Carlo Wilke

Beyond family-based exome analysis: advanced cohort-level bioinformatic approaches for assessing genetic burden in rare neurodegenerative diseases

Short Bio	I am a Clinician Scientist at the Center for Neurology and Hertie Institute for Clinical Brain Research in Tübingen, Germany, specialising in rare neurodegenerative diseases. I graduated in medicine from the University of Tübingen in 2014, having studied in Tübingen, Aberdeen and London.
Home Institution	Division Translational Genomics of Neurodegenerative Diseases, University of Tübingen, Germany
Host Institution	Radboud University Medical Center, Department of Human Genetics, Nijmegen, The Netherlands
Project description	While standard next generation sequencing analysis, mostly relying on whole exome sequencing (WES) of promising families, has allowed discovering a large number of novel genes in the last years, still >50% of all families with rare neurodegenerative diseases remain unsolved. This missing heritability in even clearly genetic diseases results from variation in non-coding space (e.g., deep-intronic/regulatory regions), but also in part from variation in exonic space, where current standard analysis might fail to identify the causative variant within long lists of variants of unknown significance. My project hypothesises that advanced cohort-level bioinformatic approaches which move beyond standard family-based WES analysis will allow discovering novel genetic causes of rare neurodegenerative diseases, even in the exonic space. As a first paradigmatic cohort-level approach, this will be demonstrated by the use case of a rare variant association study in degenerative ataxia, a disease group which is highly enriched for genetic causes.
Personal statement	My research is dedicated to elucidating the genetic basis of rare multisystemic neurodegenerative diseases, including early-onset dementias and genetic movement disorders. My research has helped to characterise the gene frequencies and mutational spectrum in early-onset dementias, using next-generation sequencing approaches, and expanded the phenotype-genotype associations of the neurodegenerative disease genes C9orf72 and TBK1. Currently, I am working to uncover novel causative mutations and genes in ataxia patients in whom the underlying genetic disease cause has not yet been solved by standard whole-exome sequencing. Moreover, I have a broad background in fluid biomarker research in rare neurodegenerative diseases to promote early diagnosis and precise monitoring of disease progression.