CONFERENCE REPORT

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Second International Conference on a Classification of Ectodermal Dysplasias: Development of a Multiaxis Model

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Ectodermal dysplasias (EDs) comprise a large clinically and etiologically heterogeneous group of genetic disorders characterized by abnormalities in tissues derived from the embryonic ectoderm. Controversy exists over which syndromes should be classified as EDs and which should be excluded from the classification. The challenge will be to balance comprehensiveness within the classification with usability and accessibility so that the benefits truly serve the needs of researchers, health-care providers, and ultimately the individuals and families directly affected by EDs. The overarching goal of the Second International Conference was to develop a consensus on EDs classifications, with the ultimate goal of creating a system that integrates clinical and molecular knowledge, using an interactive Internet-based database that clinicians, researchers, and laymen can use. The Conference, brought together a group of experts from around the world, including a diverse health-care providers, researchers, patient advocate representatives, and administrators. The Conference was modeled after the 2008 conference, with plenary sessions, scientific updates, and small group discussions. Based on the present clinical knowledge, new molecular advances and both coupled with new bioinformatics developments, the participants agree to develop a multiaxis system approach for the classification of EDs. The multiaxis approach will include a clinical/phenotype axis, a gene-based axis, and a functional/pathways axis. The significance of the conference outcomes includes, a new classification approach that will foster a better understanding of EDs, open new fields of research and develop a nosologic approach that may have broad implications for classifying other hereditary conditions.

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INTRODUCTION

Ectodermal dysplasias (EDs) comprise a large clinically and etiologically heterogeneous group of genetic disorders that are characterized by abnormalities in tissues derived from the embryonic ectoderm. As of July 2013, at least 186 distinct pathological clinical conditions have been recognized and defined as EDs. They all share common features: anomalies in hair, teeth, nails, and sweat glands, but most are associated with anomalies in other organs and systems. Some complex phenotypes are now explained in the light of the molecular causative defects involving, for instance, widely expressed proteins with essential roles in control of cell cycle progression, in replication and/or DNA repair.

The EDs are extremely variable with significant clinical overlap between many EDs, making them difficult to diagnose precisely. Indeed, controversy exists over which syndromes should be classified as EDs and which should be excluded from such a classification. The EDs have historically been diagnosed and classified based upon clinical manifestations. However, during the last few years, new advances in the molecular basis and biological functions have allowed researchers to explore the unique molecular pathways involved in the different EDs. In some cases a clinical diagnosis can now be confirmed by molecular genetics.

Since 2008, knowledge regarding the molecular nature of ED has continued to increase and new classifications have been proposed. EDs that were once thought to be distinct have been "lumped" together (e.g., Zanier-Roubicek syndrome is now thought to be the autosomal dominant form of hypohidrotic ED; and EEC2 and EEC3 were incorporated into EEC3, among others). New EDs have been described (e.g., Carvajal syndrome and SOFT syndrome). Other EDs are now thought to "overlap" with each other, presenting clinical similarities that suggest they may be variations of the same disorder. By 2008, researchers had identified 29 genes and 1 chromosomal region that are involved in the development of 39 different EDs. By 2012, 77 genes and 9 chromosomal regions had been described in relation to 75 types of ED.

With this explosion in knowledge regarding the molecular nature of ED has come a concomitant increase in available genetic testing for EDs, which is particularly useful for currently undiagnosed ED. Eleven gene tests are available for testing, most of which are performed in Clinically Laboratory Improvement Amendments (CLIA)-certified clinical laboratories; several more are conducted only in research laboratories. A number of additional genes have been associated with ED (through pathway analysis or clinical relevance) and could, therefore, also be tested to arrive at diagnoses and conduct research. With regard to cases in which clinicians and/or researchers are sure of being able to make a specific diagnosis, it is possible to test individually a prioritized list of genes available in CLIA labs and those in research settings. When a molecular diagnosis still cannot be made, whole exome sequencing can help narrow down candidate genes efficiently and cost-effectively, using a prespecified set of ED-related genes to analyze a whole exome.

Despite this progress, no universally accepted classification for EDs has been developed. There is, however, widespread agreement regarding the need for an updated classification that integrates clinical and molecular information [DiGiovanna et al., 2009; Salinas et al., 2009; Wright et al., 2009]. The challenge will be to balance comprehensiveness within the classification with usability and accessibility so that the benefits truly serve the needs of researchers, health-care providers, and ultimately the individuals and families directly affected by EDs. It is also recognized that a new classification approach is an ongoing process and will require periodical reviews or updates. Whatever scheme is developed, however, will have far-reaching application for other groups of disorders for which classification is complicated by the number of interested parties and advances in diagnostic acumen. Consensus among interested parties is necessary for optimizing communication among the diverse groups whether it be for equitable distribution of funds, correctness of diagnosis and treatment, or focusing research efforts.

CONFERENCE REPORT

To address the need for a modern classification The National Foundation for Ectodermal Dysplasias (NFED) and the Medical University of South Carolina sponsored and held the Second International Conference on Ectodermal Dysplasias Classification on October 18–20, 2012, in Charleston, South Carolina and supported by an NIDCR Conference Grant (1R13DEO23034). This is a follow up of the 2008 International Conference supported by NIDR Conference grant (1R13DEO18845-01) and the NFED. The Proceedings of the Conference were published by the *American Journal of Medical Genetics* (vol.149A, 9, Sept. 2009). The conference generated great research interest in the classification of EDs. There was general consensus regarding the need for an updated classification that integrates clinical and molecular information. A modern classification was thought that will improve patient diagnosis, treatment, counseling, research, and may also serve as a model for classifying other complex set of disorders. In addition, also as a result of the conference recommendations, The NFED Ectodermal Dysplasias International Patient Registry was implemented.

The conference was modeled after the 2008 conference, with plenary sessions, scientific updates, and small group discussions. Attendees hoped to achieve the following objectives:

1. Create an international forum of vested investigators who will outline strategies toward the development of a new classification model; and
2. Generate consensus toward the implementation of a multiple axis approach, including a clinical/phenotype axis, an etiology/gene axis, and a pathogenesis/pathways axis, coupled with a bioinformatics model appropriate for EDs.

The remainder of this report summarizes the proceedings of the conference and presents the consensus of conference participants regarding the need for an updated classification for EDs that integrates clinical and molecular data.

CHALLENGES TO A UNIFIED CLASSIFICATION

Despite ongoing progress in elucidating the molecular basis of EDs, issues regarding their classification remain similar to those discussed during the 2008 conference. There are still many ways to classify EDs. The most widely used clinical classification was

proposed by Freire-Maria [1971]. It is based on the "classical signs" of ED—trichodysplasia, dental defects, onychodysplasia, and dyshidrosis. Under the Freire-Maria classification, EDs are defined as congenital disorders characterized by alteration in two or more ectodermal structures; at least one involving hair, teeth, nails, or sweat glands. They are further broken into two groups. Group A includes those disorders with signs affecting at least two of the classical structures: (1) hair, (2) teeth, (3) nails, and (4) sweat glands. Group B includes disorders involving one of the classical signs associated with another ectodermal sign (subgroup 5). This clinical definition is the foundation for the Freire-Maria classification, which follows a mnemonic procedure with the assignment of a number for each type of structure disturbance that are catalogued in 11 subgroups [Freire-Maria, 1977; Freire-Maria et al., 2001; Freire-Maria and Pinheiro, 1988; Pinheiro and Freire-Maria, 1994].

Several classification approaches has been proposed including those from Solomon and Keuer [1980]; Itin and Fistarol [2004].

Classification approaches based on the molecular basis of EDs have been reported in the literature, such as the ones from J. Lamartine and M. Priolo. Lamartine [2003] proposed a new classification which added a dimension to the clinical classification, by grouping disorders by a functional assessment of their causative genes and proteins [Priolo et al., 2000; Priolo and Lagana, 2001]. Priolo and Lagana [2001], added yet another dimension, expanding the classification to include ectodermal–mesenchymal interactions and proposing a clinical-functional classification of EDs, based on the assumption that the ED causative genes act through two different pathogenetic mechanisms, and that all clinical findings observed in affected patients are highly specific for each of the two mechanisms identified. These types of classifications support a conceptual understanding of mechanisms, and suggest molecular functional targets to explore, but have limited use as clinical diagnostic tool. The classification system needs to address a number of challenges to developing a unified classification of EDs, which include the following:

- High number of disorders currently included under the term ectodermal dysplasia (e.g., 186 under the Freire-Maria classification);
- Variability of expression of the disorder or traits, even within individual syndromes;
- Overlapping features among EDs;
- Allelic disorders (i.e., some disorders once considered separate entities have proven to be allelic disorders, such as P63, in which different mutations on the same gene have occurred);
- Low incidence of disorders (i.e., a small n means it is hard to determine the phenotypic spectrum);
- Incomplete penetrance;
- Genetic heterogeneity;
- Pseudo-dominant inheritance; and
- Mischaracterization of disorders.

TOWARD A CONSENSUS

After receiving updated information on recent advances in classification and research, participants devoted the remaining sessions to discussing the next steps toward developing an integrated classification. Two concurrent panels of experts discussed clinical and molecular (including pathogenic) issues, respectively. The entire group then discussed the application of bioinformatics to the classification of EDs. A summary of their discussions follows.

A MULTIAXIAL MODEL

Participants agreed that each classification, whether clinically- or molecularly-based, has benefits and drawbacks associated with it. Each is useful to a particular end-user group, including clinicians, researchers, special interest groups, and pharmaceutical companies. Many user groups, while familiar with one classification, might find some functions of other classifications useful; yet each classification has limitations that make it inadequate for all user groups. Rather than limiting themselves to one classification or creating a new one, participants agreed to develop a multiaxial system of diagnosis that links existing clinical, molecular, and pathogenic classifications and allows these classifications to "talk" to each other through the use of bioinformatics.

The solution is not as simple as linking existing classifications, however. Each type of classification must be edited and refined to allow it to communicate effectively with others. An integrated classification requires, therefore, a common language, definitions, and terms. While reviewing each classification, participants agreed to focus on developing criteria and rules for inclusion and exclusion of disorders, rather than making decisions about specific disorders, which will allow the resulting classification to accommodate a fast-changing knowledge base. Issues specific to each type of classification are reviewed below.

CLINICAL ISSUES

When examining a patient who has several and diverse clinical findings, the clinician is faced with identifying the underlying disorder. To make an ED clinical diagnosis the clinician resource is the widely used Freire-Maria classification which is based on the presence of abnormalities in various ectodermal structures. The clinician can identify phenotypic abnormalities and fit them into a schema similar to combining the pieces of a jigsaw puzzle into a coherent picture. This system allows for the complexity of clinical phenotypes to be distinguished in a manner that is practical and useful for both clinical diagnosis and genetic counseling. Thus patients have a distinct name for their disease and is one which doctors can "look up" and become familiar with. Diverse specialists managing diverse clinical manifestations (dental, dermatologic, genetic, pediatric, surgical, rehabilitation medicine, orthopedic, ophthalmology, otorhinolaryngology) are able to search the medical literature for information about the etiology and management of the particular type relevant to their patient. Thus, the disorder becomes more manageable and predictions can be made about prognosis. This system works well for clinicians, which is not surprising because it was primarily developed by clinicians for diagnosis and treatment. However there is disagreement among the proponents of a clinically-based classification system about how restrictive or open-ended the inclusion/exclusion criteria should be. Participants review the following issues pertinent to the Clinical worshop.

Refine Clinical Classification

Participants agreed that the first step to creating a multiaxial system is to focus on refining a clinical classification, which will then influence how molecular information is incorporated into the revised classification. Currently, a classification system needs to be flexible and driven by clinical information—not all of the genetic causes for EDs are known and laboratory testing is still often prohibitively expensive and/or inaccessible. In addition, clinical symptoms still drive the diagnosis of ED—cases are not initially identified and diagnosed through analysis of individuals at the molecular level.

Refine Clinical Characteristics of the Disorders

The research community agreed that there is much variability in the phenotype of EDs, but that variability is not adequately quantified, even for the more common disorders. In response to this need, the NFED established the Web-based International Patient Registry which it launched on March 1, 2010. The registry is designed to support communication between affected individuals, clinicians who treat them, and scientists who strive to advance research on EDs. Its first objective was to clinically characterize and describe the ectodermal dysplasia patient population. They developed and implemented an standard protocol to recollect objective clinical signs and symptoms from the patient population.

Thus far, the registry's establishment has resulted in 27 syndromes being reported and the creation of 1,780 profiles by people from several different countries. The registry will become a good research tool to refine the clinical characteristics of the EDs.

Develop New Criteria for Inclusion

Participants focused on the need to develop clear-cut "rules" for including or excluding a disorder from the ED classification, rather than on whether individual disorders should be included. Participants noted that it is possible to have a clinical classification with specific rules in a hierarchy and a related but distinct set of rules for molecular inclusion or exclusion. To achieve this milestone, it is important to consider what individual cases represent, and how to write rules to represent them. To illustrate this point we have cases that present one structure affected and one gene mutation.

Standardized Terms

Participants agreed to use standardized terms to describe clinical findings. It was accepted to begin using the standard terminology proposed by an international group of dysmorphologist and published in six papers by the *American Journal of Medical Genetics* [Biesecker et al., 2009; Carey et al., 2009; Hall et al., 2008; Hennekam et al., 2008; Hunter et al., 2008; Allanson et al., 2008]. In addition the group will follow the guidelines proposed by papers by Allanson et al. [2009]; Biesecker and Carey [2011]; Carey et al. [2009, 2012].

Use of Freire-Maria Clinical Classification

Participants agreed to use the widely accepted Freire-Maria classification and to review each of the 186 entities Then "clean" that sample to arrive at a new version of the clinical classification that reflects the new guidelines. Participants also discussed the need to account for new clinical cases that don't trigger classic symptoms and highlighted the importance of creating a forum dedicated to research into, and discussion of, unsorted, undiagnosed "potential" EDs.

Incorporate Natural History

While ED is not a progressive disease, the disorder is also not fixed at birth. Symptoms can appear or change over time. Participants noted that symptoms can include morphological as well as functional abnormalities (e.g., an inherent hair abnormality vs. an abnormality in hair growth). A clinical classification needs, therefore, to take into account the type, timing and evolution of symptoms to present the most accurate description of EDs. This has implications for clinical diagnostics because the "quality" of an abnormality needs to be incorporated into a diagnosis; for example, the abnormal growth of a nail must be noted, not just an abnormal morphology. In addition to emphasizing the need for detailed clinical information, participants pointed out that clinicians should also be encouraged to evaluate patients at multiple points in time to capture age-related development of the phenotype (e.g., Wnt10A presents differently before and after puberty).

Clinical Descriptions

Participants stressed the need for detailed clinical descriptions, which will allow not only for an accurate diagnosis, but for the calculation of the frequency of specific phenotypic features, which would help determine in which order individuals should be tested for specific genes. As noted above, participants suggest creating hierarchies of symptoms. For example, "nail dysplasia" is a very ambiguous term. A hierarchy for nail abnormalities may include: onychodystrophy; koilonychias; candidiasis; onychoschisis, and so forth, which encourages the most specific description of symptoms possible. Participants also expressed the importance of collaborating with clinicians to ensure the quality and level of detail of phenotypic information available; clinicians are not currently trained to "ask the right questions" and therefore, participants noted, "a lot gets missed"; often with only the dominant issue being addressed, which may or may not result in an ED diagnosis.

MOLECULAR ISSUES

Participants noted that the level of complexity of molecular information related to EDs "is something we have just begun to recognize." As noted above, there are a number of challenges that complicate efforts to organize molecular information, including incomplete penetrance, variable expression, clinical heterogeneity, genetic heterogeneity, pseudo-dominant inheritance in rare diseases, and person-specific contiguous gene syndromes. In thinking about grouping molecular data, participants felt that it was important to first consider what questions will be asked about the data—to determine how the data will be used to consider how it should be put together.

The following issues were raised with regard to the organization of molecular data:

Ectodermal-Mesenchymal Interaction

Participants debated the importance of the ectodermal–mesenchymal interaction, and ultimately decided that it should be incorporated into the classification because it is integral to the development of teeth, hair, and other ectodermal derivatives. Participants also noted its limitations, however. For example, some EDs have a phenotype based on ectodermal/mesenchymal interactions, but others do not.

Animal Models

It was noted that important and relevant questions have arisen from the study of mouse and other animal models, which may also add value to the study and classification of EDs. For example, studies of breast abnormalities in mice suggest research questions to ask about similar features in humans; this demonstrates the value of linking clinical databases with molecular and pathway information. Currently, online resources such as Online Mendelian Inheritance in Man (OMIM) only work with human models, but there are opportunities to work with laboratories, such as Jackson Laboratories, that track animal studies.

Gene Lists

Participants discussed whether ED "gene lists" should include only genes considered to be causative genes, and how they would be defined as such. While the value and utility of gene lists was debated, it was noted that they would be helpful in developing an order of genes to test. They added that, at the very least, key target genes important in pathogenesis should be identified.

Pathogenic Issues

Participants discussed whether disorders should be categorized by pathway, and how knowledge of pathways might be useful in thinking about how to organize EDs. Knowledge of pathways should consider organ influences; for example, developmental signaling pathways are similar in different ectodermal derivative organs, but, when overlaid with temporal and tissue variations, they result in different gene targets and outcomes. Therefore, it is important to know under what circumstances data regarding pathways was acquired (e.g., which stage of development), to improve understanding of the complexity of the relationships and interactions.

Participants acknowledged that there is value in validating pathways, although some will prove more relevant than others. Knowledge of pathways could aid in developing a "shopping list" of genes to test in undiagnosed cases. Knowing the clinical features associated with genes in a pathway also may help in identifying other causative gene mutations. Assuming enough information is available, this can be accomplished in the following ways:

- Forward approach, which involves incorporating validated pathway biology into a more focused candidate gene approach, and
- Reverse approach, which is initiated with whole genome sequence, using genes that have been identified as potentially relevant to the disorder. Researchers go "backwards" to see if the genes are functional in the pathways that are validated as being relevant to the disorder, or to identify new pathways.

Participants noted that only pathways with confirmed involvement in the development of ED should be included, and that these should include pathways for animal models as well. This process may be time-intensive and painstaking, because it will involve reviewing previous research to determine their relevance. It was noted, however, that some pathway organization has already been completed, such as through the website at string-db.org. The question is how to access these resources, use them, and make them applicable by the ED community of researchers, clinicians, and other stakeholders.

THE ROLE OF BIOINFORMATICS

Throughout the conference, a number of participants stated that their goal should not be to "reinvent the wheel," but rather to "get on the bike and start moving." Toward this end, much of the information regarding molecular and pathway data that was discussed is already available in various databases, as noted above.

Current Resources

Many multiple current resources contain and update information about diagnostic terms, clinical features, genes, pathways, subcellular distributions, variation and its clinical significance, and the supporting literature, such as OMIM [2009], stringdb.org, Genetests, Orphanet, Genereview, the London Dysmorphology Database, PubMed, and other databases. Participants recognize that there are limitations in each of the present resources, however they represent a good starting point.

Linkages

Linking a clinical classification such as Freire-Maria to other relevant databases and resources would allow access to these frequently updated molecular biology resources. Having an accurate, precise, frequently updated clinical classification that is linked to these databases would permit the generation of "lists" of currently linked genes, proteins, and pathways. Participants also discussed linking to resources that may not exist, but would be helpful to the study and diagnosis of EDs, such as data extracted from primary research papers, and data on the probability of co-mutations and their impact on phenotype.

Bioinformatics Solutions

Participants were presented with information regarding how bioinformatics might help connect these sometimes disparate sources. Once terms are standardized and "like" concepts are identified, connections can be made between very different types of information through the use of a unique identifier, which can be assigned to terms in multiple categories, including diagnostic terms, clinical signs, and genes. A unique identifier is a stable way to refer to a concept, independent of names, and to connect names from different sources, without requiring all users from various stakeholder groups to "speak the same language." Bioinformatics can

also help connect very different types of information by assigning these unique identifiers, and also by establishing relationships between terms (such as equivalences, parent/child relationships, causative genes and mutations, and common pathways), providing cross-references, other characteristics, and an easy way to update this information.

Centralizing information in this manner has the benefit of facilitating access to both the scientific and broader stakeholder communities. Storing information in public databases is beneficial because terms and their identifiers already exist. Many databases have tools to submit and revise information, which supports cross-communication among diverse interest groups. In addition, ready access to data supports reanalysis through accumulation of new information and identification of new ways to review the data. In the interest of preserving privacy, while some information can and should be centralized and publicly available, creation of different levels of access will protect identifiable data.

NEXT STEPS

Given the rate at which new molecular information is becoming available, the expert workgroup thought it best to develop recommendations for the very short term—for the next year, rather than next five. With this in mind, the workgroup will move forward to address the issues and questions raised regarding the classification of EDs and to advance the process of developing a new classification. Such a classification holds the promise of providing clarity of diagnosis and stimulating research and discovery. To make it possible to begin connecting different data sources and classifications, next steps include (1) standardizing terms and defining them, (2) developing hierarchies of terms and phenotypes, and then (3) adapting and refining the Freire-Maria classification before linking it to other extant resources.

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APPENDIX

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