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Genetic Prevalence of Thymidine Kinase 2-Related Mitochondrial Disease: A Combined Approach Using Clinical Literature and Large-Scale Genomic Databases

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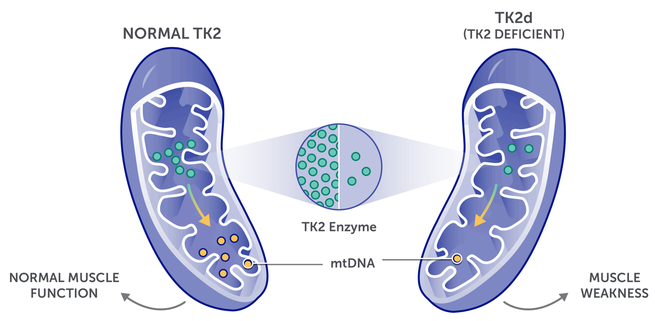
Introduction

- Mitochondrial diseases are a heterogeneous group of diseases characterized by defects in mitochondrial oxidative phosphorylation, resulting in defective cellular energy production
  - More than 350 different disease causing genes 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[2] mtDNA deletions are known as mtDNA depletion and deletion syndrome (MDDS)
- Thymidine kinase 2 deficiency (TK2d) is a rare autosomal recessive mitochondrial disorder caused by pathogenic variants in the TK2 gene[3]
- Mutations in TK2 cause mitochondrial DNA depletion and oxidative phosphorylation defects, leading to myopathy with early-onset (TK2d symptom onset ≤12 years of age) or late-onset (TK2d symptom onset >12 years of age) presentations and variable progression[3] (**Figure 1**)
- The true prevalence of TK2d remains poorly defined, as it was only first described in the literature in 2001[4]
- Accurate prevalence estimates are essential for disease awareness, diagnosis, and healthcare planning

Figure 1. Mechanism of TK2d



Objective

- The aim of this study was to estimate the genetic birth prevalence of TK2d globally and across diverse populations

Methods

- We used the Mastermind Genomic Search Engine to identify all TK2 single-nucleotide variants (SNVs) and indels from the literature, followed by a semi-automated curation and expert review to classify variants according to the American College of Medical Genetics/Association for Molecular Pathology (ACMG/AMP) criteria[5] (**Figure 2**)
- Allele frequencies from gnomAD v4 were associated with curated TK2 variants from Mastermind[6] and ClinVar
- **Figure 3** shows the algorithm that was used for inclusion of TK2 variants for prevalence analysis
- Included variants were classified as pathogenic (P), likely pathogenic (LP), variant of uncertain significance (VUS), and presumed pathogenic (PP, e.g., loss-of-function variants)
- TK2 variants were systematically filtered by allele frequency, genomic location, ACMG/AMP classification[3], and pathogenicity predictions by REVEL[7] and AlphaMissense
- Genetic prevalence and carrier frequency were calculated using a Hardy-Weinberg equilibrium-based model
- Genetic prevalence, estimated using the Hardy–Weinberg principle, reflects the expected number of affected conceptions (per million pregnancies). For TK2d, although the estimation of prenatal mortality is unknown, there is no evidence that biallelic TK2 variants are non-viable in utero. Hence genetic prevalence per million live births would be similar to genetic prevalence per million pregnancies

Figure 2. Study design

1. Extraction of TK2 clinical data from the literature (Mastermind)
2. TK2 variants classified according to the ACMG/AMP criteria
3. Removal of benign variants and variants with >0.005 allele frequencies
4. Removal of non-coding variants (5'UTR, splice site, and 3'UTR variants)
5. Final TK2 dataset (n=582)
6. Selection of TK2 variants for prevalence estimates based on Figure 3

Results

- The estimated global genetic prevalence of TK2d was 0.34 - 2.82 per million pregnancies (**Table 1, Table 2**), consistent with previous estimates of clinical prevalence based on reported patients globally (1.64 per million people)[8]
- The range reflects estimates from a conservative set of pathogenic and likely pathogenic variants (P/LP) to a more liberal set that also includes presumed pathogenic variants (PP) and VUS
- The highest genetic prevalence of TK2d was observed in the Admixed American population (as defined in gnomAD v4, which includes Mexican, Costa Rican, and Latino/a individuals), ranging from 2.80 to 13.06 per million pregnancies (**Table 3, Figure 4**)
- Other subpopulations with high genetic prevalence of TK2d were African/African American (0.36 to 8.27 per million pregnancies), South Asian (0.27 to 5.15 per million pregnancies), and Finnish (3.23 to 4.39 per million pregnancies) populations (**Table 1, Figure 4**)
- The most common TK2 variants were p.P227L, p.E207V, and p.A139T in the gnomAD database. The most common P/LP variants were p.A139T, p.R183W, and p.A139V (**Figure 5**)
- In the Admixed American population, the most common TK2 variants were p.H121N, p.V232I, and p.T108M, while the most common P/LP variants were p.H121N, p.T108M, and p.N58S (**Figure 6**)
- Overall carrier frequency was estimated at 0.12% - 0.34% (**Figure 7**)
- Marked differences in prevalence were observed across populations
- Under broader variant inclusion criteria, the highest prevalence was observed in Admixed American, African/African American, and South Asian populations
- The Finnish population showed a consistently elevated burden of definitively pathogenic variants. The results from European (non-Finnish) population were in line with previous clinical prevalence data
- The inclusion of presumed pathogenic variants and VUS substantially increased prevalence estimates, underscoring the impact of careful curation of molecular genetic data

Summary and Conclusions

These findings can inform healthcare planning by identifying at-risk populations and may provide data for evaluating the feasibility of TK2 inclusion in newborn screening programs in the future

The higher estimated genetic prevalence in some populations emphasizes the importance of clinical awareness and early diagnostic testing

Comprehensive variant classification and ancestry-aware prevalence estimation are essential for accurate diagnosis of TK2d and for optimizing the sensitivity of genomic testing for this disease.

Figure 4. The estimated genetic prevalence of TK2d varied between global subpopulations

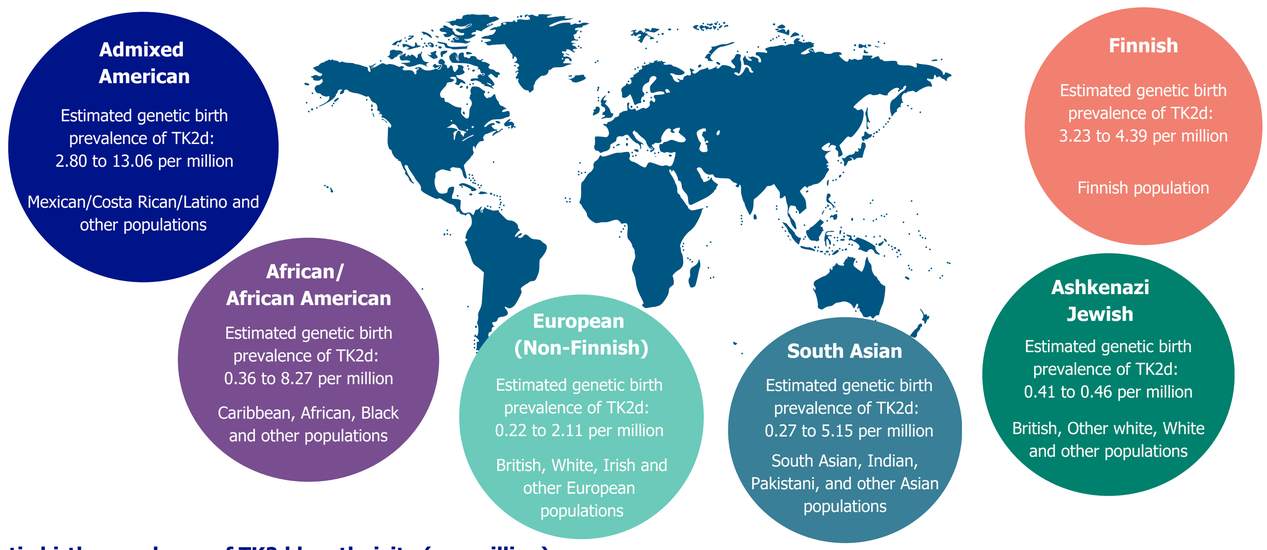


Table 1. Genetic birth prevalence of TK2d by ethnicity (per million)

Prevalence (per million)	gnomAD	African/African American	Admixed American	Ashkenazi Jewish	East Asian	Finnish	Middle Eastern*	European	South Asian	Remaining
Pathogenic+Likely pathogenic	0.34	0.36	2.8	0.41	0.42	3.23	0	0.22	0.27	0.43
Pathogenic+Likely pathogenic+Presumed Pathogenic	0.56	0.52	3.83	0.41	0.62	3.88	0.03	0.38	0.73	0.61
Pathogenic+Likely pathogenic+Presumed Pathogenic+VUS	2.82	8.27	13.06	0.46	3.98	4.39	0.69	2.11	5.15	3.11

*While gnomAD v4 includes a Middle Eastern category, the number of individuals in this group is very small compared to European and other cohorts

Table 2. Genetic birth prevalence of TK2d in gnomAD database

Prevalence	Pathogenic only	Pathogenic + Likely Pathogenic	Pathogenic + Likely pathogenic + Presumed Pathogenic
VUS excluded	0.28 per million	0.34 per million	0.56 per million
VUS included	2.11 per million	2.29 per million	2.82 per million

Table 3. Genetic birth prevalence of TK2d in Admixed American population

Prevalence	Pathogenic and Likely Pathogenic	Pathogenic + Likely pathogenic + Presumed Pathogenic
VUS excluded	2.80 per million	3.83 per million
VUS included	11.08 per million	13.06 per million

'Pathogenic only' variants are defined as: 1) pathogenic classification in Mastermind and/or ClinVar. 'Pathogenic + Likely pathogenic' variants are defined as: 1) variants with 'pathogenic' classification, and 2) variants with 'likely pathogenic' classification in Mastermind and/or ClinVar. 'Presumed pathogenic' variants are defined as variants without classification in Mastermind and ClinVar that are loss-of-function variants

Figure 5. TK2 Variant Contribution to Genetic Prevalence in gnomAD

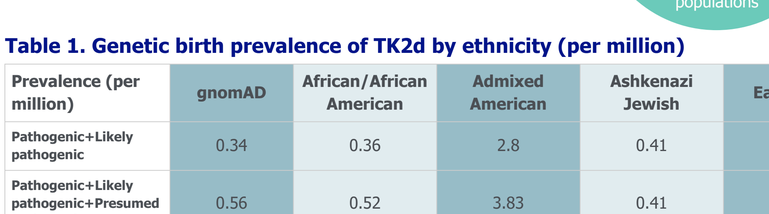
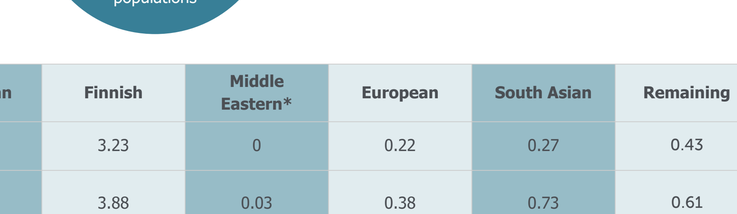


Figure 6. TK2 Variant Contribution to Genetic Prevalence in Admixed American (Latino/a) population



P, pathogenic; LP, likely pathogenic; PP, presumed pathogenic; VUS, variant of uncertain significance

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Figure 3. Methodology used for the inclusion and exclusion of variants based on the ACMG classification and scientifically based pathogenicity presumptions

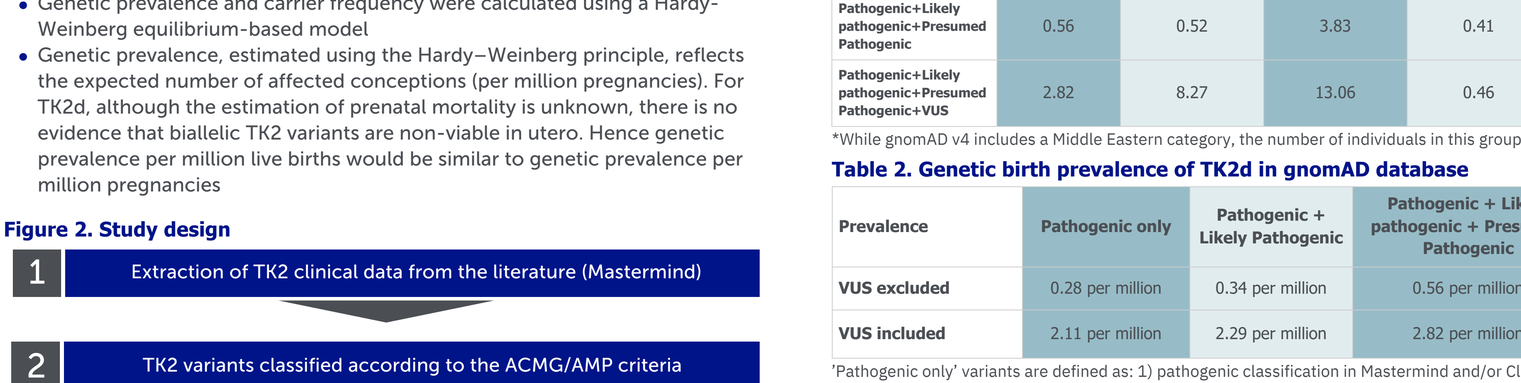
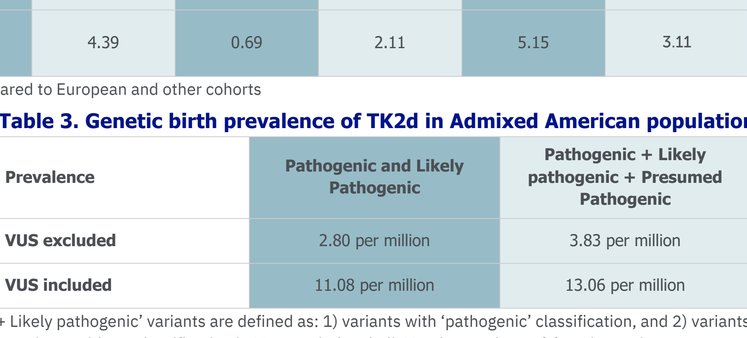


Figure 7. Carrier frequencies of TK2d in world populations



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