

Krantz ID, McCallum J, DeScipio C, et al. Cornelia de Lange syndrome is caused by mutations in *NIPBL*, the human homolog of *Drosophila melanogaster* *Nipped-B*. *Nat Genet*. 2004;36:631–635.

Tonkin ET, Wang T-J, Lisgo S, et al. *NIPBL*, encoding a homolog of fungal *Scp2*-type sister chromatid cohesion proteins and fly *Nipped-B* is mutated in Cornelia de Lange syndrome. *Nat Genet*. 2004;36:636–641.

First Editor's Comment: *Mutations in NIPBL were found in approximately 20% of patients with the clinical manifestations of the CdLS who were examined, implying that this disorder is likely to be genetically heterogeneous. Other sites that have been linked to the CdLS are located on chromosomes 2q37, 10p13, and 14q24, but an abnormality in one or more of the genes in these regions has not been detected to date. It is likely that as mutations in other genes that lead to the CdLS are identified, our understanding of the genetic regulation of somatic differentiation will be greatly enlarged.*

Allen W. Root, MD

Second Editor's Comment: *The multiplicity of clinical features of CdLS, combined with reports of chromosomal rearrangements in some patients, had long suggested that CdLS might be a contiguous gene syndrome. These papers demonstrate that the clinical manifestations reflect the diverse functions of a single gene product—delangin—during development. Most of the reported cases have severe clinical phenotypes and mutations that predict full loss of function, such as frameshift mutations leading to premature stop of translation. However, in a few cases mutations predicted to alter some, but not all functions, ie, 3 bp deletion that would remove a single amino acid appears to produce milder features, suggesting that the manifestations reflect loss or alteration of specific functions related to different regions of delangin. Correlation of clinical findings with specific mutations in more patients, combined with experimental modeling of specific CdLS mutations in mice, should help to sort out the relationship between genotype and phenotype.*

William A. Horton, MD

Metabolic Syndrome in Obese Children

The metabolic syndrome (MS) described as a link between insulin resistance, hypertension, dyslipidemia, and type 2 diabetes mellitus (T2DM), with an increased risk of atherosclerotic cardiovascular disease, has been reported to have a prevalence of 6.8% among overweight adolescents and 28.7% among obese adolescents (NHANES III). In order to determine the effect of the degree of obesity on the prevalence of the MS and its relationship to insulin resistance, Weiss and colleagues studied 439 obese (BMI >97% for age and sex), 31 overweight (BMI 85%–97% for age and sex), and 20 non-obese children and adolescents (4–20 years of age) with baseline measurements of BMI, blood pressure (BP), plasma lipids, C-reactive protein, interleukin-6, and adiponectin. Oral glucose tolerance tests were performed as well. Degree of obesity was defined by BMI z-scores (moderately obese = 2.0–2.5 and severely obese >2.5). The overall prevalence of MS was 38.7% in moderately obese subjects and 49.7% in severely obese subjects. Glucose, insulin, insulin resistance, triglycerides, C-reactive protein, interleukin-6, systolic BP, and prevalence of glucose intolerance (defined as 2hr glucose of 140–200 mg/dL) increased with increasing obesity. HDL cholesterol and adiponectin decreased with increasing adiposity. Three factors explained 58% of the variance observed: obesity and glucose metabolism, dyslipidemia and BP. Through multiple regression analysis of risk factors associated with the syndrome, a significant risk included age, sex, BMI z-score, race or ethnic group, and insulin resistance. Each half-unit increase in the BMI z-score was associated with a significant increase in the risk of the MS. White children had a higher risk than black children, and girls had a lower risk than boys.

A 2-year follow-up study was performed in 77 children; 34 with and 43 without MS. At follow-up 24 of 34 children continued to have MS. The 10 who improved had a lower BMI initially, gained less weight over the 2 years, and had decreased insulin resistance. The MS developed in 16 of 43 children who did not meet the criteria at baseline; they had gained more weight than the others. Eight subjects developed T2DM, and all had impaired glucose tolerance at baseline. The authors conclude that MS is much more common than previously reported and that each element of the syndrome is adversely affected by increasing weight. Of particular concern were the markers of inflammation, interleukin-6 and C-reactive protein, which escalated with increasing obesity and presumably put these children at high risk for cardiovascular disease.

Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med*. 2004;350:2362–2374.

Editor's Comment: *This manuscript presents some frightening data. The prevalence of MS, once a diagnosis reserved almost exclusively for adults, is very common among obese adolescents. Weiss et al showed that not only adolescents, but children meet the criteria for this diagnosis, and that markers of cardiovascular inflammation are present at a very young age. The progression to develop MS over 2 years as weight continues to increase is remarkable.*

Despite the importance of the documentation that this manuscript presents, the findings and conclusions are not surprising to most physicians who provide care to America's young. Indeed, the epidemic of childhood obesity is evident to any observer of children. It is heartening that some federal research funds are now being made available to study this problem and that Medicare is beginning to recognize

obesity as a medical condition. Regardless of the data documenting the prevalence of obesity and the morbidities and co-morbidities associated with it, the behavioral and societal interventions required to stop its progression have not been adequately addressed. Reduction in the incidence and severity of obesity will require more than medical

research—it will require significant input of pediatricians and family physicians, schools, media, and commercial enterprises. Being apprised of the seriousness of the problem is just another wake-up call.

William L. Clarke, MD

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