


## ORIGINAL ARTICLE

# Isolated positive deamidated gliadin peptide-IgG has limited diagnostic utility in coeliac disease

Nikil Vootukuru , Harveen Singh  and Edward Giles 

Department of Paediatrics, Monash University, Melbourne, Victoria, Australia

**Aim:** Deamidated gliadin peptide-IgG (DGP-IgG) antibody serology testing is widely utilised in screening for coeliac disease in Australia; however, it is used sparingly in Europe. The aim of this study was to assess the diagnostic value of a positive DGP-IgG in the setting of a negative tissue transglutaminase-IgA (tTG-IgA) for gastrointestinal pathology among paediatric patients.

**Methods:** We conducted a retrospective cohort study of all children with an elevated DGP-IgG in the setting of a negative tTG-IgA who underwent gastroscopy over a 48-month period (January 2015–December 2018) at a tertiary paediatric centre. They were identified utilising the electronic pathology database and demographic and clinical data were collected from electronic medical records. Patients who had previously been diagnosed with coeliac disease were on a gluten-free diet or over the age of 18 were excluded from the study.

**Results:** Twenty-six patients with an elevated DGP-IgG in the setting of a negative tTG-IgA underwent gastroscopy. Our study yielded a positive predictive value of 1/26 (3.9% CI 95% 0.7%, 18.9%) for the diagnosis of coeliac disease. Overall, there were 25 histopathological diagnoses including 1 diagnosis of coeliac disease among the total 26 patients who were positive DGP-IgG and negative tTG-IgA and underwent gastroscopy.

**Conclusions:** Our findings suggest that an isolated positive DGP-IgG has a very low diagnostic yield for coeliac disease in children and may be indicative of other gastrointestinal pathology.

**Key words:** coeliac disease; deamidated gliadin; DGP-IgG; gastroenterology.

## What is already known on this topic

- 1 Deamidated gliadin peptide-IgG (DGP-IgG) testing is widely used for coeliac disease screening in Australia.
- 2 Tissue transglutaminase-IgA has a higher sensitivity and specificity compared to DGP-IgG antibody.
- 3 DGP-IgG is considered a sensitive test for coeliac disease, particularly for IgA deficient patients.

## What this paper adds

- 1 Positive DGP-IgG in the setting of a negative tissue transglutaminase-IgA has a low positive predictive value for coeliac disease in children.
- 2 DGP-IgG should have a limited role in the diagnosis of coeliac disease in children.
- 3 Positive DGP-IgG may be associated with other gastrointestinal pathology in children.

Coeliac disease is a chronic autoimmune enteropathy of the small bowel triggered in individuals with a genetic predisposition by dietary gluten.<sup>1</sup> The timely and effective diagnosis of coeliac disease is essential in preventing long-term complications – particularly impaired growth and development in children, while also minimising over-investigation.<sup>2</sup> It is for this reason that it is essential to follow an evidence-based diagnostic algorithm in the diagnosis of coeliac disease.<sup>2</sup> Currently in Australia, screening guidelines recommend tissue transglutaminase-IgA (tTG-IgA) and deamidated gliadin peptide-IgG (DGP-IgG) antibody or tTG-IgA antibody and the total

IgA level.<sup>3</sup> Following screening with positive serology, a biopsy is recommended to confirm the diagnosis of coeliac disease.<sup>3</sup> However, European guidelines recommend only the tTG-IgA antibody and the total IgA level for screening; with DGP-IgG antibody recommended only if IgA levels are low.<sup>4,5</sup> Furthermore, European Society for Paediatric Gastroenterology Hepatology and Nutrition guidelines have recently recommended the no-biopsy approach to diagnosis of coeliac disease provided children meet a set criteria.<sup>5</sup>

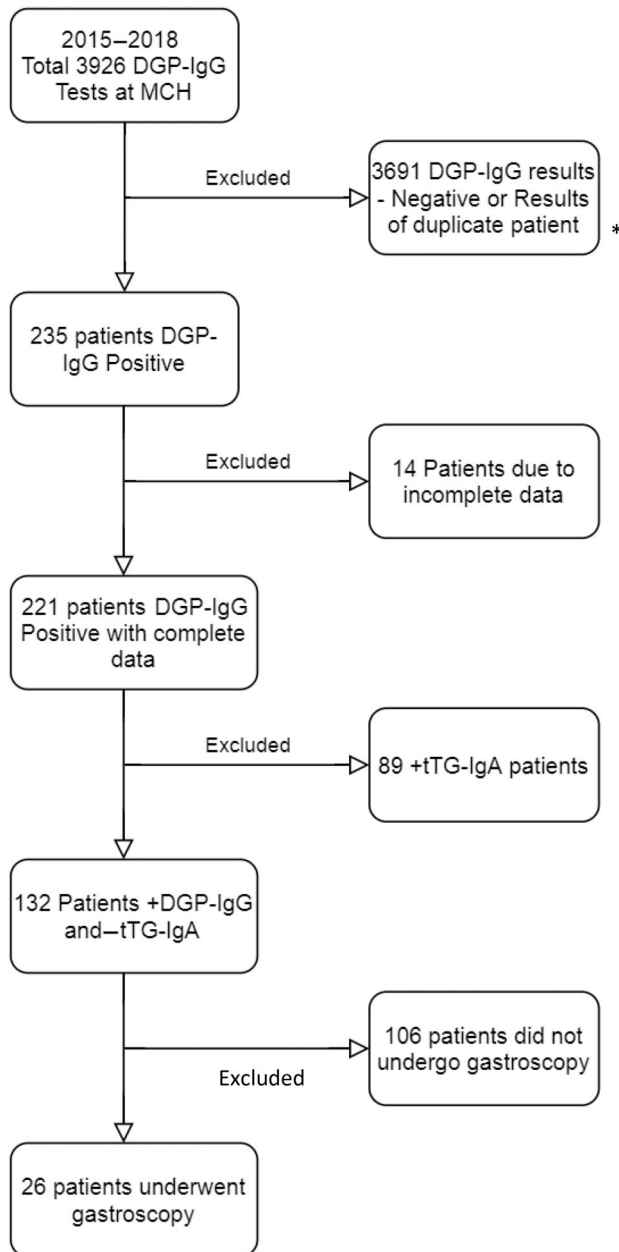
Given the high sensitivity and specificity of tTG-IgA in the diagnosis of coeliac disease, both 98%, compared to that of DGP-IgG, 80% and 98% respectively,<sup>6</sup> the utility of DGP-IgG serology in coeliac disease is unclear. Although the raised DGP-IgG has been studied in the context of a positive or negative tTG-IgA; there has been little study regarding the value of a raised DGP-IgG in the setting of a negative tTG-IgA, in particular regarding its role in diagnosing coeliac disease.<sup>7–9</sup> This is of importance in patients who lack classic symptoms where the utility of endoscopy is questionable. There is a

**Correspondence:** Dr Nikil Vootukuru, Department of Paediatrics, Monash University, Monash Children's Hospital Level 5, 246 Clayton Road Clayton, VIC 3168. Email: [Nikil.vootukuru@monash.edu](mailto:Nikil.vootukuru@monash.edu)

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need to balance the need for prompt diagnosis of coeliac disease with the risk of over-investigation. Furthermore, the role of DGP-IgG in the diagnosis of other gastrointestinal conditions has not been studied. The aim of this study was to assess the utility of an isolated positive DGP-IgG in the diagnosis of coeliac disease, and whether its presence was associated with other diagnoses.



**Fig. 1** Flowchart of patient selection for study. \*Results excluded if DGP-IgG was negative or were DGP-IgG results for duplicate patient. DGP-IgG, deamidated gliadin peptide-IgG; MCH, Monash Children's Hospital; tTG-IgA, tissue transglutaminase-IgA.

## Methods

We conducted a retrospective review of all children with an elevated DGP-IgG and a concurrent negative tTG-IgA result who underwent gastroscopy with no previous diagnosis of Coeliac Disease over a 48-month period (January 2015–December 2018) at a tertiary paediatric centre. Patients were identified by extracting all elevated DGP-IgG results from the electronic pathology system. Patients over the age of 18 at the time of serology, patients with a positive tTG-IgA and patients on a gluten-free diet at time of serology and patients who did not undergo gastroscopy were excluded. Of note, from 1 January 2015 to 2 March 2015, DGP-IgG testing was performed using the Anti-Gliadin (GAF-3X) ELISA IgG assay which was manufactured by Euroimmun in Lubeck, Germany and tTG-IgA testing was performed using the Aeskulisa tTg-A assay which was manufactured by Aesku. Diagnostics in Wendelsheim, Germany. During this time period from 1 January 2015 to 2 March 2015, an elevated DGP-IgG was defined as >25 RU/mL and elevated tTG-IgA defined as >20 U/mL. From 2 March 2015 onwards the DGP-IgG testing was performed using the Celiac DPG IgG assay manufactured and tTG-IgA testing was performed using Celiac DPG IgA assay which were both manufactured by Theradiag in Croissy Beaubourg, France. During this time period, elevated results were defined as >20 AU/mL for both serology tests. Coeliac disease was defined in the study as physician final assessment which was based on histology of the duodenal biopsies, serology testing and the clinical context. The positive predictive value (PPV), median and interquartile range (IQR) were calculated using excel, Mann–Whitney *U* test was undertaken utilising R which is developed by the R Core team and 95% confidence intervals were calculated utilising PEDro confidence interval calculator which is developed by Physiotherapy Evidence Database at Institute for Musculoskeletal Health at the University of Sydney and Sydney Local Health District.<sup>10</sup> Research ethics approval was obtained from the Monash Health Ethics Committee (RES-19-0000-629Q).

## Results

Over a 48-month period, 3926 DGP-IgG tests were undertaken in a paediatric population from which 221 (5.6%) patients were identified with a positive DGP-IgG (Fig. 1). This yielded 132 (59.73%) patients who had a positive DGP-IgG in the absence of a positive tTG-IgA.

Among the cohort with a positive DGP-IgG and –ve tTG-IgA, 24 (18.18%) patients underwent a gastroscopy, and 2 (1.5%) patients underwent both a gastroscopy and colonoscopy. One hundred and six (80.30%) patients in the cohort did not undergo gastroscopy for the following reasons: clinical decision for 73 patients (68.9%) – 12 of whom had an alternative diagnosis, serology normalisation for 20 patients (18.9%) and unknown reasons for 13 patients (12.3%). The symptoms among the 26 total patients who underwent gastroscopy include 10 patients with abdominal pain, 8 patients with failure to thrive, 5 patients with altered bowel habit, 3 patients with Iron/Folate/B12/Vitamin D deficiency and 2 patients with PR bleeding and 4 patients with unspecified symptomatology. Among the 26 patients that underwent gastroscopy – the median age was 8.80 ([5.25, 13.81]) with a median DGP-IgG was 1.65 ([1.25, 2.75]) times the upper limit (Table 1). Among these

**Table 1** Demographics and pathology results for positive DGP-IgG and negative tTG-IgA population who underwent gastroscopy

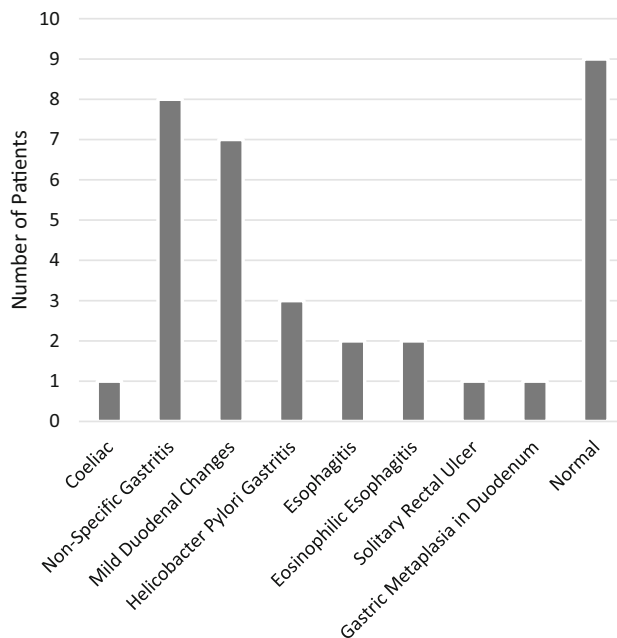
Patient demographics	n (%)
Number of patients	26 (100%)
Sex	
Males	10 (38.5%)
Females	16 (61.5%)
Age (years)	
<5	7 (26.9%)
5–10	10 (38.5%)
10–18	9 (34.6%)
DGP-IgG ULN (median [IQR])	1.65 [1.5]
Endomysial Ab IgA	
Positive	0 (0%)
Negative	0 (0%)
Not done	26 (100%)
HLA genetic testing	
Positive	1 (3.8%)
Negative	2 (7.7%)
Not done	23 (88.5%)
IgA, g/L	
Deficient	0 (0%)
Non-deficient	11 (42.3%)
Not done	15 (57.7%)

DGP-IgG, deamidated gliadin peptide-IgG; HLA, human leukocyte antigen; IQR, interquartile range; ULN, upper limit of normal; tTG-IgA, tissue transglutaminase-IgA.

patients, 0 underwent Endomysial-IgA testing, 3 (11.5%) underwent human leukocyte antigens (HLA) genetic testing (1 HLA DQ2.5 positive) and 11 (42.3%) patients underwent IgA testing with 0 IgA deficient.

From the 26 children who underwent a gastroscopy, a median of 122.5 ([23, 331]) days post DGP-IgG result, 17 children (65.4%) had the following histopathological diagnoses: coeliac (1), non-specific gastritis (8), mild duodenal changes which include mild duodenitis or mild focal villous blunting (7), *Helicobacter pylori* gastritis (3), oesophagitis (2), eosinophilic oesophagitis (2), gastric metaplasia in duodenum (1) and a solitary rectal ulcer in a patient who underwent a colonoscopy as well as gastroscopy – the remaining 9 children had normal histology (Fig. 2). This yields a PPV for coeliac disease of 1/26 (3.9% CI 95% 0.7%, 18.9%) for positive DGP-IgG Serology in the setting of a negative tTG-IgA. Overall, there were 25 histopathological diagnoses among children who underwent a gastroscopy and were positive DGP-IgG and negative tTG-IgA. There was not a statistically significant difference in the DGP-IgG upper limit of normal levels ( $W = 80$ ,  $P = 0.87$ ) between the group that had gastrointestinal pathology and the group with normal gastrointestinal histology.

The patient with positive DGP-IgG in the setting of a negative tTG-IgA who underwent gastroscopy showing coeliac disease was a 2-year-old girl who presented with vitamin D deficiency and haematochezia whose baseline and subsequent IgA levels are not known. Interestingly, serology for coeliac surveillance continued to show a positive DGP IgG – 25 in 2016 and 42 in 2018 with negative tTG-IgA. During this period, the patient was commenced



**Fig. 2** Histopathological diagnoses among positive deamidated gliadin peptide-IgG (DGP-IgG) and negative tissue transglutaminase-IgA (tTG-IgA) population who underwent gastroscopy ± colonoscopy. Note patients not equal to 26 (the number of patients who underwent gastroscopy) as some patients had multiple histopathological diagnoses.

on a gluten-free diet – however, there were some difficulties noted during follow-up with adherence. Furthermore, of the three patients who showed mild focal villous shortening and blunting – two had subsequent normalisation of DGP-IgG and one had persistently high DGP-IgG but improvement in presenting complaint (failure to thrive). These patients did not undergo further endoscopy and were not commenced on a gluten-free diet.

## Discussion

Our retrospective study suggests that a positive DGP-IgG in the setting of a negative tTG-IgA has a low diagnostic yield for coeliac disease in children as suggested by the PPV of 3.9% and therefore has limited utility in the diagnosis of coeliac disease where tTG-IgA serology testing is undertaken. This study is the first to look at the association between DGP-IgG and other gastrointestinal pathology. Our findings of 24 non-coeliac histopathological diagnoses suggest that a positive DGP-IgG may be associated with alternative gastrointestinal pathology.

Our finding, a PPV of 3.9% for a positive DGP-IgG in the setting of a negative tTG-IgA, is consistent with Gould *et al.* who reported a PPV of 2.5% in a paediatric population. However, this is significantly lower than the PPV of 15.5% reported by Hoerter *et al.* in an adult population which may be attributed to Hoerter *et al.* reporting the PPV for both DGP-IgG and DGP-IgA in the setting of a negative tTG-IgA.<sup>11–12</sup> There are conflicting data on the sensitivity and specificity of DGP assays for coeliac disease with Volta *et al.* reporting a 98.9% specificity for IgG deamidated

gliadin peptide anti-gliadin antibody (IgG DGP-AGA) in adult patients<sup>7</sup> in contrast with Olen *et al.* who reported a specificity of 26% for anti deamidated gliadin peptide (anti-DGP) assay.<sup>8</sup> We believe that higher reported rates in some studies may be guiding clinician decision-making contributing to unnecessary endoscopy.<sup>8,13</sup> This has been supported by Zucchini *et al.* who have reported a significantly lower specificity and PPV for anti-DGP assay than the anti-tTG assay.<sup>9</sup> Horwitz *et al.* reported that in order to diagnose 1 case of coeliac disease that was negative for tTG-IgA – almost 2300 tests for DGP-IgG and 4 unneeded endoscopies had to be performed.<sup>13</sup> In our study, although a total of 3926 DGP-IgG tests were undertaken during the study period, it was not within the scope of the study to assess the utility of all DGP-IgG results. Consequently, we can report that 26 gastroscopies were undertaken to diagnose one case of coeliac disease.

Our findings support the limited use of DGP-IgG in the diagnosis of coeliac disease and suggest that it is reasonable to observe in patients who have positive DGP-IgG levels and negative tTG-IgA level but minimal symptoms with serial measurements. In fact, the 2-year-old girl who was coeliac positive continued to display a positive DGP-IgG in the setting of a negative tTG-IgA during coeliac surveillance. It is therefore possible that coeliac disease may not have been cause of the positive DGP-IgG. A positive DGP-IgG in the setting of a negative tTG-IgA should not immediately lead to gastroscopy but should be interpreted in the context of clinical symptoms and suspicion of an alternative diagnosis. In our findings, only 26 of 132 children with positive DGP-IgG in the setting of a negative tTG-IgA underwent gastroscopy. This suggests that although DGP-IgG is widely utilised clinically in the screening of coeliac disease – clinicians are utilising their clinical expertise to guide decision-making regarding undertaking gastroscopy.

This study is the first of its kind to suggest a relationship between DGP-IgG and gastrointestinal conditions other than coeliac disease. Deamidated gliadin is raised in coeliac disease due to gliadin deamidation in the intestinal mucosa being catalysed by tissue transglutaminase.<sup>14</sup> In the case of non-coeliac aetiology, we speculate that deamidated gliadin as a non-specific antibody may be more likely to be elevated in the presence of inflammation. Given the scarcity of studies regarding DGP-IgG outside the context of coeliac disease, further studies are needed to evaluate the degree of association of DGP-IgG to other gastrointestinal conditions.

The limitations of this study include the retrospective study design and the small study sample. Furthermore, due to the lack of long-term follow-up in this study, it is possible that some biopsy-negative patients later develop coeliac disease. Not all patients that were positive for DGP-IgG in the absence of a positive tTG-IgA underwent endoscopy which can lead to an underestimation of the utility of DGP-IgG, particularly if these patients who did not undergo gastroscopy may later have developed coeliac disease. Additionally, the association of a positive DGP-IgG with other gastrointestinal conditions is impacted by selection bias. All patients that undergo DGP-IgG testing are either presenting with symptoms or risk factors that increase the likelihood that they have a gastrointestinal condition irrespective of the DGP-IgG result. In addition to this, we were unable to calculate odds ratio to measure this association given that data were not collected for patients who were DGP-IgG negative and tTG-IgA

positive, DGP-IgG negative and tTG-IgA negative and DGP-IgG positive and tTG-IgA positive. Finally, this study does not evaluate the utility of DGP-IgG in other clinical contexts such as monitoring of coeliac disease, among children of different age groups and IgA deficient children. Strengths of our study are that it is one of the few studies to assess the utility of an elevated DGP-IgG in the setting of a negative tTG-IgA and the only study to look at the utility of DGP-IgG in diagnosis of non-coeliac gastrointestinal pathology.

## Conclusions

In conclusion, our findings suggest that a positive DGP-IgG in the setting of a negative tTG-IgA has a low diagnostic yield for coeliac disease in children but may be elevated in a wide variety of non-coeliac gastrointestinal pathologies, the reasons for which are unclear. When considering endoscopy in the cases of positive DGP-IgG and negative tTG-IgA serology, it is important this is done in association with gastrointestinal symptoms or biochemical evidence of inflammation or malabsorption. Further studies are required to confirm the utility of the DGP-IgG in diagnosis for specific gastrointestinal pathology.

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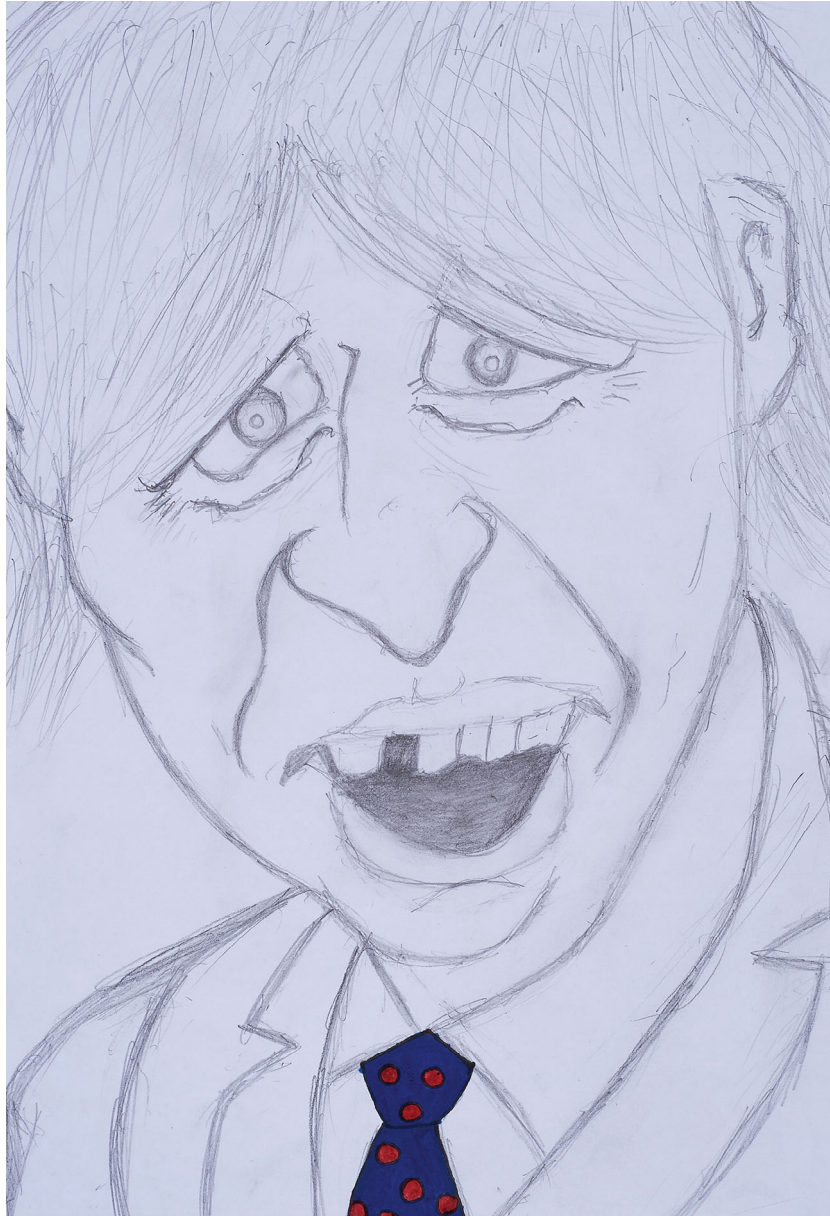
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## References

- Ludvigsson J, Leffler D, Bai J *et al.* The Oslo definitions for coeliac disease and related terms. *Gut* 2012; **62**: 43–52.
- Brigic E, Hadzic D, Mladina N. Early and correct diagnosis of celiac disease in the prevention of growth disorders and child development. *Mater. Sociomed.* 2012; **24**: 242.
- Tye-Din J. Interpreting tests for coeliac disease: Tips, pitfalls and updates. *Aust. J. Gen. Pract.* 2018; **47**: 28–33.
- Al-Toma A, Volta U, Auricchio R *et al.* European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. *United European Gastroenterol. J.* 2019; **7**: 583–613.
- Husby S, Koletzko S, Korponay-Szabó I *et al.* European Society Paediatric Gastroenterology, Hepatology and Nutrition guidelines for diagnosing coeliac disease 2020. *J. Pediatr. Gastroenterol. Nutr.* 2020; **70**: 141–56.
- Leffler D, Schuppan D. Update on serologic testing in celiac disease. *Am. J. Gastroenterol.* 2010; **105**: 2520–4.
- Volta U, Granito A, Parisi C *et al.* Deamidated gliadin peptide antibodies as a routine test for celiac disease. *J. Clin. Gastroenterol.* 2010; **44**: 186–90.
- Olen O, Gudjónsdóttir A, Browaldh L *et al.* Antibodies against deamidated gliadin peptides and tissue transglutaminase for diagnosis of pediatric celiac disease. *J. Pediatr. Gastroenterol. Nutr.* 2012; **55**: 695–700.
- Zucchini L, Giusti D, Gatouillat G *et al.* Interpretation of serological tests in the diagnosis of celiac disease: Anti-deamidated gliadin peptide antibodies revisited. *Autoimmunity* 2016; **49**: 414–20.
- Herbert R. Confidence Interval Calculator (2013). Available from: <https://www.pedro.org.au/english/downloads/confidence-interval-calculator/> [accessed 31 August 2020].



- 11 Hoerter N, Shannahan S, Suarez J *et al.* Diagnostic yield of isolated deamidated gliadin peptide antibody elevation for celiac disease. *Dig. Dis. Sci.* 2017; **62**: 1272–6.
- 12 Gould M, Brill H, Marcon M *et al.* In screening for celiac disease, deamidated gliadin rarely predicts disease when tissue transglutaminase is normal. *J. Pediatr. Gastroenterol. Nutr.* 2019; **68**: 20–5.
- 13 Horwitz A, Skaaby T, Kårhus LL *et al.* Screening for celiac disease in Danish adults. *Scand. J. Gastroenterol.* 2015; **50**: 824–31.
- 14 Lewis N, Scott B. Meta-analysis: Deamidated gliadin peptide antibody and tissue transglutaminase antibody compared as screening tests for coeliac disease. *Aliment. Pharmacol. Ther.* 2010; **31**: 73–81.



The observer by Adya Bhushan (aged 10) from “A Pop of Colour” art competition, Youth Arts, Children’s Hospital at Westmead