

## **Determinants of Linear Growth in Children with Inflammatory Bowel Disease**

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**Background:** Inflammatory Bowel Disease (IBD), particularly Crohn's Disease (CD), has long been associated with impaired linear growth in children. Though the mechanism of this impairment is unknown, we have shown, in two retrospective studies, that a mutation in CARD15 with concomitant high titer GM-CSF antibodies is associated with growth retardation without changes in serum cytokine levels, but that changes in serum LBP and IGF-1 can also independently impact linear growth. To date, there have been no prospective studies that have observed relationships between the possession of risk alleles, cytokine levels, and linear growth.

**Hypotheses:** CARD15 SNP carriage and high GM-CSF antibodies increase the risk for linear growth failure. The relative suppression of LBP and induction of IGF-1 is associated with better growth.

**Methods:** A cohort of 191 children (Tanner Stage I or II) with CD, UC, or indeterminate colitis was recruited from three locations: Cincinnati Children's Hospital; the Hospital for Sick Children, Toronto; and the IBD Program, Ottawa. Blood samples were obtained at study entry and at one or more time points during a minimum of two years follow-up. Genotyping was performed in the CCHMC sequencing core, and GM-CSF antibodies, cytokines, and growth factors were measured with ELISA.

**Results:** Among 104 children with CD, those who had both the CARD15 risk allele and high titer GM-CSF antibodies had a significantly lower height Z-score ( $p=0.0122$ ) and a greater incidence of growth retardation at diagnosis ( $p=0.012$ ). LBP dropped ( $n=108$ ,  $p<0.0001$ ) and IGF-1 rose ( $n=108$ ,  $p=0.0004$ ) from baseline to follow-up. Finally, a higher concentration of serum IGF-1 was inversely associated with serum LBP at baseline ( $n=123$ ,  $r=-0.221$ ,  $p=0.014$ ) with a similar trend during follow-up ( $n=54$ ,  $r=-0.1975$ ,  $p=0.1523$ ).

**Conclusions:** The possession of both a CARD15 risk allele and high GM-CSF antibody levels are associated with linear growth failure in CD children. Also, a decrease in LBP concentration is correlated with an increase in IGF-1 concentration at baseline and follow-up. Furthermore, an increase in IGF-1 and a decrease in LBP were achieved during the course of treatment indicating a possible role of those factors in the growth normalization process in children with IBD.