ABSTRACT

Despite the sharp rise in the prevalence of ASD, existing therapies remain unsatisfactory and development of new treatment options has been impeded due to inadequate understanding of disease mechanism and the absence of specific biomarkers. There is emerging evidence that immune system abnormalities are associated with symptoms in a substantial number of affected individuals. Recent studies point to a role for gastrointestinal (GI) symptoms and defects in GI function in the context of autism. Dietary gluten, a group of over 70 different proteins in wheat and related cereals, has been suspected of having a role in some patients with ASD. Diets that exclude gluten are increasingly popular in the autism community, although their effectiveness has not been proven in controlled studies. Despite years of speculation and immense interest by families of affected children regarding the potential connection between autism and gluten sensitivity, no well-controlled study has been performed to determine the levels of immune reactivity to gluten in patients, to characterize the antigenic specificity of this immune response, or to assess its pathogenic relevance to autism. Our newly published data indicate that children with autism exhibit significantly elevated antibody reactivity to gluten, which is associated with GI symptoms. Interestingly, the data show that the immune response to gluten in ASD is distinct from celiac disease (an autoimmune disorder triggered by gluten) and involves a different mechanism. The central hypothesis of the proposed study is that the immune response to gluten in ASD is fundamentally different from celiac disease, targeting a unique set of proteins and epitopes, which can be utilized to identify novel biomarkers and gain novel insights about mechanism. The specific aims of this proposal, which represent a systematic approach to examine this hypothesis, are: 1) to fully characterize the specific target molecules of the anti-gluten antibody response in ASD, using a gluten protein/peptide microarray system, and 2) to map the specific target sequences of the identified gluten proteins associated with the antibody response in ASD. The proposed study will utilize a novel gluten proteomic microarray system that has been developed by our team. The gluten microarray would allow sensitive, quantitative, and accurate mapping of the immune response to the complex gluten antigenic mixture. This approach has not been previously employed to profile the antibody response in autism. If the aims of the proposed project are achieved, the results would 1) offer biomarkers that may be useful in identifying subsets of ASD patients or individuals at risk of developing ASD, 2) support the examination of specific treatment strategies, including gluten exclusion diet, targeted at the identified subset of patients, and 3) yield experimental support for closer examination of the role of the identified proteins or the immune response to them in the pathogenesis of the disorder. This grant proposal is in line with the program announcement's request for Idea Development Award applications that address the following needs of the ASD community: "understanding factors underlying the heterogeneity of ASD" and "conditions co-occurring with ASD".