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CASE REPORT

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A child with Klinefelter syndrome and both IgE-mediated food allergy and low proportion of naive Treg

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Key Clinical Message

This case suggests a possible association between Klinefelter Syndrome and decreased regulatory T cells (Treg) cells, relating to an increased risk of allergic and autoimmune disorders in these patients. The immune phenotyping of the circulating FOXP3+ naive Treg populations in KS patients may help to indicate this predisposition.

KEYWORDS

FoxP3, Klinefelter syndrome, regulatory T cell

Klinefelter syndrome (KS) is the most common male sex aneuploidy. It comprises one or more additional X chromosomes, typified by a karyotype of 47 XXY, with an incidence of 1 in 500-1000 male births.[1] Other variants, 48 XXXY or 49 XXXXY, occur but are less common and associated with a more extreme phenotype.[1] The diagnosis of the 47 XXY form of KS is often delayed, and tends to present with tall stature, hypogonadism, infertility, and gynaecomastia.[1] KS is associated with increased risk of autoimmune diseases such as systemic lupus erythematosus, scleroderma, polymyositis, and rheumatoid arthritis.[2] The association between KS and atopy is less well characterised, but there appear to be higher rates of asthma and allergy, particularly in those with the more extreme forms of KS.[3]

Allergic and autoimmune conditions are linked to a breakdown in immune tolerance, and deficits in regulatory T-cell (Treg) number and/or function have been associated with these conditions.[4] The development and function of Treg is specified by transcriptional, epigenetic, and post-transcriptional regulation of the *FOXP3* gene, located on the X chromosome.[5] Although the X chromosome polypoidy associated with KS has been linked to epigenetic and transcriptional dysregulation,[6] it is unclear whether the expression of *FOXP3* is disrupted in KS, and whether potential abnormality in Treg development and function contribute to the increased risk in autoimmune and allergic conditions associated with this syndrome.[5]

Here we describe a male child with IgE-mediated food allergy and an exceptionally low proportion of $FOXP3^+$ naïve Treg (nTreg) at 1 year of age, who was subsequently diagnosed with KS. The child was a participant in the Barwon Infant Study (BIS), which is an Australian birth cohort study (n = 1074), in which participants were recruited using an unselected antenatal sampling frame.[7] The infant had no family history of food allergy or atopy. Both the perinatal and postnatal periods were uneventful. As part of the BIS protocol, at 1 year he was found to have a 3-mm positive reaction to egg and clinical allergy was confirmed using a validated food challenge protocol.[7] He remained

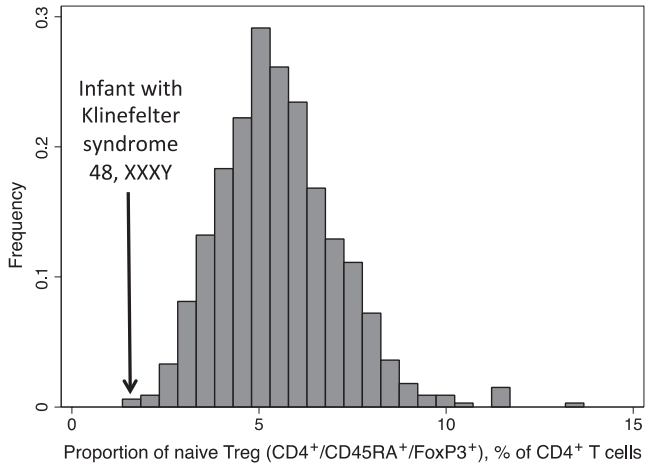

FIGURE 1 Distribution of nTreg at one year of age among participants in the Barwon Infant Study. Peripheral blood samples were collected at one year of age and the mononuclear cells (MNC) isolated. The proportion of naïve Treg (nTreg, $CD4^+/CD45RA^+/FoxP3^+$) was measured by flow cytometry and presented as a percentage of the $CD4^+$ T cells (mean = 5.53% (95% CI, 5.40%-5.65%), n = 675). The infant who was later diagnosed with Klinefelter syndrome had the lowest percentage of nTreg (1.35%)

food allergic at 4 years of age. He also had a clinical diagnosis of eczema, and has an extensive history of viral infections. In the context of speech delay, karyotype testing was conducted at 2 years, revealing a 48, XXXY chromosomal structure/pattern. Mild impairments to fine and gross motor skills, as well as motor dyspraxia, were subsequently attributed to this diagnosis.

As an additional component of the BIS protocol, immune phenotyping of the circulating nTreg populations was also performed at 1 year of age.[8] Notably, the proportion of nTreg (as a proportion of total $CD4^+$ T-cells) was found to be 1.35% - the lowest of the 675 individual infants in BIS who underwent nTreg measures (Figure 1).

There are currently no reports of the frequency of nTreg in KS. Investigations of Treg measures have been performed in Turners syndrome, a 45,X karyotype; however no changes in frequency were observed.[9] KS is associated with variable inactivation of the surplus X chromosome(s),[1] and differential expression of a number of X-chromosomal genes has been reported.[10] Our data support a link between the atypical copy number of *FOXP3* in KS, a decrease in nTreg, and an increased risk of allergic disease. Further studies regarding *FOXP3* methylation and/or gene expression in KS and its variants are required and may inform the care and monitoring of KS patients.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTION

RF: original draft; PV: draft review and edit, management of clinical case; MLKT: draft review and edit; ALP: draft review and edit; EW: draft review and edit; RS: draft review and edit; FC: investigation, methodology, original draft, draft review and edit; the Barwon Infant Study Investigator (BIS) Group - oversight of BIS cohort study.

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