

Baboons affected by hereditary chronic diarrhea as a possible non-human primate model of celiac disease

- **Background:** Celiac disease (CD) represents a unique model of autoimmunity in which, in contrast to most other autoimmune diseases, a close genetic association with HLA genes (DQ2 and/or DQ8), a highly specific humoral autoimmune response (autoantibodies to tissue transglutaminase, (TTG)), and, most importantly, the triggering environmental factor (gluten), are known. Given the undisputable role of gluten in causing inflammation and immune-mediated tissue damage, CD could provide unique opportunities to tackle the pathogenic basis of autoimmune processes. However, the lack of an animal model of the disease represents a major limitation in reaching goals.
- **Aims:** To establish if pedigreed colony of baboons with hereditary chronic diarrhea at the Southwest Foundation for Biomedical Research, could be used as a possible non-human primate model for celiac disease.
- **Methods:** Baboons from the pedigreed colony at the Southwest Foundation for Biomedical Research (SFBR) in San Antonio, Texas were reviewed. Those animals with chronic diarrhea (≥ 21 days) and more than two clinical admissions between January 1998 and December 2003 were selected. This search yielded 163 baboons. An infective cause of the diarrhea was ruled out. CD serology and intestinal histological analysis were performed on a selected number of animals.
- **Results:** The onset of diarrhea occurred at all ages (1-16 years of age) and was analyzed for distribution among the 4,200 offspring of 57 sires of the pedigreed colony. Fifty-one of the 163 cases (31%) of chronic diarrhea occurred among the offspring of 4 sires. Of the 20 cases studied, 5 (25%) tested TTG IgA and/or IgG antibodies positive, compared to 1/17 (5.9%) in healthy control baboons. Zonulin, a modulator of intestinal permeability that is up regulated in CD, resulted elevated in 8/20 (40%) baboons with chronic diarrhea and 0/17 controls. There was 80% correlation between positive TTG IgG and elevated zonulin. Duodenal samples obtained after the baboons were euthanized showed increased intraepithelial lymphocytes and, occasionally, marked lymphocytic mucosal infiltration and villi distortion and blunting. Four baboons with chronic diarrhea, weight loss, anemia, and histological findings of intestinal damage compatible with CD were individually caged and fed a gluten-free diet (GFD). After 6 weeks of diet the diarrhea persisted, however the animals began to gain weight.
- **Conclusions:** These preliminary observations suggest that a gluten-dependent enteropathy is present in the pedigreed baboon colony studied, and that it is clustered among the progeny of a few sires. This sire effect is presumptive evidence that the condition is hereditary. The clinical, serological, and histological features suggest a similarity to human CD and, therefore, that the progeny of this sire can be potentially used as a primate non-human model of CD.

Background



The Southwest Foundation for Biomedical Research in San Antonio, TX has a pedigreed baboon colony (population 3000) that has had a problem of managing chronic diarrhea since the inception of the colony in 1972.

Infectious agents have been excluded and preliminary analysis of the distribution of diarrhea in the baboons at the SFBR, shows a concentration of the affected animals among the progeny of 4 sires, that span 6 generations.

Aims

To establish if the pedigreed colony of baboons with hereditary chronic diarrhea at the Southwest Foundation for Biomedical Research, could be used as a possible non-human primate model for celiac disease.

Methods

Animal Selection:

- 4200 baboons from the pedigreed colony at the Southwest Foundation for Biomedical Research (SFBR) in San Antonio, Texas were reviewed.
- Those animals with chronic diarrhea (≥ 21 days) and more than two clinical admissions between January 1998 and December 2003 were selected.
- This search yielded 163 baboons. An infective cause of the diarrhea was ruled out.
- Celiac serology and intestinal histological analysis were performed on a selected number these animals.
- Baboons that were seen in the clinic for other reasons (such as trauma) where used as normal controls.

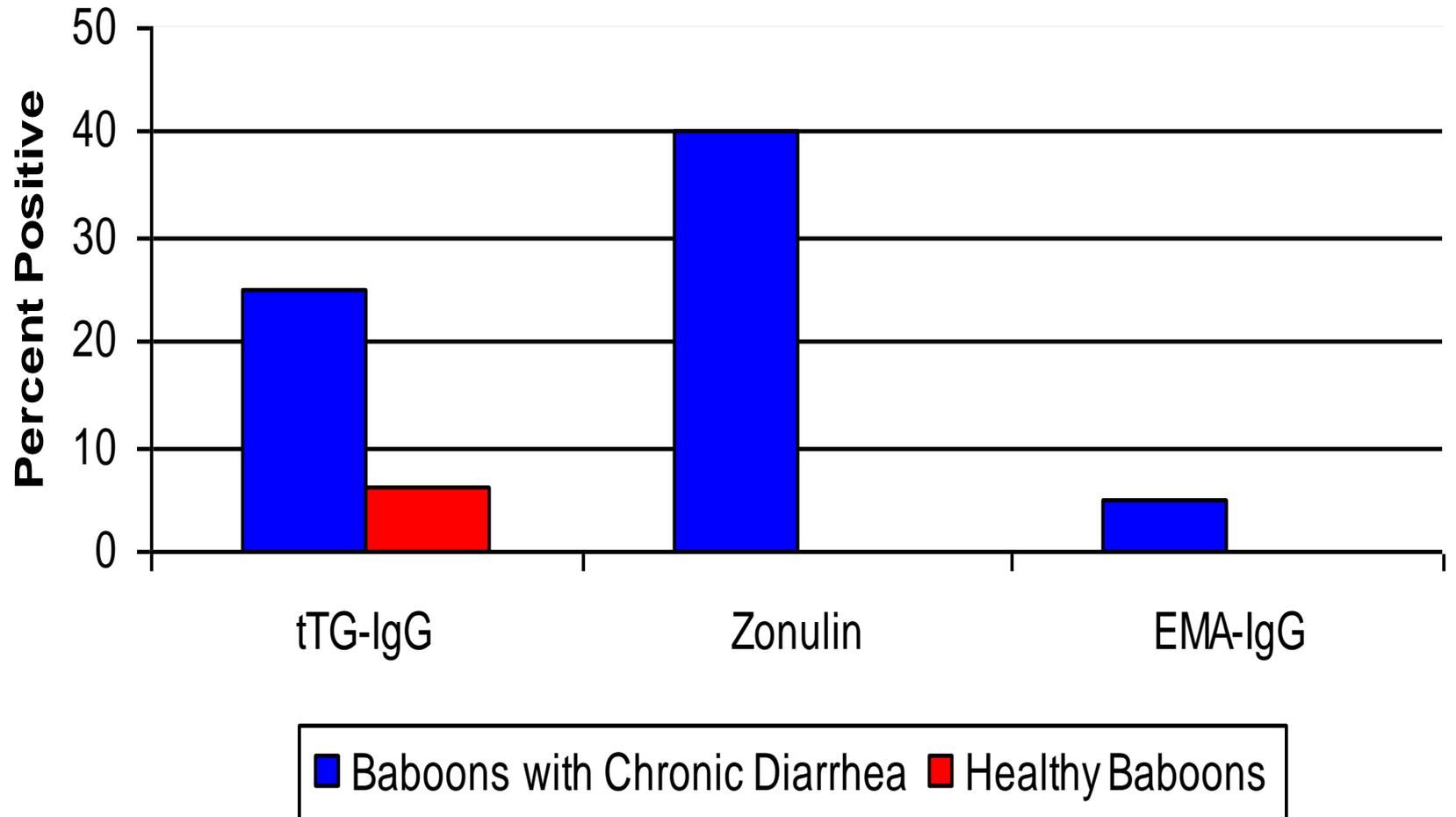
Serum biochemical tests:

- Anti-Tissue transglutaminase antibodies (tTG-IgA and tTG-IgG) (Scimedx Corporation. NJ, USA)
- Anti-Endomysial antibodies (EMA-IgA) (Scimedx Corporation. NJ, USA)
- Anti-Endomysial antibodies (EMA-IgG) (Immco Diagnostics. NY, USA)
- Anti-Gliadin antibodies (IgA and IgG) (Center for Celiac Research. MD, USA)
- Zonulin levels (Center for Celiac Research. MD, USA)

Results

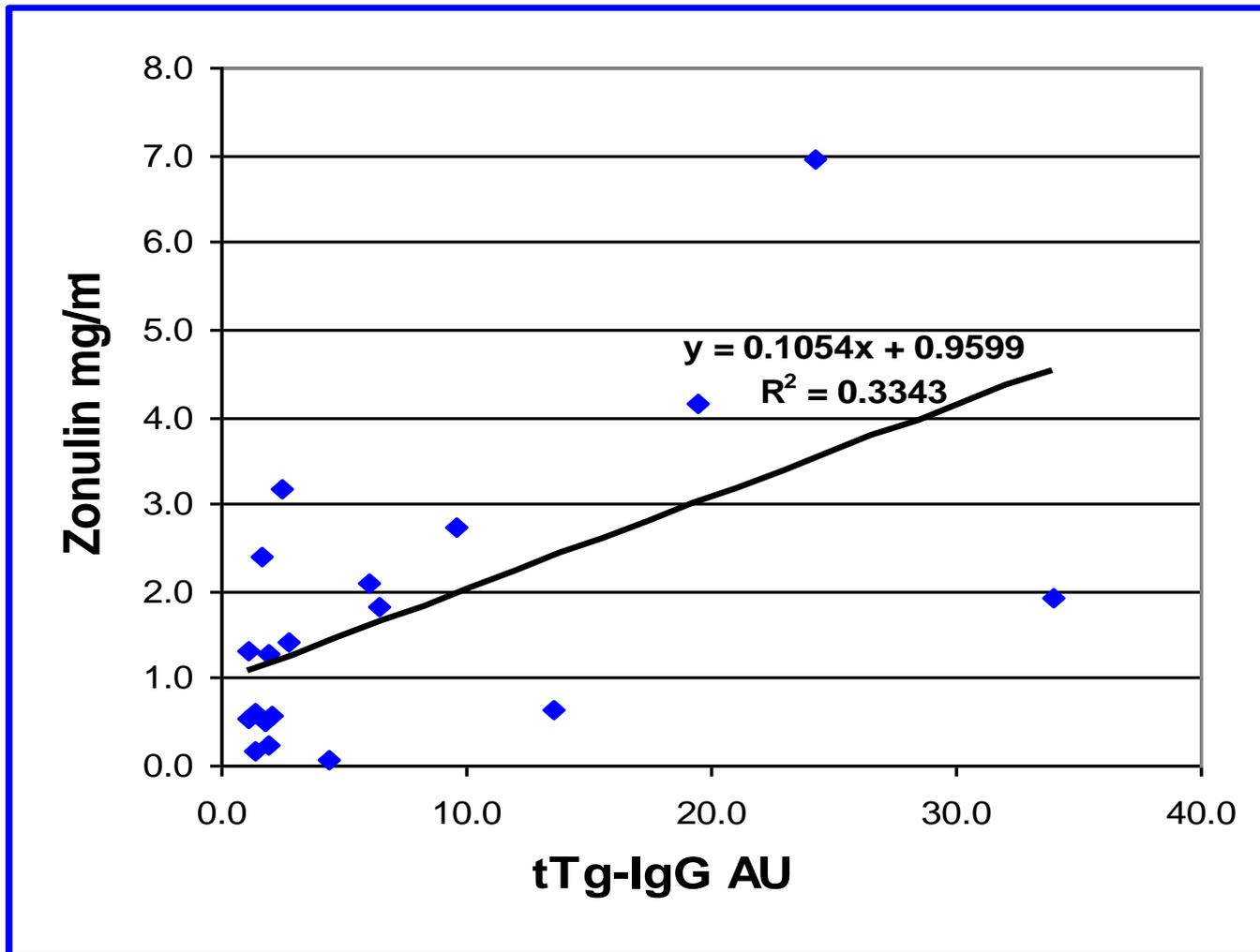
- The onset of diarrhea occurred at all ages (1-16 years of age) and was analyzed for distribution among the 4,200 offspring of 57 sires of the pedigreed colony.
- Fifty-one of the 163 cases (31%) of chronic diarrhea occurred among the offspring of 4 sires.
- Of the 20 cases studied, 5 (25%) tested TTG IgA and/or IgG antibodies positive, compared to 1/17 (5.9%) in healthy control baboons.
- Zonulin, a modulator of intestinal permeability that is up regulated in CD, resulted elevated in 8/20 (40%) baboons with chronic diarrhea and 0/17 healthy controls.
- There was 80% correlation between positive TTG IgG and elevated zonulin.
- Duodenal samples obtained after the baboons were euthanized showed increased intraepithelial lymphocytes and, occasionally, marked lymphocytic mucosal infiltration and villi distortion and blunting.
- Four baboons with chronic diarrhea, weight loss, anemia, and histological findings of intestinal damage compatible with CD were individually caged and fed a gluten-free diet (GFD). After 6 weeks of diet the diarrhea persisted, however the animals began to gain weight.

Serology Results



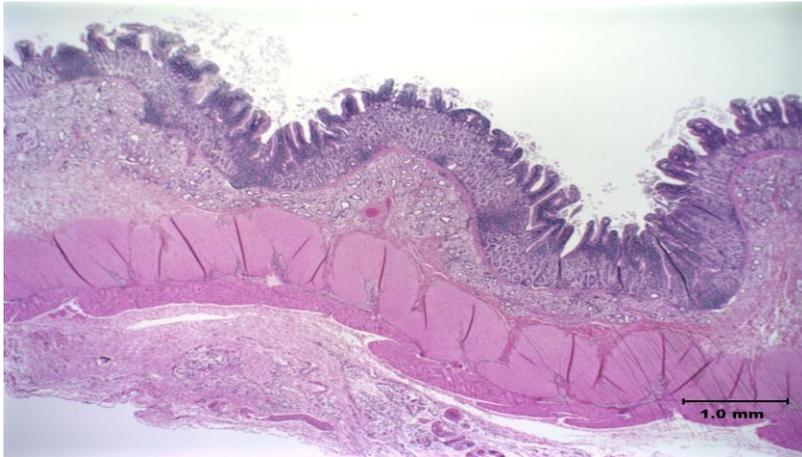
Serology

80% correlation between positive tTG-IgG and elevated zonulin Levels

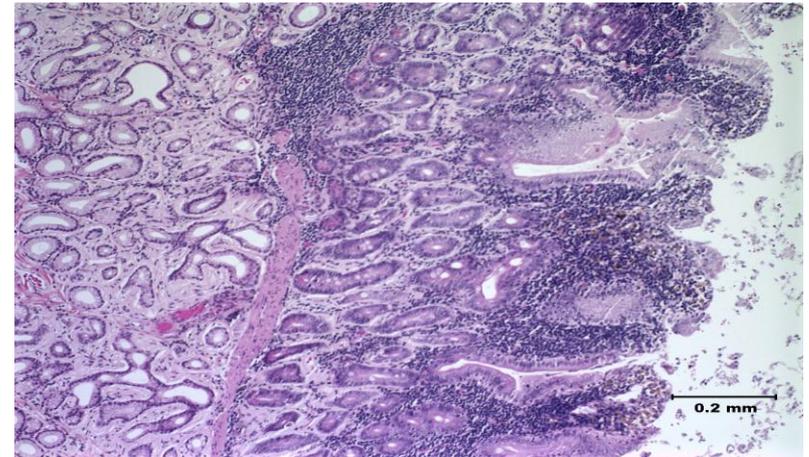


Histology

Duodenal tissues from Baboons with chronic diarrhea



Patchy Villous Blunting (2X)



Increased Intraepithelial lymphocytes (10X)



Patchy Villous Blunting (4X)

Histology

Duodenal tissues from Healthy Baboons

Conclusions

- The combination of our serological data, the intestinal biopsies, and the response to a short course of a GFD seem to suggest that a gluten-dependent enteropathy is present in the pedigreed baboon colony studied, and that it is clustered among the progeny of a few sires.
- This sire effect is presumptive evidence that the condition is hereditary. The clinical, serological and histological features suggest a similarity to human CD and, therefore, that the progeny of this sire can be potentially used as a primate non-human model of CD.

Future Directions

- We have an ongoing collaboration with the SFBR to study baboons with chronic diarrhea that will be placed on a Gluten Free Diet and monitored for 6 months.
- A blood sample and a duodenal biopsy will be collect at baseline, midway and at the conclusion of the study.