Genetics and Craniofacial & Dental Anomalies

Report of the National Institute of Dental and Craniofacial Research

Genetics Workgroup

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PREFACE

We face the world. Our face 'makes' the first impression to others: we are first judged on the basis of our face and only later, after this first impression is indelibly made, are we permitted to make our inner self known to the other, to reveal our secret self, to risk making our true-self known. Ourself, we have access only to a mirror image of our face. It is a reflection, putting our left on the right, and our right on the left. If this image is not perfect to us, the challenge of becoming known, of being fully human, is orders of magnitude more complex.

ACKNOWLEDGEMENTS

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EXECUTIVE SUMMARY

Goal:
To provide NIDCR with a set of prioritized recommendations for future directions in genomic and functional genomic research to facilitate understanding of dental, oral, and craniofacial biology and associated disorders and diseases.

Background:
During the past decade, important advances have been gained in cell, molecular and developmental biology; etiology and pathogenesis of diseases/disorders in dental, oral, and craniofacial structures; and bioinformatics and related information technology. Significant progress has been made toward completion of the human, mouse and zebrafish genomes, a number of microbial genomes representing viral, bacterial and yeast organisms, and a number of other genome projects are soon to be completed. Many of these advances have led to gene-based diagnostics for a number of dental, oral and craniofacial inherited diseases and disorders. These advances have also provided a new emphasis to be placed on understanding human complex diseases and the need for molecular "tools" to identify multiple genetic polymorphisms in microbial, animal and human organisms. Further, a number of innovative technological developments now provide approaches to high throughput genotyping, single nucleotide polymorphisms (SNPs), DNA microarray technology, and a host of transgenic animal models for diseases of the human condition. Accelerated progress has been made in part due to increased trans-NIH institute as well as private and international coalitions supporting these activities.

Objectives:
1. To assess the current status of dental, oral, and craniofacial genetics research.
2. To identify genomic resources for use by the biomedical research community.
3. To identify opportunities, obstacles and deficiencies for genomic and functional genomic research in the NIDCR research portfolio.
4. To identify the technologies that exist and that are being developed to accelerate discoveries in dental, oral, and craniofacial genetics research.
5. To assess the ability of the NIDCR scientific community to perform state-of-the-art research, including scientific expertise, infrastructure and technology accessibility.
6. To identify NIDCR's role in fostering research training and career development.
7. To develop a set of prioritized recommendations for genomic and "post-genomic" research for the next 5 years.
8. To identify opportunities for increased academic, government, non-profit foundation and private sector collaborations.
9. To identify opportunities for increased international collaborations.

Participants:
Approximately 60 scientists were invited to this workshop. This included scientists from different areas of dental, oral and craniofacial genetics. In addition, scientists outside of the NIDCR community who have expertise in genome technology and developing genomic resources were invited.

Research Priorities

I. Immediate needs

1. Current technologies are allowing for more rapid identification of gene mutations/variations that contribute to complex genetic diseases. NIDCR participation in the NHGRI/NIH funded contract at the Center for Inherited Disease Research (CIDR) genotyping facility would allow NIDCR-funded applicants to apply for access to state-of-the-art genotyping technologies without cost. (NOTE: NIDCR participation was established in February, 2000.)
2. Basic research findings are not readily communicated to the medical community. The NIDCR should facilitate the translation from bench research to clinical applications for improved diagnosis and treatment.
3. Practitioners (dentists, dental hygienists, physicians, nurses, etc.) need training for the clinical identification of genetic anomalies and diseases. Special attention should be focused on genetic counseling and bioethics training, especially as it relates to genetic testing. Genetic test development and clinical applications should be coordinated with the NHGRI ELSI program.
4. Animal models are valuable for understanding the causes of human genetic anomalies. Phenotyping assays need to be developed to identify existing craniofacial mutants in mouse, zebrafish, and other potential animal models. It is also important to archive mutants so that material is accessible to the research community.
5. Tissue-specific and stage-specific cDNA libraries are useful tools for studying normal craniofacial development. The ultimate goal will be a set of full-length cDNA clones. This would increase the capacity to compare and analyze tissues or samples of interest for specific genetic anomalies, simple or complex, rare or common.

II. Long term needs

1. Standardized criteria are needed for clinical diagnosis and phenotyping of genetic disorders.
2. Data records and sample collection and storage procedures need to be standardized as well. A controlled vocabulary should be developed for data records. Standardization will facilitate sharing of data and materials among investigators.
3. Infrastructure support (i.e. bioinformatics, databases) is needed to manage clinical craniofacial, oral, and dental genetics data.
4. Regional centers are needed for enhanced recruitment of human subjects and coordinated collection and storage of clinical samples for rare diseases, so that the samples are available for research projects.
5. Craniofacial centers are needed in academic health science centers to encourage research and improve diagnosis, treatment, and prevention for craniofacial, oral and dental anomalies.

BACKGROUND

The National Institute of Dental Research (NIDR) was established in 1948 as the third Institute of the National Institutes of Health (NIH). In 1998, the name was changed to the National Institute of Dental and Craniofacial Research (NIDCR), to reflect the scope of research supported by the Institute.

The NIDCR mission is to improve and promote craniofacial, oral and dental health through research. Extramural research programs are funded through the Division of Extramural Research, with two offices and five branches: Office of Clinical, Behavioral and Health Promotion Research, Office of Training, Craniofacial Anomalies and Injuries Branch, Infectious Diseases and Immunity Branch, Neoplastic Diseases Branch, Chronic Diseases Branch, and Biomaterials, Biomimetics, and Tissue Engineering Branch. The Division of Intramural Research includes laboratories located on the NIH campus in Bethesda, MD. There are seven branches: Craniofacial and Skeletal Diseases Branch, Craniofacial Developmental Biology and Regeneration Branch, Craniofacial Epidemiology and Genetics Branch, Gene Therapy and Therapeutics Branch, Oral and Pharyngeal Cancer Branch, Oral Infection and Immunity Branch, and Pain and Neurosensory Mechanisms Branch.

In 1949, the NIDR began to support studies of dentofacial defects, especially for cleft lip and palate, the most common facial birth defect. The first longitudinal growth study of subjects born with cleft lip or palate was established and followed the same subjects for many years. In the early 1950's, the Institute established what would be one of the first genetics programs at the NIH. The research, initiated by Dr. Carl Witkop, focused on a field study looking at an isolated southern Maryland community that had high susceptibility to defective enamel and dentin. This study came to be known as the "Brandywine Study." In addition to identifying the genetic disease dentinogenesis imperfecta, the Witkop team also identified albinism, glaucoma, ankyloglossia (tongue-tiedness), and a high percentage of sickle cell anemia. The success of this study resulted in the creation of the Human Genetics Section in the NIDR's Clinical Investigations Branch, and expanded the genetic research scope. In the early 1960's the Institute began to promote genetics research at Dental Schools, and urged dental schools to include genetics as part of their curriculum.

In recent years dramatic changes in the health care system and in genetic research have affected treatment and research priorities. Managed care practices make clinical education more restricted, resulting in a clinical community that is becoming more and more naive in terms of understanding and implementing current research advances. Yet, the scientific community is smaller in terms of access to data and the ease and speed of communication worldwide, but more fragmented in terms of disparity of technical skills in computing and molecular biology, and in access to adequate research funding. It is an era of "Big Science" in biological research, which means fewer labs with the equipment and staff to do modern research. The need for developing new research tools in the dental community continues to grow. At the same time, most dental schools in the United States have dropped the genetics curriculum, resulting in a lack of insight for many dentists when developing treatment of genetic conditions.

The NIH has become more international in its scope, in advocating patient rights worldwide, in the composition of working groups and in identifying culturally diverse people to build international collaborations. One way to accelerate technical advances is to provide funds for research for the public and private sector in the form of small projects that scientists are generally unwilling to attempt due to time or budget constraints. There is current interest in the NIH to seed centers for research efforts and foster communication between centers and the outside community.

Genomics

The National Center for Human Genetics Research was established in 1988, and the Human Genome Project was launched in 1990 with the goal of sequencing the Human Genome in 15 years - the anticipated completion date was 2005. On June 26, 2000, the Human Genome Project Public Consortium announced that it had assembled a "working draft" of the sequence of the human genome. This sequence covered 97 percent of the human genome, and 85 percent assembled in order. The final completion date has been accelerated to 2003 in consideration of the following events:

1. automation of template production;
2. technical advances in sequencing technology, especially the development of capillary sequencing;
3. the accompanying reduction in the cost of sequencing;
4. coordination of the independent centers into 1 group;
5. high quality of sequence data (50% in near-finished or better form, 24% in finished form,).

This project has implications for the future of research of interest to the NIDCR. The general understanding of the genome (number and kinds of genes) and elucidation of clusters of orthologous groups of genes will permit identification of genes important in craniofacial development and disease.

In addition to the Human Genome Project, several other genome projects will also provide very important information to the genetics community. The completion of the *Caenorhabditis elegans* and *Drosphila melanogaster* genomes, and the progress made on the mouse genome will accelerate research aimed toward understanding human disease, using these animals as models. Also underway and supported in part by NIH are the rat, zebrafish (*Danio rerio*) and *Xenopus laevis* genome sequencing efforts. Over 60 bacterial genomes have been or are currently being sequenced. The NIDCR supports genome sequencing research on several important oral pathogens. Currently, NIDCR provides funds for genome projects for *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Streptococcus mutans, Treponema denticola, Streptococcus sanguis,* and *Candida albican*s.

As the genome projects are proceeding towards completion, scientists are developing ways to use this new data. Functional genomics or proteomics will look at gene expression patterns and protein function and interactions to understand the mechanisms that are involved in life processes. In this sense, the genome projects will provide important tools for understanding gene function.

Target Diseases

Heritable diseases that affect craniofacial morphology (CFMD = CranioFacial Morphology Disorder) are of interest to the Institute (Table 1). Forty-seven disease categories have been identified and summaries of 90 members of these categories are included in Tables 3a and 3b (extracted from a more complete data set in Appendix 4). For a disease to be included in this list, it was required that, at minimum, the mode of inheritance of the disorder be known.

These summaries include information on whether a putative causal gene had been identified, if a locus is known, and if allelic variants have been reported. Many of these disease categories include phenotypically similar disorders with very different modes of transmission, being due to multiple loci, and/or described as 'genetically heterogeneous'. Genetic heterogeneity has become a complex designation. This is partially due to the recognition that many CFMDs of clinically

similar presentation are due to mutations in disparate genes at various loci, but also that the definition of allele has become problematic, notwithstanding that the current definition of a gene itself also involves a certain amount of ambiguity. Are allelic variants defined as varying mutations in a single gene anywhere within the bounds of that gene, or as varying mutations at a unique position along the linear DNA composing some part of a gene? Clearly some syndromes are multi-factorial and therefore heterogeneous, however non-complementing allelic forms can also be considered genetically heterogeneous, whether or not they include deletions or insertions.

Genetics Of Target Diseases

Tables 3a and 3b summarize the following types of genetic information for the 47 CFMDs identified:

1. whether a putative causal gene product has been identified,
2. whether a causal gene locus has been identified (regardless of whether a corresponding gene or protein is known),
3. the inheritance pattern,
4. any known allelic variants,
5. whether attempts at prenatal diagnosis has been documented,
6. any animal models (for gene mapping, determination of the functional affect of a mutation, 'naturally' occurring analogous disorders in animals, etc.),
7. whether affected individuals are susceptible or predisposed to systemic disease (e.g. neoplasia, diabetes, infections)
8. whether a paternal age effect has been documented.

A putative causal gene product has been identified for 77% of the targeted disorders yet 83% have been mapped to a causal gene locus. Allelic variants have been described for 12% of these disorders (amelogenesis imperfecta, Bloom syndrome, diGeorge syndrome, diastrophic dysplasia, hypophosphatasia, Kallman syndrome, Marfan, Reiger syndrome, Treacher-Collins mandibulofacial syndrome, velocardiofacial syndrome and Waardenburg syndrome) and attempts at prenatal diagnosis has been documented for only 7% (Achondroplasia, Apert Syndrome, Beckwith-Wiedmann Syndrome, Ehlers Danlos Syndrome, Marfan Syndrome, Osteopetrosis, Treacher Collins Mandibulofacial Dysostosis), a reflection of the sporadic nature of many of these disorders - i.e. at risk pregnancies are not easily identified as many of the causal mutations are spontaneous, not inherited. Animal models have been described in 40% of the disease categories (Achondroplasia, Amelogenesis Imperfecta, Beckwith-Wiedemann, Cleidocranial Dysplasia, DiGeorge Syndrome, Greig Cephalopolysyndactyly, Holoprosencephaly, Hypochondroplasia, Jackson-Weiss, Marfan, McCune-Albright, Metaphyseal Chondrodysplasia, Osteogenesis Imperfecta, Osteopetrosis, Reiger, Treacher-Collins, Waardenburg, And Williams-Beuren), which is very useful for identifying candidate genes. In 13% of these disorders affected individuals are predisposed to systemic disease (e.g. neoplasia, diabetes or infection). The maternal age effect of likelihood of a chromosomal anomaly in at-risk pregnancies is well known, and in 6% of these disorders a paternal age effect has been documented, i.e. case presentation is correlated with advanced age of the father.

Identified Genes

At least 60 genes have been directly implicated in the formation of craniofacial and dental anomalies (Table 2) and 77% of the targeted disorders include identified putative causal genes. These genes comprise structural (e.g.. collagen) and regulatory (e.g. growth factor, transcription factors) genes, and include gene families (e.g. keratins), receptors, DNA binding proteins (e.g. histone cell cycle regulation defective) immune system (e.g. autoanti gen) and genes known to be involved in complex traits (e.g. homeobox genes).

Periodontal Diseases

Periodontal diseases are a heterogeneous group of diseases that affect hundreds of millions worldwide. The disease presents clinically as redness and bleeding of the gingiva, detachment of the soft tissues from the teeth to produce periodontal pockets, and radiographic evidence of loss of alveolar bone height. Advanced periodontitis results in increased tooth mobility, loss of masticatory function, and tooth loss. Specific bacteria play a requisite role in periodontal disease, but microbial factors alone do not predict the presence or severity of disease. In addition to oral microbes, a variety of environmental factors, including tobacco use, diet, and stress, may be important in disease pathogenesis. Different individuals have different risk for developing periodontitis. A differential host immune response may relate to disease occurrence or severity. Periodontitis may be a group of diseases where gene-environment interactions play a major role. Several inherited diseases with immune system defects have a periodontal tissue involvement. Altered host response has also been reported for nonsyndromic, adult, and early onset periodontitis. Recent studies have shown that variations in the pro-inflammatory cytokine interleukin-1 (IL-1) gene cluster on chromosome 2 are associated with increased susceptibility to severe adult periodontitis. Also, IgG_2 levels and prostaglandin E_2 levels affect severity of early onset or adult periodontitis.

Recent studies have identified a genetic link between early onset periodontitis and mutations in the cathepsin C gene. The gene was identified as a loss-of-function mutation for Papillon-Lefevre syndrome, which is characterized by palmoplantar hyperkeratosis and severe early onset periodontitis. The gene has now also been linked to Haim-Munk syndrome, and to non-syndromic prepubertal periodontitis.

Head And Neck Cancers

Many head and neck cancers are known to have a strong environmental component, e.g. exposure to tobacco, alcohol or certain viral agents, such as Epstein-Barr virus or human papillomavirus. In addition, ultraviolet light exposure increases the risk for facial carcinomas. Genetic factors involved in head and neck cancers include the tumor protein p53, zinc finger protein 217, and tumor necrosis factor receptor superfamily and loss of heterozygosity at protein phosphatase 2, structural/regulatory subunit A, beta, to list a few examples. Susceptibility to carcinogenic agents differs among individuals, and may be related to the genetic variation and interaction of genetic and environmental factors. Correlation of factors known to be important in tumorigenesis with individual genetic susceptibility could be one way of understanding the etiology of these cancers. Defining the molecular pathogenesis of head and neck cancer may provide the basis for earlier diagnosis, treatment and prevention strategies. It may be possible to identify specific genetic targets that increase risk of cancer and to develop genetic tests to identify individuals who would be at risk. In addition, it

would be possible to identify genetic damage that predisposes to cancer, such that strategies can be developed for early detection and treatment.

Temporomandibular Disorders

An important challenge to the understanding of Temporomandibular Disorders (TMD) is the separation of proximal causes (stress, injury) from inherent causes. The etiology of TMDs is considered to be multifactorial, with psychosocial and behavioral characteristics playing important roles. Identifying biological markers for susceptibility to these disorders would provide future avenues for research on treatment and prevention.

Diagnostics

The development of reliable diagnostics is extremely important. Tests have beem developed to identify abnormalities that result in a variety of human diseases. However, in many cases there is not a genetic or biochemical test that will allow for definitive diagnosis. In addition, the presence of a mutation may indicate increased susceptibility for a disease without being able to predict the actual manifestations of the disease in a single individual. Future studies will concentrate on identifying genotype/phenotype correlations and development of successful treatments and preventive measures to decrease the burden of craniofacial diseases.

Animal Models and Gene Therapy

An animal model has been described in a rodent, primate, or ungulate for 40% of the targeted disorders. Reverse genetics, the technique of constructing a transgenic animal by introducing a mutated homologous version of a putative causal human disease gene, has been extremely useful for some disorders in identifying candidate genes, examining the consequences of particular mutations, and greatly increasing the understanding of the developmental underpinnings of the clinical presentation of the disorder.

Gene therapy as used here is restricted to the use of molecular techniques in correcting genetic disease - i.e. does not include traditional medical treatment (e.g. dietary or pharmacological management of symptoms). Gene therapy then has two manifestations - somatic correction or germ line correction. Somatic correction includes two forms. One form includes a localized correction where the gene product is provided to a specific region of the body (e.g. an expression vector containing the wild type laminin gene to a blister in Epidermolysis bullosa). A second form involves systemic correction where the introduction of the corrected gene is 'spread' to all cells in the body (either by introduction of the corrected gene early in development of the fetus so all progeny cells contain the corrected gene (using a recombination or lysogenic transgene system) or by introduction of the gene using a vector which will infect all the cells in the fetus, incorporate into the genome and thus correct the progeny cells of the infected cells). Germline correction entails correction of gametes that contain the mutation. Preferential elimination of gametes bearing the mutation, or some recombination based correction method are two possible approaches.

Gene therapy is an infant science, some success has been obtained in research on skin disorders (Bauer, et al. 1999, Bickenbach, et al. 1999) and proof of principle has been achieved for oral models (Baum and O'Connell 1999). Tissue

remodeling, and gene therapy focused on somatic therapy for tooth regeneration and repair are exciting new areas of research.

Genetics Research Funded by the NIDCR

Funding of genetics research is not restricted to the craniofacial and anomalies and injuries branch but rather is distributed among all of the Branches of the NIDCR. Figure 1 shows the FY1998 funding distribution of projects coded as genetics, or having a significant genetic component, by program area. These projects include the study of broad categories of genes as in the study of homeobox genes, growth factors and signaling peptides, genes involved in morphogenesis and patterning, as well as the study of neural crest cells and genes involved in the formation of the palate and mandibular arch, and wound healing.

Figure 2 shows the FY1998 distribution of genetics grants by subject area. The projects are subsumed in the following general categories: craniofacial development, craniofacial anomalies, teeth and bones research, periodontal disease, microbial genetics and microbial genome projects, head and neck cancer, pain, and salivary gland/saliva.

For genetics research, the majority of grants administered by the NIDCR are RO1s. Eighty-one percent are research projects in contrast to research centers (15%) and research training, contracts and other grants (4%) as presented in Figure 3.

Nearly one quarter (23%) of the funded research (n=91) is in the area of microbial genetics or genomics, an area of long standing interest to the Institute and is an area in which the NIDCR and the NIAID has held a leading role in promoting research. The study of microbes involved in dental caries provided the impetus to establishment of the microbial genome projects targeting the following microorganisms: *Streptococcus mutans, Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Treponema denticola, Streptococcus sanguis,* and *Candida albican*s. Elucidation of bacterial adhesion molecules may be the means to controlling and preventing systemic infection of these bacteria. There is also the new focus on the relationship of periodontal diseases and systemic disease, such as cardiovascular disease.

Thirty-six percent of grants are in either craniofacial, tooth or bone related research (n=144). Research projects concerning craniofacial anomalies include the study of cleft lip and cleft palate, diseases of tooth formation, ectodermal dysplasias, craniosynostosis, frontonasal dysplasia, hemifacial microsomia, diGeorge syndrome, and velo-cardio-facial syndrome. Teeth and tooth development is of particular interest to the Institute. Included in this category are dentinogenesis, amelogenesis, tooth enamel formation and mineralization, tooth eruption and cementogenesis. Bone morphology and patterning genes are important for craniofacial morphology. Genes involved in growth factor signaling events, cartilage formation, deposition and bone development, bone resorption and remodeling are part of the set of events leading to craniofacial formation. Related to these topics is the study of specific bone diseases especially osteoporosis, arthritis, and osteogenesis imperfecta. The genetic component of periodontal disease is an area of increasing interest to the Institute. Localized juvenile periodontitis appears to have a significant genetic component. Appendix 5 describes the status of genetic research for specific craniofacial, oral and dental diseases targeted by the NIDCR.

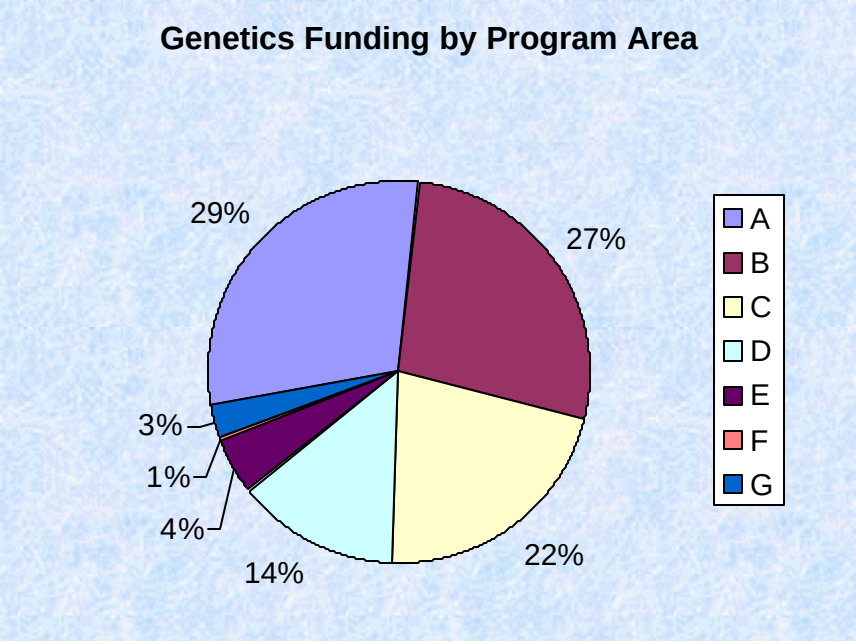
Head and neck cancer, including squamous cell carcinoma, is the sixth most prevalent type of cancer. Every hour a person dies from this disease and forty-two thousand people die from cancer of the tonsil and/or larynx annually. Eighteen percent of the genetics research at NIDCR (n=74) is in the area of head and neck cancer. Study of cell cycle, cell interactions, cytokines, growth factors, and tumor suppressor genes and the human papilloma virus is extremely promising in addressing this disease group.

The study of the salivary gland and saliva holds great promise for the development of genetic screening procedures. Identification of salivary genes and polymorphisms as well as the description of salivary mucins is an area of burgeoning research. In addition, use of the salivary gland as a delivery system for gene therapy products is being actively pursued.

Pain research of specific interest to the NIDCR includes the areas of trigeminal neuralgia, temporal mandibular joint disease, tooth pulp innervation and gender-specific pain.

New areas of study include the development of oral vaccines and gene therapy as emerging fields. This research has important application to the treatment of oral complications of HIV infection and oral pharyngeal carcinomas. In addition the identification of biomarkers for risk assessment and its application to pharmacogenetics to provide individualized medical care is the future of medicine.

Figure 1.



A: Craniofacial Anomalies and Injuries; B: Infectious Diseases and Immunity; C: Neoplastic Diseases; D: Chronic Diseases; E: Biomaterials, Biomimetics and Tissue Engineering
F: Clinical, Behavioral and Health Promotion Research; G: Training

Figure 2

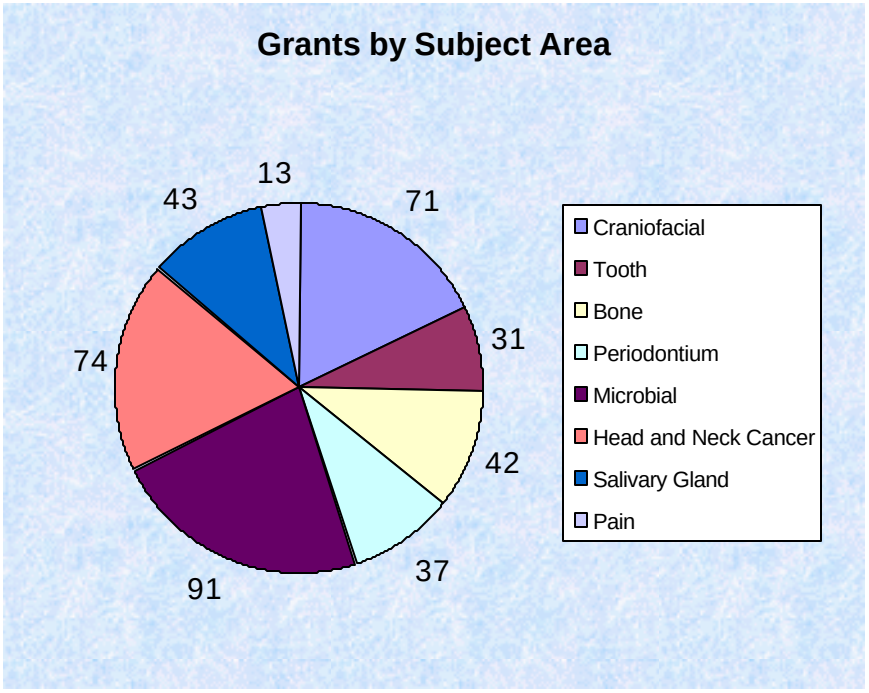
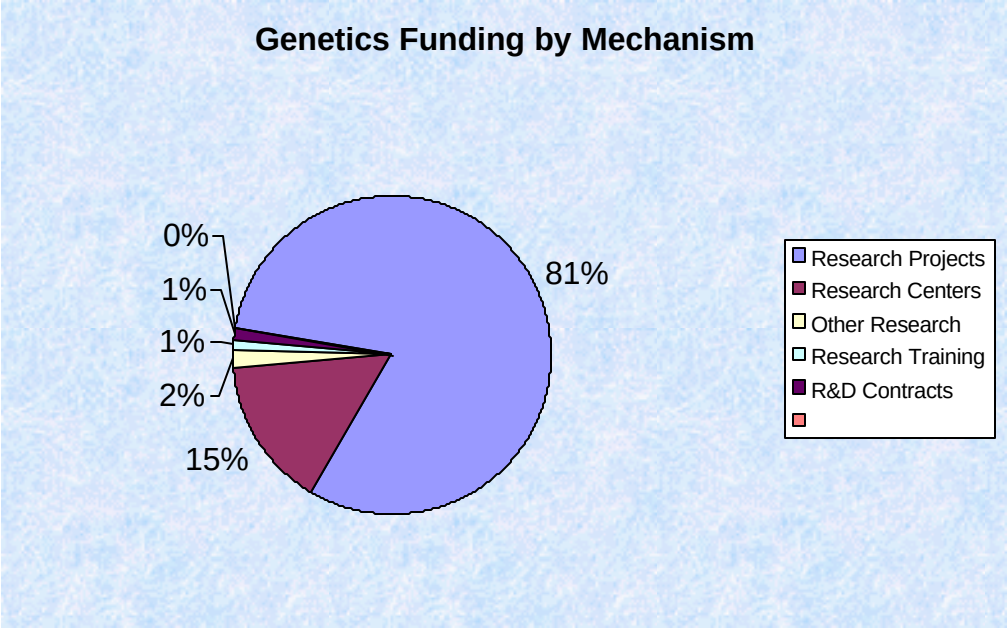


Figure 3


Genetics Funding by Mechanism
0%
1%
1%
2%
15%
81%
Research Projects
Research Centers
Other Research
Research Training
R&D Contracts

FINDINGS AND RECOMMENDATIONS

Overview

The areas of opportunity and need identified by the committee can be grouped into seven broad categories: Training, Infrastructure, Standardization, Complex or Rare Diseases, Microbial Studies**,** Animal Models, and Craniofacial Genetics.

Training

The need for continuous education and training is a priority for the members of the Genetics Work Group. Also required is the dissemination of information to the public and education of patients. The high rate of change in technology and available data means that continual training and reeducation must be implemented in both research and clinical settings. The areas identified as a priority in genetics training efforts are: informatics, statistical analysis, phenotyping, and population analysis, including new molecular technologies and data sets (for example SNPs and multilocus interactions). Training sabbaticals could be made available for senior investigators. The corollary to this would be to establish effective means of recruiting and retaining young investigators to oral, dental and craniofacial research. Dental geneticists or specialists in dental dysmorphology are declining in numbers and a need exists to prevent extinction of these clinician/scientists. Also, as the volume and complexity of data increases, it is necessary to include bioinformatics in training and research programs.

Infrastructure

The NIDCR could serve as a facilitator to develop and encourage centralized resources. Access to informatics resources, array technology and genotyping, and establishing tissue and DNA repositories with disease, organ, and developmental stage specific material is needed for significant progress in understanding morphological and developmental processes. Centralized facilities providing community access to these technologies need to be established. The Working Group unanimously agreed that the NIDCR provide support for CIDR-Genotyping Center (NOTE: NIDCR joined the CIDR contract in February, 2000). They also suggested that the NIDCR support a resource center including databases for tracking clinical information including genetic susceptibility and diagnostic testing in clinical settings for use by the research community.

Mutation analysis and characterization is a priority for any research in diagnostics. SNP identification is being funded as an NIH-wide effort. A component of this research includes the analysis of regulatory polymorphisms. The NIDCR should participate in this effort in a proactive fashion by facilitating the collection and retention of samples from patients with rare diseases. A central repository for mutagenesis data and standardized phenotyping and procurement of model animals needs to be established. Presymptomatic testing to predict risk requires new markers for prediction or identifying at-risk individuals. Information is needed by the community on the availability of knock-out mice, tissue resources and synteny. A central site would facilitate characterization and continuation of study of mutants. The need to establish focused, local centers for the repository of clinical samples, for example chondrodysplasia centers, would foster multicenter collaborations.

A technology center should be established in the NIDCR Division of Intramural Research for the use and training of extramural scientists to facilitate retraining programs and be a means of establishing a common language and standard protocols in the research community. Intramural technology training centers would also allow greater flexibility and ease in upgrading to newer technologies.

Interest in more web-based access to databases was expressed. Centralized analytical software, user friendly, web-based and centralized facilities could provide analysis.

Standardization

Clearly the need for standardization of diagnosis and phenotyping of craniofacial anomalies is of paramount importance. The determination of environmental exposures to putative teratogens involved in craniofacial anomalies is a promising area of research as evidenced by the cleft lip/cleft palate association with tobacco use. Associations with dietary components such as folate and other nutrients also need further study. Such work requires multicenter and multinational collaborations that rely upon standardized protocols for diagnosis and characterization and comparing studies requires standardized data analysis and statistical methods.

Data sharing and data release guidelines need to be established for genes involved in craniofacial anomalies. Currently the Bermuda Rules, requiring the release of human genome sequencing data within 24 hours by publicly funded labs, does not ensure that research from other sources is becoming available in a timely fashion. This rule does not protect the researcher's desire for priority of access to the data for publication. Guidelines requiring release of data upon publication or at end of funding period may be more amenable to longer-term projects and research involving large data sets. Also no benefit to negative result publication currently exists yet this information can save members of the research community time, funds and energy by avoiding potential misdirection and focusing on relevant mutations in mutation screens and other analyses.

Complex or Rare Diseases

Many craniofacial anomalies are of complex etiology or are associated with rare diseases (meeting the orphan disease criteria). It was recommended that the NIDCR manage consortia for collection of data and samples for these diseases and the banking of rare case specimens for future mining. Analysis of complex traits requires fostering research approaches and multicenter studies in order to evaluate morphogenetic vs. metabolic effects. Also complex disease is often manifested in a developmental hierarchy. Collection of such data requires multicenter and multi-investigator coordination.

Data release is also of concern to the Working Group. The need for linkage data and gene identification information to be released within six months of discovery was emphasized. Some means to ensure the interests of the investigators (priority of study, time for publication of longer term studies) was also viewed as integral to the discovery process.

Microbial Studies

Microbial research is an area of longstanding interest to the NIDCR. The need for public access to these genome databases and support for development of genetics systems for sequenced organisms was identified. Annotation of the Microbial Genetics Database was stated a priority and the databases of oral microbes would be the appropriate place to start.

Animal Models

Animal models are a means for the phenotypic characterization of genes involved in craniofacial morphology and the need exists for screening of mutants for craniofacial anomalies. Several animal models were discussed with mouse, zebrafish and fly receiving the most attention. A mammalian model is the ideal but other systems have distinct advantages. Zebrafish have the visual advantage in that the embryos are transparent making it of singular utility in the study of gene expression with mutated targets. The Tubingen database provides good access to mutants and it provides a means for a functional genomic approach compatible with small labs. The fruit fly, Drosophila melanogaster, is the classical genetic organism and its utility in studying craniofacial genes should be optimized.

In the mouse, the use of multiple inbred strains is a means to reveal modifier genes that influence inherited disease, especially those which affect expression in the study of complex traits. Also the dissection of physiology/function can be used for gene discovery. Gene knock-outs technologies have disadvantages because diseases do not always occur in the null state but are affected by the genotype. The search for naturally occurring variants was discussed and a support mechanism for comparative model analyses needs to be put in place. Mouse mutagenesis centers need to be established and phenotyping screens need to be developed.

The Working Group also supported continuing to explore the use of alternative animal models in specific areas, for example tooth development.

Craniofacial Genetics

Effective study of craniofacial anomalies requires tissue- and stage-specific cDNA libraries and the capacity to compare samples from affected individuals with "normal" phenotypes. Such analysis requires a population genetics approach in order to address, for example, epistatic interactions in human genetic studies. Teasing out the gene/environment interaction, possible maternal effects, and ethnic/race/lifestyle effects in uniform populations requires sophisticated statistical analysis and large data sets. The need exists to involve population genetics in epidemiological studies. The same enzymes may vary in importance of effect in craniofacial anomalies in different populations. Specific populations with known exposures need to be identified and analyzed.

A multidisciplinary approach is indicated for craniofacial treatment. Long-term dysmorphology follow-up to identify syndromic cases not apparent at birth is also indicated. Tissue-specific cDNAs in normalized/subtracted libraries, and/or developmentally staged, tissue-specific mouse-human hybridized libraries for sequencing could facilitate and accelerate the identification of genes involved in craniofacial development and neoplasia.

Other

Several other topics also received attention. Human clinical studies provide the opportunity for sample collection but there is minimal support for collection and storage of biological samples or for the proper characterization of patients. The situation is complicated by economics, for example, a researcher cannot provide reimbursement for follow-up, unless it has been built into the protocol. It also was suggested to leverage centers of excellence for samples and build a phenotyping database.

Teasing out factors involved in craniofacial dysmorphology requires multifaceted research efforts, as observed in folate/clefting studies. The NIDCR should fund behavioral research as a component of genetic/environmental susceptibility projects. Pharmacogenetics permits the stratification of treatment, and prospective treatment modification based on genetic markers. Typically retrospective analysis is based on outcome evaluation markers. If growth potential could be predicted particular treatment could be correlated with genotype and perhaps permit prevention of craniofacial anomalies developmentally downstream.

Funding concerns were widely discussed. Multiple suggestions were made: RFAs should be made available; inter-institute studies should be designed across NIH, not just NIDCR; some method of levaraging funds from contributors, perhaps by requiring clone submission or sharing of resources could make new technologies more widely available without a concomitant financial burden; and supplements to grants to allow for diagnostic testing be created, or perhaps to supplement existing centers to do perform this service.

Table 1. NIDCR TARGET DISEASES

1. Achrondroplasia
2. Amelogenesis imperfecta-1
3. Apert Syndrome
4. Beare-Stevenson cutis gyrata Syndrome
5. Beckwith-Wiedemann Syndrome
6. Bloom Syndrome
7. Chondrodysplasia punctata
8. Cleidocranial Dysplasia
9. Craniosynostosis
10. Crouzon syndrome
11. Dentinogenesis imperfecta
12. Diastrophic dysplasia
13. DiGeorge syndrome
14. Ectodermal dysplasia
15. Ehlers-Danlos syndrome
16. Epidermolysis bullosa
17. Greig cephalopolysyndactyly syndrome
18. Holoprosencephaly
19. Hypochondroplasia
20. Hypophosphatasia, infantile
21. Jackson-Weiss Syndrome
22. Kallmann Syndrome-1
23. Leprechaunism
24. Marfan Syndrome
25. McCune-Albright Syndrome
26. Metaphyseal chondrodysplasia, Murk Jansen type
27. Neonatal osseous dysplasia 1
28. Neuromata, mucosal, with endocrine tumors
29. Osteogenesis imperfecta
30. Osteopetrosis
31. Pachyonychia congenita, Jackson-Lawler type
32. Pallister-Hall Syndrome
33. Pfeiffer Syndrome
34. Reiger Syndrome
35. Saethre-Chotzen Syndrome
36. Shprintzen-Goldberg Syndrome
37. Simpson Dysmorphia Syndrome
38. Sjogren Syndrome
39. Temporomandibular disorders
40. Thanatophoric Dysplasia
41. Tooth agenesis, familial
42. Treacher Collins Mandibulofacial Dysostosis
43. Velocardiofacial Syndrome
44. Waardenburg Syndrome
45. Williams-Beuren Syndrome
46. Head and Neck cancers

47. Other

Table 2 GENES INVOLVED IN CRANIOFACIAL AND DENTAL DISORDERS, Sorted by acronym

OMIM number	GENE NAME Acronym	Full Name
102540	ACTC	ACTIN, ALPHA, CARDIAC MUSCLE
104760	APP	AMYLOID BETA A4 PRECURSOR PROTEIN; APP
602269	ARVCF	ARMADILLO REPEAT GENE DELETED IN VCFS
108746	ATP6E	ATPase, H+ TRANSPORTING, LYSOSOMAL, SUBUNIT E
114800	CA1	CARBONIC ANHYDRASE I
601273	CLTCL1	CLATHRIN, HEAVY POLYPEPTIDE-LIKE 1
120150	COL01A1	COLLAGEN, TYPE I, ALPHA-1
120160	COL01A2	COLLAGEN, TYPE I, ALPHA-2
120140	COL02A1	COLLAGEN, TYPE II, ALPHA-1
120131	COL04A4	COLLAGEN, TYPE IV, ALPHA-4
303630	COL04A5	COLLAGEN, TYPE IV, ALPHA-5
120215	COL05A1	COLLAGEN, TYPE V, ALPHA-1
120220	COL06A1	COLLAGEN, TYPE VI, ALPHA-1
120110	COL10A1	COLLAGEN, TYPE X, ALPHA-1
116790	COMT	CATECHOL-O-METHYLTRANSFERASE
603432	CYLN2	CYTOPLASMIC LINKER 2
125255	DCN	DECORIN
601755	DGSI	DIGEORGE SYNDROME CRITICAL REGION GENE
130160	ELN	ELASTIN
135821	FBLN2	FIBULIN 2
134797	FBN1	FIBRILLIN 1
600483	FGF8	FIBROBLAST GROWTH FACTOR 8
136350	FGFR1	FIBROBLAST GROWTH FACTOR RECEPTOR 1
176943	FGFR2	FIBROBLAST GROWTH FACTOR RECEPTOR 2
134934	FGFR3	FIBROBLAST GROWTH FACTOR RECEPTOR 3
139320	GNAS1	GUANINE NUCLEOTIDE-BINDING PROTEIN, ALPHA-STIMULATING ACTIVITY POLYPEPTIDE.
602502	GOLGA1	GOLGI AUTOANTIGEN, GOLGIN SUBFAMILY A, 1
138720	GP1BB	GLYCOPROTEIN Ib, PLATELET, BETA POLYPEPTIDE
300037	GPC3	GLYPICAN 3
300168	GPC4	GLYPICAN 4
600239	GPR1	G PROTEIN-COUPLED RECEPTOR 1
601679	GTF2I	GENERAL TRANSCRIPTION FACTOR II-I
601767	HIP1	HUNTINGTIN-INTERACTING PROTEIN 1
600237	HIRA	HISTONE CELL CYCLE REGULATION DEFECTIVE, S. CEREVISIAE, HOMOLOG OF, A
142984	HOXD10	HOMEO BOX D10
600065	ITGB2	INTEGRIN, BETA-2
123940	KRT04	KERATIN 4
148041	KRT06A	KERATIN 6A
148042	KRT06B	KERATIN 6B
148065	KRT13	KERATIN 13
148067	KRT16	KERATIN 16
148069	KRT17	KERATIN 17
150240	LAMB1	LAMININ, BETA-1
600535	MEOX2	MESENCHYME HOMEO BOX 2
142983	MSX1	MSH, DROSOPHILA, HOMEO BOX, HOMOLOG OF, 1
123101	MSX2	MSH (DROSOPHILA) HOMEO BOX HOMOLOG 2
602724	PNUTL1	PEANUT-LIKE 1
168468	PTHR1	PARATHYROID HORMONE RECEPTOR 1
600063	RO60	AUTOANTIGEN Ro/SSA, 60-KD
181500	SCZD	SCHIZOPHRENIA
600850	SCZD4	SCHIZOPHRENIA 4
603206	SCZD8	SCHIZOPHRENIA 8
190090	SRC	V-SRC AVIAN SARCOMA (SCHMIDT-RUPPIN A-2) VIRAL ONCOGENE
480000	SRY	SEX-DETERMINING REGION Y

109092 SSA1 SJOGREN SYNDROME ANTIGEN A1
109090 SSB SJOGREN SYNDROME ANTIGEN B
602643 TNFRSF11B TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY, MEMBER 11B
600415 TTPA TOCOPHEROL TRANSFER PROTEIN, ALPHA
601622 TWIST TWIST, DROSOPHILA, HOMOLOG OF
603431 WBSCR1 WILLIAMS-BEUREN SYNDROME CHROMOSOME REGION 1

Table 3a: SUMMARY OF TARGET DISEASE SUMMARIES

DISEASE CATEGORY NAME (AGGREGATE NAME OF GROUPED ENTRIES)	NUMBER OF ENTRIES	PUTATIVE CAUSAL GENE IDENTIFIED	LOCUS MAPPED	INHERITANCE PATTERN	ALLELIC VARIANTS KNOWN
Achrondroplasia	1	yes	yes	yes	no
Amelogenesis imperfecta	8	yes	yes	yes	yes
Apert Syndrome	1	yes	yes	yes	no
Beare-Stevenson cutis gyrata	1	yes	yes	yes	no
Beckwith-Wiedemann Syndrome	1	yes	yes	yes	no
Bloom Syndrome	1	yes	yes	yes	yes
Chondrodysplasia punctata	0	yes	mul	yes	no
Cleidocranial Dysplasia	3	yes	yes	yes	no
Craniosynostosis, nonsyndromic	7	yes	yes	yes	no
Crouzon syndrome with acanthosis nigricans	1	yes	yes	yes	no
Dentinogenesis imperfecta	3	no	yes	yes	no
Diastrophic dysplasia	1	yes	no	yes	yes
DiGeorge syndrome	1	yes	yes	yes	yes
Ectodermal dysplasia	nc	.	.	.	.
Ehlers-Danlos syndrome	4	yes	yes	yes	no
Epidermolysis bullosa	nc	.	.	.	.
Greig cephalopolysyndactyly	1	yes	yes	yes	no
Holoprosencephaly	4	yes	mul	yes	no
Hypochondroplasia	1	yes	yes	yes	no
Hypophosphatasia	1	yes	yes	yes	yes
Jackson-Weiss Syndrome	1	yes	yes	yes	no
Kallmann Syndrome-1	3	no	mul	yes	mul
Leprechaunism	1	yes	yes	yes	no
Marfan Syndrome	1	yes	yes	yes	mul
McCune-Albright Syndrome	1	yes	yes	yes	no
metaphyseal chondrodysplasia, Murk Jansen type	1	yes	yes	yes	no
Neonatal osseous dysplasia 1	1	yes	yes	yes	no
Neuromata, mucosal, with endocrine tumors	nc	.	.	.	.
Osteogenesis imperfecta	3	yes	mul	yes	no
Osteopetrosis	2	yes	mul	yes	no
Pachyonychia congenita	2	yes	mul	yes	no
Pallister-Hall Syndrome	1	yes	yes	yes	no
Pfeiffer Syndrome	1	yes	mul	yes	no
Reiger Syndrome, type 1	1	yes	yes	yes	yes
Saethre-Chotzen Syndrome	1	yes	yes	yes	no
Shprintzen-Goldberg Syndrome	2	yes	yes	yes	no
Simpson Dysmorphia Syndrome	1	yes	mul	yes	no
Sjogren Syndrome	1	no	no	yes	no
Temporomandibular disorders	nc	.	.	.	.
Thanatophoric Dysplasia	1	yes	yes	yes	no
Tooth agenesis, familial	2	yes	mul	yes	no
Treacher Collins mandibulofacial Dysostosis	2	no	yes	yes	yes
Velocardiofacial Syndrome	1	no	yes	yes	yes
Waardenburg Syndrome, type 1	2	yes	mul	yes	yes
Williams-Beuren Syndrome	1	mul	no	yes	no
Head and Neck cancers	nc	.	.	.	.

Other	7	yes	yes	yes	yes	.
TOTALS	**90**	**36**	**39**	**42**	**12**	**.**
PERCENT OF TOTAL		**77**	**83**	**89**	**26**	**.**

Table 3b: SUMMARY OF TARGET DISEASE SUMMARIES

DISEASE CATEGORY NAME (AGGREGATE NAME OF GROUPED ENTRIES)	PRENATAL DIAGNOSTICS DOCUMENTED	ANIMAL MODEL DESCRIBED	SYSTEMIC DISEASE PREDIPOSITION	PATERNAL AGE EFFECT POSSIBLE
Achrondroplasia	yes	yes	no	yes
Amelogenesis imperfecta	no	yes	no	no
Apert Syndrome	yes	no	no	yes
Beare-Stevenson cutis gyrata	no	no	no	yes
Beckwith-Wiedemann Syndrome	yes	yes	yes	no
Bloom Syndrome	no	no	yes	no
Chondrodysplasia punctata	no	yes	no	no
Cleidocranial Dysplasia	no	yes	no	no
Craniosynostosis, nonsyndromic	no	no	no	no
Crouzon syndrome with acanthosis nigricans	no	no	no	no
Dentinogenesis imperfecta	no	no	no	no
Diastrophic dysplasia	no	no	no	no
DiGeorge syndrome	no	yes	yes	no
Ectodermal dysplasia	.	.	.	.
Ehlers-Danlos syndrome	yes	ch	no	no
Epidermolysis bullosa	.	.	.	.
Greig cephalopolysyndactyly	no	yes	no	no
Holoprosencephaly	no	yes	no	no
Hypochondroplasia	no	yes	no	no
Hypophosphatasia	no	no	no	no
Jackson-Weiss Syndrome	no	yes	no	no
Kallmann Syndrome-1	no	no	no	no
Leprechaunism	no	no	no	no
Marfan Syndrome	yes	yes	no	no
McCune-Albright Syndrome	no	yes	yes	no
metaphyseal chondrodysplasia, Murk Jansen type	no	yes	no	no
Neonatal osseous dysplasia 1	no	no	no	no
Neuromata, mucosal, with endocrine tumors	.	.	.	.
Osteogenesis imperfecta	no	yes	no	no
Osteopetrosis	yes	yes	no	no
Pachyonychia congenita	no	no	no	no
Pallister-Hall Syndrome	no	no	no	no
Pfeiffer Syndrome	no	no	no	no
Reiger Syndrome, type 1	no	yes	no	no
Saethre-Chotzen Syndrome	no	yes	no	no
Shprintzen-Goldberg Syndrome	no	no	no	no
Simpson Dysmorphia Syndrome	no	no	yes	no
Sjogren Syndrome	no	no	no	no
Temporomandibular disorders	.	.	.	.
Thanatophoric Dysplasia	no	no	no	no
Tooth agenesis, familial	no	no	no	no
Treacher Collins mandibulofacial Dysostosis	yes	yes	no	no
Velocardiofacial Syndrome	no	no	no	no
Waardenburg Syndrome, type 1	no	yes	yes	yes
Williams-Beuren Syndrome	no	yes	no	no
Head and Neck cancers	.	.	.	.
Other	no	yes	no	no
TOTAL	**7**	**19**	**6**	**3**
PERCENT OF TOTAL	**15**	**40**	**13**	**6**

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Appendix 2: NIDCR Genetics Work Group Agenda

National Institute of Dental and Craniofacial Research
Genetics Work Group
Agenda

Holiday Inn, Bethesda
8120 Wisconsin Avenue
Bethesda, MD 20814
301-652-2000
Versailles I Ballroom

Sunday, November 14, 1999

Welcome and Reception, 6:00-9:00 PM

6:00 PM Genetics and the NIDCR
Harold Slavkin, Director, NIDCR

6:30 Genomics and Craniofacial Research
Leslie Biesecker, NHGRI

7:00 Summary of Genetics Research at the NIDCR
Judy Small, NIDCR

7:30-9:00 Reception

Monday, November 15, 1999

Session I: Genomics

Moderator, Ken Buetow, NCI

8:30 "Genomics from Microbes to Man"
George Weinstock, University of Texas Medical School

9:05 "Beyond the Genome Project"
John Quackenbush, The Institute for Genome Research

9:25 "Mouse as Models for Craniofacial/Dental Disorders"
Eric Everett, Indiana University

9:40 "Molecular Dissection of Craniofacial Development in Zebrafish"
Pam Yelick

9:50 Discussion and Instructions for Break-Out Sessions

10:10 Coffee Break

10:30 Break-Out Session I

11:15 Break-Out Group Reports

12:00 Lunch

Session II: Human Dental, Oral, and Craniofacial Diseases

Moderator: Ethylin Wang Jabs, M.D.

1:30 "Craniofacial Malformation Syndromes: General Principles"
Gregg Semenza, Johns Hopkins University School of Medicine

1:50 "Susceptibility Genes for Oral Cancer"
Stephen Schwartz, Fred Hutchinson Cancer Research Center

2:10 "Genetic Epidemiological Approaches to Clefting, Oral Cancer, and Periodontal Disease"
Scott Diehl, NIDCR

2:30 Discussion

2:40 Coffee Break

3:00 Break-Out Session II

3:45 Break-Out Group Reports

4:30 Adjourn for the Day

7:00 Dinner

Tuesday, November 16, 1999

Session III: Clinical Applications

Moderator: Mary Marazita, University of Pittsburgh

8:30 "Genes in Oral Cancer for Diagnosis and Prognosis"
Tom Carey, University of Michigan Cancer Center

8:50 "Etiology of Malocclusion"
James Hartsfield, Indiana University

9:10 "Issues in Surveillance for Genetic Conditions"
Deborah Winn, NIDCR

9:30 Discussion

9:40 Coffee Break

10:00 Break-Out Session III

10:45 Break-Out Group Reports

11:30 Lunch

Session IV: Final Recommendations and Priorities

12:30 Discussion: Implementation of Recommendations
Ken Buetow
Ethylin Wang Jabs
Mary Marazita

2:00 Adjourn Meeting

Appendix 3: Topics for Breakout Sessions

National Institute of Dental and Craniofacial Research
National Institutes of Health

Genetics Work Group
Bethesda, MD • November 14-16, 1999

Breakout Group Sessions

Discuss topic area and produce a list of recommendations for each breakout group.
Transfer recommendations to transparencies for overhead projection.
Breakout group leader will present reports to workshop participants.

General Discussion Points to Consider:

- What genomic resources are available?
- What technologies are available?
- What new technologies are needed?
- Accessibility of newly developed technologies by the NIDCR research community.
- What resources are needed? Consider the development and production of resources.
- Distribution of resources. Facilitating transfer and broad dissemination and distribution of genomic resources both widely and timely to the research community.
- Bioinformatics and databases. Accessibility of up-to-date public databases for storage, utilization and manipulation of large data sets.
- Training

Session I: Genomics
Discussion Points to Consider in Breakout Groups:

- DNA: Gene Discovery, Single Nucleotide Polymorphisms, and Full Length cDNAs
  - Tissue source and repositories. Quality, availability, and microdissection of tissue.
  - Generation of cDNA libraries for ESTs and full-length cDNAs from specific tissues of dental and craniofacial systems, considering all aspects of library production including quality control and sequencing.

    - Identification of polymorphisms in genes.
- RNA: Gene expression, microarray technologies
    - Access to microarray technology by the NIDCR community, including discussion of costs and cost sharing.
    - Specific microarray needs
    - Gene expression patterns for all genes in dental and craniofacial tissues.
    - Other technologies for gene expression such as in situ analyses
- Protein Structure and Expression
    - Technologies for high-resolution measurements of protein expression and analysis
    - Protein arrays
    - Analysis for protein-protein interactions and protein-DNA interaction
- Functional Genomics
    - Use of animal models to identify gene function
    - Other methodologies for studying gene function

Session II: Human, Dental, Oral, and Craniofacial Diseases
Discussion Points to Consider in Breakout Groups:

- Identification of Genes for Genetic Disorders
    - Genomic markers as a tool for linkage studies
    - Mutations vs. Polymorphisms
- Complex Genetic Traits
    - Risk or Susceptibility
    - Statistical Methods
    - Genotyping Centers
    - Large scale, multi-center studies of disease
        - International collaboration
    - Gene-Environment Interactions
- Data Sharing
    - Family registries
    - Tissue availability
    - Repositories for tissues, cell lines, DNA
- Animal models to study human disease
    - Naturally occurring mutants
    - Genetically engineered animals
    - Mutagenesis for production of mutants
        - Dominant negative
        - Recessive

Session III: Clinical Applications
Discussion Points to Consider in Breakout Groups:

- Translation from bench to bedside
    - Clinical trials
    - Standards of care
- Use of genetic information as a diagnostic tool
- Prevention strategies using genetic susceptibility data
- Diagnostic tests in the clinical setting

- Informed Consent
- Surveillance for occurrence of genetic traits
- Multidisciplinary approach for treatment of developmental defects
- International collaboration and data sharing (families, tissue, DNA)
  - International registries, repositories
- Vaccines for prevention of disease (periodontitis, oral cancer)
- Pharmacogenetics
- Gene Therapy

APPENDIX 4: COMPLETE LIST OF TARGET DISEASE SUMMARIES

01. #100800 ACHRONDROPLASIA
02. *104500 AMELOGENESIS IMPERFECTA 2, HYPOPLASTIC LOCAL, AUTOSOMAL DOMINANT; AIH2
03. *104510 AMELOGENESIS IMPERFECTA, HYPOMATURATION-HYPOPLASIA TYPE, WITH TAURODONTISM
04. *104530 AMELOGENESIS IMPERFECTA, HYPOPLASTIC TYPE
05. 204650 AMELOGENESIS IMPERFECTA, LOCAL HYPOPLASTIC TYPE, RECESSIVE
06. 204690 AMELOGENESIS IMPERFECTA AND NEPHROCALCINOSIS
07. *204700 AMELOGENESIS IMPERFECTA, PIGMENTED HYPOMATURATION TYPE
08. *301100 AMELOGENESIS IMPERFECTA, HYPOMATURATION TYPE; AIH
09. AMELOGENESIS IMPERFECTA 1, HYPOPLASTIC TYPE; AIH1
10. #101200 APERT SYNDROME
11. #123790 BEARE-STEVENSON CUTIS GYRATA SYNDROME
12. #130650 BECKWITH-WIEDEMANN SYNDROME
13. *210900 BLOOM SYNDROME
14. 118650 CHONDRODYSPLASIA PUNCTATA
15. *118650 CHONDRODYSPLASIA PUNCTATA, AUTOSOMAL DOMINANT
16. 118651 CHONDRODYSPLASIA PUNCTATA, TIBIA-METACARPAL TYPE
17. #215100 RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, TYPE 1; RCDP1
18. #222765 RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, TYPE 2; RCDP2
19. #302940 CHONDRODYSPLASIA PUNCTATA, BRACHYTELEPHALANGIC
20. #302950 CHONDRODYSPLASIA PUNCTATA 1, X-LINKED RECESSIVE; CDPX1
21. #302960 CHONDRODYSPLASIA PUNCTATA 2, X-LINKED DOMINANT; CDPX2
22. #600121 RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, TYPE 3; RCDP3
23. #119600 CLEIDOCRANIAL DYSPLASIA; CCD
24. 216330 CLEIDOCRANIAL DYSPLASIA, RECESSIVE FORM
25. *216340 CLEIDOCRANIAL DYSPLASIA WITH MICROGNATHIA, ABSENT THUMBS, & DISTALAPHALANGIA
26. *123100 CRANIOSYNOSTOSIS, TYPE 1; CRS1
27. 123155 CRANIOSYNOSTOSIS, SAGITTAL, WITH DANDY-WALKER MALFORMATION & HYDROCEPHALUS
28. 101120 ACROCEPHALOPOLYSYNDACTYLY TYPE III
29. 218450 CRANIOSTENOSIS, SAGITTAL, W CONGENITAL HEART DISEASE, MENTAL DEFICIENCY, & MANDIBULAR ANKYLOSIS
30. 218600 CRANIOSYNOSTOSIS WITH RADIAL DEFECTS
31. *600593 CRANIOSYNOSTOSIS, ADELAIDE TYPE; CRSA
32. 601222 CRANIOSYNOSTOSIS, PHILADELPHIA TYPE
33. #123500 CROUZON SYNDROME
34. *125420 DENTIN DYSPLASIA, TYPE II
35. *125490 DENTINOGENESIS IMPERFECTA; DGI1
36. 125500 DENTINOGENESIS IMPERFECTA, SHIELDS TYPE III
37. *222600 DIASTROPHIC DYSPLASIA; DTD
38. *188400 DIGEORGE SYNDROME; DGS
39. #130000 EHLERS-DANLOS SYNDROME, TYPE I; EDS1

40. #130050 EHLERS-DANLOS SYNDROME, TYPE IV, AUTOSOMAL DOMINANT
41. 130070 EHLERS-DANLOS SYNDROME, PROGEROID FORM
42. *130080 EHLERS-DANLOS SYNDROME, TYPE VIII
43. #175700 GREIG CEPHALOPOLYSYNDACTYLY SYNDROME; GCPS
44. *236100 HOLOPROSENCEPHALY 1, ALOBAR; HPE1
45. #157170 HOLOPROSENCEPHALY 2; HPE2
46. #142945 HOLOPROSENCEPHALY 3; HPE3
47. *142946 HOLOPROSENCEPHALY 4; HPE4
48. #146000 HYPOCHONDROPLASIA; HCH
49. #146300 HYPOPHOSPHATASIA, ADULT TYPE
50. #123150 JACKSON-WEISS SYNDROME; JWS
51. *308700 KALLMANN SYNDROME 1; KAL1
52. *147950 KALLMANN SYNDROME 2; KAL2
53. *244200 KALLMANN SYNDROME 3; KAL3
54. #246200 LEPRECHAUNISM
55. #154700 MARFAN SYNDROME; MFS
56. #174800 MCCUNE-ALBRIGHT SYNDROME; MAS
57. #156400 METAPHYSEAL CHONDRODYSPLASIA, MURK JANSEN TYPE
58. #256050 NEONATAL OSSEOUS DYSPLASIA I
59. 166230 OSTEOGENESIS IMPERFECTA WITH OPALESCENT TEETH, BLUE SCLERAE & WORMIAN BONES, BUT WITHOUT FRACTURES
60. #166200 OSTEOGENESIS IMPERFECTA, TYPE I
61. #166220 OSTEOGENESIS IMPERFECTA, TYPE IV; OI4
62. *259700 OSTEOPETROSIS, AUTOSOMAL RECESSIVE
63. *166600 OSTEOPETROSIS, AUTOSOMAL DOMINANT, TYPE II
64. *129900 ECTRODACTYLY, ECTODERMAL DYSPLASIA, AND CLEFT LIP/PALATE SYNDROME 1; EEC1
65. *129500 ECTODERMAL DYSPLASIA 2, HIDROTIC; ED2
66. *129400 ECTODERMAL DYSPLASIA, ANHIDROTIC, WITH CLEFT LIP AND CLEFT PALATE
67. #129490 ECTODERMAL DYSPLASIA 3, ANHIDROTIC; ED3
68. *129400 ECTODERMAL DYSPLASIA, ANHIDROTIC, WITH CLEFT LIP AND CLEFT PALATE
69. #224900 ECTODERMAL DYSPLASIA, ANHIDROTIC
70. *225060 ECTODERMAL DYSPLASIA, TYPE 4; ED4
71. #167210 Pachyonychia congenita, Jackson-Lawler type
72. PACHYONYCHIA CONGENITA, JADASSOHN-LEWANDOWSKY
73. #146510 PALLISTER-HALL SYNDROME; PHS
74. #101600 PFEIFFER SYNDROME
75. *119500 CLEFT LIP/PALATE, LOWER LIP PARAMEDIAN MUCOUS CYSTS, POPLITEAL PTERYGIUM, DIGITAL & GENITAL ANOMALIES
76. #180500 RIEGER SYNDROME, TYPE 1; RIEG1
77. #101400 SAETHRE-CHOTZEN SYNDROME; SCS
78. #182212 SHPRINTZEN-GOLDBERG CRANIOSYNOSTOSIS SYNDROME
79. 182210 SHPRINTZEN OMPHALOCELE SYNDROME
80. #312870 SIMPSON-GOLABI-BEHMEL SYNDROME, TYPE 1; SGBS1
81. 270150 SJOGREN SYNDROME
82. #187600 THANATOPHORIC DYSPLASIA; TD
83. #106600 HYPODONTIA, AUTOSOMAL DOMINANT Tooth agenesis, familial
84. *602639 HYPODONTIA, AUTOSOMAL RECESSIVE
85. #247200 MILLER-DIEKER LISSENCEPHALY SYNDROME; MDLS
86. *149730 LACRIMOAURICULODENTODIGITAL SYNDROME; LADD
87. *154500 TREACHER COLLINS-FRANCESCHETTI SYNDROME 1; TCOF1
88. 248390 MANDIBULOFACIAL DYSOSTOSIS, TREACHER COLLINS TYPE, AUTOSOMAL RECESSIVE
89. 154400 ACROFACIAL DYSOSTOSIS 1, NAGER TYPE; AFD1
90. #192430 VELOCARDIOFACIAL SYNDROME
91. *193500 WAARDENBURG SYNDROME, TYPE I; WS1
92. #193510 WAARDENBURG SYNDROME, TYPE IIA; WS2A
93. #194050 WILLIAMS-BEUREN SYNDROME; WBS DISORDERS NAMED BY GENE

94. *170993 PEROXISOMAL MEMBRANE PROTEIN 3; PXMP3
95. #256050 NEONATAL OSSEOUS DYSPLASIA I
96. *200990 ACROCALLOSAL SYNDROME; ACLS

Appendix 5: TARGET DISEASE SUMMARIES:
RESTRICTED TO GENETICS AND HEAD AND NECK CLINICAL PRESENTATION

01. ACHRONDROPLASIA
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?100800.cs
OMIM: #100800
GENES INVOLVED: fibroblast growth factor receptor-3 gene (FGFR3;134934)
CHROMOSOMAL LOCATION: 4p16.3.
INHERITANCE: Autosomal dominant with complete penetrance , 80% cases new mutations , Paternal age effect, Mutations in FGFR3 gene ({134934}), >99% G380R
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: 1 PCR and 1 restriction digest of ACH homozygotes in families at risk and in which the parents are heterozygous for either the 1138A or 1138C allele
ANIMAL MODEL: mouse - distribution of transcripts
CLINICAL SUMMARY:
HEAD AND NECK :: [cranium]: , Frontal bossing , Megalencephaly , Foramen magnum stenosis , [face]: , Midface hypoplasia , Low nasal bridge , [ears]: , Recurrent otitis media in infancy and childhood , Conductive hearing loss
PREDISPOSITIONS: not stated

02. AMELOGENESIS IMPERFECTA 2, HYPOPLASTIC LOCAL, AUTOSOMAL DOMINANT; AIH2
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?104500
OMIM: *104500
GENES INVOLVED: The ameloblastin gene (AMBN; 601259) maps to 4q21 and is a strong candidate gene for AIH2
CHROMOSOMAL LOCATION: 4q21
INHERITANCE : Autosomal dominant form also recessive and X-linked forms
ALLELIC VARIANTS: see INHERITANCE
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [teeth]: Soft opaque or yellowish white lusterless enamel, Anterior open bite
PREDISPOSITIONS: not stated

03. AMELOGENESIS IMPERFECTA, HYPOMATURATION-HYPOPLASIA TYPE, WITH TAURODONTISM
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?104510.cs
OMIM: *104510
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: unk
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS:
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [teeth]: Amelogenesis imperfecta, hypomaturation-hypoplasia type, Taurodontism
PREDISPOSITIONS: unk

04. AMELOGENESIS IMPERFECTA, HYPOPLASTIC TYPE
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?104530
OMIM: *104530
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: not stated

INHERITANCE: Autosomal dominant (Four types: pitted, local, smooth and rough) also autosomal recessive rough type and an X-linked smooth type (301200)
ALLELIC VARIANTS: none stated
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [teeth]: Hypoplastic amelogenesis imperfecta, Generalized microdontia
PREDISPOSITIONS: not stated

05. AMELOGENESIS IMPERFECTA, LOCAL HYPOPLASTIC TYPE, RECESSIVE
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?204650.cs
OMIM: 204650
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: not stated
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [teeth]: Crown pitting and grooving, horizontal, both dentitions
PREDISPOSITIONS: not stated

06. AMELOGENESIS IMPERFECTA AND NEPHROCALCINOSIS
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?204690.cs
OMIM: 204690
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: not stated
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [teeth]: Enamel absent
PREDISPOSITIONS: not stated

07. AMELOGENESIS IMPERFECTA, PIGMENTED HYPOMATURATION TYPE
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?204700.cs
OMIM: *204700
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: unk
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [teeth]: Enamel soft, primary and secondary dentitions Shiny agar jelly tooth appearance Brown pigment in middle layers of enamel [radiology]: Enamel and dentin contrast absent
PREDISPOSITIONS: not stated

08. AMELOGENESIS IMPERFECTA, HYPOMATURATION TYPE; AIH
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?301100.cs
OMIM: *301100
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: X

INHERITANCE: X-linked recessive, Heterozygous females have vertically banded enamel mottling
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [teeth]: Opaque white, soft enamel
PREDISPOSITIONS: not stated

09. AMELOGENESIS IMPERFECTA 1, HYPOPLASTIC TYPE; AIH1
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?301200.cs
OMIM: *301200 Alternative titles; symbols ENAMEL HYPOPLASIA, HEREDITARY AMELOGENIN; (AMELX, ALGN, AMG, AMGL, INCLUDED)
GENES INVOLVED:
CHROMOSOMAL LOCATION: Xp22.3-p22.1
INHERITANCE: X-linked dominant
ALLELIC VARIANTS: AMELOGENESIS IMPERFECTA, HYPOPLASTIC TYPE
0001 : AMELX, 5-BP DEL
0002 : AMELX, 1-BP DEL, EX5
0003 : AMELX, 9-BP DEL
0004 : AMELX, LEU126TER
0005 : AMELX, THR3ILE
0006 : AMELX, GLU129TER
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: mouse amelogenin
CLINICAL SUMMARY:
HEAD AND NECK :: [teeth]: Hypoplastic type amelogenesis imperfecta Very hard enamel Thin enamel Small teeth Rough tooth surface. Twisted enamel rods course from the dentinoenamel junction to the enamel surface Defective amelogenin
PREDISPOSITIONS: not stated

10. APERT SYNDROME
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?101200.cs
OMIM: #101200
GENES INVOLVED: fibroblast growth factor receptor-2 (176943)
CHROMOSOMAL LOCATION: 10q26
INHERITANCE: Autosomal dominant paternal age effect
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: FGFR2 mutation, either S252W (176943.0010) or P253R, was found in exon IIIa (exon U or 7); PCR-based assay, ARMS (amplification refractory mutation system), to determine the phase of the mutant allele and the natural occurring polymorphisms present in the introns flanking the Apert mutation: S252W (934C-G) and P253R (937C-G)
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: Flat facies, Shallow orbits, Hypertelorism, Narrow palate, Craniosynostosis, Brachysphenocephalic acrocephaly
PREDISPOSITIONS: not stated
NOTE: cleft palate was significantly more common in the S252W patients

11. BEARE-STEVENSON CUTIS GYRATA SYNDROME
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?123790.cs
OMIM: #123790
GENES INVOLVED: fibroblast growth factor receptor 2 (FGFR2; 176943)
CHROMOSOMAL LOCATION: 10q26
INHERITANCE: autosomal dominant, Reported cases all sporadic Increased paternal age

ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [facies]: Craniofacial anomalies [skull]: Craniosynostosis Cloverleaf skull [ears]:]: Ear defects
PREDISPOSITIONS: not stated

12. BECKWITH-WIEDEMANN SYNDROME

http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?130650

OMIM: #130650
GENES INVOLVED: p57(KIP2) gene (CDKN1C; 600856) (collagen X)
CHROMOSOMAL LOCATION: 11p15.5, 11pter-p15.4
INHERITANCE: Autosomal dominant. Many sporadic. Imprinting at 11p15.5
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: cytogenetics
ANIMAL MODEL: p57(KIP2) gene (CDKN1C; 600856) in mice
CLINICAL SUMMARY:
HEAD AND NECK :: [Cranium] Metopic ridge Large fontanelle Prominent occiput [Face] Coarse facial features [Eyes] Prominent [ears]: Linear ear lobe creases Posterior helical indentations [Mouth] Macroglossia
PREDISPOSITIONS: Wilms tumor Hepatoblastoma Adrenal carcinoma Gonadoblastoma [Cardiac] Cardiomyopathy Cardiomegaly: Advanced bone age

13. BLOOM SYNDROME

http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?210900.cs

OMIM: *210900
GENES INVOLVED: Multiple seemingly nonspecific chromosomal breaks, High sister chromatid exchange (SCE) rate Increased chromosomal breakage Hypertriglyceridemia DNA ligase I abnormal SCE normal in heterozygotes
CHROMOSOMAL LOCATION: 15q26.1
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS:
.0001 BLOOM SYNDROME [BLM, 6-BP DEL/7-BP INS]
.0002 BLOOM SYNDROME [BLM, 3-BP DEL, 631CAA]
.0003 BLOOM SYNDROME [BLM, ILE843THR]
PRENATAL DIAGNOSTICS:
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK ::[facies]: Thin Malar hypoplasia, [nose]: Large, [head]: Dolichocephaly, [voice]:]: High-pitched, [mandible]: Small
PREDISPOSITIONS: Life-threatening infections, Predisposition to neoplasia (Wilm's tumor), Tendency to diabetes mellitus, Telangiectasia Sunlight sensitive erythema

14. CHONDRODYSPLASIA PUNCTATA

OMIM: 118650
GENES INVOLVED: peroxisomal type 2 targeting signal (PTS2), and receptor PEX7 gene (601757), rhizomelic chondrodysplasia punctata (RCDP2) show deficiency of the enzyme acyl-CoA:dihydroxyacetonephosphate acyltransferase (DHAPAT; 602744). arylsulfatase E gene (ARSE; 300180), (RCDP3)is caused by mutations in the alkyldihydroxyacetonephosphate synthase (alkyl-DHAP synthase) gene (AGPS; 603051). Type 1 RCDP (215100) results from a defect in the PEX7 gene (601757). In type 2 RCDP (RCDP2; 222765), there is an isolated deficiency of DHAP acyltransferase (602744).
CHROMOSOMAL LOCATIONS: 6q22-q24, Xp22.3, CDPX2: Xp11.23-p11.22, RCDP3: 2q31
INHERITANCE:
ALLELIC VARIANTS:

PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK ::
PREDISPOSITIONS: not stated

15. CHONDRODYSPLASIA PUNCTATA, AUTOSOMAL DOMINANT
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?118650.cs
OMIM: *118650
GENES INVOLVED:
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS:
ANIMAL MODEL:
CLINICAL SUMMARY:
HEAD AND NECK :: [skin]: Hyperkeratosis with erythema [hair]: Sparse hair Coarse hair [head]: Frontal bossing [facies]: Koala bear facies Nasal bone hypoplasia [eyes]: Cataracts
PREDISPOSITIONS:

16. CHONDRODYSPLASIA PUNCTATA, TIBIA-METACARPAL TYPE
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?118651.cs
OMIM: 118651
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: not stated
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [facies]: Flat midface Flat nose
PREDISPOSITIONS: not stated

17. RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, TYPE 1; RCDP1
http://www3.ncbi.nlm.nih.gov:80/htbin-post/Omim/dispmim?215100.cs
OMIM: #215100
GENES INVOLVED:
CHROMOSOMAL LOCATION: not stated
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS:
ANIMAL MODEL: beagle
CLINICAL SUMMARY: not warfarin ingestion effector
HEAD AND NECK :: [skin]: Sparse hair Coarse hair Erythroderma [facies]: Koala bear facies due to nasal bone hypoplasia [eyes]: Congenital cataracts [nose]: Saddle nose
PREDISPOSITIONS: not stated

18. RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, TYPE 2; RCDP2
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?222765.cs
OMIM: #222765
GENES INVOLVED: deficiency of the enzyme acyl-CoA:dihydroxyacetonephosphate acyltransferase (DHAPAT; 602744)
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: not stated

ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [HEENT]: Low nasal bridge Broad nasal bridge Anteverted nostrils Cataracts
PREDISPOSITIONS: not stated

19. CHONDRODYSPLASIA PUNCTATA, BRACHYTELEPHALANGIC
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?302940
OMIM: #302940
GENES INVOLVED: arylsulfatase E gene (ARSE; 300180)
CHROMOSOMAL LOCATION: Xp22.3
INHERITANCE: X-linked
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [facies]: Facial dysmorphism
PREDISPOSITIONS: not stated

20. CHONDRODYSPLASIA PUNCTATA 1, X-LINKED RECESSIVE; CDPX1
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?302950.cs
OMIM: #302950
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: not stated
INHERITANCE: X-linked recessive milder form has cerebral involvement X-linked dominant form lethal in hemizygous males
ALLELIC VARIANTS: 118650 and 215100 for the autosomal dominant and autosomal recessive forms of chondrodysplasia punctata and 302960 for the X-linked dominant form, which maps to Xq28.
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [hair]: Coarse lusterless hair Cicatricial alopecia [skel]: Chondrodysplasia punctata [HEENT]: Nasal hypoplasia Deafness
PREDISPOSITIONS: not stated

21. CHONDRODYSPLASIA PUNCTATA 2, X-LINKED DOMINANT; CDPX2
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?302960.cs
OMIM: #302960
GENES INVOLVED: Decreased peroxisomal enzyme activity in fibroblast cultures, delta(8)-delta(7) sterol isomerase emopamil-binding protein (EBP; 300205).
CHROMOSOMAL LOCATION: Xp11.23-p11.22
INHERITANCE: X-linked dominant form lethal in hemizygous males X-linked recessive milder form has cerebral involvement
ALLELIC VARIANTS: see INHERITANCE
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: 'Tattered' (Td) is an X-linked, semidominant mouse mutation associated with prenatal male lethality. The phenotype of Td is similar to that seen in heterozygous females with human X-linked, dominant chondrodysplasia punctata as well as another X-linked semidominant mouse mutation, 'bare patches' (Bpa). Derry et al. (1999) identified the defect in Td mice as a single amino acid substitution in the delta(8)-delta(7) sterol isomerase emopamil-binding protein encoded by the Ebp gene in mouse, and identified alterations in human EBP (300205) in 7 unrelated CDPX2 patients.
CLINICAL SUMMARY:
HEAD AND NECK :: [skin]: Linear or whorled atrophic and pigmentary skin lesions Striated ichthyosiform hyperkeratosis Follicular atrophoderma

[hair]: Coarse lusterless hair Cicatricial alopecia [HEENT]: Nasal hypoplasia Deafness Frontal bossing Cataracts
PREDISPOSITIONS: not stated

22. RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, TYPE 3; RCDP3
OMIM: #600121
GENES INVOLVED: Abnormal peroxisomes Alkyldihydroxyacetonephosphate synthase (alkyl-DHAP synthase) defect
CHROMOSOMAL LOCATION: not stated
INHERITANCE: Autosomal recessive vs. X-linked recessive
ALLELIC VARIANTS: see INHERITANCE
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK ::
PREDISPOSITIONS: not stated
NOTE: Several different disorders with similar punctate cartilaginous changes have been observed; e.g., X-linked chondrodysplasia punctata (see 302960); the multiple forms of the Zellweger syndrome (see 214100); maternal ingestion of certain anticoagulants (dicoumarol or warfarin) in early pregnancy; and even occasionally trisomy 18.

23. CLEIDOCRANIAL DYSPLASIA; CCD
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?119600.cs
OMIM: #119600
GENES INVOLVED: transcription factor CBFA1 600211.
CHROMOSOMAL LOCATION: 6p21
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: Sillence et al. (1987) described cleidocranial dysplasia in mice. The change was radiation-induced and inherited as an autosomal dominant with variable expressivity but almost complete penetrance. Selby et al. (1993) investigated the interactions between 2 unlinked genes causing a semidominant skeletal dysplasia in mice: cleidocranial dysplasia (Ccd) and 'short digits' (Dsh). Each mutant is a homozygous lethal.
CLINICAL SUMMARY:
HEAD AND NECK :: [head]: Brachycephaly Arnold head [facies]: Midfacial hypoplasia [mouth]: Delayed eruption of deciduous teeth Delayed eruption of permanent teeth Supernumerary teeth
PREDISPOSITIONS:
NOTE: Pycnodysostosis (265800) and mandibuloacral dysplasia (248370) are disorders to be considered in differential diagnosis

24. CLEIDOCRANIAL DYSPLASIA, RECESSIVE FORM
OMIM: 216330
GENES INVOLVED:
CHROMOSOMAL LOCATION:
INHERITANCE: Severe autosomal recessive form, usually dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS:
ANIMAL MODEL:
CLINICAL SUMMARY:
HEAD AND NECK :: [HEENT]: Brachycephaly
PREDISPOSITIONS:

25. CLEIDOCRANIAL DYSPLASIA WITH MICROGNATHIA, ABSENT THUMBS, & DISTAL APHALANGIA
OMIM: *216340

GENES INVOLVED:
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [HEENT]: Macrocrania Diastasis of cranial sutures Micrognathia Retracted and poorly delineated lips
PREDISPOSITIONS: not stated

26. CRANIOSYNOSTOSIS, TYPE 1; CRS1
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?123100.cs
OMIM: *123100
GENES INVOLVED:
CHROMOSOMAL LOCATION: 7p21.3-p21.2
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
0001 : CRANIOSYNOSTOSIS, BOSTON TYPEMSX2, PRO148HIS
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [skull]: Scaphocephaly Dolichocephaly Oxycephaly [radiology]: Beaten copper appearance of skull
PREDISPOSITIONS: not stated

27. CRANIOSYNOSTOSIS, SAGITTAL, WITH DANDY-WALKER MALFORMATION & HYDROCEPHALUS
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?123155
OMIM: 123155
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: not stated
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [skull]:Sagittal craniosynostosis Neuro :Posterior fossa cystCerebellar vermis hypoplasiaHydrocephalus
PREDISPOSITIONS: not stated
OTHER: not stated

28. ACROCEPHALOPOLYSYNDACTYLY TYPE III
http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?101120.cs
OMIM: 101120
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: not stated
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [skull]: Craniosynostosis Acrocephaly [facies]: Flat facies Small facies Prognathism Maxillary hypoplasia [eyes]: Shallow orbits Hypertelorism [ears]: : Dysplastic [ears]: Low-set [ears]: [teeth]: Dental crowding [neck]: Short neck with low hairline
PREDISPOSITIONS: not stated

29. CRANIOSTENOSIS, SAGITTAL, WITH CONGENITAL HEART DISEASE, MENTAL DEFICIENCY, AND MANDIBULAR ANKYLOSIS (Pfeiffer type cardiocranial)

http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?218450.cs

OMIM: 218450
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: not stated
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [HEENT]: Craniosynostosis, sagittal Micrognathia Limited mouth opening
PREDISPOSITIONS: not stated

30. CRANIOSYNOSTOSIS WITH RADIAL DEFECTS

http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?218600.cs

OMIM: 218600
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: not stated
INHERITANCE: Autosomal recessive, possible genetic heterogeneity
ALLELIC VARIANTS:
CLINICAL SUMMARY: not stated
HEAD AND NECK :: [HEENT]: Oxycephaly Steep forehead High nasal bridge Prominent mandible Epicanthal folds Ocular hypotelorism Small dysplastic [ears]: Conductive hearing loss
PREDISPOSITIONS: not stated

31. CRANIOSYNOSTOSIS, ADELAIDE TYPE; CRSA

OMIM: *600593
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: 4p16
INHERITANCE: ? Autosomal dominant
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [head]: Craniosynostosis
PREDISPOSITIONS: not stated

32. CRANIOSYNOSTOSIS, PHILADELPHIA TYPE

http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?601222

OMIM: 601222
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: not stated
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [head]: Acrocephalosyndactyly Sagittal craniosynostosis
PREDISPOSITIONS: not stated

33. CROUZON SYNDROME

OMIM: #123500
GENES INVOLVED: fibroblast growth factor receptor-2 (176943). Crouzon syndrome with acanthosis nigricans results from a mutation in the FGFR3 gene (134934.0001)

CHROMOSOMAL LOCATION: 10q26
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [skull]: Craniosynostosis [eyes]: Shallow-orbits Proptosis Hypertelorism External strabismus [facies]: Parrot-beaked nose Short upper lip Hypoplastic maxilla Relative mandibular prognathism [radiology]: Pronounced digital impressions of skull Triangular optic foramen
PREDISPOSITIONS: not stated

34. DENTIN DYSPLASIA, TYPE II

OMIM: *125420
GENES INVOLVED:
CHROMOSOMAL LOCATION: 4q, 4q13-q21
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [teeth]: Coronal dentin dysplasia Opalescent deciduous teeth [radiology]: Pulp chambers obliterated Thistle-tube pulp configuration with pulp stones
PREDISPOSITIONS: not stated

35. DENTINOGENESIS IMPERFECTA; DGI1

OMIM: *125490
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: (? 4q13-q21)
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [teeth]: Dentinogenesis imperfecta Blue-gray or amber brown opalescent teeth Enamel splitting [radiology]: Teeth have bulbous crowns, narrow roots, and pulp chambers and root canals that are small or obliterated
PREDISPOSITIONS: not stated

36. DENTINOGENESIS IMPERFECTA, SHIELDS TYPE III

OMIM: 125500
GENES INVOLVED: not stated
CHROMOSOMAL LOCATION: not stated
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS: not stated
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [teeth]: Tooth crowns wear rapidly Multiple pulp exposures Smooth amber dentin Anterior open bite [radiology]: Very large pulp chambers and root canals of deciduous teeth Small or obliterated pulpal spaces of permanent teeth
PREDISPOSITIONS: not stated

37. DIASTROPHIC DYSPLASIA; DTD

OMIM: *222600
GENES INVOLVED: A defect in sulfate transport was demonstrable in fibroblasts from a DTD patient. Hastbacka et al. (1994) referred to the gene as DTDST. The DRA gene (126650), cloned by subtractive hybridization from normal colon and colon carcinoma, shows strong sequence similarity along its entire length to a sulfate transporter gene in the rat and thus may have a role in sulfate transport (3 mutations described).
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS:
.0001 DIASTROPHIC DYSPLASIA [SLC26A2, 1-BP DEL, 1751A]
.0002 ATELOSTEOGENESIS, TYPE II [SLC26A2, ARG279TRP]
.0003 ATELOSTEOGENESIS, TYPE II [SLC26A2, GLY255GLU]
.0004 ATELOSTEOGENESIS, TYPE II [SLC26A2, ALA715VAL]
.0006 ACHONDROGENESIS, TYPE IB [SLC26A2, ASN425ASP]
.0007 ACHONDROGENESIS, TYPE IB [SLC26A2, GLY678VAL]
.0008 ACHONDROGENESIS, TYPE IB [SLC26A2, VAL340DEL]
.0009 DIASTROPHIC DYSPLASIA, BROAD BONE-PLATYSPONDYLIC VARIANT [SLC26A2, GLN454PRO]
PRENATAL DIAGNOSTICS:
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [HEENT]: Normocephaly Neonatal cystic lesions of the pinnae Hypertrophic auricular cartilage Ossified pinnae Cleft palate
PREDISPOSITIONS: not stated

38. DIGEORGE SYNDROME; DGS

http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?188400

OMIM: *188400
GENES INVOLVED: Aubry et al. (1993) have identified a zinc finger gene ZNF74, Halford et al. (1993) reported the expressed sequence T10. The gene TUPLE1 (TUP-like enhancer of split gene-1; 600237) reported by Halford et al. (1993) is an attractive candidate for the central features of the syndrome. This putative transcription factor shows homology to the yeast transcription factor TUP, and to Drosophila enhancer of split. It contains 4 WD40 domains
CHROMOSOMAL LOCATION: 22q11
INHERITANCE: Autosomal dominant, possibly a contiguous gene syndrome One explanation for the wide variation in phenotype would be the need for more than 1 gene defect to produce the severe version. Usually (90%) deletion of chromosome 22q11.2, 1/3 of which are detectable cytologically A few cases have defects in other chromosomes, e.g. 10p13, 18q21.33, and 4q21.3-q25 Usually sporadic resulting from de novo 22 deletion
ALLELIC VARIANTS: See INHERITANCE
PRENATAL DIAGNOSTICS:
ANIMAL MODEL: Galili et al. (1997) documented homology of synteny between a 150-kb region on mouse chromosome 16 and the portion of 22q11.2 most commonly deleted in DiGeorge syndrome and VCFS. They identified 7 genes, all of which are transcribed in the early mouse embryo. Pizzuti et al. (1996) described the cloning and tissue expression of a human homolog of the Drosophila 'dishevelled' gene (601225), a gene required for the establishment of fly embryonic segments. The 3-prime untranslated region of the gene was positioned within the DGS critical region and was found to be deleted in DGS patients. The authors stated that the gene may be involved in the pathogenesis of DGS. Demczuk et al. (1996) described the cloning of a gene, which they referred to as DGCR6 (601279), from the DGS critical region. The putative protein encoded by this gene shows homology with Drosophila melanogaster gonadal protein (gdl) and with the gamma-1 chain of human laminin (150290), which maps to chromosome 1q31.

CLINICAL SUMMARY:
HEAD AND NECK :: [ears]: : Low-set [ears]: Short [ears]: Abnormal folded pinna Deafness [eyes]: Telecanthus Short palpebral fissures Upward/downward slanting eyes [nose]: Bulbous nose Square nasal tip Short philtrum [mouth]: Small mouth Submucous or overt palatal cleft, Cleft lip [voice]: : Hypernasal speech
PREDISPOSITIONS: Susceptibility to infection
NOTE: The acronym CATCH22 derives from the phrase Catch 22, which was used by Joseph Heller as the title of his book (Heller, 1962).

39. EHLERS-DANLOS SYNDROME, TYPE I; EDS1

OMIM: #130000
GENES INVOLVED: COL5A1 (120215) and COL5A2 (120190), type III collagen (COL3A1; 120180), dermatan sulfate proteoglycan
CHROMOSOMAL LOCATION: 2q31, 9q34.2-q34.3
INHERITANCE: Autosomal dominant Genetic-heterogeneity likely
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [eyes]: Retinal detachment [skin]: Fragile skin Easy bruisability Cigarette-paper scars Loose skin Velvety skin
PREDISPOSITIONS: not stated
NOTE: EDS I, or gravis type, is the severe classic form. EDS II (130010), or mitis type, is the mild classic form. EDS III (130020) is the benign hypermobility form. EDS IV (130050, 225350) is the arterial, ecchymotic or Sack type. EDS V (305200) is the X-linked form. EDS VI (225400) is the form due to deficiency of lysyl hydroxylase. EDS VII (225410) is the form due to deficiency of procollagen protease. EDS VIII (130080) is the form with accompanying periodontosis. EDS IX (304150) is the form with occipital horns. EDS X (225310) is the form with a possible fibronectin defect. EDS XI (147900) is the familial joint instability syndrome. The severe form of EDS reported by Friedman and Harrod (1982)

40. EHLERS-DANLOS SYNDROME, TYPE IV, AUTOSOMAL DOMINANT

OMIM: #130050
GENES INVOLVED: Type III collagen defect
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal dominant form genetic-heterogeneity likely
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: Johnson et al. (1995) were successful in demonstrating mutations in all 13 patients with typical or acrogeric EDS IV using denaturing gradient gel electrophoresis (DGGE) in the study of PCR-amplified cDNA from the C-terminal domain of type III collagen.
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [facies]: Pinched nose Thin lips
PREDISPOSITIONS: not stated

41. EHLERS-DANLOS SYNDROME, PROGEROID FORM

OMIM: 130070
GENES INVOLVED: Defective dermatan sulfate proteoglycan
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:

HEAD AND NECK :: [facies]: Progeroid facies Wrinkled facies Scanty eyebrows and eyelashes Telecanthus [teeth]: Defective deciduous teeth Periodontosis [hair]: Scanty scalp hair Curly and fine hair
PREDISPOSITIONS: not stated

42. EHLERS-DANLOS SYNDROME, TYPE VIII

OMIM: *130080
GENES INVOLVED:
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [mouth]: Periodontal disease Alveolar bone loss [teeth]: Early loss of teeth
PREDISPOSITIONS: not stated

43. GREIG CEPHALOPOLYSYNDACTYLY SYNDROME; GCPS

OMIM: #175700
GENES INVOLVED: GLI3 gene (165240)
CHROMOSOMAL LOCATION: 7p13
INHERITANCE: Autosomal dominant (7p13-p12.3) ? same as frontodigital syndrome or acrocallosal syndrome
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: Greig cephalopolysyndactyly syndrome is homologous to the mouse mutant 'extra toes' (Xt) on mouse chromosome 13. The pattern of polydactyly in the 2 species is very similar and both conditions probably map close to the T-gamma receptor locus (TCRG; 186970). Vortkamp et al. (1992) reported deletion in the 5-prime end of the Gli-3 gene in an Xt mutant, and Schimmang et al. (1992) reported that expression of Gli-3 is reduced in this mutant. Hui and Joyner (1993) described the molecular characteristics of the Xt mutation. They found that deficiency of expression of Gli-3 in the mutant mouse is due to a deletion within the 3-prime end of the gene. Furthermore, structures affected in the mouse mutant and in the human syndrome were found to correlate with expression domains of Gli-3 in the mouse.
CLINICAL SUMMARY:
HEAD AND NECK :: [skull]: Peculiar skull shape Expanded cranial vault No precocious closure of cranial sutures [facies]: High forehead and bregma Frontal bossing
PREDISPOSITIONS: not stated

44. HOLOPROSENCEPHALY 1, ALOBAR; HPE1

OMIM: *236100
GENES INVOLVED:
CHROMOSOMAL LOCATION: 21q22.3
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [HEENT]: Cyclopia Ethmocephaly Cebocephaly Agenesis of nasal bones Ocular hypotelorism Facial cleft [mouth]: Median cleft lip/palate
PREDISPOSITIONS: not stated

45. HOLOPROSENCEPHALY 2; HPE2

OMIM: #157170
GENES INVOLVED: homeo box-containing SIX3 gene (603714)
CHROMOSOMAL LOCATION: 2p21
INHERITANCE: Autosomal dominant (? 2p21)
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [mouth]: Cleft lip/palate Submucous cleft palate [eyes]: Hypotelorism [nose]: Absent nasal septal cartilage [head]: Microcephaly [teeth]: Single central incisor [mouth]: Bifid uvula
PREDISPOSITIONS: not stated

46. HOLOPROSENCEPHALY 3; HPE3
OMIM: #142945
GENES INVOLVED: human sonic hedgehog homolog (600725)
CHROMOSOMAL LOCATION: 7q36
INHERITANCE: Autosomal dominant (7q36)
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: Roessler et al. (1996) noted that in humans loss of one SHH allele is sufficient to cause HPE, whereas in the mouse both alleles need to be lost to produce a similar CNS phenotype.
CLINICAL SUMMARY:
HEAD AND NECK :: [eyes]: Cyclopia Ocular hypotelorism [facies]: Proboscis Midface hypoplasia
PREDISPOSITIONS: not stated

47. HOLOPROSENCEPHALY 4; HPE4
OMIM: *142946
GENES INVOLVED:
CHROMOSOMAL LOCATION: 18p11.3
INHERITANCE: Autosomal dominant (14q11.1-q13)
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [facies]: Flat nasal bridge Flattened nasal tip Absent nasal septum [eyes]: Hypotelorism Ptosis [mouth]: Wide midline cleft lip/palate
PREDISPOSITIONS: not stated

48. HYPOCHONDROPLASIA; HCH
OMIM: #146000
GENES INVOLVED: fibroblast growth factor receptor-3 (FGFR3; 134934), located on 4p
CHROMOSOMAL LOCATION: 4p16.3
INHERITANCE: Autosomal dominant ? allele of achondroplasia
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [head]: Normocephaly or occasional brachycephaly Mild frontal bossing [facies]: Normal
PREDISPOSITIONS: not stated

49. HYPOPHOSPHATASIA, ADULT TYPE
OMIM: #146300

GENES INVOLVED: ALPL gene (171760),Hypophosphatasia Elevated urinary phosphoethanolamine
CHROMOSOMAL LOCATION: 1p36.1-p34
INHERITANCE: Autosomal dominant ? allelic to recessive infantile hypophosphatasia (241500)
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [teeth]: Early dental loss
PREDISPOSITIONS: not stated
NOTE: Three more or less distinct types can be identified: (1) type 1 with onset in utero or in early postnatal life, craniostenosis, severe skeletal abnormalities, hypercalcemia, and death in the first year or so of life; (2) type 2 with later, more gradual development of symptoms, moderately severe 'rachitic' skeletal changes and premature loss of teeth; (3) type 3 with no symptoms, the condition being determined on routine studies.

50. JACKSON-WEISS SYNDROME; JWS

OMIM: #123150
GENES INVOLVED: fibroblast growth factor receptor-2 (176943)
CHROMOSOMAL LOCATION: 10q26
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: Legouis et al. (1993) determined the entire coding sequence of chicken and quail KAL cDNAs and demonstrated an overall identity of 73% and 72%, respectively, with human KAL cDNA. This corresponds to 76% and 75% identity at the protein level.
CLINICAL SUMMARY:
HEAD AND NECK :: [skull]: Craniosynostosis [facies]: Midfacial hypoplasia
PREDISPOSITIONS: not stated

51. KALLMANN SYNDROME 1; KAL1

OMIM: *308700
GENES INVOLVED:
CHROMOSOMAL LOCATION: Xp22.3
INHERITANCE: X-linked
ALLELIC VARIANTS
0001 : KAL1, 3300-BP DEL
0002 : KAL1, TRP237TER
0003 : KAL1, ARG257TER
0004 : KAL1, TRP258TER
0005 : KAL1, 1-BP DEL, PRO277FS
0006 : KAL1, EX3-5DEL
0007 : KAL1, GLU514LYS
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [nose]: Anosmia [mouth]: High-arched palate, Partial or complete anosmia in some heterozygous females
PREDISPOSITIONS: not stated

52. KALLMANN SYNDROME 2; KAL2

OMIM: *147950
GENES INVOLVED:
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal dominant genetic heterogeneity

ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [nose]: Choanal atresia [ears:]: Neurosensory hearing loss
PREDISPOSITIONS: not stated

53. KALLMANN SYNDROME 3; KAL3
OMIM: *244200
GENES INVOLVED:
CHROMOSOMAL LOCATION: See INHERITANCE
INHERITANCE: Autosomal recessive also dominant and X-linked forms
ALLELIC VARIANTS: See INHERITANCE
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [HEENT]: Anosmia Midline cranial fusion defect Cleft lip Cleft palate Hypotelorism
PREDISPOSITIONS: not stated

54. LEPRECHAUNISM
OMIM: #246200
GENES INVOLVED: insulin receptor gene (INSR; 147670), Insulin receptor defect Fasting hypoglycemia Postprandial hyperglycemia Profound hyperinsulinemia Hypertrophy of pancreatic beta cells Abnormal epidermal growth factor receptor function Histologic changes in ovaries, pancreas and breasts Low serum alkaline phosphatase
CHROMOSOMAL LOCATION: 19p13.2
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [HEENT]: Elfin facies Protuberant [ears]: Low-set [ears]: Poorly developed ears Flat nasal bridge Flared nostrils [mouth]:Thick lips Macrostomia Microcephaly Hypertelorism High arched palate
PREDISPOSITIONS: not stated

55. MARFAN SYNDROME; MFS
OMIM: #154700
GENES INVOLVED: fibrillin-1 gene (134797)
CHROMOSOMAL LOCATION: 15q21.1
INHERITANCE: Autosomal dominant, About 25% of cases due to new mutations in FBN1
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: Godfrey et al. (1993) reported prenatal diagnosis by the linkage method in a 4-generation Marfan kindred. The diagnosis was made using CVS material at 11 weeks' gestation. At birth the infant showed skeletal changes suggestive of the Marfan syndrome. The mutation involved a donor splice site in the FBN1 gene (134797.0014). In a pregnant affected female in a third generation, Rantamaki et al. (1995) succeeded in the prenatal diagnosis by chorionic villus sampling.
ANIMAL MODEL: Besser et al. (1990) described the Marfan syndrome in Limousin cattle. Tilstra et al. (1994) found that the cDNA sequence for the bovine fibrillin gene corresponds closely to the human gene and that it maps to bovine chromosome 10. The identity between human and bovine sequences was

97.8% at the amino acid level and 92% at the nucleotide level. The bovine fibrillin sequence contains the same number and types of motifs as the FBN1 sequenc

CLINICAL SUMMARY:

HEAD AND NECK :: [Cranium] Dolichocephaly [Face] Long and narrow face Enophthalmos [Eyes] Ectopia lentis Myopia Increased axial globe length Corneal flatness Retinal detachment Iris hypoplasia Early glaucoma Early cataracts Down-slanting palpebral fissures [Mouth] High arched palate Narrow palate Micrognathia Retrognathia Molar hypoplasia [Teeth] Crowded teeth

PREDISPOSITIONS: not stated

56. MCCUNE-ALBRIGHT SYNDROME; MAS

OMIM: #174800

GENES INVOLVED: GNAS1 gene (139320)

CHROMOSOMAL LOCATION: 20q13.2

INHERITANCE: Autosomal dominant lethal mosaic postzygotic somatic mutation in the GNAS1 gene

ALLELIC VARIANTS:

PRENATAL DIAGNOSTICS:

ANIMAL MODEL: Transplantation of clonal populations of normal cells into the subcutis of immunocompromised mice resulted in normal ossicle formation. In contrast, transplantation of clonal populations of mutant cells always led to the loss of transplanted cells from the transplantation site and no ossicle formation. However, transplantation of a mixture of normal and mutant cells reproduced an abnormal ectopic ossicle recapitulating human fibrous dysplasia and providing an in vivo cellular model of this disease. The results provided experimental evidence for the need of both normal and mutant cells in the development of McCune-Albright syndrome fibrous dysplastic lesions in bone. This study confirmed the hypothesis of Happle (1986).

CLINICAL SUMMARY:

HEAD AND NECK :: [skull]: Cranial foramen impingement Craniofacial hypertosis [ears]:]: Deafness [eyes]: Blindness [neck]: Multinodular toxic goiter

PREDISPOSITIONS: Pituitary adenoma

57. METAPHYSEAL CHONDRODYSPLASIA, MURK JANSEN TYPE

OMIM: #156400

GENES INVOLVED: parathyroid hormone receptor (PTHR; 168468)

CHROMOSOMAL LOCATION: 3p22-p21.1

INHERITANCE: Autosomal dominant

ALLELIC VARIANTS:

PRENATAL DIAGNOSTICS:

ANIMAL MODEL: Karaplis et al. (1994) disrupted the parathyroid hormone-related peptide in murine embryonic stem cells by homologous recombination, and introduced the null allele into a mouse germline. Mice homozygous for the null mutation died postnatally, probably from asphyxia, and exhibited widespread abnormalities of endochondral bone development. Histologic examination revealed a diminution of chondrocyte proliferation, associated with premature maturation of chondrocytes and accelerated bone formation.

CLINICAL SUMMARY:

HEAD AND NECK :: [skull]: Sclerosis of cranial bones Wide cranial sutures [facies]: Supraorbital hyperplasia Prominent supraorbital ridges Frontonasal hyperplasia Micrognathia [ears]:]: Variable hearing loss [eyes]: Prominent eyes [nose]: Choanal stenosis [mouth]: High arched palate

PREDISPOSITIONS: not stated

58. NEONATAL OSSEOUS DYSPLASIA I

OMIM: #256050
GENES INVOLVED: diastrophic dysplasia sulfate transporter gene (222600)
CHROMOSOMAL LOCATION: 5q32-q33.1
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL:
CLINICAL SUMMARY:
HEAD AND NECK :: [HEENT]: Cleft palate
PREDISPOSITIONS: not stated

59. OSTEOGENESIS IMPERFECTA WITH OPALESCENT TEETH, BLUE SCLERAE AND WORMIAN BONES, BUT WITHOUT FRACTURES

OMIM: 166230
GENES INVOLVED: COL1A1 gene (120150) or the COL1A2 gene (120160) and possibly in other genes.
CHROMOSOMAL LOCATION: 17q21.31-q22.05, 7q22.1
INHERITANCE: Autosomal dominant ? same as OI type I (166200)
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS:
ANIMAL MODEL:
CLINICAL SUMMARY:
HEAD AND NECK :: [teeth]: Opalescent teeth [eyes]: Blue sclerae [ears]:]: Hearing loss uncommon [skull]: Wormian bones
PREDISPOSITIONS:

60. OSTEOGENESIS IMPERFECTA, TYPE I

OMIM: #166200
GENES INVOLVED: COL1A1 gene (120150) or the COL1A2 gene (120160) and possibly other genes.
CHROMOSOMAL LOCATION: 17q21.31-q22.05, 7q22.1
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS:
ANIMAL MODEL: Bonadio et al. (1990) reported that the heterozygous Mov-13 mouse, which has a murine retrovirus integrated within the first intron of the COL1A1 gene, is a good model for the mild autosomal dominant form of OI. The animals showed morphologic and functional defects in mineralized and nonmineralized connective tissue and progressive hearing loss.
CLINICAL SUMMARY:
HEAD AND NECK :: [head]: Normocephaly. Eyes: Blue sclerae [ears]:]: Progressive conductive and/or neurisensorial hearing loss during adulthood Otosclerosis [skull]: Wormian bones Platybasia
PREDISPOSITIONS:

61. OSTEOGENESIS IMPERFECTA, TYPE IV; OI4

OMIM: #166220
GENES INVOLVED:
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal dominant, likely a COL1A1 (17q21.31-q22.05) or COL1A2 (7q22.1) gene mutant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: Wenstrup et al. (1986) found that fibroblasts from 2 affected persons synthesized 2 populations of alpha-2 chains: one normal population and one with a deletion of about 10 amino acids from the middle of the triple helical domain. In a family with type IV OI genetically linked

to the COL1A2 gene, Tsipouras et al. (1987) showed by linkage analysis that a fetus was unaffected, having inherited the normal COL1A2 allele from her affected parent.

ANIMAL MODEL:

CLINICAL SUMMARY:

HEAD AND NECK :: [skull]: Wormian bones Platybasia [eyes]: Normal sclerae [ears]:]: Progressive hearing loss during adulthood in some kindreds Otosclerosis [mouth]: Hypoplastic dentin Multiple carries

PREDISPOSITIONS:

62. OSTEOPETROSIS, AUTOSOMAL RECESSIVE

OMIM: *259700

GENES INVOLVED:

CHROMOSOMAL LOCATION: 11q12-q13, 1p21

INHERITANCE: Autosomal recessive also mild autosomal dominant and autosomal recessive forms

ALLELIC VARIANTS:

PRENATAL DIAGNOSTICS: Ogur et al. (1995) established the prenatal diagnosis of osteopetrosis at 25 weeks of pregnancy by fetal x-ray evaluation which showed typical changes.

ANIMAL MODEL: Brown and Dent (1971) reviewed theories of pathogenesis and described probable models in the mouse and rabbit. Similarities to the gray-lethal mutation in the mouse, which seemed to be a thyrocalcitonin excess disease, stimulated search for abnormality of this hormone in osteopetrosis and other osteosclerotic conditions. However, Walker (1973) presented evidence that the osteopetrosis of the gray-lethal and microphthalmic mice is not primarily related to calcitonin or parathyroid hormone overproduction. Walker (1975) showed that osteopetrosis could be induced in normal mice by intravenous injection of splenic cells into the lethally irradiated recipient from osteopetrotic sibs.Yoshida et al. (1990) demonstrated that the defect in the osteopetrotic mouse (op/op) resides in the gene for macrophage colony-stimulating factor (CSF1; see 120420). The op/op mouse is not cured by transplant of normal bone marrow cells, suggesting that the defect is an abnormal hematopoietic microenvironment rather than an intrinsic defect in progenitors of mature macrophages and osteoclasts. Mice homozygous for the op mutation suffer from congenital osteopetrosis due to severe deficiency of osteoclasts and macrophages. The unimpaired ability of macrophage progenitors from op/op mice to generate macrophages in vitro when incubated with macrophage growth factors suggested that absence or deficiency of a macrophage growth factor and/or an overabundance of macrophage growth inhibitor was responsible. Wiktor-Jedrzejczak et al. (1990) demonstrated that serum, 11 tissues, and different cell- and organ-conditioned media from op/op mice were devoid of biologically active colony-stimulating factor 1, whereas all of these preparations from heterozygous or homozygous normal littermates contained the growth factor.

CLINICAL SUMMARY:

HEAD AND NECK :: [head]: Macrocephaly Hydrocephaly Peculiar facies [eyes]: Blindness due to cranial nerve II compression Primary retinal atrophy Hypertelorism Strabismus Nystagmus [ears]:]: Hearing loss [nose]: Chronic rhinitis due to narrow nasal airway [teeth]: Delayed dentition Severe dental caries [Neuro]: Nerve compression of cranial nerves II, VII, and VIII Normal intelligence

PREDISPOSITIONS: not stated

63. OSTEOPETROSIS, AUTOSOMAL DOMINANT, TYPE II

OMIM: *166600

GENES INVOLVED:

CHROMOSOMAL LOCATION: 1p21
INHERITANCE: Autosomal dominant also a mild autosomal recessive form and a lethal autosomal recessive form 1p21
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [skull]: Cranial hyperostosis [teeth]: Dental abscess [nose]: Chronic rhinitis due to narrow nasal airway [Neuro]: Facial palsy due to cranial nerve VII compression Normal intelligence
PREDISPOSITIONS: not stated

64. ECTRODACTYLY, ECTODERMAL DYSPLASIA, AND CLEFT LIP/PALATE SYNDROME 1; EEC1
OMIM: *129900
GENES INVOLVED:
CHROMOSOMAL LOCATION: 7q11.2-q21.3
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
CLINICAL SUMMARY:
HEAD AND NECK : Skin : Ectodermal dysplasia Hypohidrosis Hair : Hypotrichosis Facies : Maxillary hypoplasia Short philtrum Eyes : Blepharitis Keratitis Dacryocystitis Nose : Choanal atresia Broad nasal tip Mouth : Cleft lip Cleft palate Cleft lip/palate Teeth : Anodontia
PREDISPOSITIONS:
OTHER:

65. ECTODERMAL DYSPLASIA 2, HIDROTIC; ED2
OMIM: *129500
GENES INVOLVED:
CHROMOSOMAL LOCATION: 13q11-q12.1
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
CLINICAL SUMMARY:
HEAD AND NECK : Skin : Normal sweating Palmoplantar hyperkeratosis Hair : Variable focal alopecia to total balding Nails : Severe nail dystrophy Skin hyperpigmentation, esp. over joints Teeth : Normal teeth Eyes : Strabismus Neuro : Variable mental retardation Lab : Disorganized fibrillar hair structure by light microscopy, reduced birefringence in polarized light, and increased amount of reactive SH groups
PREDISPOSITIONS:
OTHER:

66. ECTODERMAL DYSPLASIA, ANHIDROTIC, WITH CLEFT LIP AND CLEFT PALATE
OMIM: *129400
GENES INVOLVED:
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
CLINICAL SUMMARY:
HEAD AND NECK : Skin : Anhidrotic ectodermal dysplasia Mouth : Cleft lip Cleft palate Small mouth Cleft uvula Nose : Narrow nose Hair : Pili torti Coarse, dry and wiry scalp hair Alopecia in adulthood Teeth : Hypodontia Eyes : Ptosis Tear duct anomalies Ears : Atretic ear canals Dysplastic eustachian orifices Lab : Pili canaliculi by scanning EM
PREDISPOSITIONS:
OTHER:

67. ECTODERMAL DYSPLASIA 3, ANHIDROTIC; ED3

OMIM: #129490
GENES INVOLVED: human homolog of the mouse 'downless' gene (DL; 604095) can cause autosomal dominant hypohidrotic ectodermal dysplasia.
CHROMOSOMAL LOCATION: 2q11-q13
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS: (arg358 to ter, 604095.0005; arg420 to gln, 604095.0006
CLINICAL SUMMARY:
HEAD AND NECK : Skin : Hypohidrotic ectodermal dysplasia Variable hypohidrosis Hair : Mild hypotrichosis Teeth : Mild hypodontia Lab : Defective cuticular layer of hair shafts with longitudinal grooves by scanning EM
PREDISPOSITIONS:
OTHER:

68. ECTODERMAL DYSPLASIA, ANHIDROTIC, WITH CLEFT LIP AND CLEFT PALATE
OMIM: *129400
GENES INVOLVED:
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
CLINICAL SUMMARY:
HEAD AND NECK : Skin : Anhidrotic ectodermal dysplasia Mouth : Cleft lip Cleft palate Small mouth Cleft uvula Nose : Narrow nose Hair : Pili torti Coarse, dry and wiry scalp hair Alopecia in adulthood Teeth : Hypodontia Eyes : Ptosis Tear duct anomalies Ears : Atretic ear canals Dysplastic eustachian orifices Lab : Pili canaliculi by scanning EM
PREDISPOSITIONS:
OTHER:

69. ECTODERMAL DYSPLASIA, ANHIDROTIC
OMIM: #224900
GENES INVOLVED: human homolog of the mouse 'downless' gene (604095) on 2q11-q13 can cause autosomal recessive hypohidrotic ectodermal dysplasia (HED). Autosomal recessive HED does not map to that locus in all families, implying the existence of at least 1 additional human locus.
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS:
CLINICAL SUMMARY:
HEAD AND NECK :Skin : Anhidrotic ectodermal dysplasia Hypohydrosis Thin, smooth skin Dry skin Hypoplastic skin Dermatoglyphic changes Wrinkled skin Orbital darkening Hair : Scalp hair sparse Scalp hair brittle Scalp hair lightly pigmented Scalp hair lanugo-like Absent or scanty eyebrows Absent or scanty eyelashes Absent or scanty body hair Facies : Saddle nose Frontal bossing Hypertelorism Teeth : Hypodontia Anodontia Conical teeth Eyes : Lacrimal duct hypoplasia Photophobia Nose : Chronic rhinitis Ears : Prominent auricles Sensorineural hearing loss Voice : Hoarse
PREDISPOSITIONS: Unexplained infantile fever Hyperthermia
OTHER:

70. ECTODERMAL DYSPLASIA, TYPE 4; ED4
OMIM: *225060
GENES INVOLVED:
CHROMOSOMAL LOCATION: 11q23
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS:
CLINICAL SUMMARY:

HEAD AND NECK :Skin : Ectodermal dysplasia Scanty eyebrows and eyelashes Normal sweating Hair : Sparse scalp hair Short and dry scalp hair Teeth : Hypodontia, esp. upper lateral incisors Abnormal size and shape Mouth : Cleft lip/palate
PREDISPOSITIONS:
OTHER:

71. Pachyonychia congenita, Jackson-Lawler type

OMIM: #167210
GENES INVOLVED: keratin 17 (KRT17; 148069).
CHROMOSOMAL LOCATION: 17q12-q21
INHERITANCE: Autosomal dominant (? 17q12-q21)
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [eyes]: Corneal dystrophy [mouth]: No oral leukoplakia Subungual hyperkeratoses [teeth]: Natal teeth [Resp]: Laryngeal lesions Respiratory distress in childhood [voice]:]: Hoarseness [hair]: Hair anomalies Alopecia
PREDISPOSITIONS: not stated

72. PACHYONYCHIA CONGENITA, JADASSOHN-LEWANDOWSKY

OMIM: #167200
GENES INVOLVED: keratin 16 gene (KRT16; 148067) or in the keratin 6A gene (KRT6A; 148041)
CHROMOSOMAL LOCATION: 17q12-q21, 12q13
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [mouth]: Oral leukoplakia Subungual hyperkeratoses [teeth]: Neonatal teeth [Resp]: Laryngeal lesions Respiratory distress in childhood [voice]:]: Hoarseness [hair]: Hair anomalies Alopecia
PREDISPOSITIONS: not stated

73. PALLISTER-HALL SYNDROME; PHS

OMIM: #146510
GENES INVOLVED: frameshift mutations in the GLI3 gene (165240)
CHROMOSOMAL LOCATION: 7p13
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: Nails : Nail dysplasia [ears]:]: Abnormal auricles [nose]: Short nose Flat nasal bridge [mouth]: Multiple buccal frenula Microglossia Micrognathia Cleft palate
PREDISPOSITIONS: not stated

74. PFEIFFER SYNDROME

OMIM: #101600
GENES INVOLVED: fibroblast growth factor receptor-1 (FGFR1; 136350), fibroblast growth factor receptor-2 (FGFR2; 176943)
CHROMOSOMAL LOCATION: 10q26, 8p11.2-p11.1
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:

PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [facies]: Flat facies [eyes]: Shallow orbits Hypertelorism [skull]: Mild craniosynostosis Acrocephaly
PREDISPOSITIONS: not stated

75. CLEFT LIP/PALATE, PARAMEDIAN MUCOUS CYSTS OF THE LOWER LIP, POPLITEAL PTERYGIUM, DIGITAL AND GENITAL ANOMALIES

OMIM: *119500
GENES INVOLVED:
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [mouth]: Lower lip pits Cleft lip Cleft palate Lower lip cysts Filiform alveolar bands Ankyloglossia [eyes]: Congenital ankyloblepharon filiforme
PREDISPOSITIONS:

76. RIEGER SYNDROME, TYPE 1; RIEG1

OMIM: #180500
GENES INVOLVED: homeo box transcription factor gene, PITX2 (601542)
CHROMOSOMAL LOCATION: 4q25-q25
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS: CASPASE 6, APOPTOSIS-RELATED CYSTEINE PROTEASE; CASP6 (*601532 Reiger syndrome (180500) is a candidate genetic disease at the 4q25-q26 locus. homeo box transcription factor gene, PITX2 (601542). Linkage studies indicated that a second type of Rieger syndrome maps to chromosome 13q14 (RIEG2; 601499)
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: Semina et al. (1996) reported the isolation of a homeo box gene, designated RIEG (601542) by them, mutations in which cause this disorder. They found 6 mutations in RIEG in individuals with Rieger syndrome. The cDNA sequence of Rieg, the murine homolog of RIEG, was also isolated and shares strong homology with the human sequence. Semina et al. (1996) showed that in mouse embryos the homologous mouse Rieg transcript localized in the periocular mesenchyme, maxillary and mandibular epithelia, and umbilicus, all consistent with abnormalities found in the Rieger syndrome.The finding by Semina et al. (1996) that in mouse embryos the Rieg gene is expressed in Rathke pouch suggests that the gene may be important in the development of the anterior pituitary.
CLINICAL SUMMARY:
HEAD AND NECK :: [eyes]: Iris dysplasia Microcornea Anterior chamber synechiae Glaucoma Corneal opacity Hypertelorism Telecanthus [facies]: Maxillary hypoplasia Mild prognathism [nose]: Broad nasal root Short philtrum [mouth]: Protruding lower lip[teeth]: Microdontia Hypodontia Cone-shaped teeth Ear : Abnormal ear
PREDISPOSITIONS: not stated

77. SAETHRE-CHOTZEN SYNDROME; SCS

OMIM: #101400
GENES INVOLVED: TWIST transcription factor gene (601622), FGFR3 gene (134934.0014), FGFR2 gene (176943.0023)
CHROMOSOMAL LOCATION: 7p21
INHERITANCE: Autosomal dominant

ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: The MEOX2 gene (600535), which maps to the same region of 7p as SCS, is a major candidate gene in SCS because it is expressed in the mesenchyma of craniofacial and limb structures during early mouse embryogenesis.Howard et al. (1997) and El Ghouzzi et al. (1997) demonstrated that the Saethre-Chotzen syndrome results from mutations in the TWIST gene (601622). They were prompted to evaluate the TWIST gene, which encodes a basic helix-loop-helix transcription factor, because its expression pattern and mutant phenotypes in Drosophila and mouse are consistent with the SCS phenotype in humans.
CLINICAL SUMMARY:
HEAD AND NECK :: [facies]: Flat facies Thin, long, pointed nose [eyes]: Shallow orbits Hypertelorism Plagiocephaly (asymmetry of orbits) Strabismus Hydrophthalmos [ears]:]: Long and prominent ear crus [mouth]: Cleft palate [skull]: Craniosynostosis Acrocephaly Cranial asymmetry
PREDISPOSITIONS: not stated

78. SHPRINTZEN-GOLDBERG CRANIOSYNOSTOSIS SYNDROME
OMIM: #182212
GENES INVOLVED: fibrillin-1 gene (134797)
CHROMOSOMAL LOCATION: 15q21.1
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK: [head]: Craniosynostosis [eyes]: Exophthalmos No ectopia lentis [facies]: Maxillary hypoplasia Mandibular hypoplasia [mouth]: Palatal shelf soft tissue hypertrophy Pseudocleft palate [ears]:]: Low-set [ears]: Soft and pliable auricles
PREDISPOSITIONS: not stated

79. SHPRINTZEN OMPHALOCELE SYNDROME
OMIM: 182210
GENES INVOLVED:
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [facies]: Mildly dysmorphic facies Unusual eyebrow pattern [eyes]: Epicanthus [nose]: Short columella Flared nostrils [mouth]: Pharyngeal hypoplasia [voice]:]: High pitched [voice]: [Resp]: Neonatal respiratory distress Laryngeal hypoplasia Constricted glottic and subglottic airway Anteroposteriorly shortened larynx Omega-shaped epiglottis
PREDISPOSITIONS: not stated

80. SIMPSON-GOLABI-BEHMEL SYNDROME, TYPE 1; SGBS1
OMIM: #312870
GENES INVOLVED: glypican-3 (300037), which maps to Xq26. A second SGBS locus (SGBS2; 300209) is located on Xp22
CHROMOSOMAL LOCATION: Xq26
INHERITANCE: X-linked (Xcen-q21.3)
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated

ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [head]: Disproportionately large head [facies]: Coarse facies Large protruding jaw [nose]: Wide nasal bridge Upturned nasal tip [eyes]: Cataract Hypertelorism Upward slanting palpebral fissures Retinal detachment [ears]:]: Peculiar cup-shaped [ears]: Earlobe creases [mouth]: Large mouth Central cleft of lower lip Midline groove of tongue and inferior alveolar ridge Enlarged tongue Tethered tongue Submucous cleft palate High-arched palate [voice]:]: Low-pitched [voice]:
PREDISPOSITIONS: risk of embryonal tumors

81. SJOGREN SYNDROME
OMIM: 270150
GENES INVOLVED:
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [HEENT]: Xerostomia Xerophthalmia
PREDISPOSITIONS: not stated

82. THANATOPHORIC DYSPLASIA; TD
OMIM: #187600
GENES INVOLVED: fibroblast growth factor receptor-3 gene (134934)
CHROMOSOMAL LOCATION: 4p16.3
INHERITANCE: Usually autosomal dominant possibly some autosomal recessive cases
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [head]: Megalencephaly Small foramen magnum Cloverleaf skull [Neuro]: Temporal lobe malformations [facies]: Small facies
PREDISPOSITIONS: not stated

83. HYPODONTIA, AUTOSOMAL DOMINANT Tooth agenesis, familial
OMIM: #106600
GENES INVOLVED: MSX1 gene (142983)
CHROMOSOMAL LOCATION: 4p16.1
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [teeth]: Hypodontia
PREDISPOSITIONS: not stated
OTHER:see also 603446 OROACRAL SYNDROME, VERLOES-KOULISCHER TYPE

84. HYPODONTIA, AUTOSOMAL RECESSIVE
OMIM: *602639
GENES INVOLVED:
CHROMOSOMAL LOCATION: 16q12.1
INHERITANCE:
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated

CLINICAL SUMMARY:
HEAD AND NECK ::
PREDISPOSITIONS: not stated

85. MILLER-DIEKER LISSENCEPHALY SYNDROME; MDLS

OMIM: #247200
GENES INVOLVED:
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal recessive cases, with about 90% having visible or submicroscopic 17p13.3 deletions
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: Because of the close location of MDCR to tumor antigen p53 (TP53; 191170) and MYHSA1 (160730) in man, the homologous locus in the mouse is probably close to the corresponding loci in that species. Several neurologic mutants in the mouse map to that region.
CLINICAL SUMMARY:
HEAD AND NECK :: [HEENT]: Hypertelorism Microcephaly Bitemporal hollowing Prominent forehead Broad nasal bridge Epicanthus Short nose Upturned nares Prominent upper lip Micrognathia Thin vermilion border of upper lip Malformed [ears]: Malpositioned ears [teeth]: Late tooth eruption
PREDISPOSITIONS: not stated

86. LACRIMOAURICULODENTODIGITAL SYNDROME; LADD

All of the features of this syndrome have been reported as isolated traits inherited as autosomal dominants (see 149700, 128600, 150400, etc.)
OMIM: *149730
GENES INVOLVED:
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal dominant
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [eyes]: Aplasia/hypoplasia of lacrimal puncta Nasal lacrimal duct obstruction Poor tear production [ears]:]: Cup-shaped pinnas Mixed hearing deficit [mouth]: Poor saliva production [teeth]: Small and peg-shaped lateral maxillary incisors Enamel dysplasia Delayed tooth eruption [head]: Broad anterior fontanel High forehead Deep metopic fissure Microretrognathia
PREDISPOSITIONS: not stated

87. TREACHER COLLINS-FRANCESCHETTI SYNDROME 1; TCOF1

OMIM: *154500
GENES INVOLVED:
CHROMOSOMAL LOCATION: 5q32-q33.1
INHERITANCE: Autosomal dominant (5q32-q33.1)
ALLELIC VARIANTS
.0001 [TCOF1, GLN-TER] C-to-T transition at nucleotide 703
.0002 [TCOF1, 1-BP INS, FS174TER] single adenine after nucleotide 422 in exon 5 (422insA)
.0003 [TCOF1, 4-BP DEL, FS210TER] deletion of 4 bp, ATAC, after nucleotide 497 (497delATAC)
PRENATAL DIAGNOSTICS: Edwards et al. (1996) used 7 short tandem repeat polymorphic probes closely linked to the TCOF1 locus for prenatal diagnosis of the Treacher Collins syndrome in the fetus of an affected father. A chorionic villus sample was used as a source of fetal DNA. The at-risk fetus, his father, and half-sister shared the same haplotype, indicating a

very high probability that the fetus inherited the TCOF1 gene. Ultrasound examination at 20 weeks of gestation confirmed the diagnosis.

ANIMAL MODEL: Sulik et al. (1987) suggested that the malformations produced in mice by isotretinoin represent a useful model for the pathogenesis of Treacher Collins syndrome. Lungarotti et al. (1987) described changes strikingly similar to those of vitamin A toxicity in both animals and humans in an infant born of a mother who took 2000 IU of vitamin A daily as a supplement during pregnancy. Facial changes resembled those of mandibulofacial dysostosis. Lungarotti et al. (1987) speculated that the mother might have hypersensitivity to vitamin A.

CLINICAL SUMMARY:

HEAD AND NECK :: [facies]: Malar hypoplasia [eyes]: Anti-mongoloid slant Lower eyelid coloboma Partial absence of lower eyelashes [ears]:]: Microtia Conductive hearing loss [mouth]: Cleft palate Mandibular hypoplasia Macrostomia

PREDISPOSITIONS: not stated

OTHER:

88. MANDIBULOFACIAL DYSOSTOSIS, TREACHER COLLINS TYPE,AUTOSOMAL RECESSIVE

OMIM: 248390

GENES INVOLVED:

CHROMOSOMAL LOCATION:

INHERITANCE: Autosomal recessive vs. gonadal mosaicism most cases autosomal dominant

ALLELIC VARIANTS:

PRENATAL DIAGNOSTICS: not stated

ANIMAL MODEL: not stated

CLINICAL SUMMARY:

HEAD AND NECK :: [HEENT]: Mandibulofacial dysostosis Downward slanting palpebral fissures Lower eyelid coloboma Malar hypoplasia Abnormal pinnae

PREDISPOSITIONS: not stated

89. ACROFACIAL DYSOSTOSIS 1, NAGER TYPE; AFD1

OMIM: 154400

GENES INVOLVED:

CHROMOSOMAL LOCATION: 9q32

INHERITANCE: Paternal age effect Autosomal dominant heterogeneity

ALLELIC VARIANTS:

PRENATAL DIAGNOSTICS: not stated

ANIMAL MODEL: not stated

CLINICAL SUMMARY:

HEAD AND NECK :: [eyes]: Anti-mongoloid slant Ptosis of lower lids Hypoplasia of lower lid eyelashes [facies]: Malar hypoplasia Micrognathia Mandibular hypoplasia [ears]:]: Conductive hearing loss [ears]:]: Microtia Cartilaginous pegs between the antitragus and lobule

PREDISPOSITIONS: not stated

90. VELOCARDIOFACIAL SYNDROME

OMIM: #192430

GENES INVOLVED: velocardiofacial syndrome and DiGeorge syndrome (188400) may result from mutations in the same gene. The nature of that gene remains to be determined.

CHROMOSOMAL LOCATION: 22q11

INHERITANCE: Autosomal dominant, Neonatal hypocalcemia, rare T-lymphocyte dysfunction, rare Monosomy for 22q11

ALLELIC VARIANTS: Edelmann et al. (1999) developed hamster-human somatic hybrid cell lines from VCFS/DGS patients and showed by use of haplotype analysis with a set of 16 ordered genetic markers on 22q11 that the

breakpoints occurred within similar low copy repeats, designated LCR22s. Models were presented to explain how the LCR22s can mediate different homologous recombination events, thereby generating a number of rearrangements that are associated with congenital anomaly disorders.
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK: [Mouth] Cleft palate Velopharyngeal insufficiency Small open mouth Pharyngeal hypotonia [Face] Long Pierre Robin syndrome Retrognathia [Eyes] Narrow palpebral fissures Small optic discs Tortuous retinal vessels Posterior embryotoxon [Nose] Square nasal root Decreased nasopharyngeal lymphoid tissue Prominent tubular nose Hypoplastic nasal alae Bulbous nasal tip [Cranium] Microcephaly [ears]: Minor auricular anomalies
PREDISPOSITIONS: not stated

91. WAARDENBURG SYNDROME, TYPE I; WS1
OMIM: *193500
GENES INVOLVED:
CHROMOSOMAL LOCATION: 2q35
INHERITANCE: Autosomal dominant (2q35)
ALLELIC VARIANTS:
0001 : WAARDENBURG , TYPE IPAX3, 18-BP DEL, EX2
0002 : WAARDENBURG , TYPE IPAX3, PRO-LEU, EX2
0003 : WAARDENBURG , TYPE IPAX3, 14-BP DEL, EX2
0004 : WAARDENBURG , TYPE IPAX3, 1-BP DEL, FS
0005 : WAARDENBURG , TYPE IPAX3, 2-BP DEL, CA, EX4
0006 : WAARDENBURG , TYPE II PAX3, GLY48ALA
0007 : RHABDOMYOSARCOMA, ALVEOLAR PAX3/FKHR HYBRID
0008 : WAAR W MENINGOMYELOCELEPAX3, 5-BP DEL, EX5
0009 : WAARDENBURG , TYPE III PAX3, SER84PHE
0010 : CRANIOFACIAL-DEAFNESS-HAND SYNDROME; CDHS PAX3, ASN47LYS
0011 : WAARDENBURG , TYPE III PAX3, ASN47HIS
PRENATAL DIAGNOSTICS:
ANIMAL MODEL: Since a plausible mouse model is 'Steel' (Sl), a dominant mutation on mouse chromosome 10 closely linked to Pep-2, Read et al. (1989) studied polymorphic probes for loci on human chromosome 12 close to PEPB, the human homolog, in 7 families. They excluded a sizable region of 12q as the site of this gene. On the basis of an analysis of mouse and hamster mutants as models for Waardenburg syndrome(s), Asher and Friedman (1990) predicted that the gene(s) would be found to be on chromosome 2q near fibronectin-1, on chromosome 3p near the protooncogene RAF1 or 3q near rhodopsin, or on chromosome 4p near the protooncogene KIT. Based on amino acid sequence homology and common genomic exon/intron organization (Goulding et al., 1991), the human homolog of the mouse Pax-3 gene is thought to be the HUP2 gene (Burri et al., 1989). Chalepakis et al. (1994) studied the functional consequence of the mutations described in 193500.0001 and 193500.0006 on DNA binding and compared the results with those in the 'splotch' mouse. Combining the phenotypic features of heterozygous mutants and considering that molecular defects ranging from single point mutations to large deletions cause similar phenotypes, they excluded the possibility that the mutated allele in heterozygotes interferes with the function of the wildtype allele. Contrariwise, they considered both WS and 'splotch' mutants to represent loss-of-function mutations. Other genes in the 9q34 band have homologs on mouse chromosome 2. In the mouse, the 'lethal-spotted' (ls) mutation, which results not only in spotting but also in failure of the entire ganglia to colonize the gut, is located on chromosome 2. Chakravarti (1988) suggested that this and other possibly homologous mouse mutations

might be used as a clue to the chromosomal location of the WS1 gene in the human. Epstein et al. (1991) studied a deletion of mouse chromosome 1 that involved the 'splotch' locus. The murine equivalent of the ALPP gene was included in the deletion, thus supporting the notion that 'splotch' is the equivalent of WS1. Steel and Smith (1992) found that, unlike individuals with Waardenburg syndrome, the splotch mouse has normal hearing. They suggested that the difference in expression of the genes in the 2 species may result from different parts of the gene being mutated or from modifying influences as yet undefined. In mice with certain 'splotch' mutations, influence of the genetic background and sex of the individual on penetrance and expressivity is demonstrable.

CLINICAL SUMMARY:

HEAD AND NECK :: [hair]: White forelock White eye lashes Premature graying of hair [eyes]: Laterally displaced inner canthi Normal inner canthal distance (e.g. Waardenburg syndrome, Type II .0006) Heterochromia iridis Hypoplastic iris stroma Fundus albinotic [ears]:]: Cochlear deafness [nose]: Wide nasal bridge Short philtrum [mouth]: Cleft lip/palate Bilateral cleft lip

PREDISPOSITIONS: Rhabdomyosarcoma (e.g. Rhabdomyosarcoma, alveolar .0007)

92. WAARDENBURG SYNDROME, TYPE IIA; WS2A

OMIM: #193510

GENES INVOLVED: microphthalmia-associated transcription factor (MITF; 156845)

CHROMOSOMAL LOCATION: 3p14.1-p12.3

INHERITANCE: Autosomal dominant (3p13) heterogeneous

ALLELIC VARIANTS: not stated

PRENATAL DIAGNOSTICS: not stated

ANIMAL MODEL: not stated

CLINICAL SUMMARY:

HEAD AND NECK :: [hair]: White forelock White eye lashes Premature graying of hair [eyes]: No dystopia canthorum Normal inner canthal distance (e.g. Waardenburg syndrome, Type II .0006) Heterochromia iridis (more frequent than in Type I) Hypoplastic iris stroma Fundus albinotic [ears]:]: Cochlear deafness (more frequent than in Type I) [nose]: Wide nasal bridge Short philtrum [mouth]: Cleft lip/palate Bilateral cleft lip

PREDISPOSITIONS: Rhabdomyosarcoma (e.g. Rhabdomyosarcoma, alveolar .0007)

93. WILLIAMS-BEUREN SYNDROME; WBS

OMIM: #194050

GENES INVOLVED: Contiguous gene deletion syndrome of 7q11.2, usually involving the elastin gene (ELN) ({130160}) usually sporadic elastin gene (130160), LIM kinase-1 (LIMK1; 601329) Haploinsufficiency of the RFC2 gene (600404,)hemizygosity for the LIMK1

CHROMOSOMAL LOCATION: not stated

INHERITANCE: Autosomal dominant usually sporadic

ALLELIC VARIANTS: not stated

PRENATAL DIAGNOSTICS: not stated

ANIMAL MODEL: Li et al. (1998) generated mice hemizygous for the elastin gene (ELN +/-). ELN +/- mice have an expected reduction in ELN mRNA and protein of 50% but nearly normal arterial compliance at physiologic pressures. ELN hemizygosity in mice and humans induces a compensatory increase in the number of rings of elastic lamellae and smooth muscle during arterial development. Animal models exposed to hypervitaminosis D gave birth to offspring that developed SVAS (Friedman and Roberts, 1966; Chan et al., 1979). These findings supported the model of Li et al. (1998) of reduced gestational ELN expression resulting in abnormal vascular development and obstructive vascular disease.

CLINICAL SUMMARY:

HEAD AND NECK :: [Face] Medial eyebrow flare Flat midface Periorbital fullness (puffy eyes) Epicanthal folds Long philtrum Thick lips [Eyes] Stellate pattern of iris [Nose] Depressed nasal bridge Anteveted nares [Teeth] Hypodontia Microdontia [VOICE]: : Harsh, brassy, or hoarse [voice]: Vocal cord paralysis
PREDISPOSITIONS:

DISORDERS NAMED BY GENE

94. PEROXISOMAL MEMBRANE PROTEIN 3; PXMP3
http://www3.ncbi.nlm.nih.gov:80/htbin-post/Omim/dispmim?170993.cs
OMIM: *170993
GENES INVOLVED:
CHROMOSOMAL LOCATION:
INHERITANCE: Autosomal recessive Zellweger-3 (8q21.1)
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [head]: High forehead Dolichoturricephaly Large fontanels [facies]: Flat face Round face [eyes]: Puffy lids Mongoloid slant Hypertelorism Epicanthic folds Brushfield spots Cloudy cornea Cataracts Pigmentary retinopathy Optic nerve dysplasia [mouth]: Cleft palate [mandible]: Micrognathia [ears]:]: Low set [ears]: Helix abnormal
PREDISPOSITIONS: not stated

95. NEONATAL OSSEOUS DYSPLASIA I
OMIM: #256050
GENES INVOLVED: diastrophic dysplasia sulfate transporter gene (222600)
CHROMOSOMAL LOCATION: 5q32-q33.1
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [HEENT]: Cleft palate
PREDISPOSITIONS: not stated

96. ACROCALLOSAL SYNDROME; ACLS
OMIM: *200990
GENES INVOLVED:
CHROMOSOMAL LOCATION: 12p13.3-p11.2
INHERITANCE: Autosomal recessive
ALLELIC VARIANTS:
PRENATAL DIAGNOSTICS: not stated
ANIMAL MODEL: not stated
CLINICAL SUMMARY:
HEAD AND NECK :: [head]: Macrocephaly Forehead protruding Occiput prominent Calvarian defect [facies]: Hypertelorism [neck]: Clavicle bipartite
PREDISPOSITIONS: not stated