



**Collaboration Education and
Test Translation Program**

Collaboration Education and Test Translation Program

www.cettprogram.org

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NIH ORD CETT Program Director

ICORD September, 2007

- CLIA RULE - "Sec.493.3 Applicability.=3D20
- (a) Basic rule. Except as specified in paragraph (b) of this section, a laboratory will be cited as out of compliance with section
- 353 of the Public Health Service Act unless it--
- (1) Has a current, unrevoked or unsuspended certificate of waiver, registration certificate, certificate of compliance, certificate for
- (2) Is CLIA-exempt. (*NY state and Washington state*)
- (b) Exception. These rules do not apply to components or functions of--
- (1) Any facility or component of a facility that only performs testing for forensic purposes;
- (2) Research laboratories that test human specimens **but do not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients; or...**"
- <http://www.cms.hhs.gov/clia/default.asp?>

- 2004
 - 33% - testing is available only from “research” labs
 - 22% - clinical testing is available only outside US
- July 2007
 - 20% - testing is available only from “research” labs
 - 19% - clinical testing is available only outside US

Laboratories Listed in GeneTests

- 2004
- 40% - “Research only”
- 31% - Non US labs
- 40% - clinical testing in only 1 lab
- July 2007
- 47% - “Research only”
- 38% - Non US labs
- 28% - clinical testing in only 1 lab



Rare Disease Test Translation

Major Participants

- Conference Organizers

CDC, NIH ORD, Emory University

- Planning Committee

Joe Boone (CDC)

Bin Chen (CDC)

Carol Greene (HHS)

David Ledbetter (Emory)

Giovanna Spinella (NIH)

Mike Watson (ACMG)

Joann Boughman (ASHG)

Andy Faucett (CDC)

Steve Groft (NIH)

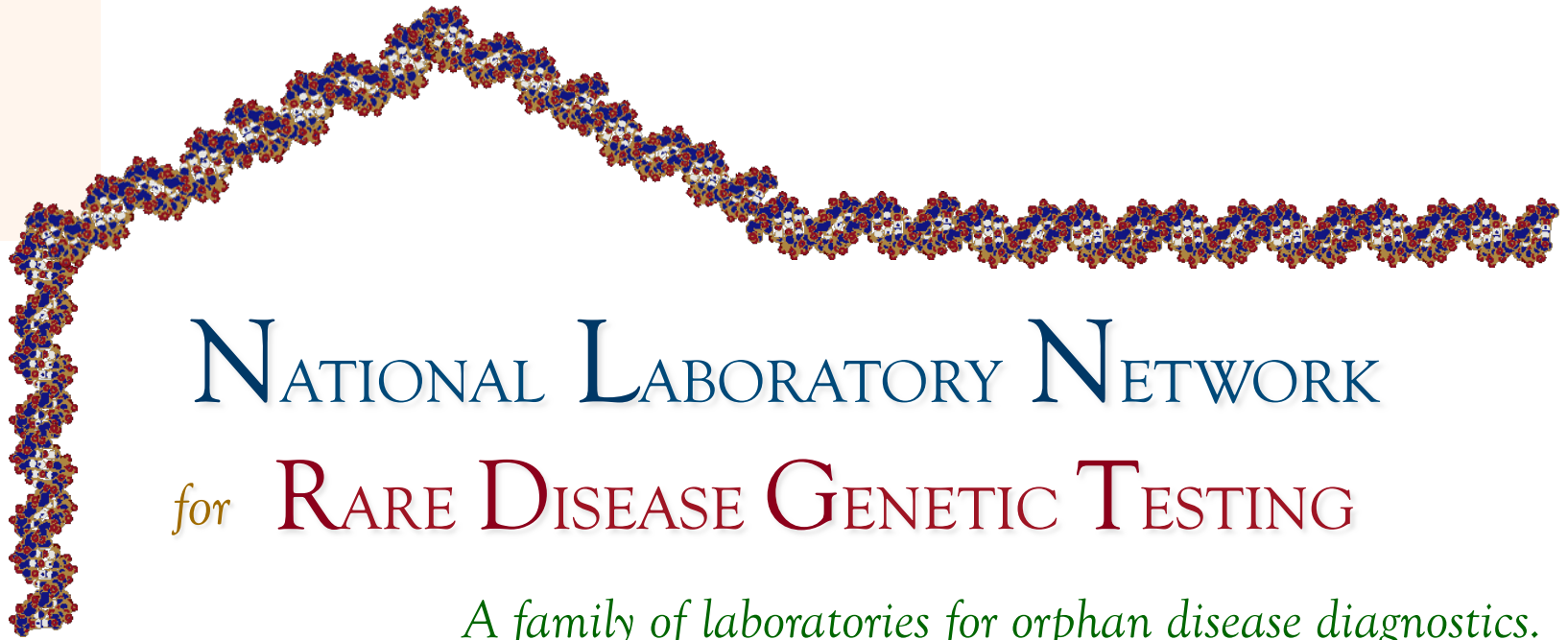
Michele Puryear (HRSA)

Sharon Terry (Genetic Alliance)

- CDC Staff

- ASHG

- ❖ May 19–21, 2004 Atlanta, GA
 - ❖ Workgroup meeting of invited experts
 - <http://www.phppo.cdc.gov/dls/genetics/RareDiseaseConf.aspx>
- ❖ March 17, 2005 ACMG Satellite
 - ❖ Workgroup meeting of invited experts (CETT idea)
- ❖ September 26–27, 2005 Washington, DC
 - ❖ Open national meeting
- ❖ October 6–7, 2006 Atlanta, GA
 - ❖ Workgroup meeting of invited experts with focus on Biochemical Genetics



NATIONAL LABORATORY NETWORK *for* RARE DISEASE GENETIC TESTING

A family of laboratories for orphan disease diagnostics.

Six laboratories formed the NLN in May 2004 and agreed to share a commitment to ensure that quality, affordable genetic testing services are accessible to all.

NLN website:

www.rarediseasetesting.org



www.cettprogram.org

Collaboration Education and Test Translation Program

ORD Program Director: Giovanna Spinella, MD
Project Coordinator: Andrew Faucett, MS
Scientific Advisor: Suzanne Hart, PhD
Review Board Coordinator: Roberta Pagon, MD
NCBI Liaison: Lisa Forman, PhD
Biochemical Advisor: William Gahl, MD, PhD

- ❖ To promote the development of new genetic tests for rare diseases.
- ❖ To facilitate the translation of genetic tests from research laboratories to clinical practices.



CETT Program Objectives

- ❖ To establish collaborations and provide education about each rare genetic disease; related genetic research & the clinical impact of testing.
- ❖ To support the collection and storage of genetic test result information in publicly accessible databases to leverage the information into new research and new treatment possibilities.

All parties benefit when:

- ❖ Quality of testing for rare disorders meets or **exceeds** existing standards

All parties benefit when:

- ❖ Clinical laboratories, researchers, clinicians, and disease specific advocacy groups collaborate
- ❖ High-quality educational materials explain what the test can and cannot tell you and how best to use the test

❖ Required

- ❖ Clinical (CLIA-certified) laboratory
- ❖ Researcher (laboratory and/or clinician)
- ❖ Disease specific advocacy group

❖ Recommended

- ❖ Genetic Counselor
- ❖ Clinical and laboratory research expert

- ❖ First applications accepted Feb-March 2006
- ❖ First Review Board evaluation in April 2006
- ❖ Facilitated application process
 - Constructive feedback
- ❖ Applications
 - Accepted monthly
 - Electronic submission
 - Reviewed in 2-3 month cycle

❖ Success Summary

- August 2007 – 27 tests reviewed
- 26 approved
- 3 in submission now
- 2 returned and re-submission encouraged
- 1 resubmitted

❖ Test Development Summary

- Sept 2007 – 16 tests available

❖ Review to Test Release

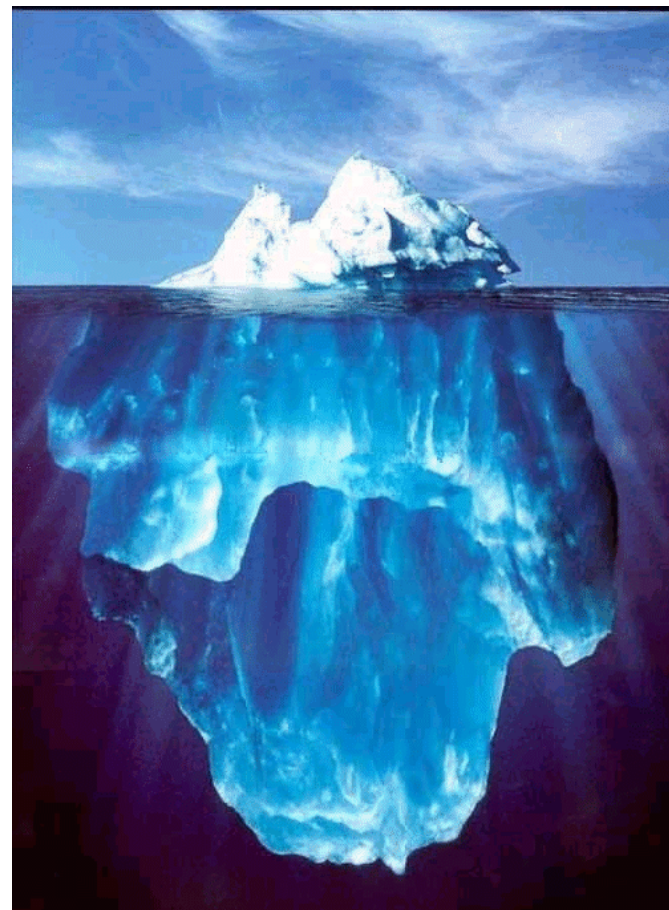
- 1 month to 12 months
- 5 month Average for released tests

❖ Anticipated Reviews

- Averaging 2 per month

NCBI (NIH) National Center for Biotechnology Information

- Help develop a useful data collection scheme and HIPPA compliant web based form
- Put data in a broader context to help advance knowledge about the disorder



Collaboration, Education and Test Translation (CETT) Program:
Cornelia de Lange Syndrome

clinical questionnaire

Please include copy of form with sample

Submit to Lab

Print Form

Patient Name	<input type="text"/>	<input type="radio"/> Male	DOB	<input type="text"/>	Today's Date	<input type="text"/>
		<input type="radio"/> Female				
Wt.:	<input type="radio"/> lbs <input type="text"/>	Ht.:	<input type="radio"/> in. <input type="text"/>	Age at Onset:	<input type="text"/>	Submitting Dr. contact information
	<input type="radio"/> Kg <input type="text"/>		<input type="radio"/> cm. <input type="text"/>	Age Now:	<input type="text"/>	<input type="text"/>
Ancestral Background: (As reported by Patient. Please check as many as apply. Text boxes will expand as you type))						
<input type="checkbox"/> Native American Specify <input type="text"/>		<input type="checkbox"/> African American <input type="checkbox"/> Black <input type="radio"/> Not African Amer.		<input type="radio"/> Latino or Hispanic <input type="checkbox"/> Caucasian <input type="radio"/> Not Lat. or Hisp.		
<input type="checkbox"/> Asian Specify <input type="text"/>		<input type="checkbox"/> Native Hawaiian <input type="checkbox"/> Other Pacific Islander		<input type="checkbox"/> Other Ethnicity Specify <input type="text"/>		

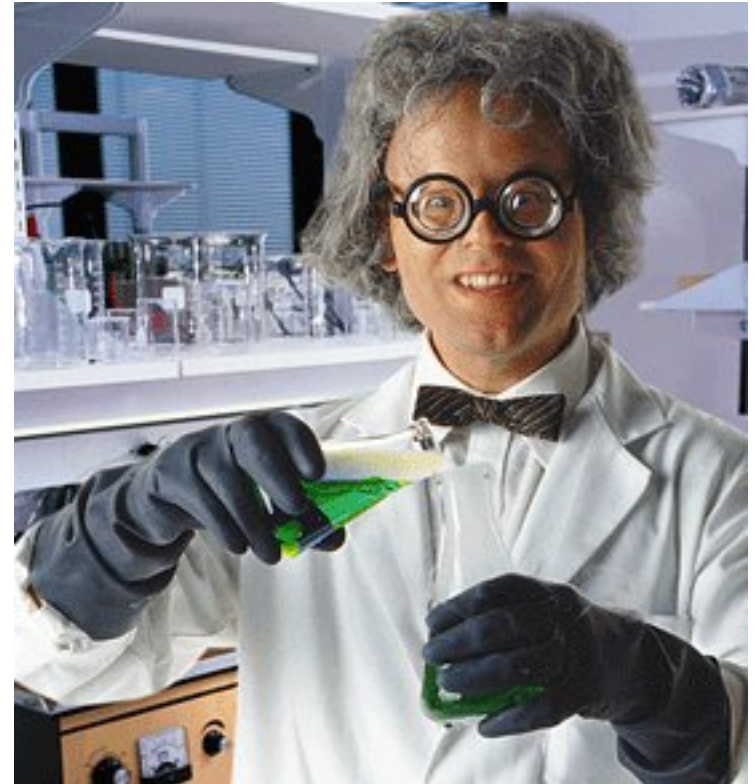
Features	Present:	Yes	No
Growth			
IUGR		<input type="radio"/>	<input type="radio"/>
Failure to Thrive		<input type="radio"/>	<input type="radio"/>
Gestational Age (wks)	<input type="text"/>		
Birth Weight (gms)	<input type="text"/>		
Birth Length (cm)	<input type="text"/>		
Birth OFC (cm)	<input type="text"/>		
Current OFC (CM)	<input type="text"/>		

Features	Present:	Yes	No
Craniofacial			
Microbrachycephaly		<input type="radio"/>	<input type="radio"/>
Synophrys/ arched eyebrows		<input type="radio"/>	<input type="radio"/>
Long, thick eyelashes		<input type="radio"/>	<input type="radio"/>
Low-Set ears		<input type="radio"/>	<input type="radio"/>

Features	Present:	Yes	No
Limb Abnormalities			
Upper extremity deformed		<input type="radio"/>	<input type="radio"/>
Describe	<input type="text"/>		
Small Hands		<input type="radio"/>	<input type="radio"/>
Thumbs Proximal		<input type="radio"/>	<input type="radio"/>
5th finger clinodactyly		<input type="radio"/>	<input type="radio"/>
Limited elbow extension		<input type="radio"/>	<input type="radio"/>
Lower extremity involvement		<input type="radio"/>	<input type="radio"/>
Small feet		<input type="radio"/>	<input type="radio"/>
2-3 toe syndactyly		<input type="radio"/>	<input type="radio"/>

Features	Present:	Yes	No
Gastrointestinal			
GER		<input type="radio"/>	<input type="radio"/>
Pyloric stenosis		<input type="radio"/>	<input type="radio"/>
Intestinal malrotation		<input type="radio"/>	<input type="radio"/>

- Data are de-identified and sent to NCBI.
 - Purpose: create opportunities that improve the clinical test interpretation by identifying genotype/ phenotype associations that can lead to targeted treatments for a disorder.
 - The more explicit the genotype information, the more likely such leveraging can occur



NCBI Entrez Gene

Search Gene for [] Go Clear

Limits Preview Index History Clipboard Details

Display: Full Report Show 10 Send to

All: 1 Current Only: 1 Genes Genomes: 1 SNP GeneView: 1

1: TSC2 tuberous sclerosis 2 [Homo sapiens]
GeneID: 7249 Primary source: HGNC:12363

Summary

Official Symbol: TSC2 and Name: See related: HPRD:01850, MDM19
Gene type: protein coding
Gene name: TSC2
Gene description: tuberous sclerosis
RefSeq status: Reviewed
Organism: Homo sapiens
Lineage: Eukaryota; Metazoa; Chordata
Gene aliases: LAM; TSC4; uberin;
Summary: Mutations in this gene lead to hamartin. Three splice variants for this gene have been identified.

Genomic regions, transcripts, and products

RefSeq below

NC_000016

2008640 5' 3' 2014500
NM_021545.2
NM_021546.1
NM_021547.1
■ = coding region ■ = untranslated region

Genomic context

chromosome: 16, Location: 16p13.3

2014930
SLC6A20 TSC2
NTSL1

Bibliography

PubMed links

GeneRIFs:

1. Data show that tuberin protein levels are decreased in TSC2-deficient cells.
2. study provides new insights into cellular mechanisms of tuberous sclerosis.
3. patient should be considered as having tuberous sclerosis.
4. Growth of smooth muscle cells depends on tuberin.
5. Reduced expression of tuberin might be a cause of tuberous sclerosis.
6. identified three sites of TSC2 phosphorylation and a novel site of TSC1 phosphorylation, and investigated the roles of these sites in regulating the activity of the TSC1-TSC2 complex.
7. Cortical tuberous cells in a case of embryonic tuberous sclerosis showed predominantly nuclear hamartin, cytoplasmic tuberin, and hyperphosphorylation of TSC2.

Sequence Updated On: 05-Oct-2005
Annotation Updated On: 05-Oct-2005

LinkOut

LINKING TO A WORLD OF RESOURCES

HOME HELP FAQ Provider Lists Journal Lists File Validation Library Submission

Welcome Libraries Full-Text Providers Other Resource Providers

LinkOut is a service of Entrez that allows you to link directly from PubMed and other Entrez databases to a wide range of information and services beyond the Entrez system. LinkOut aims to facilitate access to relevant online resources in order to extend, clarify, and supplement information found in the Entrez databases. Examples of LinkOut Resources include full-text publications, biological databases, consumer health information, research tools, and more.

All links are specially assigned to specific database records. When accessing a link through LinkOut, no additional searching should be necessary to access the relevant resource that has been linked to the record. Please encourage online resources that may be valuable to Entrez users to participate in LinkOut.

Click on the applicable tab to access documentation on becoming a LinkOut provider and linking your resources from PubMed and other Entrez databases. Specific documentation is available for libraries, full-text providers and providers of other resources.

Send questions or comments to linkout@ncbi.nlm.nih.gov.

Viewing LinkOut Resources in Entrez Records

Viewing Links as Icons in PubMed

Obtaining the Full Text of an Article

LinkOut Provider and Journal Lists

Last updated: January 9, 2006

Entrez Gene Home

Table of Contents

Summary

Genomic regions, transcripts, and products

Genomic context

Bibliography

Interactions

General gene information

General protein information

Reference Sequences

Related Sequences

Additional Links

Links

Books

Conserved Domains

Genome

GEO Profiles

HomoloGene

Map Viewer

Nucleotide

OMIM

Full text in PMC

Probe

Protein

PubMed

PubMed (GeneRIF)

SNP

SNP: Genotype

SNP: GeneView

Taxonomy

UniSTS

AcView

CCDS

Cardiff Rotterdam Tuberous Sclerosis

Evidence Viewer

GOB

Gene Tests for MIM: 191092

Entrez Gene Info

Feedback

Subscriptions

PubMed

PubMed

PubMed

PubMed

PubMed

PubMed

- ❖ Group of disease specific advocate leaders
- ❖ Resource to each collaborative group
- ❖ Assigned early in the process
- ❖ Option for “involved” genetic counselors to participate

- ❖ 15 Members in year one
- ❖ Three teams of five members from:
 - Laboratory genetics
 - Medical genetics
 - Research
 - Primary care
 - Disease specific advocacy
- ❖ 18 Members – 3/07 – Add biochemical expertise

- ❖ Vet guidelines by which applications are evaluated
- ❖ Evaluates quality of each application
- ❖ Provides constructive feedback for each application

- ❖ Scientific Evidence
- ❖ Proposed Methodology
- ❖ Impact on Healthcare
- ❖ Laboratory Qualifications
- ❖ Data Collection and Sharing Plan
- ❖ Educational Materials
- ❖ Evidence of Collaboration – Empowered Roles
- ❖ Shared Development Costs

- ❖ Cornelia de Lange Syndrome – (U Chicago)
 - ❖ 2 genes – NIPBL & SMC1L1
- ❖ Joubert Syndrome (Prevention Genetics)
- ❖ Cherubism (Toronto Sick Children)
- ❖ X-linked Chondrodysplasia Punctata (U Chicago)
- ❖ Kallman Syndrome (Gene DX)
- ❖ Progressive Familial Intrahepatic Cholestasis (Baylor)
- ❖ Russell Silver (Emory)

- ❖ MPS VI (Emory)
- ❖ Niemann Pick A/B (Emory)
- ❖ X-Linked Periventricular nodular heterotopia
 - ❖ (Harvard U)
- ❖ Primary Ciliary Dyskinesia (UNC)
 - ❖ Targeted mutations – full sequencing under development
- ❖ Infantile Neuroaxonal dystrophy (Oregon HS)
- ❖ MADD (U of CO at Denver)

Approved – In Development

- ❖ Arginase (UCLA)
- ❖ Allan Herndon Dudley - MCT8 (U Chicago)
- ❖ 9q34 deletion (Emory)
- ❖ Epimerase GALE (Emory)
- ❖ PXE (GeneDX)
- ❖ Familial Focal Segmental Glomerulosclerosis –
NPHS2, ACTN4, TRPC6 – (Sick Kids)

Approved – In Development

- ❖ Arrhythmogenic Right Ventricular Cardiomyopathy – DSG2, DSP, PKP2 – (Sick Kids)
- ❖ X-linked Recessive Brachytelephalangic Chondrodysplasia Punctata – ARSE – (GeneDX)
- ❖ Bilateral Frontoparietal Polymicrogyria – GPR56 – (U Chicago)
- ❖ Autosomal Recessive Agammaglobulinemia –IGHM – (Correlagen)
- ❖ Urea Cycle Disorders – CPS1 & ASL – (Baylor)

- ❖ Variability in Collaborative Group Composition
- ❖ Need for Educational Material Guidelines
- ❖ Laboratory Guidelines – CETT
 - VOUS (variants of unknown significance)
 - Reports
 - Turn-around time, control materials
 - Informed Consent
 - Role of Research / Clinical clarification for variants

Developing CETT Standards- March 2007 Meeting

❖ Laboratory CETT Guidelines:

VOUS, TAT, Pre-Implantation Genetic DX, Validation, Prenatal DX, Interpretation of Sequence Diff., Deletions and Duplications, Quality Control.

❖ Clinical Test Result Report Forms suggested framework/language

❖ Educational Materials Guidelines

❖ Pubic Databases and Rare Diseases Testing



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Genetic Testing for Cornelia de Lange Syndrome

Information for Patients and Families

What do I need to know about testing my child for Cornelia de Lange syndrome?

Cornelia de Lange syndrome (CdLS) is caused by a change in someone's DNA. People with CdLS are small for their age, have learning problems and look more like each other than their family members. This blood test may prove that your child has CdLS. However, half of the children with CdLS will have a negative result, so this test will not rule out CdLS. There is also a chance that the test will find something that we do not understand. Thus, we may need to test the child's parents to learn more. This information sheet will provide more details about CdLS and this testing. Please talk to a genetic counselor, if you have more questions about testing.

What is Cornelia de Lange syndrome?

Cornelia de Lange syndrome (CdLS) is a rare genetic condition. As with other syndromes, individuals with CdLS look alike. Common findings in these children include: small size at birth (often under five pounds), slow growth and small stature, and small head size (microcephaly). Typical facial features include thin eyebrows which frequently meet at midline (synophrys), long eyelashes, short upturned nose and thin, downturned lips.

Other frequent findings include extra body hair (hirsutism), small hands and feet, joining of the second and third toes, incurved fifth fingers, indigestion, seizures, heart defects, cleft palate, problems feeding, and learning problems. Limb differences, including missing limbs or portions of limbs, usually fingers, hands or forearms, are also found in some individuals. Not everyone with CdLS has all of the findings or is affected to the same degree.

What causes CdLS?

CdLS is caused by a change (mutation) in the *NIPBL* (Nipped-B-like) gene on chromosome 5. We each have two copies of the *NIPBL* gene. Half the individuals with CdLS have a change in one copy of the *NIPBL* gene. Genes are written instructions to make proteins. When there is a change in the instructions, the protein may not be made or may not work properly. Thus, the smaller amount of good protein from the *NIPBL* gene causes the features in CdLS. Research continues to look for other causes of CdLS.

Can my child be tested? Can I be tested? Can my family members be tested?

The first person to be tested in any family would be the individual thought to have CdLS. Testing for mutations in the CdLS gene is complex because it is a very large gene. It is like reading a very long book and looking for a single spelling mistake. You may read the whole book and miss the "typo," however when you do find it, then it is easy to test other family members (i.e. you know that the change is on page 875 in the second paragraph). Once a change is found in the person with CdLS, testing other family members, even during a pregnancy, is easy and fast because we know where to look. Testing is now available at The University of Chicago Genetics Services Laboratory.

Reasons for genetic testing for CdLS:

- confirm the diagnosis
- reassure that other family members are not affected
- provide information and resources for future pregnancies

GeneReviews: Author Template – Single Disease

(Customized template for author to enter text directly)

X-linked Dominant Chondrodysplasia Punctata 2

[Synonyms; Includes]

Authors: **Richard Kelley, MD**
 Melissa A. Dempsey, MS, CGC



Summary

1. Rare disease tests can be successfully translated
2. Using a Review Board of experts is a model for test review
3. Collaboration between research, clinical and advocates is beneficial
4. Clinical laboratories continue to need:
 - Improved educational materials on testing
 - Improved laboratory reports



THANKS TO

Office of Rare Diseases (ORD)
Stephen Groft, Pharm D, Director
National Institutes of Health

www.cettprogram.org