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A longitudinal study of neurocognition and behavior in patients with Hurler-Scheie syndrome heterozygous for the L238Q mutation

Alia Ahmed[a,*], Li Ou[b], Kyle Rudser[c], Elsa Shapiro[a], Julie B. Eisengart[a], Kelly King[a], Agnes Chen[d], Patricia Dickson[d,e], Chester B. Whitley[a,b]

[a] Department of Pediatrics, University of Minnesota, Minneapolis, MN 55455, USA
[b] Gene Therapy Center, Department of Pediatrics, University of Minnesota, Minneapolis, MN 55455, USA
[c] Division of Biostatistics, University of Minnesota, Minneapolis, MN 55455, USA
[d] Department of Pediatrics, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA
[e] Department of Pediatrics, Washington University in St. Louis, St. Louis, MO, USA

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ABSTRACT

Previous research has demonstrated the mutation, c.712T > A (p.L238Q) of the gene for α-L- iduronidase (IDUA) in patients with Hurler-Scheie syndrome is relatively severe when paired with a nonsense or deletion or splice-site mutation. This mutation was also found to be associated with psychiatric symptoms. This research presents longitudinal data and protein analysis to further investigate the severity and natural history of these unique patients.

Methods: Six patients heterozygous for L238Q were compared to six patients with Hurler-Scheie without the L238Q mutations. Somatic burden of disease, IQ, memory, attention, adaptive functioning and behavioral measures were given yearly over 2 to 4 years from 2009 to 2014. The impact of L238Q on the IDUA enzyme was examined using 7 bioinformatics tools and a 3D structural analysis.

Results: Similar to the cross sectional study, the L238Q patients had more severe abnormalities in IQ, attention, adaptive functioning, and behavioral functioning than the comparison group. There were no major differences between the two groups in change over time; IQ for both groups was stable with some behavioral areas showing improvement. Over time, both groups declined in visual spatial memory and, attention/visual processing. They also showed increased anxiety. Structural and bioinformatics analysis of the L238Q suggest that this mutation causes a significant reduction in the IDUA enzyme's potential catalytic activity, and this mutation may be more severe than other mutations contributing to the Hurler-Scheie syndrome phenotype, presumably causing the psychiatric disease.

Conclusion: L238Q patients demonstrate severe neurocognitive and neurobehavioral deficits but are relatively stable. Like the comparison group, decreasing visual spatial memory and attention and increasing anxiety suggest more intervention in life skills and emotional social supports are needed.

1. Introduction

A missense mutation, L238Q, in patients with Hurler-Scheie syndrome, has been described as having a spectrum of clinical severity. In the literature, this IDUA (α-L- iduronidase) mutation has been mentioned in different levels of severity [1–4]. Previous cross sectional research of six heterozygous patients has documented the mutation, c.712T > A (p.L238Q) of the gene for IDUA in Hurler-Scheie syndrome as relatively severe when paired with a nonsense or other severe mutation, manifested by medical, cognitive complications and also identified the mutation L238Q as uniquely associated with a neuropsychiatric phenotype [5]. Although heterozygosity of mutations of the GLB gene in Gaucher disease has been associated with Parkinson's disease [6], no other specific mutation of the IDUA gene has been associated with neuropsychiatric symptoms.

This study extends prior cross-sectional work by investigating how this same cohort of patients has functioned over time and whether their life adjustment has been affected. These longitudinal findings are compared to a comparison group of non-L238Q patients with Hurler-Scheie. It was of particular interest to find out whether these patients showed decline in functioning over time. The primary hypothesis tested in this analysis is that while medical symptoms were likely to worsen

* Corresponding author at: 717 Delaware St. SE, 353-25, Minneapolis, MN 55414, USA.
E-mail address: ahmed306@umn.edu (A. Ahmed).

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Table 1
Mutation and medical data of L238Q and comparison group.

	Mutation	Mutation type	Hydrocephalus	Shunt placement	Cord compression	Psychiatric problem	Sleep problem
L238Q group							
1	L238Q/63delC	Missense/Deletion	Absent	Absent	Present	Present	Present
2	L238Q/W402X	Missense/Nonsense	Present	Present	Present	Present	Present
3	L238Q/W402X	Missense/Nonsense	present	Absent	Present	Present	Present
4	L238Q/W402X	Missense/Nonsense	Present	Present	Absent	Present	Present
5	L238Q/W402X	Missense/Nonsense	Present	Present	Present	Present	Present
6	L238Q/Int3-2a > g	Missense/Splice Site	Absent	Absent	Absent	Present	Present
Compari-son group							
7	G256R/ W402X	Missense/Nonsense	Absent	Absent	Absent	Absent	Absent
8	G265R/A327P	Missense/Missense	Absent	Absent	Absent	Absent	Absent
9	Q380R/Q70X	Missense/Nonsense	Absent	Absent	Absent	Absent	Absent
10	P533R/P533R	Missense/Missense	Absent	Absent	Absent	Absent[a]	Absent
11	R89W/W402X	Missense/Nonsense	Present	Absent	Present	Absent	Absent
12	W402X/Int11-7c > t	Nonsense/Splice Site	Absent	Absent	Present	Absent	Absent

[a] This patient has a diagnosis of depression after his 3rd visit and was on anti-depressant thereafter.

over time as in other patients with Hurler-Scheie syndrome, their neurocognitive and neuropsychiatric status would be stable, but remain within the abnormal range.

In addition, to further understand the impact of L238Q on the IDUA enzyme, a 3D structural analysis and a combination of bioinformatics tools were used [7,8] to determine its consequences.

2. Methods

Patients were identified from MPS I participants with Hurler-Scheie syndrome in the age range of 14 to 25 years from an NIH-supported study which is a part of the Lysosomal Disease Network (LDN) (U54-NS065768). The six patients in the L238Q group were compared to 6 age-matched Hurler-Scheie patients without the L238Q mutation as a comparison group. All participants are on enzyme replacement therapy (ERT) and had DNA analysis. Specifics of their mutations can be found in Table 1.

2.1. Patients

Of the six patients with L238Q mutation, four were paired with a nonsense mutation, one with a deletion, and one with a splice site mutation. For the comparison group, three patients had a missense paired with nonsense, two patients with missense paired with missense, and one patient with nonsense paired with splice site mutation.

2.2. Procedures

2.2.1. Somatic disease burden

To measure the somatic disease burden, the Physical Symptom Score (PSS) [9] was used. It quantifies severity using medical data from history and by interviewing the research participants or their caregivers.

2.2.2. Neurocognitive, adaptive, and psychological status

Assessment of neurocognitive functioning, including IQ, memory, attention, adaptive skills and behavioral function, used following measures:

- WASI (Wechsler Abbreviated Scale of Intelligence) [10] to obtain the Full Scale IQ (FSIQ),
- BVMT (Brief Visual Spatial Memory Test) [11] to measure nonverbal memory,
- TOVA (Test of Variables of Attention) [12] to assess attention,
- VABS-II (Vineland Adaptive Behavior Scales, Second Edition) [13] to assess adaptive functioning
- BASC-PRS and BASC–SRP (Behavior Assessment System for Children-Parent Rating Scale and Self-Report of Personality) [14] to assess psychological status.

2.2.3. DNA analysis

For DNA analysis molecular diagnosis was performed by Sanger sequencing of all exomes of the IDUA gene at the Gene Therapy and Diagnostics Lab, University of Minnesota. DNA was isolated from leukocyte pellets, PCR amplified, and then sequenced with BigDye® Terminator (Life Technologies). The reactions were sequenated on an ABI 3130 Avant sequencer (Life Technologies) with subsequent analysis on Sequencer software (Gene Codes Corporation).

2.2.4. In silico analysis of L238Q

A total of 7 bioinformatics tools were used as described in a previous study [7,8]. These tools were listed as follows: SIFT (Sorting Intolerant From Tolerant), PolyPhen (Polymorphism Phenotyping), I-Mutant, PROVEAN (Protein Variation Effect Analyzer), PANTHER (Protein Analysis Through Evolutionary Relationships), SNPs&GO (Single Nucleotide Polymorphism Database & Gene Ontology) and PHD-SNP (Predictor of Human Deleterious Single Nucleotide Polymorphisms). SIFT and PROVEAN predict the consequences of a single amino acid substitution by utilizing multiple alignment information. PolyPhen predicts the impact of an amino acid substitution using straightforward physical and comparative considerations. I-Mutant can predict protein stability changes upon single amino acid substitution. PANTHER makes prediction with hidden Markov model (HMM) based statistical modeling methods and multiple sequence alignments (MAS). Both PHD-SNP and SNPs&GO are support vector machine (SVM) classifiers using supervised training to predict functional impacts of amino acid substitutions.

The impact of L238Q was predicted by a total of 7 bioinformatics tools using different methodologies. The associated index that indicates the confidence of prediction was given and explained as followed:

SIFT: tolerated, if the index is < 0.05; and damaging, if the index is ≥ 0.05.
PolyPhen: benign, if the index is < 0.15; probably damaging, if the index is > 0.85; and possibly damaging; > 0.15.
I-Mutant: neutral, if the index is -0.5 to < 0.5; and large decrease, if the index is < -0.5.
PROVEAN: neutral, if the index is > -2.5; and deleterious, if the index is < -2.5.
PANTHER, SNPs&GO and PHD-SNP are using a probability score (0 to 1).

2.2.5. 3D Structural Analysis

A 3D structural analysis was performed to reveal the impact of the

L238Q on the IDUA enzyme.

2.3. Ethical considerations

All patients and/or their legal guardians provided written informed consent to participate in the study. This study was approved by the University of Minnesota Institutional Review Board: Human Subjects Committee. The protocol was approved by each site's institutional review board or independent research ethics committee. The authors confirm independence from any of the funder of this research; the content of the article has not been influenced by any of the funder.

2.4. Statistical analysis

Descriptive statistics were tabulated separately for L238Q and comparison Hurler-Scheie groups. These included the mean and standard deviation for continuous variables and frequency with percentages for categorical variables. Linear regression based on generalized estimating equations was used to estimate the first-order trend in neurocognition and behavioral scores over time separately for each group and compared to each other. Confidence intervals and *P*-values were based on robust variance estimation to account for the correlated nature of longitudinal measurements. The Holm procedure was used for statement on multiple comparisons [15]. All analyses were conducted using R v3.2.4 [16].

3. Results

1. Mutation and medical data are presented in Table 1.

Table 2 summarizes the demographic, PSS, neurocognitive and behavioral/psychological data. Higher physical symptom scores reflect greater disease burden. IQ, BVMT, TOVA, VABS scores are reported as standard scores with a mean of 100 and standard deviation of 15; higher scores reflect better abilities. BASC scores are reported as T scores with a mean of 50 and standard deviation of 10; higher scores reflect increased psychological problems.

Table 2
Patient descriptive: values are mean (SD) or N (%) where indicated. PSS and below are calculated from within individual average across visits.

Covariates	L238Q group	Comparison group
	N = 6	N = 6
Male	3 (50%)	5 (83.3%)
2 Visits	0 (0.0%)	1 (16.7%)
3 Visits	3 (50.0%)	2 (33.3%)
4 Visits	3 (50.0%)	3 (50.0%)
Age (years)	17.6 (1.54)	19.2 (4.72)
Age at 1st treatment (years)	10.6	10.6
Number of years on treatment	8.3 (1.3)	9.9 (1.2)
Physical Symptom Score (PSS)	11.2 (0.9)	10.5 (1.8)
Number of surgeries	6.0 (1.4)	9.4 (3.2)
Neuropsychological measures: standard scores 100 ± 15		
WASI IQ	75.0 (5.06)	99.4 (13.2)
BVMT	63.2 (17.4)	82.5 (15.7)
TOVA-d prime	80.1 (11.8)	98.4 (16.2)
TOVA-reaction time	92.3 (20.6)	104 (16.0)
TOVA-variability	77.2 (18.5)	94.6 (24.8)
VABS-composite	69.9 (3.12)	88.7 (14.0)
VABS-daily living skills	68.2 (4.27)	84.9 (13.7)
BASC: T scores 50 ± 10		
Parent report (PR); Anxiety	53.1 (8.3)	48.5 (7.5)[2a]
Parent report (PR); depression	57.9 (12.4)	45.4 (6.6) [2]
Parent report (PR); withdrawal	63.3 (12.3)	50.2 (11.5) [2]
Parent report; atypicality	57.0 (12.1)	42.1 (3.0) [2]
Self-report (SR); anxiety	53.5 (10.3)	49.6 (9.8)
Self-report (SR); depression	58.5 (14.3)	45.8 (7.0)
Self; atypicality	68.2 (4.27)	84.9 (13.7) [1]

[a] Superscripts indicate number of cases with missing data.

There were three males in the L238Q group and five males in the comparison group. Age of first assessment was slightly earlier in L238Q group. No difference was found in age at which ERT treatment was started between the two groups, but the comparison group had a longer history of ERT treatment. The PSS average was similar between the two groups, although more surgeries occurred in the comparison group as the two oldest patients were included in that group, reflecting the increase in surgeries with age.

2. Neuropsychological and behavioral results indicated continued lower functioning in the L238Q group relative to the comparison group as seen in Table 2. However, comparing slopes across time between the two groups suggested relative stability in functioning with the exception of a few variables described below. Table 3 describes the slopes for the two groups and the comparisons between them.

3. MPS-specific physical symptom score (PSS) increased with age in both groups indicating progressive somatic burden of diseases (See Fig. 2). The difference of the marginal slopes between the two groups is not statistically significant (See Table 3).

4. FSIQ scores increased 0.45 point in the L238Q group and 1.68 point in the comparison group, on average, per year. The difference of the marginal slopes between the two groups is not statistically significant (0.295) (See Table 3); although the mean FSIQ was below the average range in the L238Q group and in the average range in the comparison group (See Table 2, Fig. 3).

5. The visual spatial memory score was almost 2 SD below average in the L238Q group and just below average for the comparison group (See Table 2, Fig. 4). The difference of the marginal slopes across individuals per year between the two groups was statistically significant (0.05) (See Table 3).

6. Average attention scores were within the lower average range in TOVA-d prime (See Table 2, Fig. 5) and almost 1 SD below the average range for TOVA- variability in L238Q group (See Table 2, Fig. 6). For the comparison group all these scores in TOVA were within the average range (See Table 2). The differences of the marginal slopes between the two groups were not statistically significant (See Table 3).

7. Adaptive functioning scores did not change over time but the range was almost 1.5 SD below average in the L238Q group and average in the comparison group (See Table 2, Fig. 7). While both groups declined in adaptive skills over time, the marginal slopes between the two groups was not statistically significant (See Table 3).

8. On the behavioral measures, average scores on PR-anxiety increased in severity (See Fig. 8) but scores on PR-depression (See Fig. 9), PR-withdrawal, and PR-atypicality (e.g. stares blankly, says things that do not make sense, seems unware of those around him/her) were improved by parent-report (PR) over time. The differences of the marginal slopes of PR-anxiety, PR-depression, PR-withdrawal between the two groups were not statistically significant (See Table 3). The difference of the marginal slopes between the two groups for PR-atypicality was statistically significant ($p < .001$) with both groups improving. The statistical significance of each of the parent and self-report on atypicality BASC domain is retained after accounting for multiple comparisons.

9. Average scores on SR-depression worsened in the L238Q group and were still below average (See Fig. 11). Scores on SR-anxiety

Table 3
Marginal slope across individuals per year in age.

Score	N	L238Q Group	Comparison Group	Slope L238Q vs	P-value
		Slope per year (95%CI)	Slope per year (95% CI)	Comparison (95% CI)	
PSS	12	0.16 (−0.09, 0.40)	0.25 (0.04, 0.46)	−0.09 (−0.42, 0.23)	0.566
IQ	12	0.45 (−1.15, 2.05)	1.68 (0.03, 3.33)	−1.23 (−3.53, 1.07)	0.295
BVMT	12	−5.32 (−9.03, −1.62)	−1.08 (−3.15, 0.98)	−4.24 (−8.48, 0.00)	0.050
TOVA: d prime	12	−1.47 (−4.45, 1.51)	0.48 (−0.67, 1.62)	−1.95 (−5.14, 1.25)	0.232
TOVA: reaction time	12	−3.99 (−9.70, 1.72)	−2.43 (−4.12, −0.74)	−1.56 (−7.52, 4.40)	0.608
TOVA: variability	12	−4.13 (−7.45, −0.82)	−2.76 (−4.77, −0.74)	−1.38 (−5.25, 2.50)	0.487
Vineland: composite	12	0.00 (−1.28, 1.28)	−0.34 (−2.92, 2.24)	0.34 (−2.54, 3.22)	0.818
Vineland: DLS	12	−0.45 (−2.13, 1.22)	−1.04 (−3.53, 1.46)	0.58 (−2.42, 3.59)	0.704
BASC PR: anxiety	10	1.59 (−0.73, 3.91)	0.22 (−1.92, 2.36)	1.37 (−1.79, 4.52)	0.395
BASC PR: depression	10	−1.77 (−6.16, 2.62)	−0.69 (−2.33, 0.95)	−1.08 (−5.77, 3.61)	0.652
BASC PR: atypicality	10	−4.69 (−7.24, −2.13)	−0.29 (−0.80, 0.23)	−4.40 (−7.01, −1.80)	< 0.001
BASC PR: withdrawal	10	−3.63 (−5.18, −2.08)	−1.83 (−4.15, 0.48)	−1.79 (−4.58, 0.99)	0.207
BASC SR: anxiety	12	1.11 (−2.37, 4.58)	1.42 (0.32, 2.53)	−0.32 (−3.97, 3.33)	0.864
BASC SR: depression	12	−1.74 (−7.82, 4.33)	1.11 (0.35, 1.87)	−2.86 (−8.98, 3.27)	0.361
BASC SR: atypicality	10	−5.03 (−6.19, −3.87)	−0.92 (−3.05, 1.21)	−4.10 (−6.53, −1.68)	< 0.001

worsened for both groups, but especially the L238Q group (See Fig. 10). SR-atypicality scores were improved by self-report (SR) over time for both groups. The difference of the marginal slopes between the two groups for SR-atypicality is statistically significant ($p < .001$) with more improvement in the comparison group (See Table 3).

10. All tools predicted L238Q to be damaging or pathogenic with the associated index shown in Table 4.

L238Q leads to conversion of leucine into glutamine at position 238. As shown in Fig. 1, the wildtype residue leucine is smaller and buried in the core of the protein; thereby the mutant residue glutamine probably will not fit. Further, this mutation will cause loss of hydrophobic interactions in the core of the protein. In addition, L238 is located in the TIM barrel domain that is important for catalytic activity and in contact with residues in another domain. The interaction between these domains could be disturbed by the mutation, which may affect the function of IDUA enzyme.

11. The 3D structure of native IDUA protein was retrieved from the RCSB database (PDB ID: 3w81). The mutant model of L238Q was built through the online server of SWISS-MODEL (https://swissmodel.expasy.org/interactive) using the native structure as the template. The Swiss-PDB Viewer, a free molecular graphics program was used for viewing the modeled structures. In addition, Project Have Our Protein Explained (HOPE; http://www.cmbi.ru.nl/hope/home) was used to analyze the structural impact of L238Q on the whole IDUA protein (Fig. 11).

4. Discussion

No biochemical or clinical guidelines have been established that reliably distinguish among the three clinical descriptions; severe Hurler syndrome, attenuated Scheie syndrome, or the intermediate Hurler-Scheie syndrome in mucopolysaccharidosis type I (MPS I). Hurler-Scheie and Scheie syndrome, are a spectrum of disorders without clearly defined diagnostic criterion [17,18]. Genotype-phenotype associations for missense mutations are not clearly defined. Missense mutations have widely variable presentations in individuals ranging from mild to severe [19]. Missense mutations can prevent any functional enzyme activity or can allow for some functional enzyme to be produced [19,20].

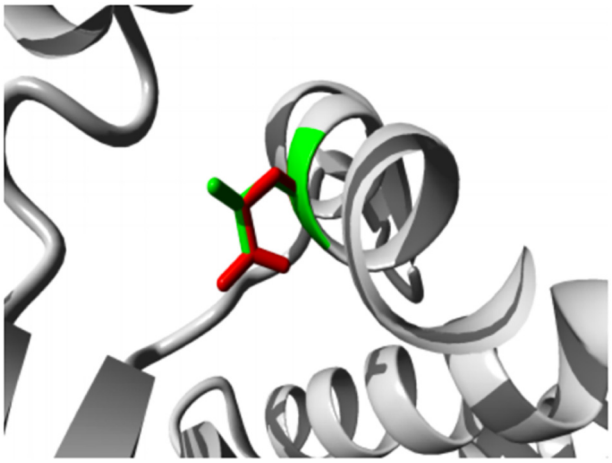

Fig. 1. Close-up view of superimposed structure of native and mutant residues of L238Q. The main protein core is shown in white color while the wild type and mutated residues are shown in red and green color, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The missense mutation, L238Q, is associated with significant cognitive impairment and psychological impacts. L238Q mutation, when paired with nonsense, deletion or splice site mutation is more severe than most other patients with Hurler-Scheie syndrome [5]. Therefore, we examined the structure of the mutation as well as used bioinformatics tools to examine the severity of the mutation. The structural analysis suggests the L238Q mutation may have disturbing influences on the function of the IDUA enzyme. Further analysis using bioinformatics tools suggests that all tools used (SIFT, PolyPhen, I-Mutant, PROVEAN, PANTHER, SNPs&GO and PHD-SNP) predicted the damaging effect of L238Q to the functional enzyme [7,8].

Table 4
Prediction of L238Q by multiple bioinformatics tools.

	SIFT	PolyPhen	I-MUTANT	PROVEN	PANTHAR	SNPs&GO	PHD-SNP
Prediction	Damaging	Probably damaging	Large decrease	Deleterious	Disease	Disease	Disease
Associated Index	0.002	1	−2.05	−5.33	0.553	0.513	0.777

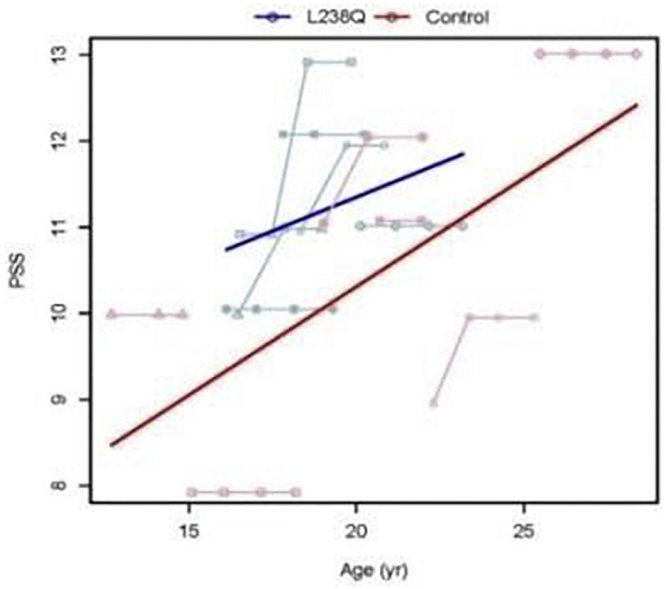

Fig. 2. PSS of L238Q vs comparison.

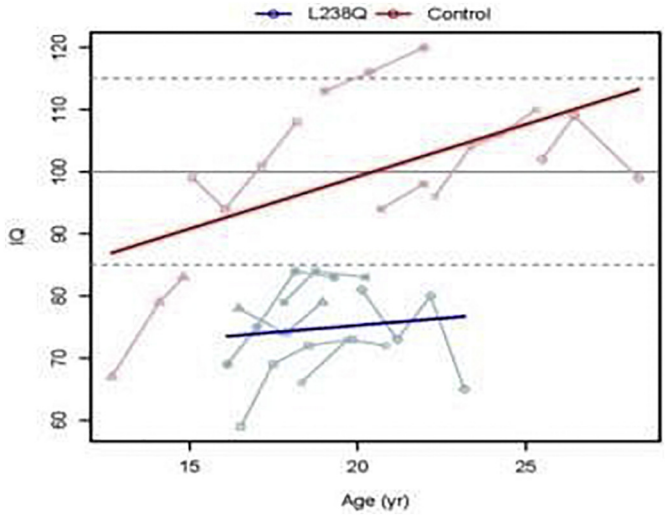

Fig. 3. IQ of L238Q vs comparison.

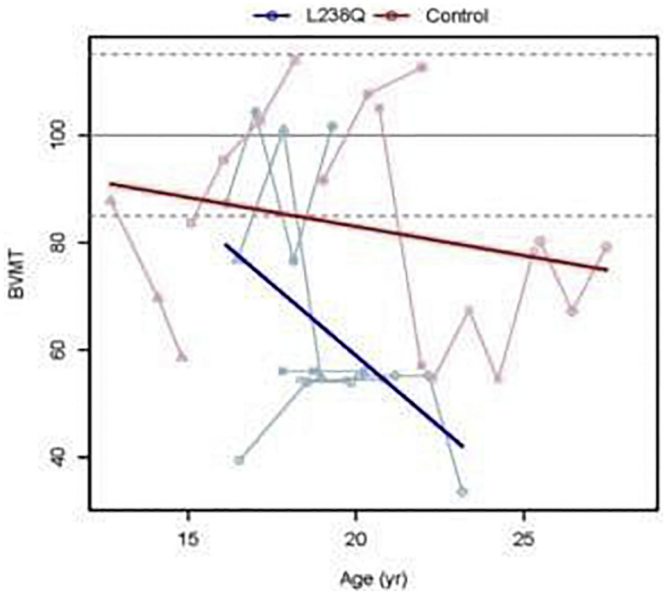

Fig. 4. BVMT of L238Q vs Comparison.

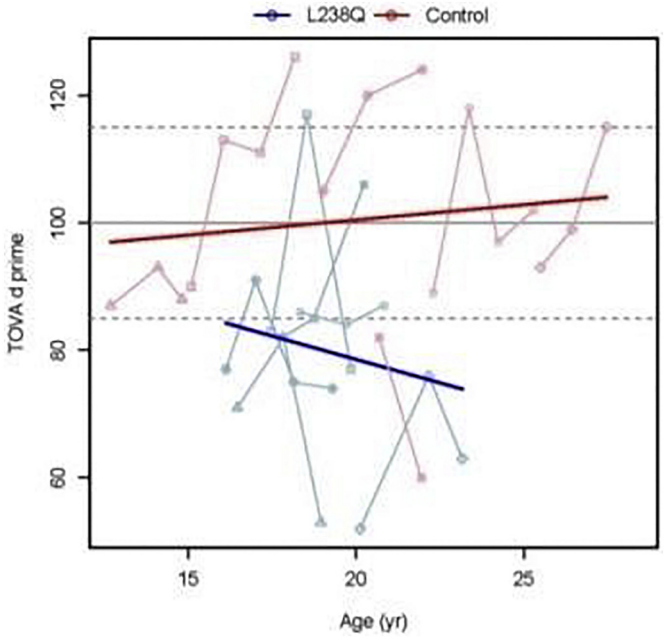

Fig. 5. TOVA d prime of L238Q vs Comparison.

This study is the first to track the longitudinal neurocognitive and neurobehavioral functioning of patients with L238Q mutations paired with a severe mutation. Given previous cross sectional findings that these patients have more impairment in cognition, memory, attention, and adaptive behavior than patients with Hurler-Scheie with other mutation types, it was crucial to clarify whether the pairing of L238Q mutations with a severe mutation could be associated with any worsening across time. We followed these patients over a 2 to 4 year period of time and the same differences were found in level of impairment between the two groups as the cross sectional study. IQ scores stayed the same in the L238Q group but slightly improved in the comparison group although not statistically significant. Stability in IQ is consistent with previous cross-sectional findings in patients with Hurler-Scheie [21].

There were a few cognitive areas that did suggest some worsening, even in the face of stable IQ scores. Visual spatial memory worsened in both groups, with a marked statistically significant decrease in the L238Q group. Similarly, measures of processing speed (reaction time and variability) slightly worsened in both groups, but did not differ between groups. The d′ prime score (a measure of accuracy of response), while not statistically significant, showed a slightly worsening pattern in the L238Q patients with a slightly improving pattern in the comparison group. Poor and worsening performance on these tasks may be associated with white matter abnormalities in these patients [22,23]. Neurocognitive outcomes are functional marker that can be used to identify the disease severity in Hurler syndrome [24,25] and are now being used as endpoints for clinical trials of new treatments [26].

Adaptive functioning, while showing impairment in the L238Q group and normal range function in the comparison group appeared to show a slight decline over time, especially in the comparison group. The two groups were not different in their slopes. However, the finding of increasing somatic involvement as measured by the PSS over time is very likely contributing to decreasing ability to carry out activities of daily living resulting in decreased scores on the measure of adaptive functioning. Also physical disability can lead to psychological impacts

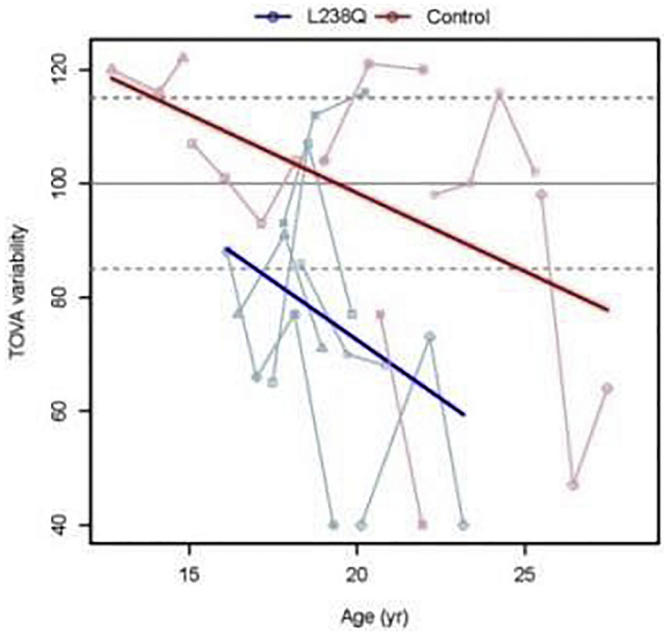

Fig. 6. TOVA-Variability of L238Q vs Comparison.

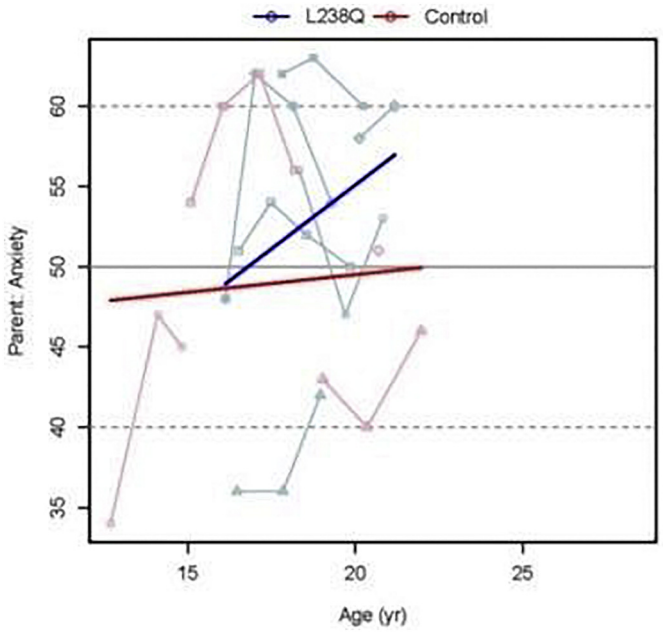

Fig. 8. Parent Anxiety of L238Q vs Comparison.

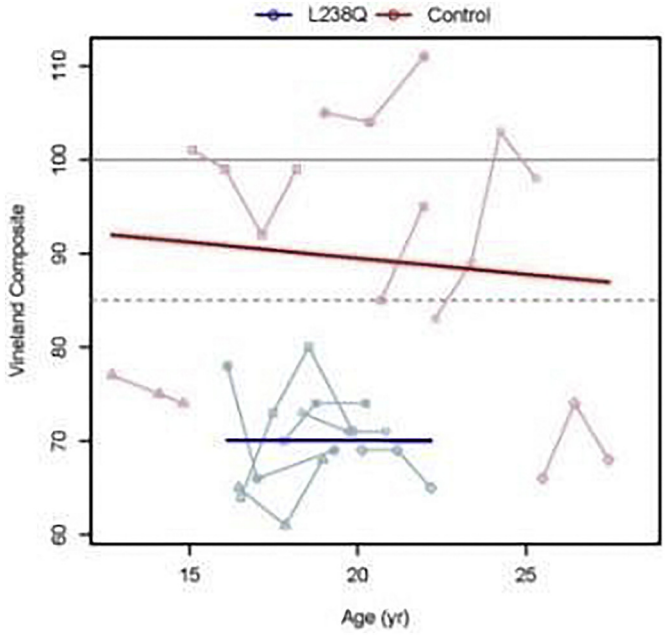

Fig. 7. Vineland Composite of L238Q vs Comparison.

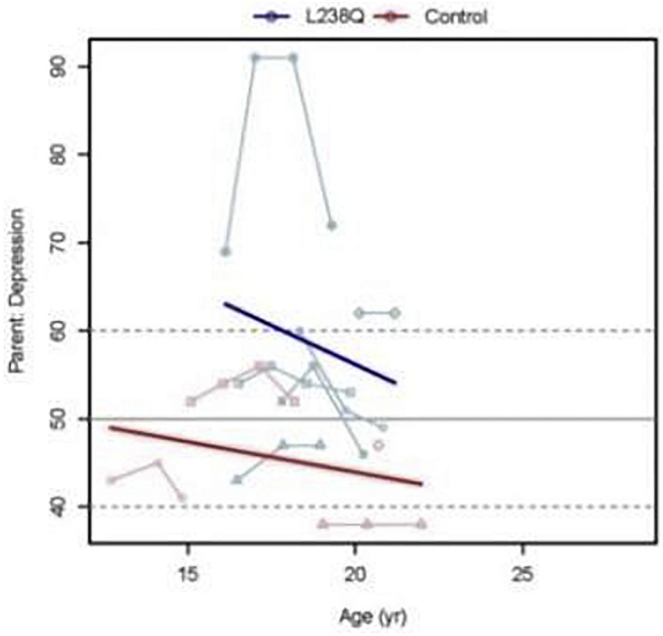

Fig. 9. Parent Depression of L238Q vs Comparison.

and eventually decrease motivation to perform in school or daily living skills.

From the medical history, three patients had shunted hydrocephalus in the L238Q group compared with one patient with hydrocephalus without shunt placement in the comparison group. Four patients had cord compressions in the L238Q group compared with two in the comparison group. All of the L238Q patients had at least one episode of depression, psychosis, or autism and they all were on psychotropic medications and all had sleep problems. None of the comparison subjects had such episodes except one, who had a diagnosis of depression after his 3rd visit and started anti-depressant medication. On ratings of behavior and psychological status, parents reported improvement in the L238Q patients in depression, level of withdrawal and atypical behaviors, but an increase in anxiety. Atypical behaviors improved significantly in the L238Q group. Parents of the comparison group reported stability in these behaviors, all within the normal range, with a slight improvement in the withdrawal score.

Self-report is somewhat different with increasing anxiety and decreasing atypical behaviors in both groups, perhaps reflecting the improving awareness of the patients over time. The presence of atypical behaviors was statistically significantly improved in the L238Q group compared to the comparison group (See Table 3). A difference is seen in the self-report of depression with the L238Q group reporting slight improvement and the comparison group slight worsening (not statistically different). It should be noted that the scores on these measures of behavior are very variable, contributing to the lack of statistical significance. However, that variability may reflect the actual fluctuation in behavioral or psychological status in these children who may suffer rejection and other stresses, in addition to direct disease effects. It is possible that the increased incidence of spinal cord compression and

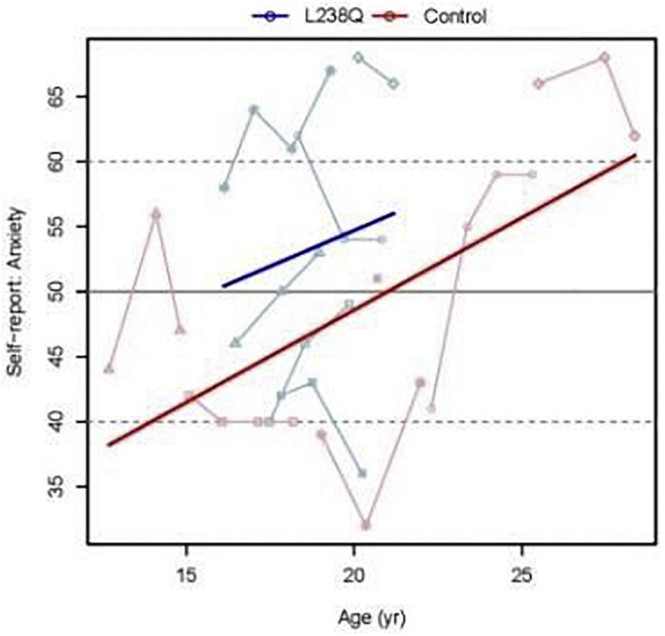

Fig. 10. Self-report of Anxiety of L238Q vs Comparison.

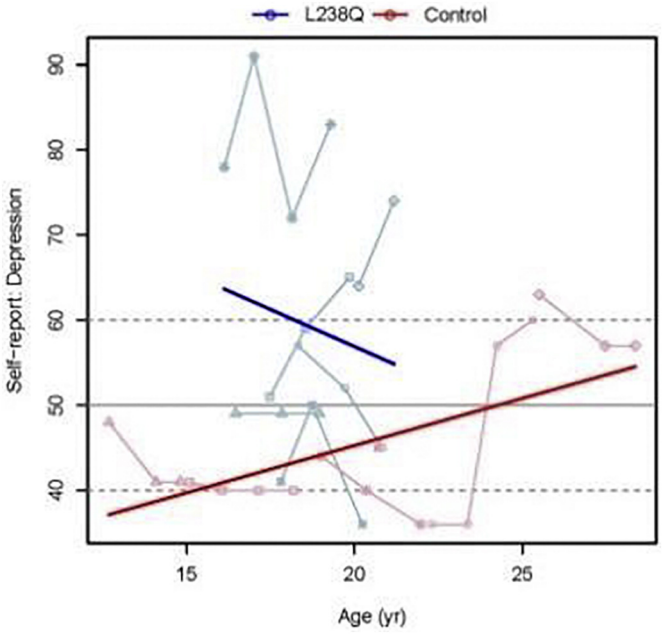

Fig. 11. Self-Report Depression of L238Q vs Comparison.

hydrocephalus may have had an impact on the behavioral status of these patients. Previous research has found hydrocephalus also common in MPS II and MPS VI but they do not present with significant neurocognitive or psychiatric manifestations [27].

With regard to limitations of this study, two of the patients in the comparison group did not have equivalent mutations (had two missense mutations). However, their data does not indicate that these two patients had different PSS, cognitive, or behavioral scores than those with other types of mutations. Finding comparable mutations is challenging in such a rare disease. Another limitation is the lack of knowledge about the polymorphism variants in IDUA gene which may have played a role in their genotype-phenotype correlation. It is mentionable that four patients from the L238Q group and two patients from the control group were eligible for and participated in a Food and Drug Administration Investigational New Drug (IND) approved clinical trial of intrathecal (IT) enzyme replacement therapy.

5. Conclusions

It can be concluded that Hurler-Scheie patients heterozygous for the L238Q mutation together with a severe mutation appear to have a greater significant central nervous system impact compared to the comparison group. The L238Q mutation is associated with a significant impact on FSIQ, memory, attention, adaptive functioning, and behavioral/psychological measurements with below average functioning. IQ appears stable but visual spatial memory and attention/processing abilities appear to decline relative to normal values in both the L238Q and in the comparison group. Somatic symptoms and adaptive functioning worsen in both groups. Depression, withdrawal, and atypicality improve, but anxiety is worsen as these patients grow older. Because the L238Q patients seem to be more severely impacted neurocognitively and vulnerable to neuropsychiatric abnormalities than other Hurler-Scheie syndrome patients, they will need even more attention to life skills, educational interventions, emotional/social supports, and efforts at improving the quality of life. Methods of early treatment need to be considered that will impact the brain in MPS I patients heterozygous for the L238Q mutation.

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