

## **The European Skeletal Dysplasia Network: a pan-European research and diagnostic network for rare bone diseases**

The bone dysplasias are a diverse and complex group of rare genetic disorders affecting the development of the skeleton. Due to the rarity of these conditions, which also exhibit extensive clinical variability and genetic heterogeneity, determining an accurate diagnosis can be an extremely difficult, time-consuming and expensive undertaking for the non-expert.

In order to address these diagnostic problems within the wider European Community the European Skeletal Dysplasia Network (ESDN) was established as a referral and communication network to provide help and diagnostic expertise to the medical community. In this context ESDN employs state-of-the-art DNA diagnostic and research technologies to provide diagnostic services and research collaborations respectively.

ESDN is composed of eight partners from six European countries and is coordinated by Dr Mike Briggs, a bone biologist at the University of Manchester. The project was initially established in January 2002 with funding from the European Commission's Fifth Framework Programme (contract number QLG1-CT-2001-02188) and financial support from the Swiss Government (contract number OFES 01.0258). The primary goal of the project was to provide an integrated research and diagnostic network for skeletal dysplasias, which will ultimately provide a better understand the cellular, molecular and genetic factors that cause bone dysplasias and to develop effective approaches for their diagnosis. Using a unique web-based electronic referral system ESDN partners in the United Kingdom, Belgium, Germany, Finland Switzerland and France provide medical practitioners from any where in the world with specialist clinical advice and expert molecular diagnosis services for bone dysplasias.

The European Skeletal Dysplasia Network comprises two major components:

***ESDN-Diagnostics*** offers diagnostic review of patients and families with bone dysplasias and provides molecular analysis of over 21 genes associated with more than 28 different bone dysplasias. Diagnostic review is undertaken by the clinical review panel, which includes clinicians from across Europe who are leading experts in the clinical and radiographic diagnosis of bone dysplasias. To enable efficient management of the diagnostic network a web-based case management system was launched in September 2003. This secure server, which was developed in collaboration with Certus Technology Associates, guarantees the protection of patient confidentiality.

The ESDN Case Manager allows a clinician from anywhere in the world to submit an initial diagnosis supported by x-ray images. The system coordinator then refers the submitted case to the expert clinical and radiographic review panel, which uses an electronic discussion forum to consider the case and direct investigations. Following their recommendation, materials from the originating clinician (such as DNA) are directed to the appropriate laboratory and molecular testing can be completed as appropriate.

Since January 2002, ESDN has received approximately 2000 patient referrals and performed over 1500 molecular diagnostic tests. Over 430 cases have now been referred using the ESDN Case Manager.

In summary, robust referral pathways with appropriate sample routing, quality assessment schemes and efficient dissemination of results and clinically relevant information are amongst the major achievements of the ESDN diagnostics service. The deployment of the

ESDN Case Manager system has fostered major improvements in the diagnosis of skeletal dysplasias including accelerated clinical diagnosis or review of cases with an unknown diagnosis, increased sensitivity and specificity of DNA testing through clinical pre-review and finally the further delineation of new skeletal dysplasia phenotypes by the referral and discussion of unknown cases.

**ESDN-Research** focuses on identifying the genes, mutations and disease processes that underpin the pathophysiology of skeletal dysplasias. The complexity and heterogeneous presentation of this group of skeletal diseases requires the application of a multi-disciplined and integrated research approach. Thus, the overall methodology consists of three basic elements: patient ascertainment and comprehensive clinical and radiographic diagnosis; molecular genetic investigations and approaches to determine the molecular cell pathology and structure/function relationships of the relevant gene products.

Several complementary programmes have been developed to achieve this, which include identifying novel genes involved in human skeletal development, the identification of new diseases genes and mutations through the use of genetic linkage and positional candidate cloning the identification, analysis of protein function and dysfunction through structural & functional studies and finally a systems biology approach for investigating the molecular cell pathology of skeletal dysplasias.

“There is no one centre with all the necessary experience or facilities to cope with the diagnosis of so many types of bone disorder,” project administrator Dr. Jacky Taylor from Manchester, UK stated in a press release. “There are more than 200 different kinds of complaints ranging from mild to life-threatening, so clinicians face significant problems identifying which condition their patient has. This web-based, case-management system overcomes geographical barriers and brings together the scarce clinical resources for these rare conditions. By providing efficient access to a pan-European network of experts and genetic-testing facilities, doctors can make accurate diagnoses enabling patients to receive the best treatment for their particular condition.”

As the first pan-European approach to the diagnosis of rare diseases, the ESDN project has major implications for the future of diagnostic service delivery. The model established by the ESDN is applicable to the diagnosis and management of any group of rare disease.

Since January 2006, ESDN has been maintained by various National and European sources of funding.

Visit the ESDN website:

<http://www.esdn.org/>