Publications du centre de référence des maladies rares de la peau et des muqueuses d'origine génétique - Année 2017

1. Hereditary epidermolysis bullosa: French national guidelines (PNDS) for diagnosis and treatment. Chiaverini C, Bourrat E, Mazereeuw-Hautier J, Hadj-Rabia S, Bodemer C, Lacour JP. Ann Dermatol Venereol. 2017 Jan;144(1):6-35.

   Hereditary epidermolysis bullosa (EB) is a heterogeneous group of rare genetic diseases characterized by fragile skin and/or mucous membrane, and it may be either local or generalized. It is caused by mutations in genes encoding different proteins involved mainly in the structure and function of the dermal-epidermal junction. Nineteen genes have so far been identified. They are classified by level of skin cleavage (from top to bottom) into four groups: EB simplex, junctional EB, dystrophic EB and Kindler syndrome. Clinically suspected diagnosis is confirmed by immunohistochemical examination of a skin biopsy at specialized centres in order to determine the level of cleavage and the deficient protein. This first step may be followed by genetic analysis. The severity of the disease is highly variable, ranging from localized forms with little effect on quality of life to rapidly lethal forms. In generalized severe forms, the extent and chronicity of lesions, as well as mucosal involvement, can lead to systemic complications: malnutrition, pain, joint contractures, chronic inflammation, amyloidosis, cutaneous squamous cell carcinoma. Some specific forms are associated with other cutaneous signs (nail involvement, alopecia, hyperpigmentation, palmoplantar keratoderma) or extracutaneous involvement (muscular dystrophy or pyloric atresia). No curative treatment of EB is available today. EB requires multidisciplinary medical care, nursing, psychological and social management. This is best provided by a specialized network, involving reference centres, centres of expertise and daily caregivers. The goal of treatment is the prevention and treatment of lesions with specific non-adherent dressings and the prevention, detection and treatment of complications. It is essential not to traumatize the skin (bandaging, friction, etc.). Protein, gene or cell replacement therapy, and allogeneic bone marrow, cord blood or pluripotent stem-cell transplantation are currently being assessed. The aim of these French recommendations (national diagnostic and treatment protocol [PNDS]) is to provide healthcare professionals with guidance on the course of EB and on optimal patient management.

2. A stereotypical clinical presentation of childhood linear purpura of the arms: Analysis of six cases. Hosteing S, Uthurriague C, Boralevi F, Mazereeuw-Hautier J. Arch Pediatr. 2017 Jan;24(1):45-51

   Among causes of childhood purpura, other- or self-induced mechanical purpura, such as factitious purpura, needs to be considered. This cause is unfamiliar to pediatricians, usually compromising early diagnosis. We report on the cases of six children, seen between 1998 and 2014 at the Toulouse and Bordeaux Departments of Dermatology, presenting with a stereotypical linear purpura on the arms. All were females, aged 6-14 years. One patient had a psychiatric history, whereas the others were undergoing a stressful time period. All had several relapses and diagnosis was delayed in all. The patients presented with multiple oval or square purpuric macules, forming a discontinuous linear band. Some patients reported functional discomfort such as pain or pruritus. Lesions were always located on the arms and sometimes on other areas of the body. Biological assessments were normal and there was no vasculitis at skin histology. We retained the diagnosis of induced mechanical purpura. Psychological support was offered to four patients. One of them declared that the lesions were induced by classmates using suction. Another child declared that she caused the lesions herself, without explaining the mechanism. Outcome was favorable in five children (one was lost to follow-up), 1-4 years after diagnosis. In conclusion, induced mechanical purpura in

children, although rarely described in the medical literature, must be kept in mind. Investigations should be carried out in cases with uncertain diagnosis. Underlying psychological distress should be sought.

3. KLICK syndrome: recognizable phenotype and hot-spot POMP mutation. Morice-Picard F, Jonca N, Pichery M, Mermin D, Leauté-Labrèze C, Taïeb A, Mazereeuw-Hautier J, Boralevi F. J Eur Acad Dermatol Venereol. 2017 Mar;31(3):e154-e156.

4. Systemic allergic contact dermatitis caused by methyl aminolaevulinate in a patient with keratosis-ichthyosis-deafness syndrome. Al Malki A, Marguery MC, Giordano-Labadie F, Konstantinou MP, Mokeddem L, Lamant L, Paul C, Maza A, Mazereeuw-Hautier J. Contact Dermatitis. 2017 Mar;76(3):190-192.

5. The scalp hair collar and tuft signs: A retrospective multicenter study of 78 patients with a systematic review of the literature. Bessis D, Bigorre M, Malissen N, Captier G, Chiaverini C, Abasq C, Barbarot S, Boccara O, Bourrat E, El Fertit H, Eschard C, Hubiche T, Lacour JP, Leboucq N, Mahé E, Mallet S, Marque M, Martin L, Mazereeuw-Hautier J, Milla N, Phan A, Plantin P, Picot MC, Puzenat E, Rigau V, Vabres P, Fraitag S, Boralevi F; Groupe de Recherche Clinique en Dermatologie Pédiatrique. J Am Acad Dermatol. 2017 Mar;76(3):478-487.

BACKGROUND:

Hair collar sign (HCS) and hair tuft of the scalp (HTS) are cutaneous signs of an underlying neuroectodermal defect, but most available data are based on case reports.

OBJECTIVE:

We sought to define the clinical spectrum of HCS and HTS, clarify the risk for underlying neurovascular anomalies, and provide imaging recommendations.

METHODS:

A 10-year multicenter retrospective and prospective analysis of clinical, radiologic, and histopathologic features of HCS and HTS in pediatric patients was performed.

RESULTS:

Of the 78 patients included in the study, 56 underwent cranial and brain imaging. Twenty-three of the 56 patients (41%) had abnormal findings, including the following: (1) cranial/bone defect (30.4%), with direct communication with the central nervous system in 28.6%; (2) venous malformations (25%); or (3) central nervous system abnormalities (12.5%). Meningeal heterotopia in 34.6% (9/26) was the most common neuroectodermal association. Sinus pericranii, paraganglioma, and combined nevus were also identified.

LIMITATIONS:

The partial retrospective design and predominant recruitment from the dermatology department are limitations of this study.

CONCLUSIONS:

Infants with HCS or HTS are at high risk for underlying neurovascular anomalies. Magnetic resonance imaging scans should be performed in order to refer the infant to the appropriate specialist for management

6. Extensive Post-zygotic Mosaicism of KRT1 or KRT10 Mutation Mimicking Classical Epider-molytic Ichthyosis.Severino-Freire M, Jonca N, Pichery M, Tournier E, Chassaing N, Mazereeuw-Hautier J.Acta Derm Venereol. 2017 Mar 10;97(3):387-388.

7. Special Considerations in Children with Vitiligo. Taïeb A, Seneschal J, Mazereeuw-Hautier J. Dermatol Clin. 2017 Apr;35(2):229-233.

   Childhood vitiligo differs from adult-onset vitiligo for several features including increased incidence of the segmental variant, higher prevalence of halo nevi, and more common family history for autoimmune diseases and atopic diathesis. The major differential diagnoses are the postinflammatory hypomelanoses for nonsegmental vitiligo and nevus depigmentosus for segmental vitiligo. From a therapeutic standpoint, early awareness of the diagnosis seems to correlate with a good treatment outcome in this age group.

8. PNPLA1 defects in patients with autosomal recessive congenital ichthyosis and KO mice sustain PNPLA1 irreplaceable function in epidermal omega-O-acylceramide synthesis and skin permeability barrier. Pichery M, Huchenq A, Sandhoff R, Severino-Freire M, Zaafouri S, Opálka L, Levade T, Soldan V, Bertrand-Michel J, Lhuillier E, Serre G, Maruani A, Mazereeuw-Hautier J, Jonca N. Hum Mol Genet. 2017 May 15;26(10):1787-1800.

   Autosomal recessive congenital ichthyosis (ARCI) is a heterogeneous group of monogenic genodermatoses that encompasses non-syndromic disorders of keratinization. The pathophysiology of ARCI has been linked to a disturbance in epidermal lipid metabolism that impaired the stratum corneum function, leading to permeability barrier defects. Functional characterization of some genes involved in ARCI contributed to the identification of molecular actors involved in epidermal lipid synthesis, transport or processing. Recently, PNPLA1 has been identified as a gene causing ARCI. While other members of PNPLA family are key elements in lipid metabolism, the function of PNPLA1 remained unclear. We identified 5 novel PNPLA1 mutations in ARCI patients, mainly localized in the putative active enzymatic domain of PNPLA1. To investigate Pnpla1 biological role, we analysed Pnpla1-deficient mice. KO mice died soon after birth from severe epidermal permeability defects. Pnpla1-deficient skin presented an important impairment in the composition and organization of the epidermal lipids. Quantification of epidermal ceramide species highlighted a blockade in the production

of ω-O-acylceramides with a concomitant accumulation of their precursors in the KO. The virtually loss of ω-O-acylceramides in the stratum corneum was linked to a defective lipid coverage of the resistant pericellular shell encapsulating corneocytes, the so-called cornified envelope, and most probably disorganized the extracellular lipid matrix. Finally, these defects in ω-O-acylceramides synthesis and cornified envelope formation were also evidenced in the stratum corneum from PNPLA1-mutated patients. Overall, our data support that PNPLA1/Pnpla1 is a key player in the formation of ω-O-acylceramide, a crucial process for the epidermal permeability barrier function.

9. Pain and quality of life evaluation in patients with localized epidermolysis bullosa simplex. Brun J, Chiaverini C, Devos C, Leclerc-Mercier S, Mazereeuw J, Bourrat E, Maruani A, Mallet S, Abasq C, Phan A, Vabres P, Martin L, Bodemer C, Lagrange S, Lacour JP; Research Group of the French Society of Pediatric Dermatology. Orphanet J Rare Dis. 2017 Jun 28;12(1):119.

BACKGROUND:

A localized form of epidermolysis bullosa simplex (EBS-l) is considered one of the mildest forms of epidermolysis bullosa (EB), with blisters limited to the palms and soles. However, these lesions can be very painful. The aim of the study was to characterize pain in patients with EBS-l and evaluate its impact on quality of life (QoL). Patients were contacted via the Research Group of the French Society of Pediatric Dermatology and the association of EB patients (DEBRA France). One investigator used a standardized questionnaire that included validated scales for pain and QoL for a telephone interview.

RESULTS:

We included 57 patients (27 children). All patients had pain: the mean pain on a 10-mm visual analog scale was >5 for most adults (90%) and children ≥8 years old (94%) when blisters were present and for most adults (73%) and about half of the children ≥ age 8 (53%) during dressing changes. Similar results were found for younger patients. Overall, 75% of patients had neuropathic pain; for 55% of children and 73% of adults, the pain had a moderate to severe impact on QOL. Only seven patients used premedication before changing dressings and seven regularly used oral treatment for chronic pain. A total of 21% and 23% of patients used non-steroidal anti-inflammatory drugs and grade 2 analgesics, respectively. These treatments were not effective for neuropathic pain. Six patients tried 5% lidocaine plasters on their feet, with good efficacy.

CONCLUSIONS:

EBS-l patients have frequent and severe pain with neuropathic characteristics. This pain is undertreated and affects QoL.

KEYWORDS:

Localized epidermolysis bullosa simplex; Neuropathic pain; Quality of life

10. Mosaic Focal Dermal Hypoplasia (Goltz Syndrome) in Two Female Patients. Severino-Freire M, Maza A, Lombardi MP, Tournier E, Chassaing N, Mazereeuw-Hautier J. Acta Derm Venereol. 2017 Jul 6;97(7):853-854.

11. Molecular diagnosis of PIK3CA-related overgrowth spectrum (PROS) in 162 patients and recommendations for genetic testing. Kuentz P, St-Onge J, Duffourd Y, Courcet JB, Carmignac V, Jouan T, Sorlin A, Abasq-Thomas C, Albuisson J, Amiel J, Amram D, Arpin S, Attie-Bitach T, Bahi-Buisson N, Barbarot S, Baujat G, Bessis D, Boccara O, Bonnière M, Boute O, Bursztejn AC, Chiaverini C, Cormier-Daire V, Coubes C, Delobel B, Edery P, Chehadeh SE, Francannet C, Geneviève D, Goldenberg A, Haye D, Isidor B, Jacquemont ML, Khau Van Kien P, Lacombe D, Martin L, Martinovic J, Maruani A, Mathieu-Dramard M, Mazereeuw-Hautier J, Michot C, Mignot C, Miquel J, Morice-Picard F, Petit F, Phan A, Rossi M, Touraine R, Verloes A, Vincent M, Vincent-Delorme C, Whalen S, Willems M, Marle N, Lehalle D, Thevenon J, Thauvin-Robinet C, Hadj-Rabia S, Faivre L, Vabres P, Rivière JB. Genet Med. 2017 Sep;19(9):989-997.

PURPOSE:

Postzygotic activating mutations of PIK3CA cause a wide range of mosaic disorders collectively referred to as PIK3CA-related overgrowth spectrum (PROS). We describe the diagnostic yield and characteristics of PIK3CA sequencing in PROS.

METHODS:

We performed ultradeep next-generation sequencing (NGS) of PIK3CA in various tissues from 162 patients referred to our clinical laboratory and assessed diagnostic yield by phenotype and tissue tested.

RESULTS:

We identified disease-causing mutations in 66.7% (108/162) of patients, with mutant allele levels as low as 1%. The diagnostic rate was higher (74%) in syndromic than in isolated cases (35.5%; $P = 9.03 \times 10^{-5}$). We identified 40 different mutations and found strong oncogenic mutations more frequently in patients without brain overgrowth (50.6%) than in those with brain overgrowth (15.2%; P = 0.00055). Mutant allele levels were higher in skin and overgrown tissues than in blood and buccal samples ($P = 3.9 \times 10^{-25}$), regardless of the phenotype.

CONCLUSION:

Our data demonstrate the value of ultradeep NGS for molecular diagnosis of PROS, highlight its substantial allelic heterogeneity, and confirm that optimal diagnosis requires fresh skin or surgical samples from affected regions. Our findings may be of value in guiding future recommendations for genetic testing in PROS and other mosaic conditions.Genet Med advance online publication 02 February 2017.

12. Germline Loss-of-Function Mutations in EPHB4 Cause a Second Form of Capillary Malformation-Arteriovenous Malformation (CM-AVM2)

Deregulating RAS-MAPK Signaling.Amyere M, Revencu N, Helaers R, Pairet E, Baselga E, Cordisco M, Chung W, Dubois J, Lacour JP, Martorell L, Mazereeuw-Hautier J, Pyeritz RE, Amor DJ, Bisdorff A, Blei F, Bombei H, Dompmartin A, Brooks D, Dupont J, González-Enseñat MA, Frieden I, Gérard M, Kvarnung M, Hanson-Kahn AK, Hudgins L, Léauté-Labrèze C, McCuaig C, Metry D, Parent P, Paul C, Petit F, Phan A, Quere I, Salhi A, Turner A, Vabres P, Vicente A, Wargon O, Watanabe S, Weibel L, Wilson A, Willing M, Mulliken JB, Boon LM, Vikkula M. Circulation. 2017 Sep 12;136(11):1037-1048.

BACKGROUND:

Most arteriovenous malformations (AVMs) are localized and occur sporadically. However, they also can be multifocal in autosomal-dominant disorders, such as hereditary hemorrhagic telangiectasia and capillary malformation (CM)-AVM. Previously, we identified RASA1 mutations in 50% of patients with CM-AVM. Herein we studied non-RASA1 patients to further elucidate the pathogenicity of CMs and AVMs.

METHODS:

We conducted a genome-wide linkage study on a CM-AVM family. Whole-exome sequencing was also performed on 9 unrelated CM-AVM families. We identified a candidate gene and screened it in a large series of patients. The influence of several missense variants on protein function was also studied in vitro.

RESULTS:

We found evidence for linkage in 2 loci. Whole-exome sequencing data unraveled 4 distinct damaging variants in EPHB4 in 5 families that cosegregated with CM-AVM. Overall, screening of EPHB4 detected 47 distinct mutations in 54 index patients: 27 led to a premature stop codon or splice-site alteration, suggesting loss of function. The other 20 are nonsynonymous variants that result in amino acid substitutions. In vitro expression of several mutations confirmed loss of function of EPHB4. The clinical features included multifocal CMs, telangiectasias, and AVMs.

CONCLUSIONS:

We found EPHB4 mutations in patients with multifocal CMs associated with AVMs. The phenotype, CM-AVM2, mimics RASA1-related CM-AVM1 and also hereditary hemorrhagic telangiectasia. RASA1-encoded p120RASGAP is a direct effector of EPHB4. Our data highlight the pathogenetic importance of this interaction and indicts EPHB4-RAS-ERK signaling pathway as a major cause for AVMs.

13. Mutations in ACTRT1 and its enhancer RNA elements lead to aberrant activation of Hedgehog signaling in inherited and sporadic basal cell carcinomas. Bal E, Park HS, Belaid-Choucair Z, Kayserili H, Naville M, Madrange M, Chiticariu E, Hadj-Rabia S, Cagnard N, Kuonen F, Bachmann D, Huber M, Le Gall C, Côté F, Hanein S, Rosti RÖ, Aslanger AD, Waisfisz Q, Bodemer C, Hermine O, Morice-Picard F, Labeille B,

Caux F, Mazereeuw-Hautier J, Philip N, Levy N, Taieb A, Avril MF, Headon DJ, Gyapay G, Magnaldo T, Fraitag S, Crollius HR, Vabres P, Hohl D, Munnich A, Smahi A. Nat Med. 2017 Oct;23(10):1226-1233.

Basal cell carcinoma (BCC), the most common human cancer, results from aberrant activation of the Hedgehog signaling pathway. Although most cases of BCC are sporadic, some forms are inherited, such as Bazex-Dupré-Christol syndrome (BDCS)-a cancer-prone genodermatosis with an X-linked, dominant inheritance pattern. We have identified mutations in the ACTRT1 gene, which encodes actin-related protein T1 (ARP-T1), in two of the six families with BDCS that were examined in this study. High-throughput sequencing in the four remaining families identified germline mutations in noncoding sequences surrounding ACTRT1. These mutations were located in transcribed sequences encoding enhancer RNAs (eRNAs) and were shown to impair enhancer activity and ACTRT1 expression. ARP-T1 was found to directly bind to the GLI1 promoter, thus inhibiting GLI1 expression, and loss of ARP-T1 led to activation of the Hedgehog pathway in individuals with BDCS. Moreover, exogenous expression of ACTRT1 reduced the in vitro and in vivo proliferation rates of cell lines with aberrant activation of the Hedgehog signaling pathway. In summary, our study identifies a disease mechanism in BCC involving mutations in regulatory noncoding elements and uncovers the tumor-suppressor properties of ACTRT1.