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Lifespan in rodents with MYT1L heterozygous mutation

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MYT1L syndrome is a newly recognized disorder characterized by intellectual disability, speech and motor delay, neuroendocrine disruptions, ADHD, and autism. In order to study this gene and its association with these phenotypes, our lab recently created a *Myt1l* heterozygous mutant mouse inspired by a clinically relevant mutation. This model recapitulates several of the physical and neurologic abnormalities seen in humans with MYT1L syndrome, such as weight gain, microcephaly, and behavioral disruptions. The majority of patients with this syndrome are young, and little is known about the impact of age on health and mortality in these patients. Using a *Myt1l* mutant mouse, we examined the impact of *Myt1l* mutation on body weights, lifespan, and histopathology findings of mice at the end of life. This cohort of heterozygous mice demonstrated increased body weight across the lifespan, however there was no significant difference in lifespan, apparent cause of death, or end of life histopathological findings between *Myt1l* heterozygous and wildtype mice. These findings suggest while *Myt1l* heterozygous mutation may influence overall brain development, it does not strongly impact other organ systems in the body over time.

Keywords Lifespan, Obesity, MYT1L syndrome, Neurodevelopmental disorders

Neurodevelopmental disorders, including autism spectrum disorder, intellectual disability, and attention deficit hyperactivity disorder, affect more than 3% of children worldwide and lead to impaired cognition, communication, adaptive behavior, and psychomotor skills[1,2]. Multiple genetic syndromes have been associated with neurodevelopmental disorders including autism. People with neurodevelopmental disorders often have shorter lifespans than the general population, likely due to a variety of factors including comorbid conditions and health care disparities[3,4].

Recently, the gene Myelin Transcription Factor 1 Like (*MYT1L*) has been associated with neurodevelopmental disorders (NDD), with *MYT1L* loss of function now recognized as MYT1L Syndrome[5]. Hallmark features of MYT1L Syndrome include intellectual disability, obesity, speech and motor delay, neuroendocrine disruptions, ADHD, and autism. Epilepsy, microcephaly, and white matter thinning are also observed in a portion of patients[6–10]. While significant progress has been made in characterizing the molecular and cellular mechanisms that underlie MYT1L syndrome[11–14], the majority of identified patients are young (< 35 years), and there is still much to learn about the long-term impact of *MYT1L* gene mutations on overall health outcome. Notably, it is unknown if *MYT1L* mutation may result in any recurrent comorbidities that would influence overall lifespan and cause of death.

While waiting for definitive studies in humans, study of lifespan in animal models can be helpful to understand potential long-term health impacts of newly discovered genetic mutations. Mice have substantially shorter lifespans than humans, enabling studies of how a particular genetic mutation intersects with time to impact health. Most mouse strains are generally considered geriatric at approximately 24 months[15]; however, lifespan is reported to vary between strains, with C57BL/6 mice known to be long-lived with 50% survival at approximately 900 days of life[16]. Importantly, study of lifespan in other mouse models of NDDs is sparse with mixed results. Large studies of well-defined mouse models such as Down Syndrome, Prader-Willi, and Rett syndrome show decreased lifespan[17–19]; however, studies of more newly discovered NDDs have not yet been studied.

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We previously generated and characterized a mouse mutant disrupting the *Myt1l* gene, with a basepair insertion resulting in frameshift and predicted stop-gain mutation (Fig. 1)[11]. These mice were confirmed to have decreased *MYT1L* transcripts and protein, consistent with haploinsufficiency[14]. These studies demonstrated that *Myt1l* mutant mice exhibit a range of neurological and physical abnormalities, including altered neuronal function, behavior, and body weight regulation. As *Myt1l* is only expressed in neuronal populations, characterization of the brain was an initial focus for our group and others. *Myt1l* mutant mice have smaller brain volumes, specifically lower cortical volumes and volumes of white matter tracts such as the corpus callosum[14]. In addition, we determined that decreased function of *Myt1l* impacts deep layer excitatory neurons of the cortex, resulting in delayed neuronal maturation and persistent regulatory dysregulation throughout development[11,20].

The impact of *Myt1l* gene mutations on lifespan and cause of death in *Myt1l* mutant mice has not yet been explored. Studying the lifespan and cause of death in *Myt1l* mutant mice will be helpful in understanding the potential health implications of *MYT1L* gene mutations in humans. In this paper, we examine differences in lifespan, gross necropsy, and histopathological findings between *Myt1l* heterozygous mutant and wildtype mice at the end of life.

Methods

Animals

All experimental protocols were approved by and performed in accordance with the relevant guidelines and regulations of the Institutional Animal Care and Use Committee of Washington University in St. Louis and were in compliance with US National Research Council's Guide for the Care and Use of Laboratory Animals, the US Public Health Service's Policy on Humane Care and Use of Laboratory Animals, Guide for the Care and Use of Laboratory Animals, and the ARRIVE guidelines 2.0.

All mice used in this study were bred and maintained in the vivarium at Washington University in St. Louis School of Medicine. *Myt1l* heterozygous mouse line was created at Washington University St. Louis as previously described[11], and the line maintained for future studies. The colony room lighting was on a 12:12 h light/dark cycle (lights on at 6a.m.); room temperature (20–22C) and relative humidity (50%) were controlled automatically. Standard lab diet and water were available *ad lib*. Upon weaning at postnatal day (P)21, mice were group housed according to sex and experimental condition. The mice used in this study harbor a frameshift mutation in exon 11 of the *Myt1l* gene on a C57BL/6 J background, as previously described[11]. The cohort used herein consisted of 16 *Myt1l* heterozygous mutants ('Het', 8 males, 8 females) and 21 wildtype littermate controls ('WT', 8 males, 13 females). All mice reported here were used for behavioral testing and magnetic resonance imaging between P33 and P287, as published in Chen et al.[14]. A subset of animals including five Hets (two males, three females) and six WT (two males, four females) were submitted for gross necropsy and histopathological examination. At the end of experimentation, at the end of the study, all animals were humanely sacrificed via euthanasia by CO2 inhalation and cervical dislocation consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association and following the NIH Guidelines for Euthanasia of Rodents Using Carbon Dioxide.

Genotyping

Myt1l mutation within litters was determined by genotyping as previously described[14]. Genotyping was conducted using allele-specific PCR using MYT1L Mutant primers (F(5′–3′): ATGTCGCAGTAGCCAAGT C; R(5′–3′): TCTTGCTACACGTACTGGA) and Control primers (F(5′–3′): ATGTCGCAGTAGCCAAGTC; R(5′–3′): TCTTGCTACACGTGCTACT), amplified using Phusion and the following conditions: 98C for 10 s, 61C for 20 s, 72C for 20 s, repeat 2–4 for 35 cycles, 72C for 5 min and hold at 4C.

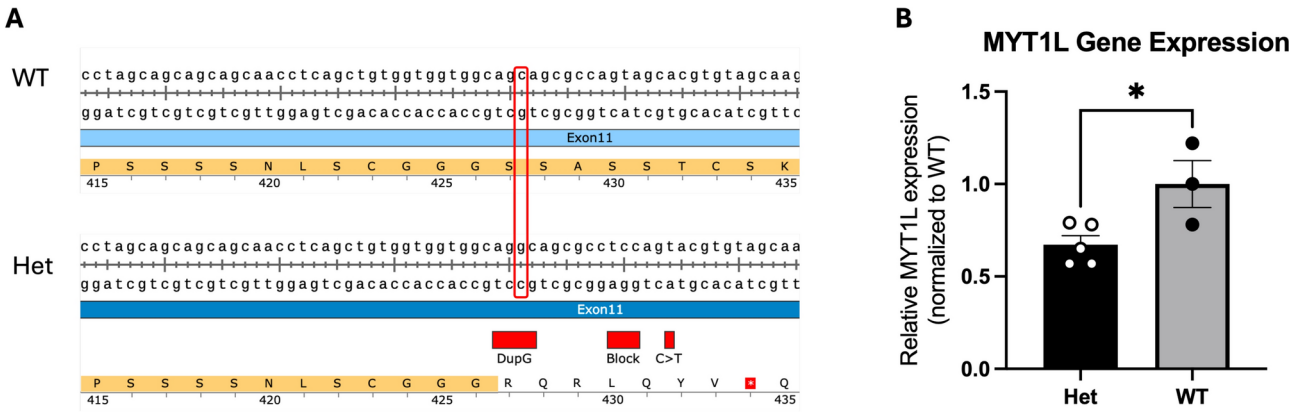

Fig. 1. Basepair insertion in Exon 11 of *Myt1l* Het mice leads to decreased *Myt1l* expression in the brain. (**A**) Schematic of basepair insertion in Exon 11 of *Myt1l* gene (Duplicate G—outlined in red) in *Myt1l* Het mouse resulting in frameshift and stop-gain mutation. (**B**) Whole brain *Myt1l* gene expression normalized to WT mice. Filled circles represent individual animals. *T-test, p = 0.027*.

Moribund status determination

General health status and body weight were monitored on a weekly basis from P383 until P720. Monitoring continued for moribund state or mortality until P1013–1015. Moribund mice were euthanized if judged to be severely ill and/or exhibiting signs such as gulping or irregular breathing; severe motor/gait disturbance (lack of spontaneous movement and little to no movement when prompted); ulcerated skin, or abdominal distension. The date of euthanasia was used as an estimate of natural lifespan in these cases. The experiment was continued until day 1013–1015, and mice that had survived to that point were considered censored (not plotted in figures).

Histopathology

Gross necropsy, tissue processing, and slide staining were performed by the Research Animal Diagnostic Laboratory at Washington University in St. Louis School of Medicine. Tissues collected at the time of gross necropsy were fixed in 10% neutral buffered formalin for 24–48 h, paraffin embedded, sectioned at 5-µm thickness and stained with hematoxylin and eosin (H&E, Harris Hematoxylin Nuclear Stains, Cat. No. 3801560). Histopathological evaluation was performed by a board-certified veterinary pathologist. Animals examined included five *Myt1l* Hets (two males, three females) and six WT (two males, four females).

RNA extraction and RT-qPCR

A separate cohort of mice, consisting of 5 *Myt1l* Het and 3 WT, were used to assess *Myt1l* mRNA levels in the brain as previously described[14]. Briefly, brains were dissected out at adulthood and homogenized in lysis buffer (10 mM Tris–HCl, pH 7.4, 10 mM NaCl, 3 mM MgCl2, 0.1% IGELPAL-CA-630, 0.1% RNase inhibitor) on ice. Lysates were mixed with Trizol LS and chloroform. After centrifugation, RNA was extracted from the aqueous layer with Zymo RNA Clean and ConcentratorTM-5 kit. cDNA libraries were prepared using qScript cDNA synthesis Kit (QuantaBio). RT-qPCR were performed using SYBR Green Master Mix (Thermo Fisher) on QuantStudio 6 Flex Real Time PCR System using MYT1L Specific Primers (F(5′–3′): ACTATCAAGCAGCGAG CCAG; R(5′–3′): CATGTCAGCCTCCATCTGGG). We normalized cycle counts to b-actin (Primers: F(5′–3′): CAATAGTGATGACCTGGCCGT; R(5′–3′): AGAGGGAAATCGTGCGTGAC) and calculated normalized relative gene expression using ΔΔCT (Fig. 1).

Statistical analysis

Statistical analyses and data visualization were conducted using IBM SPSS Statistics (v.28). Prior to analyses, weight data was screened for missing values and fit of distributions with assumptions underlying univariate analysis. This included the Shapiro–Wilk test on z-score-transformed data and qq-plot investigations for normality, Levene's test for homogeneity of variance, and boxplot and z-score (± 3.29) investigation for identification of influential outliers. Analysis of variance (ANOVA) was used to analyze weight data, and simple main effects were used to dissect significant interactions. Kaplan–Meier survival analysis was conducted to assess lifespan. Sex was included as a biological variable in all analyses across all experiments. Multiple pairwise comparisons were subjected to Bonferroni correction. The critical alpha value for all analyses was $p < 0.05$. Illustration of mouse *Myt1l* mutation generated using SnapGene. All other figure illustrations were generated using Prism software. The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Results

At the end of our initial behavioral and neuroimaging-based characterization of *Myt1l* mutants[14], we continued housing the animals until they became moribund. This allowed us to examine the health and lifespan of a cohort of Het and WT littermates, over two to three years, with a subset further assessed grossly and histologically at time of death.

Myt1l heterozygous mutant mice weigh more than wild type mice into old age

Previously, we observed a significant increase in body weight starting in early adulthood in mice harboring a *Myt1l* mutation (Fig. 2A)[14]. Here, we have extended the analysis of body weight into old age (to P720) to determine if *Myt1l* mutation effects on body weight persisted. We ran a three-way ANOVA to examine the effect of sex, genotype, and age on weight data collected weekly between approximately P530 and P720 (Fig. 2B). There was no significant three-way interaction, $F(21,671) = 48.03$, $p = 1.00$, but significant main effects of sex ($F(1,671) = 57.35$, $p = 0.000$), genotype ($F(1,671) = 80.16$, $p = 0.000$) and a significant sex*genotype interaction ($F(1,671) = 32.15$, $p = 0.000$) were found. There was no significant main effect of age or significant interactions with age. Female Het mice ($M = 36.98$, $SE = 0.52$) were significantly heavier than female WT mice ($M = 30.50$, $SE = 0.35$), $F(1,671) = 106.40$; $p = 0.00$. Male Het mice ($M = 37.83$, $SE = 0.44$) were significantly heavier than male WT mice ($M = 36.37$, $SE = 0.44$), $F(1,671) = 5.42$, $p = 0.02$. Expected sex differences were found in WT animals, with males heavier than females, $F(1,671) = 107.6$, $p = 0.00$., but there was no significant difference in weight between male and female Het mice, $F(1,671) = 1.52$; $p = 0.136$.

Myt1l heterozygous mutation does not impact lifespan in mice

To understand if heterozygous mutation for *Myt1l* influences lifespan, we continuously monitored the status of our mice into their old age. We performed a Kaplan–Meier survival analysis over the lifespan of male and female Hets and WT littermates. Date and cause of death were noted for all mice. At ~ P1014 or > 33 months, all surviving animals were euthanized, which included 4 Het males, 1 WT male and 3 WT females. We found a significant difference in survivability between males and females ($\chi = 9.61$, $p = 0.002$; Fig. 3A, B). Specifically, males in our cohort lived longer than females. Males, pooled across genotypes, had a longer median lifespan (958.5 days) than females (777 days). However, we did not observe a significant difference between Het and WT

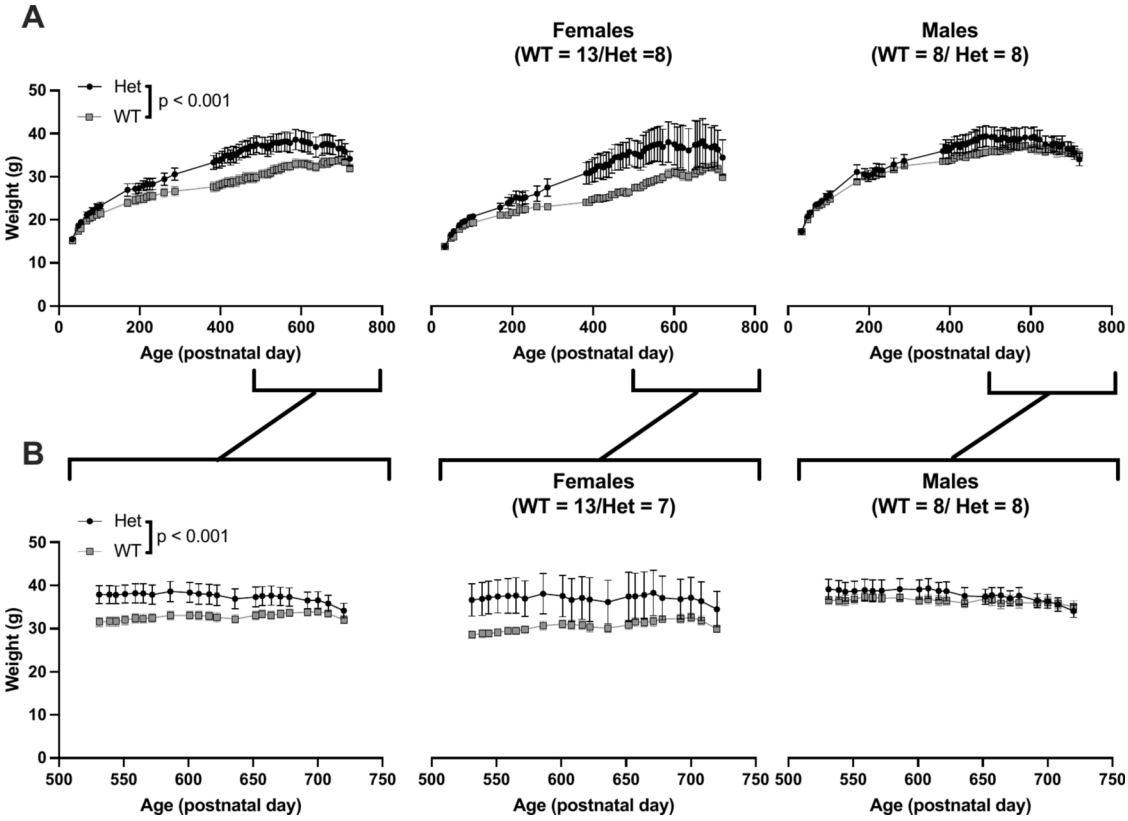

Fig. 2. Het mice weighed more than WT throughout the lifespan. (**A**) Weights of cohort across age, including data previously reported in Chen et al. (prior to P500), and newly collected data. Left panel, all mice, right panels, subsetted by sex. (**B**) As above, plotting only newly collected data, *3 way ANOVA, for age sex and genotype, main effect of genotype shown.*

animals ($\chi = 0.95$, $p = 0.330$; Fig. 3C, D), with WT animals achieving a median lifespan of 875 days compared to 762.5 days for Hets. Due to small group sizes (< 20/group), genotype*sex interactions were not analyzed or interpreted.

Myt1l heterozygous mutation does not result in significantly different pathology at death

To understand if *Myt1l* Het mice experienced similar health outcomes with old age as compared to their WT littermates, a subset of animals were submitted for gross necropsy and histopathological examination once they were judged to be moribund or found dead. The subset of mice that were examined for gross necropsy and histopathology were on average 820.9 days old (2.2 years old) for WT mice and 773.5 days old (2.1 years old) for Het mice, both groups well into old age and not statistically different from each other ($p = 0.34$)[15,21]. We found that mice harboring a *Myt1l* mutation had similar gross and histopathological findings as compared to WT littermate controls (Tables 1 and 2). Specifically, we found similar age-related lesions including cancers and changes in liver, kidney and bone marrow morphologies. Cancers, such as lymphoma, leukemia, and hepatocellular carcinoma were identified in most animals of both genotypes (4/5 WT animals, 3/5 Het animals). Extramedullary hematopoiesis, the production of red and white blood cells outside of bone marrow, was found in both groups (2/5 WT animals, 5/5 Het animals). Underlying causes of extramedullary hematopoiesis include anemia, chronic inflammation, and neoplasia, including lymphoma and leukemia. Membranoproliferative glomerulopathy, a kidney disorder that ultimately affects the kidney's ability to adequately filter blood and create urine, was found in both WT (3/5) and Het animals (3/5). Liver changes, such as oval cell and Kupffer cell hyperplasia were also observed (both 2/5). Biliary cyastadenoma was found in two WT animals. This benign liver malformation is uncommonly described in mice and best characterized as a bile duct hamartoma (von Meyernburg complex). In these two animals, the masses were large enough to cause abdominal distension with compression of other internal organs, resulting in rectal prolapse in one mouse. Following statistical analysis, we did not determine there to be an increased incidence in specific organ changes or disease processes in *Myt1l* Het mice as compared to WT littermates.

Discussion

MYT1L Syndrome is a newly defined monogenic form of NDD, and by studying recently generated mutant mouse models, we are beginning to understand how *MYT1L* mutations alter brain development and contribute to NDD-related features. Using mouse models of disease, we can study pathologies across lifespan and into old

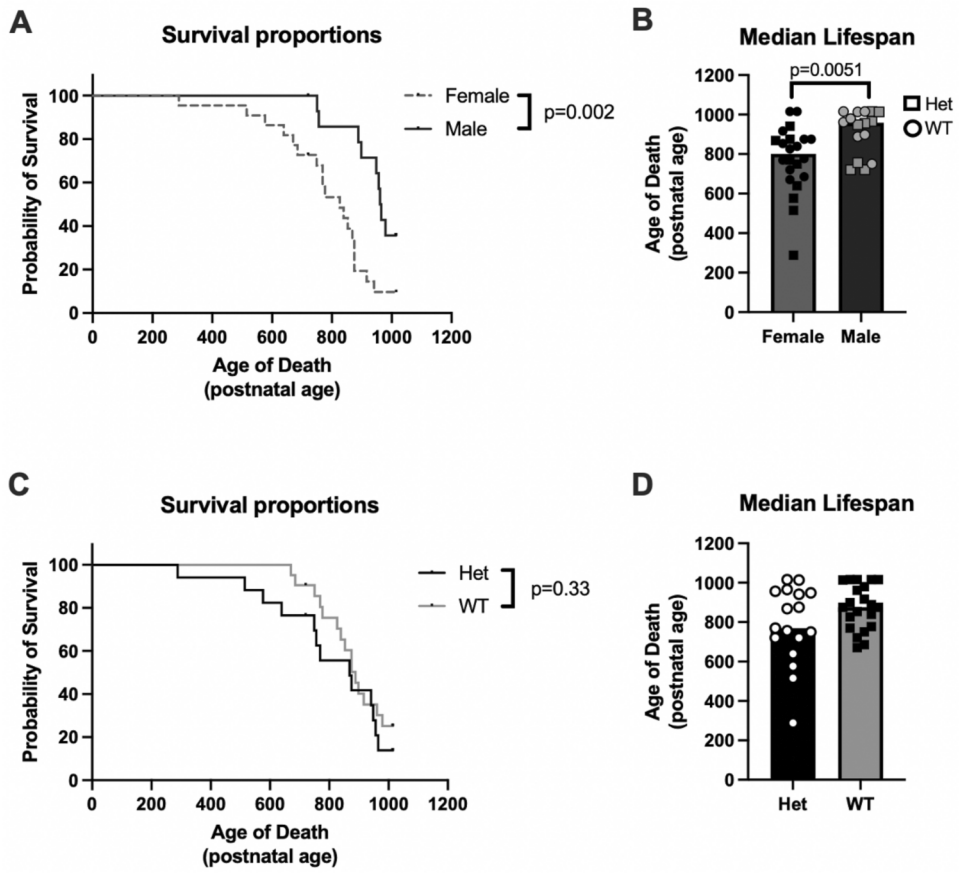

Fig. 3. Het and WT mice have similar lifespans. (**A**) A Kaplan–Meier plot of survival comparing male and female collapsed for genotype mice show longer lifespans in males. (**B**) Bar chart illustrating median lifespan for age of death, including animals at end of experiment (p1013–1015). Filled circles are individual animals. (**C**) A Kaplan–Meier plot of survival comparing Het and WT mice shows no significant genotype difference in lifespan. (**D**) Bar chart illustrating median lifespan for age of death across genotype, including animals at end of experiment (p1013–1015). Filled circles are individual animals.

Finding	WT (%) N = 10 (M = 2/F = 8)	Het (%) N = 8 (M = 2/F = 6)	Total (%)
Alopecia	20.0	25.0	22.2
Dermatitis	30.0	25.0	27.8
Distended abdomen	30.0	25.0	27.8
Malocclusion	0	25.0	11.0
Ocular issue (sunken, cloudy, swollen, discharge)	40.0	25.0	33.3
Rectal prolapse	20.0	0	11.0

Table 1. Gross necropsy findings.

age, in hopes of identifying potential clinical complications and comorbidities in human patients as they age. In this paper, we examined the lifespan of a cohort of *Myt1l* mutant mice and cataloged gross and histological changes to understand possible end of life consequences of *Myt1l* mutation. This cohort of *Myt1l* heterozygous mice continued to have increased body weight into old age compared to WT counterparts, but did not have consistent differences in lifespan or necropsy findings.

Approximately 50% of people with MYT1L syndrome exhibit overweight/obesity, potentially due to hyperphagia or neuroendocrine disturbances[5]. Previously we have shown that this cohort of adult heterozygous MYT1L mice had higher body weights, compared to wildtype controls[14], which was maintained through the duration of this study. However, we do note that an obesity-related increase in weight was not reliably found in all future cohorts[22]. Although there was no significant effect of age on weight in this aging cohort, there was greater variability in weight scores in Het mice than WT mice, especially at the later timepoints and heavily

Finding	WT (n = 5; M = 1; F = 4)	Het (n = 5; M = 2, F = 3)	Total
Neoplasia (lymphoma, leukemia, hepatocellular carcinoma)	4	3	7
Membranoproliferative glomerulopathy (PGN)	3	3	6
Extramedullary hematopoiesis (EMH)	2	5	7
Oval cell hyperplasia	2	2	4
Kupffer cell hyperplasia	2	2	4
Biliary cystadenoma	2	0	2
Alveolar histiocytosis	1	1	2

Table 2. Histopathology findings.

driven by females. Finally, although not examined specifically in great detail, there did not appear to be any increased weight-related changes related to cause of death at time of histopathological analysis. Importantly, here we did not examine differences in neuroendocrine phenotypes that may be mediating the increased weight in female Het mice as this is a focus of a parallel study examining the role of sex and *Myt1l* gene mutation on specific hormones that regulate feeding behavior and weight gain[22]. In that study we found that Het mice did not show signs of metabolic dysfunction as measured by fasting blood glucose, free fatty acids, triglycerides, or cholesterol, at comparable weights to controls or at a heavier weight following high fat diet exposure[22]. Future studies will be necessary in mice and humans to determine if altered metabolism contributes to the increased weight gain in *Myt1l* Het mice and patients with MYT1L Syndrome.

We did not see a significant difference in survival between *Myt1l* Het mice and WT mice, whereas mortality studies in other animal models of NDD genetic liability have demonstrated mixed results depending on the type of genetic model used[18,19,23,24]. With additional, novel discoveries of genetic causes of NDD such as MYT1L syndrome, studies on aging and lifespan will hopefully provide additional insight into the pathophysiology of aging in individuals with this disorder, in hopes of identifying potential causes of comorbidities and death. However, these studies are currently limited or still in progress.

Despite no group effects on survival between *Myt1l* Het mice and WT mice, there was a significant sex difference on overall lifespan, with male mice living significantly longer than female mice. Sex differences on lifespan of various inbred mouse strains, including the C57Bl/J have been reported, but have been mixed across studies and institutions, with some showing males outlive females, others showing females outlive males, and some showing no difference in lifespan at all[25]. Thus, the sex difference found in our survival analysis could be an effect of background strain or the influence of a number of facility-specific and/or cohort-specific factors, such as the handling and behavioral testing experience of these animals.

We also examined histopathology in a subset of animals. *Myt1l* Het mice had similar histopathological findings as their WT littermate controls. Common findings in the histological examination were likely related to old age including benign and malignant neoplasms, membranoproliferative glomerulonephropathy, extramedullary hematopoiesis, and aging changes in the liver. In human studies, people with MYT1L syndrome primarily have central nervous system and endocrine-related pathologies, which we did not specifically see in our histopathological analysis[5]. In this study, we did not see differences in histopathological changes between *Myt1l* Het mice and WT controls, suggesting old age had a bigger impact on organ function than loss of *Myt1l*. However, more natural history studies in humans and aging studies in mice are needed to definitively rule out potential pathological organ changes in MYT1L syndrome.

This study did not examine changes in the brain associated with aging. Previous studies have focused primarily on brain-related changes in *Myt1l* Het mice[11,14,20]. *Myt1l* Het mice have smaller brain volumes in adulthood compared to WT mice[14]. These studies suggest that decreased cortical volumes may be due to disrupted neuronal maturation of cortical excitatory neurons early in development[20]. We suspect the brain changes may be related to developmental changes, rather than old-age related changes as we observed these neuronal phenotypes as early as E14.5 and confirmed the smaller brain phenotypes at P60. In addition, we've observed cortical cell loss due to insufficient expansion of neuronal progenitors, neuronal immaturity, and disrupted gene expression in the cortex of developing and adult *Myt1l* het mice[20]. Future studies will be necessary to examine any further changes in brain processes related to age such as neurodegeneration, and age-related behavioral decline in domains such as learning and memory.

The purpose of this study was to understand if the presence of *Myt1l* mutation impacts lifespan. While mortality in old age may have been similar between Het mice and their wildtype littermates, this study did not target potential sub-lethal disease states throughout life. If there were earlier onset comorbidities, overall age-related changes at > 24 months could have masked differences between the two groups. Thus, it remains uncertain whether any pathologies could have presented at an earlier age, as this study provided only a snapshot of health and disease at the end of life. A similar, future study with a larger cohort of mice, to include groups sampled for necropsy and histopathology at early adulthood (2–3 months), mid life (10–14 months) and early onset of old age (18 months) could provide greater insight into potential sub-lethal disease states or other pathophysiologies associated with MYT1L syndrome in humans. In addition to examining a wider breadth of ages, it would also be worthwhile to examine specific organs, hormonal changes, and/or cell types, in hopes of possibly elucidating more subtle changes potentially contributing to the overall morbidity of MYT1L heterozygotes that were not examined in this survey study. If these differences do exist in our mutant model, they did not influence overall lifespan.

Finally, this study included only a small number of animals tested on a single background strain (C57BL/6 J), which is consistently reported as especially long-lived among inbred mouse strains[16,26], with a max lifespan estimated at 1075 ± 13 days in females and 1061 ± 17 days in males[16]. As there are known differences in disease development and progression between mouse strains, as well as documented species differences between mice and humans, it remains possible that increased morbidity and/or mortality in humans with MYT1L syndrome might not be detected in this particular mouse model. Also not recapitulated in animal models, causes of decreased lifespan amongst people with neurodevelopmental disorders and autism are presumed to be multifactorial, including influencers such as social determinants of health and access to healthcare[3,4]. Therefore, although there were no definitive differences in lifespan or cause of death between our *Myt1l* Het mice and WT controls, this does not preclude potential lifespan differences in humans with MYT1L syndrome. As MYT1L syndrome becomes recognized and diagnosed with increasing frequency, future studies in animals and humans will be essential for understanding both the lifespan and the healthspan as these patients age. Nonetheless, the current findings suggest a robust lifespan in the context of MYT1L mutation is possible.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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Author contributions

J.D.D. and S.E.M. designed the study. R.G.S. and L.W. collected and analyzed the data. R.G.S., A.S., and S.E.M.

wrote the manuscript. A.S., K.L.K, S.E.M, and J.D.D. revised the manuscript and secured funding for the project.

Competing interests
The authors declare no competing interests.

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