cerebral atrophy, neonatal choleastasis, muscular hypotension, infantile hepatopathy and hypomyelination to speech disorders and aggressive behavior. Finally, it should be mentioned that the non-canonical functions of ARSs could also be responsible for the wide phenotypic spectra that can be observed in the diseases related to their mal- or dysfunction.

### Mitochondrial ARSs

Human mitochondrial ARSs (mt-ARSs) are essential for the synthesis of 17 mt-DNA-encoded proteins, which are all subunits of the respiratory chain complexes. Therefore, they are involved in the generation of the major source of cellular energy, i.e., ATP. Like cytosolic ARSs, all mt-ARSs are encoded by nuclear genes, which are, however, different from those coding for the cytosolic ARSs. Three *ARS* genes encode enzymes that are active in both mitochondria and cytosol: glycyl-tRNA synthetase (GARS), lysyl-tRNA synthetase (KARS), and glutaminyl-tRNA synthetase (QARS). Only QARS, however, has so far been found to be associated with an ID phenotype [Table 1B]. The first correlation between an mt-ARS mutation and a human disorder was published in 2007 by Scheper *et al.*[222], who found autosomal recessive mutations in the *DARS2* gene in individuals suffering from leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation (LBSL). Since then, numerous other pathogenic mutations in mt-ARSs have been described, so that to date, at least 17 out of the 19 *mt-ARSs* genes have been implicated in human genetic disorders involving damage to the central nervous system[35].

It is noteworthy at this point that in 2017, Moulinier *et al.*[223] introduced MiSynPat, an integrated knowledge base that links clinical, genetic, and structural data for disease-causing mutations in human *mt-ARSs*. According to the authors, this tool provides a "comprehensive knowledge base together with an ergonomic Web server designed to organize and access all pertinent information (sequences, multiple sequence alignments, structures, disease descriptions, mutation characteristics, original literature) (http://misynpat.org/misynpat/AboutMisynpat.rvt last accessed 2020-01-09).

Mutations in at least six *mt-ARS* genes (Table 1B - aminoacylation, including *QARS*) are involved in the etiology of ID. All of these lead to a syndromic phenotype. Mutations in *NARS2* and *PARS2*, for example, cause Alpers syndrome, and homozygous *RARS2* defects lead to pontocerebellar hypoplasia, which is characterized by not only overall delayed development, impaired brain development, movement problems and ID but also progressive atrophy, particularly of the pons and cerebellum. *WARS2* mutation carriers show a phenotype that is very similar to patients with mutations in cytosolic *SARS* (Table 1B - aminoacylation). Other than that seen for ct-ARSs, there are no clearly prominent recurrent motives in homozygous or compound heterozygous carriers of mt-ARS mutations (Table 1B - aminoacylation) with the possible exception of seizures that are observed with a notably increased frequency (*NARS2*, *PARS2* and *QARS*).

## CONCLUSION

The literature compilation we present here makes a compelling case for an important if not pivotal role of a fully functional tRNA complement for the development and maintenance of higher cognitive functions. Interestingly, disease-causing *ARSs* mutations often only result in a reduction of enzyme activity without causing complete inhibition[158,224,225]. This points to the sensitivity of cognitive features towards even slight disturbances in this basic cellular process.

In addition, there is much evidence that tRNA molecules assume possibly unknown biological functions in eukaryotes, which have not yet been fully elucidated[17] but could be influenced by disruption of tRNA function. This opens up a myriad of further possibilities for tRNA involvement in the formation of cognitive features and underlines the importance of further research in this field.

## DECLARATIONS

### Authors' contributions

Made substantial contributions to the conception and design of the article, performed literature research and interpretation and were involved in the writing and editing of the manuscript as well: Franz M, Hagenau L, Jensen LR, Kuss AW

Franz M and Hagenau Lcontributed equally to the article.

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All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

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