AI-DRIVEN DELINEATION OF DISTINCT PHENOTYPES ASSOCIATED WITH N-TERMINAL TRUNCATIONS OF THE *MN1* GENE – BEYOND A NEW SYNDROME DISCOVERY FROM HONG KONG

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Background

MN1 C-Terminal Truncation (MCTT) syndrome is a rare autosomal dominant disorder characterized by intellectual disability, mid-face hypoplasia, severe expressive speech delay, and an atypical form of rhombencephalosynapsis (Mak et al. Brain 2020 and GeneReviews®). The *MN1* gene is comprised of only two exons. Individuals with distinct features of MCTT harbour truncating variants at the C-terminal (within exon 2 or the last 55bp of exon 1), which are predicted to escape nonsense-mediated decay (NMD). Individuals affected by N-terminal (MNTT) truncations (predicted to induce NMD) have milder developmental phenotypes than MCTT patients.

Methods

Since our discovery of the syndrome, an expanded clinical case series was recruited to review 45 subjects (mean age 12.9, range 2-44) from North America, Europe and Asia. We performed deep phenotyping on patients affected by MNTT (n=13) and MCTT (n=32) mutations both clinically and using AI-based facial recognition software GestaltMatcher (Hsieh et al.). GestaltMatcher trains deep convolutional neural networks on 22,619 frontal images with 299 different rare disorders to learn the facial features, and it further converts facial images into feature vectors to form a Clinical Face Phenotype Space. The facial syndromic similarities among the patients are quantified by cosine distance in this space.

Results

Delineation of phenotype both clinically and by GestaltMatcher identifies two distinct groups when comparing MNTT with MCTT. Clinically, patients with MNTT have unique facial features, a disproportionate abundance of cleft palate (33% vs 7%) and conductive hearing loss (82% vs 35%). Compared to the MCTT group where 33% of individuals with MCTT rely on non-verbal communication only, and the remaining expressing first words at the mean age of 4.03 (range 2-6.75 years). Speech delay is less severe in the MNTT group with mean age first words at 2 (range 1.3-3 years). The distinction of MNTT and MCTT is supported by GestaltMatcher where clustering of MNTT and MCTT facial gestalt is observed and delineates from other syndromes in an unsupervised manner. Using this approach, GestaltMatcher also helps identify atypical cases where the phenotype does not follow the predicted rule of NMD.

Conclusions

Truncating mutations can have a region-specific effect on phenotype. Supported by AI-based approaches, MNTT and MCTT are two distinct facially recognisable syndromes in the same gene and are distinct from other known syndromes.

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