The Natural History of Facial Features Observed in Sanfilippo Syndrome (MPSIIIB) Using a Next Generation Phenotyping Tool

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INTRODUCTION

Sanfilippo Syndrome (MPSIII) is the most prevalent of the MPS (mucopolysaccharidosis) disorders, resulting from deficiency of 1 of 4 enzymes in the degradative pathway of heparan sulfate. It leads to progressive neurodegeneration and systemic disease. Diagnostic delay is common due to less obvious physical features, particularly early in its course. Classic facial features include progressive coarsening facies, prominent eyebrows, full lips, and frontal bossing.

Face2Gene is a suite of next-generation phenotyping applications that uses facial Analysis, deep Learning and artificial intelligence to highlight possible syndrome matches from a 2D photograph. Our previous work leveraged the patient community's engagement in order to collect disease-specific images to establish an accurate facial gestalt of MPSIIIB for use in the Face2Gene tool.

OBJECTIVES

- Assess Face2Gene technology's capability to differentiate the unique facial phenotype of MPSIIIB across different age groups.
- Establish a visual composite facial phenotype natural history of MPSIIIB.
- Assess the tool's ability to distinguish patient images from other syndromes and normal controls at a time when clinical symptoms begin to appear (1-3yo age range).

METHODS

- Collaboration between Cure Sanfilippo Foundation, Jonah's Just Begun and FDNA was established
- Campaign targeted MPS III patient families through social media, email, webinar, conferences, personal communications
- Photographs were uploaded via HIPAA-compliant online portal
- Statistical analyses of the receiver operating characteristic (ROC) curve was performed to calculate the area under curve (AUC) to determine classification accuracy
- Multiple Separate Binary Analyses performed: MPS IIIB Images divided into different age groups (see Key) vs. each subsequently higher age group; Age Group 3 (n=40) vs. Other Syndromes (n=40) and vs. Unaffected Normal Controls (n=40).

KEY

- Age Group = AG
- AG 2 = 1 month-1 year
- AG 3 = 1-3 years
- AG 4 = 3-6 years
- AG 5 = 6-12 years

RESULTS

- Composite images of the different Age Groups participating in this study are represented in Fig.1.
- Comparisons of advancing MPSIIIB Age Groups revealed significant results for 2 age group comparisons: <1yo vs. 1-3yo yielded AUC of 0.86 (p=0.005); 1-3yo vs. 3-6yo yielded AUC of 0.817 (p=0.009); the 3-6yo vs. 6-12yo comparison yielded AUC of 0.68 (p=0.211). (Fig. 2)
- Composite images of MPSIIIB Age Group 3 (1-3yo), Other Syndromes Controls and Unaffected Controls are seen in Fig. 3.
- Confusion matrix of MSPIIIB Age Group 3 vs other syndromes and unaffected controls yielded high accuracy of placing images in the correct category.

Figure 2. *Detection score and ROC curves obtained for the best performing split in 3 MPSIIIB patient age groups. When the AUC is 1 it expresses "perfect" separation between the age groups compared.*

Figure 1. *Composite images of MPSIIIB patient photos grouped by age.*

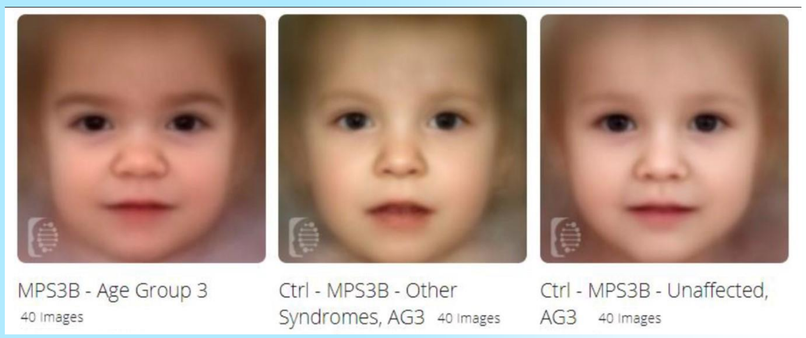

Figure 3. *Composite images of MPSIIIB patient photos grouped by age.*

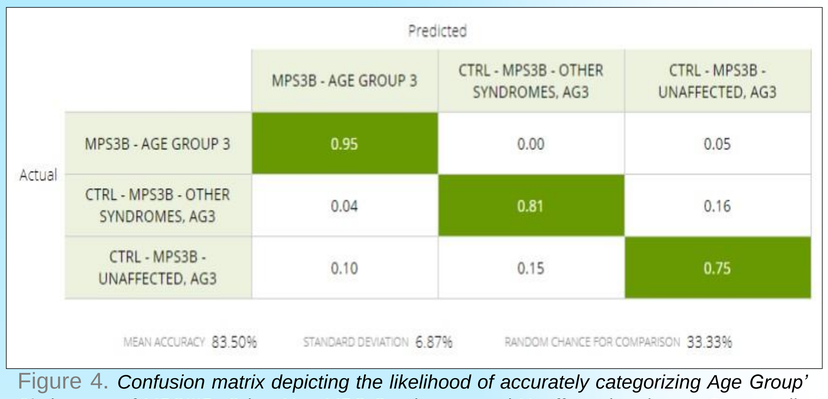

Figure 4. *Confusion matrix depicting the likelihood of accurately categorizing Age Group' 3's images of MPSIIIB, Other Non-MPS Syndromes and Unaffected patients . Green cells show the true positive values, which compared to the random chance of 33.3%, indicate a high classification ability.*

CONCLUSIONS

Collaborative efforts between FDNA and Patient Groups have enabled the creation of a facial phenotype natural history for MPSIIIB. Most distinct changes in facies occur from infancy through age 3 years. Phenotyping software detected differences between ages 3-6 years vs. 6-12 years, but was not statistically significant.

Age Group 3 (1-3 years) was examined more closely due to its clinical relevance in relation to the appearance of early symptoms. MPSIIIB patient photos in this age range were reliably distinguished from other non-MPS syndromes and normal controls. This underscores that the tool may be quite useful in helping to identify MPSIIIB patients at an early age.

In this study, we sought to better understand and define the facial phenotype as patients progress through the course of MPSIIIB. To date, characterization of MPSIII facies has been conveyed by subjective observation and dysmorphology. This is the first effort, to our knowledge, to use objective, artificial intelligence facial phenotyping in MPSIII. Future work could expand on the diversity of included images and may explore if emerging treatments alter the facial natural history of this disease.

ACKNOWLEDGEMENTS

We are grateful to all of the patient families for submitting images of their children for this important research.

Jonah's Just Begun
www.jonahsjustbegun.org

CURE SANFILIPPO FOUNDATION