Impact of Newborn Screening for Early Identification and Management of MPS I in Siblings with W402X/L238Q Genotype

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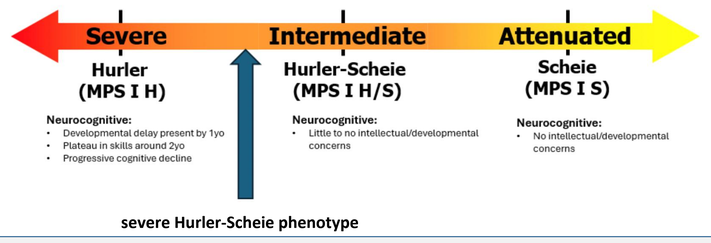
OVERVIEW

- Biallelic mutations in *IDUA* result in Mucopolysaccharidosis I (MPS I) which presents along a spectrum of clinical severity:
  - Hurler Syndrome (severe neuronopathic phenotype)
  - Hurler-Scheie Syndrome (intermediate phenotype)
  - Scheie Syndrome (attenuated phenotype without neurological involvement)
- The compound heterozygous genotype, W402X/L238Q, is predicted to cause neuronopathic MPS I, previously characterized as “severe Hurler-Scheie" phenotype with unique neuropsychiatric involvement[1]



NEWBORN SCREENING FOR MPS I

Newborn screening (NBS) is a public health initiative that is conducted shortly after birth, testing newborns for serious and treatable medical conditions that can affect their long-term health and survival.

The recommended uniform screening panel (RUSP) is a list of disorders recommended for screening. Most states screen for most disorders recommended, but ultimately, each state decides which disorders they screen for, with some states screening for additional non-RUSP disorders.

MPS I was added to the Recommended Uniform Screening Panel in the United States in February 2016

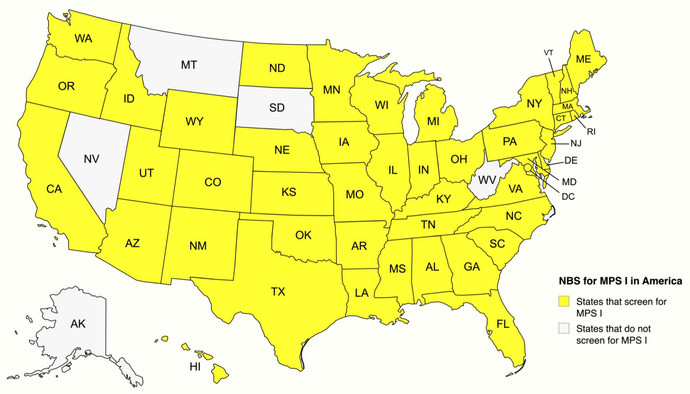


Image 1. Yellow areas represent the states in the United States that currently screen for MPS I

https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp

CASE PRESENTATION

Case #1 (newborn proband)

Age at diagnosis: Newborn

NBS results: α-iduronidase enzyme 1.44% daily mean, 2nd-tier MPS I marker positive (Revvity assay ratio = 22.2, normal range <= 3.27)

Follow up: Echo and abdominal ultrasound normal, started on enzyme replacement therapy 9-weeks-old

Current Status: No developmental concerns, exploring CNS-targeted treatment options

Case #2 (older sibling)

Age at diagnosis: 4y10m

Medical History: Hernia s/p repair, joint restriction, protuberant abdomen

Diagnostic evaluation: α-iduronidase enzyme (0.02 nmol/mL), urine GAG (results below)

Follow up: baseline assessments with hepatosplenomegaly and mitral and aortic valve thickening, started on enzyme replacement therapy at 4y11m

Current Status: No developmental concerns, exploring CNS-targeted treatment options

Figure 1. Comparison of siblings total glycosaminoglycans, dermatan sulfate and heparan sulfate levels

	Newborn proband	4 year old sibling
TOTAL GAGS	2x upper normal	4x upper normal
DERMATAN SULFATE	6x upper normal	11x upper normal
HEPARAN SULFATE	53x upper normal	53x upper normal

Figure 2. Four-year-old sibling Vineland Third Edition Scores and Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV) Scores

ADAPTIVE BEHAVIOR COMPOSITE STANDARD SCORE:	89 (23rd percentile)
Vineland-3 Domains	
Communication	94 (34th percentile)
Daily Living Skills	95 (37th percentile)
Socialization	88 (21st percentile)
Motor Skills	89 (23rd percentile)

FULL SCALE IQ	89 (23rd percentile)
WPPSI-IV Domains	
Verbal comprehension	99 (47th percentile)
Visual Spatial	89 (23rd percentile)
Fluid Reasoning	85 (16th percentile)

L238Q Variant

When the L238Q (c.712T>A) variant is seen in combination with a null variant (nonsense, deletion, splice site variant, etc) it is predicted to result in a severe phenotype as compared to typical Hurler-Scheie presentation.

Longitudinal studies demonstrated that individuals with the L238Q variant had lower IQ and more severe deficits in attention, adaptive functioning and behavior when compared to their non-L238Q Hurler-Scheie counterparts.[1]

Structural and functional modeling studies suggest the L238Q variant causes a significant reduction in catalytic activity.[3]

Figure 4. Ahmed et al longitudinal study of 6 individuals with L238Q variant

	L238Q Mutation Cohort (n=6)	Hurler-Scheie (no L238Q) Comparator Cohort (n=6)
Psychiatric History	6/6	0/6
Sleep Problems	6/6	0/6
Shunted or Unshunted Hydrocephalus	4/6 hydrocephalus 3/6 shunted	1/6 hydrocephalus 0/6 shunted
Cervical Cord Compression	4/6	2/6

Figure 5: Two additional individuals seen at UNC Muenzer MPS Center with W402X/L238Q genotype

UNC Patient #1
Early developmental delays - walked at 2yo, first words at 3yo Diagnosed with autism at age 5 MPS I diagnosis at 32 years old Pediatric genetics was consulted and notes course facial features, stiff gait, some contractures of hands Urine GAGs were obtained showing elevated dermatin and heparin sulfate Passed away at 36 years old

UNC Patient #2
MPS I diagnosis at age 10 years old Reduced shoulder and joint mobility noted in childhood Cognitive abilities in the low average range, IQ 87 Graduated college but started having outbursts of aggression towards professors In 30s, lives at home with parents now as patient struggles with regulation and understanding

CONCLUSION

- Newborn screening allowed for early identification and treatment of a newborn with MPS I genotype predictive of severe intermediate phenotype
- Identification of the newborn allowed for rapid testing of asymptomatic older siblings with diagnosis and rapid referral to treatment for affected 4-year-old sibling with subclinical evidence of disease
- Challenges highlighted by this case include:
  - Imperfect genotype-phenotype prediction leading to uncertainty regarding treatment options
  - Uncertainty around the timing of intervention for later-onset phenotypes
  - Uncertainty of benefit vs. risk profile of CNS-targeted treatments such as HSCT for intermediate phenotypes

SIGNIFICANCE

The sibling pair in this study represent a unique opportunity to understand the early natural history of the W402X/L238Q genotype. While HSCT has demonstrated the ability to stabilize neurological disease in severe Hurler syndrome, it remains unknown whether early transplant could mitigate the neuropsychiatric phenotype associated with this genotype. To our knowledge, most individuals have been diagnosed at a later age and after the onset of neurological symptoms.

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