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ASAH1 pathogenic variants associated with acid ceramidase deficiency (ACD): Farber disease and spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME)

Running title: *ASAH1* pathogenic variants

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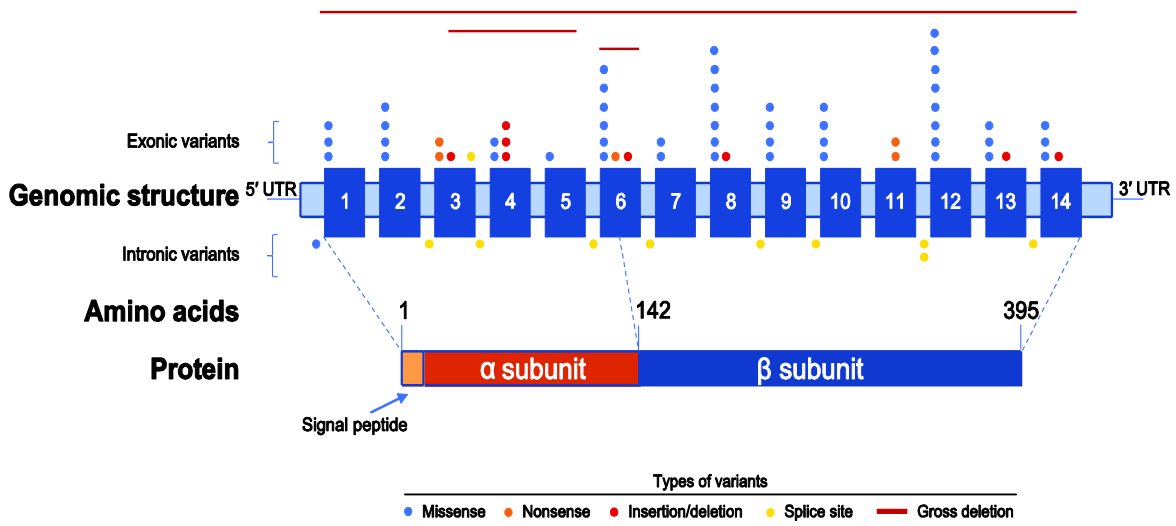
Abstract

Farber disease and spinal muscular atrophy with progressive myoclonic epilepsy are a spectrum of rare lysosomal storage disorders characterized by acid ceramidase deficiency (ACD), resulting from pathogenic variants in *ASAH1*. Other than simple listings provided in literature reviews, a curated, comprehensive list of *ASAH1* mutations associated with ACD clinical phenotypes has not yet been published. This publication includes mutations in *ASAH1* collected through the Observational and Cross-Sectional Cohort Study of the Natural History and Phenotypic Spectrum of Farber Disease (NHS), ClinicalTrials.gov identifier NCT03233841, in combination with an up-to-date curated list of published mutations. The NHS is the first to collect retrospective and prospective data on living and deceased patients with ACD presenting as Farber disease, who had or had not undergone hematopoietic stem cell transplantation. Forty-five patients representing the known

clinical spectrum of Farber disease (living patients aged 1 to 28 years) were enrolled. The curation of known *ASAH1* pathogenic variants using a single reference transcript includes 10 previously unpublished from the NHS and 63 that were previously reported. The publication of *ASAH1* variants will be greatly beneficial to patients undergoing genetic testing in the future by providing a significantly expanded reference list of disease-causing variants.

Graphical Abstract

Farber disease and spinal muscular atrophy with progressive myoclonic epilepsy are a spectrum of rare lysosomal storage disorders characterized by acid ceramidase deficiency (ACD), resulting from pathogenic variants in ASAH1. We provide a comprehensive assessment of variants in ASAH1 collected through the Observational and Cross-Sectional Cohort Study of the Natural History and Phenotypic Spectrum of Farber Disease (NHS), ClinicalTrials.gov identifier NCT03233841, in combination with an up-to-date curated list of published mutations describing the spectrum of acid ceramidase deficiency.



Keywords

Acid ceramidase deficiency (ACD); Farber disease; spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME); lysosomal storage disorder; N-acylsphingosine amidohydrolase 1, ASAH1, acid ceramidase

1. INTRODUCTION

Farber disease [MIM# 228000, ORPHA 333] and spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME) [MIM# 159950, ORPHA 2590] are part of a spectrum of lysosomal storage disorders that are characterized by acid ceramidase deficiency (ACD) (Yu et al. 2018). They are caused by pathogenic variants in *ASAH1* (located on chromosome 8p22) [MIM# 613468], which encodes acid ceramidase (AC) (Koch et al. 1996; Alayoubi et al. 2013; Burek et al. 2001). Inheritance of both of these diseases is autosomal recessive. Acid ceramidase primarily acts in the lysosome to degrade ceramide into sphingosine and fatty acid, but can also catalyze the synthesis of ceramides (Gatt 1963). Ceramide is a bioactive lipid with pro-inflammatory and pro-apoptotic properties (Koch et al. 1996; Alayoubi et al. 2013; Burek et al. 2001). Abnormal accumulation of ceramide leads to a multiple organ system pathology, including potential impacts on the bone, cartilage, immune system, central nervous system (CNS), lungs, and other internal organs (Alayoubi et al. 2013). Acid ceramidase deficiency leads invariably to progressive disease with profound morbidity and premature death (Yu et al. 2018).

1.1 Farber disease (Farber lipogranulomatosis)

Farber disease was first characterized by Dr. Sidney Farber in 1947, and the first cases were published in the 1950s (Farber 1952; Farber, Cohen, and Uzman 1957). A literature review by Yu and colleagues demonstrated that approximately 201 cases of Farber disease and SMA-PME were reported between 1952 and 2018 (Yu et al. 2018). As is the case with many other lysosomal storage disorders, Farber disease and SMA-PME have a broad range of age at onset and rapidity of disease progression, and the severity of

symptoms within an individual patient may also be quite variable (Ferreira and Gahl 2017). Initial reports of patients with Farber disease divided the population into multiple subtypes, but Farber himself (Farber, Cohen, and Uzman 1957) and other experts in the field (Moser 1983) recognized that it was likely most accurate to describe a spectrum of disease, which is reflected in recent papers (Bonafe et al. 2016; Schuchman, Mitchell, and Solyom 2017; Ferreira et al. 2014). The cardinal triad of symptoms common to almost all reported patients with Farber disease are subcutaneous nodules (lipogranulomas consisting of ceramide engorged macrophages), joint disease (arthritis and/or contractures), and a hoarse voice (dysphonia) (Figure 1a and b).

Farber disease is characterized by activation of the innate immune system and local and systemic inflammation (Alayoubi et al. 2013; Dworski et al. 2017; Schuchman, Mitchell, and Solyom 2017). Additional clinical manifestations are variable and may include neurological, ophthalmic, respiratory, gastrointestinal, liver, bone, dermatological, and/or hematopoietic symptoms. Symptoms may appear in any order, and it may take years for the cardinal symptoms to appear together. The complexity and variability of clinical features creates a diagnostic challenge, and patients are often initially misdiagnosed as having juvenile idiopathic arthritis (Hugle, Mueller, and Levade 2014). Milder involvement with prolonged survival has been associated with peripheral osteolysis of bones in the wrist (distal radius and ulna) and hands (carpals, metacarpals and phalanges), with consequent finger shortening and skin redundancy (Bonafe et al., 2016). There have been cases of patients with combined Farber and Sandhoff diseases (Fusch et al. 1989), presenting with a similar clinical picture due to deficiency of saposins (Hulkova et al. 2001). Further, additional disorders have a range of symptoms that

overlap with Farber disease and are therefore part of a broad differential diagnostic spectrum with implications for diagnostic testing strategies, including composition of gene panels (Supp. Table S1).

Generally speaking, from the perspective of prognosis, the relative severity of the disease may be considered to be associated with the rapid progression of symptoms and the presence or absence of lung and CNS involvement. In patients with rapidly progressive (severe) disease, symptoms may emerge in the first days or weeks of life, and affected children usually do not survive beyond their second or third birthday (Farber, Cohen, and Uzman 1957) (Figure 1c).

A few cases of Farber disease in infants with nonimmune hydrops fetalis have been reported (Kattner, Schafer, and Harzer 1997; Schafer et al. 1996). Individuals with more moderately or slowly progressive forms of Farber disease may survive into adolescence or early adulthood (Bonafe et al. 2016; Hugle, Mueller, and Levade 2014; Yu et al. 2018) (Figure 1d).

1.2 Spinal muscular atrophy with progressive myoclonic epilepsy

Previously known as Jankovic-Rivera Syndrome, SMA-PME as a distinct clinical entity was first described by Jankovic and colleagues in 1978 (Jankovic and Rivera 1978), and the association with the *ASAH1* gene and ACD was reported by Zhou and colleagues in 2012 (Zhou et al. 2012). The recent expansive paper by Yu and colleagues collected reports of 43 patients, including 23 cases of SMA-PME associated with *ASAH1* mutations and 20 patients who were described as having SMA-PME prior to the elucidation of the genetic background (Yu et al. 2018). Initial symptoms usually include

those typical of lower motor neuron disease, including progressive muscle weakness, increasing number of falls, difficulty in walking, and tremors. However, myoclonic epilepsy may also appear first and can vary in severity. Seizures generally increase in frequency and are difficult to control with medication (Yu et al. 2018; Dyment et al. 2014). Patients may experience generalized seizures or tremors and swallowing difficulty, eventually reaching a state of severely impaired mobility, with respiratory failure occurring in the last stages of the disease course. Cognitive decline may occur as a result of high seizure activity in some cases (Yildiz et al. 2018), whereas full intellectual capacity may remain in others until the end of life. Death can occur in childhood (Teoh et al. 2016), but a greater number of patients are reported to live into early adulthood (Gan et al. 2015; Rubboli et al. 2015; Dyment et al. 2014). The variability in age at presentation, rapidity of progression, and relative severity of symptoms mirrors that of patients with Farber disease. The earliest recorded symptoms have appeared at 2 years of age (Rubboli et al. 2015), and presentation in adulthood has been recorded (van der Beek et al. 2019), although the majority of patients begin to experience symptoms in late childhood to early teenage years (Dyment et al. 2014). Adding to the spectrum of phenotypes, recent cases have been published of patients who have only SMA symptoms (Filosto et al. 2016), onset of eyelid myoclonic status epilepticus (Oguz Akarsu et al. 2016), sensorineural hearing loss, or a Farber-SMA-PME overlap phenotype (Teoh et al. 2016). Similar to Farber disease, SMA-PME patients have been reported from diverse countries and geographies. A selected list of differential diagnoses related to the known spectrum of SMA-PME phenotypes is proposed in Supp. Table S2.

Clinical reports suggest that ACD is an extremely rare condition; however, due to the relatively few reports of SMA-PME and the recent establishment of the association of this clinical phenotype with ACD and *ASAH1* mutations, the prevalence of ACD overall has not been accurately determined to date. An epidemiological Orphanet report predicted the prevalence of Farber disease as <1/1,000,000 (Orphanet 2019).

When indicative clinical symptoms are present, Farber disease and SMA-PME are most often diagnosed by genetic testing that confirms pathogenic variants in *ASAH1* and/or by measuring enzyme activity that confirms ACD. In rare cases, when other testing is not available, biopsy of the subcutaneous nodules has been used to confirm the diagnosis of Farber disease (Schmoeckel and Hohlfed 1979). Establishing deficient activity of AC in peripheral blood leukocytes, cultured lymphoid cells, or cultured skin fibroblasts is the ideal method for confirming a diagnosis. However, the availability of such testing is extremely limited, and consensus levels representing a clear deficiency or the lower limit of normal AC have not yet been definitively standardized across laboratories and methods. There have been published reports of activity levels of 32% of activity of controls in patients with clinically and genetically confirmed ACD, with levels <10% having been also previously cited (Yu et al. 2018; Chatelut et al. 1996).

Prior to this publication, 61 pathogenic variants associated with Farber disease or SMA-PME had been published. More than 165 genetic variants, including pathogenic and nonpathogenic variants, have been submitted to the National Center for Biotechnology Information ClinVar public archive, including copy number, single nucleotide variants, and insertions/deletions. The majority of the reported *ASAH1* pathogenic variants are missense mutations and nonsense mutations, with most of the mutations associated with

Farber disease in the region encoding the β-subunit, and most of the mutations associated with SMA-PME predominantly in the region encoding the α-subunit, especially p.Thr42Ala and p.Thr42Met in exon 2 (Yu et al. 2018). At present, no definitive genotype-phenotype correlations have been confirmed due to a lack of systematically collected natural history data across all phenotypes.

Prenatal diagnosis is possible in families known to carry mutations associated with ACD or can also be performed by measuring AC activity in cultured amniocytes or chorionic villi (Bedia et al. 2010); however, the availability of this testing is extremely limited.

A disease-specific therapy for ACD is not currently available. Symptoms are managed with anti-inflammatory medications, analgesics, and occasionally surgical intervention (Yu et al. 2018). Allogenic hematopoietic stem cell transplantation (HSCT) has provided some benefit for patients with regard to joint and other peripheral symptoms, but HSCT does not appear to prevent the development or progression of neurological symptoms (Cappellari et al. 2016; Yu et al. 2018; Ehlert et al. 2007; Ehlert et al. 2019). Gene therapy for ACD has been previously investigated in animal models (Alayoubi et al. 2013). Enzyme replacement therapy has been proposed as a therapeutic intervention for Farber disease, and proof of concept experiments in cultured cells and mice have yielded promising results (He et al. 2017).

2. MUTATIONAL SPECTRUM

The Observational and Cross-Sectional Cohort Study of the Natural History and Phenotypic Spectrum of Farber Disease (NHS) was designed to collect retrospective and prospective data, including demographics, clinical presentation, phenotype, and

diagnostic history, such as specific prospective clinical evaluations (e.g., measures of symptom impact through standardized physical assessments and patient-reported outcomes) of living patients diagnosed with Farber disease who have or have not undergone HSCT. Consideration of the need to include historical (deceased) patients, as well as living patients, in order to collect as much relevant data as possible on this very rare disease led to the adoption of the inclusion criteria listed below.

- Living or deceased subjects with a diagnosis of Farber disease, based on clinical (typical clinical symptoms) and biochemical or genetic criteria, as follows:

    a. Biochemical: An AC activity value in white blood cells, cultured skin fibroblasts or other biological sources (e.g., plasma) that is <30% of control (normal) values established by the testing laboratory. For deceased subjects only, storage of ceramide in cells from histopathologic sections is also adequate to confirm the diagnosis.

    b. Genetic: Nucleotide changes within both alleles of the AC gene (*ASAH1*) or complementary DNA (cDNA) that indicate, through bioinformatic analysis, gene expression studies, or other methods, a possible loss of function of the AC protein.

Patient recruitment was conducted by investigators who had known patients or who function as recognized experts in rare diseases in the fields of genetics, inherited metabolic diseases, pediatric neurology, or pediatric rheumatology. The scope of the study was global, with patient countries of birth that include Afghanistan, Argentina,

Canada, Egypt, Germany, India, Iraq, Italy, Mexico, Sweden, Syria, Turkey, and the United States; however, it was still not possible to enroll every known Farber disease patient in every country due to logistical and operational limitations.

The study was approved by the appropriate regulatory entities, ethics committees, and internal review boards according to the laws and regulations in each country where a study site was established and patients enrolled. The conduct of the study was in accordance with International Council of Harmonization and Good Clinical Practice standards and directives.

Analysis of data available from enrollment over the period from November 2017 to July 2019 included 45 patients (27 living, 18 deceased); 40% were female and 60% were male (Table 1). The average age of the living patients was 9 years (range 1–28 years). Twenty-three living patients (85%) were less than 18 years old and 16 (59%) were less than 6 years old, whereas 89% (16/18) of deceased patients died before the age of 6 years. Three of the living patients and four deceased patients had undergone HSCT. In the population of patients enrolled in the NHS, diagnostic confirmation was achieved by *ASAH1* mutational analysis (40 patients), AC activity testing (7 patients), and nodule biopsy (14 patients). Multiple modalities were used in some patients.

2.1 *ASAH1* mutations identified in the Natural History Study

Reports on *ASAH1* pathogenic variants were available from 38 patients in the NHS (Table 1). Identified variants included previously reported *ASAH1* variants, as well as novel disease-causing variants. Most patients carried missense mutations, and known or

putative splice site variants were also frequently identified. Fewer patients carried larger deletions encompassing *ASAH1*.

Elements of the data set have been submitted to ClinVar for review (submission ID: SUB5958214).

2.2 *ASAH1* variants previously reported by other groups

A comprehensive review of the literature was conducted using the search terms “Farber disease”, “ASAH1”, “SMA-PME”, “acid ceramidase deficiency”, “acid ceramidase”, to identify all published *ASAH1* variants associated with ACD. Inclusion criteria required any of the following: documented ACD by enzyme analysis, the triad of features consistent with Farber disease, or in trans inheritance of alleles with features associated with SMA-PME.

The genotypes of 76 previously reported patients with ACD are shown Table 2, representing a range of phenotypes spanning the spectrum of ACD, including Farber disease and SMA-PME. Most variants leading to the more severe Farber phenotype represent founder mutations in specific populations (geographical or ethnic) or private mutations within a family that are not represented in public genome databases. A patient reported by Chikova and colleagues (Chikova et al. 2014) was excluded from the analysis, as one of the reported variants likely represents a polymorphism, with a minor allele frequency of 3.7% in the general population and as high as 6.9% in some populations.

3. IMPACT OF VARIANTS ON AC FUNCTION

Due to the historical nature of the data available on enzyme activity and the variability in the laboratories and techniques used, not enough information is available to present conclusions on the impact of specific variants on AC function. It is clear that the vast majority of reported variants are missense mutations (>90%), likely resulting in some remaining functional enzyme, with likely null alleles (truncated protein products and significant splice variants) typically found in the heterozygous state along with a missense variant in more than 85% of cases. There are very few published cases of ACD with AC activity below the level of detection by the available assay; these patients had a rapidly progressive phenotype representing the most severe end of the spectrum of ACD (Alves et al. 2013; Antonarakis et al. 1984). This, as well as evidence from studies showing that *Asah1*$^{-/-}$ knockout mice had an early embryonic lethal phenotype (Li et al. 2002), indicates that almost all patients within the currently established spectrum of ACD who are likely to be seen in the clinic have some residual enzyme production.

4. GENOTYPE-PHENOTYPE CORRELATION

Table 3 provides a curated list of the 63 previously reported pathogenic variants in *ASAH1* that are associated with ACD, in addition to the 10 new variants identified in the NHS. The vast majority of variants are associated with features of Farber disease, whereas a subset of more recently described *ASAH1* variants are associated with SMA-PME or epilepsy. The location of the variants in the canonical transcript of the gene (NM_177924.5) is shown in Figure 2.

Although ACD is a spectrum disorder and variants that affect enzyme function are located throughout the gene, a high number of variants associated with an SMA-PME

phenotype have been reported in exons 1 and 2, likely affecting the α-subunit of the AC protein (Filosto et al. 2016; Rubboli et al. 2015; Yildiz et al. 2018; Zhou et al. 2012; Giraldez et al. 2015; Behin et al. 2015). Overall, 18 reports of mutations affecting the α-subunit of AC have been reported in SMA-PME, with 12 of these being the pathogenic variant c.125C>T (p.Thr42Met) located in exon 2.

However, there are reports of patients with the SMA-PME phenotype and variants that have no apparent effect on the α-subunit (Kernohan et al. 2017; Dyment et al. 2014; Gan et al. 2015; Teoh et al. 2016), as well as patients with a Farber phenotype and no reported typical symptoms of SMA-PME who have reported pathogenic variants that are likely to affect the α-subunit (Zhang et al. 2000).

5. ANIMAL MODELS

Initial efforts to produce a mouse model of ACD focused on achieving a systemic phenotype resembling Farber disease. Generation of *Asah1*$^{-/-}$ knockout mice led to embryonic lethality, with heterozygotes showing some signs of lipid ceramide accumulation long term (Eliyahu et al. 2007). A Farber disease mouse model reflecting a rapidly progressive clinical phenotype was achieved by knocking-in a mutation (*Asah1*$^{P361R/P361R}$) from a severely affected Farber patient who died before the age of 2 years (Alayoubi et al. 2013; Li et al. 1999). Characterization of the knock-in mouse model has been extensive and demonstrates systemic ceramide accumulation with a resultant inflammatory phenotype with organ system pathology overlapping significantly with that seen in the Farber disease spectrum (Yu et al. 2019; Yu et al. 2018; Dworski et al. 2017; Sikora et al. 2017). Reflecting the severity of the human clinical phenotype

associated with the same mutation, the Farber mice have a profoundly limited lifespan. Early experimentation with gene therapy demonstrated that supplying functional AC showed therapeutic promise (Alayoubi et al. 2013), and enzyme replacement therapy has been demonstrated to have a broad impact on inflammation, ceramide storage, and organ system pathology in mice models of Farber disease (He et al. 2017).

6. CONCLUSION AND FUTURE PROSPECTS

The data presented in this paper significantly expand the number of pathogenic variants in *ASAH1* that are associated with ACD, thus facilitating the appropriate classification of variants identified in diagnostic testing. Furthermore, although there have been several summary and review publications related to *ASAH1* mutations, this paper establishes a comprehensive curated list of nucleotide changes with consistent notation, allowing for the accurate and reproducible analysis of data associated with mutations in relation to one another, to the structure of the AC enzyme, and potentially to biochemical and clinical phenotypes. The importance of an up-to-date and comprehensive list of known *ASAH1* variants associated with clinical disease is demonstrated by the fact that the majority of patients in the Farber disease NHS were diagnosed primarily using genetic testing.

The distribution of known mutations and their association with clinical phenotypes would seem to indicate that the majority of mutations associated with Farber disease are predominantly found in the region encoding the β-subunit of AC and that mutations associated with SMA-PME are more often found in the region encoding the α-subunit (Yu et al. 2018). However, there are cases that do not seem to support definitive acceptance of such associations. In such a rare disease, encompassing a broad clinical spectrum, we feel it is important to acknowledge the potential role of ascertainment bias

and the need for papers like this one, which help to collate diagnostic information and contribute to standardized reporting.

The phenotypes associated with ACD and *ASAH1* variants may represent distinct clinical entities in certain cases, such as moderately progressive Farber disease without CNS involvement versus SMA-PME, but the existence of overlapping phenotypes (Teoh et al. 2016) indicates that it is reasonable to consider both Farber disease and SMA-PME as clinical variants on the ACD spectrum. Future studies to elucidate the differences in phenotypes between Farber disease and SMA-PME, including cell-type specific needs for adequate levels of enzyme activity and/or cell-specific expression of AC isoforms are required to better understand the association between *ASAH1* mutations and biochemical and clinical phenotypes across the AC deficiency spectrum. These studies may lead to better elucidation of the complex interactions in the sphingolipid metabolic pathways that underly the variability in the phenotypes across this broad spectrum of ACD, as well as other potential targets for therapy.

The *ASAH1* mutation data combined with the biochemical, biomarker, and clinical data being collected in the Farber disease NHS will be important for establishing additional tools and methods to enhance diagnostic testing, evaluate prognosis, monitor disease progression, and potentially evaluate response to disease-specific therapies once they become available. The Farber disease NHS is the first substantial step in moving toward this possibility, and the publication of known disease-causing mutations from the study, along with the curation of all mutations known to date, will hopefully substantially enhance the ability of genetic testing laboratories to provide clear results to patients and physicians seeking a diagnosis.

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CONFLICTS OF INTEREST

SHE reports personal fees from Enzyvant and Takeda and grants received from NIH and Shire Genetic Therapies. AS is an employee of Enzyvant. PH reports personal fees from Enzyvant. JM reports consulting fees from Enzyvant. CL reports grants, advisor fees, and honorarium from Shire/Takeda, Sanofi Genzyme, Biomarin, Amicus, Alexion, Actelion. CG reports cost of investigations paid to hospital only and travel support from Enzyvant and Sanofi Genzyme. SO reports serving on an advisory board with Pfizer and speakers bureau with Novartis and SOBI. KM, LS, NOM, NG, BM, ES, RP, SK, NA, MD, MZ, IGM, KE, AH, GG, MT, and CRF have nothing to disclose.

Author contributions

AS, KM, SHE, and CRF collected and assessed variant data; PH, JM, CL, CG, LS, NOM, NG, BM, ES, RP, SK, NA, MD, MZ, SO, IGM, KE, AH, GG, MT enrolled patients and collected clinical and molecular data for patients in the natural history study; AS, SHE, and CRF drafted the manuscript; all authors read, edited, and approved the manuscript prior to submission.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Figures

FIGURE 1 Typical features of patients with Farber disease. (a) Feet of a 3-year-old child with moderately progressive Farber disease (subcutaneous nodules circled). (b) Right ear of a teenage patient with Farber disease. (c) Hand of 3-year-old child with moderately progressive Farber disease (subcutaneous nodules circumscribed). (d) Left hand of a 28-year-old patient with Farber disease. Source of photos: Enzyvant NHS.

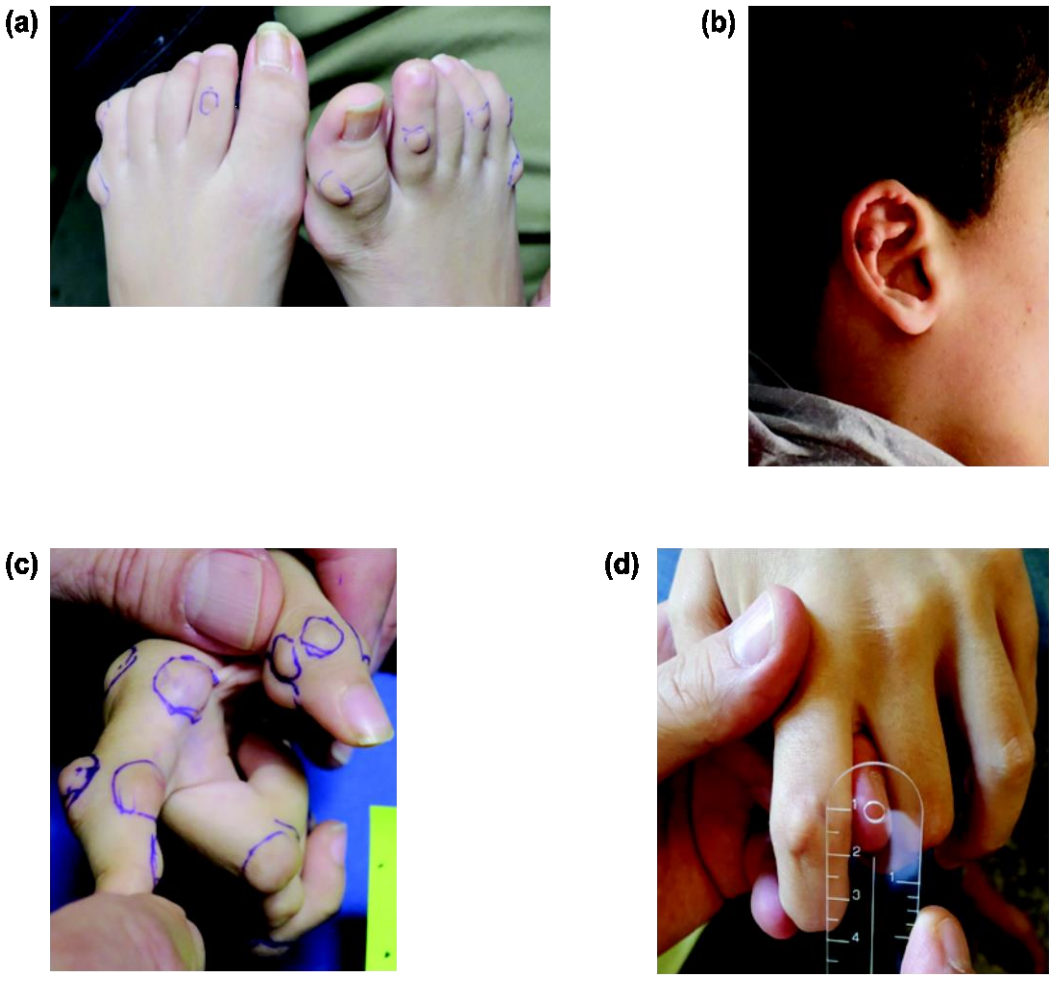
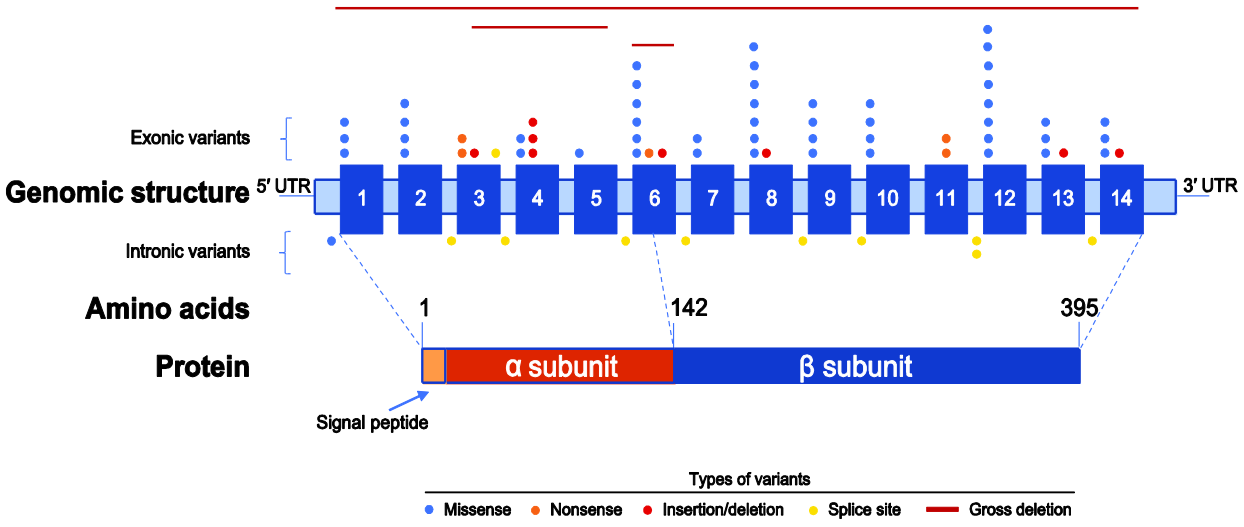


FIGURE 2 Quantitative distribution of ASAH1 mutations. Each mutation is represented by a single circle.



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Tables

TABLE 1 *ASAH1* genotypes identified in the Natural History Study

Patient	gDNA (Chr8; GRCh38)	GT2_MUT1 [NM_177924.5]	Protein [NP_808592.2]	gDNA (Chr8; GRCh38)	GT2_MUT2 [NM_177924.5]	Protein [NP_808592.2]	Phenotype
1	g.18075574C>A	c.92G>T	p.Cys31Phe	g.18075574C>A	c.92G>T	p.Cys31Phe	Farber
2	g.18075574C>A	c.92G>T	p.Cys31Phe	g.18075574C>A	c.92G>T	p.Cys31Phe	Farber
3	g.18075559T>C	c.107A>G	p.Tyr36Cys	g.18059385G>C	c.997C>G	p.Arg333Gly	Farber
4	g.18075559T>C	c.107A>G	p.Tyr36Cys	g.18075559T>C	c.107A>G	p.Tyr36Cys	Farber
5	g.18075559T>C	c.107A>G	p.Tyr36Cys	g.18075559T>C	c.107A>G	p.Tyr36Cys	Farber
6	g.18075559T>C	c.107A>G	p.Tyr36Cys	g.18075559T>C	c.107A>G	p.Tyr36Cys	Farber
7	g.18075559T>C	c.107A>G	p.Tyr36Cys	g.18075559T>C	c.107A>G	p.Tyr36Cys	Farber
8	g.18075559T>C	c.107A>G	p.Tyr36Cys	g.18075559T>C	c.107A>G	p.Tyr36Cys	Farber

9	g.18075559T>C	c.107A>G	p.Tyr36Cys	g.18075559T>C	c.107A>G	p.Tyr36Cys	Farber
10	g.18071344dup	c.174dup	p.Tyr59LeufsTer6	g.18062301C>T	c.626G>A	p.Gly209Asp	Farber
11	g.18071297T>A	c.216+3A>T	p.=	g.18063185C>A	c.503G>T	p.Gly168Val	Farber
12	g.18064506A>T	c.408T>A	p.Phe136Leu	g.18059385G>C	c.997C>G	p.Arg333Gly	Farber
13	g.18064504_18064505delTA	c.410_411delAT	p.Tyr137Ter	g.18061458C>T	c.704G>A	p.Gly235Asp	Farber
14	g.18064504T>C	c.410A>G	p.Tyr137Cys	g.18064504T>C	c.410A>G	p.Tyr137Cys	Farber+CNS
15	g.18064504T>C	c.410A>G	p.Tyr137Cys	g.18064504T>C	c.410A>G	p.Tyr137Cys	Farber+CNS
16	g.18064501T>A	c.413A>T	p.Glu138Val	g.18064504_18064505delTA	c.410_411delAT	p.Tyr137Ter	Farber+CNS
17	g.18064457C>T	c.457G>A	p.Gly153Ser	g.18059462A>C	c.920T>G	p.Leu307Arg	Farber
18	g.18064457C>T	c.457G>A	p.Gly153Ser	g.18059462A>C	c.920T>G	p.Leu307Arg	Farber
19	g.18062422A>G	c.505T>C	p.Trp169Arg	g.18062422A>G	c.505T>C	p.Trp169Arg	Farber
20	g.18062422A>G	c.505T>C	p.Trp169Arg	g.18062422A>G	c.505T>C	p.Trp169Arg	Farber
21	g.18062422A>G	c.505T>C	p.Trp169Arg	g.18062422A>G	c.505T>C	p.Trp169Arg	Farber
22	g.18062383G>C	c.544C>G	p.Leu182Val	g.18062383G>C	c.544C>G	p.Leu182Val	Farber
23	g.18061712C>G	c.677G>C	p.Arg226Pro	g.18058849G>T	c.1084C>A	p.Pro362Thr	Farber
24	g.18061686C>G	c.703G>C	p.Gly235Arg	g.18061686C>G	c.703G>C	p.Gly235Arg	Farber
25	g.18061458C>T	c.704G>A	p.Gly235Asp	g.18061458C>T	c.704G>A	p.Gly235Asp	Farber
26	g.18061458C>T	c.704G>A	p.Gly235Asp	g.18061458C>T	c.704G>A	p.Gly235Asp	Farber

27	g.18061458C>T	c.704G>A	p.Gly235Asp	g.18061458C>T	c.704G>A	p.Gly235Asp	Farber
28	g.18061458C>T	c.704G>A	p.Gly235Asp	g.18061458C>T	c.704G>A	p.Gly235Asp	Farber
29	g.18061458C>T	c.704G>A	p.Gly235Asp	g.18061458C>T	c.704G>A	p.Gly235Asp	Farber
30	g.18061440A>G	c.722T>C	p.Leu241Pro	g.18061440A>G	c.722T>C	p.Leu241Pro	Farber
31	g.18061440A>G	c.722T>C	p.Leu241Pro	g.18061440A>G	c.722T>C	p.Leu241Pro	Farber
32	g.18059388C>G	c.994G>C	p.Asp332His	g.18059384C>T	c.998G>A	p.Arg333His	Farber
33	g.18059436C>G	c.994G>C	p.Asp332His	g.18059436C>G	c.994G>C	p.Asp332His	Farber
34	g.18059384C>T	c.998G>A	p.Arg333His	g.18059384C>T	c.998G>A	p.Arg333His	Farber
35	g.18058848G>C	c.1085C>G	p.Pro362Arg	g.18058848G>C	c.1085C>G	p.Pro362Arg	Farber
36	g.18058845_18058847delinsTGTTTT	c.1086_1088delinsAAAACA	p.Val363delinsLysHis	g.18064505A>T	c.409T>A	p.Tyr137Asn	Farber
37	g.18057544A>C	c.1178T>G	p.Ile393Arg	g.18071300C>T	c.216G>A	p.V72=	Farber
38	g.18057537C>A	c.1185G>T	p.Trp395Cys	g.18057537C>A	c.1185G>T	p.Trp395Cys	Farber

TABLE 2 *ASAH1* genotypes previously reported by other groups

Genotype	**gDNA (Chr8; GRCh38)**	**NM_177924.5**	**NP_808592.2**	**gDNA (Chr8; GRCh38)**	**NM_177924.5**	**NP_808592.2**	**Phenotype**	**Reference**
1	g.18083982G>T	c.77C>G	p.Pro26Arg	g.18075540C>T	c.125+1G>A	p.=	SMA-PME	(van der Beek et al. 2019)
2	g.18075574C>A	c.92G>T	p.Cys31Phe	g.18075574C>A	c.92G>T	p.Cys31Phe	Farberdis	(Cozma et al. 2017)

							ease	
3	g.18075574C>A	c.92G>T	p.Cys31Phe	g.18075574C>A	c.92G>T	p.Cys31Phe	Farber disease	(Saygi et al. 2015)
4	g.18075559T>C	c.107A>G	p.Tyr36Cys	g.18075559T>C	c.107A>G	p.Tyr36Cys	Farber disease	(Bar et al. 2001)
5	g.18075559T>C	c.107A>G	p.Tyr36Cys	g.18075559T>C	c.107A>G	p.Tyr36Cys	Farber disease	(Cozma et al. 2017)
6	g.18075559T>C	c.107A>G	p.Tyr36Cys	g.18059385G>C	c.997C>G	p.Arg333Gly	Farber disease	(Cozma et al. 2017)
7	g.18075542T>C	c.124A>G	p.Thr42Ala	g.18062391G>A	c.536C>T	p.Thr179Ile	SMA-PME	(Cozma et al. 2017)
8	g.18075542T>C	c.124A>G	p.Thr42Ala	g.18075542T>C	c.124A>G	p.Thr42Ala	SMA-PME	(Filosto et al. 2016)
9	g.18075542T>C	c.124A>G	p.Thr42Ala	g.18075542T>C	c.124A>G	p.Thr42Ala	SMA-PME	(Filosto et al. 2016)
10	g.18075542T>C	c.124A>G	p.Thr42Ala	g.18062391G>A	c.536C>T	p.Thr179Ile	SMA-PME	(Sathe and Pearson 2014)
11	g.18075540C>T	c.125+1G>A	p.=	g.18064458T>G	c.456A>C	p.Lys152Asn	SMA-PME	(Cozma et al. 2017)
12	g.18075541G>A	c.125C>T	p.Thr42Met	g.18075541G>A	c.125C>T	p.Thr42Met	SMA-	(Shervin Badv et al. 2019)

							PME	
13	g.18075541G>A	c.125C>T	p.Thr42Met	g.18075541G>A	c.125C>T	p.Thr42Met	SMA-PME	(Giraldez et al. 2015)
14	g.18075541G>A	c.125C>T	p.Thr42Met	g.18075541G>A	c.125C>T	p.Thr42Met	SMA-PME	(Oguz Akarsu et al. 2016)
15	g.18075541G>A	c.125C>T	p.Thr42Met	g.18075541G>A	c.125C>T	p.Thr42Met	SMA-PME	(Rubboli et al. 2015)
16	g.18075541G>A	c.125C>T	p.Thr42Met	g.18075541G>A	c.125C>T	p.Thr42Met	SMA-PME	(Yildiz et al. 2018)
17	g.18075541G>A	c.125C>T	p.Thr42Met	g.18075541G>A	c.125C>T	p.Thr42Met	SMA-PME	(Zhou et al. 2012)
18	g.18075541G>A	c.125C>T	p.Thr42Met	g.18075541G>A	c.125C>T	p.Thr42Met	SMA-PME	(Zhou et al. 2012)
19	g.18075541G>A	c.125C>T	p.Thr42Met	g.18075541G>A	c.125C>T	p.Thr42Met	SMA-PME	(Zhou et al. 2012)
20	g.18075541G>A	c.125C>T	p.Thr42Met	g.18075541G>A	c.125C>T	p.Thr42Met	SMA-PME	(Zhou et al. 2012)
21	g.18075541G>A	c.125C>T	p.Thr42Met	g.18075541G>A	c.125C>T	p.Thr42Met	SMA-PME	(Zhou et al. 2012)
22	g.18075541G>A	c.125C>T	p.Thr42Met	chr8:17,909,063-17,964,559x1(hg19)	*ASAH1* gene deletion	entire *ASAH1* deletion	SMA-PME	(Zhou et al. 2012)

23	g.18065862_18075331del	c.126-3941_382+1358del	p.=	g.18059568T>C	c.917+4A>G	p.=	Farber disease	(Alves et al. 2013)
24	g.18071339G>C	c.177C>G	p.Tyr59Ter	g.18064458T>G	c.456A>C	p.Lys152Asn	SMA-PME	(Rubboli et al. 2015)
25	g.18069871_18069872insG	c.223_224insC	p.Val75AlafsTer25	g.18075541G>A	c.125C>T	p.Thr42Met	SMA-PME	(Rubboli et al. 2015)
26	g.18069839dup	c.256dup	p.Thr86AsnfsTer14	g.18067288A>G	c.314T>C	p.Leu105Pro	Farber disease	(Bao et al. 2017)
27	g.18069808_18069810delCAC	c.286_288delGTG	p.Val96del	g.18069808_18069810del	c.286_288delGTG	p.Val96del	Farber disease	(Muramatsu et al. 2002)
28	g.18069805A>T	c.290T>A	p.Val97Glu	g.18061686C>G	c.703G>C	p.Gly235Arg	Farber disease	(Muramatsu et al. 2002)
29	g.18069805A>C	c.290T>G	p.Val97Gly	g.18069805A>C	c.290T>G	p.Val97Gly	Farber disease	(Chedrawi et al. 2012)
30	g.18069805A>C	c.290T>G	p.Val97Gly	g.18069805A>C	c.290T>G	p.Val97Gly	Farber disease	(Chedrawi et al. 2012)
31	g.18064532_18064548delGAAAA	c.383-16delTTTTC	p.=	g.18062389C>T	c.538G>A	p.Glu180Lys	Farber disease	(Bashyam et al. 2014)
32	g.18064506A>T	c.408T>A	p.Phe136Leu	g.18059385G>C	c.997C>G	p.Arg333Gly	Farber	(Bashyam et al. 2014)

							disease	
33	g.18064504_18064505delTA	c.410_411delAT	p.Tyr137Ter	g.18061458C>T	c.704G>A	p.Gly235Asp	Farber disease	(Torcoletti et al. 2014)
34	g.18064504T>C	c.410A>G	p.Tyr137Cys	g.18064458T>G	c.456A>C	p.Lys152Asn	SMA-PME	(Kernohan et al. 2017)
35	g.18064502C>A	c.412G>T	p.Glu138Ter	g.18059391C>T	c.991G>A	p.Asp331Asn	Farber disease	(Bar et al. 2001)
36	g.18064502C>A	c.412G>T	p.Glu138Ter	g.18059391C>T	c.991G>A	p.Asp331Asn	Farber disease	(Ehlert et al. 2019)
37	g.18064501T>A	c.413A>T	p.Glu138Val	g.18064501T>A	c.413A>T	p.Glu138Val	Farber disease	(Bar et al. 2001)
38	g.18064501T>A	c.413A>T	p.Glu138Val	g.18064504_18064505delTA	c.410_411delAT	p.Tyr137Ter	Farber disease	(Ehlert et al. 2019)
39	g.18064453T>C	c.457+4A>G	p.=	g.18064453T>C	c.457+4A>G	p.=	Farber disease	(Bashyam et al. 2014; Muranjan et al. 2012)
40	g.18063186C>A	c.502G>T	p.Gly168Trp	g.18063186C>A	c.502G>T	p.Gly168Trp	Farber disease	(Cvitanovic-Sojat et al. 2011)
41	g.18062422A>G	c.505T>C	p.Trp169Arg	g.18062422A>G	c.505T>C	p.Trp169Arg	Farber dis	(Moghadam et al. 2019)

							ease	
42	g.18062422A>G	c.505T>C	p.Trp169Arg	g.18062422A>G	c.505T>C	p.Trp169Arg	Farber disease	(Bashyam et al. 2014)
43	g.18062422A>G	c.505T>C	p.Trp169Arg	g.18061402T>C	c.760A>G	p.Arg254Gly	Farber disease	(Bonafe et al. 2016)
44	g.18062422A>G	c.505T>C	p.Trp169Arg	g.18061402T>C	c.760A>G	p.Arg254Gly	Farber disease	(Bonafe et al. 2016)
45	g.18062422A>G	c.505T>C	p.Trp169Arg	g.18061402T>C	c.760A>G	p.Arg254Gly	Farber disease	(Bonafe et al. 2016)
46	g.18062422A>G	c.505T>C	p.Trp169Arg	g.18062422A>G	c.505T>C	p.Trp169Arg	Farber disease	(Cozma et al. 2017)
47	g.18062409T>A	c.518A>T	p.Asn173Ile	g.18062328_18062333dup	c.594_599dup	p.Phe199_Lys200insAsnPhe	Farber disease + SMA	(Teoh et al. 2016)
48	g.18062383G>C	c.544C>G	p.Leu182Val	g.18062383G>C	c.544C>G	p.Leu182Val	Farber disease	(Bashyam et al. 2014)
49	g.18062383G>C	c.544C>G	p.Leu182Val	g.18062383G>C	c.544C>G	p.Leu182Val	Farber disease	(Bashyam et al. 2014; Devi et al. 2006)
50	g.18062383G>C	c.544C>G	p.Leu182Val	g.18062383G>C	c.544C>G	p.Leu182Val	Farber	(Bashyam et al. 2014)

							disease	
51	g.18062334A>G	c.593T>C	p.Val198Ala	g.18059385G>C	c.997C>G	p.Arg333Gly	Farber disease	(Bashyam et al. 2014)
52	g.18062301C>T	c.626G>A	p.Gly209Asp	g.18071344dup	c.174dup	p.Tyr59LeufsTer5	Farber disease	(Ehlert et al. 2019)
53	g.18061724G>T	c.665C>A	p.Thr222Lys	g.18061724G>T	c.665C>A	p.Thr222Lys	Farber disease	(Koch et al. 1996; Bar et al. 2001)
54	g.18061712C>G	c.677G>C	p.Arg226Pro	g.18058849G>T	c.1084C>A	p.Pro362Thr	Farber disease	(Bashyam et al. 2014)
55	g.18061687C>G	c.702G>C	p.Gly235Arg	g.18059385G>A	c.997C>T	p.Arg333Cys	Farber disease	(Kim et al. 2016)
56	g.18061686C>G	c.703G>C	p.Gly235Arg	g.18061686C>G	c.703G>C	p.Gly235Arg	Farber disease	(Bashyam et al. 2014)
57	g.18061686C>A	c.703G>T	p.Gly235Cys	g.18061686C>A	c.703G>T	p.Gly235Cys	Farber disease	(Geraghty et al. 2005)
58	g.18061460T>C	c.704-2A>G	p.=	g.18061460T>C	c.704-2A>G	p.=	Farber disease	(Cozma et al. 2017)
59	g.18061440A>G	c.722T>C	p.Leu241Pro	g.18061440A>G	c.722T>C	p.Leu241Pro	Farber dis	(Hugle, Mueller, and Levade 2014)

							eas e	
60	g.18061402 T>C	c.760A> G	p.Arg2 54Gly	g.18057547 C>T	c.1175 G>A	p.Cys392 Tyr	Far ber dis eas e	(Ehlert et al. 2019)
61	g.18061402 T>C	c.760A> G	p.Arg2 54Gly	g.18061402T >C	c.760A >G	p.Arg254 Gly	Far ber dis eas e	(Kostik et al. 2013)
62	g.18061402 T>C	c.760A> G	p.Arg2 54Gly	g.18064501T >A	c.413A >T	p.Glu138 Val	Far ber dis eas e	(Li et al. 1999)
63	g.18061402 T>C	c.760A> G	p.Arg2 54Gly	g.18064501T >A	c.413A >T	p.Glu138 Val	Far ber dis eas e	(Li et al. 1999)
64	g.18059656 G>A	c.833C> T	p.Pro2 78Leu	g.18059656 G>A	c.833C >T	p.Pro278 Leu	Far ber dis eas e	(Ehlert et al. 2019)
65	g.18059656 G>A	c.833C> T	p.Pro2 78Leu	g.18059656 G>A	c.833C >T	p.Pro278 Leu	Far ber dis eas e	(Ehlert et al. 2019)
66	g.18059639 C>A	c.850G> T	p.Gly2 84Ter	g.18064458T >G	c.456A >C	p.Lys152 Asn	SM A-PM E	(Dyment et al. 2014)
67	g.18059603 G>A	c.886C> T	p.Arg2 96Ter	g.18064458T >G	c.456A >C	p.Lys152 Asn	SM A-PM E	(Gan et al. 2015)
68	g.18059567 C>T	c.917+5 G>A	p.=	g.18059567 C>T	c.917+ 5G>A	p.=	Far ber dis eas e	(Ehlert et al. 2019)

69	g.18059424T>C	c.958A>G	p.Asn320Asp	g.18059424T>C	c.958A>G	p.Asn320Asp	Farber disease	(Bar et al. 2001)
70	g.18059423T>C	c.959A>G	p.Asn320Ser	g.18059423T>C	c.959A>G	p.Asn320Ser	Farber disease	(Bashyam et al. 2014)
71	g.18059385G>A	c.997C>T	p.Arg333Cys	g.18059385G>A	c.997C>T	p.Arg333Cys	Farber disease	(Cozma et al. 2017)
72	g.18059384C>T	c.998G>A	p.Arg333His	g.18059384C>T	c.998G>A	p.Arg333His	Farber disease	(Bashyam et al. 2014)
73	g.18058848G>C	c.1085C>G	p.Pro362Arg	g.18058848G>C	c.1085C>G	p.Pro362Arg	Farber disease	(Li et al. 1999)
74	g.18058837T>G	c.1096A>C	p.Lys366Gln	g.18062422A>G	c.505T>C	p.Trp169Arg	Farber disease	(Al Jasmi 2012)
75	g.18058837T>G	c.1096A>C	p.Lys366Gln	g.18062422A>G	c.505T>C	p.Trp169Arg	Farber disease	(Cozma et al. 2017)
76	g.18058834C>A	c.1098+1G>T	p.=	-	-	-	Farber disease	(Bar et al. 2001)

TABLE 3 All known reported *ASAH1* variants: curated according to NM_177924.5 (HGVS notation GRch 38)

***ASAH1* variant**	**Transcript by HGVS notation, GRch 38**	***ASAH 1* NP_80 8592.2**	**Canonical Allele Identifier**	**dbSNP**	**ExAC MAF**	**gnoMAD MAF**	**Type**	**Exon**	**Subunit**	**Reference**
c.66G>C	NM_177924.5:c.66G>C	p.Gln22His	CA370435723		not found	not found	Missense	1	Alpha	(Zhang et al., 2000)
c.67C>G	NM_177924.5:c.67C>G	p.His23Asp	CA370435721		not found	not found	Missense	1	Alpha	(Zhang et al., 2000)
c.77C>G	NM_177924.5:c.77C>A	p.Pro26Gln	CA370435698		not found	not found	Missense	1	Alpha	(van der Beek et al., 2019)
c.92G>T	NM_177924.5:c.92G>T	p.Cys31Phe	CA370434634		not found	not found	Missense	2	Alpha	NHS (Cozma et al., 2017; Saygi, Haytoglu, Savas, Alkan, & Erol, 2015)
c.107A>G	NM_177924.5:c.107A>G	p.Tyr36Cys	CA113842	rs137853595	not found	not found	Missense	2	Alpha	NHS (Bar et al., 2001; Cozma et al., 2017)
c.124A>G	NM_177924.5:c.124A>G	p.Thr42Ala	CA4651074	rs779888892	2.47E-05	1.59E-05	Missense	2	Alpha	(Filosto et al., 2016; Sathe & Pearson, 2014)

c.125+1G>A	NM_177924.5:c.125+1G>A	p.=	CA370434569		not found	not found	Splice site	Intron 2	Alpha	van der Beek 2018 (Cozma et al., 2017)
c.125C>T	NM_177924.5:c.125C>T	p.Thr42Met	CA129940	rs145873635	2.47E-05	1.19E-05	Missense	2	Alpha	(Giraldez et al., 2015; Oguz Akarsu et al., 2016; Rubboli et al., 2015; Shervin Badv, Nilipour, Rahimi-Dehgolan, Rashidi-Nezhad, & Ghahvechi Akbari, 2019; Yildiz et al., 2018; Zhou et al., 2012)
c.126-3941_382+1358del	NM_177924.5:c.126-3941_382+1358del	Deletion	CA658821173		not found	not found	Gross deletion	3 to 5	Alpha	(Alves et al., 2013)
c.147G>A	NM_177924.5:c.147G>A	p.Trp49Ter	CA4651001	rs369707059	1.20E-05	1.13E-05	Nonsense	3	Alpha	ClinVar
c.174dup	NM_177924.5:c.174dup	p.Tyr59LeufsTer6	CA4650994	rs771718522	1.12E-05	4.12E-06	Indel	3	Alpha	NHS (Ehlert et al., 2018)

c.177C>G	NM_177924.5:c.177C>G	p.Tyr59Ter	CA370433961		not found	not found	Nonsense	3	Alpha	(Rubboli et al., 2015)
c.216+3A>T	NM_177924.5:c.216+3A>T	p.=			not found	not found	Splice site	Intron 3	Alpha	NHS
c.216G>A	NM_177924.5:c.216G>A	p.V72=	CA4650980	rs753035061	3.74E-05	4.30E-06	Likely splice site	3	Alpha	NHS
c.223_224insC	NM_177924.5:c.223_224insC	p.Val75AlafsTer25			not found	not found	Indel	4	Alpha	(Rubboli et al., 2015)
c.256dup	NM_177924.5:c.256dup	p.Thr86AsnfsTer14	CA580092784	rs1336696568	not found	4.01E-06	Indel	4	Alpha	(Bao, Tian, Ji, & Chang, 2017)
c.286_288delGTG	NM_177924.5:c.286_288delGTG	p.Val96del			not found	not found	Indel	4	Alpha	(Muramatsu et al., 2002)
c.290T>A	NM_177924.5:c.290T>A	p.Val97Glu	CA370433053		not found	not found	Missense	4	Alpha	(Muramatsu et al., 2002)
c.290T>G	NM_177924.5:c.290T>G	p.Val97Gly	CA370433049		not found	not found	Missense	4	Alpha	(Chedrawi et al., 2012)
c.314T>C	NM_177924.5:c.314T>C	p.Leu105Pro	CA370432878		not found	not found	Missense	5	Alpha	(Bao et al., 2017)
c.383-16delTTTTC	NM_177924.5:c.383-16delTTTTC	p.=		rs761372687	1.831E-05	not found	Indel/Likely splice site	Skips exon 6	Alpha	(Bashyam et al., 2014)

c.408T>A	NM_177924.5:c.408T>A	p.Phe136Leu	CA370431730		not found	not found	Missense	6	Alpha	(Bashyam et al., 2014)
c.409T>A	NM_177924.5:c.457T>A	p.Tyr137Asn	CA370431728		not found	not found	Missense	6	Alpha	NHS
c.410_411delAT	NM_177924.5:c.410_411delAT	p.Tyr137Ter	CA580091718	rs1281024431	not found	8.51E-06	Indel/Nonsense	6	Alpha	NHS (Ehlert et al., 2018; Torcolletti et al., 2014)
c.410A>G	NM_177924.5:c.410A>G	p.Tyr137Cys	CA4650862	rs371666412	1.42E-05	2.26E-05	Missense	6	Alpha	NHS (Cozma et al., 2017) (Kernohan et al., 2017)
c.412G>T	NM_177924.5:c.412G>T	p.Glu138Ter	CA370431703		not found	not found	Nonsense	6	Alpha	(Bar et al., 2001)
c.413A>T	NM_177924.5:c.413A>T	p.Glu138Val	CA113840	rs137853594	not found	4.25E-06	Missense	6	Alpha	NHS (Bar et al., 2001; Ehlert et al., 2018; Koch et al., 1996; Zhang et al., 2000)

c.456A>C	NM_177924.5:c.456A>C	p.Lys152Asn	CA185930	rs200455852	1.04E-04	5.83E-05	Missense	6	Beta	(Cozma et al., 2017; Dyment et al., 2014; Gan et al., 2015; Kernohan et al., 2017; Rubboli et al., 2015)
c.457+4A>G	NM_177924.5:c.457+4A>G	p.=	CA4650854	rs767864356	1.15E-05	4.11E-06	Splice site	Intron 6	Beta	(Bashyam et al., 2014)
c.457G>A	NM_177924.5:c.457G>A	p.Gly153Ser	CA370431449		not found	8.24E-06	Missense	6	Beta	NHS
c.502G>T	NM_177924.5:c.502G>T	p.Gly168Trp	CA370430988		not found	not found	Missense	7	Beta	(Cvitanovic-Sojat et al., 2011)
c.503G>T	NM_177924.5:c.503G>T	p.Gly168Val	CA370430979		not found	not found	Missense	7	Beta	NHS

c.505T>C	NM_177924.5:c.505T>C	p.Trp169Arg	CA236461	rs756455049	8.24E-06	3.98E-06	Missense	8	Beta	ClinVar, NHS (Al Jasmi, 2012; Bashyam et al., 2014; Bonafe et al., 2016; Cozma et al., 2017; Moghadam, Tavasoli, Modaresi, & Ziaee, 2019)
c.518A>T	NM_177924.5:c.518A>T	p.Asn173Ile	CA370430268		not found	not found	Missense	8	Beta	(Teoh et al., 2016)
c.536C>T	NM_177924.5:c.536C>T	p.Thr179Ile	CA4650789	rs766257867	8.24E-06	7.96E-06	Missense	8	Beta	(Cozma et al., 2017; Sathe & Pearson, 2014)
c.538G>A	NM_177924.5:c.538G>A	p.Glu180Lys	CA4650788	rs762756953	2.471E-05	1.21863E-05	Missense	8	Beta	(Bashyam et al., 2014)
c.544C>G	NM_177924.5:c.544C>G	p.Leu182Val	CA113846	rs137853597	not found	1.21858E-05	Missense	8	Beta	NHS (Bashyam et al., 2014; Devi et al., 2006)
c.593T>C	NM_177924.5:c.593T>C	p.Val198Ala	CA370429986		not found	not found	Missense	8	Beta	(Bashyam et al., 2014)

c.594_599dup	NM_177924.5:c.594_599dup	p.Phe199_Lys200insAsnPhe			not found	not found	Indel	8	Beta	(Teoh et al., 2016)
c.626G>A	NM_177924.5:c.626G>A	p.Gly209Asp	CA3704 29876		not found	not found	Missense	8	Beta	NHS (Ehlert et al., 2018)
c.648+1G>C	NM_177924.5:c.648+1G>C	p.=	CA3704 29792	rs1411 267767	not found	not found	Splice site	Intron 8	Beta	ClinVar
c.665C>A	NM_177924.5:c.665C>A	p.Thr222Lys	CA1138 38	rs1378 53593	2.954E-05	5.2211E-06	Missense	9	Beta	(Bar et al., 2001; Koch et al., 1996; Zhang et al., 2000)
c.677G>C	NM_177924.5:c.677G>C	p.Arg226Pro	CA3704 29643	rs3777 49094	not found	8.48E-06	Missense	9	Beta	NHS (Bashyam et al., 2014)
c.703G>C	NM_177924.5:c.703G>C	p.Gly235Arg	CA3704 29556	rs1554 808625	not found	not found	Missense	9	Beta	NHS (Bashyam et al., 2014; Kim et al., 2016; Muramatsu et al., 2002)
c.703G>T	NM_177924.5:c.703G>T	p.Gly235Cys	CA3704 29555		not found	not found	Missense	9	Beta	Geraghty 2005
c.704-2A>G	NM_177924.5:c.704-2A>G	p.=	CA3704 29519		not found	not found	Splice site	Intron 9	Beta	(Cozma et al., 2017)
c.704G>A	NM_177924.5:c.704G>A	p.Gly235Asp	CA1063 0531	rs8860 62781	not found	not found	Missense	10	Beta	NHS (Torcoletti et al., 2014)

c.722T>C	NM_177924.5:c.722T>C	p.Leu241Pro	CA370429449		not found	not found	Missense	10	Beta	Hügle 2014, NHS
c.760A>G	NM_177924.5:c.760A>G	p.Arg254Gly	CA370429322		not found	not found	Missense	10	Beta	(Bonafe et al., 2016; Ehlert et al., 2018; Kostik et al., 2013; Li et al., 1999)
c.833C>T	NM_177924.5:c.833C>T	p.Pro278Leu	CA370428191		not found	not found	Missense	10	Beta	(Ehlert et al., 2018)
c.850G>T	NM_177924.5:c.850G>T	p.Gly284Ter	CA185927	rs794729663	not found	not found	Nonsense	11	Beta	(Dyment et al., 2014)
c.886C>T	NM_177924.5:c.886C>T	p.Arg296Ter	CA4650644	rs771847002	not found	4.062E-06	Nonsense	11	Beta	(Gan et al., 2015)
c.917+4A>G	NM_177924.5:c.917+4A>G	p.=	CA144005	rs397509415	not found	not found	Splice site	Intron 11	Beta	(Alves et al., 2013)
c.917+5G>A	NM_177924.5:c.917+5G>A	p.=			not found	not found	Splice site	Intron 11	Beta	(Ehlert et al., 2018)
c.920T>G	NM_177924.5:c.920T>G	p.Leu307Arg	CA370427668		not found	not found	Missense	12	Beta	NHS
c.958A>G	NM_177924.5:c.958A>G	p.Asn320Asp	CA113844	rs137853596	not found	not found	Missense	12	Beta	(Bar et al., 2001; Zhang et al., 2000)
c.959A>G	NM_177924.5:c.959A>G	p.Asn320Ser	CA370427525		not found	not found	Missense	12	Beta	(Bashyam et al., 2014)

c.991G>A	NM_177924.5:c.991G>A	p.Asp331Asn	CA370427406	rs1354060089	not found	not found	Missense	12	Beta	(Bar et al., 2001; Ehlert et al., 2018)
c.994G>C	NM_177924.5:c.994G>C	p.Asp332His	CA16042634	rs941670381	not found	3.98E-06	Missense	12	Beta	NHS
c.997C>G	NM_177924.5:c.997C>G	p.Arg333Gly	CA4650601	rs543697946	5.77E-05	5.57E-05	Missense	12	Beta	(Bashyam et al., 2014)
c.997C>T	NM_177924.5:c.997C>T	p.Arg333Cys	CA370427378	rs543697946	not found	3.19E-05	Missense	12	Beta	NHS (Cozma et al., 2017; Kim et al., 2016)
c.998G>A	NM_177924.5:c.998G>A	p.Arg333His	CA370427376		not found	not found	Missense	12	Beta	NHS (Bashyam et al., 2014)
c.1084C>A	NM_177924.5:c.1084C>A	p.Pro362Thr	CA370426993		not found	not found	Missense	13	Beta	NHS (Bashyam et al., 2014)
c.1085C>G	NM_177924.5:c.1085C>G	p.Pro362Arg	CA370426988		not found	not found	Missense	13	Beta	NHS (Li et al., 1999)
c.1086_1088delinsAAAACA	NM_177924.5:c.1086_1088delinsAAAACA	p.Val363delinsLysHis			not found	not found	Indel	13	Beta	NHS
c.1096A>C	NM_177924.5:c.1096A>C	p.Lys366Gln	CA370426949		not found	not found	Missense	13	Beta	(Al Jasmi, 2012; Cozma et al., 2017)

c.1098+1G>T	NM_177924.5:c.1098+1G>T	p.=	CA4650546	rs763842677	8.29E-06	7.97E-06	Splice site	Intron 13	Beta	(Bar et al., 2001)
c.1175A>G	NM_177924.5:c.1175G>A	p.Cys392Tyr	CA4650490	rs746513660	8.28E-06	7.96E-06	Missense	14	Beta	(Ehlert et al., 2018)
c.1178T>G	NM_177924.5:c.1178T>G	p.Ile393Arg	CA4650489	rs376831762	8.29E-06	3.98E-06	Missense	14	Beta	NHS
c.1185G>T	NM_177924.5:c.1185G>T	p.Trp395Cys	CA370442568		not found	not found	Missense	14	Beta	NHS
c.1186dup	NM_177924.5:c.1186dup	p.Ter396LeuextTer21			not found	not found	Indel	14	Beta	(Zhang et al., 2000)
GRCh37 8p22(chr8:17909063-17964559)x1	GRCh38 8p22(chr8:18051554 - 18107050)x1	*ASAH1* deletion					Gross deletion	Exons 1-14	Gene deletion	(Zhou et al., 2012)