Further evidence for de novo variants in SYNCRIP as the cause of a neurodevelopmental disorder

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Abstract

SYNCRIP encodes for the Synaptotagmin-binding cytoplasmic RNA-interacting protein, involved in RNA-binding and regulation of multiple cellular pathways. It has been proposed as a candidate gene for neurodevelopmental disorders (NDDs) with autism spectrum disorder (ASD), intellectual disability (ID), and epilepsy. We ascertained genetic, clinical, and neuroradiological data of three additional individuals with novel de novo SYNCRIP variants. All individuals had ID. Autistic features were observed in two. One individual showed myoclonic-atonic epilepsy. Neuroradiological features comprised periventricular nodular heterotopia and widening of subarachnoid spaces. Two frameshift variants in the more severely affected individuals, likely result in haploinsufficiency. The third missense variant lies in the conserved RNA recognition motif (RRM) 2 domain likely affecting RNA-binding. Our findings support the importance of RRM domains for SYNCRIP functionality and suggest genotype-phenotype correlations. Our study provides further evidence for a SYNCRIP-associated NDD characterized by ID and ASD sporadically accompanied by malformations of cortical development and myoclonic-atonic epilepsy.
Neurodevelopmental disorders (NDDs) typically manifest in early childhood and frequently affect cognition, language, behavior, and motor skills. In the past decade, progress in sequencing technologies substantially contributed to the identification of an increasing number of candidate genes associated with NDDs (Guo et al., 2019; Lelieveld et al., 2016; Mefford et al., 2012; Rauch et al., 2012; Schaal et al., 2020). In recent comprehensive studies deciphering the genetic etiology of intellectual disability (ID) and autism spectrum disorders (ASD), SYNCRIP (MIM #616686), encoding for Synaptotagmin-binding cytoplasmic RNA-interacting protein, has been proposed as a candidate gene for NDD with ASD and epilepsy (Guo et al., 2019; Lelieveld et al., 2016; Rauch et al., 2012). SYNCRIP, also known as hnRNP Q, is an evolutionarily conserved RNA-binding protein involved in multiple cellular pathways, many of which have been associated with neuronal and muscular developmental disorders. SYNCRIP plays an important role in the regulation of RNA metabolism, including sequence recognition as well as pre-messenger RNA (mRNA) splicing, translation, transport, and degradation (Blanc et al., 2001; Cappelli et al., 2018; Chen et al., 2020; Mizutani et al., 2000; Titlow et al., 2020). In particular, SYNCRIP modulates alternative splicing of the SMN2 transcript postulated to compensate for the loss of SMN1 in spinal muscular atrophy (Chen et al., 2008). Further RNA-interacting proteins, such as argonaute-2 as well as the hnRNP family members HNRNPU and HNRNPD, have previously been associated with developmental and epileptic encephalopathies (Epi4K et al., 2013; Hinokuma et al., 2020; Lessel et al., 2020). The involvement of SYNCRIP in RNA-binding and regulation of multiple pathways suggests its relevance in several important functions including neurodevelopment.

In this study, we present genetic and clinical data of three unrelated individuals with epileptic and nonepileptic NDDs associated with three novel de novo SYNCRIP variants providing further evidence for a SYNCRIP-associated NDD.

Data of three previously unreported individuals with de novo variants in SYNCRIP were collected from institutions in Germany and the Netherlands. Genetic testing was performed using trio (individuals #2 and #3) or singleton (individual #1) exome sequencing within scientific studies or as part of the clinical diagnostics in individuals with ID and/or epilepsy. Available clinical, genetic, and neuroradiological information was obtained for all individuals. Detailed phenotypic information was ascertained based on the phenotypic spectrum of previously reported individuals. All participating families gave their informed consent for genetic testing and publication of clinical data. The study was approved by the ethics committee of the University of Heidelberg (S-318/2018).

Localization of variants reported here and structural consequence of the identified missense variant c.734T>C p.(Leu245Pro) in the SYNCRIP tertiary structure was assessed and visualized using PyMol (v. 2.5.0a; Schrödinger, LLC) installed through Anaconda (v. 2020.11 with Python 3.8.5; Anaconda Inc.) and the existing PDB template 6KOR of the human SYNCRIP crystal structure (amino acid sequence 242-428) (Chen et al., 2020). To visualize differences in variant distribution between affected individuals and healthy controls, we compiled pathogenic and benign SYNCRIP variants using the databases PubMed and gnomAD (Karczewski et al., 2020). PubMed literature research was performed using the search terms “SYNCRIP” and “HNRNPQ,” GnomAD (v.3.1) variants were selected by the consequences “missense_variant,” “stop_gained,” “inframe deletion,” and “inframe insertion.” All databases were most recently accessed 31st January 2021. All variants were harmonized with the canonical Ensembl feature ENST00000369622.8 (RefSeq NM_006372.5) of the GRCh38/hg38 human reference genome build. To evaluate the likelihood of pathogenic variant effects, all biologically possible SYNCRIP missense variants of ENST00000369622.8 and corresponding values of the established variant effect prediction (VEP) scores CADD, M-CAP, MetaLR, MetaSVM, PolyPhen-2, PROVEAN, REVEL, and SIFT were compiled and annotated using the recent dbNSFP v.4.1a database (Adzhubei et al., 2010; Choi et al., 2012; Dong et al., 2015; Ioannidis et al., 2016; Jagadeesh et al., 2016; Liu et al., 2016; Rentzsch et al., 2019; Sim et al., 2012; Yates et al., 2020). Resulting VEP scores and gnomAD variant distributions were plotted along the SYNCRIP primary structure using the geom_tile, geom_smooth, and geom_density function, respectively, of the ggplot2 library in RStudio (v. 1.2.5042; RStudio, Inc.). Arithmetic means of VEP scores for all possible amino acid substitutions at the respective protein position were calculated for heatmap visualization. The REVEL ensemble score showed high overall performances regarding discrimination between pathogenic and benign single nucleotide variants in different variant data sets (Li et al., 2018). Therefore, the REVEL score is primarily used in this study to assess the pathogenicity of variants. For comparison, plots using further established VEP scores are depicted in Figure S1.

Clinical and neuroradiological features of individuals reported here and in the literature are delineated in Table 1. Detailed case reports are provided in the Supplementary Information. In all three individuals, exome sequencing was performed due to NDDs characterized by a delay in speech and language development (#3) as well as ID (#1, #2), respectively. Behavioral abnormalities as well as ASD and autistic features, respectively, were described in two cases (#1, #3). Epilepsy was present in one of three individuals (#2) and characterized by epilepsy with myoclonic atonic seizures (MAE) with myoclonic reflex seizures partially triggered by tactile stimuli. Seizures started at 10 months of age and were refractory to multiple treatments. Eventually, a reduction in seizure frequency was
**TABLE 1** Summary of phenotypes associated with SYNCRIP variants

| Individual | Variant | Inheritance | Sex | Age at last FU (years) | Cognition | ASD | Epilepsy | Further clinical features | Neuroradiological features | Reference |
|------------|---------|-------------|-----|------------------------|-----------|-----|----------|---------------------------|-----------------------------|-----------|
| #1         | c.858_859del p.(Gly287Leufs*5) | *de novo* | m   | 14                     | ID, DD    | +   | −        | Hirschsprung disease       | Unspecific widening of outer CSF spaces | This report |
| #2         | c.854dupA p.(Asn285Lysfs*8)   | *de novo* | f   | 3                      | ID, DD    | −   | + MAE   | −                         | Periventricular nodular heterotopia       | This report |
| #3         | c.734T>C p.(Leu245Pro)       | *de novo* | m   | 3.8                    | Mild ID, DD | + Autistic features | − | − | n/a                      | This report |
| #4         | Whole gene deletion         | n/a        | m   | n/a                    | ID        | n/a | n/a      | n/a                       | n/a                         | DECIPHER |
| #5         | c.629T>C p.(Phe210Ser)       | *de novo* | m   | n/a                    | ID        | +   | −        | n/a                       | n/a                         | Guo et al. (2019) |
| #6         | c.1573_1574delinsTT p.(Gln525Leu) | *de novo* | m   | n/a                    | n/a       | +   | −        | n/a                       | n/a                         | Guo et al. (2019) |
| #7         | c.1247_1250del p.(Arg416Lysfs*145) | *de novo* | n/a | n/a                    | ID        | −   | −        | n/a                       | n/a                         | Lelieveld et al. (2016) |
| #8         | c.1518_1519insC p.(Ala507Argfs*14) | *de novo* | f   | 1                      | ID        | −   | + MAE   | n/a                       | Prominent lat. ventricles               | Rauch et al. (2012) |

Note: Variants based on NM_006372.5.  
Abbreviations: ASD, autism spectrum disorder; CSF, cerebrospinal fluid; DD, developmental delay; f, female; GW, gestational week; ID, intellectual disability; MAE, myoclonic-astatic epilepsy; m, male; n/a, not assessed.
FIGURE 1  (See caption on next page)
observed after initiation of the ketogenic diet. Additional features included facial dysmorphisms in individuals #1 and #3, macrocephaly (#1), and Hirschsprung disease requiring transanal rectosigmoidectomy in individual #1.

Brain MRI was performed in two of three individuals, which revealed widening of subarachnoid spaces in individual #1 and periventricular nodular heterotopic tissue (PVNH) in the right frontal lobe of individual #2 (Figure S2). Given the impairment due to the reflex seizures, treatment of the PVNH was attempted using stereotactic thermoagulation but failed to decrease seizure burden.

Exome sequencing identified three novel variants in SYNCRIP (Figure S3a; Table 1; Table S1). Concomitant exome sequencing of parental samples (individuals #2 and #3), as well as subsequent Sanger sequencing (individual #1), confirmed a de novo status of the changes in all individuals. In individuals #1 and #2, frameshift variants were detected: c.858_859del p.(Gly287Leufs*5) and c.854dupA p.(Asn285Lysfs*8), respectively. The small deletion of two nucleotides and the single nucleotide insertion both are predicted to result in a premature stop codon after five and eight amino acids, respectively. Subsequently, both frameshift variants putatively either cause a truncated SYNCRIP protein lacking parts of the RNA recognition motif (RRM) domain 2, all of domain RRM 3, and all C-terminal domains or lead to mRNA being degraded by nonsense-mediated decay. In individual #3, the missense variant c.734T>C p.(Leu245Pro) was identified, resulting in a substitution of leucine by proline at amino acid position 245, located at the beginning of the highly conserved RRM 2 domain, within a region of the protein completely spared from variation in healthy gnomAD controls (Figure S3B and Figure 1a–c). The vast majority of established VEP scores predict the substitution from leucine to proline at amino acid 245 as one of the most damaging among all biologically possible substitutions at this residue, suggesting high pathophysiological relevance (Table S2). To assess regions of functional conservation and vulnerability to missense variation, we generated heatmaps of all biologically possible SYNCRIP missense variants and their corresponding pathogenicity scores. In synopsis with gnomAD variant distribution, especially the central part (residues 150-400) of the protein, comprising the three RRM domains, is predicted to be highly vulnerable and is widely spared from polymorphisms in the general population. In contrast, N- and C-terminal regions show higher variability and lower vulnerability (Figure 1a–c). To analyze possible alterations from p.(Leu245Pro) on the tertiary structure of SYNCRIP, we generated a three-dimensional protein model, including the RRM 2 and RRM 3 domains (Figure 1d–f). Leu245, localized in the RNA binding pocket of RRM 2, maintains two polar hydrogen bonds to the neighboring residue Leu291 (Figure 1e). Substitution with Pro245 abolishes one of these H-bonds, thereby likely altering the tertiary structure and RNA binding capacity of RRM 2 (Figure 1f).

Progress in genome-wide genetic testing enabled the identification of a large number of genes associated with NDDs as well as developmental and epileptic encephalopathies (Guo et al., 2019; Lelieveld et al., 2016; Mefford et al., 2012; Rauch et al., 2012). According to recent estimations, up to 1000 additional NDD candidate genes remain to be identified (Kaplans et al., 2020). SYNCRIP encodes for the Synaptotagmin-binding cytoplasmic RNA-interacting protein that plays an essential role in mRNA splicing, editing, transport, and maturation (Blanc et al., 2001; Cappelli et al., 2018; Chen et al., 2020; Mizutani et al., 2000; Titlow et al., 2020). So far, de novo SYNCRIP variants have only been identified in four individuals with ID and ASDs in studies with large cohort sizes providing limited phenotypic details (Guo et al., 2019; Lelieveld et al., 2016; Rauch et al., 2012). Another individual with ID harboring a 77.92 kb deletion, including SYNCRIP, as the only protein-encoding gene is reported in the DECIPHER database (Firth et al., 2009). Here, we present genetic and clinical data of three additional individuals with de novo variants in SYNCRIP providing further evidence for its role in NDDs.

In line with previous reports, all individuals in our study presented with ID of various severity. Together with the individuals described here, autistic features or formal ASD were present in 4/8 individuals and epilepsy in 2/8 individuals. In both cases, seizures were triggered by tactile stimuli, widely affecting the quality of life, and largely refractory to different treatments. Failure of a surgical thermoagulation of one heterotopic nodule and the positive effects from the ketogenic diet are in line with the suspected diagnosis of idiopathic MAE. Interestingly, seizures in individual #2 were triggered by tactile stimuli, widely affecting the quality of life, and largely refractory to different treatments. Failure of a surgical thermoagulation of one heterotopic nodule and the positive effects from the ketogenic diet are in line with the suspected diagnosis of idiopathic MAE. Interestingly, the first reported child carrying a truncating SYNCRIP variant also presented with MAE underscoring the role of SYNCRIP as another candidate gene for this rare epilepsy

FIGURE 1 Two- and three-dimensional localization of SYNCRIP variants. (a) Linear representation of the SYNCRIP protein with highlighted functional domains as well as localization of pathogenic variants reported in the literature (black) and in this study (red). (b) Heatmap visualization of mean REVEL score values (score range: 0–1) of all biologically possible SYNCRIP missense variants. Functional domains are highlighted with dashed lines. (c) Regional density of tolerated (benign) gnomAD variants without respect to allele frequency. All three variants reported here are localized in the RNA-binding RRM 2 domain. Distributions of prediction score values and gnomAD variants suggest variation intolerance and functional conservation of RRM domains in contrast to the N-terminal and C-terminal sections containing R-G-G and Y-Y-G-Y repeats. (d) 3D ribbon model of the SYNCRIP protein region containing the RNA-binding domains RRM 2 (turquoise) and RRM 3 (orange), corresponding to residues 242-428 (PDB model 6KOR). Localization of the two novel frameshift variants p.(Asn285Lysfs*8) and p.(Gly287Leufs*5) is highlighted in red. Leu245 is shown as a red stick model. (e, f) Close-up views on Leu245 (e) and its substitution Pro245 (f). Hydrogen bonds to the neighboring residue Leu291 (turquoise sticks) are shown as dashed yellow lines. The substitution p.(Leu245Pro) leads to the loss of one hydrogen bond between amino acids 245 and 291, possibly affecting the tertiary structure of the RRM 2 RNA-binding pocket and subsequently altering protein function.
syndrome (Rauch et al., 2012). In line with this report, individuals with MAE frequently present with ID and ASD, but so far only a few genes have been associated, including SLC2A1, SLC6A1, several ion channels, as well as HNRNPU, another member of the hnRNP family (de Kovel et al., 2016; Hinokuma et al., 2020; Tang et al., 2020).

Individual #1 showed Hirschsprung disease, which has been observed in rare monogenic NDDs, such as Mowat-Wilson syndrome and Shprintzen-Goldberg syndrome (Heinritz et al., 2006). Therefore, we speculate that SYNCRIP-associated disorders not only affect the development of the central but also the enteric nervous system, possibly by interfering with the migration of neuronal progenitors during embryogenesis (Luzón-Toro et al., 2020).

All identified variants are absent in controls in the comprehensive gnomAD database. Two of our reported variants cause a frameshift with the formation of a premature stop codon, likely resulting in nonsense-mediated decay and haploinsufficiency (Lykke-Andersen & Jensen, 2015). The presence of only two C-terminal, truncating gnomAD variants further supports intolerance of SYNCRIP for loss-of-function variation (predicted loss-of-function index: 1.0).

In one individual, we identified a missense variant leading to a predicted amino acid exchange from leucine to proline at the evolutionarily highly conserved position 245 in the RRM 2 domain of SYNCRIP (Leu245Pro). RRM domains are widely spared from missense variations, which rather occur in the N- and C-terminal regions. Although leucine and proline both have nonpolar side chains, the introduced proline has a cyclic structure, higher hydrophilicity, and disrupts one of two hydrogen bonds, likely affecting the tertiary structure of the RRM 2 domain within SYNCRIP. These structural changes might lead to an impaired protein function due to a dysfunctional RNA-recognition domain that has been shown to be essential for RNA-binding and consequently for proper SYNCRIP functionality (Chen et al., 2020). Further, the conserved RRM domains are partly shared by other members of the large hnRNP family comprising multiple genes encoding for ribonucleoproteins. Similar to SYNCRIP, central RRM domains of other hnRNP family members are spared from variation in the general population supporting the essential role of these motifs. Besides SYNCRIP/hnRNPQ, hnRNPU has previously been associated with developmental and epileptic encephalopathies highlighting the importance of this gene family for physiological neurodevelopment and making genes within this family putative candidates for NDDs (Ep4K et al., 2013; Hinokuma et al., 2020).

By reporting three additional individuals with de novo SYNCRIP variants within this study, we expand the number of individuals with pathogenic variants in this gene. Comparison of clinical phenotypes of all eight individuals with de novo SYNCRIP variants suggests ID as a shared phenotype with variable additional neurological manifestations, such as ASD and epilepsy. Being present in two individuals, MAE is also included in the spectrum of SYNCRIP-associated disorders. With four truncating frameshift variants and one gene deletion, haploinsufficiency appears to be the most likely mechanism of disease. The milder phenotype of individual #3 carrying a missense variant further suggests genotype-phenotype correlations.

In conclusion, our study further establishes SYNCRIP variants as a cause for ID, ASD, variable malformations of cortical development and the enteric nervous system, as well as MAE in a subset of affected individuals.

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CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT
All data that supports the findings of this study are available in the manuscript and in the supplementary material of this article.

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