
White Rose Research Online

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk
Universities of Leeds, Sheffield and York

Deposited via The University of Sheffield.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/id/eprint/133110/

Version: Accepted Version

Article:
Kanani, F., Study, D. and Balasubramanian, M. (2018) SHANK3 variant as a cause of nonsyndromal autism in an 11-year-old boy and a review of published literature. Clinical Dysmorphology, 27 (4). pp. 113-115. ISSN: 0962-8827

https://doi.org/10.1097/MCD.0000000000000232

© 2018 Wolters Kluwer Health, Inc. This is an author produced version of a paper subsequently published in Clinical Dysmorphology. Uploaded in accordance with the publisher's self-archiving policy.

Reuse
Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



SHANK3 variant as a cause of non syndromal autism in an 11-year old boy and review of published literature

Kanani F[1], Balasubramanian M[1]

[1]Sheffield Clinical Genetics Service, Sheffield Children's NHS Foundation Trust, UK

*Author to whom correspondence should be addressed

Dr. Meena Balasubramanian, Sheffield Clinical Genetics Service, Sheffield Children's Hospital NHS Foundation Trust, Western Bank, Sheffield S10 2TH; Phone: +44 114 2717025; Fax: +44 114 2737467; E-mail: meena.balasubramanian@nhs.net

KEYWORDS: Autism; genomics; *SHANK3*; social communication

CONFLICTS OF INTEREST: None to declare

Abstract:

Autism spectrum disorder (ASD) encompasses a spectrum of pervasive neuropsychiatric disorders characterised by deficits in social interaction, communication, unusual and repetitive behaviour. The aetiology of ASD is believed to involve complex interactions between genetic and environmental factors; it can be further classified as syndromic or non-syndromic, according to whether it is the primary diagnosis or secondary to an existing condition where both common and rare genetic variants contribute to the development of ASD or are clearly causal.

The prevalence of ASD in children is increasing with higher rates of diagnosis and an estimated 1 in 100 affected in the UK.[i] Given that heritability is a major contributing factor, we aim to discuss research findings to-date in the context of a high risk autism candidate gene, *SHANK3* (SH3 and multiple ankyrin repeat domain 3), with its loss resulting in synaptic function disruption.

We present a 10-year old patient with a pathogenic *de novo* heterozygous c.1231delC, p.Arg411Val frameshift variant in *SHANK3*. He presented with severe autism, attention deficit hyperactivity disorder and pathological demand avoidance, on a background of developmental impairment and language regression.

The number of genes associated with autism is ever increasing. It is a heterogeneous group of disorders with no single gene conferring pathogenesis in the majority of cases. Genetic abnormalities can be detected in approximately 15% of ASD and these range from copy number variants in 16p11.2 and 15q13.2q13.3 to several well-known genetic disorders including Tuberous Sclerosis and Fragile X syndrome. Further high confidence autism genes include but are not limited to: *NRXN*, *NLGN 3*, *NLGN 4*, *SHANK 2* and *SHANK3*.

Introduction:

Autism has a worldwide childhood prevalence of approximately 1 in 160 children[ii] and has become a frequent reason for referral to paediatric genetic services. Due to its clinical and genetic heterogeneity, the underlying cause for ASD remains unclear. However, advances in genetic testing have led to the discovery of several high risk autism candidate genes.[iii]

Here, we focus our attention on one of these high risk genes, *SHANK3*. This gene is strongly expressed in the cerebral cortex and cerebellum and encodes a scaffold protein involved in the postsynaptic density (PSD) of excitatory synapses.[iv]

It is widely known that microdeletions of 22q13 region involving *SHANK3* are responsible for the clinically recognizable Phelan-McDermid syndrome (PMS)[v] characterised by global developmental delay, intellectual disability (ID), absent or severely delayed speech, autism spectrum disorder, hypotonia, and distinctive facial dysmorphic features. However, *SHANK3* variants have also been reported in individuals with autism and/or intellectual disability.[vivii]

The SHANK3 protein is a crucial component of the postsynaptic density that takes part in the neuroligin-neurexin interaction at glutamate synapses. Genetic studies show that the neurexin-neuroligin (NRXN-NLGN) pathway genes contribute susceptibility to ASD, which include cell adhesion molecules *NLGN3*, *NLGN4* (also named *NLGN4X*), *NRXN1* and scaffolding proteins *SHANK2* and *SHANK3* [viii]

Clinical report:

This 10-year old boy was the fifth pregnancy to healthy non-consanguineous, Caucasian parents. There had been two miscarriages prior to this pregnancy. He was born at term with a birth weight of 4.5kg. There was bleeding throughout pregnancy but antenatal scans were normal. There was an increased risk of Down syndrome reported on antenatal screening.

In terms of his development, he could sit unaided at 7 months and walked at 10 months. He had multiple words at 11 months, but subsequently lost speech until the age of 4. At his 2 year check, there were concerns regarding poor eye contact and limited speech. Following a clinical psychologist assessment, he fulfilled the criteria for severe autism. His parents reported episodes consistent with absence seizures at this stage too.

At age 5, he was attending mainstream school with additional support of two teaching assistants. Communication and social skills were noted to be poor. In terms of behaviour, frustration and violent traits were noted. He was late to develop imaginary play and weakness in social interaction with peers was noted. At age 10, he was attending a special needs school. He was exhibiting pathological demand avoidance and complex social impairments.

Clinical examination did not reveal any dysmorphic features (Figure 1).
Investigations so far have included: an EEG which was unremarkable; Cytogenetics showing a normal male karyotype (46XY) and Fragile X testing which was also negative. A microarray revealed no clinically significant imbalances, after which the patient was enrolled in the Deciphering Developmental Delay (DDD) study which identified a *de novo* heterozygous c.1231delC, p.Arg411Val frameshift variant in *SHANK3*.

Discussion:

Patients with ASDs and ID carrying *SHANK3* variants have been described in the literature. Several papers have reported *SHANK3* variants in ASD patients, consisting of copy number variants,[ix] point variants,[xxixiiixiii] and polymorphisms.[xiv]

De novo pathogenic variants in *SHANK 3* accounted for 1.4% and 0.75% of ASD cohort subjects in studies conducted in 2007 by Durand et al and Moessner et al respectively. [xv] Bozdagi et al in 2011 reported that the loss of one copy of *SHANK3* correlates with behavioural issues reproducing most of the ASD traits, such as deficits in social interaction, social communication, and compulsive/repetitive actions.[xvi]

Buccuto et al in 2013 assessed the prevalence of variants in *SHANK3* in two cohorts of patients with different subtypes of ASD. [xvii] Pathogenic alterations in *SHANK3* were found in 2.3% of cases (5 patients): one 106 kb deletion encompassing the *SHANK3* gene, two frameshift variants leading to premature stop codons, one missense variant (p.Pro141Ala), and one splice site variant (c.1820-4G>A). It was also noted that in the cases of the *SHANK3* deletion and frameshift variants, the patients showed some degree of speech or developmental delay in association with autistic traits, similar to the patient we report here. It is plausible that the overall level of functional SHANK3 protein is lower as a result of these variants compared to cases with different types of variants.

Nemirovsky et al in 2015 described three siblings with ASD, intellectual disability and absence of language to have germline mosaicism for a heterozygous deletion of a cytosine in the exon 21 of the *SHANK3* gene. This resulted in the substitution of five amino acids followed by a premature stop codon (NM_033517:c.3259_3259delC, p.Ser1088Profs*6).[xviii]

Terrone et al in 2017 went on to describe a family with four members carrying an interstitial microdeletion within *SHANK3* leading to intellectual disability[xix]. This involved a mother and three children and was the first report of a familial microdeletion. Each carrier in this family presented with symptoms of autism.

However, Liu et al in 2013 did not find any significant association between four high risk genes (*NLGN3, NLGN4, SHANK 2 and SHANK 3*) and ASD cases in a Chinese population. [xx] This perhaps highlights the heterogeneous nature of ASD, variability of gene function in different populations but also the role of environmental factors and their potential contribution to the phenotype.[xxi]

Conclusion

Autism spectrum disorders (ASD) describes a heterogeneous spectrum of disorders with no single causal gene conferring pathogenicity in the majority of cases. The disease process comprises great genetic and phenotypic complexity.

Our report details a 10-year old boy with a *de* novo heterozygous c.1231del, p.Arg411Val frameshift variant in *SHANK3, a* high risk candidate autism gene. We report significant speech delay and seizures as an association with this phenotype.

Our case findings appear to be in line with previous findings for *SHANK3* and other genes involved in the neurexin-neuroligin complex. Further case reports of this nature will continue to expand the phenotype and understand the variable expressivity of *SHANK3*.

Acknowledgements

The DDD study presents independent research commissioned by the Health Innovation Challenge Fund [grant number HICF-1009-003], a parallel funding partnership between the

Wellcome Trust and the Department of Health, and the Wellcome Trust Sanger Institute [grant number WT098051]. The views expressed in this publication are those of the author(s) and not necessarily those of the Wellcome Trust or the Department of Health. The study has UK Research Ethics Committee approval (10/H0305/83, granted by the Cambridge South REC, and GEN/284/12 granted by the Republic of Ireland REC). The research team acknowledges the support of the National Institute for Health Research, through the Comprehensive Clinical Research Network.

We would also like to thank the family for consenting to this publication.

Conflicts of interest

None to declare

References:-

[i] The National Autistic Society [accessed 16 October 2017] http://www.autism.org.uk/about/what-is/myths-facts-stats.aspx

[ii] Autism Spectrum Disorders. World Health Organisation. [date updated April 2017, date accessed 16 October 2017] http://www.who.int/mediacentre/factsheets/autism-spectrum-disorders/en/

[iii] SFARIGENE. c2017[accessed 16 October 2017] http://gene.sfari.org/

[iv] Boeckers, T.M, Bockmann, J, Kreutz M.R and Gundelfinger E.D. 2002. ProSAP/Shank proteins – a family of higher order organizing molecules of the postsynaptic density with an emerging role in human neurological disease. J Neurochem. 2002; 81: 903–910

[v] Kolevzon A, Angarita B, Bush L, Wang A.T, Frank Y, Yang A, Rapaport R, Saland J, Srivastava S, Farrell C, Edelmann L.J, and Buxbaum J.D. 2014. Phelan-McDermid syndrome: a review of the literature and practice parameters for medical assessment and monitoring. J Neurodev Disord. 2014;6: 39

[vi] Durand C.M, Betancur C, Boeckers T.M, Bockmann J, Chaste P, Fauchereau F, Gillberg I.C, Sponheim E, Goubran-Botros H, Mouren-Simeoni M.C et al. 2007. Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nat Genet*. 2007; 39: 25–27

[vii] Gauthier J, Spiegelman D, Piton A, Lafreniere RG, Laurent S, St-Onge J, Lapointe L, Hamdan FF, Cossette P, Mottron L et al. 2009. Novel de novo SHANK3 mutation in autistic patients. Am J Med Genet B Neuropsychiatr Genet 150B: 421–424

[viii] Craig AM, Kang Y. 2007. Neurexin-neuroligin signaling in synapse development. Curr Opin Neurobiol17: 43–52

[ix] Marshall CR, Noor A, Vincent JB, Lionel AC, Feuk L, Skaug J, Shago M, Moessner R, Pinto D, Ren Y et al. 2008. Structural variation of chromosomes in autism spectrum disorder. Am J Hum Genet 2008; 82: 477–488.

[x] Moessner R, Marshall CR, Sutcliffe JS, Skaug J, Pinto D, Vincent J, Zwaigenbaum L, Fernandez B, Roberts W, Szatmari P et al. 2007. Contribution of SHANK3mutations to autism spectrum disorder. Am J Hum Genet 2007; 81: 1289–1297.

[xi] Gauthier J, Spiegelman D, Piton A, Lafrenière RG, Laurent S, St-Onge J, Lapointe L, Hamdan FF, Cossette P, Mottron L et al. 2009. Novel de novo SHANK3 mutation in autistic patients. Am J Med Genet 2009; 150B: 421–424.

[xii] Waga C, Okamoto N, Ondo Y. 2011. Novel variants of the SHANK3 gene in Japanese autistic patients with severe delayed speech development. Psychiatr Genet 2011; 21: 208–211.

[xiii] Buxbaum JD. 2009. Multiple rare variants in the etiology of autism spectrum disorders. Dialogues Clin Neurosci 11: 35–43

[xiv] Mashayekhi F, Mizban N, Bidabadi E, Salehi Z. 2016. The association of SHANK3 gene polymorphism and autism. Minerva Pediatr. 2016.

[xv]Moessner R, Marshall CR , Sutcliffe JS, Skaug J, Pinto D, Vincent J, Zwaigenbaum L, Fernandez B, Roberts W, Szatmari P et al. 2007. Contribution of SHANK3 Mutations to Autism Spectrum Disorder. Am J Hum Genet. 2007 Dec; 81(6): 1289–1297.

[xvi] Bozdagi O, Sakurai T, Papapetrou D, Wang X, Dickstein DL, Takahashi N, Kajiwara Y, Yang M, Katz AM, Scattoni ML et al. 2011. Haploinsufficiency of the autism-associated Shank3 gene leads to deficits in synaptic function, social interaction, and social communication. Mol Autism 2011; 1: 1–15.

[xvii] Boccuto L, Lauri M, Sarasua SM, Skinner CD, Buccella D, Dwivedi A, Orteschi D, Collins JS, Zollino M, Visconti P et al. 2013. Prevalence of SHANK3 variants in patients with different subtypes of autism spectrum disorders. Eur J Hum Genet. 2013 Mar;21(3):310-6.

[xviii] Nemirovsky SI, Córdoba M, Zaiat JJ, Completa SP, Vega PA, González-Morón D, Medina NM, Fabbro M, Romero S, Brun B et al. 2015. Whole genome sequencing reveals a de novo SHANK3 mutation in familial autism spectrum disorder. PLoS One 3;10(2):e0116358.

[xix] Terrone G, Vitiello G, Genesio R, D'Amico A, Imperati F, Ugga L, Giugliano T, Piluso G, Nitsch L[3], Brunetti-Pierri N et al. A novel SHANK3 interstitial microdeletion in a family with intellectual disability and brain MRI abnormalities resembling Unidentified Bright Objects.
Eur J Paediatr Neurol. 2017 Nov;21(6):902-906.

[xx] Liu Y, Du Y, Liu W, Yang C, Liu Y, Wang H, Gong X. 2013. Lack of association between NLGN3, NLGN4, SHANK2 and SHANK3 gene variants and autism spectrum disorder in a Chinese population.
PLoS One 8(2):e56639.

[xxi] Grabrucker AM. 2013. Environmental factors in autism. Front Psychiatry 3:118. doi: 10.3389/fpsyt.2012.00118.