NATIONAL HUMAN GENOME RESEARCH INSTITUTE
NATIONAL INSTITUTES OF HEALTH

1st NIH CONFERENCE ON HOLOPROSENCEPHALY

SPONSORS: Division of Intramural Research, NHGRI, NIH
Office of Rare Diseases, NIH, and the
Crowley-Carter Centers for Research in
Holoprosencephaly and Related Brain Malformati

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PLACE: Pookshill Marriott, Bethesda, Maryland

DATES: April 3-4th, 2000

Introduction

Holoprosencephaly (HPE) is the most common structural anoma
forebrain in humans. It occurs in about 1:250 pregnancies.
cent of affected fetuses survive to delivery, however, so t
about 1:16,000 live births. The disorder occurs when the p
fails to divide during the first few weeks of fetal life to
and right cerebral hemispheres. Incomplete cleavage of the
forebrain results in defects in brain structure and functio
development of the face. Brain malformations in HPE can ra
to severe.

Although the causes of HPE is unknown are not known in mos
least four genes are known to be involved in HPE, inclu
Hedgehog (SHH) gene on chromosome 7, ZIC2 on chromosome 13, S
chromosome 2, and TGIF on chromosome 18. HPE occurs in up to
cent of infants born to diabetic mothers. Veratrum alkal

well-established cause of HPE in animals, making exposure
environmental factors a possible cause of other cases of HP

The 1st National Institutes of Health Conference on Holopros
held April 3-4, 2000 in Bethesda, Maryland. With oral p
basic and clinical HPE research, and special family-or
sessions, it was the largest program yet held on this im
understood cause of congenital malformations. The cor
organized and sponsored by the National Human Genome
Institute, the NIH Office of Rare Diseases, and the (
Foundation of Dallas, Texas, which has established a netw
and treatment centers for HPE.

Organizers regarded the conference as a mechanism for
overview on the present state of understanding the causes
genetic defects that interfere with body patterning during
the role of cholesterol in modifying embryonic signaling p
concepts about the prognosis and care of infants born wit
undergone significant change, which were addressed in the p

The first session on Monday, April 3rd, titled Holoprosencephaly:
A Paradigm for the Complex Genetics of Brain Development.
session was by invitation only because of its highly techn
the fact that some of the work presented had not yet been
reviewed journals and hence might be far too preliminar
specialists. Nevertheless, valuable insights were presen
experts in their respective fields that should lead to a be
both normal and abnormal brain development exemplified by
C. Urschel III, and his family represented the families
session.

The morning session opened with an introduction by Franc
M.D./Ph.D. who as the Director of the National Human Genor
Institute leads the government and university-based pursui
genetic blueprint for human beings contained in the geneti
He announced that tremendous progress is being made towa
wherein a complete set of human genes will be determined f
in history. The significance of this milestone will be t
rapidly use this information to better understand many di

human beings, including HPE. He also noted that “HPE is short of HOPE” which helped to set the tone, and add a prop the talks that followed.

The first presentation was by Jeffery A. Golden M.D. (University Pennsylvania) who is an embryologist, neuropathologist, a developing chick. He uses this model system, to obt understanding of early steps in the formation of the brai Dr. Golden described the current understanding of th environmental influences that help to determine the form o was followed by Kathleen K. Sulik Ph.D (University of North Caroli Chapel Hill) who reviewed the early development of th emphasized that many environmental agents (chemicals, dr excess, etc.) could cause birth defects in animals very sim Clearly a better understanding of the way that genes environmental factors will lead to progress in HPE resea conclusion could be drawn from the presentation by Drs. Helm D.D.S., Ph.D.(University of California, San Francisco). Dr. Helm that retinoic acid (Vitamin A) in excessive amounts or e amounts could dramatically affect the development of the b laboratory animals in a manner that may hold clues to the humans. Next, Philip A. Beachy Ph.D (Johns Hopkins University reviewed the latest research on the components of the first to be shown to cause human HPE (Sonic hedgehog, named afte the video game) as well as similar malformations in th abnormal gene function. The Acting Scientific Director Institute of Child Health and Human Development, Ian Dawi described the fruitful approach of using additional model o the frog and the laboratory fish to better understand the brain development. The final talk of the morning session A. Brown M.D(Columbia University) who has identified a ge ZIC2, whose loss can lead to HPE in humans and animals. Th families with HPE can be attributed to either mutations in of the gene’s actions through the absence of the genetic ma region of human chromosome 13. It is hoped that a better the function of this gene will lead to progress in HPE rese

The keynote speaker for the afternoon session was Max Muenk is the Branch Chief of the Medical Genetics Branch, the N Genome Research Institute and one of the meeting organize

genetics of HPE into focus as it affects humans. There a
HPE genes: SHH (discussed by Dr. Beachy), ZIC2 (discussed by Dr.
Brown), SIX3 and TGIF. For each of these genes, there are fa
alterations in gene function that are presumed to be the
these cases. However, at present the majority of families
cause has been sought do not have alterations in thes
emphasizes the complexity of HPE that is known to have man
causes including the environment as well as genetics. The
one to two dozen additional HPE loci. However, these gene
been identified. Dr. Muenke leads an active research p
complex genetics of HPE on the NIH campus aimed at ident
genes. The participation of the families has been essent
effort.

Only one of the invited speakers was unable to attend the
M. Casey M.D. (Baylor College of Medicine) was to speak a
emerging evidence that a disorder that he studies, called
related to the defects in the midline of the developing f
HPE. It is known that the events leading to HPE occur ex
the pregnancy: gastrulation and early neurulation (during
after conception). It has been hypothesize that many of t
direct the positioning of these organs also are involved
which is the basis for HPE. This area is actively being
Muenke lab.

The next two speakers, Michael M. Shen Ph.D. (Robert Wood Johnson
Medical School) and Alexander F. Schier PhD. (Skirball Institute, Ne
York University School of Medicine) both provided evid
laboratory animals such as the mouse and the fish that t
indeed correct. Defects in the developmental program gui
nodal can result in abnormal positioning of internal body
features similar to HPE. Both of these investigators are
the Muenke lab to see if abnormal gene function of the hum
also be responsible for HPE.

The final presentation was by David Wotton Ph.D. (Wotton at the University
of Virginia, and previously in Joan Massague's lab at M
Kettering in New York). Dr. Wotton's basic research ha
mutations in the TGIF gene from HPE families can lead to a loss o
in the altered protein. These studies confirm that changes in TGIF

HPE in humans and provide detailed information as to how occurring at the molecular level.

On Tuesday April 4th, 2000 the session "Holoprosencephaly: A Update" was introduced by the Honorable William Frist, M.D. United States Senator (R-Tenn). Senator Frist was kind enough attendees and some of the families about his commitment in for seeking increased funding for research exemplified by the National Institutes of Health. Senator Frist, who was Dr. Collins of the NHGRI and Dr. Urschel of the Carter Cent that the partnership between the Carter Centers and the NHG an excellent example of productive cooperation to achieve r in the pursuit of treatments for HPE. Although he empha nation we have many competing goals in the budget, biomed has historically fared well in the view of most members Senator Frist's speech was preceded by a moving 10-minu prepared by the Carter Centers which is the first install documentary to serve to educate the public about HPE and i families.

The first talk of the morning session was by M. Michael D.M.D., Ph.D. (Dalhousie University) who described the broad HPE. The range of clinical severity in HPE is extensive a are confronted by exactly the same medical problems. Maso (University of Michigan) described that there are common between different families who have a child with HPE. Some relate to feeding, growth, irritability, sleeping pro developmental delays, and difficulty with communication o muscle difficulties. There is no substitute for experien these challenges. Often the medical literature paints an gloomy picture of HPE. This was further emphasized by the Nancy Clegg Ph.D. who as the National HPE Project Director Centers at the Texas Scottish Rite Hospital for Children i her presentation reported on the survival and performance HPE. These results are re-writing the textbooks on HPE. the treatments with medications, such as Artane for the m and a greater appreciation for the variations between pati better result than traditional textbooks would indicate.

James Barkovich M.D. (University of California, San Francisco)
the evolving understanding of the diagnosis of HPE made c
magnetic resonance imaging (MRI) which speaks to the spectr
the brain that can be affected by HPE and the means of ma
diagnoses. The final talk of the morning was by April A. Bensky Ph.D.
and Hillary J. Leevers, Ph.D. (Rutgers University) who as speciali
developmental assessment reviewed the test batteries and ne
which they use to more precisely asses the strengths and
children with HPE.

The information provided to the families during “Holopro
family-Oriented Conference” was similar the morning sessio
Barbara B. Biesecker (Senior Genetic Counselor, NHGRI) outl
some of the psychosocial issues revolving around HPE and p
to the diagnosis and coping strategies with the condition a
for their family. Maximilian Muenke, M.D gave a brief summary of t
research efforts of his lab and the key role that parents
research effort play in providing the motivation and sub
progress in the field of HPE research. Based on questions
children that arose during this session, his group will be
for families on the genetics of HPE.

A “Thank-You Picnic” followed the afternoon session and
videotape seen previously in the morning so that the famil
attend the morning session could also view this “work in pr

The Crowley-Carter Foundation and members of the Carter Center
were kind enough to not only help organize and partici
conference events, but also funded the elegant meals for th
and attendees both before and during the conference. They
funds for the “Thank-you Picnic” for the families at the
family conference.

It is the intention of the Carter Centers to plan and
conferences so that families and specialists can remain fo
of the better understanding HPE, its root causes, treatme
term goal of possible cures.