup>116</sup>	—	rs2906569, rs2301963 <sup>115,116</sup>	rs2301963 (associated with decreased orbitofrontal cortex white matter volume) <sup>117</sup>	Chien et al. <sup>115</sup> Li et al. <sup>116</sup> Wu et al. <sup>117</sup>
<i>SHANK3</i>	—	rs9616915 <sup>118,119</sup> Independent studies did not find association with autism spectrum disorder <sup>120,121</sup>	—	—	Shao et al. <sup>118</sup> Mashayekhi <sup>119</sup> Sykes et al. <sup>120</sup> Qin et al. <sup>121</sup>
<i>HOMER1</i>	rs4704560, rs2290639 <sup>122</sup> , rs9293785 <sup>123</sup>	—	—	rs4704560 C allele (associated with hallucinations in patients with Parkinson's disease) <sup>124</sup> rs2290639 (associated with substance abuse) <sup>125</sup>	Spellmann et al. <sup>122</sup> Zhao et al. <sup>123</sup> De Luca et al. <sup>124</sup> Strauss et al. <sup>125</sup>
<i>HOMER2</i>	rs2306428, rs86949, SNP20 <sup>126</sup>	—	—	—	Gilks et al. <sup>126</sup>

SNP = single nucleotide polymorphism.

autism-spectrum disorders, respectively. In contrast, SNVs have been associated with both disorders (Table 2).

Among these variants, the SNP rs13331 (T/C), located at the 3'UTR of the gene, is especially interesting because the T allele was first associated with schizophrenia, and a posterior reporter gene assay indicated that subjects carrying this allele had decreased DLG4 protein activity. Based on these results, the authors suggested that reduced DLG4 activity or expression may increase the risk of developing schizophrenia.<sup>112</sup>

Alterations in mRNA and protein expression have been reported in postmortem brain samples of patients with schizophrenia (Table 4), although the direction of the results is inconsistent. Up to now, no expression studies have been performed in patients with autism-spectrum disorders.

Animal-model studies also appear to support an important role for DLG4 in regulating excitatory synapses and synaptic plasticity, while mutant mice also displayed clinical phenotypes related to schizophrenia and autism-spectrum disorders, such as impaired learning, abnormal

**Table 2: Single nucleotide variants in scaffolding genes associated with schizophrenia, autism-spectrum disorders and other clinical phenotypes of interest (part 1 of 3)**

Gene	Single nucleotide variants				Sources
	Schizophrenia	Autism-spectrum disorders	Schizophrenia and autism-spectrum disorders	Other associated phenotypes	
<i>DLG1</i>	g.196863463C>T <sup>49</sup> g.196812562A>T, g.196812614A>T, g.196842947T>C, g.196867096C>A <sup>50</sup> g.196863502G>C* <sup>127</sup>	g.196817764T>C <sup>59</sup>	—	—	Fromer et al. <sup>49</sup> Purcell et al. <sup>50</sup> Iossifov et al. <sup>59</sup> Xing et al. <sup>127</sup>
<i>DLG2</i>	g.83194295C>T <sup>49</sup> g.83180351C>T, g.83180371T>G, g.83243821T>G, g.83497759G>A <sup>50</sup>	—	—	—	Fromer et al. <sup>49</sup> Purcell et al. <sup>50</sup>
<i>DLG4</i>	g.7096826C>T <sup>50</sup>	g.7106562G>Aa <sup>127</sup>	—	—	Purcell et al. <sup>50</sup> Xing et al. <sup>127</sup>
<i>DLGAP1</i>	c.1922A>G <sup>114</sup>	—	—	—	Li et al. <sup>114</sup>
<i>DLGAP2</i>	g.1497520G>A <sup>50</sup> c.-69+9C>T, c.-69+13C>T, c.-69+47C>T, c.-69+55C>T, c.-32A>G, c.341A>G,* c.438C>T, c.990+60T>C, c.1192G>A, c.1920+37A>G, c.1920+94T>A, c.1927G>A, c.2493G>C, c.2634C>T, c.2797G>A,* c.2884G>A,* c.2663G>A <sup>116</sup>	c.44C>T,* c.277C>A,* c.545G>A,* c.574G>T, c.1516T>C,* c.2392G>C,* c.970A>T <sup>115</sup> g.1616734C>T* <sup>127</sup> g.1626547G>C <sup>59</sup>	c.841C>G,*† c.2135C>T,†† c.2750C>T*†† <sup>115,116</sup>	—	Purcell et al. <sup>50</sup> Iossifov et al. <sup>59</sup> Chien et al. <sup>115</sup> Li et al. <sup>116</sup> Xing et al. <sup>127</sup>
<i>DLGAP3</i>	c.1141G>A, c.1759G>C, c.2309G>T, c.2578-11C>T <sup>128</sup>	35365700G>A <sup>59</sup>	—	—	Iossifov et al. <sup>59</sup> Li et al. <sup>128</sup>
<i>SHANK1</i>	g.51205733T>A <sup>50</sup>	g.51220161C>T, g.51206952G>A,* g.51205840C>T,* g.51170826G>A, g.51170775G>A, g.51165632C>T <sup>129</sup> g.51220076C>T, g.51219998C>T, g.51215287C>T,* g.51206988G<T, g.51205886C>T,* g.51191281C>T,* g.51172180G>A, g.51171270C>T,* g.51170856C>T, g.51170854C>T,* g.51170779C>T, g.51170674C>A,* g.51170418G>A, g.51170407G>T, g.51170362A>T,* g.51170359T>C,* g.51170046A>T,* g.51169830C>T,* g.51165932C>T, g.51165929C>T,* g.51165767G>A,* g.51165574C>A* <sup>130</sup>	—	—	Purcell et al. <sup>50</sup> Leblond et al. <sup>129</sup> Sato et al. <sup>130</sup>

**Table 2: Single nucleotide variants in scaffolding genes associated with schizophrenia, autism-spectrum disorders and other clinical phenotypes of interest (part 2 of 3)**

Single nucleotide variants					
Gene	Schizophrenia	Autism-spectrum disorders	Schizophrenia and autism-spectrum disorders	Other associated phenotypes	Sources
<i>SHANK2</i>	g.70666649G>A, g.70666499C>A, g.70544817G>T, g.70349029T>C, g.70333526G>T, g.70333043G>T, g.70333967G>A, g.70331576C>T, g.70331462G>T, g.70319333C>A <sup>131</sup> , g.70644595G>A* <sup>132</sup>	c.76C>T, c.622C>T, c.3380C>T, c.4048G>A, c.467A>G, c.492C>T, c.527-18C>A, c.640+11C>T, c.80033C>T, c.942+19G>A, c.924+133G>C, c.1061-81C>T, c.1141+49G>A, c.1148-109C>T, c.1201A>C, c.1264G>A, c.1302+35G>A, c.1303-54C>T, g.70336411G>A,* c.1392G>T, c.1923G>A, c.2052G>A, c.2823C>T, c.3135C>T, c.3843-12C>T, g.70666749G>A,* g.70644566G>A,* g.70331881G>A,* g.70319339C>T <sup>133</sup> , g.70666635G>A,* g.70544853C>A,* g.70348949C>A,* g.70348913C>T,* g.70332914C>T,* g.70332890C>T,* g.70332272C>T,* g.70331795C>T,* g.70319359A>G* <sup>134</sup> , g.70821018C>G, g.70858273A>C <sup>59</sup>	—	c.76C>T, c.467A>G, c.942+19G>A, c.924+133G>C, c.1141+49G>A, c.1148-109C>T (associated with intellectual disability) <sup>133</sup>	Iossifov et al. <sup>59</sup> , Peykov et al. <sup>131</sup> , Homann et al. <sup>132</sup> , Berkel et al. <sup>133</sup> , Leblond et al. <sup>134</sup>

communication, altered motor coordination or other abnormal behaviour (Table 4).

### Summary

These findings suggest that mutations in *DLG* genes might increase the risk of developing schizophrenia and autism-spectrum disorders, as well as related cognitive deficits, by contributing to the disruption of glutamatergic synapses. Although the neurobiological mechanisms underlying these disruptions are still unknown, some pathways can be inferred. For instance, mutations affecting *DLG2* might modify the tyrosine phosphorylation-based regulation of NMDA receptors, altering NMDA-receptor-related signaling. Similarly, mutations in *DLG4* might dysregulate NMDA receptor activity, because this protein also anchors different protein tyrosine kinases.<sup>229</sup> Other mechanisms might explain the association between *DLG4* and both schizophrenia and autism-spectrum disorders. It has been reported that *DLG4* inhibits the interaction between dopamine receptor D1 and the NMDA receptor, preventing a reciprocal damaging overactivation of both receptors.<sup>86</sup> This suggests that reduced expression or dysfunction of this protein might dysregulate glutamatergic and dopa-

minergic homeostasis. Finally, since *DLG4* enhances the expression of NMDA receptor subunits NR2A and NR2B<sup>230</sup> and the traffic of the NMDA receptor to synapses,<sup>231</sup> diminished expression or alterations in protein function might also compromise NMDA-receptor-mediated signaling transduction.

### The *DLGAP* protein family

Some SNPs (Table 1) and SNVs (Table 2) in the *DLGAP1* gene and SNVs (Table 2) in the *DLGAP3* gene have been associated with schizophrenia. No studies have assessed the association between *DLGAP4* and schizophrenia or autism-spectrum disorders.

There is more evidence for an association between the *DLGAP2* gene and both disorders. The SNPs (Table 1), SNVs (Table 2) and CNVs (Table 3) in this gene have been associated with both schizophrenia and autism-spectrum disorders. Interestingly, some variants were coincident in both disorders (Table 1, Table 2 and Table 3).

On one hand, the SNP rs2906569 (A>G) in intron 1 and the missense SNP rs2301963 (C>A; P384Q) in exon 3 have been associated with both autism-spectrum disorders<sup>115</sup> and



**Table 2: Single nucleotide variants in scaffolding genes associated with schizophrenia, autism-spectrum disorders and other clinical phenotypes of interest (part 3 of 3)**

Single nucleotide variants					
Gene	Schizophrenia	Autism-spectrum disorders	Schizophrenia and autism-spectrum disorders	Other associated phenotypes	Sources
<i>SHANK3</i>	g.49484091C>T g.49506476C>T <sup>46,135</sup> g.51117040G/A, g.51117200G/T, g.51117489C/T, g.51117580C/T, g.51117585G/A, g.51137217A/G, g.51143287C/T, g.51144513C/G, g.51153371G/A, g.51159735C/T, g.51159798A/G, g.51159802C/T, g.51159828G/A, g.51160154G/A, g.51169180A/G <sup>51</sup>	g.51117341C>G, g.51159953G>A, g.51169240A>G <sup>136</sup> g.51159293G>T <sup>*129,136</sup> c.670G>A <sup>136,138</sup> g.51121780C>T,* g.51159458G>T,* g.51113103C>T <sup>136,140</sup> g.51117094C>G,* g.51160615G>T <sup>137</sup> g.51142357C>T, g.51153464G>A,* g.51158686G>T,* g.51158945T>C,* g.51159965C>A,* g.51159988C>T,* g.51160086A>T,* g.51160057G>A <sup>129</sup> c.1527G>A <sup>138</sup> g.51113615T>C <sup>*139</sup> g.51121844A>G,* g.51123071C>T,* g.51159169G>T,* g.51160477C>G, g.51169213G>A,* g.51160589T>C <sup>141</sup> g.51159778G>A,* g.51160049C>T,* <sup>§ 141,142</sup> c.1563G>A, c.1967G>A, c.4908C>T <sup>142</sup> g.1159884G>A,* g.51160018A>T, g.51169259C>T* (p.1572A>V), 51169364C>T,* 51169442G>A,* 51169459C>T, 51169463C>T,* 51169480G>A, g.51169207C>T* g.51169499G>A <sup>143</sup> c.612C>A, c.763C>T, c.898C>T, c.920C>G, c.1315C>T, c.1337G>T, c.3761C>T, c.3764C>T, c.3836C>T, c.4025C>T, c.4405G>C, c.4406G>T, c.4490G>A, c.4720G>A <sup>144</sup> c.5008A>T <sup>145</sup>	g.49506159G>T <sup>129,135,136</sup>	g.49506476C>T, c.5008A>T, c.1527G>A (associated with intellectual disability) <sup>46,138,145</sup>	Awadalla et al. <sup>46</sup> Girard et al. <sup>51</sup> Leblond et al. <sup>129</sup> Gauthier et al. <sup>135</sup> Durand et al. <sup>136</sup> Boccutto et al. <sup>137</sup> Soorya et al. <sup>138</sup> Gauthier et al. <sup>139</sup> Durand et al. <sup>140</sup> Moessner et al. <sup>141</sup> Waga et al. <sup>142</sup> Schaaf et al. <sup>143</sup> Kelleher et al. <sup>144</sup> Cochoy et al. <sup>145</sup>
<i>HOMER1</i>	IVS4 p <sup>146</sup>	c.195G>T, c.290C>T, c.425C>T, c.968G>A, c.1090C>T <sup>144</sup>			Kelleher et al. <sup>144</sup> Norton et al. <sup>146</sup>

\*These variants have functional impact on the protein using the PolyPhen-2 or the Pmut computer program.

†Chien and colleagues also found this variant in controls.<sup>115</sup>‡Li and colleagues also found this variant in controls.<sup>116</sup>§Waga and colleagues also found this variant in controls.<sup>142</sup>

schizophrenia.<sup>116</sup> Although the functional significance of rs2906569 is difficult to infer, it could affect either the final protein function or the regulation of gene expression by altering different processes, such as splicing, translation regulation or mRNA polyadenylation.<sup>232</sup> The missense variant rs2301963, in which CC homozygotes were overrepresented in patients with schizophrenia and patients with autism-spectrum disorders, could affect final protein activity according to bioinformatics analyses.<sup>115</sup>

On the other hand, 3 nonsynonymous exonic de novo variants (c.841C>G, c.2135C>T and c.2750C>T) have been identified in both schizophrenia<sup>116</sup> and autism spectrum disorders.<sup>115</sup> The c.841C>G and c.2750C>T mutations were predicted to damage protein function using PolyPhen-2 or Pmut.

Moreover, deletion of the chromosomal region 8p23.3 has been detected in patients with schizophrenia and patients with autism-spectrum disorders. This deletion and other CNVs spanning this gene have been found in patients with

**Table 3: Copy number variants in scaffolding genes associated with schizophrenia, autism-spectrum disorders and other clinical phenotypes of interest (part 1 of 2)**

Gene	Copy number variants				Sources
	Schizophrenia	Autism-spectrum disorders	Schizophrenia and autism-spectrum disorders	Other associated phenotypes	
<i>DLG1</i>	—	del:195971510_197675831 <sup>147</sup>	del:3q29 <sup>45,50,57,148–156</sup>	Deletion of 3q29 has been associated with intellectual disability, <sup>148,149,154–156</sup> developmental delay, <sup>152</sup> impaired social skills and repetitive behaviour <sup>150,152</sup>	Sanders et al. <sup>45</sup> Purcell et al. <sup>50</sup> Kirov et al. <sup>57</sup> Pinto et al. <sup>147</sup> Levinson et al. <sup>148</sup> Mulle et al. <sup>149</sup> Magri et al. <sup>150</sup> Szatkiwicz et al. <sup>151</sup> Quintero-Rivera et al. <sup>152</sup> Levy et al. <sup>153</sup> Willatt et al. <sup>154</sup> Ballif et al. <sup>155</sup> Sagar et al. <sup>156</sup>
<i>DLG2</i>	del:83472750_83842973 del:84006106_84226064 <sup>57</sup> del:83680969_83943977 <sup>158</sup>	del:84032216_84276593 <sup>157</sup> dup:83108466_83378706 <sup>159</sup>	—	—	Kirov et al. <sup>57</sup> Cuscó et al. <sup>157</sup> Walsh et al. <sup>158</sup> Egger et al. <sup>159</sup>
<i>DLG4</i>	—	dup:17p13.1_p13.2 <sup>153,160</sup>	—	—	Levy et al. <sup>153</sup> Sanders et al. <sup>160</sup>
<i>DLGAP2</i>	dup:1436299_1642837 <sup>40</sup>	dup:704383_1521910 <sup>60,147</sup> del:1130900_6780950 <sup>162</sup>	del:8p23.3 <sup>161,163–165</sup>	Duplication of 1436299_1642837 has been associated with intellectual disability <sup>40</sup> Deletion of 8p23.3 has been associated with intellectual disability <sup>161</sup>	Guilmatre et al. <sup>40</sup> Pinto et al. <sup>60</sup> Pinto et al. <sup>147</sup> Chien et al. <sup>161</sup> Szatmari et al. <sup>162</sup> Costain et al. <sup>163</sup> Marshall et al. <sup>164</sup> Ozgen et al. <sup>165</sup>
<i>SHANK1</i>	—	del:55872189_55935995, del:55808307_55871709 <sup>130</sup> del:19q13.33 <sup>166</sup>	—	Deletion of 55872189_55935995 has been associated with impaired social communication skills, repetitive behaviours and higher functioning <sup>130</sup> Deletion of 55808307_55871709 has been associated with developmental abnormalities and disrupted social skills <sup>130</sup>	Sato et al. <sup>130</sup> Prasad et al. <sup>166</sup>
<i>SHANK2</i>	—	del:70154458_70220632 <sup>60</sup> del:70077507_70506315, del:70119917_70187872, del:70154458_70220632 <sup>147</sup> del:70220882_70154208 <sup>133</sup> dup:70520567_71017315 <sup>167</sup> del:70332092(2)CTG > C <sup>59</sup>	—	Deletion of 70154458_70220632, 70077507_70506315 and 70119917_70187872 has been associated with language delay <sup>60,147</sup> Deletion of 70220882_70154208, 70077507_70506315 and 70119917_70187872 has been associated with intellectual disability <sup>133,147</sup>	Iossifov et al. <sup>59</sup> Pinto et al. <sup>60</sup> Berkel et al. <sup>133</sup> Pinto et al. <sup>147</sup> Gai et al. <sup>167</sup>

**Table 3: Copy number variants in scaffolding genes associated with schizophrenia, autism-spectrum disorders and other clinical phenotypes of interest (part 2 of 2)**

Gene	Copy number variants				Sources
	Schizophrenia	Autism-spectrum disorders	Schizophrenia and autism-spectrum disorders	Other associated phenotypes	
<i>SHANK3</i>	—	del:c.1320_1338, dup:c.1497+910bp/ins, del:c.1497+910bp/del <sup>142</sup> del:c.3259 <sup>168</sup> del:48927548_51224208, del:48444959_51224208, del:49114430_51224208, del:44321641_51224208, del:46143471_51224208, del:44427703_51224208, del:46905533_51224208, del:49028732_51224208, del:43745129_51224208, del:50267252_51224208, del:45902119_51224208, del:42918711_51224208, del:45583935_51224208, del:48551989_51206201, del:51083118_51224208, del:45428606_51224208, del:44800014_51224208, del:44023173_51224208, del:43218614_51224208, del:46787434_51224208, del:49460840_51224208, del:51115526_51234443, del:45705241_51224208, del:49004395_51224208, del:42822943_51224208118, del:45159185_49582267 <sup>169</sup> del:45159185_49582267, del:47996161_49512530, del:49468716_49485255, del:49470371_49567383, del:49470371_49480446 <sup>147</sup>	del:22q13.3 40,60,136,137,141,164,170–174	Deletion of 22q13.3 has been associated with intellectual disability, language alteration, <sup>60,137,139,170,174</sup> developmental delay and impaired social interaction <sup>140</sup> Deletion of 45159185_49582267 has been associated with intellectual disability, hyperactivity, attention deficits and aggressiveness <sup>147</sup> Deletion of 47996161_49512530 has been associated with severe intellectual disability and cortical atrophy <sup>147</sup> Deletion of 49470371_49567383 and 49470371_49480446 have been associated with language delay <sup>147</sup>	Guilmatre et al. <sup>40</sup> Pinto et al. <sup>60</sup> Durand et al. <sup>136</sup> Boccutto et al. <sup>137</sup> Gauthier et al. <sup>139</sup> Moessner et al. <sup>141</sup> Waga et al. <sup>142</sup> Pinto et al. <sup>147</sup> Marshall et al. <sup>164</sup> Nemirovsky et al. <sup>168</sup> Yuen et al. <sup>169</sup> Failla et al. <sup>170</sup> Crespi et al. <sup>171</sup> Sebat et al. <sup>172</sup> Wang et al. <sup>173</sup> Bonaglia et al. <sup>174</sup>
<i>HOMER1</i>	dup:78375511_78797532 <sup>167</sup>	—	—	—	Gai et al. <sup>167</sup>

del = deletion; dup = duplication.

schizophrenia and patients with autism-spectrum disorders who have intellectual disability.<sup>40,161</sup>

To the best of our knowledge, there are no studies of the expression of *DLGAP2* in either autism-spectrum disorders or schizophrenia. Animal-model studies have suggested that alterations in this gene might lead to disadaptative social behaviour (Table 4).

Taken together, these findings suggest that disruptions of this gene might alter the function or expression of *DLGAP2* and ultimately dysregulate its interplay with other PSD proteins, which could underlie the development of both schizophrenia and autism-spectrum disorders, as well as the manifestation of related clinical phenotypes, such as abnormal social behaviour. Interestingly, animal studies have found that *DLGAP2* is vital for normal synaptic structure and function of the orbitofrontal cortex, a brain region that is implicated in the self-regulation of social-emotional behaviour.<sup>233</sup> There is also evidence that the orbitofrontal cortex is disrupted in patients with autism, and animal studies have indi-

cated that a lesion of the orbitofrontal cortex may cause aggressive behaviour.<sup>234</sup>

### *The Shank protein family*

#### **Protein Shank1**

Up to now, most of the SNVs in *SHANK1* have been associated with autism-spectrum disorders and not schizophrenia (Table 2). Deletions in *SHANK1* have also been associated with autism-spectrum disorders (Table 3), with some detected in patients with pronounced social dysfunction.

No expression studies have been carried out for either schizophrenia or autism-spectrum disorders, but animal-model studies seem to indicate that alterations in *SHANK1* could lead to impaired social skills (Table 4).

#### **Protein Shank2**

While SNVs in this gene have been identified in patients with schizophrenia and patients with autism-spectrum disorders

(Table 2), CNVs have been found only in people with autism-spectrum disorders, particularly with respect to intellectual disability or language delay (Table 3).

Among these mutations, the SNV (A1731S) detected in patients with schizophrenia is noteworthy. The authors of a study involving a functional assay in HEK293 cells reported that this variant has a significant effect on the F/G-actin ratio and concluded that diminished actin polymerization could

lead to impairments in synapse formation and maintenance by reducing the presynaptic contacts.<sup>131</sup>

To the best of our knowledge, no expression studies have been performed for this gene. However, animal-model studies suggest that disruption of this gene could lead to the cognitive and social dysfunction associated with schizophrenia or autism-spectrum disorders by altering NMDA receptor function (Table 4).

**Table 4: Expression, animal model and pharmacological studies on the reviewed scaffolding genes (part 1 of 2)**

Gene	Expression studies	Functional studies	Sources
<i>DLG1</i>	Reduced expression of <i>DLG1</i> mRNA in PFC of schizophrenia patients <sup>68</sup> Reduced expression of <i>DLG1</i> protein in PFC of schizophrenia patients <sup>175</sup>	Administration of the NMDA receptor antagonist PCP caused an upregulation of <i>DLG1</i> gene transcription in the neocortex of rats <sup>176</sup>	Dracheva et al. <sup>68</sup> Toyooka et al. <sup>175</sup> Hiraoka et al. <sup>176</sup>
<i>DLG2</i>	Increased <i>DLG2</i> mRNA and decreased protein expression in prefrontal cortex and anterior cingulate cortex of schizophrenia patients <sup>177</sup>	PSD-93 mutant mice exhibited deficits in LTP <sup>178</sup> PSD-93 mutant mice showed cognitive abnormalities <sup>179</sup> PSD-93 mutant mice did not show any abnormality of synaptic structure or function in cerebellum <sup>180</sup>	Kristiansen et al. <sup>177</sup> Carlisle et al. <sup>178</sup> Nithianantharajah et al. <sup>179</sup> McGee et al. <sup>180</sup>
<i>DLG3</i>	Increased <i>DLG3</i> mRNA and protein expression in the thalamus of schizophrenia patients <sup>181</sup> Decreased <i>DLG3</i> protein expression in the thalamus of schizophrenia patients <sup>182</sup>	Mice lacking <i>DLG3</i> exhibited impairments of spatial learning <sup>183</sup>	Clinton et al. <sup>181</sup> Clinton et al. <sup>182</sup> Cuthbert et al. <sup>183</sup>
<i>DLG4</i>	Increased <i>DLG4</i> mRNA and decreased protein expression in ACC of schizophrenia patients <sup>177</sup> Increased <i>DLG4</i> mRNA and protein expression in thalamus of schizophrenia patients <sup>182,185</sup> Increased <i>DLG4</i> mRNA expression in the occipital cortex of schizophrenia patients <sup>186</sup> Decreased <i>DLG4</i> mRNA expression in the PFC of schizophrenia patients <sup>69</sup> Decreased <i>DLG4</i> mRNA and protein expression in the DLPFC of schizophrenia patients <sup>187</sup> Decreased <i>DLG4</i> protein expression in thalamus of schizophrenia patients <sup>182</sup> Decreased <i>DLG4</i> protein expression in hippocampus <sup>188,189</sup> Decreased mRNA expression in the striatum <sup>190</sup> No changes in either <i>DLG4</i> mRNA or protein expression in PFC of schizophrenia patients <sup>175,186</sup> No changes in either <i>DLG4</i> mRNA or protein expression in the hippocampus of schizophrenia patients <sup>69,182</sup>	<i>DLG4</i> mutant mice displayed schizophrenia and autism-spectrum disorder-like phenotypes <sup>184</sup> <i>DLG4</i> mutant mice displayed aberrant AMPA receptor-mediated transmission <sup>178,191</sup> <i>DLG4</i> mutant mice exhibited enhancement in LTP and deficit in LTD <sup>178,192-194</sup> <i>DLG4</i> mutant mice exhibited disrupted synaptic plasticity and impaired learning <sup>192</sup> Ketamine reduced <i>DLG4</i> mRNA in cortical regions of rats <sup>195</sup>	Ohnuma et al. <sup>69</sup> Toyooka et al. <sup>175</sup> Kristiansen et al. <sup>177</sup> Carlisle et al. <sup>178</sup> Clinton et al. <sup>179</sup> Clinton et al. <sup>182</sup> Feyder et al. <sup>184</sup> Clinton et al. <sup>185</sup> Dracheva et al. <sup>186</sup> Funk et al. <sup>187</sup> Toro et al. <sup>188</sup> Matosin et al. <sup>189</sup> Kristiansen et al. <sup>190</sup> Nakagawa et al. <sup>191</sup> Migaud et al. <sup>192</sup> Ehrlich et al. <sup>193</sup> Xu et al. <sup>194</sup> de Bartolomeis et al. <sup>195</sup>
<i>DLGAP2</i>	—	<i>DLGAP2</i> knockout mice displayed abnormal social behaviour <sup>196</sup>	Jiang-Xie et al. <sup>196</sup>
<i>SHANK1</i>	—	<i>SHANK1</i> mutant mice showed alterations in motor system and social behaviour <sup>197-199</sup> <i>SHANK1</i> mutant mice showed social communication deficits <sup>200</sup>	Silverman et al. <sup>197</sup> Hung et al. <sup>198</sup> Wöhr et al. <sup>199</sup> Sungur et al. <sup>200</sup>
<i>SHANK2</i>	—	<i>SHANK2</i> (-/-) mutant mice were hyperactive and displayed autism-like behaviours, including social interaction and repetitive jumping <sup>201,202,203</sup> <i>SHANK2</i> (-/-) mutant mice exhibited fewer dendritic spines, reduced basal synaptic transmission and reduced frequency of miniature excitatory postsynaptic currents <sup>201,203</sup> <i>SHANK2</i> (-/-) mutant mice showed a decrease in NMDA receptor function. Direct stimulation of the NMDA receptor with a partial agonist normalized its function and improved social interaction. <sup>202</sup>	Schmeisset et al. <sup>201</sup> Won et al. <sup>202</sup> Ha et al. <sup>203</sup>

Table 4: Expression, animal model and pharmacological studies on the reviewed scaffolding genes (part 2 of 2)

Gene	Expression studies	Functional studies	Sources
<i>SHANK3</i>	—	<p><i>SHANK3</i> mutant mice exhibited self-injurious repetitive grooming behaviours<sup>204,206,207</sup> and social interaction,<sup>204,205,207,209,210</sup> learning and memory<sup>205</sup> deficits. They also showed anxiety and motor deficits<sup>206,208,209</sup></p> <p><i>SHANK3</i> mutant mice showed deficits in glutamatergic transmission and synaptic plasticity and reduced synaptic concentrations of scaffolding proteins (e.g., DLGAP3, Homer1).<sup>204,208-210</sup> Re-expression of the <i>SHANK3</i> gene in adults led to improvements in synaptic protein composition, spine density and neural function, as well as selective rescue in autism-related phenotypes.<sup>208</sup></p> <p>Insulin-like growth factor-1 reversed synaptic and behavioural deficits in <i>SHANK3</i> mutant mice<sup>206</sup> and phenotypic changes in human neuronal models of Rett syndrome.<sup>211</sup></p> <p><i>SHANK3B</i> knockout mice exhibited early hyperactivation and precocious maturation of corticostriatal circuits<sup>212</sup></p>	<p>Arons et al.<sup>204</sup> Wang et al.<sup>205</sup> Bozdagi et al.<sup>206</sup> Peça et al.<sup>207</sup> Mei et al.<sup>208</sup> Bozdagi et al.<sup>209</sup> Yang et al.<sup>210</sup> Marchetto et al.<sup>211</sup> Peixoto et al.<sup>212</sup></p>
<i>HOMER1</i>	<p>Increased Homer1a protein expression in hippocampal interneurons of schizophrenia patients<sup>213</sup></p> <p>Increased Homer1a and decreased Homer1b protein expression in hippocampus of schizophrenia patients<sup>189</sup></p>	<p><i>HOMER1</i> knockout mice displayed impaired fear memory formation<sup>214</sup> and impaired LTP<sup>215</sup></p> <p><i>HOMER1</i> knockout mice showed abnormalities in motivational, emotional, cognitive and sensorimotor processing<sup>216</sup></p> <p><i>HOMER1</i> knockout mice also showed somatic growth retardation, poor motor coordination, enhanced sensory reactivity, learning deficits and increased aggression in social interaction<sup>218</sup></p> <p>Overexpression of <i>HOMER1</i> in knockout mice reverted the cognitive and behavioural impairments<sup>217</sup></p> <p>Exposure to novel environments upregulated <i>HOMER1</i> mRNA in the hippocampus of rats<sup>219</sup></p> <p>Methamphetamine or cocaine administration upregulated <i>HOMER1</i> mRNA in the neocortex of rats<sup>220</sup></p> <p>LSD or PCP administration upregulated <i>HOMER1</i> mRNA in the PFC of rats<sup>221,222</sup></p> <p>10Ketamine increased <i>HOMER1</i> mRNA in the cortical regions, striatum and nucleus accumbens of rats<sup>195,223</sup></p> <p>Antipsychotics (haloperidol, olanzapine or clozapine) induced an increment of Homer1 protein expression in the cortex, the striatum, the caudate-putamen or nucleus accumbens of rats<sup>107,224-228</sup></p>	<p>de Bartolomeis et al.<sup>107</sup> Matosin et al.<sup>189</sup> de Bartolomeis et al.<sup>195</sup> Leber et al.<sup>213</sup> Inoue et al.<sup>214</sup> Gerstein et al.<sup>215</sup> Szumlinski et al.<sup>216</sup> Lominac et al.<sup>217</sup> Jaubert et al.<sup>218</sup> Vazdarjanova et al.<sup>219</sup> Fujiyama et al.<sup>220</sup> Cochran et al.<sup>221</sup> Nichols et al.<sup>222</sup> Iasevoli et al.<sup>223</sup> Iasevoli et al.<sup>224</sup> Iasevoli et al.<sup>225</sup> Ambesi-Impiombato et al.<sup>226</sup> Polese et al.<sup>227</sup> Tomasetti et al.<sup>228</sup></p>

ACC = anterior cingulate cortex; AMPA =  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4 propionic acid; LSD = lysergic acid; LTD = long-term depression; LTP = long-term potentiation; NMDA = N-methyl-D-aspartate; PCP = phencyclidine; PFC = prefrontal cortex; PSD = postsynaptic density.

### Protein Shank3

There is accumulating evidence that *SHANK3* mutations contribute to the pathology of neurodevelopment disorders. Two SNVs in the *SHANK3* gene have been identified in patients with schizophrenia (Table 2), and different variants (SNPs, SNVs and CNVs) have been associated with autism-spectrum disorders (Table 1, Table 2 and Table 3). Among them, the missense variant G1011V (g.49506159G>T) located in exon 21 has been identified in patients with schizophrenia and patients with autism-spectrum disorders (Table 2). Further studies are needed to test whether this variant has any consequence for the protein function.

The R1117X nonsense mutation (g.49484091C>T) has been identified in exon 21 of the *SHANK3* gene in patients with schizophrenia and intellectual disability. This amino acid

change resulted in a truncated form of the Shank3 protein that lacked the Homer-binding site, causing its loss of function.<sup>46,135</sup>

The A198G (g.51117341C>G) identified in people with autism-spectrum disorders generated a frameshift mutation that introduced a premature STOP codon at position 1227, leading to a truncated form of Shank3 that also caused its loss of function. This mutation disrupted actin polymerization, the regulation of spine formation and the molecular organization of the PSD.<sup>136</sup>

Two frameshift mutations causing premature STOP codons (g.51117094C>G and g.51160615G>T) resulted in the loss of protein function by losing the C-terminal region of the protein, which is crucial for interactions with other PSD proteins.<sup>137</sup>

Regarding CNVs, different studies have identified deletions in the *SHANK3* gene in patients with schizophrenia and patients with autism-spectrum disorders with intellectual

disability, developmental delay, language alterations or impaired social interaction (Table 3). Similarly, Phelan McDermid Syndrome (22q13.3 deletion syndrome), which includes deletion of the *SHANK3* gene, is characterized by neonatal hypotonia, global developmental delay, absence of speech, autistic behaviour and intellectual disability.<sup>235</sup>

Animal-model studies also appear to support a role for this gene in the cognitive and behavioural clinical phenotypes related to schizophrenia and autism-spectrum disorders. Shank3 mutant mice display reduced social interaction, affiliative behaviour, repetitive behaviour and communicative deficits (Table 4).

### Summary

In summary, results for Shank proteins suggest that their disruption might underlie some of the cognitive and social dysfunction present in schizophrenia and autism-spectrum disorders. This is in line with the latest data showing that the prevalence of *SHANK3* mutations in people with autism-spectrum disorders is 0.5% to 0.7%, and that a *SHANK3* mutation is present in approximately 2% of people with both an autism-spectrum disorder and intellectual disability.<sup>129,138,236</sup> More specifically, from animal-model studies it has been suggested that these dysfunctions might be caused by alterations in the NMDA-receptor-related signalling pathway. There is evidence that *SHANK2* (–/–) mutant mice display abnormal NMDA receptor function and show alterations in behaviour and social skills.<sup>201</sup> Interestingly, when mutant mice were stimulated with NMDA receptor agonists, NMDA receptor function was normalized and their social interactions improved.<sup>202</sup> Regarding the pathophysiological mechanisms underlying the social deficits in *SHANK3* mutation, it has been reported that knockdown of the *SHANK3* gene in rat cortical cultures causes a loss of NMDA receptor function and alterations in its membrane trafficking through the disruption of the actin cytoskeleton.<sup>237</sup> Furthermore, Arons and colleagues showed that the loss of function of the *SHANK3* gene resulted in reduced glutamatergic synaptic transmission, whereas overexpression of this gene increased the number and size of excitatory synapses and the expression levels of other PSD proteins, such as *DLG4* and *Homer1*.<sup>204</sup> Therefore, the behavioural and cognitive alterations present in patients carrying mutations in *SHANK* genes might be related to dysfunctions in NMDA-receptor-related glutamatergic signalling, which in turn might be caused by abnormalities in the interactions between Shank and other PSD proteins or anomalies in the actin polymerization processes.

### The Homer protein family

Although 1 study reported a putative role for the *HOMER2* gene in schizophrenia (Table 1), it is principally the *HOMER1* gene that has been associated with schizophrenia and autism-spectrum disorders.

Three SNPs in *HOMER1* have been associated with schizophrenia (Table 1). Among them, rs4704560 has also been associated with the risk of developing psychotic symptoms in Parkinson disease (Table 1). In addition, 1 SNV and 1 CNV

have been found in patients with schizophrenia (Table 2 and Table 3). As well, SNVs (Table 2) and CNVs (Table 3) have been detected in people with autism-spectrum disorders.

Expression studies have reported increases in *Homer1a* protein and decreases in *Homer1b* in the hippocampus of postmortem brain samples of schizophrenia (Table 4).

Animal-model studies suggest that *HOMER1* transcripts might control cognitive and behaviour functions (Table 4). It has also been suggested that mutations in *HOMER1* might increase the risk of developing schizophrenia by dysregulating NMDA receptors and their associated signalling pathway. Pharmacological studies have shown that the NMDR inhibitor phencyclidine (PCP) and the NMDA receptor antagonist ketamine increase *HOMER1* mRNA in rat prefrontal cortex and ventral striatum and nucleus accumbens, respectively. Other studies show that *HOMER1* mRNA and/or related protein expression levels are modified by psychotomimetic drugs and the antipsychotic haloperidol (Table 3).

### Summary

Overall, although *HOMER1* has been associated with both schizophrenia and autism-spectrum disorders, genetic, expression and animal model studies do not provide conclusive results. This could be because different *Homer1* isoforms have different functions. It has been suggested that the long isoform *Homer1c* is implicated in the regulation of working memory and sensorimotor function, whereas *Homer1a* could modulate the behavioural and emotional area.<sup>217</sup> Additionally, some studies report that the balance between long and short *Homer* forms determines the normal functioning of the synaptic architecture and function and influences synaptic plasticity dynamics<sup>238</sup>; therefore, an alteration of this balance could dysregulate synaptic signalling, leading to neurochemical, structural and behavioural changes.<sup>217,218</sup>

### Discussion

Accumulating evidence supporting biological overlap between schizophrenia and autism-spectrum disorders has fuelled research into common underlying mechanisms to provide a better understanding of the etiology of these disorders, their diagnosis and treatment. One such mechanism involves the synaptic plasticity in which the PSD structure plays a key role. This review has summarized genetic variants in the main scaffolding genes of the PSD that have been associated with schizophrenia and/or autism-spectrum disorders to date. Moreover, evidence coming from genetic, brain expression and animal model studies suggests that genetic variants in scaffolding genes could contribute to the deregulation of the glutamate receptor signalling pathways of the PSD, which may be involved in the pathophysiology of schizophrenia and autism-spectrum disorders, and the development of related shared phenotypes, such as cognitive or social dysfunction.

Such a cross-disorder effect of scaffolding gene and protein dysregulation seems consistent with their role as a dynamic complex that regulates cell signalling pathways and determines the specificity of information flow in intracellular networks.<sup>72</sup> Because scaffolding proteins coordinate the excitatory

synaptic transmission and mediate functional changes at the synapse, thus regulating synaptic plasticity among other processes,<sup>73</sup> they can be seen as crucial pieces of the complex puzzle of synaptic homeostasis maintenance. The fact that common (SNPs) and rare (SNVs and CNVs) variants have been identified in scaffolding genes in both schizophrenia and autism-spectrum disorders is in agreement with the view that both kinds of variants complementarily and heterogeneously underlie the shared genetic susceptibility to these disorders (Table 5) by generating synaptic instability.

From the present review, it is possible to infer that patients with schizophrenia or autism-spectrum disorders primarily share CNVs that include the complete length of one or more genes. In this regard, CNVs in the PSD genes seem to increase the risk of developing either schizophrenia or autism-spectrum disorders. For instance, deletions of the chromosomal region 3q29, which includes the *DLG1* gene, have been related to both schizophrenia and autism-spectrum disorders.<sup>45,49</sup> Taking into account the usually large effect size of rare variants on a phenotype, we should not be surprised that alterations in the number of copies (deletions or duplications) of these genes have an impact on PSD functioning and plasticity. In addition to being associated with specific disorders, these variants have been associated with certain phenotypes in these or other disorders, or even in healthy controls. Pocklington and colleagues showed that rare CNV burden may be relevant to cognitive dysfunction in patients with schizophrenia,<sup>239</sup> and Stefansson and col-

leagues found that CNVs conferring risk of either schizophrenia or autism-spectrum disorders, including CNVs in the *DLG1* and *DLG2* genes, also affect cognitive function in healthy controls.<sup>240</sup> Other studies have similarly detected that mutations in PSD genes, including some of the scaffolding genes reviewed here, such as *DLG3*<sup>83</sup> or *SHANK3*,<sup>241</sup> are present in patients with intellectual disability.

This review has also provided evidence that, although several SNPs and SNVs in the scaffolding genes have been associated with schizophrenia or autism-spectrum disorders, only a few have been reported in both: 2 SNPs and 3 SNVs in the *DLGAP2* gene and 1 SNV in the *SHANK3* gene (Table 5). Variants that occur in both diagnoses might be targets of special interest for our understanding of common pathophysiological mechanisms and shared clinical features. Although it is difficult to infer the functional significance of these variants, bioinformatic analyses have indicated that some of the *DLGAP2* gene variants (rs2301963, c.841C>G and c.2750C>T) might affect final protein function or expression. In relation to *SHANK3*, to our knowledge, there is no available information about the functionality of the missense SNV (G1011V) that has also been found associated with both disorders.

Nevertheless, the general lack of specificity observed here can be explained in terms of the pleiotropic nature of scaffolding genes. Variants in different scaffolding genes, either at the allelic or the gene level, may dysregulate the homeostasis of the PSD, which is finally expressed as features associated with different neurodevelopment disorders. In addition

**Table 5: Summary of variants in scaffolding genes associated with both schizophrenia and autism-spectrum disorders**

Genes	SNPs	SNVs	CNVs	Sources
<i>DLG1</i>	—	—	del:3q29 <sup>45,50,57,148–156</sup>	Sanders et al. <sup>45</sup> Purcell et al. <sup>50</sup> Kirov et al. <sup>57</sup> Levinson et al. <sup>148</sup> Mulle et al. <sup>149</sup> Magri et al. <sup>150</sup> Szatkiewicz et al. <sup>151</sup> Quintero-Rivera et al. <sup>152</sup> Levy et al. <sup>153</sup> Willatt et al. <sup>154</sup> Ballif et al. <sup>155</sup> Sagar et al. <sup>156</sup>
<i>DLGAP2</i>	rs2906569, rs2301963 <sup>115,116</sup>	c.841C>G, c.2135C>T c.2750C>T <sup>115,116</sup>	del:8p23.3 <sup>161,163–165</sup>	Chien et al. <sup>115</sup> Li et al. <sup>116</sup> Chien et al. <sup>161</sup> Costain et al. <sup>163</sup> Marshall et al. <sup>164</sup> Ozgen et al. <sup>165</sup>
<i>SHANK3</i>	—	g.49506159G>T <sup>129, 135,136</sup>	del:22q13.3 <sup>40,60,136,137,141,164,170–174</sup>	Guilmatre et al. <sup>40</sup> Pinto et al. <sup>60</sup> Leblond et al. <sup>129</sup> Gauthier et al. <sup>135</sup> Durand et al. <sup>136</sup> Boccutto et al. <sup>137</sup> Moessner et al. <sup>141</sup> Marshall et al. <sup>164</sup> Failla et al. <sup>170</sup> Crespi et al. <sup>171</sup> Sebat et al. <sup>172</sup> Wang et al. <sup>173</sup> Bonaglia et al. <sup>174</sup>

CNV = copy number variant; del = deletion; SNP = single nucleotide polymorphism; SNV = single nucleotide variant.

to this pleiotropy, the polygenic nature of psychiatric disorders and the polygenic nature of the intermediate molecular pathways known to underlie at least part of the autism-spectrum disorders/schizophrenia pathology (such as the proper functioning of the PSD) should also be considered. This directly links with additional genetic phenomena, such as gene-gene interactions. In recent years, the gene-pathways methodology has been developed to study whether different genes with similar functions are jointly associated with a single phenotype. So far, only a few studies have assessed the effect of common variance in scaffolding genes as a functional gene set or the epistatic effects of other related PSD functional gene sets on the risk of schizophrenia or autism-spectrum disorders. One recent study explored the enrichment of schizophrenia-associated ultra-rare variants and found a significant enrichment of disrupting ultra-rare variants among genes defined as encoding interactors with *DLG4* and *ARC* and *NMDA* receptors.<sup>70</sup> Another study observed an enrichment of SNPs associated with autism-spectrum disorders in gene sets related to synaptic structure and function, including genes related to scaffolding proteins,  $\beta$ -catenin nuclear pathways, glutamate receptor activity and adherents junctions.<sup>67</sup> In addition, although not significant after correction, a nominal association between a PSD protein defined gene set (including *ARC* and *NMDA* receptor complexes) with schizophrenia has been reported.<sup>36</sup> In all, the effect of common and rare variants in scaffolding genes on schizophrenia and autism-spectrum disorders reflects the complex and heterogeneous genetic architecture of these disorders, and further analyses of gene sets could facilitate the untangling of this complexity.

In addition to genetic data, expression and animal-model studies have indicated the importance of scaffolding genes in schizophrenia and autism-spectrum disorders. There is evidence that patients with schizophrenia or autism-spectrum disorders display deviations from normal scaffolding protein brain expression levels, supporting the hypothesis that the deregulation of these genes might underlie the neurobiology of both disorders. However, to our knowledge, there are no brain expression studies of the 2 genes (*DLGAP2* and *SHANK3*) in which overlapping variants that predispose individuals to schizophrenia and/or autism-spectrum disorders were found.<sup>52,115,116,135,242</sup> Further research is required to test whether these coincident genetic variants contribute to modifying protein expression levels. In contrast, studies with animal models have shown the importance of scaffolding genes in ensuring cognitive and social function. We have reviewed different studies in which mice with scaffolding protein mutations show schizophrenia and autistic-like phenotypes.<sup>184,205</sup> The use of animal models is extremely useful for understanding how changes in the gene sequence can affect phenotypes. As an example of the potential importance of animal models, there are *SHANK3*-deficient mice in which synaptic deficits were reversed with insulin-like growth factor-1.<sup>206</sup> In a recent pilot study, insulin-like growth factor-1 has been used to treat 9 children with autism, and preliminary results have shown a reduction in social deficits.<sup>243</sup>

### Limitations

Some limitations of this review should be acknowledged. First, since the reviewed association studies do not always include the same genetic regions or variants, coincident variants can be linked to shared genetic variability between schizophrenia and autism-spectrum disorders, but noncoincidence cannot be interpreted as a lack of it. Second, patients with low IQ scores are generally excluded from association studies. Since the scaffolding genes reviewed here seem to contribute to cognitive phenotypes, it is plausible to hypothesize that the effects of SNPs and SNVs in these genes were detected less often than they actually occur. Third, the relationship between the effect size associated with common and rare variants, the statistical power needed to detect these effects and the sample sizes in the studies reported in the different articles reviewed should be considered. The odds ratios associated with schizophrenia risk SNPs are typically about 1.10 to 1.50, whereas schizophrenia-associated CNVs confer a significantly increased risk of illness (odds ratios for several CNVs exceed 8).<sup>244</sup> Therefore, rare variants can more easily create significant genome-wide associations than common variants.<sup>245</sup>

### Conclusion

Advances in genetic technologies, together with the assembly of large patient cohorts, have made it possible to identify some genes and biological pathways involved in both schizophrenia and autism-spectrum disorders. Among them, scaffolding genes implicated in the PSD have been repeatedly associated with schizophrenia and autism-spectrum disorders, pointing toward these genes' common involvement in the neurobiology of these disorders and in some shared clinical phenotypes, such as cognitive and social impairment. This review summarizes evidence that many different variants could introduce numerous slight alterations in the PSD pathway, leading to its inappropriate development or insufficiently robust response to environmental insults.

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