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Prevalence estimation of thymidine kinase 2 deficiency, an ultra-rare autosomal recessive mitochondrial disease

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Introduction

- Mitochondrial diseases are a heterogeneous group of diseases characterized by defects in mitochondrial oxidative phosphorylation, resulting in defective cellular energy production
  - More than 350 gene mutations in either mitochondrial (mt)DNA or nuclear (n)DNA are known to cause primary mitochondrial diseases[1]
  - The subset of these diseases that cause mtDNA depletion and/or multiple mtDNA deletions are known as mtDNA depletion syndromes (MDDS)[2]
- Thymidine kinase 2 deficiency (TK2d) is an ultra-rare, autosomal recessive MDDS, in which the lack of mtDNA synthesis leads to substantial morbidity driven by progressive muscle weakness and can lead to premature death[3,4]
- The first cases of TK2d were described in 2001;[2] by 2018 there were approximately 107 published cases worldwide[4]
  - The rarity of TK2d and a similarity in presentation to other neuromuscular conditions such as spinal muscular atrophy or general myopathy means underdiagnosis and misdiagnosis are common[2]
- Although some estimates suggest there could be between 600 and 2700 cases in the USA,[2] the prevalence of TK2d is unknown

Objective

- The aim of this study was to provide a robust estimate for the prevalence of TK2d

Methods

Study design

- Given that published data on TK2d prevalence are limited and narrow in scope, a three-step indirect approach was used to generate a prevalence estimate (**Figure 1**):
  - comprehensive literature search to identify sources reporting mitochondrial disease prevalence and the proportion with MDDS and/or TK2d
  - ranking of the papers to qualify robustness (high/medium/low tiers)
  - statistical meta-analysis based on Monte Carlo simulation methodology
- A funnel approach was used to estimate prevalence of patients with genetically confirmed mitochondrial disease first, followed by the percentage of those with MDDS, and then the percentage of MDDS cases with TK2d

Figure 1. Study design

1 Epidemiology database creation

Collection of relevant literature on disease prevalence for mitochondrial disease, mtDNA depletion and TK2d

2 Source strength characterization

Ranking into tiers (high, medium, low) according to degree of robustness (based on inclusion criteria, methodology, founder effect, relative sample size)

Prevalence will be driven by weighting of the most robust papers

3 Statistical analysis

Monte Carlo simulations to estimate prevalence rate, based on reported findings in each paper and their estimated weight (rank)

nDNA correction application to mitochondrial disease prevalence to allow comparison across sources

mtDNA, mitochondrial DNA; nDNA, nuclear DNA; TK2d, thymidine kinase 2 deficiency.

Literature search and ranking strategy

- To identify the required sources, the following search terms were used in PubMed
  - Mitochondrial Disease Prevalence: [Prevalence OR Incidence] AND [Mitochondrial Disease OR Mitochondrial Respiratory Chain Disorder]
  - Proportion with MDDS: [Prevalence OR Incidence] AND [Mitochondrial Disease OR Mitochondrial Respiratory Chain Disorder] AND [Proportion OR Percentage] WITH [mitochondrial DNA mutations; mtDNA; mitochondrial DNA depletion; mtDNA depletion]
  - Proportion with TK2d: [Prevalence OR Incidence] AND [Mitochondrial Disease OR Mitochondrial Respiratory Chain Disorder] AND [mtDNA] AND [Proportion OR Percentage] WITH [TK2d; thymidine kinase 2 deficiency]
- Papers were ranked into tiers according to degree of methodological robustness (**Table 1**)

Statistical meta-analysis

- Monte Carlo simulations were performed for each subpopulation (for patients with mitochondrial disease, the proportion with MDDS and the proportion with TK2d; three simulations in total)
  - Individual papers were randomly selected in proportion with their ranked tier; high-tier papers were selected more often to ensure the prevalence rate was weighted towards comprehensive papers with robust methods
  - A prevalence rate was taken from within the reported prevalence confidence interval (CI) in the selected paper
    - When no CI was provided, the sample size was used to estimate the sampling distribution (95% CI)
- Each simulation was repeated 10 000 times to sample across and within sources randomly to calculate a range over which there was confidence it would contain the true prevalence
  - No additional burn-in or thinning of samples was required because this was a Monte Carlo simulation with independent pulls
  - Given that some papers reported only mtDNA disease prevalence, a standardized nDNA correction factor (x1.3, based on published observations[5]) was applied to enable direct comparison across sources
- Distribution curves of outcomes were obtained, reporting the median prevalence and uncertainty (25th to 75th percentile) range, and combined to calculate a final prevalence estimate of TK2d
- Analyses were performed in Microsoft Excel and R for Statistical Computing

Please use this QR code to download a PDF of the poster.

Abbreviations: CI, confidence interval; MDDS, mitochondrial DNA depletion syndromes; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; TK2d, thymidine kinase 2 deficiency.

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Results

- The literature search revealed 173 potential sources in total, with 19 papers found to report data of interest
- In total, 17 manuscripts were included and ranked according to robustness of data (**Table 2**)
  - Seven manuscripts that reported prevalence values for mitochondrial disease were included
    - One review article was excluded because it only referenced values from other sources; one manuscript was excluded because the values reported were limited to a subset of mitochondrial diseases
  - Five manuscripts that reported percentages of MDDS were included
    - One manuscript was excluded because the participant population included patients who did not meet biopsy criteria
  - Eight manuscripts reported percentages of TK2d, with no exclusions
- The Monte Carlo meta-analysis (**Figure 2**) estimated a median [25th, 75th percentiles] prevalence of approximately 8.92 [6.2, 12.2] per 100 000 people for mitochondrial disease as a whole, of which:
  - 23% [12%, 38%] were estimated to be caused by MDDS
  - 8% [4%, 15%] of the MDDS cases were estimated to be caused by TK2d
- Based on these proportions, the estimated prevalence [25th, 75th percentiles] of TK2d is 1.64 [0.5, 3.1] per million people (**Figure 2**)
- Application of the prevalence rate to the USA and the populations of European countries including France, Germany, Spain, Italy and the UK suggests that there are approximately 1080 [25th, 75th percentiles: 330, 2030] people with TK2d across these countries (**Table 3**)

Table 1. Ranking scale

Ranking scale	
High robustness	Studies that are sound in methodology, relevant to the US and EU4/UK populations, with no concerns (or few concerns within subpopulation)
Medium robustness	Studies that are relatively sound, with select questions about methodology owing to considerations other than consanguinity
Low robustness	Studies that are likely outliers owing to high consanguinity or with significant methodology concerns
Considerations	
Degree of consanguinity (or founder effect) in study population	- Study populations with known founder effects and consanguinity - Consanguineous populations exist in the USA and EU4/UK, but to a relatively smaller extent
Appropriateness of inclusion criteria	- Inclusion of too few subtypes (e.g. only late infantile) or too many disease types (e.g. non-pathogenic mutations) in total diagnoses or age group did not align with the majority of studies - Inclusion of prenatal diagnoses
Timeline of data sample	- Incidence based on diagnostic data over the course of a very short time frame, or data considered outdated by new study conducted by same study group
Comprehensiveness of data	- Data collected from multiple, potentially incomplete sources owing to a highly decentralized diagnostic pathway in some regions
Clarity/robustness of epidemiological calculation	- Disclosing inadequate or unclear methodological data - Calculating incidence using number of diagnoses per live births during diagnosis years

EU4/UK, European countries including France, Germany, Spain, Italy and the UK.

Summary and Conclusions

This analysis provides an up-to-date estimated prevalence of TK2d of 1.64 [25th, 75th percentiles: 0.5, 3.1] per million people

As with most ultra-rare disorders, accurate prevalence estimation of TK2d is challenging owing to low disease awareness, multiple pathogenic variants and lack of inclusion in gene panels for neuromuscular diseases and muscular dystrophies[2]

Given that TK2d is underdiagnosed and underrecognized,[2] the true prevalence may be higher if 'population at risk' of mitochondrial disease is considered, which would include all individuals with pathogenic mutations

These results emphasize the need to increase healthcare professional awareness, support earlier diagnosis in patients, and develop clear referral guidelines for this progressive, debilitating and often life-threatening disease

Further research is ongoing to better understand the global prevalence of TK2d

Table 3. Estimation of numbers of patients with TK2d in the USA and EU4/UK

	USA	EU4/UK
Total population, in millions	**335**	**321**
Number of patients with TK2d [25th, 75th percentiles] (1.64/million TK2d prevalence × total population)	**~550 [170, 1040]**	**~530 [160, 1000]**

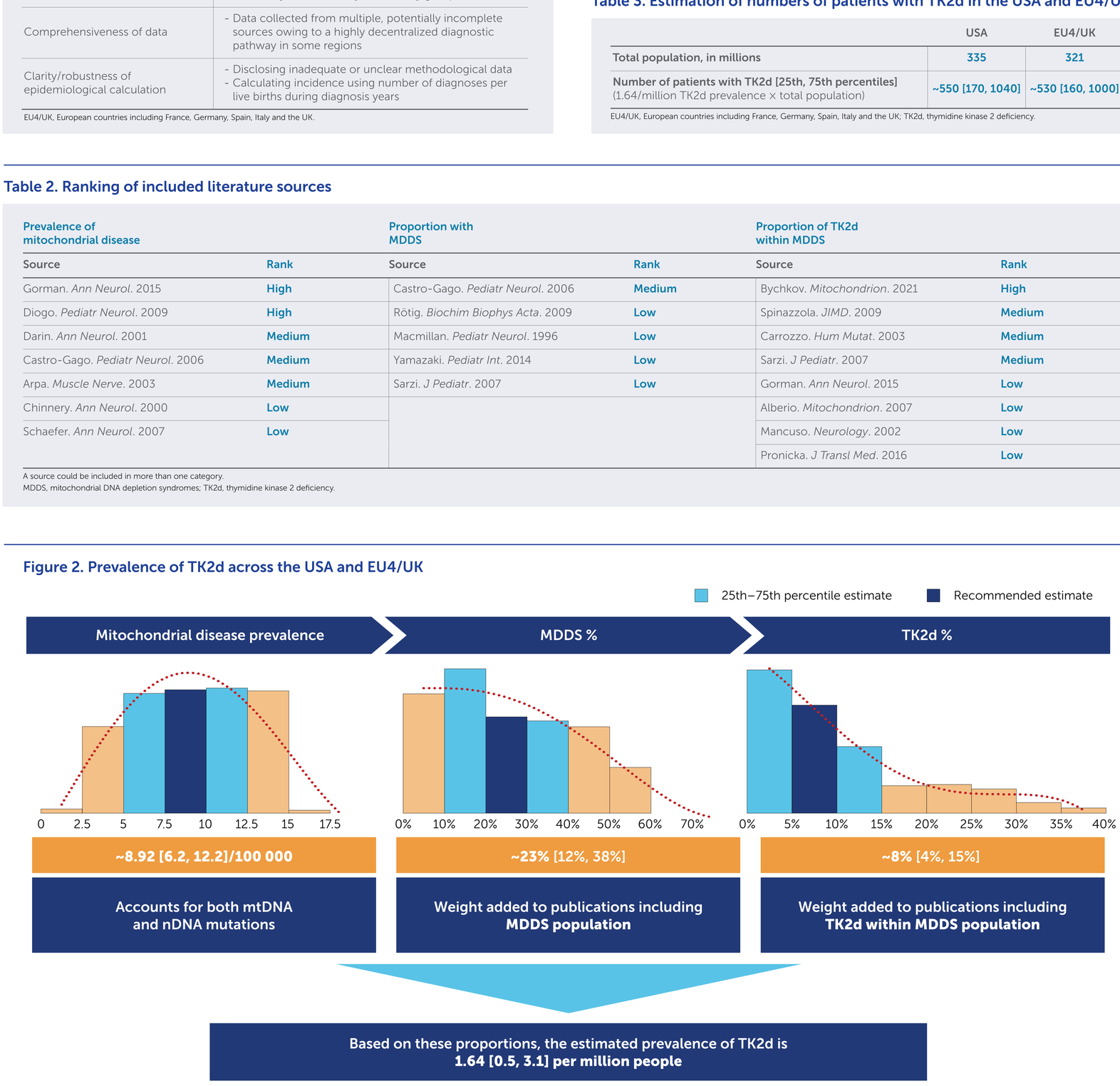
EU4/UK, European countries including France, Germany, Spain, Italy and the UK; TK2d, thymidine kinase 2 deficiency.

Table 2. Ranking of included literature sources

Prevalence of mitochondrial disease		Proportion with MDDS		Proportion of TK2d within MDDS	
Source	**Rank**	**Source**	**Rank**	**Source**	**Rank**
Gorman. *Ann Neurol*. 2015	**High**	Castro-Gago. *Pediatr Neurol*. 2006	**Medium**	Bychkov. *Mitochondrion*. 2021	**High**
Diogo. *Pediatr Neurol*. 2009	**High**	Rötig. *Biochim Biophys Acta*. 2009	**Low**	Spinazzola. *JIMD*. 2009	**Medium**
Darin. *Ann Neurol*. 2001	**Medium**	Macmillan. *Pediatr Neurol*. 1996	**Low**	Carrozzo. *Hum Mutat*. 2003	**Medium**
Castro-Gago. *Pediatr Neurol*. 2006	**Medium**	Yamazaki. *Pediatr Int*. 2014	**Low**	Sarzi. *J Pediatr*. 2007	**Medium**
Arpa. *Muscle Nerve*. 2003	**Medium**	Sarzi. *J Pediatr*. 2007	**Low**	Gorman. *Ann Neurol*. 2015	**Low**
Chinnery. *Ann Neurol*. 2000	**Low**			Alberio. *Mitochondrion*. 2007	**Low**
Schaefer. *Ann Neurol*. 2007	**Low**			Mancuso. *Neurology*. 2002	**Low**
				Pronicka. *J Transl Med*. 2016	**Low**

A source could be included in more than one category.
MDDS, mitochondrial DNA depletion syndromes; TK2d, thymidine kinase 2 deficiency.

Figure 2. Prevalence of TK2d across the USA and EU4/UK



Distributional curves showing the prevalence for mitochondrial disease, MDDS and TK2d. Median values are reported with the interquartile range [25th, 75th percentiles].
EU4/UK, European countries including France, Germany, Spain, Italy and the UK; MDDS, mitochondrial DNA depletion syndromes; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; TK2d, thymidine kinase 2 deficiency.