Clinical and translational research in epilepsy and neurology

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Summary
Epilepsy is the most common chronic neurological disorder in dogs and human medicine. Many of the features of epilepsy in dogs, e.g. pathophysiology, clinical manifestations, and therapeutic options and the life-long burden of epilepsy are similar in dogs and man. Moreover, dogs are currently underutilized as a translational model for epilepsy and also for other neurologic diseases in man. Therefore, the aim of our research was to define canine models for human neurologic disorders from a clinical, pathophysiological, neuroimaging and genetic perspective. In detail, we utilized phenotyping of cohorts of dogs suffering from a particular genetic disorders and genetic analysis as part of a European-Canadian-consortium. For precise description of the phenotype we adapted routine clinical and advanced neurodiagnostic techniques including electroencephalography and magnetic resonance imaging to our patient cohorts. A better description of the parallels and differences of epilepsy and other neurologic disorders in humans and dogs will assist both, dog and men vice versa.

Research Objectives
Our current research goals are the discovery of animal models of human disease in dogs. Therefore, we aim to characterize the disorders at a clinical, neurophysiologic, imaging and molecular level. As a secondary research goal we aim to clarify the genetic mechanisms of idiopathic-genetic epilepsy and other neurodegenerative and neuromuscular disorders in dogs breeds with a high burden of disease to enable comparison with the human counterpart and define the animal model more closely. Lastly, our consortium provides genetic tests for dog owners and breeding purposes and advances diagnosis and therapy of neurologic disorders in a translational setting.

Key Findings
We discovered a genetic epilepsy in dogs which closely resembles juvenile myoclonic epilepsy (JME) in humans. In these dogs, a new epilepsy gene was identified, *diras1* coding for a GTPase which is known to be involved in presynaptic acetylcholine release. Juvenile myoclonic epilepsy is the most frequent idiopathic epilepsy in children and juveniles. The discovery of JME in dogs

was a mile stone in the definition of animal models for human epilepsies. Furthermore, it demonstrated the value of a novel ambulatory electroencephalography with intermittent light stimulation for the diagnosis of epilepsy in dogs. Gene discovery in canine epilepsy is of specific relevance due to high frequency of epilepsy in dogs and humans. Besides canine epilepsy our phenotype-characterization- approach initiated also discovery of animal models, novel genes and variants in myelin disorders (*napepld*), myotonia congenita (*clcn1*), Leigh syndrome (*slc19a3*), dyskinesia (*pck2*), and cerebellar hypoplasia (*vldlr*).

Selected Publications

1. Fischer, A. Idiopathic epilepsy in dogs: insights into factors that may predict upcoming seizure activity. Veterinary Record 2020; 187: 149-151.
2. Nessler, J, Hug, P., Mandigers, PJJ, Leegwater, PAJ, Jagannathan, V, Das, AM, Rosati, M, Matiasek, K, Sewell, AC, Kornberg, M, Homann, M, Wolf, P, Fischer, A, Tipold, A, Leeb, T. Mitochondrial PCK2 Missense Variant in Shetland Sheepdogs with Paroxysmal Exercise-Induced Dyskinesia (PED). Genes (Basel) 2020; 11: 774.3
3. Buhmann, G, Paul, F, Herbst, W, Melzer, F, Wolf, G, Hartmann, K, Fischer, A. Canine Brucellosis: Insights Into the Epidemiologic Situation in Europe. Frontiers Veterinary Sciences 2019; 6: 151.
4. Minor, KM, Letko, A, Becker, D, Drögemüller, M, Mandigers, PJJ, Bellekom, SR, Leegwater, PAJ, Stassen, QEM, Putschbach, K, Fischer, A, Flegel, T, Matiasek, K, Ekenstedt, KJ, Furrow, E, Patterson, EE, Platt, SR, Kelly, PA, Cassidy, JP, Shelton, GD, Lucot, K, Bannasch, DL, Martineau, H, Muir, CF, Priestnall, SL, Henke, D, Oevermann, A, Jagannathan, V, Mickelson, JR, Drögemüller, C. Canine NAPEPLD-associated models of human myelin disorders. Scientific Reports 2018; 8(1): 5818.
5. Quitt, PR, Hytönen, MK, Matiasek, K, Rosati, M, Fischer, A (shared last authorship), Lohi, H. Myotonia congenita in a Labrador Retriever with truncated CLCN1. Neuromuscular Disorders 2018; 28: 597–605.
6. Lauda, A, Bruehschwein, A, Ficek, J, Schmidt, MJ, Klima, A, Meyer-Lindenberg, A, Fischer, A. Caudal Fossa Ratio in Normal Dogs and Eurasier Dogs with VLDLR-Associated Genetic Cerebellar Hypoplasia. Frontiers Veterinary Sciences 2018; 4: 241.
7. Wielaender, F, Sarviaho, R, James, F, Hytönen, MK, Cortez, MA, Kluger, G, Koskinen, LLE., Arumilli, M, Kornberg, M, Bathen-Noethen, A, Tipold, A, Rentmeister, K, Bhatti, SFM, Hülsmeyer, V, Boettcher, IC, Tästensen, C, Flegel, T, Dietschi, E, Leeb, T, Matiasek, K, Fischer, A (shared last authorship), Lohi, H. Generalized myoclonic epilepsy with photosensitivity in juvenile dogs caused by a defective DIRAS family GTPase 1. Proceedings of the National Academy of Sciences 2017; 114: 2669–2674.
8. Wielaender, F, James, FMK, Cortez, MA, Kluger, G, Neßler, JN, Tipold, A, Lohi, H, Fischer, A. Absence Seizures as a Feature of Juvenile Myoclonic Epilepsy in Rhodesian Ridgeback Dogs. Journal of Veterinary Internal Medicine 2017; 32: 428-432.
9. Koskinen, LLE, Seppälä, EH, Weissl, K, Jokinen, TS, Viitmaa, R, Hänninen, RL, Quignone, P, Fischer, A, Andre, C, Lohi, H. ADAM23 is a common risk gene for canine idiopathic epilepsy. BMC Genetics 2017; 81: 8.
10. Potschka, H, Fischer, A, Löscher, W, Patterson, N, Bhatti, S, Berendt, M, De Risio, L, Farquhar, R, Long, S, Mandigers, P, Matiasek, K, Munana, K, Pakodzy, A, Penderis, J, Platt, S, Podell, M, Rusbridge, C, Stein, V, Tipold, A, Volk, H. International veterinary epilepsy task force consensus proposal: outcome of therapeutic interventions in canine and feline epilepsy. BMC Veterinary Research 2015; 11: 177.

Funding

Funder	Project title	Start date	End date
Clinical research grant Anicura	A open-label prospective drug trial in idiopathic epilepsy	2019	2021
Gesellschaft für kynologische Forschung	Accelerometric investigation of sleep in dogs	2019	2020
Gesellschaft für kynologische Forschung	Investigation of inflammatory markers of epilepsy	2018	2020
Pharmaceutical company	A double-blinded prospective treatment trial in paroxysmal dyskinesia	2016	2020