



**MHE
Research
Foundation**

Multiple Hereditary Exostoses

www.MHEResearchFoundation.org

Toll Free: 1-877-486-1758

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The American Association of Multiple Enchondroma Diseases



www.aamed.net

The MHE Research Foundation is a nonprofit 501(c)(3) Organization for researchers, physicians & families dealing with Multiple Hereditary Exostoses a rare genetic bone disease.

The MHE Research Foundation has a five point mission to
REACH advance and support the following.

- ❖ **RESEARCH**, to help researchers one day find a treatment for MHE. Our foundation works hand in hand with researchers from around the world on this mission.
- ❖ **EDUCATION**, to provide clinical information, guides to help benefit both families and physicians.
- ❖ **ADVOCACY**, bring awareness about this disease throughout the world.
- ❖ **CLINICAL**, to help provide resources to families enabling them to find the medical care they need.
- ❖ **HOPE**, is that the research being conducted on MHE, the informational resources will bring a better quality of life to the families affected by this disease.

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The MHE Research Registry



- ✓ Researchers are required by our foundation to sign a certificate of corporation and confidentiality .
- ✓ Researchers are required to give a full set of project paperwork to our foundation.
- ✓ Research Projects are explained in lay terms and there is no cost to participate in research.
- ✓ Research projects are submitted to different hospitals around the USA where there are pockets of patients.



The MHE Research Registry



- ✓ People interested in participating in Research are required to fill out a registry form to insure informed consent and interest in research.
- ✓ Participants can register online or by hard copy.
- ✓ When a child or adult has a surgery scheduled they can go onto the foundations website and fill out the online form for collection of samples or contact the foundation directly.
- ✓ In the cases where hospitals have obtained the IRB project approvals, the hospital contact Sarah Ziegler directly
- ✓ The MHE Research Foundation sends a research collection box via Fed Ex directly to the patient or hospital. (including consent forms)
- ✓ A phone call is made by Sarah Ziegler to go over all consent forms and what needs to be done with the collection box.
- ✓ The collection box is sent directly back to the laboratory via Fed Ex after surgery.



Researchers that have on going projects



Collection of tumor & blood samples

Samples have been sent to the following labs for study

- **Jacqueline T Hecht, PH.D.** Professor of Pediatrics, University of Texas Houston Medical Center
- **Jeffrey D Esko, PH.D.** Professor, Dept. of Cellular Molecular Medicine, Associate Director the Glycobiology Research & Training Center, UCSD, CA
- **Wim Wuyts, PH.D.** Supervisor DNA Diagnostics, Department of Medical Genetics University & University Hospital of Antwerp, Belgium
- **Yu Yamaguchi, M.D., PH.D.** Professor Developmental Neurobiology Program, The Burnham Institute, La Jolla, CA
- **Luca Sangiorgi, M.D., PH.D.** Head of the Genetics Unit, Lab Oncology Research Coordinator, Rare Skeletal Diseases Rizzoli Orthopaedic Institute, Bologna, Italy Coordinator of the Italian Registry of Hereditary Multiple Exostoses Coordinator Virtual Lab of Bioinformatics for Genetics and Biotech (Gebba-Lab)

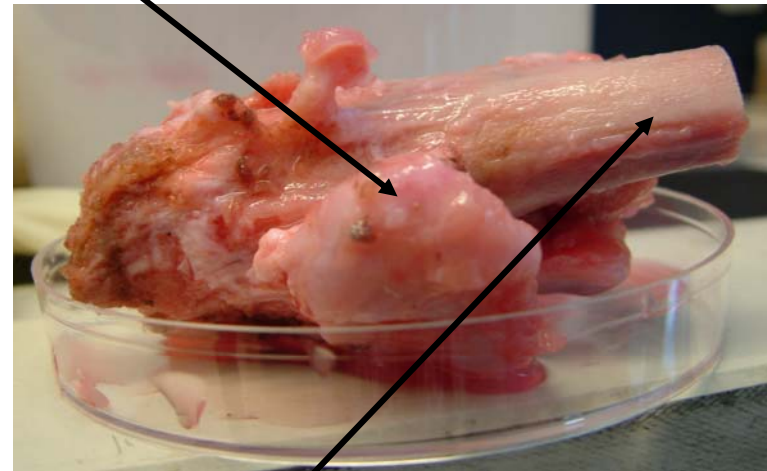
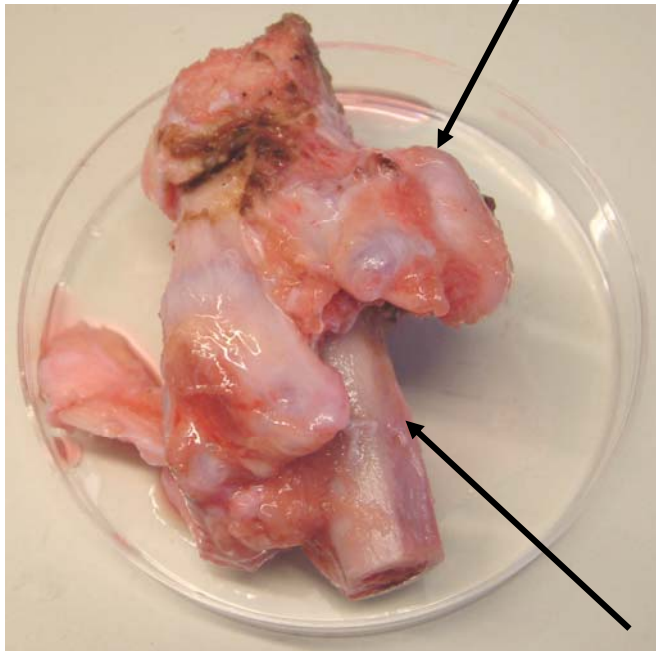
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Clinical Case of a 12 Year Old Boy with MHE

Sample was sent to Jeffrey Esko, Ph.D. at UCSD

Exostoses



Bone (fibula)

Thank you goes to Jeffrey D Esko, PH.D for the use of the graphics located on this slide



Advocacy / Research Connections & Trust Does Translate into Collaborations !



- ❖ Working directly with researchers allows us to give insight into secondary symptoms that have been over looked in many clinical settings.
- ❖ Results of this work
 - Hereditary Multiple Exostosis and Pain, has been published in the Journal of Pediatric Orthopaedics, Volume 25, Number 3, May/June 2005, pps 369-376.
 - Keloid Formation Following Surgical Treatment of Multiple Hereditary Exostoses
Sumeet Garg, Greenberg, J., Hosalkar, H.S., Garg, S., Dormans, J.P
 - Yu Yamaguchi, M.D., PH.D. Informal survey The Possible Relationship of Heparan Sulfate and Nerve Cell Function to Neurological Clinical Symptoms in patients with Multiple Hereditary Exostoses

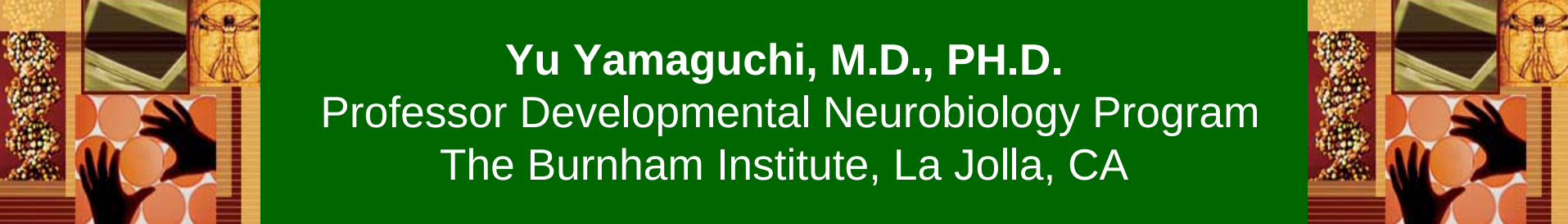
Hereditary multiple exostoses and pain

Darkle S, Wicklund C, Novy D, Scott A, Gambello M, Johnston D, Hecht J.

Department of Pediatrics, University of Texas-Houston Medical School, Houston, TX 77225, USA.

This study was undertaken to characterize pain in individuals with hereditary multiple exostoses

- Two hundred ninety-three patients with HME completed a questionnaire designed to assess pain as well as its impact on their life.
- 84% of participants reported having pain, indicating that pain is a real problem in HME.
- Of those with pain, 55.1% had generalized pain
- Two factors were found to be associated with pain outcome:
 - ✓ HME-related complications and surgery. Individuals who had HME-related complications were five times more likely to have pain.
 - ✓ While those who had surgery were 3.8 more likely to have pain.
- ❖ **The results of this study indicate that the number of individuals with HME who have pain has been underestimated and that pain is a problem that must be addressed when caring for individuals with HME.**



Yu Yamaguchi, M.D., PH.D.

Professor Developmental Neurobiology Program

The Burnham Institute, La Jolla, CA

Informal survey The Possible Relationship of Heparan Sulfate and Nerve Cell Function to Neurological Clinical Symptoms in patients with Multiple Hereditary Exostoses conducted by Yu Yamaguchi, M.D., PH.D. and Sarah Ziegler.

- Such symptoms include:
- MHE patients tend to have some mental, neurological, and muscular symptoms.
- Mild social interaction deficits (excessive shyness, adherence to routines)
- Heightened sensitivities to sensory stimulation (sounds, touch, taste)
- Difficulties to concentrate
- Muscle weakness (easy to get tired)
- We believe these symptoms can be explained by the deficiency of heparan sulfate in nerve and muscle cells.
- Yu Yamaguchi's recent analysis of knockout mouse behavior has suggested that these mice have deficits in social interaction and reduced levels of fear / anxiety.



Our Networking with Researchers gets Results !



Examples

Yu Yamaguchi, M.D., PH.D. Burnham Institute- EXT1 conditional knockout mice

Mammalian Brain Morphogenesis and Midline Axon Guidance Require Heparan Sulfate Masaru Inatani,¹ Fumitoshi Irie,¹ Andrew S. Plump,^{2*} Marc Tessier-Lavigne,² Yu Yamaguchi¹
Science 7 November 2003:Vol. 302. no. 5647, pp. 1044 – 1046 DOI: 10.1126/science.1090497

Jeffrey Esko, PH.D. UCSD- EXT1 & EXT2 knockout mice

Hereditary multiple exostoses and heparan sulfate polymerization, Beverly M. Zak, Brett E. Crawford and Jeffrey D. Esko
Biochimica et Biophysica Acta (BBA) – General Subjects, Volume 1573, Issue 3, 19 December 2002, Pages 346-355

Dan Wells, PH.D. Houston University of Houston - EXT1 knockout mice

EXT1 Regulates Chondrocyte Proliferation and Differentiation During Endochondral Bone Development, M. J. Hilton, L. Gutiérrez, D. A. Martinez, and D. E. Wells
Development. Bone 2005, 36, 379-386

Dominique Stickens, PH.D. - EXT2 knockout mice

Glen Evans M.D., PH.D.

Zena Werb, PH.D. UCSF

Mice deficient in Ext2 lack heparan sulfate and develop exostoses, Dominique Stickens, Beverly M. Zak, Nathalie Rougier, Jeffrey D. Esko, and Zena Werb*
Development 132, 5055-5068 (2005)

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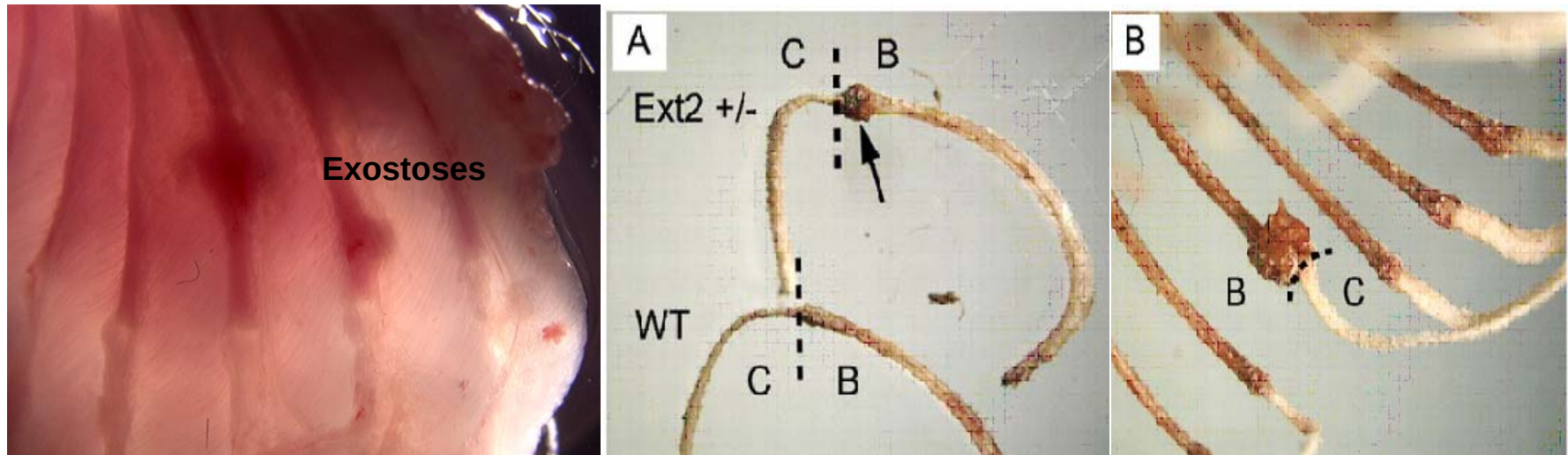
Mice deficient in Ext2 lack heparan sulfate and develop exostoses

- Mice have been created with mutations in EXT1 and EXT2
- Exostoses arise in EXT deficient mice that resemble exostoses in humans

Back-lighting rib mice cage shows irregular contours of exostoses

(A) Dissected rib of a wild-type mouse and an *Ext2*^{+/-}

(B) Higher magnification showing larger exostosis on a rib of an *Ext2*^{+/-} mouse.



Thank you goes to Jeffrey D Esko, PH.D and Dominique Stickens, PH.D for the use of the graphics located on this slide



On going & future research



- Genotype / Phenotype correlations
- Animal model development
- Neurological secondary symptoms
- The study of chronic pain in MHE Patients
- Scar formation
- Malignant transformation of Exostoses
- Stomach and Intestinal issues as they may be related as secondary symptoms in MHE Patients.
- Tooth Development, Dental problems in MHE Patients
- Bone Density Issues



International MHE Conferences



- ❖ First Oct 2002 organized by Scott B Selleck, M.D., PH.D., Jeffrey D Esko, PH.D., Sarah Ziegler. Held at the Arizona Cancer Center
- ❖ Second Nov 2005 organized by Dan Wells, PH.D., Jacqueline T Hecht, PH.D., Sarah Ziegler. Held at the Shriners Hospital in Houston Texas
- ❖ Third scheduled for July 8-11, 2009 to be held in San Diego CA & organized by Yu Yamaguchi, M.D., PH.D., Dominique Stickens, PH.D., Sarah Ziegler





Comments from the Conference



Dear Sarah

The MHE Research Foundation collectively you are making a vital contribution to stimulating research into a human condition which will hopefully provide the platform for breakthroughs to new treatments to alleviate the Symptoms of MHE.

At the same time you are supporting research that will provide unique and important clues to the wider functions of heparan sulfate itself; this has the potential to create knowledge that can be applied in other therapeutic applications including inflammation, cancer, neuron degeneration and cardiovascular disorders.

*What you are doing is a valuable contribution. Keep up the good work !
best regards, Jerry*

*Jeremy Turnbull PH.D. Prof. of Biochemistry & MRC Senior Research Fellow
Molecular Glycobiology Group School of Biological Sciences University of
Liverpool*

- ❖ The MHE Research Foundations website includes comprehensive sections related to Research being conducted, Conferences, Orthopaedics, Genetics and Chronic pain, Directories to find physicians. Includes many guides written by professionals related to each subject. Our website is both user and printer friendly.
- ❖ Our website is regularly reviewed by the Scientific & Medical Advisory Board of the MHE Research Foundation
- ❖ Our website is accredited by the [Health on the Net Foundation](#), is linked to NIH National Library of Medicine, Directory of Health Organizations ([SIS](#)), the link for Patient Information on The Diseases [Database](#) a cross-referenced index of human disease, and the [Intute](#): health & life sciences a free online service providing access to the very best Web resources for education and research UK.
- ❖ Our organization is an Affiliate of the [Society for Glycobiology](#) and has a link with the [American Society for Matrix Biology](#)





The MHE Research Foundation

Scientific and Medical Advisory Board

- **David E Donati, M.D.**, Director of Musculoskeletal Regeneration Tissue laboratory the Rizzoli Institute, Professor Orthopaedics at the University of Bologna, Italy
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- **Dominique Stickens, Ph.D.**, Senior Research Biologist, Merck Research Laboratories, NJ
- **Dan Wells, Ph.D.**, Professor of Biology & Biochemistry, University of Huston Texas
- **Wim Wuyts, Ph.D.**, Supervisor DNA Diagnostics, Department of Medical Genetics University and University Hospital of Antwerp, Belgium
- **Yu Yamaguchi, M.D., Ph.D.**, Professor Developmental Neurobiology Program, The Burnham Institute, La Jolla, CA



The MHE Research Foundation Board of Directors



- **Craig A Eaton, Esq.:** President
- **David Brooks:** Vice President
- **Suzanne Caputo:** Secretary and Chair of fund raising
- **Dan Caputo:** Treasurer
- **Sarah Ziegler:** National Director of Research and Coordinator of Clinical Information, Executive Director of the National MHE Research Registry



Other Organizations you should be aware of



Chondrosarcoma Support Group has over 400 members from all over the world.

<http://health.groups.yahoo.com/group/Chondrosarcoma>

Support Group and Resource Site for Adults with Primary Bone Cancers

www.abc-survivors.net

International WAGR Syndrome Association -**W**-Wilm's tumor **A**-Aniridia
G-Genital and/or urinary tract abnormalities **R**-mental retardation)

www.wagr.org

The CDG Family Network - Congenital Disorders of Glycosylation (CDG), formerly called carbohydrate-deficient glycoprotein syndrome, are a group of inherited disorders that affect a process called glycosylation.

www.cdgs.com

Multiple Hereditary Exostoses



**Wings of hope as we help
researchers reach for the
way to find a cure**