"Splicing it all together": Discovery of a novel likely pathogenic *CDH1* variant using RNA analysis

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Background and Aim

Hereditary Diffuse Gastric Cancer (HDGC) syndrome increases the risk of diffuse gastric cancer (DGC) and lobular breast cancer (LBC), often caused by truncating variants in the *CDH1* gene. Non-truncating variants are generally classified as variants of uncertain significance (VUS). Herein we describe the identification of a novel likely pathogenic *CDH1* variant through use of RNA analysis.

Clinical Presentation

A 41-year-old man presented for consultation following a DGC diagnosis. Previous multi-gene panel testing identified a *CDH1* VUS called c.944A>G (p.Asn315Ser). Family history was notable for early-onset breast cancer in his mother (subtype unknown) and early-onset thyroid cancers in siblings, but no known gastric cancer (**Figure 1**).

The c.944A>G (p.Asn315Ser) variant is predicted to cause an amino acid change from asparagine to serine, which are both neutral and polar. This germline variant was not previously reported in publicly available databases or in the literature but was reported somatically in two LBCs. The laboratory indicated that this variant was of interest for RNA analysis due to possible creation of a donor splice site.

Paired DNA and RNA analysis detected an abnormal transcript, r.945_1009del, which arises from use of a novel donor site predicted by *in silico* tools and is expected to cause a frameshift and nonsense-mediated decay (p.Asn315Lysfs*13) (**Figure 2**). Using the patient's clinical and RNA data, the variant was classified as likely pathogenic.

Conclusions

To our knowledge, this is the first reported case of this *CDH1* variant in an individual with DGC. This case illustrates the importance of including RNA analysis upfront when possible, as it may provide a clinically actionable result for a patient and family. Follow up of suspicious VUS identified by DNA analysis with RNA should be discussed with the laboratory. We confirm consent of the relevant patient was obtained to submit this Case Report abstract.

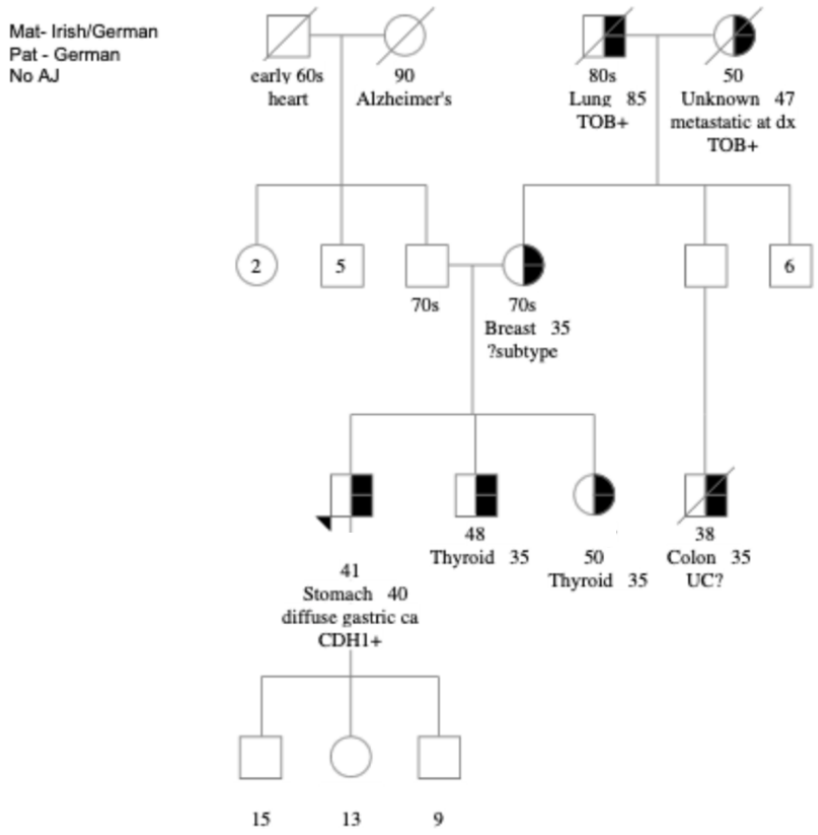

Fig 1. Pedigree.
Abbreviations: TOB+ - history of tobacco use, UC – ulcerative colitis

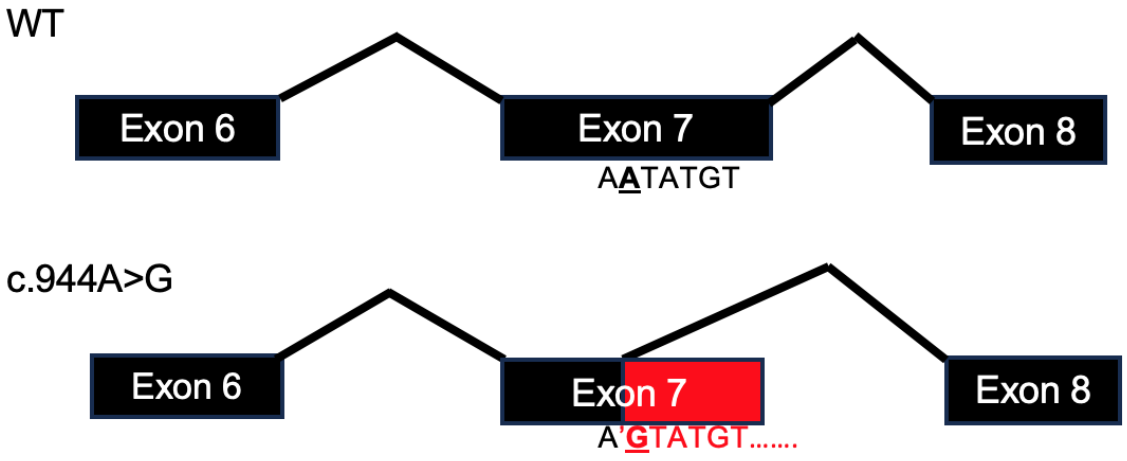

Fig 2. Splicing diagram showing the creation of a new donor site by the c.944A>G and the removal of 65 intronic nucleotides (depicted in red) from exon 7. The location of the novel donor splice site is depicted below exon 7 in red letters. The location of the variant is underlined.