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Variable immune deficiency related to deletion size in chromosome 22q11.2 deletion syndrome

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Abstract

The clinical features of 22q11.2 deletion syndrome include virtually every organ of the body. This review will focus on the immune system and the differences related to deletion breakpoints. A hypoplastic thymus was one of the first features described in this syndrome and low T cell counts, as a consequence of thymic hypoplasia, are the most commonly described immunologic feature. These are most prominently seen in early childhood and can be associated with increased persistence of viruses. Later in life, evidence of T cell exhaustion may be seen and secondary deficiencies of antibody function have been described. The relationship of the immunodeficiency to the deletion breakpoints has been understudied due to the infrequent analysis of people carrying smaller deletions. This manuscript will review the immune deficiency in 22q11.2 deletion syndrome and describe differences in the T cell counts related to the deletion breakpoints. Distal, non-*TBX1* inclusive deletions, were found to be associated with better T cell counts. Another new finding is the relative preservation of T cell counts in those patients with a 22q11.2 duplication.

Keywords

breakpoints; deletion size; DiGeorge; IgG; low copy number repeats; T cells

1 | INTRODUCTION

There is a spectrum of immune deficiency recognized in 22q11.2 deletion syndrome (22q11.2del) and some of the more common clinical features related to immune deficiency will be reviewed here. Some patients have completely normal T cells and other infants have no T cells detectable on laboratory studies (Kwan et al., 2014; Ryan et al., 1997). This variability in severity is not conceptually different from that seen with other end organs (Botto et al., 2003; McDonald-McGinn et al., 1999). One of the differences is that there is a linear quantitative scale for T cells, whereas definition of severity in other organs is more qualitative. The explanation for the variability appears to reflect stochastic effects during embryonic development although there are suggestions that background genes may modify

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the effects of the deletion (Bassett et al., 2017; Driscoll et al., 2006; Lindsay et al., 1999; Lopez-Rivera et al., 2017; Stalmans et al., 2003; Widdershoven et al., 2013). Supporting the concept that features may reflect early binding of *TBX1* to target genes are family studies showing differences in members of multiplex kindreds (Digilio, Marino, Giannotti & Dallapiccola, 1997; Driscoll et al., 1995; Yamagishi et al., 1998) (McDonald-McGinn et al., 2001). Several studies have attempted to use clinical features to predict the extent of the immune deficiency. There may be some statistical association of immune deficiency with hypoparathyroidism, however, this has not been observed in other studies and certainly there are no strict predictors of the severity of the immune deficiency in 22q11.2del (Herwadkar, Gennery, Moran, Haeney, & Arkwright, 2010; Sullivan et al., 1998). Thus, current recommendations emphasize that clinical testing for the immunodeficiency should be performed in all patients since there are no robust clinical predictors (Bassett et al., 2011; Habel et al., 2014).

It has been recognized that there is variability in the deletion breakpoints, however, clinical detection of the deletion often does not distinguish specific breakpoints and instead utilizes either PCR detection of a region within the deleted region, multiple ligation probe amplification, or fluorescent in situ hybridization with the probe homologous to a region that is deleted. Thus, our knowledge of the relationship of the deletion breakpoints to the immune deficiency severity is very limited. In addition to reviewing the immune deficiency in 22q11.2del, this manuscript will also present new data on the influence of breakpoints on the immune deficiency. This study of deletion breakpoint size effect on the immune system is of practical value to clinicians managing patients with 22q11.2del and we will review the immunologic context of the condition.

2 | DYNAMIC CHANGES IN THE IMMUNODEFICIENCY

There are some aspects of the immune deficiency that evolve over time. The direct effect of thymic hypoplasia on peripheral blood T-cell counts is most apparent in early infancy (Chinen, Rosenblatt, Smith, Shearer, & Noroski, 2003; Dar et al., 2015; Kanaya et al., 2006; Lima et al., 2010; Sullivan et al., 1999). The T-cell counts in early infancy are strongly associated with thymic output and functional thymic size (Dar et al., 2015). Thymic size observable on imaging may not accurately reflect the functional thymic size because the thymus can arrest in its descent into the anterior mediastinum leaving small thymic remnants in the neck, not apparent on imaging (Lima et al., 2010). Low T-cell counts are normally corrected physiologically by increased secretion of IL-7 (Tan et al., 2001). IL-7 acts to increase thymic output and increases peripheral proliferation of T cells (Tan et al., 2001; Tchao & Turka, 2012). These combined effects serve to normalize T-cell counts and by adulthood most adults with 22q11.2del will have normal or nearly normal peripheral blood T-cell counts. These T cell counts in adulthood belie the acquisition of some dysfunctional features that compromise the ability of the T cells to contribute to host defense (Piliero, Sanford, McDonald-McGinn, Zackai, & Sullivan, 2004; Zemble et al., 2010). Understanding the dynamic nature of the immune deficiency in 22q11.2del is critical for providing care to patients.

A second aspect of the immunodeficiency is the secondary humoral immune deficiency, an aspect reviewed here but not studied in the cohort descibred below. This is presumed to be secondary to compromised T cell help for B cell development. Nevertheless, it remains unexplained why this aspect of immunodeficiency is most often seen in older children and adults. Described humoral defects include an increased rate of IgA deficiency, compromised differentiation of B cells into the switched memory compartment and decline in immunoglobulin production and function (Derfalvi et al., 2016; Finocchi et al., 2006; McLean-Tooke, Spickett, & Gennery, 2007; Patel et al., 2012; Smith et al., 1998; Zemble et al., 2010). IgM levels appear to decline and this may be a marker for humoral dysfunction in general (Patel et al., 2012). Natural IgM antibodies appear to be diminished in 22q11.2del and these key antibodies have a non-redundant function in the defense against gram negative bacteria (Klocperk, Mejstrikova, Kayserova, Kalina, & Sediva, 2015). In addition, poor responses to vaccines have been described in adults with 22q11.2del (McLean-Tooke et al., 2007). There is still much to learn about the humoral immune deficiency and specifically the evolution of the immunodeficiency in adulthood. While these humoral defects are presumed to be secondary to insufficient T cell help, there has not been an exhaustive study of *TBX1* expression or dysregulation of downstream genes in secondary lymphoid organs such as lymph node and spleen. Recently, natural killer cell function and T cell function were shown to be compromised due to haplosufficiency for other genes in the deleted region (Giacomelli et al., 2016; Zheng et al., 2015). Therefore, the humoral defects could be a direct result of the deletion and not due to compromised T cell help.

3 | DELETION ENDPOINTS AND LYMPHOCYTE COUNTS

To address the issue of breakpoint contributions to the immune deficiency, we examined our data on 52 infants with deletion testing and a full immunologic evaluation near 1 year of age. Two patients were removed from the analysis due to chylous losses (one patient in each of the deletion cohorts). We compared lymphocyte counts between those with a *TBX1* deletion (A–B, A–C, A–D deletions) with those who did not have a *TBX1* deletion (B–D, C–D, D–E, D–F deletions) and a set of patients with a 22q11.2 duplication including *TBX1*. The cohorts consisted of 52 subjects with a deletion that included *TBX1*, eight patients with a distal deletion that did not include *TBX1*, and six patients with a duplication that included *TBX1*. Lymphocyte subset absolute counts for each group were analyzed by *t*-test, and are shown in Figure1. CD3 counts were significantly lower in the *TBX1*-deleted cohort compared to the other two cohorts (Figure 2). Similarly, CD4 counts were lower in the *TBX1*-deleted patients compared to the other two cohorts. CD8 (not shown), CD19, and NK call counts were not different between the three cohorts. The relation of phenotype to deletion breakpoints and *TBX1* function has been described in murine models but the T cell phenotype has not been previously reported in clinical cohorts of patients with defined deletions (Jerome & Papaioannou, 2001; Lindsay et al., 1999, 2001; Vitelli et al., 2003). These clinical data provide important information for immune monitoring of patients followed for 22q11.2 deletions and duplications.

4 | AUTOIMMUNE DISEASE

Autoimmune diseases occur with high frequency in 22q11.2del (Davies, Stiehm, Woo, & Murray, 2001; Davies, Telfer, Cavenagh, Foot & Neat, 2003; Jawad, McDonald-Mcginn, Zackai, & Sullivan, 2001; Kratz et al., 2003). There have been several proposed mechanisms including altered regulatory T cell development in the face of limited thymic tissue, increased responses to self-antigens with homeostatic proliferation, and dysregulation due to lymphopenia (Di et al., 2015; Ferrando-Martinez et al., 2014; McLean-Tooke et al., 2007; Milner, Ward, Keane-Myers, & Paul, 2007; Sullivan, McDonald-McGinn, & Zackai, 2002; Tison et al., 2011). The most common autoimmune disease affecting 22q11.2 patients in childhood is idiopathic thrombocytopenic purpura, and the second most common in juvenile idiopathic arthritis (Bjork, Oskarsdottir, Andersson, & Friman, 2012; Gennery et al., 2002; McLean-Tooke et al., 2007). Platelet size and number are lower at baseline in most patients with the deletion, which may cause confusion with idiopathic thrombocytopenia purpura (Lawrence, McDonald-McGinn, Zackai, & Sullivan, 2003). Adults with 22q11.2 deletion syndrome have a high rate of hypothyroidism but this has not been definitely shown to be secondary to autoimmune destruction (Bassett et al., 2005). Celiac disease may be increased over the frequency in the general population (Digilio et al., 2003). The mechanism underlying the susceptibility to autoimmune disease is probably multifactorial. One study found that low T cells in early childhood were more common in those with subsequent autoimmune disease (Tison et al., 2011).

Therapy for autoimmune disease remains undefined. Standard approaches are most often used although sometimes an effort is made to limit the suppression of T cells. Rituximab has been useful in autoantibody-mediated disorders. There is a growing appreciation that low T cells in early infancy are a marker for subsequent dysregulation, although more study is required.

5 | ATOPY

Extreme lymphopenia can drive a Th2 skewing, strongly associated with atopy (Khiong et al., 2007; Milner et al., 2007; Wada et al., 2000). Nevertheless, it was only recently appreciated that allergies and Th2 skewing of T cells were identified in patients with 22q11.2del (Morsheimer, Brown Whitehorn, Heimall, & Sullivan, 2017; Staple, Andrews, McDonald-McGinn, Zackai, & Sullivan, 2005; Zemble et al., 2010). Low T cell counts in infancy were associated with an increased risk of atopy, similar to what was described for autoimmune disease (Morsheimer et al., 2017).

6 | SUMMARY

The 22q11.2del syndrome is associated with a broad range of end organ effects. Prolonged viral infections have long been known to be associated with compromised T cells. Secondary consequences related to T cell lymphopenia include an increased risk of atopy and autoimmune disease. A key aspect of the immunodeficiency is the relationship of CD4 + lymphopenia to deletion breakpoints including the *TBX1* region, a previously unappreciated association.

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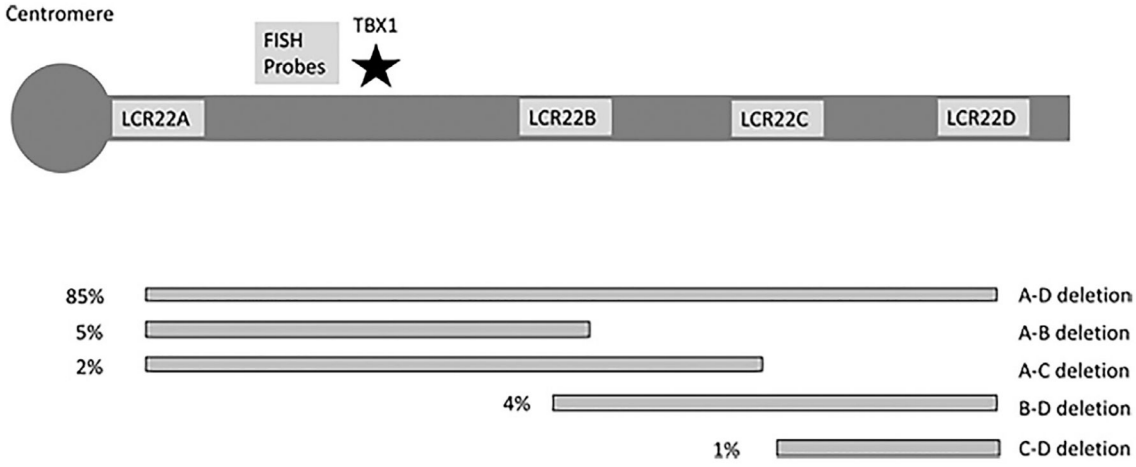

FIGURE 1.

Chromosome 22q11.2del breakpoints commonly observed. This schematic diagram demonstrates the most common breakpoints observed in 22q11.2del. The most common deletion is A–D and includes *TBX1*. The location of *TBX1* is shown with a star. The percentages next to each deletion schematic indicate the frequency. In addition, there are rarer deletions not mediated by the low copy number repeats (LCRs) indicated in the figure and larger deletions that extend distal to the region shown in the figure. Duplications are similarly variable but most often lead to duplication of the A–D region

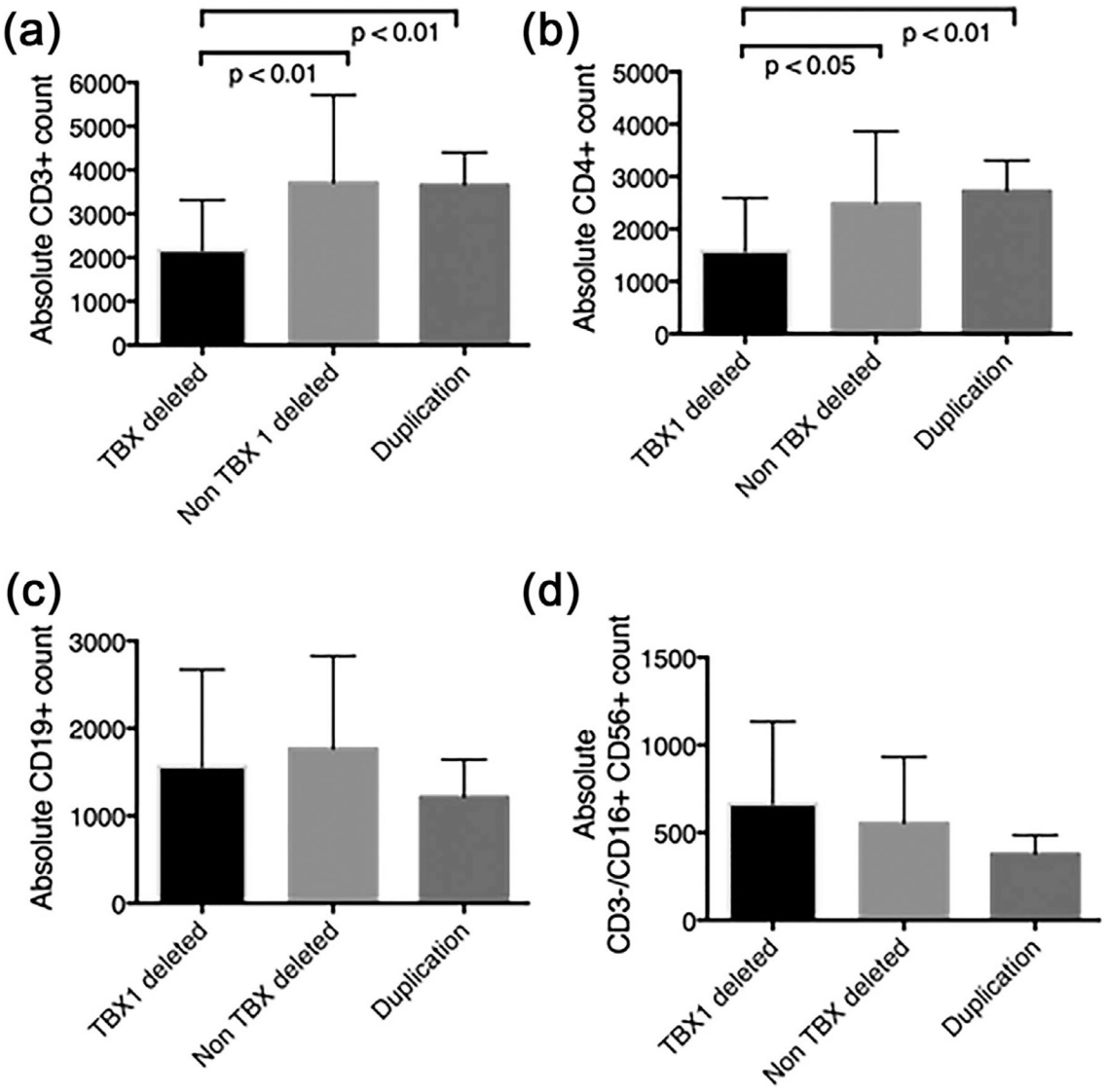

FIGURE 2.

22q11.2 deletions including *TBX1* gene region are associated with CD3+ lymphopenia due to decreased CD4+ count. Charts of patients were retrospectively reviewed following approval from the Children's Hospital of Philadelphia Institutional Review Board. Peripheral blood absolute (a) CD3+ counts, (b) CD4+ counts, (c) CD19 counts, and (d) natural killer CD3−/CD16+ CD56+ counts were determined by flow cytometry. Data were extracted from the patients' medical records from Immunology visit near 12 months' of age. 22q11.2 deletion patients with a *TBX1* containing deletion (A–B, A–C, A–D deletions, $n = 52$), were compared to patients with 22q11.2 deletion with deletions not containing *TBX1* (B–D, C–D, D–E, D–F deletions, $n = 8$), and patients with 22q11.2 duplications ($n = 11$). Bars demonstrate mean and error bars indicate standard deviation. p values refer to an unpaired t-test