PTEN RESEARCH

Estimation of the Prevalence of PTEN Hamartoma Tumour Syndrome and Opportunities for Orphan Drug Designation

Abstract

The true prevalence of PTEN Hamartoma Tumour Syndrome (PHTS) remains uncertain. However, recent large-scale genomic data provide more robust estimates. Analysis of whole-genome sequencing data from over 700,000 individuals suggests that the prevalence of constitutional *PTEN* pathogenic or likely pathogenic variants, and by extension PHTS, ranges from approximately 1 in 9,000 to 1 in 13,000 in the general population. This is 10- to 20-fold higher than previous estimates cited in the literature.

PHTS is a rare genetic condition caused by constitutional heterozygous pathogenic variants in the Phosphatase and Tensin Homolog (*PTEN*) tumour suppressor gene. Before the *PTEN* gene was identified and before routine genetic testing for rare congenital conditions, several syndromes were described based on clinical features. These clinical syndromes included Cowden syndrome (CS), Bannayan–Riley–Ruvalcaba syndrome (BRRS), Proteus syndrome (PS) and Proteus-like syndrome. Some, but not all, patients with these syndromes have been found to have constitutional *PTEN* variants and are now recognised as having PHTS.

Historically, estimating the prevalence of PHTS has been complex. This is partly due to the variability in patients' phenotypic and genotypic presentation. Additionally, several of the features of PHTS, such as benign lesions of the breast and uterus, are relatively common in the general population. As a result, some patients may not have been recognized as having a syndrome, and PHTS in particular[1]. Moreover, because PHTS is defined by the presence of pathogenic constitutional variants in the *PTEN* gene, disparities in access to genetic testing further complicate efforts to accurately estimate its prevalence.

Until recently, prevalence estimates for PHTS were based on estimates for the clinical syndromes associated with a PHTS-like phenotype (for details, see Appendix 1 – Literature review of the prevalence of clinical syndromes related to PHTS). A prevalence estimate of 1/200,000-1/250,000 is frequently cited, based on a study of the prevalence of CS in the Netherlands [2]. A more recent and accurate study, together with other supporting evidence as outlined below, suggest that the prevalence of PHTS is much higher.

Recently, a study assessed the prevalence of constitutional pathogenic/likely pathogenic *PTEN* variants in two research cohorts. A PHTS prevalence of approximately 1/9,000 was found in the US-based All of Us Research Program (245,000 participants). A similar estimate of 1/13,000 was found in the UK Biobank cohort (470,000 participants) [3]. These estimates are 10-20x higher than the previous estimate of 1/200,00-250,000 (for CS in the Netherlands).

Even higher estimates of prevalence (as high as 4-5 in 10,000 ie. ~1 in 2000) can be derived from the prevalence of *PTEN* variants in individuals with autism spectrum disorder (ASD) and macrocephaly (for details, see Appendix 2 – Additional supporting information based on the prevalence of *PTEN* variants in autism spectrum disorders).

Recent data from the French National Database of Rare Diseases (BNDMR) suggests a combined prevalence of PHTS and associated clinical syndromes of approximately 1/101,000 (for details, see Appendix 3 - French National Database of Rare Diseases (BNDMR)) [4]. It is not unexpected that the prevalence of individuals who have been diagnosed with PHTS is lower than the prevalence of individuals with a constitutional *PTEN* pathogenic/likely pathogenic variant given the diagnostic challenges outlined above.

Orphan Drug Designation Criteria

United States[5]

Within the US, to meet the criteria of the Orphan Drug Act of January 1983 (ODA) for Orphan Drug Designations, the molecule under assessment must be indicated for the prevention, diagnosis or treatment of diseases or conditions affecting fewer than 200,000 persons in the US. **It is noted that this designation is given to a drug for a disease or condition, and is not granted to the indication.** (There are additional criteria for drugs that will not be profitable within 7 years following approval by the FDA.)

In the context of PHTS:

- The maximum published prevalence estimate for PHTS is 1 in 9,000 [3].
- With the current US population[6], a disease prevalence of 1 /9,000 would mean approximately 38,000 individuals with PHTS in the US (well within the requirement for Orphan Drug Designation).
- The following limitations should be noted:
    - The estimation of population prevalence is based on research cohorts experiencing likely recruitment biases, such as the 'healthy volunteer effect' and the ancestry of participants is not representative of these populations.
    - The penetrance of a clinical phenotype associated with *PTEN* variants in a population-based cohort has not yet been characterised.
- Despite these caveats, even if the prevalence were 5 times higher (5/9,000), PHTS would still meet the US criteria for orphan drug designation.

European Union[7], [8]

The Committee for Orphan Medicinal Products (COMP) is the European Medicines Agency's (EMA) committee responsible for recommending orphan designation of medicines for rare diseases. The COMP was established in 2000, in line with Regulation (EC) No 141/2000.

To qualify for orphan designation in the EU, a medicine must meet several criteria:

- It must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating.

- The prevalence of the condition in the EU must not be more than 5 in 10,000 (i.e. 1 in 2,000) or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development.
- No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

Based on the COMP criteria and a PHTS prevalence estimate of 1/9,000, it may be inferred that a drug being developed to treat any or all PHTS subsets could meet the definition for orphan drug designation within the EU. The lack of existing therapeutic interventions and the fact that most, if not all, PHTS subsets may be considered life-threatening or chronically debilitating, also supports orphan designation for a drug developed for PHTS in the EU.

Discussion and Further Activity

The published prevalence data for PHTS is limited although the recent assessment of constitutional pathogenic/likely pathogenic *PTEN* variants in research cohorts provides the first robust data supporting the population prevalence of PHTS. Estimating PHTS prevalence is also complicated because:

i) Not all the clinical conditions associated with PHTS have formal consensus diagnostic criteria.
ii) Where consensus diagnostic criteria do exist, not all patients meeting the clinical criteria also express an identified *PTEN* constitutional variant.
iii) The penetrance of the *PTEN* variants in cohorts not evaluated in a clinical setting is unknown.

However, despite these caveats, the existing prevalence data would indicate that a molecule developed for the treatment of PHTS would likely meet the criteria for orphan drug designation in both the US and EU.

Importantly, a marketing approval would almost certainly be limited to the PHTS patient subpopulation studied in the pivotal trial(s) (e.g. PHTS patients with ASD) and not the entire PHTS patient population. This would further reduce the patient population considered in the context of an orphan drug designation application.

Consultation with a Regulatory Affairs professional would be advisable to validate the above assessment and to gain insights into recent Health Authority precedents for other orphan drug designations.

Other potential ways to obtain enhanced estimates on PHTS prevalence would include interrogating anonymised electronic medical records (EMR) or health care provider's claims data. However, it should be noted that the applicable ICD-10-CM and ICD-11 codes were only implemented for PHTS in late 2022 and early 2023, respectively. A lack of appropriate coding in affected individual's electronic medical records is likely to hamper accurate prevalence estimations for several years.

Regardless, a better understanding of PHTS prevalence would be valuable to support not only future Health Authority interactions and potential orphan drug designation applications but also to guide future drug development efforts and assessment of the burden of PHTS on payors and healthcare systems.

APPENDIX 1 – LITERATURE REVIEW OF THE PREVALENCE OF CLINICAL SYNDROMES RELATED TO PHTS

Cowden Syndrome (CS)

Consensus clinical diagnostic criteria for CS have been developed and are updated each year by the National Comprehensive Cancer Network (NCCN)[9]. Approximately 25-85% of patients meeting these criteria also have a constitutional pathogenic *PTEN* variant[10].

Nelen and colleagues[2] have estimated that the prevalence of CS in the Dutch population is between 1 in 200,000 and 1 in 250,000 based on a database of > 4.5 million individuals. The authors also highlight the possibility of misdiagnosis. Given the phenotypic variability of CS, this may represent an underestimate.

MedlinePlus, maintained under the auspices of the US National Library of Medicine and the NIH and the European Union supported Orphanet both list that the exact prevalence of Cowden syndrome is unknown, but it is estimated that it affects about 1 in 200,000 individuals[11], [12], but it is noted that the condition is likely underdiagnosed[9].

Bannayan–Riley–Ruvalcaba syndrome (BRRS)

At present no formal consensus criteria exist for the diagnosis of BRRS[9]. Approximately 60% of BRRS patients have pathogenic constitutional *PTEN* variants[10].

The prevalence of BRRS is unknown[13], [14] although it appears to be rare. As with CS, the disorder is likely to be underdiagnosed due to the variability of patients and lack of formal consensus diagnostic criteria.

Proteus syndrome (PS) and Proteus-like syndrome

Proteus syndrome (PS) is an extremely rare and highly variable condition and affects individuals in a mosaic distribution. Thus, it is frequently misdiagnosed despite the development of consensus clinical diagnostic criteria[9]. There are no clinical consensus criteria for Proteus-like syndrome[9] but the condition encompasses individuals with significant clinical features of PS but who do not meet the diagnostic criteria. It is estimated that between 7-67% of PS and Proteus-like syndrome patients have constitutional pathogenic *PTEN* variants[10].

The prevalence of Proteus syndrome is estimated as less than 1 in 1 million individuals worldwide. Only a limited number of affected individuals have been reported in the medical literature[15], [16].

APPENDIX 2 – ADDITIONAL SUPPORTING INFORMATION BASED ON THE PREVALENCE OF *PTEN* VARIANTS IN AUTISM SPECTRUM DISORDERS

Further supporting evidence for the potential PHTS prevalence can be obtained from extrapolation of other literature sources.

- It is estimated that autism spectrum disorder (ASD) affects approximately 2.2% of adults in the United States[17], and 1% of individuals in Europe[18].
- Further, estimates suggest that~15% of ASD cases have macrocephaly defined as >2 SDs per age norms[19].
- A meta-analysis of 9 studies indicated approximately 17% of macrocephalic ASD patients also had *PTEN* constitutional variants[20].
- In the light of last two findings, Frazier has suggested approximately 2% of all individuals with ASD will also have a *PTEN* constitutional variants[21].

On this basis the prevalence of PHTS with ASD may be estimated to be as high as 4 patients in 10,000 in the US and 2 patients per 10,000 in the EU. However, the lack of formal statistical analyses in deriving this estimate, and likely ascertainment biases in the source datasets, must be underlined. (Also noteworthy is that in a recent large study with sequencing data from 5100 individuals with ASD, *PTEN* was one of the most common genes with ASD associated rare variants[22].) Even with this estimation it is still expected that any drug developed for PHTS would fulfil the criteria for an orphan drug designation in both the US and European Union.

APPENDIX 3 - FRENCH NATIONAL DATABASE OF RARE DISEASES (BNDMR)

Currently, limited data sets exist containing systematic population level data about the prevalence of PHTS or associated clinical syndromes. One such source is the French National Database of Rare Diseases (BNDMR), where the most recent report, dated Dec 2024 detailed at least 674 living patients as having PHTS (n=62) or the clinical diagnoses of CS (n=573), BRRS (n=38) or Proteus-like syndrome (n≤10) corresponding to a combined prevalence of approximately 1:101,000 [4]. Of note, with each iterative update (published approximately every 6 months) this prevalence has been increasing (in 2023 the prevalence was approximately 1:120,000).

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