

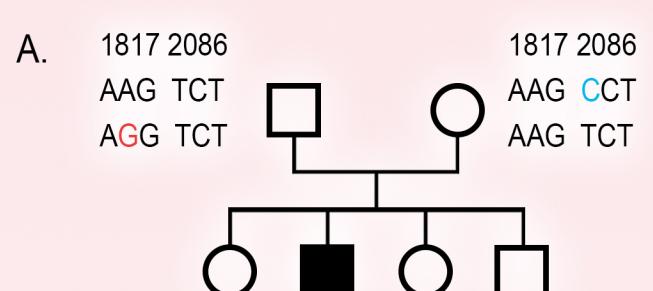
# A case presenting with common variable immunodeficiency with enteropathy caused by mutations in tetratricopeptide repeat domain 7a (ttc7a)

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TTC7A deficiency typically causes severe gastrointestinal manifestations such as multiple intestinal atresia or early onset inflammatory bowel disease. In some cases this is associated with severe combined immunodeficiency. Partial loss-of-function mutations appear to be associated with a milder phenotype resulting in common variable immunodeficiency-like (CVID) condition with enteropathy. We present here a case with clinical features consistent with this CVID and enteropathy phenotype. Compound heterozygous mutations were identified in TTC7A by whole exome sequencing.

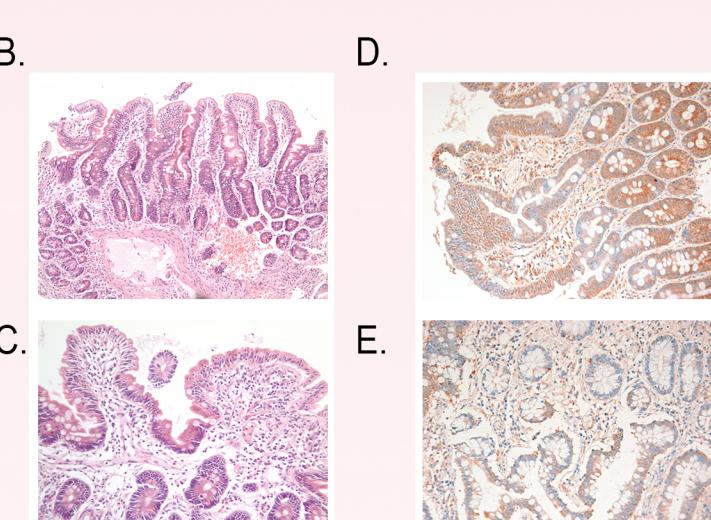
## Results

Whole exome sequencing performed on Illumina HiSeq with SureSelect XT and analysis with GATK and vcfhacks command line tools.



A. Pedigree and mutation inheritance pattern of K606R and S696P.

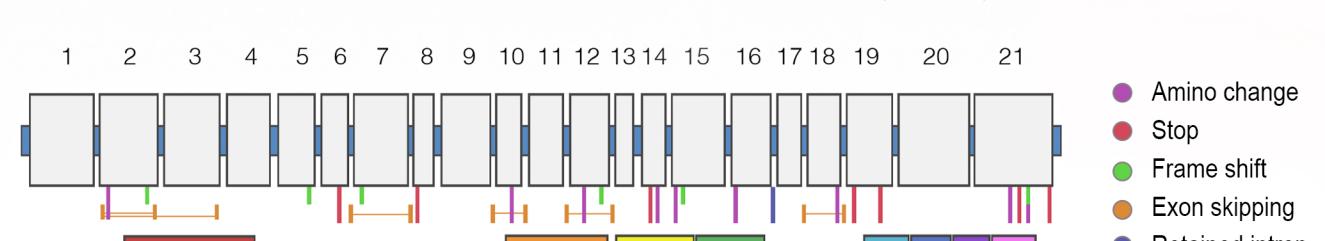
B. Gastrointestinal pathology. Duodenal biopsy with subtotal villous atrophy, marked crypt hyperplasia and villous tip lymphocytosis. Goblet and Paneth cells are preserved. C. Higher magnification. Shortened villi with lymphocytosis and conspicuous lack of plasma cells within the lamina propria.



D. Staining with TTC7A antibody in enterocytes indicates no loss of protein expression in a patient biopsy. E. Healthy control.

F. TTC7A gene and position of mutations identified to date in apop totic enterocolitis, multiple intestinal atresias, combined immunodeficiency, and enteropathy-lymphocytopenia-alopecia.

A Phyre2 model was generated based on the similar protein TTC7B and several TPR domain containing proteins. Missense mutations of non-TPR domain regions produce a phenotypic presentation of reduced severity.



## Clinical Features

Presentation at the age of 15 with lethargy, pallor and a low BMI. Anaemic with low levels of ferritin, folate, calcium and Vitamin D.

No history of unusual infections. No report of any overt diarrhoea, abdominal pain or any symptoms suggestive of small bowel obstruction.

An oesophago-gastroduodenoscopy showed an atrophic duodenal mucosa with no evidence of atresia. Variable villous atrophy and marked lymphocytosis with absence of plasma cells.

Immunoglobulin replacement therapy for severe panhypogammaglobulinaemia.\*

Normal T and B cell numbers but almost absent class-switched memory B cells. Normal proliferative T cell response to PHA and anti-CD3 stimulation and normal neutrophil function tests.

Diagnosed with type 1 diabetes mellitus at age 17. Remains free from infections, but continued difficulty with malabsorption and poor weight gain.

### Immunological assessments

Tests	2012	2016	Normal ranges
IgG (g/l)	2.9	5.4 (on IVIG)	5.4-16.1
IgA (g/l)	0.07	<0.06	0.8-2.80
IgM (g/l)	0.18	0.16	0.5-1.90
IgE ku/l	<2.0		0.5-120
Pneumococcal Ab µg/ml	4.1		Adequate >30
Total lymphocytes (cells/µl)	1930	1897	1000-2800
CD3+ Lymphocytes (cells/µl)	1170	1286	800-3500
CD4+ T cells (cells/µl)	677	664	300-1400
CD8+ T cells (cells/µl)	420	540	200-900 cells/µl
NK cells CD56+ (cells/µl)	97	163	90-600 cells/µl
B cells (CD19+) cells/µl	570	379	100-500 cells/µl
Ratio	1.61	1.23	1.07-1.87
Marginal zone B cells	5		0.5-8%*
CD19+ CD27+ IgD+ (% of CD19+)			
Class switched memory B cells CD19+ CD27+ IgD- (% of CD19+)	1		3-18%
PHA induced lymphocyte proliferation		Normal	N/A
Anti-CD3 induced lymphocyte proliferation		Normal	N/A
Neutrophil function test		Normal	N/A
Autoimmune screen [ANA, AMA, ACPA, Endomysial Ab (IgG and IgA)]	Negative		N/A

## Conclusion

Our case expands the clinical phenotype associated with biallelic TTC7A mutations. Missense mutations in regions outside of tetratricopeptide repeat domains allow expression of protein with presumably reduced function.

Enteropathy is a relatively common complication of CVID, and as we continue to use more advanced genetic techniques to study this condition, it is possible that these less severe TTC7A variants will be found more frequently in this patient population.

