NIPBL Gene Responsible for Cornelia de Lange Syndrome, a Severe Developmental Disorder

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The *NIPBL (IDN3)* gene encodes a key protein, delangin, responsible for the correct development of many organs in the growing embryo. It was identified in June 2004 by two independent studies, published back to back, as the gene causing Cornelia de Lange syndrome (CdLS) [1,2]. Named after the Dutch physician who first described it in 1933, this syndrome occurs in one of every 10,000 individuals. It includes mental retardation, self-injurious behavior, impaired growth, heart defects, hearing and visual loss, distinctive facial features and severe limb abnormalities [Figure 1].

In the first study [1] a whole genome scan was performed of affected and non-affected members in 12 families, in which four candidate genomic regions for CdLS were identified. Further cytogenetic analyses of chromosomal rearrangements have narrowed the search down to an interval of 1.1 Mb on chromosome 5p13.1–13.3. Mutational analysis of the first three exons of all 11 genes in this genomic region led to the identification of the causative gene, *NIPBL*. Subsequently, mutations spread throughout the gene were identified in all the affected individuals, confirming the discovery of the gene responsible for CdLS.

NIPBL stands for "Nipped B-like," named after its counterpart in Drosophila fruit flies, "Nipped B." Fruit flies having the mutated gene show abnormally nipped wing structure [Figure 2A]. *Nipped-B* is an essential regulator of several developmental genes, including the homeobox *Ultrabithorax* (*Ubx*), whose mutations display a double thorax fly [Figure 2B], and *Notch* that displays aberrant wing phenotype. Interestingly, two other genes involved in Notch signaling are implicated in human developmental disorders: mutations in *JAG1* result in Alagille syndrome [3], and mutations

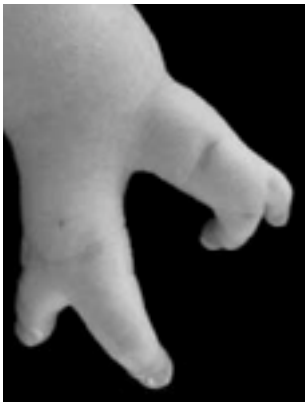

Figure 1. Distal reduction defect with missing and fused digits.

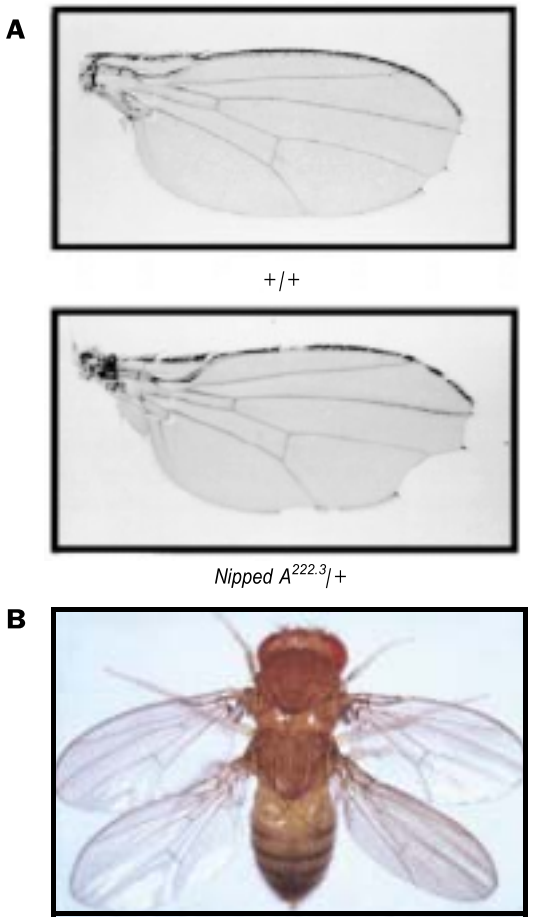

Figure 2. [A] Dominant enhancement of the cut wing phenotype of flies wuth the cut *wing* mutation by *Nipped* heterozygous mutations (lower left). A control cut wing with a few margin nicks is shown in the upper left (+/+). The additional *Nipped* $A^{222.3}$ mutation enhances the marginal nicks. (Rollins et al., 1999, with permission [5]). **[B]** Drosophila *bithorax* mutation.

in *DLL3* result in spondylocostal dysostosis [4]. In yeast and similar fungal species, proteins encoded by *NIPBL* homologs function in sister chromatid cohesion, in meiotic chromosome pairing and in DNA repair. *NIPBL* counterparts in higher species are akin to chromosomal adherins and have an architectural role in facilitating long-distance interactions between enhancers and promoters of the homeobox genes' regulatory elements. This explains the profound developmental outcome of *NIPBL* mutations.

In order to substantiate a role for *NIPBL* in development, the authors of the second study [2] carried out *NIPBL in situ* hybridization analyses on human embryonic tissue sections. These showed an expression pattern consistent with the CdLS phenotype. The gene was expressed in developing limbs and later in cartilage primordia of the ulna and of various hand bones. Sites of craniofacial expression included the cartilage primordium of the basioccipital and basisphenoid skull bones and elsewhere in the head and face, including a region encompassing the mesenchyme adjacent to the cochlear canal. Furthermore, the first study [1] included a similar examination of the expression of the mouse *NIPBL* ortholog. Signals were detected widely at gestation days 9.5 and 10.5, with notable accumulations in limb buds, branchial arches and craniofacial mesenchyme. These regions are involved in patterning of the skeleton and soft tissues of the limbs, jaw and face.

The identification of mutations in a single allele of *NIPBL* in individuals with CdLS is consistent with a dominant pattern of inheritance. All mutations identified so far predict a truncated protein product and probably result in functional haplo-insufficiency. That haplo-insufficiency is a mechanism in CdLS is confirmed by a child with a large deletion of the region (encompassing *NIPBL*) and severe manifestations of CdLS, and by a child with translocation who also has severe manifestations [1].

Although CdLS has been known for decades, the disease was a challenge to scientists. It was difficult to trace any one source for its multiple effects on many organs. The disease is also variable – some patients have much milder forms of CdLS. In addition, because few individuals with CdLS had children, it is rare to find parents and children who both have the disease.

This discovery is exciting since it will pave the way for genetic tests to confirm or rule out a clinical diagnosis. Furthermore, it will assist genetic counselors in detecting affected embryos prenatally. Fortunately CdLS has a low (1%) recurrence risk, so the availability of prenatal diagnosis will allow virtually all families to eventually have healthy offspring.

References

1. 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;36:631–5.
2. Tonkin ET, Wang TJ, Lisgo S, Bamshad MJ, Strachan T. NIPBL, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteins and fly Nipped-B, is mutated in Cornelia de Lange syndrome. *Nat Genet* 2004;36:636–41.
3. Li L, Krantz ID, Deng Y, et al. Alagille syndrome is caused by mutations in human Jagged1, which encodes a ligand for Notch1. *Nat Genet* 1997;16:243–51.
4. Bulman MP, Kusumi K, Frayling TM, et al. Mutations in the human delta homologue, DLL3, cause axial skeletal defects in spondylocostal dysostosis. *Nat Genet* 2000;24:438–41.
5. Rollins RA, Morcillo P, Dorsett D. Nipped-B. A Drosophila homologue of chromosomal adherins participates in activation by remote enhancers in the cut and Ultrabithorax genes. *Genetics* 1999;152:577–93.

Fore more information on this gene, search for IDN3 or NIPBL in http://Genecards.weizmann.ac.il/

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No one tests the depth of the river with both feet

Indian proverb

Capsule

Helicobacter pylori and American Indians

The gastric bacterium *Helicobacter pylori* is peculiarly specific to human beings and infects nearly half the population. Decades-long infections can result in gastritis, peptic ulcers, and even cancer. Aspholm-Hurtig et al. have explored the marked biogeography observed in the severity of *H. pylori* infections in relation to the known ability of the pathogen to bind to the carbohydrates of human blood group antigens. The bacterial adhesin BabA determines blood group binding and governs the distribution of disease prevalence. American-Indian populations, who almost exclusively possess blood group O, and the strains of *H. pylori* that infect these people exhibit a high frequency of strains that only bind the carbohydrates displayed by this blood group. This finding also explains the high prevalence of peptic ulcer disease in these peoples. The Amerindian strains have derived from European strains within the past 500 years by an attrition of "generalist" bacteria that can also bind to other blood group types.

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