Hong Kong College of Pathologists 18th Trainee Presentation

Rewriting the future of newborns with a newly treatable rare disease

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Background

Allan-Herndon-Dudley syndrome (MCT8 deficiency) is an X-linked recessive condition caused by pathogenic variants in the *SLC16A2* gene that encodes the monocarboxylate transporter 8, a crucial thyroid hormone transporter in the brain. It is featured by global developmental delay and neuromotor deficits onset in infancy, accompanied by characteristic abnormal thyroid function with high T3, low reverse T3, low-normal T4 and usually normal TSH.

Diagnosis is by genetic confirmation of a hemizygous pathogenic variant in *SLC16A2*. Current newborn screening would easily miss a prompt to diagnosis due to a normal TSH.
In 2019, Remerand et al. proposed a T3:T4 ratio >0.75 to facilitate diagnosis[1]. In the same year, a new treatment "TRIAC" was proven effective in improving clinical phenotypes, especially when started before the age of 4[2].

Patient 1

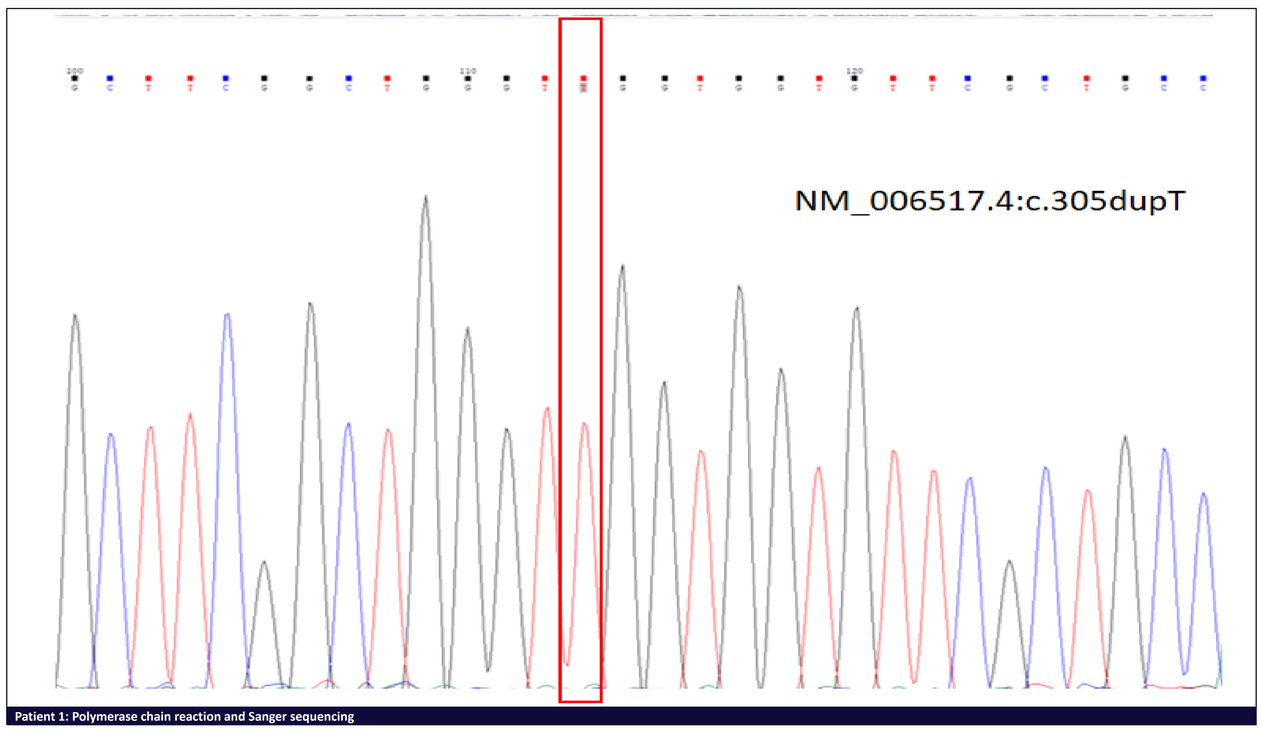
A Chinese boy, born to non-consanguineous marriage, presenting with global developmental delay, head lag and dystonia at 6 months of life. TSH was normal. He was deceased at age 18, genetic variant identified by PCR and Sanger sequencing post-mortem.

- Hemizygous NM_006517.4:c.305dupT;NP_006508.2:p.(Val103fs)
- TSH 0.51 mIU/L (RI 0.3-4.0 mIU/L)
- Free T4 12.3 pmol/L (RI 13.9-22.1 pmol/L)
- Free T3, Reverse T3 not done

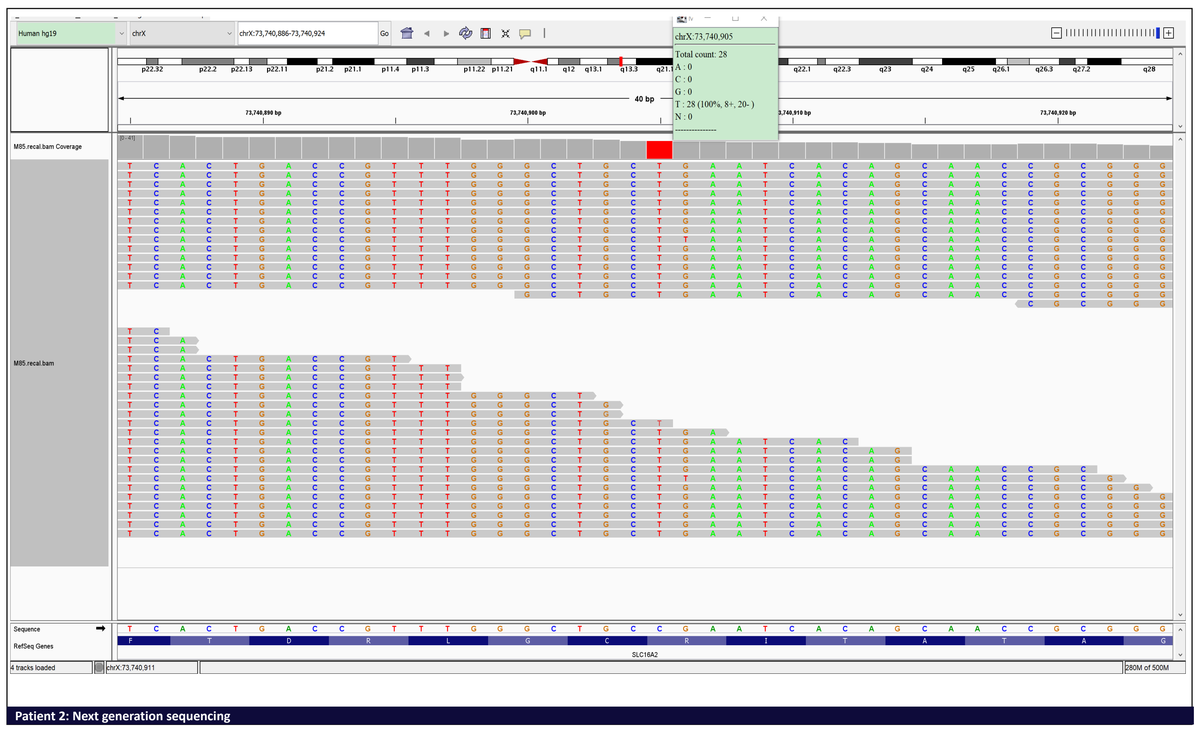
Patient 2

A Chinese boy, born to non-consanguineous marriage, presenting with global developmental delay and epilepsy in infancy. There was strong family history of intellectual disability (mother, 1 sister, 2 brothers). He was deceased at age 17, genetic variant identified by whole exome sequencing post-mortem.

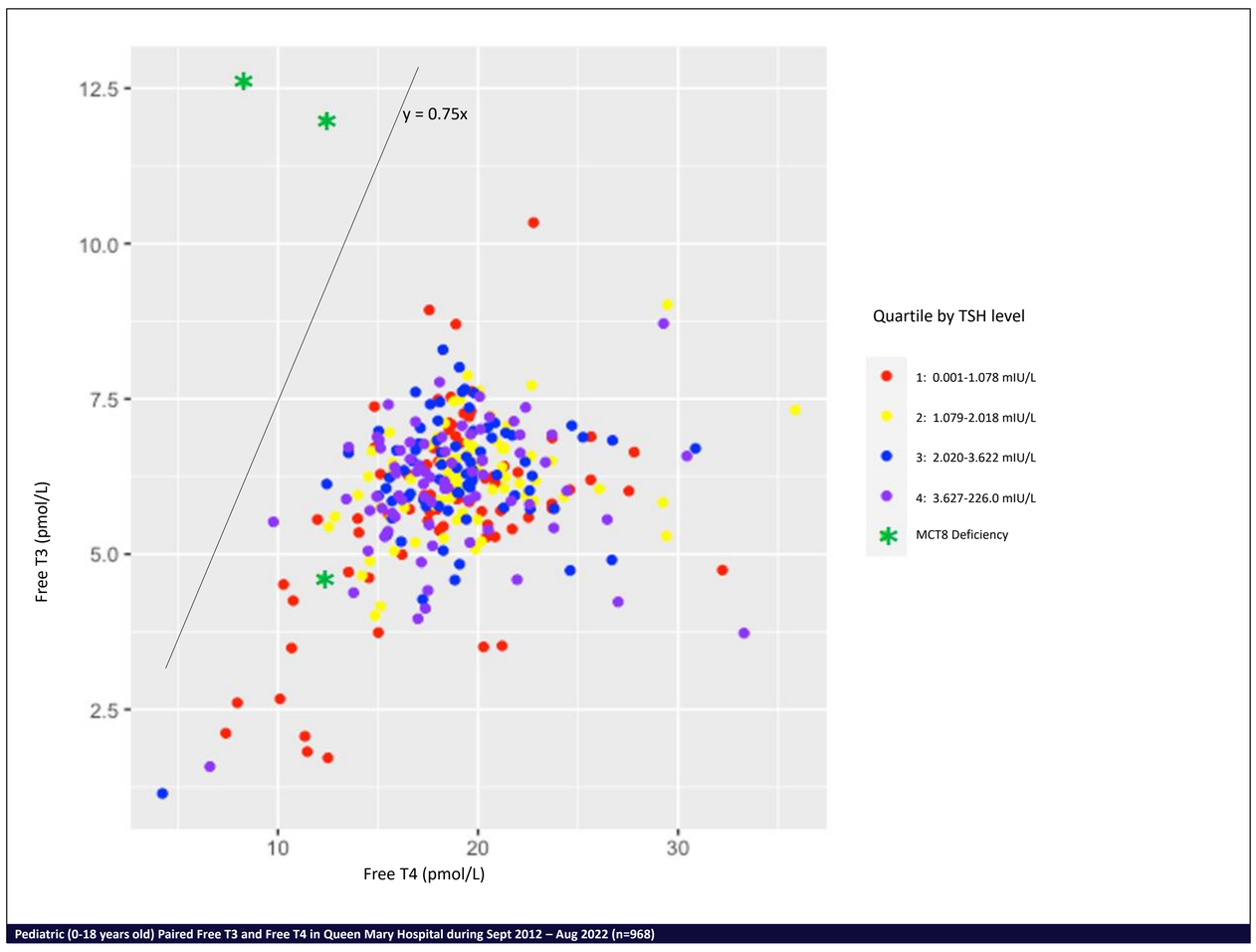
- Hemizygous NM_006517.4:c.511C>T(p.Arg171*); NP_006508.2:p.(Val103fs)
- Free T4, TSH, Free T3, Reverse T3 not done



Patient 1: Polymerase chain reaction and Sanger sequencing



Patient 2: Next generation sequencing



Pediatric (0-18 years old) Paired Free T3 and Free T4 in Queen Mary Hospital during Sept 2012 – Aug 2022 (n=968)

Conclusion

Complete thyroid function investigation (TSH, T4, T3 and reverse T3) should be performed for male pediatric patients presenting with developmental delay and/or neuromotor abnormalities, to facilitate early diagnosis of MCT8 deficiency, a "rare" genetic condition with new treatment.

Reference
1. Remerand G, Boespflug-Tanguy O, Tonduti D, Touraine R, Rodriguez D, Curie A, et al. Expanding the phenotypic spectrum of Allan-Herndon-Dudley syndrome in patients with SLC16A2 mutations. Dev Med Child Neurol. 2019 Dec;61(12):1439–47.
2. Groeneweg S, Peeters RP, Moran C, Stoupa A, Auriol F, Tonduti D, et al. Effectiveness and safety of the tri-iodothyronine analogue Triac in children and adults with MCT8 deficiency: an international, single-arm, open-label, phase 2 trial. Lancet Diabetes Endocrinol. 2019 Sep;7(9):695–706.