



CdLS Foundation

Cornelia de Lange Syndrome Foundation, Inc.
Reaching Out, Providing Help, Giving Hope

A Journey, Not a Destination

By Laird Jackson, M.D., Clinical Advisory Board Member and former CdLS Foundation Medical Director

In the beginning there were two West Coast mothers – Carol Welsh and Sue Anthony, who met in 1970 because their children shared the same rare condition, called CdLS. Frustrated by the appalling lack of available medical information about their children’s condition, they scraped up a supply of paper, an old duplicating setup with imprinting gel, master forms for typing and appealed to the March of Dimes for a mailing list of their clinical grantees. Working far into the waning Northwestern nights, they cranked out a newsletter, licked hundreds of stamps and sent the product forth in the mail. Thus began a journey that has just reached an important milestone.

That 1977 newsletter reached a clinician/researcher at Jefferson Medical College, Laird Jackson, and a subsequent issue had a medical question, which I answered initiating a correspondence. In 1980, Sue and the Matheson and Sharrard families arranged an eastern vacation to meet CdLS families at a Pennsylvania picnic. There, I met Sue and the other families, some of whom I knew from my work. There, I also met Julie Mairano and was asked, “Who are you and what do you want?” My answer (met with some skepticism) was simple – “I’m just someone who is interested in CdLS and want to help the children and families if I can.” I met a few families, took some notes and realized that this experience was unique so my wife, Marie Barr, and I began holding “clinic” at a picnic table outside to afford some privacy.

These gatherings moved to Maryland where families stayed overnight at the “Red Horse Motel.” In three years I had seen more children with CdLS than anyone and Marie had become a fast friend of the children and the families. Marie and I missed the 1984 picnic because of personal illness. The “picnics” transformed into “conventions” in 1985-86 in Indianapolis, sponsored by the American Legion. Families met at a hotel and the “clinic” and informational meetings were held at a school facility nearby. More families were recorded and the children’s medical information gathered. Close to 100 children had been seen.

In summer 1986, I traveled to a Los Angeles picnic arranged by Sue Salmons to film and examine children. Sue brought Dr. Dick Mungo to talk about dental problems and he became the beginning of a medical team. At the 1987 Philadelphia meeting, Marie arranged facilities at a medical school for pediatrics, genetics, orthopedics, ENT, neurology, radiology and ophthalmology to see children. The head of children’s service at the Wills Eye Hospital assigned a young resident in ophthalmology, Dr. Alex Levin to the task of seeing patients. The medical team was growing.



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The 1988 convention was in Chicago and the 1989 convention was in San Francisco. A collaboration began in 1989 with other researchers into genetic causes of CdLS. We needed blood samples for cells and DNA from children and their parents and our first collections were aided by Kathy Wagner in York Harbor, ME (in late summer sun) and Linda Hasecke in Toledo, OH (in early fall snow). Thereafter, blood samples were collected at many family meetings and conferences. At the 1990 and 1991 conference we were joined by two new faces – Dr. Antonie Kline and Dr. Joan Overhauser, both from Jefferson. Many more came aboard and the Scientific Advisory Council was officially born.

In 1991 Dr. Kline and I attended a CdLS symposium where Dr. Maggie Ireland announced that her team in Newcastle, U.K., had “found the gene.” I cautioned her that their finding of a chromosome #3 break in a CdLS child was a wonderful discovery (#3 had long been suspected to be the site of a gene on other evidence), but did not quite constitute “finding the gene.” Drs. Overhauser and Kline attempted to formulate a collaboration with the Newcastle group but were not successful. So the Jefferson researchers along with Dr. Antonio Baldini of Houston, extended their current efforts and initiated a research approach termed “linkage.” Here, they had to trace the inheritance of specific chromosomes (especially #3) from parents to their children by using DNA markers such as one sees in TV crime shows. This required the participation of families where the occurrence of more than one individual with the syndrome suggested that a gene is transmitted within the family to cause the syndrome. I was alerted to one such family in 1987, so I started looking for others.

In 1992, Marie and I missed the Boston conference. Marie had become the President of the Foundation’s Advisory Board and she attended her last conference in Columbus in 1993. Because of her long devotion to the families, I continued, after her death in 1995, to search for the gene in spite of my laboratory’s limitations. In late January, I collected more DNA samples from “transmitting families” in Denmark. Then a Finnish colleague and I went up the coast of Sweden across the border and down the coast of Finland in a week-long trip to visit and collect samples from three more families. In April, I traveled across Canada and the U.S. visiting yet more families. On this trip I met a child in Idaho with a chromosome break that would prove critical to the research. At first it did not seem important because it was on chromosome #5 not #3. But by late summer my linkage attempts showed that #3 might not be the place to look for the gene. So I arranged with this child’s family to obtain DNA and a small piece of tissue for creating long lasting cell cultures. A month later I met (and later married) the driving force that would keep me in focus until the riddle was solved – a new Marie.

Shortly after the 1996 Nashville conference another mother was having a pregnancy which might benefit from knowledge about the gene. She had two children with CdLS and was at increased risk for another. I desperately looked at her #3 chromosomes for some linkage and a way to predict the outcome of her pregnancy. Alas, there was not only no evidence that the gene might be on #3 – there was a strong suggestion that it was not. One of her #3 chromosomes had gone to one child with CdLS but not the other, and the same #3

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chromosome had gone to a third unaffected child. Barring an infrequent accident, this suggested that the gene should not be on chromosome #3. More evidence was obviously needed.

In Stratford, England in 1997 I met Prof. Tom Strachan, the head of the Newcastle research team in the U.K. I told him of my suspicions about #3. We struck an informal agreement that he would continue to use chromosomal breaks in their research while I would try linkage. We would keep each other informed. I thus arranged transfer of DNA and cell cultures from two more children with chromosome breaks to Newcastle (including the DNA from the Idaho child).

Then in late '97 I received a call from the Children's Hospital of Philadelphia (CHOP) from a young clinical and research fellow, Dr. Ian Krantz, asking if he could refer a child to me for a possible diagnosis. The referral was made, I saw the child, and made the report and forgot about the incident until early the next year when another important "mother" interceded. I was on the telephone with Dr. Nancy Spinner, director of cytogenetics at CHOP, when Ian walked into her office. Nancy reminded me that Ian had spoken to me before and, now that he was close to finishing his fellowship and becoming a faculty member, he was looking for a challenging research project. "How about collaborating on your interest in the Cornelia de Lange Syndrome," she said. "Let's meet," I said and the collaboration was born. The only intelligent thing I said at the meeting was "I don't think the gene is on chromosome #3."

In early 1998, I began transferring frozen DNA and cell cultures to Ian's lab. Ian began going to gatherings and attended his first CdLS conference in Minneapolis that July. Ian, Tonie, Marie and I watched the 4th of July fireworks together from atop the conference hotel. Ian initiated the ultimately successful applications for NIH grant sponsorship that would make continuing the research possible. The research first showed that chromosome #3 could not be the site of the gene in at least half of 10 families studied. Then Ian began a long search through the rest of the human chromosomes to eliminate as many as possible as sites. By late summer 2003 the number of remaining sites had been reduced and one of the remaining candidates was #5. This now made the Idaho child's chromosome break very important. Another fortuitous report of a fetus with a missing piece of #5 and a CdLS phenotype completed the clues pointing to #5. Ian immediately informed the Newcastle team and both teams went to work. The rest of the story belongs to Ian and his incredible crew of young lab research associates. Working nearly around the clock, they unearthed the solution using a combination of clever insight and planning, and a lot of plain hard work.

I have met many inspiring mothers in my journey. Each and every one – many more than are mentioned above – has contributed to and made possible the discovery we now have. Every family – every child – has given more than asked – without reserve. Thanks for the wonderful journey – and it's not over.