COFFIN-LOWRY SYNDROME

A 3-in-1 Medical Reference

A Bibliography and Dictionary
for Physicians, Patients,
and Genome Researchers

TO INTERNET REFERENCES

ICON Group International, Inc.

Coffin-Lowry Syndrome

A Bibliography and Dictionary for Physicians, Patients, and Genome Researchers

James N. Parker, M.D.
and Philip M. Parker, Ph.D., Editors

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FORWARD

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading."[1] Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with Coffin-Lowry syndrome is indexed in search engines, such as **www.google.com** or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about Coffin-Lowry syndrome, using the most advanced research tools available and spending the least amount of time doing so.

In addition to offering a structured and comprehensive bibliography, the pages that follow will tell you where and how to find reliable information covering virtually all topics related to Coffin-Lowry syndrome, from the essentials to the most advanced areas of research. Special attention has been paid to present the genetic basis and pattern of inheritance of Coffin-Lowry syndrome. Public, academic, government, and peer-reviewed research studies are emphasized. Various abstracts are reproduced to give you some of the latest official information available to date on Coffin-Lowry syndrome. Abundant guidance is given on how to obtain free-of-charge primary research results via the Internet. **While this book focuses on the field of medicine, when some sources provide access to non-medical information relating to Coffin-Lowry syndrome, these are noted in the text.**

E-book and electronic versions of this book are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). If you are using the hard copy version of this book, you can access a cited Web site by typing the provided Web address directly into your Internet browser. You may find it useful to refer to synonyms or related terms when accessing these Internet databases. **NOTE:** At the time of publication, the Web addresses were functional. However, some links may fail due to URL address changes, which is a common occurrence on the Internet.

For readers unfamiliar with the Internet, detailed instructions are offered on how to access electronic resources. For readers unfamiliar with medical terminology, a comprehensive glossary is provided. We hope these resources will prove useful to the widest possible audience seeking information on Coffin-Lowry syndrome.

The Editors

[1] From the NIH, National Cancer Institute (NCI): **http://www.cancer.gov/**.

CHAPTER 1. STUDIES ON COFFIN-LOWRY SYNDROME

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on Coffin-Lowry syndrome. For those interested in basic information about Coffin-Lowry syndrome, we begin with a condition summary published by the National Library of Medicine.

Genetics Home Reference

Genetics Home Reference (GHR) is the National Library of Medicine's Web site for consumer information about genetic conditions and the genes or chromosomes responsible for those conditions. Here you can find a condition summary on Coffin-Lowry syndrome that describes the major features of the condition, provides information about the condition's genetic basis, and explains its pattern of inheritance. In addition, a summary of the gene or chromosome related to Coffin-Lowry syndrome is provided. [2]

The Genetics Home Reference has recently published the following summary for Coffin-Lowry syndrome:

What Is Coffin-Lowry Syndrome?[3]

Coffin-Lowry syndrome is a condition associated with mental retardation and delayed development, short stature, and skeletal abnormalities. Distinctive facial features (including wide-spaced and downward-slanting eyes, a short nose with a wide tip, and full lips) and soft hands with short, tapered fingers are also characteristic of this condition. Males are usually more severely affected than females, but the signs and symptoms of Coffin-Lowry syndrome range from very mild to severe in affected women.

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[2] This section has been adapted from the National Library of Medicine: **http://ghr.nlm.nih.gov/**.

[3] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/condition=coffinlowrysyndrome**.

How Common Is Coffin-Lowry Syndrome?

The incidence of this condition is uncertain, but the disorder probably affects 1 in 40,000 to 50,000 births.

What Genes Are Related to Coffin-Lowry Syndrome?

Mutations in the **RPS6KA3** (**http://ghr.nlm.nih.gov/gene=rps6ka3**) gene cause Coffin-Lowry syndrome.

The RPS6KA3 gene makes a protein that is involved in signaling within cells. Researchers believe that the protein helps control the activity of other genes and may play an important role in the central nervous system. Mutations in the RPS6KA3 gene disturb the function of the protein, but it is not well understood how mutations lead to the signs and symptoms of Coffin-Lowry syndrome.

Some people with the features of Coffin-Lowry syndrome do not have identified mutations in the RPS6KA3 gene. In these cases, the cause is unknown.

How Do People Inherit Coffin-Lowry Syndrome?

This condition is inherited in an X-linked dominant pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes. The inheritance is dominant if one copy of the altered gene in each cell is sufficient to cause the condition. In most cases, males (who have one X chromosome in each cell) experience more severe signs and symptoms of the disorder than females (who have two X chromosomes in each cell). A striking characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Most people with Coffin-Lowry syndrome have no history of the condition in their families. These cases are caused by new mutations in the RPS6KA3 gene.

Where Can I Find Additional Information about Coffin-Lowry Syndrome?

You may find the following resources about Coffin-Lowry syndrome helpful. These materials are written for the general public.

NIH Publications - National Institutes of Health

- **http://www.ninds.nih.gov/disorders/coffin_lowry/coffin_lowry.htm**

MedlinePlus - Health Information

- Health Topic: Developmental Disabilities:
  http://www.nlm.nih.gov/medlineplus/developmentaldisabilities.html

- Health Topic: Facial Injuries and Disorders:
  http://www.nlm.nih.gov/medlineplus/facialinjuriesanddisorders.html
- Health Topic: Head and Brain Malformations:
  http://www.nlm.nih.gov/medlineplus/headandbrainmalformations.html

Educational Resources - Information Pages

- Madisons Foundation:
  http://www.madisonsfoundation.org/content/3/1/display.asp?did=185
- Orphanet:
  http://www.orpha.net//consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=192

Patient Support - for Patients and Families

- National Organization for Rare Disorders:
  http://www.rarediseases.org/search/rdbdetail_abstract.html?disname=Coffin+Lowry+Syndrome
- Resource list from the University of Kansas Medical Center:
  http://www.kumc.edu/gec/support/coffin_l.html
- The Arc of the United States:
  http://www.thearc.org/

Professional Resources

You may also be interested in these resources, which are designed for healthcare professionals and researchers.

- Gene Reviews - Clinical summary:
  http://www.genetests.org/query?dz=cls
- Gene Tests - DNA tests ordered by healthcare professionals:
  http://www.genetests.org/query?testid=2415
- PubMed - Recent literature:
  http://ghr.nlm.nih.gov/condition=coffinlowrysyndrome/show/PubMed;jsessionid=CEDDD3898934E1783DFADF71221CEC34
- OMIM - Genetic disorder catalog:
  http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=303600

References

These sources were used to develop the Genetics Home Reference condition summary on Coffin-Lowry syndrome.

- Gene Review
- Hanauer A, Young ID. Coffin-Lowry syndrome: clinical and molecular features. J Med Genet. 2002 Oct;39(10):705-13. Review. PubMed citation

- Hunter AG. Coffin-Lowry syndrome: a 20-year follow-up and review of long-term outcomes. Am J Med Genet. 2002 Sep 1;111(4):345-55. Review. PubMed citation
- Jacquot S, Zeniou M, Touraine R, Hanauer A. X-linked Coffin-Lowry syndrome (CLS, MIM 303600, RPS6KA3 gene, protein product known under various names: pp90(rsk2), RSK2, ISPK, MAPKAP1). Eur J Hum Genet. 2002 Jan;10(1):2-5. PubMed citation

A summary of the gene related to Coffin-Lowry syndrome is provided below:

What Is the Official Name of the RPS6KA3 Gene?[4]

The official name of this gene is "ribosomal protein S6 kinase, 90kDa, polypeptide 3."

RPS6KA3 is the gene's official symbol. The RPS6KA3 gene is also known by other names, listed below.

What Is the Normal Function of the RPS6KA3 Gene?

The RPS6KA3 gene makes a protein that is part of a protein family called ribosomal S6 kinases, or RSKs. The proteins in this family are kinases, enzymes that change the activity of other proteins by adding a cluster of oxygen and phosphate atoms (a phosphate group) at certain positions. RSKs probably help regulate other genes by activating specific proteins called transcription factors. RSKs are involved in signaling within cells and are thought to play a role in several important cellular processes, including cell growth and division (proliferation), cell specialization (differentiation), cell response to stress, and programmed cell death (apoptosis).

The protein made by the RPS6KA3 gene appears to play an important role in the central nervous system. The protein is involved in cell signaling pathways that are required for learning, the formation of long-term memory, and the survival of nerve cells in the brain.

What Conditions Are Related to the RPS6KA3 Gene?

Coffin-Lowry Syndrome - Caused by Mutations in the RPS6KA3 Gene

More than 90 mutations in the RPS6KA3 gene have been identified in people with Coffin-Lowry syndrome, a condition associated with mental retardation and skeletal abnormalities. Many of these mutations create an abnormally short, nonfunctional version of the protein or prevent any protein from being produced. Other mutations substitute one amino acid (a building block of proteins) for another amino acid in a critical region of the protein, disturbing the protein's function. Researchers do not fully understand how mutations in the RPS6KA3 gene lead to the signs and symptoms of Coffin-Lowry syndrome. A functional RPS6KA3 protein appears to be important in the central nervous system, but the protein's role in the formation of the skeleton is unknown.

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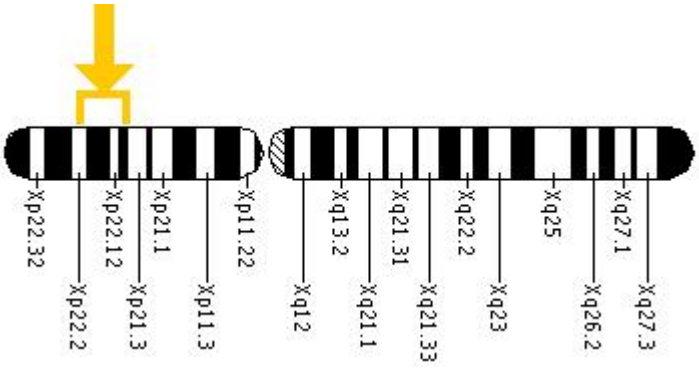
[4] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/gene=rps6ka3;jsessionid=CEDDD3898934E1783DFADF71221CEC34**.

Where Is the RPS6KA3 Gene Located?

Cytogenetic Location: Xp22.2-p22.1

Molecular Location on the X chromosome: base pairs 20,077,949 to 20,194,670



The RPS6KA3 gene is located on the short (p) arm of the X chromosome between positions 22.2 and 22.1.

More precisely, the RPS6KA3 gene is located from base pair 20,077,949 to base pair 20,194,670 on the X chromosome.

References

These sources were used to develop the Genetics Home Reference gene summary on the RPS6KA3 gene.

- Delaunoy J, Abidi F, Zeniou M, Jacquot S, Merienne K, Pannetier S, Schmitt M, Schwartz C, Hanauer A. Mutations in the X-linked RSK2 gene (RPS6KA3) in patients with Coffin-Lowry syndrome. Hum Mutat. 2001 Feb;17(2):103-16. PubMed citation
- Guimiot F, Delezoide AL, Hanauer A, Simonneau M. Expression of the RSK2 gene during early human development. Gene Expr Patterns. 2004 Jan;4(1):111-4. PubMed citation
- Hanauer A, Young ID. Coffin-Lowry syndrome: clinical and molecular features. J Med Genet. 2002 Oct;39(10):705-13. Review. PubMed citation
- Zeniou M, Ding T, Trivier E, Hanauer A. Expression analysis of RSK gene family members: the RSK2 gene, mutated in Coffin-Lowry syndrome, is prominently expressed in brain structures essential for cognitive function and learning. Hum Mol Genet. 2002 Nov 1;11(23):2929-40. PubMed citation
- Zeniou M, Gattoni R, Hanauer A, Stevenin J. Delineation of the mechanisms of aberrant splicing caused by two unusual intronic mutations in the RSK2 gene involved in Coffin-Lowry syndrome. Nucleic Acids Res. 2004 Feb 18;32(3):1214-23. Print 2004. PubMed citation

Federally Funded Research on Coffin-Lowry Syndrome

The U.S. Government supports a variety of research studies relating to Coffin-Lowry syndrome. These studies are tracked by the Office of Extramural Research at the National Institutes of Health.[5]

CRISP (Computerized Retrieval of Information on Scientific Projects)

CRISP is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other institutions. Search the CRISP Web site at **http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen**. You will have the option to perform targeted searches by various criteria, including geography, date, and topics related to Coffin-Lowry syndrome.

For most of the studies, the agencies reporting into CRISP provide summaries or abstracts. As opposed to clinical trial research using patients, many federally funded studies use animals or simulated models to explore Coffin-Lowry syndrome. The following is typical of the type of information found when searching the CRISP database for Coffin-Lowry syndrome:

- **Project Title: ATF4 IS DOWNSTREAM EFFECTOR OF BONE ANABOLIC GROWTH FACTORS**

  Principal Investigator & Institution: Yang, Xiangli; Cellular & Structural Biology; University of Texas Hlth Sci Ctr San Ant 7703 Floyd Curl Dr San Antonio, Tx 78229

  Timing: Fiscal Year 2006; Project Start 01-FEB-2006; Project End 14-AUG-2006

  Summary: (provided by applicant): The differentiation and function of osteoblasts are controlled by a series of incompletely defined growth factors, cytokines, hormones, and ultimately transcription factors that act in sequence. We have recently identified that ATF4 and its upstream regulator, RSK2, a kinase that, when mutated, causes **Coffin-Lowry syndrome** (CLS), a mental retardation condition associated with skeletal manifestations. Inactivation of Atf4 in mice causes severe osteoporosis. Mice lacking Rsk2 have similar skeletal abnormalities to that of CLS patients. In order to search for upstream regulators of ATF4 and RSK2, we tested IGF1, an important bone anabolic growth factor, and found that IGF1 induced the phosphorylation of RSK2 and ATF4. We have also observed that PKA, a downstream protein kinase of PTH, is also able to phosphorylate ATF4 and increase its transactivation ability. These data suggest that IGF1 and PTH use ATF4 as their transcription factor via the action of RSK2 or PKA to execute the anabolic function on osteoblasts. To test this hypothesis, we propose in this application with the following Specific Aims: 1. To analyze whether IGF1 and PTH activate RSK2 or PKA, which then phosphorylate ATF4 at serines 251 and 254, respectively, to enhance its transcription activity in osteoblasts. 2. To test whether phosphorylations of ATF4 accounts for its cell-specificity by increasing ATF4's stability in osteoblasts. 3. To establish transgenic mice overexpressing ATF4-S251A and ATF4-S254A, two mutant forms of ATF4 that are no longer phosphorylated by RSK2 and PKA, to study the functional relevance of RSK2- and PKA-phosphorylation in vivo. The

[5] Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

knowledge gained from this study will improve our understanding of the mechanisms governing osteoblast differentiation, skeletal development and bone remodeling throughout life, as well as assist therapeutic drug discoveries in the future.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: RECRUITMENT AND ACTIVATION OF RSK2 BY HIV TAT**

  Principal Investigator & Institution: Ott, Melanie; J. David Gladstone Institutes 1650 Owens St San Francisco, Ca 94158

  Timing: Fiscal Year 2005; Project Start 01-MAR-2005; Project End 28-FEB-2007

  Summary: (provided by applicant): The transcriptional machinery of HIV-1 remains a therapeutic target that has not been exploited in current therapeutic regimens. The viral transactivator Tat and its cellular interaction partners play a critical role in the regulation of HIV transcription. We have obtained evidence that Tat also interacts with the p90 ribosomal S6 kinase 2 (RSK2). Dominant-negative RSK2 or siRNAs directed against RSK2 inhibited Tat transactivation, indicating that RSK2 is important for Tat function. Reconstitution of RSK2 in cells from individuals with a genetic defect in RSK2 expression (**Coffin-Lowry syndrome**) enhanced Tat transactivation. RSK2 is normally activated through the pp44/42MAPK/ERK signal transduction pathway after mitogenic stimulation and has been implicated in the phosphorylation of histone H3 and CREB/ATF transcription factors. We find that Tat activated the RSK2 kinase activity in cells. We propose to identify the mechanism of Tat-induced RSK2 activation by performing in vitro kinase assays of recombinant RSK2 in the presence of synthetic Tat. In addition, we will identify the target(s) of activated RSK2 at the HIV promoter by performing chromatin immunoprecipitation experiments using modification-specific antibodies against histone H3 and CREB/ATF transcription factors. We have recently obtained the first selective cell-permeable RSK inhibitor generated by the laboratory of Jack Taunton at the University of California San Francisco. Our preliminary experiments show that this inhibitor suppresses Tat transactivation. We will therefore study the relevance of RSK2 activation for HIV infection by testing the effect of RSK2 inhibition and RSK2 knockdown in T cells infected with HIV-1. We anticipate that these studies will substantially further our understanding of the role of RSK2 in HIV transcription and explore its potential as a novel target for anti-HIV therapy.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: REGULATION OF RAS-SIGNALING PATHWAYS BY SYNGAP**

  Principal Investigator & Institution: Carlisle, Holly; None; California Institute of Technology Office of Sponsored Research, Mail Code 201-15 Pasadena, Ca 91125

  Timing: Fiscal Year 2004; Project Start 01-MAR-2004; Project End 28-FEB-2007

  Summary: (provided by applicant): The overall objective of this project is to further elucidate the role of SynGAP, a synapse specific Ras GTPase activating protein, in the regulation of activity-dependent Ras activation and downstream Ras effectors. The specific aims are to (1) determine if homeostasis of active Ras is perturbed in the absence of SynGAP in mature synapses, (2) examine whether regulation of actin remodeling through a Ras/PI3K/Rac pathway is influenced by SynGAP activity, and (3) test whether phosphorylation of KV4.2 channels via the Ras/MAPK pathway is altered by disruption of SynGAP activity. The research methods will include techniques routinely performed in the Kennedy lab (Ras activation assays, western immunoblotting, immunocytochemistry, and confocal microscopy) combined with techniques that I learned during my graduate work (hippocampal slice preparation and

electrophysiology). Abnormal regulation of Ras and its downstream effectors has been implicated in several human cognitive disorders including Neurefibromatosis, **Coffin-Lowry Syndrome,** Rubinstein-Taybi Syndrome, and Fragile X Syndrome. Understanding how Ras signaling pathways are regulated in adult neurons may further our understanding of the molecular underpinnings of these disorders.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: TARGETING AND TRAFFICKING OF 5-HT2A SEROTONIN RECEPTORS**

  Principal Investigator & Institution: Roth, Bryan L.; Professor; Biochemistry; Case Western Reserve University 10900 Euclid Ave Cleveland, Oh 44106

  Timing: Fiscal Year 2005; Project Start 01-SEP-2000; Project End 31-MAR-2010

  Summary: (provided by applicant): 5-HT2A serotonin receptors represent the principal neuropharmacological target for LSD-like hallucinogens and an important molecular target for many psychiatric medications (e.g. selected atypical antipsychotics, antidepressants and atypical anxiolytics). Not surprisingly, 5-HT2A receptors continue to be actively targeted for psychiatric drug discovery in many therapeutic areas including schizophrenia, sleep disorders and cognition enhancement. Thus, study of 5-HT2A receptors is likely to lead to novel insights into psychiatric drug actions as well as insights into the molecular mechanisms responsible for psychosis and related disorders. We have recently discovered that 5-HT2A receptors functionally interact with RSK-2 and that knocking-out RSK-2 augments 5-HT2A mediated signaling (see Preliminary studies). These results imply that the psychosis and impaired cognition, which occur in **Coffin-Lowry Syndrome,** are due, in part, to over-active 5-HT2A signaling. In favor of this hypothesis are findings that 5-HT2A receptor agonists induce psychosis and cognitive impairment reminiscent of schizophrenia in humans and that 5-HT2A antagonists improve cognition and reduce psychosis in schizophrenia. For more than 50 years it has been suggested that the psychosis, which occurs in schizophrenia is due, in part, to dysregulation of serotonergic signaling-without any direct evidence. These findings represent the first direct evidence in favor of the hypothesis that psychosis is associated with augmented 5-HT2A receptor signaling. The ultimate goal of these studies is to elucidate the molecular actions by which 5-HT2A receptors are regulated and targeted to neuronal subdomains and how this system is dysregulated in various psychotic states: Specific Aim 1: To determine the relevance of 5-HT2A receptor interactions with PDZ-domain containing proteins on the functional activity and sorting of 5-HT2A receptors in vitro and, ultimately, in vivo. Specific Aim 2: To determine the relevance of 5-HT2A receptor interactions with caveolins-1 and flotillin, which target 5-HT2A receptors. Specific Aim 3: To determine whether the interaction between ribosomal S6-kinase-2 (RSK2) and 5-HT2A receptors has functional significance.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

The National Library of Medicine: PubMed

One of the quickest and most comprehensive ways to find academic studies in both English and other languages is to use PubMed, maintained by the National Library of Medicine.[6]

[6] PubMed was developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM) at the National Institutes of Health (NIH). The PubMed database was developed in conjunction with publishers of biomedical literature as a search tool for accessing literature citations and linking to full-text

The advantage of PubMed over previously mentioned sources is that it covers a greater number of domestic and foreign references. It is also free to use. If the publisher has a Web site that offers full text of its journals, PubMed will provide links to that site, as well as to sites offering other related data. User registration, a subscription fee, or some other type of fee may be required to access the full text of articles in some journals.

To generate your own bibliography of studies dealing with Coffin-Lowry syndrome, simply go to the PubMed Web site at **http://www.ncbi.nlm.nih.gov/pubmed**. Type **Coffin-Lowry syndrome** (or synonyms) into the search box, and click **Go**. The following is the type of output you can expect from PubMed for Coffin-Lowry syndrome (hyperlinks lead to article summaries):

- **"Cataplexy" and muscle ultrasound abnormalities in Coffin-Lowry syndrome.**
  Author(s): Crow YJ, Zuberi SM, McWilliam R, Tolmie JL, Hollman A, Pohl K, Stephenson JB.
  Source: Journal of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9507386&query_hl=3&itool=pubmed_docsum

- **"Cataplexy" in Coffin-Lowry syndrome.**
  Author(s): Fryns JP, Smeets E.
  Source: Journal of Medical Genetics.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9719387&query_hl=3&itool=pubmed_docsum

- **A case of Coffin-Lowry syndrome with premature exfoliation of primary teeth.**
  Author(s): Igari K, Hozumi Y, Monma Y, Mayanagi H.
  Source: International Journal of Paediatric Dentistry / the British Paedodontic Society [and] the International Association of Dentistry for Children.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16643544&query_hl=3&itool=pubmed_docsum

- **A case suggesting Coffin-Lowry syndrome.**
  Author(s): Iwasaki K, Tamura Y, Nishimura K, Sakai N, Miyagi A, Higaki M.
  Source: Bull Kanagawa Dent Coll.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=2133800&query_hl=3&itool=pubmed_docsum

- **A female with Coffin-Lowry syndrome and "cataplexy".**
  Author(s): Fryssira H, Kountoupi S, Delaunoy JP, Thomaidis L.
  Source: Genet Couns.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12558110&query_hl=3&itool=pubmed_docsum

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