EPH197

An Integrated Modelling Methodology for Estimating Global, Regional, and Country-Specific Incidence and Prevalence of Tay-Sachs Disease at the Subtype Level

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Tay-Sachs disease (TSD) is a rare autosomal recessive disorder causing progressive neurodegeneration due to HEXA deficiency. Infantile, juvenile, and late-onset subtypes are described based on the age of symptom onset.
Despite genotype variability between certain ethnicities, there are well-established associations between common mutations and subtypes. Limited published evidence is available on prevalence for large regions of the world, especially for the late-onset subtype, which may be underdiagnosed. This prevents a realistic estimate of the current disease burden. The objective of this study was to develop an epidemiological model of the prevalence and patient pool per TSD subtype at the global, regional, and country levels.

251
Articles identified through keyword search using MEDLINE/PubMed

Studies were screened for the potential to offer the best available evidence on model inputs

Criteria for exclusion	Criteria for inclusion
Animal/cell models	Subtype frequency
Treatment effects only	Subtype distribution
Focus on another disease	Incidence, prevalence, onset
Symptom-based cohorts	Survival/mortality
Single cases	Screening/carrier data

99
Studies selected after screening by title/abstract

1,088
Total TSD patients identified

434
Subtype cases

45,742
TSD carriers identified

A data triangulation approach was used to combine evidence on carrier frequency, genotype, modifying factors, (birth) prevalence, survival, and onset from multiple sources.

Key countries were selected based on available evidence, region representativity, and expected size of rare disease market. For other countries, calculations were based on averages of the most populated countries in the region.

Infantile subtype
Birth prevalence calculation from carrier screening[92]
Validation with referred cases (mostly Caucasian)[3, 18,19,20,21,22,26,30]
0.29

Juvenile subtype
Birth prevalence from referred cases study[22]
0.07

Late-onset subtype
Birth prevalence from referred cases study[6]
Given uncertainty, a range of birth prevalence was used
0.20 – 0.30

Base-case birth prevalence used in the model (per 100k)

Individual patient data was used to build onset and survival curves in STATA[1,4,6,7,8,10,44,45,48,49,50,51,82,88,89,90,96,98].
The curves were corrected based on UN income regions to account for differences in life expectancy between countries.

Ethnicities' risk[17,22,32,50,92]
Risk ratios calculated from available evidence for each subtype

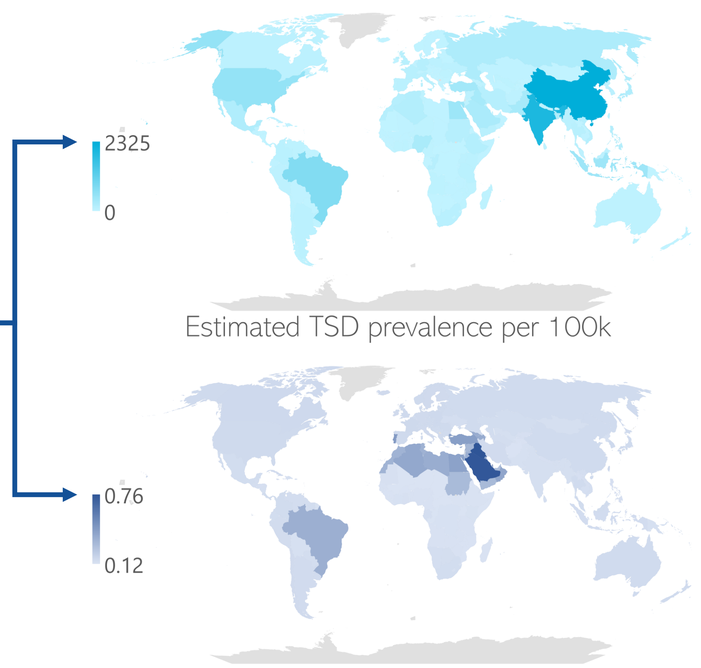
Consanguinity risk[102]
Risk ratios calculated from available inbreeding coefficients for high-risk countries

Ethnicity matrix
Ethnicity matrix for key countries and regions was constructed from available population data

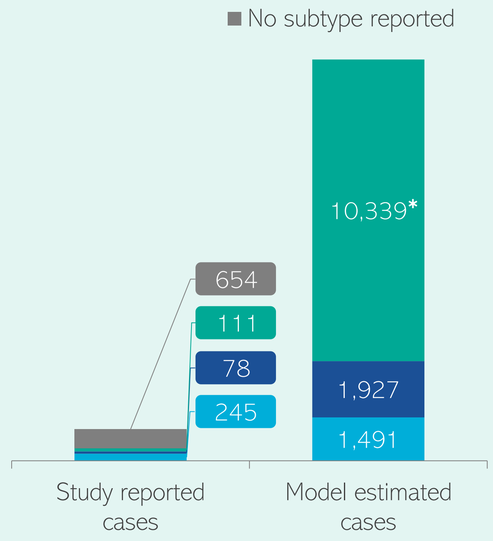
Screening factor[92]
Carrier screening impact factor was integrated to capture lower risk in screened populations

Point prevalence was calculated and a deterministic sensitivity analysis was used to generate a range for the late-onset subtype, reflecting the uncertainty in birth prevalence. Results shown represent a conservative scenario (birth prevalence of 0.20).

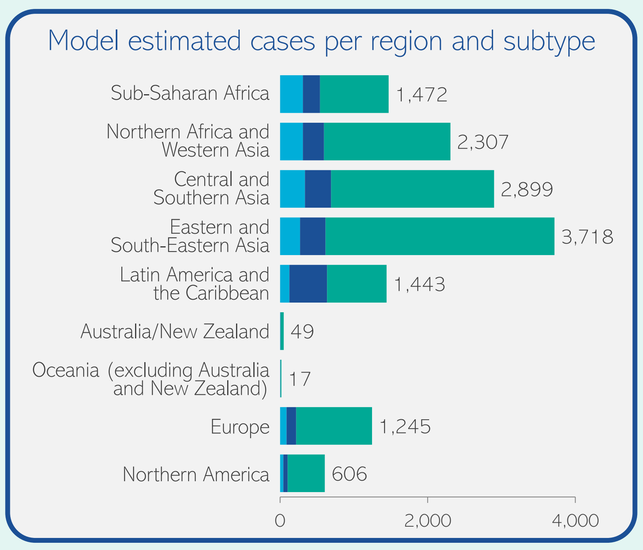
Estimated number of TSD patients



Model results show an underdiagnosis across all TSD subtypes, especially in the late-onset subtype



**Upper range of late-onset birth prevalence (0.30) results in 15,920 total cases of the late-onset subtype*



This is the first reported epidemiological model of TSD at the subtype and country level. By combining limited evidence, the estimates better capture the unmet need of the late-onset subtype. This method can be applied in other rare genetic diseases to quantify uncertainty and inform clinical program planning and health economic modelling.

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