

# Heiko Brennenstuhl, MD, MBA

## Professional Address

Institute of Human Genetics  
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## SUMMARY

Heiko Brennenstuhl is an accomplished MD and board-certified pediatrician with extensive experience in clinical medicine and research. He completed clinical rotations in Germany, the US, the U.K., China, and Switzerland and has been the recipient of several prestigious grants and awards, including a DAAD stipend to study at Brown University. He holds an MBA degree in Leadership and Management in Healthcare from the University of Applied Sciences Neu-Ulm and is currently leading a study on the technical feasibility of genomic newborn screening. This project combines his clinical and research skills to improve early detection and treatment of genetic diseases in newborns.

## EDUCATION

**Board-Certified Pediatrician**, Ärztekammer Baden-Württemberg April 2023

**Master of Business Administration**, Management and Leadership in Health Care July 2021  
University of Applied Sciences, Neu-Ulm, Germany

Thesis title: "Development of recommendations for the implementation and quality assurance of an innovative gene therapy approach as well as derivation of a cost calculation for an outpatient follow-up model"

Degree: 1.7

**Medical Degree**, Eberhard Karls Universität Tübingen, Germany July 2016

Doctoral thesis work performed at the Hertie Institute for Clinical Brain Research, Department for General Neurology, Laboratory for Molecular Neuro-Oncology

Thesis title: "IKB $\zeta$ , an atypical inhibitor of NF $\kappa$ B-mediated cell death in glioblastoma"

Degree: *Magna cum laude*

## PROFESSIONAL EXPERIENCE

**Institute of Human Genetics, University Heidelberg, Germany** Since May 2022

Medical Doctor at the Institute for Human Genetics

- Diagnostic workup and consulting of patients suffering from genetic diseases

**Center for Child and Adolescent Medicine, Heidelberg, Germany** October 2016 - May 2022

Medical Doctor at the Department of General Pediatrics, Metabolism, Gastroenterology, Nephrology

- Clinical care of children and adolescents with congenital and acquired diseases in the field of neurometabolism, pediatric infectious diseases, autoimmune diseases and childhood cancers.
- Subinvestigator for the Natural History Study of Patients with Succinic Semialdehyde Dehydrogenase (SSADH) Deficiency; ClinicalTrials.gov: NCT03758521.
- Elected resident representative assigned to plan and coordinate regular rotation schedules.

**Dietmar-Hopp Metabolic Center, Heidelberg, Germany** October 2018 - May 2022

Post-doctoral researcher at the group of inborn errors of neurotransmitters and pterins

- Exploring congenital disorders of neurotransmission with induced pluripotent stem cells to generate cerebral organoids.
- Improving diagnostic capabilities for early detection of congenital neurotransmitter disorders in newborn screening.

## FUNDING / GRANTS (Competitively acquired third-party funds)

- Klinz Foundation project funding: “Human stem cell-based cerebral organoids for research of diagnostics and therapy of succinate-semialdehyde dehydrogenase deficiency”, sum 20.000 €
- APS project funding: ”Investigation of the pathophysiology of primary neurotransmitter defects using induced pluripotent stem cells (iPS) and iPS-based cerebral organoids“, sum 10.000 €
- Innovation award for outstanding SSADH research, SSADH Defizit e.V., sum 1.000 €
- Physician Scientist scholarship, Medical Faculty University Heidelberg
- Project funding, SSADH Defizit e.V., structured course in organoid generation at LMU Munich, sum 3.000 €
- Project funding, SSADH Defizit e.V., ”Immunohistochemical characterization of SSADH organoids“, sum 5.000 €
- DAAD scholarship to study at Warren Alpert Medical School, Brown University, Providence, Rhode Island, USA
- IZKF scholarship, Medical Faculty University Tübingen, sum 13.500 € (divided to 6.000 € personal budget and 7.500 € consumables)

## PUBLICATIONS (First / Co-First or Last Author)

- Christmann, M., Opladen, T., **Brennenstuhl, H.** (2023). Sprachliche Auffälligkeiten bei Succinat-Semialdehyd-Dehydrogenase-Mangel – die Untersuchung der Sprache bei drei von SSADHD betroffenen Personen. *Praxis Sprache* 2023.
- Schröter, J., Dattner, T., Hüllelein, J., Jayme, A., Heuveline, V., Hoffmann, G. F., Kölker, S., Lenz, D., Opladen, T., Popp, B., Schaaf, C. P., Stauffer, C., Syrbe, S., Uhrig, S., Hübschmann, D., **Brennenstuhl, H.** (2022). aRgus: Multilevel visualization of non-synonymous single nucleotide variants & advanced pathogenicity score modeling for genetic vulnerability assessment. (2023). *Computational and Structural Biotechnology Journal*. <https://doi.org/10.1016/j.csbj.2023.01.027>
- Keller, M., **Brennenstuhl, H.**, Kuseyri Hübschmann, O., Manti, F., Julia Palacios, N. A., Friedman, J., Yildiz, Y., Koht, J. A., Wong, S. N., Zafeiriou, D. I., Lopez-Laso, E., Pons, R., Kulhanek, J., Jeltsch, K., Serrano-Lomelin, J., Garbade, S. F., Opladen, T., Goez, H., International Working Group on Neurotransmitter related, Disorders (2021). Assessment of intellectual impairment, health-related quality of life, and behavioral phenotype in patients with neurotransmitter related disorders: Data from the iNTD registry. *J Inherit Metab Dis*, 44(6), 1489-1502.
- **Brennenstuhl, H.**, Nashawi, M., Schroter, J., Baronio, F., Beedgen, L., Gleich, F., Jeltsch, K., von Landenberg, C., Martini, S., Simon, A., Thiel, C., Tsiakas, K., Opladen, T., Kolker, S., Hoffmann, G. F., Haas, D., Unified Registry for Inherited Metabolic Disorders, C., and the European Registry for Hereditary Metabolic, D. (2021). Phenotypic diversity, disease progression, and pathogenicity of *MVK* missense variants in mevalonic aciduria. *J Inherit Metab Dis*, 44(5), 1272-1287.
- **Brennenstuhl, H.**, Christ, S., Kock, V. (2021). The ”Young Metabolic Society“: An interest group for young professionals in the field of metabolic medicine. *J Inherit Metab Dis*, 44(4), 789.
- **Brennenstuhl, H.**, Will, M., Ries, E., Mechler, K., Garbade, S., Ries, M. (2021). Patterns of extreme temperature-related catastrophic events in Europe including the Russian Federation: a cross-sectional analysis of the Emergency Events Database. *BMJ Open*, 11(6), e046359.
- **Brennenstuhl, H.**, Opladen, T. (2021). Neue biochemische Methoden zur Diagnose des Aromatischen L-Amino-säure Decarboxylase (AADC)-Mangels. *Neuropädiatrie in Klinik und Praxis*, 20. Jg.
- **Brennenstuhl, H.**, Didiasova, M., Assmann, B., et al. Succinic Semialdehyde Dehydrogenase Deficiency: in vitro and in silico characterization of a novel pathogenic missense variant and analysis of the mutational spectrum of *ALDH5A1*. *Int. J. Mol. Sci.*, 2020, 21(22), 8578.
- **Brennenstuhl, H.**, Garbade, S.F., Okun, J.G., et al. Semi-quantitative detection of a vanillic acid / vanillylmandelic acid ratio in urine is a reliable diagnostic marker for aromatic L-amino acid decarboxylase deficiency. *Mol Genet Metab*. 2020; 1096-7192(20)30151-7.
- **Brennenstuhl, H.**, Kohlmüller, D., Gramer, G., et al. High throughput newborn screening for aromatic L-amino-acid decarboxylase deficiency by analysis of concentrations of 3-O-methyldopa from dried blood spots. *J Inherit Metab Dis*. 2020;43(3):602-610.
- **Brennenstuhl, H.**, Jung-Klawitter, S., Assmann, B., Opladen, T.. Inherited Disorders of Neurotransmitters: Classification and Practical Approaches for Diagnosis and Treatment. *Neuropediatrics*. 2019;50(1):2-14.
- **Brennenstuhl, H.**, Armento, A., Braczynski, A.K., Mittelbronn, M., Naumann, U. (2015).  $\text{I}\kappa\text{B}\zeta$ , an atypical member of the inhibitor of  $\text{NF}\kappa\text{B}$  family, is induced by gamma-irradiation in glioma cells, regulating cytokine secretion and associated with poor prognosis. *Int J Oncol*. 2015;47(5):1971-1980.

## PUBLICATIONS (Co-Authorships)

- Maaß, G.F., **Brennenstuhl, H.**, Schaaf, C.P. (2023). Morbidity and mortality in Schaaf-Yang syndrome. *Annals of Translational Medicine*, <https://dx.doi.org/10.21037/atm-23-1718>
- Szakszon, K., Lourenco, C. M., Callewaert, B. B., Geneviève, D., Rouxel, F., Morin, D., Denommé-Pichon, A.S., Vitobello, A., Patterson, W., Louie, R., Pinto E, V. F., Klee, E., Kaiwar, C., Gavrilova, R., Agre, K., Jacquemont, S., Khadijé, S., Giltay, J., van Gassen, K., Merő, G., Gerkes, E., Van Bon, B., Rinne, T., Pfundt, R., Brunner, H.G., Caluseriu, O., Grasshoff, U., Kehrer, M., Haack, T.B., Khelifa, M.M., Bergmann, A.K., Cueto-González, A.M., Martorell, A.C., Ramachandrappa, S., Sawyer, L., Fasel, P., Braun, D., Isis, A., Superti-Furga, A., McNiven, V., Chitayat, D., Ahmed, S.A., **Brennenstuhl, H.**, Schwaibold, E., Battisti, G., Parmentier, B., Stevens, S. Further delineation of the rare GDACCF (global developmental delay, absent or hypoplastic corpus callosum, dysmorphic facies syndrome): genotype and phenotype of 22 patients with ZNF148 mutations. *J Med Genet.* 2023 Aug 14;jmg-2022-109030. <http://dx.doi.org/10.1136/jmg-2022-109030>
- Roubertie, A., Opladen, T., **Brennenstuhl, H.**, Hübschmann, O. K., Flint, L., Willemsen, M. A., Leuzzi, V., Cazorla, A. G., Kurian, M. A., François-Heude, M. C., Hwu, P., Ben Zeev, B., Kiening, K., Roujeau, T., Pons, R., Pearson, T. S. (2023). Gene therapy for aromatic L-amino acid decarboxylase deficiency: requirements for safe application and knowledge-generating follow-up. *Journal of inherited metabolic disease*, 10.1002/jimd.12649. <https://doi.org/10.1002/jimd.12649>
- Käseberg, S., Bertin, M., Menon, R., Gabassi, E., Todorov, H., Frank, S., **Brennenstuhl, H.**, Lohrer, B., Winter, J., Krummeich, J., Winkler, J., Winner, B., Weis, E., Hartwich, D., Diederich, S., Luck, K., Gerber, S., Lunt, P., Berninger, B., Falk, S., Schweiger, S., Karow, M. (2023). Dynamic X-chromosomal reactivation enhances female brain resilience. *bioRxiv* 2023.06.17.545424; doi: <https://doi.org/10.1101/2023.06.17.545424>
- Vogel, G. F., Mozer-Glassberg, Y., Landau, Y. E., Schlieben, L. D., Prokisch, H., Feichtinger, R. G., Mayr, J. A., **Brennenstuhl, H.**, Schröter, J., Pechlaner, A., Alkuraya, F. S., Baker, J. J., Barcia, G., Baric, I., Braverman, N., Burnyte, B., Christodoulou, J., Ciara, E., Coman, D., Das, A. M., ... Wortmann, S. (2022). Genotypic and phenotypic spectrum of infantile liver failure due to pathogenic TRMU variants. *Genetics in medicine*, S1098-3600(22)00953-4. Advance online publication. <https://doi.org/10.1016/j.gim.2022.09.015>
- Goetz, M., Schröter J., Dattner, T., **Brennenstuhl, H.**, Lenz, D., Opladen, T., Hörster, F., Okun, J. G., Hoffmann, G. F., Kölker, S., Staufner, C. (2022). Genotypic and phenotypic spectrum of cytosolic phosphoenolpyruvate carboxykinase deficiency. *Molecular Genetics and Metabolism*. Volume 137, Issues 1–2, September–October 2022, Pages 18–25. <https://doi.org/10.1016/j.ymgme.2022.07.007>
- Scharping, M., **Brennenstuhl, H.**, Garbade, S.F., Wild, B., Posset, R., Zielonka, M., Kölker, S., Haun, M.W., Opladen, T. Unmet Needs of Parents of Children with Urea Cycle Disorders. *Children* 2022, 9, 712. <https://doi.org/10.3390/children9050712>
- Schröter, J., Popp, B., **Brennenstuhl, H.**, Döring, J. H., Donze, S. H., Bijlsma, E. K., van Haeringen, A., Huhle, D., Jestaedt, L., Merckenschlager, A., Arelin, M., Gräfe, D., Neuser, S., Oates, S., Pal, D. K., Parker, M. J., Lemke, J. R., Hoffmann, G. F., Kölker, S., Harting, I., Syrbe, S. (2022). Complementing the phenotypical spectrum of *TUBA1A* tubulinopathy and its role in early-onset epilepsies. *European journal of human genetics : EJHG*, 10.1038/s41431-021-01027-0. Advance online publication. <https://doi.org/10.1038/s41431-021-01027-0>
- Weiß, C., Ziegler, A., Becker, L. L., Johannsen, J., **Brennenstuhl, H.**, Schreiber, G., Flotats-Bastardas, M., Stoltenburg, C., Hartmann, H., Illsinger, S., Denecke, J., Pechmann, A., Müller-Felber, W., Vill, K., Blaschek, A., Smitka, M., Stam, L. v. d., Weiss, K., Winter, B., Goldhahn, K., Plecko, B., Horber, V., Bernert, G., Husain, R. A., Rauscher, C., Trollmann, R., Garbade, S. F., Hahn, A., v.d. Hagen, M., Kaindl, A. M. (2021). Gene replacement therapy with onasemnogene abeparvovec in children with spinal muscular atrophy aged 24 months or younger and bodyweight up to 15 kg: an observational cohort study. *Lancet Child Adolesc Health*. 2021 Oct 28:S2352-4642(21)00287-X.
- Opladen, T., **Brennenstuhl, H.**, Kuseyri Hübschmann, O., Call, D., Green, K., Schara, U., Rascher, W., Hövel, A., Assmann, B., Kölker, S., Westhoff, J. H., Walter, M., Ziegler, A., Hoffmann, G. F., Kiening, K. (2021). Die intrazerebrale Gentherapie des Aromatischen-L-Aminosäure-Decarboxylase-Mangels mit Eladocagene exuparvovec. *Monatsschrift Kinderheilkunde*, 169(8), 738-747.
- Longo, C., Montioli, R., Bisello, G., Palazzi, L., Mastrangelo, M., **Brennenstuhl, H.**, de Laureto, P. P., Opladen, T., Leuzzi, V., Bertoldi, M. (2021). Compound heterozygosis in AADC deficiency: A complex phenotype dissected through comparison among heterodimeric and homodimeric AADC proteins. *Mol Genet Metab*, 134(1-2), 147-155.
- Semino, F., Schroter, J., Willemsen, M. H., Bast, T., Biskup, S., Beck-Woedl, S., **Brennenstuhl, H.**, Schaaf, C. P., Kolker, S., Hoffmann, G. F., Haack, T. B., Syrbe, S. (2021). Further evidence for de novo variants in SYNCRIP as the cause of a neurodevelopmental disorder. *Hum Mutat*, 42(9), 1094-1100.

- Döring, J. H., Schröter, J., Jüngling, J., Biskup, S., Klotz, K. A., Bast, T., Dietel, T., Korenke, G. C., Christoph, S., **Brennenstuhl, H.**, Rubboli, G., Möller, R. S., Lesca, G., Chaix, Y., Kölker, S., Hoffmann, G. F., Lemke, J. R., Syrbe, S. (2021). Refining Genotypes and Phenotypes in KCNA2-Related Neurological Disorders. *International Journal of Molecular Sciences*, 22(6).
- Lenz, D., Stahl, M., Seidl, E., **Brennenstuhl, H.**, et al. Rescue of respiratory failure in pulmonary alveolar proteinosis due to pathogenic MARS1 variants. *Pediatric Pulmonology*. 2020;55:3057–3066.
- Lenz, D., Smith, D.E.C., Crushell, E., ..., **Brennenstuhl, H.**, et al. Genotypic diversity and phenotypic spectrum of infantile liver failure syndrome type 1 due to variants in LARS1. *Genetics in Medicine*. 22, 1863–1873 (2020)
- Didiasova, M., Banning, A., **Brennenstuhl, H.**, et al. Succinic Semialdehyde Dehydrogenase Deficiency: An Update. *Cells*. 2020;9(2).
- Schotterl, S., **Brennenstuhl, H.**, Naumann, U. Modulation of immune responses by histone deacetylase inhibitors. *Crit Rev Oncog*. 2015;20(1-2):139-154.

### PUBLICATIONS (ABSTRACTS)

- Schröter, J., Dattner, T., Hüllelein, J., Jayme, A., Heuveline, V., Hoffmann, G. F., Kölker, S., Lenz, D., Opladen, T., Popp, B., Schaaf, C. P., Stauffer, C., Syrbe, S., Uhrig, S., Hübschmann, D., **Brennenstuhl, H.** (2022). aRgus: a versatile tool for variant visualization and advanced prediction score modeling in inherited metabolic diseases. Abstracts 2022: 35th Annual Symposium Arbeitsgemeinschaft Pädiatrische Stoffwechselstörungen (APS; Society for Pediatric Metabolic Medicine). *Monatsschr Kinderheilkd* (2022). <https://doi.org/10.1007/s00112-022-01624-3>
- Juliá-Palacios, N., Kuseyri Hübschmann, O., Olivella, M., Pons, R., Horvath, G., Lücke, T., Fung, C.W., Cortès-Saladelafont, E., Yildiz, Y., Mercimek-Andrews, S., Assmann, B., Stevanovic, G., Manti, F., **Brennenstuhl, H.**, Jung-Klawitter, S., Jeltsch, K., Sivri, S., Garbade, S. F., García-Cazorla, A., Opladen, T. Succinic Semialdehyde Dehydrogenase deficiency: Expanding the phenotypic and genotypic spectrum. *J Inherit Metab Dis*. Vol 45, Issue S1, 0141-8955, <https://doi.org/10.1002/jimd.12536>.
- Weiß, C., Ziegler, A., Becker, L. L., Johannsen, J., **Brennenstuhl, H.**, Schreiber, G., Flotats-Bastardas, M., Stoltenburg, C., Hartmann, H., Illsinger, S., Denecke, J., Pechmann, A., Müller-Felber, W., Vill, K., Blaschek, A., Smitka, M., Stam, L. v. d., Weiss, K., Winter, B., Goldhahn, K., Plecko, B., Horber, V., Bernert, G., Husain, R. A., Rauscher, C., Trollmann, R., Garbade, S. F., Hahn, A., v.d. Hagen, M., Kaindl, A. M. (2021). Real-World Data for Onasemnogen Asepavovec (Zolgensma) in Spinal Muscular Atrophy. *Neuropediatrics*, 52(S 01), FV5.09.
- Schröter, J., Popp, B., **Brennenstuhl, H.**, Döring, J. H. , Donze, S. H., Bijlsma, E. K. , van Haerlingen, A. , Huhle, D. , Jestaedt, L. , Merckenschlager, A., Arelin, M., Gräfe, D., Neuser, S., Oates, S., Pal, D. K., Parker, M. J., Lemke, J. R., Hoffmann, G. F. , Kölker, S., Harting, I., Syrbe, S. Complementing the Phenotypical Spectrum of *TUBA1A* Tubulinopathy and Its Role in Early-Onset Epilepsies. *Neuropediatrics* 2021; 52(S 01): S1-S53. DOI: 10.1055/s-0041-1739684
- Eckhardt, I., Merbecks, M. B., Jacobi, S. F., Lechner, C., Becker, L. L., Balks, M. F., Scala, M., Kampmann, K., Ortner, G. R., Schmid, F., Hensel, K. O., Pokora, R., Eichinger, M., Drossard, S., **Brennenstuhl, H.**, Christ, S., Kock, V., Krey, I., Meyer, R., Schulz, J., Ferger, M. D., Nissen, G., Happle, C., Kohlfürst, D.S., Jakob, J. (2021). "Gemeinsam stark – für eine bessere Kinder- und Jugendmedizin!". *Monatsschrift Kinderheilkunde*, 169(11), 1083-1087.
- Scharping, M., **Brennenstuhl, H.**, Garbade, S.F., Posset, R., Zielonka, M., Wild, B., Kölker, S., Haun, M., Opladen, T. Evaluation of the family burden of parents of children with urea cycle defects. *Monatsschrift Kinderheilkunde*.
- **Brennenstuhl, H.**, Kohlmüller, D., Gramer, G., et al. The quantification of 3-O-methyldopa in dried blood spots enables high-throughput newborn screening for aromatic L-amino-acid decarboxylase deficiency. *Monatsschrift Kinderheilkunde*. 168:277–290, 2020.
- **Brennenstuhl, H.**, Opladen, T., Ebrahimi-Fakhari, D., et al. Induced pluripotent stem cells (iPSCs) and iPSC-derived cerebral organoids as a tool to model Succinic Semialdehyde Dehydrogenase Deficiency. *J Inherit Metab Dis*. Vol 42, Issue S1.
- **Brennenstuhl, H.**, Opladen, T., Ebrahimi-Fakhari, D., et al. The use of patient-derived induced pluripotent stem cells (iPSCs) and iPSC-derived cerebral organoids to explore pathomechanisms of succinic semialdehyde dehydrogenase deficiency. *Monatsschrift Kinderheilkunde*. 167:365, 2019.

## MEMBERSHIPS

- Founding member and current chairman of the Young Metaboliician Society within the Association for Pediatric Metabolic (APS) to improve educational opportunities and resources for young professionals in the field of inherited metabolic disorders
- Member of the Association for Pediatric Metabolic (APS)
- Member of the German Society of Human Genetics (GfH)
- Member of the German Society of Pediatrics and Adolescent Medicine (DGKJ)

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Neckargemünd, August 30, 2023