UKE Paper of the Month September 2019

Phenotype in an Infant with *SOD1* Homozygous Truncating Mutation

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STATEMENT:

This paper is the first description of a novel disease. For the first time we describe a congenital neurometabolic disorder which causes by a complete loss of enzymatic activity of superoxide dismutase-1 (SOD1), a ubiquitously expressed antioxidant enzyme in the human organism. Genetic variants of SOD1 have been associated with dominantly-inherited amyotrophic lateral sclerosis (ALS) in the past, probably rather caused by acquired toxic effects of the protein and accompanied even by a gain of enzymatic function. In our paper we report the detection of the genetic defect by whole exome sequencing of the patient and both parents (trio analysis), we describe the phenotype of the patient homozygous for a truncating SOD1 variant, we characterize the mutant mRNA and the truncated protein and we describe ways to overcome the extreme oxygen sensitivity of patient cells in culture. Thus, our observation is important for individual patients in whom, if diagnosed, treatment with antioxidants might be helpful, Our findings further suggest, however, that caution should be taken in those ongoing gene therapy trials of ALS patients that aim at depressing production of pathogenic SOD1 proteins but may result in extensive lowering of SOD1 activity.

BACKGROUND:

This work is the result of an ongoing successful cooperation of the Department of Pediatrics (Dir. Prof. Muntau) and the Institute of Human Genetics (Dir. Prof. Kubisch) aiming at a higher diagnostic yield by using most advanced diagnostic approaches (genomic, exomic, metabolomic and others). The investigations resulting in this paper were coordinated together by Prof René Santer who holds a professorship in Pediatrics and Inborn Metabolic Disease at UKE since 2004 and PD Dr Maja Hempel who works at UKE since 2013 and recently qualified as a University Lecturer (Habilitation). Further collaborators are from the Department of Neurology, Umeå University, Sweden, a renowned center for ALS research.