Actas Dermosifiliogr. 2018;109(2):104–122

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org

SPECIAL ARTICLE

Genetic Diagnosis of Epidermolysis Bullosa: Recommendations From an Expert Spanish Research Group☆

C. Sánchez-Jimeno,[a] M.J. Escámez,[b] C. Ayuso,[a] M.J. Trujillo-Tiebas,[a,*] M. del Río[b,*], en representación de la Cátedra de la Fundación Jiménez Díaz de Medicina Regenerativa y Bioingeniería Tisular, DEBRA-España y de otros profesionales sanitarios◊

[a] *Departamento de Genética, IIS-Fundación Jiménez Díaz, Universidad Autónoma de Madrid, CIBER de Enfermedades Raras (ISCIII) U704, Madrid, Spain*
[b] *Departamento de Bioingeniería, Universidad Carlos III de Madrid; Unidad de Medicina Regenerativa, Centro de Investigaciones Energéticas Medioambientales y Tecnológicas (CIEMAT), IIS-Fundación Jiménez Díaz, CIBER de Enfermedades Raras (ISCIII) U714, Madrid, Spain*

Received 2 February 2017; accepted 30 August 2017
Available online 15 February 2018

KEYWORDS
Genodermatosis;
Epidermolysis bullosa;
Epidermolysis bullosa simplex;
Epidermolysis bullosa junctional;
Epidermolysis bullosa dystrophic;
Kindler syndrome;
Genetic diagnosis;
Antigen mapping;
Prenatal diagnosis;
Preimplantation diagnosis

Abstract Epidermolysis bullosa (EB) is a rare genetic disease that causes mucocutaneous fragility. It comprises a clinically and genetically heterogeneous group of disorder characterized by spontaneous or contact/friction–induced blistering. EB is classified into 4 types–simplex, junctional, dystrophic, and Kindler syndrome–and 30 subtypes. The disease is caused by defects in proteins implicated in dermal-epidermal adhesion. At least 19 genes have been characterized and more than 1000 mutations identified, thus rendering diagnosis complex. Molecular diagnosis of EB is the last stage of a laborious process that starts with a detailed clinical history compilation and careful procurement of a skin fresh biopsy that includes an area where the epidermis detaches from the dermis. The detachment area makes it possible to establish the cleavage plane by antigen mapping and, in the best scenario, to identify a single candidate gene to search for pathogenic mutations. The results of the molecular diagnosis enable the physician to provide appropriate genetic counseling (inheritance pattern, risk of recurrence, and options for prenatal and preimplantation diagnosis) and implement subsequent preventive programs, as well as to establish a reasonable clinical prognosis facilitating access to specific therapy and rehabilitation. Lastly, molecular diagnosis is essential for the participation of patients in clinical trials, a critical issue given the current incurable status of EB. The present guidelines

☆ Please cite this article as: Sánchez-Jimeno C, Escámez MJ, Ayuso C, Trujillo-Tiebas MJ, del Río M, en representación de la Cátedra de la Fundación Jiménez Díaz de Medicina Regenerativa y Bioingeniería Tisular, et al. Diagnóstico genético de la epidermólisis bullosa: recomendaciones de un grupo español de expertos. Actas Dermosifiliogr. 2018;109:104–122.

* Corresponding author.
E-mail addresses: mjtrujillotiebas@gmail.com (M.J. Trujillo-Tiebas), mrnechae@ing.uc3m.es (M. del Río).

◊ The names of all the health professionals are listed in Appendix A. C. Sánchez-Jimeno and M.J. Escámez are both first authors: they have contributed equally to this paper.

aim to disseminate the procedure for diagnosing EB in our laboratory and thus avoid suboptimal or incomplete clinical diagnoses. The recommendations we provide are the result of more than 10 years' experience in the molecular diagnosis of EB in Spain.

PALABRAS CLAVE
Genodermatosis;
Epidermólisis bullosa;
Epidermólisis bullosa simple;
Epidermólisis bullosa juntural;
Epidermólisis bullosa distrófica;
Síndrome de Kindler;
Diagnóstico genético;
Mapeo antigénico;
Diagnóstico prenatal;
Diagnóstico preimplantacional

Diagnóstico genético de la epidermólisis bullosa: recomendaciones de un grupo español de expertos

Resumen La epidermólisis bullosa (EB), enfermedad genética de fragilidad mucocutánea rara y devastadora, es clínica y genéticamente heterogénea. Se caracteriza por la aparición de ampollas inducidas por contacto/fricción o de forma espontánea. La EB se clasifica en 4 tipos: simple, juntural, distrófica y síndrome de Kindler y en 30 subtipos. Esta genodermatosis está causada por defectos en proteínas implicadas en la adhesión dermoepidérmica, con al menos 19 genes caracterizados hasta el momento y más de 1.000 mutaciones identificadas, que explican la complejidad de su diagnóstico. El diagnóstico molecular de la EB es el último paso de un proceso laborioso que se inicia con la recogida de una historia clínica detallada y la toma de una biopsia cutánea, que incluya una zona de despegamiento entre la dermis y la epidermis inducida, en el momento de la recolección. Dicho despegamiento permite establecer el plano de rotura por mapeo antigénico y, en el mejor de los casos, un único gen candidato en el que realizar la búsqueda de las mutaciones patogénicas. Finalizado el diagnóstico molecular, se está en condiciones de ofrecer al paciente un asesoramiento genético adecuado (patrón de herencia, riesgo de recurrencia y opciones de diagnóstico prenatal y preimplantacional) y los consecuentes programas preventivos, así como un pronóstico clínico razonable que facilite su acceso a opciones terapéuticas y de rehabilitación específicas. Por último, el diagnóstico molecular es imprescindible para la participación de los pacientes en ensayos clínicos, de gran importancia en una enfermedad como la EB, que no tiene cura. El objetivo de la presente guía es difundir el procedimiento de diagnóstico de la EB tal y como se está llevando a cabo en nuestro laboratorio y, así, evitar diagnósticos clínicos subóptimos o incompletos. Las recomendaciones recogidas son fruto de nuestra experiencia de más de 10 años de diagnóstico molecular de EB en España.

Background on Epidermolysis Bullosa

Definition

The term epidermolysis bullosa (EB), often known as butterfly skin, refers to a genetically and clinically heterogeneous group of rare diseases, characterized by muco-cutaneous fragility. The disorder leads to the formation of blisters and erosions that may arise due to friction or even spontaenously.[1,2] Other complications associated with EB are the appearance of hypoplastic lesions of dental enamel; airway, gastrointestinal, and urogenital stenosis or narrowing; pyloric atresia; muscular dystrophy; and cancer.[2–4] Therefore, management of patients with EB requires a multidisciplinary team (for further information, see Guide for Integrated Care of Hereditary Epidermolysis Bullosa published by the Spanish Ministry of Health and Consumer Affairs[5]).

EB affects people of all ethnic origins and both sexes equally. The overall incidence in the United States is estimated to be 1/53 000 and the prevalence to be 1/125 000. Similar estimates have been reported in some European countries, including Spain[6] (1/166 000; www.orpha.net).

EB is classed as an orphan disease; as there is no specific and effective treatment, current treatments aim merely to alleviate symptoms.[7] The scientific community is going to great lengths to offer innovative solutions based on so-called advanced therapies: cell therapy, tissue genetics and engineering, and protein therapy.[8–12]

Main Types of Epidermolysis Bullosa

Four types of EB are defined according to the level of cleavage when a blister develops: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome (KS). In EBS, fragility is detected at an intraepidermal level (and can involve both basal or suprabasal keratinocytes). In JEB, blister formation occurs in the lamina lucida while in DEB it occurs below the lamina densa (in the papillary dermis). In KS, cleavage can occur at any level except in suprabasal layers[2] (Fig. 1).

Pathogenesis

EB is caused by mutations in genes that encode proteins responsible for the integrity and mechanical stability of