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Extended Conventional Therapy In Adult Xlh Patients

Jessica Ann Connor
Yale University, jessicaconnor091@gmail.com

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Jessica Connor[1], Elizabeth Olear M.S.[2], Karl Insogna M.D.[3] Lee Katz M.D.[4], Suher Baker D.M.D.[5], Raghbir Kaur D.M.D.[5], Christine Simpson M.S.[3], John Sterpka[3], Robert Dubrow M.D. Ph.D.[1], Jane Zhang Ph.D.[6], Thomas Carpenter M.D.[2]

Yale University School of Medicine (Epidemiology and Public Health[1] and Departments of Medicine[2], Pediatrics[3], and Diagnostic Imaging[4]); Yale-New Haven Hospital Dentistry Program[5], The Cooperative Studies Program Coordinating Center, VA Connecticut Healthcare System[6]

Abstract

Context: Treatment of X-linked hypophosphatemia (XLH) with active vitamin D metabolites and phosphate can partially correct skeletal deformities. It is unclear if therapy influences the occurrence of two major long-term morbidities in XLH: enthesopathy and dental disease.

Objective: To investigate the relationship between treatment and enthesopathy and dental disease in adult XLH patients.

Design: Observational and cross-sectional.

Setting: Academic medical center's hospital research unit.

Participants: 52 XLH patients aged >= 18 at time of study.

Interventions: None

Main outcome measures: Number of enthesopathy sites identified by radiographic skeletal survey and dental disease severity (>5 or <=5 dental abscesses), identified historically.

Methods: Associations between proportion of adult life and total life with treatment and number of enthesopathy sites were assessed using multiple linear regression, while associations between these exposure variables and dental disease severity were assessed using multiple logistic regression. All models were adjusted for confounding factors.

Results: Neither proportion of adult nor total life with treatment was a significant predictor of extent of enthesopathy. In contrast, both of these treatment variables were significant predictors of dental disease severity (multivariate-adjusted global p-value =0.0080 and =0.0010 respectively). Participants treated 0% of adulthood were more likely to have severe dental disease than those treated 100% of adulthood (adjusted OR 25 [95% CI 1.2-520]). As proportion of total life with treatment increased, the odds of having severe dental disease decreased (multivariate-adjusted p-value for trend=0.015).

Conclusions: Treatment in adulthood may not promote or prevent enthesopathy; however it may be associated with lower risk of experiencing severe dental disease.

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Introduction

X-linked hypophosphatemia (XLH), the most common form of heritable rickets, is a dominant disorder of phosphate homeostasis whose prevalence is estimated at 1 in 20,000 (1). The pathophysiology of this disease is related to loss of function mutations in the phosphate-regulating endopeptidase gene (PHEX) (2). PHEX is normally expressed in bone and teeth and its disruption results in increased circulating levels of fibroblast growth factor 23 (FGF23) (3). FGF23 acts in an endocrine manner at the kidney to both decrease renal tubular reabsorption of phosphate and renal 1-α-hydroxylase activity resulting in the combined findings of hypophosphatemia and inadequate levels of circulating $1,25(OH)_2D$ observed in XLH (2).

Hypophosphatemia, low $1,25(OH)_2D$, and perhaps independently, elevated FGF23 and disruption of PHEX contribute to the broad range of severity in the skeletal and dental morbidities in XLH(1). Common skeletal abnormalities observed in XLH include bowing of the legs, anteromedial rotation and torsion of the tibiae, and poor bone mineralization (osteomalacia) with resultant growth retardation and bone disease (4). However, later in life, patients often experience mineralization of tendons and ligaments (enthesopathy) (1). Dental morbidities include delayed dentition and dental abscesses with the latter continuing throughout adult life (1).

The current standard of therapy for XLH is a regimen of active vitamin D metabolites, usually calcitriol, and phosphate beginning at time of diagnosis and continuing to growth completion (1). The administration of these therapies intermittently increases serum phosphate, providing necessary mineral to the growing skeleton and thereby partially correcting leg deformities (5). After growth completion, the rationale for therapy is directed toward symptomatic osteomalacia and prevention or correction of fractures or insufficiency fractures (1). It remains to be established whether therapy affects the other major adult sequelae of XLH, particularly enthesopathy and dental disease.

Continuing conventional treatment into adulthood has been controversial both because its efficacy is not well studied, and because it is burdensome and potentially toxic (4). Long-term

therapy with calcitriol and phosphate may result in hyperparathyroidism, hypercalcemia, hypercalciura, nephrocalcinosis, and in extreme cases, chronic kidney disease (4). However, if monitored for safety, treatment has been shown to improve certain features of the disease, including pain and osteomalacia (6). Therefore, it is of great clinical importance to establish the effect of therapy on enthesopathy and dental disease during adult life. Using data from a relatively large cohort of XLH patients this study examined the association between conventional XLH therapy and two significant morbidities experienced in the adult phase of the disease: enthesopathy and dental abscess formation.

Materials and Methods

Subjects and Design

The study sample included 52 XLH patients age 18 or older. Patients were offered participation during clinical visits to the Yale Bone Center or upon referral from other physicians. The study population consisted of 18 males and 34 females. Exclusion criteria included presence of other diseases likely to impact bone and mineral metabolism (e.g. renal, hepatic, gastrointestinal disorders, and malignancy), treatment with estrogen or bisphosphonates, and pregnancy.

Data Collection

Biochemical measures reflecting pathophysiology or therapeutic toxicity were obtained for each study participant. Serum PTH was measured as area under the curve from samples obtained at 4-hour intervals for 8 consecutive intervals using a mid-region assay (7). FGF23 was measured as a single value from a fasting morning sample using the Kainos intact ELISA kit (kindly provided by Kyowa Hakko Kirin Pharma, Inc.). Participant characteristics, including age at onset of treatment, years with treatment, frequency of pain medication use, previous osteotomies, and number of dental abscesses were obtained from both medical records and extensive questioning of history. Research nursing staff measured participant height using a stadiometer and weight using a calibrated scale. These measurements were used to calculate both

height z-scores and body mass index (BMI) with the latter calculated as kilogram body weight per height in meters squared. Participants were genotyped by Sanger sequencing to determine the nature of their PHEX mutations. We categorized frame-shift and splice-site mutations as "severe" and missense and point mutations as "non-severe". Sites of enthesopathy were determined via skeletal survey examined by a radiologist. The specific anatomic sites surveyed included shoulders, elbows, hands, wrists, pelvis, knees, ankle, and thoracic-lumbar spine.

Exposures of Interest

The primary exposure of interest in this study was treatment with calcitriol (or high dose vitamin D) and phosphate. Because of the importance of age in the natural history of this disease, treatment exposure was assessed as a proportion of both total years of life and total years of adult life. All years of life age 18 and over were counted towards adult life. Proportion of adult life with treatment was calculated by dividing total years of treatment in adult life by total years of adult life. This exposure variable was categorized into three levels based on the distribution of the sample: 0.0 of adult life with treatment, greater than 0.0 but less than 1.0 of adult life with treatment, and 1.0 of adult life with treatment. Proportion of total life with treatment was calculated by dividing total years of treatment throughout life by total years of life. This exposure variable was categorized into four levels based on the quartile distribution of the sample: <0.436, 0.436-<0.588, 0.588-0.881, 0.881<=1.0.

Outcomes of Interest

There were two primary outcomes of interest in this study: number of sites of enthesopathy identified on an a priori designed skeletal survey, and number of dental abscesses experienced per participant. Enthesopathy was assessed as a continuous variable. Dental disease severity was assessed as a dichotomous variable: a history of >5 dental abscesses ("severe" dental disease) versus a history of ≤ 5 dental abscesses ("non-severe" dental disease).

Statistical Analysis

The association between each of our two primary exposure variables, proportion of adult life and proportion of total life with treatment, and number of sites of enthesopathy was assessed using multiple linear regression. The association between each of our two primary exposure variables and dental disease severity was assessed using multiple logistic regression, modeling the odds of having "severe" versus "non-severe" dental disease. Because of the importance of age in the natural history of XLH, all models included age as a covariate. Age-adjusted models included only the primary exposure variable of interest and age. In addition, the following variables were assessed as potential confounders of the relationship between the respective exposure variables and enthesopathy: sex, body mass index, mutation severity, PTHauc, and FGF23. Covariates were retained in the model if their addition resulted in a 10% or greater change in the parameter estimate for the primary exposure variable. Both fully adjusted models for enthesopathy included age, sex, body mass index, mutation severity, and PTHauc. Both fully adjusted models for dental disease included age, sex, and mutation severity. For all models assessing proportion of life with treatment as the primary predictor, proportion of childhood with treatment was also included as a covariate. Proportion of childhood with treatment was assessed as a dichotomous variable: <0.80 of childhood versus >= 0.80 of childhood. P-values for trend and global p-values were obtained for the primary predictor variables. All analyses were performed using the statistical software package SAS 9.3.

Descriptive Statistics

Table 1 presents selected participant characteristics across three groups defined by proportion of adult life with treatment. The mean age of the study sample was 39 years. The total years of childhood treatment (before age 18) was relatively similar across all groups with an overall sample average of 13.9 years. For the entire sample (as well as for each treatment category) there were approximately 35% males and 65% females, consistent with the X-linked dominant mode of inheritance. The majority of participants had severe vs. not severe mutations

(65% vs. 25%). On average, 1.8 sites of enthesopathy were identified per patient. Average sites of enthesopathy across the three proportional treatment categories did not differ notably. A majority of our sample had severe dental disease versus non-severe dental disease (61.5% vs. 38.5%). There were notable differences in dental disease severity across the adult life treatment categories: 75% of those participants with no (0%) treatment during adult life had severe dental disease while only 47% of those treated throughout all (100%) of adult life had severe dental disease.

Enthesopathy

Table 2 presents both age-adjusted and multivariate-adjusted multiple linear regression models of the relationship between proportion of adult life with treatment, as well as other predictors, and number of sites of enthesopathy. We found that after adjusting for age, proportion of adult life with treatment was not a significant predictor of number of sites of enthesopathy (age-adjusted global p-value=0.96) and this finding remained after adjusting for confounders (multivariate-adjusted global p-value=0.90). We did, however, find that age, BMI, and sex were important predictors of the number of sites of enthesopathy. Age and body mass index were positively associated with number of sites of enthesopathy ($p<0.001$ for each covariate). Female sex was negatively associated with number of sites of enthesopathy (p=0.0080). We found that females on average had 0.42 less sites of enthesopathy compared to males. We found borderline significant positive association between PTHauc and number of sites of enthesopathy. In contrast, mutation severity and proportion of treatment in childhood did not predict extent of enthesopathy (p=0.42 and p=0.10 respectively). Table 3 presents age-adjusted and multivariate-adjusted multiple linear regression models of the relationship between proportion of total life, as well as other predictors, and number of sites of enthesopathy for the purposes of comparison. Proportion of total life with treatment was also not a significant predictor of this outcome (age-adjusted global p-value= 0.18; multivariate-adjusted global p-value=0.90). Results for other covariates were similar to those seen in the model for proportion of adult life with treatment: age, BMI, and

PTHauc were positively associated with number of sites of enthesopathy while female sex was negatively associated with this outcome. However, the PTHauc association did not achieve borderline significance in this model (p=0.10).

Dental Disease

Table 4 presents age-adjusted and multivariate-adjusted multiple logistic regression models of the relationship between proportion of adult life with treatment, as well as other predictors, and severity of dental disease. In both the age-adjusted and multivariate-adjusted analyses, proportion of adult life with treatment was negatively associated with the odds of having severe dental disease (global p-value=0.038 and 0.0080 respectively). After adjustment for confounders, we found a borderline significant trend between increasing proportion of adult life with treatment and decreasing odds of having severe dental disease (p-value for trend=0.066). Those who were not treated at all during adult life were more likely to experience severe dental disease than those who were treated for 100% of adulthood (adjusted OR 25 [95% CI 1.2-520]). We found that age was a significant predictor of dental disease severity: for a 1 year increase in age, the odds of having severe dental disease increased by 10% (OR: 1.1 [95% CI 1.0-1.2]). Furthermore, we found that sex was a borderline significant predictor of dental disease severity (p=0.061). Females had lower odds of experiencing severe dental disease compared to males (OR 0.15 [95% CI 0.020-1.1]). Those treated for less than 80% of childhood had higher odds of experiencing severe dental disease compared to those treated for 80% or greater of childhood (OR: 7.2 [95% CI 0.71-73]). Mutation severity was positively associated with severity of dental disease: those with severe mutations had higher odds of experiencing severe dental disease compared to those who did not have severe mutations (OR 3.9 [95% CI 0.63-25)]. These relationships did not, however, achieve statistical significance. Table 5 presents age-adjusted and multivariate-adjusted multiple linear regression models of the relationship between proportion of total life, as well as other predictors, and severity of dental disease. Proportion of total life with treatment was negatively associated with severity of dental disease (age-adjusted global p-value

0.012; multivariate-adjusted global p-value 0.0010). As proportion of total life with treatment increased, the odds of having severe dental disease decreased (age-adjusted p-value for trend=0.046; multivariate-adjusted p-value for trend=0.015). Results for other covariates were similar to those seen in the model for proportion of adult life with treatment: age and mutation severity were positively associated with dental disease severity while female sex was negatively associated with this outcome.

Discussion

The results of this study suggest that the extension of treatment for XLH with calcitriol and phosphate into adulthood neither prevents nor promotes enthesopathy, but may prove beneficial for the prevention of dental abscesses. Most previous work on the efficacy of this therapeutic regimen has focused on the pediatric XLH population and as a result there is currently not an established consensus regarding treatment of the adult patient. Moreover, the limited studies in the adult XLH population have not assessed the effect of therapy on the specific outcomes that were the focus of our study. Sullivan et al. conducted a prospective study of the relationship between phosphate and calcitriol treatment and biochemical, clinical, and histological responses in 16 adult XLH patients (7). They found that 87% of participants reported significant improvement in musculoskeletal symptoms and osteoid thickness was significantly reduced as well (7). Costa et al. assessed 5 “adult” patients (defined as >15 years of age) and 6 children with XLH and found that skeletal improvements were most pronounced in, but not limited to, the pre-pubescent patients (8). Although these studies examined certain skeletal outcomes, neither assessed enthesopathy as an outcome and the sample sizes were too small to assess possible associations with treatment duration and skeletal outcomes.

Although enthesopathy is well described in XLH patients, previous studies have not examined treatment effects on this complication. More numerous reports of dental complications exist; however a beneficial effect of medical therapy on dental outcomes has yet to be established (4). Furthermore, it is established that the management of dental abscesses via pulpectomy and

root canal often fails (11). Moreover, one dental abscess tends to predict the occurrence of future abscesses (10). In light of this information, our findings suggest that conventional therapy extended into adulthood may be particularly beneficial for XLH patients that have particularly burdensome dental disease. If management via traditional dental methods fails and one abscess predicts the next, continuation of pharmaceutical therapy may be indicated for these particular patients.

Our finding of higher odds of severe dental disease in males versus females is consistent with clinical observation: male patients have been shown to have more extensive dental disease than females (12). It is believed that the more severe dental phenotype in males can be at least partially explained by the hemizygous nature of the disease allele in males, and that a more striking gene dose effect is evidence for the teeth than the skeleton (12). This theory may also explain our finding of a negative association between female sex and number of sites of enthesopathy. The positive association between age and the two outcomes of interest may be explained by the natural history of XLH: enthesopathy is known to be a morbidity of aging and the more time that elapses, the more opportunity there is for dental abscess to occur. Although we did not find proportion of adult life or proportion of total life to be important predictors of enthesopathy, the finding that body mass index was positively associated with number of sites of enthesopathy may be of clinical importance in that the increased load to insertion sites evident with increasing BMI, may accelerate the disease process (13). Thus, greater body mass index, and resultant increased load on the insertion sites may be an important factor in accelerating the development of this complication. Our findings suggest that although pharmacological therapy may not be effective for preventing enthesopathy, weight-loss interventions may be helpful in the long-term.

In sum, we have assessed clinically significant outcomes of adult XLH that have not previously been adequately explored. Although the cross-sectional nature of this study limits its interpretation, the identification and use of a database for cumulative treatment history in adult

patients with XLH is unique and informative. A randomized control trial directed toward adult morbidities in XLH patients would be important to confirm the safety and efficacy of continued treatment through adult years, however such a study is likely to require a lengthy follow up period to capture sufficient for these age-dependent outcomes to develop.

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Table 1. Selected participant characteristics by proportion of adult Life with treatment [a]

Characteristic	**0% of Adult life with treatment** [b]	**0%<x<100% of Adult life with treatment** [b]	**100% of Adult life with treatment** [b]	**Full sample** [b]
N	***8***	***27***	***17***	***52***
Age (yrs)	31.8 (11.3)	40.7 (11.9)	39.9 (18.4)	39.0 (14.4)
Age at onset of treatment (yrs)	4.7 (8.3)	6.6 (11.5)	4.0 (6.9)	5.4 (9.7)
Yrs of treatment >= age 18	1.6 (4.3)	6.4 (6.7)	20.9 (17.8)	10.5 (13.5)
Yrs of treatment <18	14.0 (6.3)	13.5 (6.1)	14.5 (4.6)	13.9 (5.6)
Sex				
Male	3 (37.5)	9 (33.3)	6 (35.3)	18 (34.6)
Female	5 (62.5)	18 (66.7)	11 (64.7)	34 (65.4)
BMI (kg/m^2)	34.1 (11.2)	34.2 (10.4)	31.4 (5.9)	33.3 (9.2)
Body fat %	36.9 (11.1)	34.3 (11.7)	35.4 (12.4)	35.1 (11.5)
Height Z-score				
>= -1.0	0 (0.0)	4 (14.8)	0 (0.0)	4 (7.7)
-1.1=<z<= -1.5	1 (12.5)	2 (7.4)	3 (17.7)	6 (11.5)
-1.6 -2.0	2 (25.0)	2 (7.4)	2 (11.8)	6 (11.5)
-2.1	5 (62.5)	19 (70.4)	12 (70.6)	36 (69.2)
Use of pain meds				
Never	1 (12.5)	7 (25.9)	5 (31.3)	13 (25.5)
Less frequently	2 (25.0)	4 (14.8)	5 (31.3)	11 (21.6)
Weekly	3 (37.5)	5 (18.5)	2 (12.5)	10 (19.6)
Daily	1 (12.5)	7 (25.9)	4 (25.0)	12 (23.5)
> once/day	1 (12.5)	4 (14.8)	0 (0.0)	5 (9.8)
Previous no. of osteotomies				
none	4 (50.0)	11 (40.7)	3 (17.7)	18 (34.6)
1	0 (0.0)	0 (0.0)	2 (11.8)	2 (3.9)
2	2 (25.0)	7 (25.9)	3 (17.7)	12 (23.1)
>2	2 (25.0)	9 (33.3)	9 (52.9)	20 (38.5)

Mutation status[c]				
Not severe	1 (12.5)	9 (33.3)	3 (17.7)	13 (25.0)
Severe	6 (75.0)	17 (63.0)	11 (64.7)	34 (65.4)
No. of sites of enthesopathy	1.63 (0.74)	1.85 (0.86)	1.82 (0.64)	1.81 (0.77)
No. of dental abscesses	2 (25.00)	9 (33.3)	9 (52.9)	20 (38.5)
<=5	6 (75.00)	18 (66.7)	8 (47.1)	32 (61.5)
>5				
PTH[d]	1068.5 (889.9)	985.6 (392.4)	1260.7 (751.8)	1088.3 (616.5)
FGF23	1976.5 (972.4)	6156.9 (140508.8)	4604.2 (7260.8)	5006.2 (11233.0)

[a] Table values are mean ± SD for continuous variables and n (column %) for categorical variables.
[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.
[c] 5 missing values for mutation severity were included in a "missing category"
[d]PTH, area under the curve measure for PTH samples taken every 4 hours over a 26-hr period

Table 2. Age-adjusted and multivariate-adjusted multiple linear regression models of the relationship between proportion of adult life with treatment, other predictors, and sites of enthesopathy

Characteristic	Age-adjusted		Multivariate-Adjusted	
	β(SE)	P-value	β (SE)	P-value
Proportion of adult life with treatment				
0	0.071 (0.27)	0.80	-0.092 (0.23)	0.69
0<x<1	0.0040 (0.19)	0.99	-0.0000015 (0.17)	1.0
1	Reference	-	Reference	-
Global p-value		0.96		0.90
P-value for trend		0.68		0.50
Age (years)	0.033 (0.010)	<0.0010	0.023 (0.006)	<0.0010
Sex				
Male	-	-	Reference	
Female	-	-	-0.42 (0.16)	0.0080
Body mass index (kg/m^2)	-	-	0.034 (0.0090)	<0.0010
Mutation severity[a]				
Not Severe	-	-	Reference	
Severe	-	-	0.14 (0.18)	0.42
PTH[b]	-	-	0.00028 (0.00014)	0.051
Proportion of treatment in childhood				
<0.80	-	-	0.30 (0.18)	0.10
≥0.80	-	-	Reference	

[a] Mutation analyses from 5 subjects were either not preformed or not definitive and were included in a "missing" category

[b]PTH, area under the curve measure for PTH samples taken every 4 hours over a 26-hr period

Table 3. Age-adjusted and multivariate-adjusted multiple linear regression models of the relationship between proportion of total life with treatment, other predictors, and number sites of enthesopathy

Characteristic	Age-adjusted		Multivariate-Adjusted	
	β(SE)	P-value	β (SE)	P-value
Proportion of total life with treatment				
0<=x<0.436	0.012 (0.24)	0.96	0.094 (0.21)	0.66
0.436<=0.588	0.19 (0.24)	0.43	0.027 (0.23)	0.91
0.588<=x<0.881	-0.20 (0.24)	0.41	-0.050 (0.21)	0.81
0.881<=x<=1.0	Reference	-	Reference	-
Global p-value		0.18		0.90
P-value for trend		0.72		0.54
Age (years)	0.031 (0.0060)	<0.0010	0.027 0(0.0060)	<0.0010
Sex				
Male	-	-	Reference	-
Female	-	-	-0.42 (0.60)	0.012
Body mass index (kg/m^2)	-	-	0.030 (0.010)	0.0020
Mutation severity[a]				
Not Severe	-	-	Reference	-
Severe			0.17 (0.18)	0.34
PTH[b]	-	-	0.00025 (0.00015)	0.10

[a]5 missing values for mutation severity were included in a "missing category"
[b]PTH, area under the curve measure for PTH samples taken every 4 hours over a 26-hr period

Table 4. Age-adjusted and multivariate-adjusted multiple logistic regression models of the relationship between proportion of adult life with treatment, other predictors, and severity of dental disease

Characteristic	Age-adjusted		Multivariate-Adjusted	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Proportion of adult life with treatment				
0	7.8 (0.85-71)	0.069	25 (1.2-520)	0.038
0<x<1	2.3 (0.51-11)	0.27	7.1 (0.88-58)	0.067
1	1.0	-	1.0	-
Global p-value		0.038		0.0080
P-value for trend		0.20		0.066
Age (years)	1.1 (1.0-1.2)	0.0030	1.1 (1.0-1.2)	0.019
Sex				
Male	-	-	1.0	-
Female	-	-	0.15(0.020-1.1)	0.061
Mutation severity[a]				
Not Severe	-	-	1.0	
Severe	-	-	3.9 (0.63-25)	0.14
Proportion of treatment in childhood				
<0.80	-	-	7.2 (0.71-73)	0.10
≥0.80	-	-	1.0	-

[a]5 missing values for mutation severity were included in a "missing category"

Table 5. Age-adjusted and multivariate-adjusted multiple linear regression models of the relationship between proportion of adult life with treatment, other predictors, and sites of enthesopathy

Characteristic	Age-adjusted		Multivariate-Adjusted	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Proportion of total life with treatment				
0<0.436	8.8 (1.1-70)	0.040	31 (2.2-450)	0.012
0.436≤0.588	5.6 (0.84-38)	0.075	25 (1.8-340)	0.017
0.588≤0.881	2.0 (0.33-12)	0.45	4.8 (0.49-51)	0.20
0.881≤1.0	1.0	-	1.0	-
Global p-value		0.012		0.0010
P-value for trend		0.046		0.015
Age (years)	1.1 (1.0-1.1)	<0.0010	1.1 (1.0-1.2)	0.010
Sex				
Male	-	-	1.0	
Female	-	-	0.080 (0.0090- 0.71)	0.023
Mutation severity				
Not Severe	-	-	1.0	
Severe	-	-	5.2 (0.82-33)	0.080

*5 missing values for mutation severity were included in a "missing category"