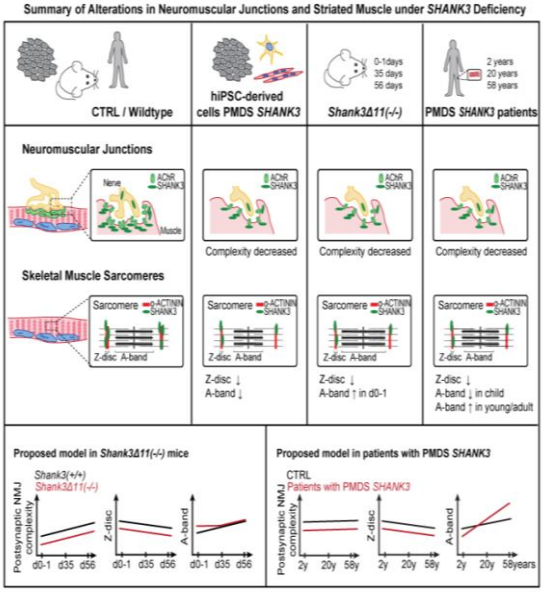
Autism-associated SHANK3 mutations impair maturation of neuromuscular junctions and striated muscles

Anne-Kathrin Lutz [1], Stefanie Pfaender [1], **Berra Incearap** [1], Valentin Ioannidis [1], Ilaria Ottonelli [1], Karl J Föhr [2], Judith Cammerer [1], Marvin Zoller [1], Julia Higelin [1], Federica Giona [3 4], Maximilian Stetter [1], Nicole Stoecker [1], Najwa Ouali Alami [5], Michael Schön [1], Michael Orth [5], Stefan Liebau [6], Gotthold Barbi [7], Andreas M Grabrucker [8 9 10], Richard Delorme [11], Michael Fauler [12], Benjamin Mayer [13], Sarah Jesse [5], Francesco Roselli [5], Albert C Ludolph [5], Thomas Bourgeron [14], Chiara Verpelli [3 4], Maria Demestre [15], Tobias M Boeckers [15 5]

[1]Institute for Anatomy and Cell Biology, Ulm University, 89081 Ulm, Germany.
[2]Department of Anesthesiology, Ulm University Hospital, 89081 Ulm, Germany.
[3]CNR Neuroscience Institute, University of Milan, 20129 Milan, Italy.
[4]BIOMETRA University of Milan, 20129 Milan, Italy.
[5]DZNE, Ulm Site, 89081 Ulm, Germany.
[6]Institute of Neuroanatomy and Developmental Biology, Eberhard Karls University Tübingen, 72074 Tübingen, Germany.
[7]Institute for Human Genetics, Ulm University Hospital, 89081 Ulm, Germany.
[8]Cellular Neurobiology and Neuro-Nanotechnology Lab, Department of Biological Sciences, University of Limerick, V94PH61 Limerick, Ireland.
[9]Bernal Institute, University of Limerick, V94T9PX Limerick, Ireland.
[10]Health Research Institute (HRI), University of Limerick, V94T9PX Limerick, Ireland.
[11]Child and Adolescent Psychiatry Department, APHP, Robert-Debré Hospital, 750197 Paris, France.
[12]Institute of General Physiology, Ulm University, 89081 Ulm, Germany.
[13]Institute of Epidemiology and Medical Biometry, Ulm University, 89075 Ulm, Germany.
[14]Génétique Humaine et Fonctions Cognitives, Université Paris Diderot, Institut Pasteur, 75015 Paris, France.
[15]Institute for Anatomy and Cell Biology, Ulm University, 89081 Ulm, Germany. mdemestre@ibecbarcelona.eu tobias.boeckers@uni-ulm.de.

Abstract:

Heterozygous mutations of the gene encoding the postsynaptic protein SHANK3 are associated with syndromic forms of autism spectrum disorders (ASDs). One of the earliest clinical symptoms in SHANK3-associated ASD is neonatal skeletal muscle hypotonia. This symptom can be critical for the early diagnosis of affected children; however, the mechanism mediating hypotonia in ASD is not completely understood. Here, we used a combination of patient-derived human induced pluripotent stem cells (hiPSCs), *Shank3Δ11(-/-)* mice, and Phelan-McDermid syndrome (PMDS) muscle biopsies from patients of different ages to analyze the role of SHANK3 on motor unit development. Our results suggest that the hypotonia in SHANK3 deficiency might be caused by dysfunctions in all elements of the voluntary motor system: motoneurons, neuromuscular junctions (NMJs), and striated muscles. We found that SHANK3 localizes in Z-discs in the skeletal muscle sarcomere and co-immunoprecipitates with α-ACTININ. SHANK3 deficiency lead to shortened Z-discs and severe impairment of acetylcholine receptor clustering in hiPSC-derived myotubes and in muscle from *Shank3Δ11(-/-)* mice and patients with PMDS, indicating a crucial role for SHANK3 in the maturation of NMJs and striated muscle. Functional motor defects in *Shank3Δ11(-/-)* mice could be rescued with the troponin activator Tirasemtiv that sensitizes muscle fibers to calcium. Our observations give insight into the function of SHANK3 besides the central nervous system and imply potential treatment strategies for SHANK3-associated ASD.



Biography:



Berra Incearap is a PhD student at the Institute for Anatomy and Cell Biology at the University of Ulm lead by Prof. Dr. Tobias Böckers. As a student from the International Graduate School in Molecular Medicine Ulm, she is interested in investigating the effects of an autism-associated *SHANK3* mutation on the myelin sheath.

From 2014 to 2017 Mrs. Incearap studied Biology at the University of Ulm, Germany. She completed this study course with a Bachelor of Science and continued her scientific education with the master's course Molecular and Translational Neuroscience at the same institution. In 2019 she was able to finish this course with a master's degree. In her master´s thesis, she was focusing on understanding the concept of an autism-associated *SHANK3* mutation on neonatal skeletal muscle hypotonia utilizing human induced pluripotent stem cell techniques, a transgenic mouse model, and skeletal muscle biopsies from Phelan-McDermid Syndrome patients with *SHANK3* deletions.

Email: berra.incearap@uni-ulm.de

Presenting author details:
Full name: Berra Incearap
Contact number: +4917634589957

Twitter account: -
LinkedIn account: https://www.linkedin.com/in/berra-incearap-3568aa210/
Facebook account: -
Session name/ number:
Category: Oral Presentation