

# Global strategies to reduce the health-care burden of craniofacial anomalies

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*Report of WHO meetings on International  
Collaborative Research on Craniofacial Anomalies*

*Geneva, Switzerland, 5-8 November 2000*

*Park City, Utah, USA, 24-26 May 2001*



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*THIS REPORT IS DEDICATED TO THE MEMORY OF*  
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# Acronyms and abbreviations

<b>AED</b>	<b>anti-epileptic drugs</b>
<b>AZT</b>	<b>azidothymidine</b>
<b>BCLP</b>	<b>bilateral cleft lip and palate</b>
<b>CAPS</b>	<b>Cleft Audit Protocol for Speech</b>
<b>CAT (scan)</b>	<b>computerized axial tomography</b>
<b>CDC</b>	<b>Centers for Disease Control and Prevention (United States of America)</b>
<b>CFA</b>	<b>craniofacial anomalies</b>
<b>CI</b>	<b>confidence interval</b>
<b>CIDR</b>	<b>Centre for Inherited Disease Research</b>
<b>CIOMS</b>	<b>Council for International Organizations of Medical Science</b>
<b>CL</b>	<b>cleft lip</b>
<b>CL/P</b>	<b>cleft lip – with or without cleft palate</b>
<b>CLP</b>	<b>cleft lip and palate</b>
<b>COR</b>	<b>Craniofacial Outcomes Registry</b>
<b>CP</b>	<b>isolated cleft palate</b>
<b>CPAP</b>	<b>continuous airway pressure</b>
<b>DNA</b>	<b>deoxyribonucleic acid</b>
<b>ECLAMC</b>	<b>Estudio Colaborativo Latino Americano Malformaciones Congenita</b>
<b>ENT</b>	<b>ear, nose and throat</b>
<b>ESF</b>	<b>European Science Foundation</b>
<b>EU</b>	<b>European Union</b>
<b>EUROCAT</b>	<b>European Registry for Congenital Anomalies and Twins</b>
<b>EUROCRAN</b>	<b>European Collaboration on Craniofacial Anomalies</b>
<b>FAS</b>	<b>fetal alcohol syndrome</b>
<b>FFQ</b>	<b>food-frequency questionnaire</b>
<b>GEI</b>	<b>gene/environment interaction</b>

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<b>GOS.SP.ASS</b>	<b>Great Ormond Street speech assessment</b>
<b>HIV</b>	<b>human immunodeficiency virus</b>
<b>IARC</b>	<b>International Agency for Research on Cancer</b>
<b>IFR6</b>	<b>interferon regulatory factor 6</b>
<b>IMR</b>	<b>infant mortality rate</b>
<b>IU</b>	<b>international units</b>
<b>LRT</b>	<b>likelihood ratio test</b>
<b>mg</b>	<b>milligrams</b>
<b>MRC</b>	<b>Medical Research Council (United Kingdom)</b>
<b>MRI</b>	<b>magnetic resonance imaging</b>
<b>MSX</b>	<b>muscle-specific homeobox factor</b>
<b>NGO</b>	<b>non-governmental organization</b>
<b>NIH</b>	<b>National Institutes of Health (United States of America)</b>
<b>NTD</b>	<b>neural tube defects</b>
<b>OFC</b>	<b>orofacial clefts</b>
<b>OR</b>	<b>odds ratio</b>
<b>RCT</b>	<b>randomized controlled trial</b>
<b>RNA</b>	<b>ribonucleic acid</b>
<b>RR</b>	<b>relative risk</b>
<b>TCS</b>	<b>Treacher Collins syndrome</b>
<b>TDT</b>	<b>transmission disequilibrium test</b>
<b>TGF</b>	<b>transforming growth factor</b>
<b>UCLP</b>	<b>unilateral cleft of the lip and palate</b>
<b>VCF</b>	<b>velo-cardio-facial syndrome</b>
<b>VPI</b>	<b>velo-pharyngeal incompetence</b>
<b>WHO</b>	<b>World Health Organization</b>
<b>WMA</b>	<b>World Medical Association</b>

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# Executive summary

In 2000, the WHO Human Genetics Programme, with financial support from the United States National Institute of Dental and Craniofacial Research, launched a five-year project designed to take forward an international research strategy on craniofacial anomalies (CFA). The specific objectives of this initiative are:

- to develop an international network for consensus building, planning and protocol development for international, collaborative, biomedical, epidemiological and behavioural studies in the core areas of CFA research;
- to create a directory of CFA research resources, and
- to establish a publicly-accessible research database on the Internet.

As a first step of this initiative, a consensus conference of international experts covering the four selected areas for research – treatment of CFA, gene/environment interaction (GEI), genetics, and prevention – was held under the auspices of the World Health Organization (WHO). The conference comprised two meetings – the first, held in Geneva from 5-8 November 2000, included concurrent workshops on research concerning the genetic basis of CFA, gene/environment interactions, and the treatment of CFA; the second, held in Utah from 24-26 May 2001, considered the prevention of CFA.

The aims and objectives of the WHO consensus meetings were to:

- (1) obtain counsel from experts involved in CFA research around the world;
- (2) describe the “state-of-the-science” with regard to treatment, genetics, gene/environment interaction and prevention, and highlight recent relevant research;
- (3) discuss requirements for future research in all areas of craniofacial anomalies; and

- 
- (4) arrive at a consensus on approaches to address data gaps and proceed with strategies, methodologies and protocols to advance knowledge.

## A. Treatment

Three interrelated research issues were addressed within the clinical theme:

- (1) **Evidence-based care:** the identification and dissemination of optimal clinical interventions for the management of CFA.
- (2) **Quality improvement:** the development and dissemination of methodologies for monitoring and improving the delivery of clinical services.
- (3) **Access and availability:** the identification of strategies to maximize access to adequate levels of care for all affected individuals, irrespective of nationality.

## B. Gene/environment interaction

Issues discussed in relation to the planning of future collaborative gene/environment interaction (GEI) research were:

### ■ Identification of data gaps

- (1) Use birth surveillance systems to determine the frequency of craniofacial anomalies and sources in ascertainment.
- (2) Identify areas of the world where interesting populations or patterns of craniofacial anomalies exist, and gain access to those populations.
- (3) Evaluate whether an established infrastructure exists to allow research in GEI to proceed.
- (4) For GEI research it will be essential to carefully categorize samples by type of defect, to identify (and exclude) syndromes that are known to have a genetic etiology and, where possible, to control methodologic and demographic parameters which might confound biochemical and genetic analyses. This type of research is therefore predominantly applied to non-syndromic orofacial clefts.
- (5) GEI research should seek to establish the frequency of genotypes in different populations and ethnic groups and establish the risk of orofacial clefts associated with:
  - (a) the gene variant alone,
  - (b) environmental exposures alone, and
  - (c) gene/environment interaction.

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## ■ Study design and standardization issues

Having identified data gaps, appropriate research hypotheses can be generated. Agreement will be required on the data to be collected, the methods of sample collection and the geographical areas where research would be carried out. In time it would be anticipated that the research would address the data gaps identified and would raise further issues that would be addressed by generating further hypotheses to be tested in a cycle of enquiry and research.

## ■ Common core protocols

It was agreed that the standardization of research would require the development of guidelines to provide consistency between groups collecting data. Such common core protocols would be developed in the areas of:

- (a) nutritional, lifestyle and occupational factors;
- (b) medical, obstetric and drug histories;
- (c) genetic and biochemical data collection;
- (d) assessment of clinical dysmorphology and collection of consistent family history data;
- (e) agreed guidelines for ascertainment of cases and, where appropriate, controls.

## C. Genetics

While there is an inevitable overlap between research in genetics and in gene/environment interaction, CFA research will benefit from an intensive genetics approach.

- (1) The discussions on the genetics component of the WHO CFA Conference focused on those technologies, analytic approaches, and populations that will best advance our understanding of the etiologies of craniofacial abnormalities, with particular reference to those with strong genetic components.
- (2) While recognizing that the environment and stochastic events play an important and, often, major role in predisposing to craniofacial anomalies, the role of genetics is compelling in many situations.
- (3) Funding, manpower training, bioethical and government policy issues also influence research. These should be discussed and addressed in the light of identified differences in the demographics and infrastructure in different regions, and research priorities should be established geographically and according to agreed criteria.

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## **D. Prevention**

- (1) Identify environmental and behavioural factors with established associations with orofacial clefts and other CFA.
- (2) Review evidence on the role of specific maternal nutritional factors in the etiology of orofacial clefts and other CFA.
- (3) Reach a consensus regarding the role and importance of nutritional supplementation trials in evaluating the causal role of specific nutrients in the etiology of orofacial clefts and other CFA.
- (4) Discuss aspects of the design of orofacial cleft and CFA prevention trials and their ethical, legal, social and financial implications.
- (5) Make recommendations on the resources needed to implement international collaborative studies of CFA prevention with common core protocols.

Section 8 provides details of the recommendations for future research arising out of these two WHO consensus meetings.