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Hirschsprung Disease: A new phenotype of *H1-4* associated Rahman syndrome?

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Background

- Rahman syndrome is a rare genetic disorder observed 48 documented case in global incidence.
- Rahman syndrome is characterized by intellectual disability, distinctive facial features, and a spectrum of developmental anomalies.
- The *H1-4* which encodes for a protein member of the histone H1 has been implicated in the etiology of Rahman syndrome.
- Hirschsprung disease, medically termed congenital megacolon, represents a congenital condition.
- Although primarily attributed to genetic factors, environmental influences are also considered contributory in the pathogenesis of Hirschsprung disease.
- Main causative genes of Hirschsprung's disease are Ret proto-oncogene(RET), Endothelin receptor type B(EDNRB) and SRY-box transcription factor 10(SOX10).
- Among the 48 confirmed cases of Rahman syndrome, no cases with concomitant congenital megacolon were identified.
- Herein, we report a patient diagnosed with Rahman syndrome in the presence of Hirschsprung's disease, suggesting the possibility of congenital megacolon as a novel phenotype of Rahman syndrome.

Case Report

- A boy born at 37 weeks and 4 days gestation, presented to our clinic at the age of 6 years and 3 months with developmental delay.
- He had a history of congenital megacolon and underwent two surgeries.
- Upon evaluation at our clinic, the patient exhibited overall developmental delay.
- At the corrected age of 6 years and 6 months, Bayley developmental assessment rated motor development at 11 months, fine motor skills at 10 months, receptive language at 15 months, expressive language at 13 months, and cognitive abilities at 12 months.
- The patient underwent chromosome microarray analysis and clinical exome sequencing, but pathogenic variants associated with developmental delay or Hirschsprung disease were not identified.

Whole Genome Sequencing

- Trio whole genome sequencing was performed and a *de novo* heterozygous variant was observed in *H1-4*: NM_005321.3:c.410dup.
- It was classified as a pathogenic variant (PVS1,PS2,PM2) according to the American College of Medical Genetics and Genomics guidelines.
- The variant was confirmed by conventional Sanger sequencing (**Figure1**).

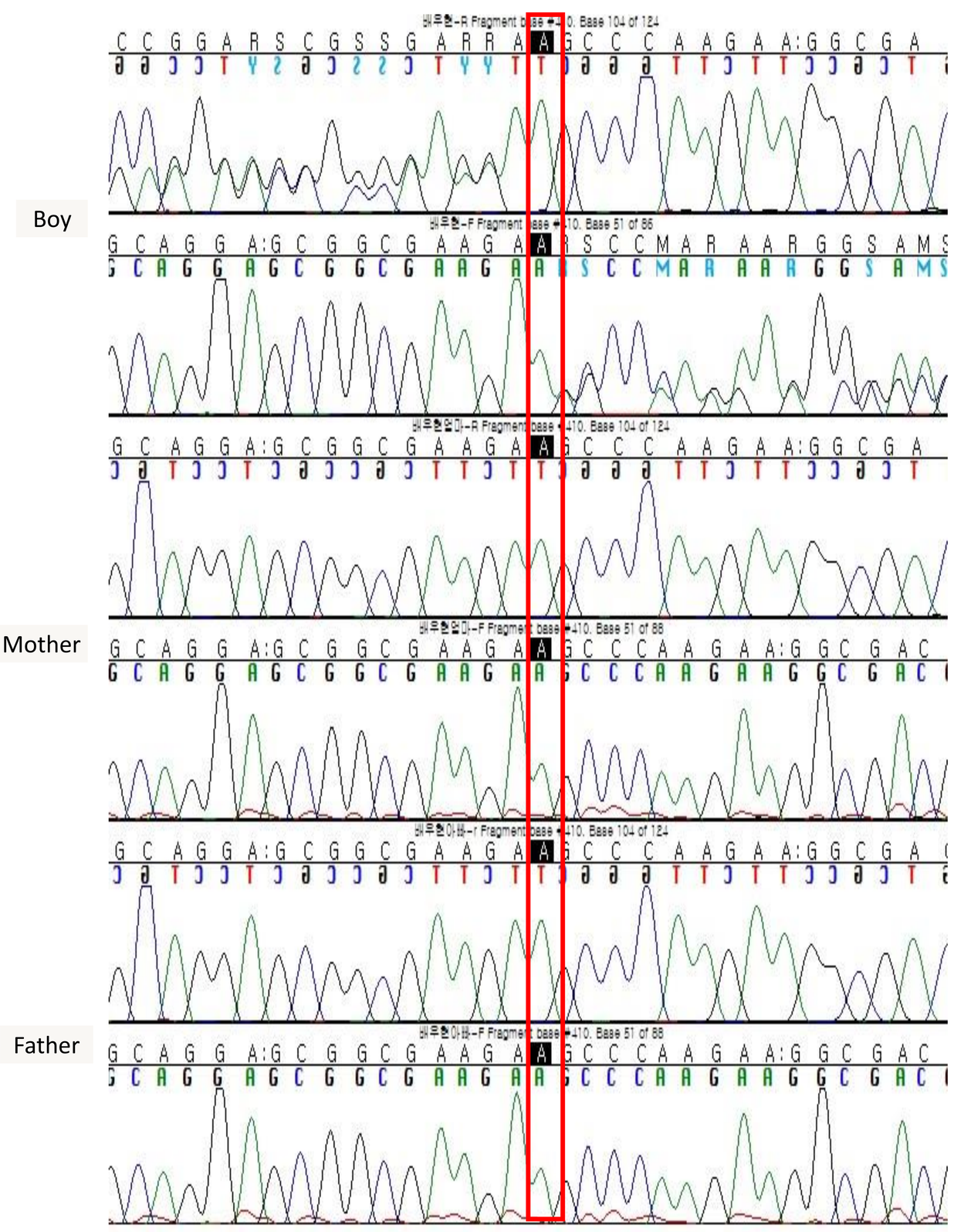

Figure 1.

- Sanger sequencing results of the boy (1st and 2nd row), mother (3rd and 4th row), and father (5th and 6th row).
- It was confirmed that the variant of the boy was *de novo*.
- This variant resulted in frameshift mutation in *H1-4*, leading to the loss of normal protein function through truncation (p. Pro138AlafsTer58).

Conclusion

- This patient was diagnosed with both Rahman syndrome and Hirschsprung disease, with a *de novo* heterozygous pathogenic variant identified in *H1-4*.
- In the case, where Rahman syndrome coexists with Hirschsprung disease, further research is needed to determine whether the expression process of the *H1-4* has contributed to the development of Hirschsprung disease.