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Epileptologie

GENETIK

Conséquences pratiques du diagnostic génétique des épilepsies mendéliennes

Genetics in Epilepsy "plus": Focus on the Role of CGH Array

Seizures and Epilepsies due to Channelopathies and Neurotransmitter Receptor Dysfunction: A Parallel Between Genetic and Immune Aspects

Genetic Testing for Epilepsy Surgery

Somatic Mosaicism in Epilepsy with Focal Cortical Dysplasia

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1. Privitera M., Efficacy of Levetiracetam: A Review of Three Pivotal Clinical Trials; Epilepsia, 42 (Suppl. 4):31-35; 2001

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Richtlinien für die Autoren

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Alle Manuskripte sind inklusive Abbildungen und Tabellen in dreifacher Ausführung einzureichen. Bevorzugt wird eine elektronische Manuskripteinreichung per e-mail (Textverarbeitung: MS Word).

PD Dr Fabienne Picard, PD Dr Christian M. Korff

Chers Collègues,

Des avancées majeures se sont poursuivies ces dernières années dans le domaine de la génétique des épilepsies, avec de plus en plus de conséquences thérapeutiques et une implication dans la compréhension de certains mécanismes de genèse de l'épilepsie. Depuis le dernier numéro sur le même thème (Epileptologie 2015), nous sommes en effet confrontés à une explosion de nouveaux gènes identifiés, liée à une amélioration technique des méthodes d'analyse, un accès facilité et meilleur marché au séquençage d'exome. Une avancée dans la compréhension de la physiopathologie des dysplasies corticales focales, grandes pourvoyeuses d'épilepsies focales pharmacorésistantes est également constatée. Un numéro faisant part de ces nouveautés nous paraissait indispensable à ce stade. Nous avons souhaité mettre l'accent sur certains aspects potentiellement utiles dans la pratique quotidienne des cliniciens, en particulier sur le plan thérapeutique.

Le but de ce numéro est donc d'apporter un nouvel éclairage sur les découvertes récentes et les progrès en génétique des épilepsies effectués depuis 2015, en insistant sur certaines implications pratiques.

Gaëtan Lesca, du service de Génétique des Hospices Civils de Lyon (Bron, France), en association avec Christian Korff, de l'Unité de Neuropédiatrie des HUG (Genève) propose une mise à jour des gènes impliqués dans des formes mendéliennes d'épilepsie et décrit les conséquences thérapeutiques de l'identification de certaines mutations.

Sarah Bürki, du département de neuropédiatrie de l'Inselspital de Bern (Suisse) nous décrit le rôle de l'analyse CGH array dans l'épilepsie "plus", c'est-à-dire une épilepsie associée à au moins un des troubles neurologiques ou psychiatriques suivants : retard du développement, déficit intellectuel, autisme ou anomalies congénitales multiples.

Adoptant la possibilité désormais offerte aux auteurs de ce Journal de publier des textes au format moins classique que les traditionnels articles de revue, nous soussignés proposons le résumé d'un article que nous avons publié avec Agustina Lascano en 2016 portant sur le parallèle entre les étiologies génétiques et auto-immunes de certaines épilepsies liées à des canalopathies et des dysfonctions d'autres récepteurs de neurotransmetteurs. Ce résumé inclut une mise à jour de l'article.

Bobby Koeleman et son équipe du département de neuropédiatrie du « Brain Center Rudolf Magnus » de la Faculté de médecine d'Utrecht (Pays-Bas) nous apporte une revue inédite de l'implication des découvertes génétiques chez des patients souffrant d'épilepsie dans le cadre de la chirurgie de l'épilepsie.

Enfin, Sara Baldassari et Stéphanie Baulac de l'Institut du Cerveau et de la Moelle épinière de Paris proposent une revue sur le sujet des mutations somatiques identifiées dans les épilepsies avec dysplasies corticales focales, en complément aux mutations germinales identifiées depuis 2013 dans les gènes de la voie GATOR1.

Nous remercions chaleureusement les auteurs de ce numéro, pour leur implication et la qualité de leurs articles, et vous souhaitons une excellente lecture !

Fabienne Picard

Christian M. Korff

PD Dr. Fabienne Picard, PD Dr. Christian M. Korff

Verehrte Kolleginnen und Kollegen

In den letzten Jahren gab es in der Epilepsiegenetik grosse Fortschritte zu verzeichnen. Diese zeitigen immer mehr Auswirkungen in der Therapie und wirken sich auch im Verständnis bestimmter Entstehungsprozesse aus. Seit der letzten Ausgabe zu diesem Thema (Epileptologie 2015) erleben wir in der Tat einen explosionsartigen Anstieg neu identifizierter Gene, im Verbund mit einer verbesserten Analysetechnik und eines leichteren und kostengünstigeren Zugangs zur Exom-Sequenzierung. Fortschritte gab es auch im Verständnis der Physiopathologie fokaler kortikaler Dysplasien, die als signifikante Ursache für fokale pharmakoresistente Epilepsien stehen. Angesichts dieser Entwicklungen erschien es uns daher angebracht, in dieser Ausgabe darüber zu berichten. Dabei wollten wir unser Hauptaugenmerk auf bestimmte Aspekte richten, die – insbesondere in der Therapie – vor allem im praktischen Klinikalltag potenziell relevant sind.

Es ist unser Bestreben, jüngste Entdeckungen und Fortschritte in der Epilepsiegenetik seit 2015 intensiver zu beleuchten und vor allem vor dem Hintergrund praktischer Implikationen darzustellen.

Gaëtan Lesca von der Humangenetik der Hospices Civils de Lyon (Bron, Frankreich) befasst sich zusammen mit Christian Korff von der Neuropädiatrie der HUG (Genf) mit einer Aktualisierung der in monogenetischen Epilepsien implizierten Gene und beschreibt die therapeutischen Folgen, die sich durch die Identifizierung bestimmter Mutationen ergeben.

Sarah Bürki von der Neuropädiatrie des Inselspitals in Bern beschreibt uns die Rolle der Array-CGH-Untersuchung bei GEFA+, d. h. bei einer generalisierten Epilepsie mit Fieberanfällen, bei der zumindest eine der nachfolgenden neurologischen oder psychiatrischen Störungen auftritt: Entwicklungsstörung, intellektuelle Retardierung, Autismus oder multiple kongenitale Anomalien.

Künftig können die Autoren dieser Fachzeitschrift Texte nicht nur als klassische Fachartikel veröffentlichen, sondern auch in weniger traditionellen Formaten. Vor diesem Hintergrund bieten die Unterzeichneten die Zusammenfassung eines 2016 zusammen mit Agustina Lascano publizierten Artikels zu den Parallelen zwischen den genetischen und autoimmunen Ätiologien bestimmter Epilepsien im Verbund mit Kanalopathien und Dysfunktionen anderer Neurotransmitter-Rezeptoren. Das Resumé enthält eine aktualisierte Version des Artikels.

Bobby Koeleman und sein Team von der Neuropädiatrie des «Brain Center Rudolf Magnus» der medizinischen Fakultät der Universität Utrecht (Niederlande) bieten uns eine bislang unveröffentlichte Darstellung der Implikationen, die sich aus genetischen Entdeckungen bei Epileptikern im Rahmen der Epilepsiechirurgie ergeben.

Und last but not least geben uns Sara Baldassari und Stéphanie Baulac vom Institut du Cerveau et de la Moelle épinière in Paris einen Überblick über die somatischen Mutationen in Epilepsien mit fokalen kortikalen Dysplasien, ergänzend zu den seit 2013 in den Genen des Signalwegs GATOR1 identifizierten Keimbahnmutationen.

Wir danken allen Autoren dieser Ausgabe herzlich für ihr Engagement und die Qualität ihrer Texte und wünschen Ihnen eine angenehme Lektüre!

Fabienne Picard

Christian M. Korff

PD Dr. Fabienne Picard, PD Dr. Christian M. Korff

Dear Colleagues,

Major advances have continued to be made in recent years in the area of the genetics of epilepsy with an increasing number of treatment-related consequences and an implication for how we understand certain mechanisms of epileptogenesis. As a matter of fact, since the last issue on the same topic (Epileptologie 2015), we have been confronted with an explosion of newly identified genes, associated with a technical improvement in analysis methods, easier and cheaper access to exome sequencing. We have also confirmed an advance in our understanding of the physiopathology of focal cortical dysplasia, a significant cause of drug-resistant focal epilepsy. An issue announcing these new discoveries seemed essential to us at this stage. We wanted to highlight certain aspects, which could potentially be useful in daily clinical practice, particularly in terms of treatment.

Therefore, the aim of this issue is to shed more light on recent discoveries and progress made since 2015 in the genetics of epilepsy, underlining certain practical implications.

Gaëtan Lesca, from the Genetics Department of the Hospices Civils de Lyon (Bron, France), in association with Christian Korff, from the Paediatric Neurology Unit of Geneva University Hospitals, proposes updating the genes involved in Mendelian forms of epilepsy and described the treatment-related consequences of identifying certain mutations.

Sarah Bürki, from the Paediatric Neurology Department of the Inselspital in Bern (Switzerland) describes for us the role of array CGH analysis in "plus" epilepsy, i.e. a form of epilepsy associated with at least one of the following neurological or psychiatric disorders: developmental delay, intelligence deficit, autism or multiple congenital anomalies.

Making it possible from now on for authors of this Journal to publish texts in a less conventional format than traditional review articles, we, the undersigned, submit the extract of an article we published with Agustina Lascano in 2016 concerning the parallel between the genetic and autoimmune aetiologies of certain forms of epilepsy associated with channelopathies and dysfunctions of other neurotransmitter receptors. This extract includes an update to the article.

Bobby Koeleman and his team at the Paediatric Neurology Department of the "Rudolf Magnus Brain Center" at the Medical Faculty of the University of Utrecht (Netherlands) contribute a new review of the implication of genetic discoveries in epilepsy sufferers as part of epilepsy-related surgery.

Finally, Sara Baldassari and Stéphanie Baulac from the Brain & Spine Institute in Paris, submit a review on the subject of somatic mutations identified in forms of epilepsy with focal cortical dysplasia, in addition to germline mutations identified since 2013 in the genes of the GATOR1 pathway.

Thank you very much to the authors of this issue for their involvement and the quality of their articles. We hope you enjoy reading the issue!

Fabienne Picard

Christian M. Korff

Conséquences pratiques du diagnostic génétique des épilepsies mendéliennes

Gaëtan Lesca [1,2,3,4] et Christian M. Korff [4,5]

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Résumé

L'évolution rapide des technologies de séquençage a permis l'identification de nombreux gènes responsables de formes mendéliennes d'épilepsie et de confirmer la très grande hétérogénéité génétique de certains syndromes électro-cliniques, particulièrement marquée dans le cas des encéphalopathies épileptiques. Ces nouvelles données ont permis de faire évoluer la classification internationale des épilepsies et sont maintenant transférées dans la pratique clinique quotidienne, permettant d'analyser de nombreux gènes de façon simultanée et de porter un diagnostic étiologique chez un nombre croissant de patient. L'identification de la mutation causale d'une forme mendélienne d'épilepsie représente une étape indispensable pour prodiguer un conseil génétique fiable et peut avoir des conséquences au niveau thérapeutique. Le regroupement de patients porteurs d'une forme donnée d'épilepsie mendélienne rare autours d'équipes médico-scientifiques pratiquant une recherche de pointe est une condition indispensable au développement d'une médecine de précision, permettant de cibler le mécanisme pathologique au niveau moléculaire.

Epileptologie 2018; 35: 4 – 9

Mots clés : Génétique, épilepsie, séquençage à haut débit, conseil génétique, médecine personnalisée

Practical consequences of the genetic diagnosis of Mendelian epilepsies

The rapid evolution of sequencing technologies has made it possible to identify numerous genes responsible for Mendelian forms of epilepsy and to confirm the high level of genetic heterogeneity of many electro-clinical syndromes, which is particularly marked in the case of epileptic encephalopathies. This new genetic data influenced the evolution of the international classification of the epilepsies and is now transferred to daily clinical practice, allowing the simultaneous analysis of high numbers of genes, and achieving an etiological diagnosis in a growing number of patients. Identifying the causal mutation of a Mendelian form of epilepsy is a mandatory step to provide accurate genetic counseling and may have therapeutic consequences. Gathering patients with a given form of rare Mendelian epilepsy and medical-scientific teams conducting cutting-edge research is a prerequisite for the development of precision medicine, which aims at targeting the pathological mechanism at the molecular level.

Key words: Genetics, epilepsy, high-throughput sequencing, genetic counseling, personalized medicine

Praktische Konsequenzen der genetischen Diagnose Mendelscher Epilepsien

Die rasante Entwicklung der Sequenzierungstechnologien hat die Identifizierung zahlreicher für mendelsche Epilepsieformen verantwortlicher Gene und die Bestätigung der enormen genetischen Heterogenität bestimmter elektroklinischer Syndrome, die bei epileptischen Enzephalopathien besonders ausgeprägt ist, ermöglicht. Diese neuen Daten führten zur Weiterent-

wicklung der internationalen Klassifikation der Epilepsien und finden nun Eingang in die tägliche klinische Praxis, wo sie bei einer zunehmenden Zahl von Patienten die simultane Multigenanalyse und eine ätiologische Diagnosestellung gestatten. Die Feststellung der ursächlichen Mutation einer mendelschen Epilepsie ist ein unverzichtbarer Schritt im Rahmen einer fundierten genetischen Beratung und kann einen Einfluss auf das therapeutische Vorgehen haben. Patienten mit bestimmten seltenen mendelschen Epilepsien mit Teams aus der medizinisch-wissenschaftlichen Spitzenforschung zusammenzubringen, ist eine unabdingbare Voraussetzung für die Entwicklung einer Präzisionsmedizin zur Aufklärung des pathologischen Mechanismus auf Molekülebene.

Schlüsselwörter: Genetik, Epilepsie, Hochdurchsatz-Sequenzierung, genetische Beratung, personalisierte Medizin

Introduction

L'évolution des technologies d'analyse génétique a été abordée dans un précédent article publié dans ce même journal [1]. Le séquençage à haut débit, qui a d'abord été un outil puissant pour l'identification des gènes impliqués dans les maladies humaines, et qui a été ensuite transféré au diagnostic, permet d'étudier des panels de plusieurs dizaines ou centaines de gènes et même l'exome, c'est-à-dire l'ensemble des régions codantes des gènes humains. Dans cet article, nous allons aborder les conséquences pratiques de la confirmation moléculaire d'une forme mendélienne d'épilepsie.

Evolution récente des connaissances des bases génétiques des épilepsies

Les premiers gènes impliqués dans les épilepsies mendéliennes ont été identifiés grâce aux études de liaison génétiques, qui étaient basées sur des grandes familles dont les membres présentaient des syndromes électro-cliniques bien caractérisés. Le premier gène d'épilepsie monogénique à avoir été identifié est *CHRNA4*, qui code pour une sous-unité du récepteur muscarinique à l'acétylcholine, dont certains variants causent une forme d'épilepsie frontale nocturne autosomique dominante (« autosomal dominant nocturnal frontal lobe epilepsy », récemment rebaptisée « sleep-related hypermotor epilepsy ») [2]. D'autres gènes ont été identifiés de cette manière, la plupart codant pour des canaux ioniques, donnant naissance au concept de canalopathie. Cependant, c'est l'évolution considérable des technologies, à la fin des années 2000, qui a permis une accélération exponentielle des découvertes, en permettant l'identification de formes d'épilepsies causées par des mutations de novo, comme c'est fréquemment le cas des encéphalopathies épileptiques, et de faciliter l'étude des formes autosomiques récessives, même à partir d'un nombre limité de familles. On connait à l'heure actuelle plus d'une centaine de gènes dont les mutations peuvent être tenues pour responsables de différentes formes d'épilepsies mendéliennes **(Tableau 1)**. L'hétérogénéité est considérable en ce qui concerne les encéphalopathies épileptiques et en particulier celles qui débutent au cours des premiers jours ou de la première année de vie. Ainsi, alors que les bases génétiques du syndrome de West demeuraient encore obscures il y a quelques années seulement, en dehors des causes classiques comme la trisomie 21 ou la sclérose tubéreuse de Bourneville, on a maintenant identifié plus d'une cinquantaine de gènes dont les mutations peuvent causer ce syndrome, d'autres étant encore régulièrement découverts.

Sur le plan des mécanismes physiopathologiques, ces nombreuses découvertes génétiques ont permis de confirmer le concept de canalopathie, puisqu'environ un tiers des gènes responsables d'épilepsies mendéliennes codent pour des canaux ioniques. Ces travaux ont également montré la très grande diversité des mécanismes impliqués, puisque d'autres gènes codent pour des protéines synaptiques, des récepteurs, des transporteurs, des facteurs de transcription, des protéines impliquées dans le remodelage de la chromatine, dans le métabolisme de nombreuses molécules et neurotransmetteurs, etc..

Initialement utilisées en recherche, la cytogénétique moléculaire et le séquençage à haut débit ont maintenant remplacé, dans la plupart des indications, les outils traditionnels comme le séquençage par la méthode de Sanger ou le caryotype. Le séquençage à haut débit permet d'étudier de nombreux gènes de façon simultanée, souvent pour le même coût que l'étude d'un ou de quelques gènes par la méthode de Sanger.

Conséquences sur la classification des épilepsies

L'évolution très rapide de la connaissance des bases génétiques des épilepsies a eu des conséquences majeures sur la classification proposée par la ligue internationale contre l'épilepsie (ILAE, International League Against Epilepsy). Depuis 1989, celle-ci distinguait trois grandes catégories étiologiques, caractérisées à l'aide des données électro-cliniques et de l'imagerie cérébrale : idiopathique, cryptogénique et symptomatique. Il a été proposé en 2010 de remplacer les termes d'idiopathique par génétique et de cryptogénique par structural/métabolique. Ces modifications introduisaient toutefois plusieurs niveaux de confusion. Le premier concernait la notion même de facteur génétique. En effet, le plus souvent, les épilepsies idiopathiques ne suivent pas un mode d'hérédité mendélien mais plutôt multifactoriel, dans lequel les facteurs génétiques exercent chacun un effet modéré et interagissent entre eux et avec des

Tableau 1: Liste (non exhaustive) des gènes impliqués dans des formes mendéliennes d'épilepsie. Les gènes figurés en gras sont ceux qui sont les plus fréquemment impliqués.

Syndrome épileptique	Gène
Epilepsie familiale néonatale bénigne	*KCNQ2, KCNQ3*
Epilepsie familiale néonatale infantile précoce	*SCN2A*
Epilepsie familiale infantile bénigne	*PRRT2, SLC9A1*
Epilepsies génétiques avec crises fébriles plus	*SCN1A, PCDH19, SCN1B, GABRG2, GABRD, STX1B*
Syndrome de Dravet	*SCN1A, PCDH19, SCN1B, HCN1, CHD2, KCNA2, GABRA1, GABRG2, GABRB3, STX8P1*
Rigidité avec crises multifocales et déficit intellectuel sévère	*BRAT2*
Encéphalopathie épileptique précoce	*STXBP1, KCNQ2, AARS, ALDH7A1, ARHGEF9, ARHGEF15, ARX, BRAT1, CASK, CDKL5, CHD2, DNM1, FOXG1, GABRA1, GABRB3, GNAO1, GNB1, GRIN1, GRIN2A, GRIN2B, HCN1, KCNA2, KCNB1, KCNT1, MECP2, MED12, MEF2C, NEDD4L, PIGA, PLCB1, PNKP, PNPO, SCN1A, SCN2A, SCN8A, SIK1, SLC12A5, SLC13A5, SLC25A22, SLC35A2, SPTAN1, ST3GAL3, ST3GAL5, STX1B, TBC1D24, UBA5, WDR45*
Spasmes infantiles / syndrome de West	*CDKL5, STXBP1, ALG13, ARX, CHD2, DLG3, DNM1, DOCK7, FOXG1, GABRA1, GABRB3, GABRG2, GNAO1, GRIN1, GRIN2A, GRIN2B, KCNQ3, KCNT1, MEF2C, NEDD4L, PIGA, PLCB1, SCN1A, SCN2A, SCN8A, SETBP1, SLC25A22, SLC35A2, SPTAN1, ST3GAL3, ST3GAL5, TBC1D24, TCF4, WWOX, WDR45*
Epilepsie partielle migrante du nourrisson	*KCNT1, PLCB1, PNKP, SCN1A, SCN2A, SCN8A, SLC12A5*
Epilepsie familiale myoclonique précoce	*TBC1D24*
Encéphalopathie épileptique infantile	*ATP1A3, CHD2, DNM1, DYRK1A, GABBR2, GABRB2, GABRB3, GRIN2A, KCNA2, KCNC2, PNPO, PNKP, PIGA, PIGN, PIGQ, QARS, RARS, SLC6A8, SYNGAP1, TBC1D24, UBA5, WWOX*
SLEAHML syndrome	*KCNJ10*
Absences myocloniques	*SLC2A1*
Epilepsie faciale avec soins oraux continus et sommeil	*GRIN2A*
Epilepsie myoclonique atonique	*SLC6A1, SLC2A1, SYNGAP1, GABRB3, KCNA2, GABRA1, GABRG2, SCN1A*
Epilepsie généralisée et dyskinésies paroxystiques	*KCNMA1*
Syndrome de Lennox-Gastaut	*ALG13, CACNA1A, CDKL5, CHD2, DNM1, FLNA, GABRB2, GRIN2B, HIVEP2, KCNB1, KCNC2, SCN1A, SCN2A, Xq28*
Epilepsies myoclonotoniques progressives	*CSTB, EPM2A, NHLRC1, CERS1, GOSR2, KCNC1, LAMP2, PRDM8, SCARB2, PRICKLE1, ZFYVE26, Amphiphysine, GBA (Gaucher), SERPINI1, DRPLA, NAF (Goodspeed), SCARB2*
Epilepsie temporale latérale autosomique dominante	*LGI1, RELN, CNTNAP2, DEPDC5, SCN1A*
Epilepsie focale autosomique dominante	*CHRNA4, CHRNB2, CHRNA2, DEPDC5, GABRA1, NPRL3, KCNT1*
Epilepsie familiale focale à foyer variable	*DEPDC5, NPRL2, NPRL3*

facteurs environnementaux. Ces facteurs de prédisposition génétique sont encore mal compris et exercent de toute façon un effet modeste, contrairement aux mutations responsables des épilepsies mendéliennes. Le deuxième niveau de confusion était lié à la mise sur le même plan des facteurs étiologiques et pronostiques, les épilepsies idiopathiques étant considérés comme ayant globalement un pronostic moins sévère. Or, l'utilisation du terme « génétique » avec cette signification pronostique a créé une ambiguïté puisque de nombreuses formes d'encéphalopathies épileptiques développementales ou d'épilepsies associées à des troubles cognitifs sévères sont précisément causées par des mutations génétiques. La version récemment révisée de cette classification distingue différents niveaux de description : sémiologique, syndromique, radiologique et étiologique, plaçant ainsi plus clairement les données génétiques dans la catégorie étiologique [3]. Cette évolution montre aussi que désormais, les tests génétiques sont entrés dans la démarche diagnostique quotidienne des épilepsies, comme l'avaient fait auparavant l'EEG puis l'imagerie cérébrale, en apportant un nouveau niveau de description.

Conséquences du diagnostic génétique pour le patient et sa famille

L'établissement d'un diagnostic de certitude

Outre la contribution du test génétique à la caractérisation étiologique de certains syndromes épileptiques, l'identification de la cause moléculaire d'une épilepsie mendélienne est une étape importante pour les patients et leurs familles. Il peut être la conclusion d'une véritable odyssée diagnostique en permettant de mettre fin aux investigations répétées, coûteuses et parfois invasives, comme les ponctions lombaires ou les biopsies, et parfois en évitant une intervention chirurgicale dont l'efficacité pourrait être limitée.

Des informations à visée pronostique

Un diagnostic établi précocement peut aussi avoir un intérêt en termes pronostiques. Dans le cas des épilepsies débutant dans les premiers jours ou semaines de vie, la mise en évidence d'une mutation du gène *PRRT2* ou d'une mutation du gène *KCNQ2* conduisant à une perte de fonction, seront plutôt en faveur d'un pronostic favorable. Les données pronostiques ont encore un impact limité parce que trop peu de variants identifiés chez les patients ont été suivis d'études fonctionnelles. Ce type d'études, réalisé sur des modèles cellulaires ou animaux ne peut être effectué que dans le cadre de collaborations internationales permettant de regrouper les données des patients ayant bénéficié d'un diagnostic génétique autour d'équipes pratiquant une recherche de haut niveau.

Le conseil génétique

L'une des conséquences pratiques du diagnostic moléculaire est la possibilité d'apporter un conseil génétique fiable. A un syndrome électrochimique donné peuvent correspondre plusieurs modes de transmission. Par exemple, le syndrome de West peut être causé par des mutations du gène *AP3B2*, de transmission autosomique récessive, du gène *ARX*, situé sur le chromosome X ou par une mutation de novo du gène *STXBP1*. Evidemment, les conséquences en termes de risque de récurrence familiale ne sont pas du tout les mêmes. Les options pour les couples à risque de récurrence d'une épilepsie monogénique ou pour les apparentés potentiellement conducteurs, telles que le diagnostic prénatal ou préimplantatoire, ne sont possibles que si la mutation pathogène a été identifiée chez le cas index. La mise en évidence d'une mutation de novo chez un patient limite le risque de transmission dans la famille. Toutefois, le risque pour un futur enfant du couple parental (ou de chacun des parents s'ils sont séparés) ne peut pas être considéré comme nul. Cela est lié à l'impossibilité d'exclure une mosaïque germinale, qui correspond au fait que seule une petite proportion de cellules sont porteuses de la mutation, celles-ci étant parfois limitées aux gonades. L'existence de mosaïques parentales a pu être démontrée chez environ 9% des parents d'enfant atteint du syndrome de Dravet, par exemple, avec un taux de mosaïcisme variant entre 4 et 85% des cellules [4]. Dans ces situations, un diagnostic anténatal est également possible. L'estimation précise du risque de récurrence permet, pour les couples qui le souhaitent, d'éviter la naissance d'un autre enfant porteur d'une affection neurologique associée à un handicap sévère.

Conséquences thérapeutiques

Adaptations thérapeutiques

La confirmation diagnostique peut, dans certains cas, avoir un impact thérapeutique immédiat. C'est le cas du déficit en transporteur du glucose (Glut-1), lié à des mutations du gène *SLC2A1*, qui peut être à l'origine de syndromes épileptiques et neurologiques de sévérité variable, incluant le syndrome de De Vivo « classique » et les absences myocloniques pharmacorésistantes mais répondant de façon spectaculaire au régime cétogène, qui permet d'apporter des corps cétoniques comme source alternative d'énergie pour les neurones. C'est également le cas des déficits du métabolisme de la vitamine B6, liés à des mutations des

gènes *ALDH7A1* ou *PNPO*, qui causent des épilepsies à début néonatal, mal contrôlées par les anti-épileptiques mais répondant à la pyridoxine ou au pyridoxal phosphate, selon le gène impliqué. Cette substitution, lorsqu'elle est mise en place précocement, permet de contrôler l'épilepsie et de limiter le risque de séquelles neurologiques, en particulier cognitives [5, 6]. Dans d'autres cas, même en l'absence de traitement spécifique, la confirmation du diagnostic étiologique permet d'adapter le traitement antiépileptique, en évitant certains médicaments, comme par exemple les bloqueurs de canaux sodiques chez des patients avec syndrome de Dravet lié à une mutation du gène *SCN1A*, alors que d'autres molécules sont au contraire bénéfiques comme le Topiramate ou le Stiripentol [7]. Les bloqueurs des canaux sodiques sont particulièrement efficaces chez les patients porteurs de certaines mutations faux-sens du gène *SCN8A* causant un gain de fonction, c'est-à-dire une hyperactivité du canal, souvent à l'origine d'encéphalopathies avec épilepsie pharmacorésistante. Enfin, une étude collaborative internationale a permis de distinguer plusieurs catégories de mutations de *SCN2A*, en fonction de leur effet fonctionnel et de la présentation électro-clinique des patients [8]. Les bloqueurs de canaux sodiques sont, dans ce cas également, plus efficaces lorsque la mutation cause un gain de fonction.

Vers une médecine personnalisée

Développement de traitements ciblés

L'enjeu ultime de l'identification des gènes responsables d'épilepsies mendéliennes est bien sûr le développement de traitements qui, contrairement à la majorité des traitements antiépileptiques disponibles à l'heure actuelle, permettrait de cibler de manière spécifique les mécanismes physiopathologiques liés aux mutations d'un gène donné, voire même d'une mutation donnée, exerçant un effet fonctionnel particulier. Quelques traitements ont déjà été proposés sur la base des mécanismes physiopathologiques. Le cas le plus notable est celui de la sclérose tubéreuse de Bourneville, liée à des mutations des gènes *TCS1* et *TSC2*, qui conduit à un défaut de répression de la voie mTORC1 qui régule, au niveau cérébral, la neurogénèse, la morphologie axono-dendritique, ainsi que le fonctionnement et la plasticité synaptique. La Rapamycine, un inhibiteur de la voie mTORC1 a montré son efficacité dans le traitement de l'épilepsie réfractaire chez les patients atteints de sclérose tubéreuse de Bourneville [9]. Or, il a été récemment montré que les mutations des gènes *DEPDC5*, *NPRL2* et *NPRL3*, qui codent pour des protéines du complexe GATOR1, qui inhibe également la voie mTORC1, étaient une cause fréquente d'épilepsies familiales focales, parfois associées à des dysplasies cérébrales [10]. Chez ces patients dont l'épilepsie est fréquemment pharmacorésistante, les inhibiteurs de la voie mTORC1 représentent également une option prometteuse. Les mutations du gène *KCNT1*, qui code pour un canal potassique activé par le calcium, sont une autre cause fréquente d'épilepsies focales familiales [11]. Des mutations de ce gène, provoquant un gain de fonction, sont également retrouvées dans la moitié des épilepsies avec crises focales migrantes du nourrisson, ainsi que dans d'autres formes d'encéphalopathies avec épilepsie à début précoce, pharmacorésistantes et de pronostic sévère [12]. Des études réalisées in vitro et sur des modèles animaux ont montré un effet inhibiteur de la quinidine sur ces canaux mutés, mais les premiers essais chez l'homme, réalisés sur un nombre limité de patients, n'a pour l'instant pas montré d'efficacité notable [13].

La rétigabine, qui favorise l'ouverture des canaux potassiques K_V7, a été proposée pour traiter les patients porteurs de mutations faux-sens du gène *KCNQ2* qui causent une encéphalopathie épileptique à début néonatal. L'utilisation de ce traitement a cependant dû être interrompue du fait d'effets secondaires, comme une coloration bleue des muqueuses et des doigts [14]. D'autres exemples illustrant bien le fait que l'identification des mutations causales d'une épilepsie mendélienne et les mécanismes physiopathologiques qu'elles engendrent peut permettre de concevoir des thérapeutiques ciblées, comme par exemple certaines mutations faux-sens des gènes *GRIN2A* ou *GRIN2D*, causant un gain de fonction du récepteur *NMDA*, pour lesquels un traitement par la mémantine, un inhibiteur de ce récepteur, a été prescrit chez quelques enfants [15, 16]. Ces approches thérapeutiques ciblées n'en sont encore qu'à leurs prémices. Elles seront facilitées par le regroupement de patients présentant des mutations d'un gène donné avec des effets semblables. On peut penser que ces traitements auront plus de chance d'être efficaces s'ils sont prescrits plus précocement, ce qui implique la réalisation d'un diagnostic moléculaire rapide.

La pharmacogénétique

Au cours des prochaines années, les données de séquençage à haut débit apporteront probablement également des données pharmacogénétiques concernant le métabolisme et les effets secondaires potentiels des traitements [17]. L'exemple classique est celui de l'hépatotoxicité liée au Valproate chez les patients porteurs de mutations du gène *POLG* [18]. Dans ce cas, les effets secondaires du médicament sont liés à la cause de la maladie. La plupart des antiépileptiques ont des effets secondaires qui sont probablement, en partie, liés à des facteurs génétiques, impliquant en particulier des gènes de protéines impliquées dans le métabolisme de ces molécules [19]. L'exemple le mieux étudié est celui de certains allèles des gènes *CYPC9* et *CYPC19* du sys-

tème des cytochromes P450 qui influencent le métabolisme des anti-épileptiques, pouvant favoriser une neurotoxicité ou des réactions cutanées sévères. Un autre exemple classique est celui de l'allèle HLA-B*15-02, particulièrement associé au risque de syndrome de Stevens-Johnson induit par la Carbamazépine chez les patients Chinois ou du Sud-Est asiatique [20]. La recherche dans ce domaine n'en est qu'à ses débuts mais représente un champ d'application prometteur.

Conclusion

L'évolution rapide des technologies de séquençage du génome humain a permis l'identification de nombreux gènes responsables de formes mendéliennes d'épilepsie. Ces technologies sont maintenant transférées dans la pratique clinique, permettant d'analyser de nombreux gènes de façon simultanée et de porter un diagnostic étiologique chez un nombre croissant de patient. Une telle confirmation représente une étape indispensable pour le conseil génétique et peut avoir des conséquences importantes dans le domaine thérapeutique.

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Genetics in Epilepsy “plus”: Focus on the Role of CGH Array

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Summary

Up to 30 - 40% of children with epilepsy are refractory to treatment, and despite numerous invasive and costly investigations, approximately 30% of cases will not identify the cause. Array comparative genomic hybridization (CGH array) as a diagnostic tool in molecular genetics has facilitated recognition of microdeletions and microduplications as risk factors for both generalized and focal epilepsies. There is evidence that many microdeletions/duplications or so called copy number variants (CNVs) predispose to a range of epilepsy plus at least one other neurological/psychiatric disorder including developmental delay, neuropsychiatric intellectual disability, autism or multiple congenital anomalies (epilepsy “plus”). Studies suggest a diagnostic yield of 15 - 20% of CGH array for this type of condition. Furthermore, CGH array can lead to the discovery of candidate epilepsy or other disease associated genes, providing insight into new treatment and control of seizures.

The identification of pathogenic CNVs implicated in epilepsy can have a significant impact on early diagnosis and successful treatment of childhood epilepsy. Proper management of seizures can prevent negative effects on a child’s brain development, offer the possibility of genetic counselling for families and avoid costly testing for other rare forms of seizure disorders.

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Key words: Array Comparative Genomic Hybridization (CGH array), Copy Number Variant (CNV), childhood epilepsy, Intellectual Disability (ID), Autism Spectrum Disease (ASD)

Genetische Abklärung bei Epilepsie “plus” mit Fokus auf die Rolle von CGH Array-Analysen

Mehr als ein Drittel der Kinder mit Epilepsie leiden unter einer therapierefraktären Form, und bei vielen dieser Patienten findet man trotz unzähligen invasiven und teuren Zusatzuntersuchungen keine Ursache. Die Entdeckung der diagnostischen Methode der sogenannten CGH array (Comparative Genomic Hybridization)-Analyse hat es möglich gemacht, dass genetische Veränderungen in Form von Mikrodeletionen und Mikroduplikationen als Ursache beziehungsweise Risikofaktoren sowohl für generalisierte als auch für fokale Epilepsien gefunden wurden. Es gibt Hinweise darauf, dass viele dieser sogenannten CNVs (Copy Number Variants) zu einem breiten Spektrum von Epilepsie plus mindestens einer anderen neurologischen oder psychiatrischen Erkrankung wie generelle Entwicklungsverzögerung, geistige Behinderung, Autismus-Spektrum-Störung oder multiple kongenitale Anomalien führen (Epilepsie “plus”). Studien lassen den Schluss zu, dass die diagnostische Ausbeute einer CGH array bei dieser Art von Symptomkomplex 15 - 20% betragen kann. Forschungsmässig konnte mehrfach gezeigt werden, dass mittels CGH array-Analysen neue Epilepsiekandidaten oder andere krankheitsassoziierte Gene entdeckt wurden.

Die Ermittlung einer potenziell pathogenen CNV kann grossen Einfluss haben auf eine frühe Diagnose und bestenfalls entsprechend erfolgreiche Behandlung der Epilepsie, was sich wiederum positiv auf die kindliche Hirnentwicklung auswirkt. Ausserdem kann den Familien eine spezifische genetische Beratung angeboten werden, und andere Zusatzuntersuchungen können vermieden werden.

Schlüsselwörter: Array-CGH (Comparative Genomic Hybridization), CNV (Copy Number Variant), kindliche Epilepsie, geistige Behinderung, Autismus-Spektrum-Störung

Tests génétiques en cas d'épilepsie "plus": rôle de la CGH-Array

Jusqu'à 30 - 40% des enfants avec épilepsie sont réfractaires au traitement. Dans environ 30% des cas la cause reste inconnue, malgré de nombreux tests invasifs et coûteux. L'arrivée de la CGH array (Comparative Genomic Hybridization) a permis d'identifier des modifications génétiques telles que microdélétions et microduplications, concernant aussi bien les épilepsies généralisées que focales. Il semblerait que de nombreuses microdélétions ou duplications (aussi appelées CNVs, Copy Number Variants) soient un facteur de prédisposition pour toute une série d'épilepsies accompagnées d'au moins un autre symptôme neurologique ou psychiatrique, tel que retard du développement, retard intellectuel, autisme, ou autre anomalie congénitale (épilepsie « plus »). Des études suggèrent que la CGH array peut contribuer au diagnostic dans jusqu'à 15% des cas. De plus la CGH array peut conduire à la découverte de nouveaux syndromes ou gènes associés à une maladie, ce qui augmente notre connaissance du traitement et du contrôle des crises.

L'identification de CNVs pathogènes impliquées dans l'épilepsie peut avoir un impact important sur le diagnostic précoce et le traitement de l'épilepsie chez l'enfant. Une thérapie adéquate des crises peut empêcher les effets néfastes sur le développement du cerveau de l'enfant, offre des possibilités de conseil pour des familles, et évite des examens coûteux pour d'autre maladies rares.

Mots clés: CGH array (Comparative Genomic Hybridization), CNVs (Copy Number Variants), épilepsie chez l'enfant, retard intellectuel, autisme

Introduction

About one percent of children are affected by epilepsy and in most cases onset occurs in infancy or early childhood. Unfortunately, 30 - 40% of children with epilepsy will be refractory to treatment, and despite numerous invasive and costly investigations, 30% of cases will not identify the cause [1]. Prolonged uncontrolled seizures especially in the developing immature brain can impair the functional development, resulting in disorders such as developmental delay/intellectual disability, psychiatric illnesses (epilepsy "plus"). However, it is likely that the underlying genetic cause also explains the developmental encephalopathy, as many of the associated epilepsies are suspected to be caused or influenced by genetic factors [2].

Clinical cytogenetic testing, in the past, relied on g-banded karyotyping. This technique only detects abnormalities in about 3% of patients with unexplained global developmental delay/intellectual disability (GDD/ID), autism spectrum disorder (ASD), or multiple congenital anomalies (MCA), whereas with using CGH array (array comparative genomic hybridization), a molecular cytogenetic method for analysing copy number variations (CNVs), the diagnostic yield rises to 15 - 20% [3]. Prospective and observational studies of patients with genetic generalized, idiopathic focal epilepsies, or epileptic encephalopathies have provided similar diagnostic yields of CGH array [4]. However, a case-control study has shown that CNVs were more common in individuals with a combination of intellectual disability (ID) and genetic generalized epilepsy (GGE) than in those with either phenotype alone [5]. These findings reflect data that have been published very recently, where Borlot et al. found that in a large cohort of adults with childhood-onset epilepsy and intellectual disability pathogenic and/or likely pathogenic copy number variations in 16.1% of the 143 probands investigated using CGH array. In this cross-sectional study eight non-recurrent rare CNVs that overlapped one or more genes associated with intellectual disability, autism, and/or epilepsy were identified [6]. In addition, the method of CGH array has a significant impact on epilepsy research and could lead to the discovery of candidate epilepsy genes.

To illustrate the complexity and broad variability of genotype-phenotype correlations this brief overview will focus on recurrent and rare microdeletion and duplication syndromes and their association with epilepsy "plus". The genetic variability of epilepsy "plus" associated with CNVs e.g. involving known epilepsy genes will be addressed by providing recent examples from the literature.

Methodical aspects of CGH array

CGH array, also referred to as the "molecular karyotype", has replaced the routine karyotype, because the resolution of CGH array is 100 - 1000 times greater than that of routine karyotyping, meaning that CGH array can detect CNVs as small as ~1 kb. CNVs could contain zero up to several genes and be both, normal genetic variants and or pathogenic mutations. The technique of CGH array is based on competitive hybridization of reference and patient DNA to an immobilized target sequence on a glass platform or other flat surface [7]. Copy number variants (CNVs) are deletions and duplications ranging from 1 kilobase (kb) to an entire chromosome. They are an important source of normal genomic variation, but some act as risk factors or causes of disease. The interpretation of results may be challenging for different reasons, first of all one has to consider technical aspects of the analysis such as the applied platform, accuracy of reference databases, filter settings determining threshold values (e.g. 200 kb) for deletions and 400 kb for duplications and number of probes (e.g. 50 markers). In terms of potential pathogenicity of a deletion or duplication many factors have

to be considered: location, size, contented gene(s), parental inheritance, presence or absence in control studies and of course any of the individual's phenotypes are all very relevant. Furthermore, one has to consider an extensive phenotypic heterogeneity as well as incomplete penetrance, variable expressivity and susceptibility loci of CNVs [8]. In general, de novo CNVs, larger CNVs (> 500 kb) and deletions more often than duplications have a higher likelihood to be possibly pathogenic. CNVs are usually categorized as either pathogenic, benign or variants of unknown significance (VUS).

CNVs predisposing to epilepsy in individuals in microdeletion syndromes associated with epilepsy

A way to classify CNVs in general is to group them in so called recurrent and non-recurrent CNVs. Recurrent CNVs are deletions and duplications which occur as a result of nonallelic homologous recombination at meiosis due to a predisposing sequence architecture being consisting with particularly unstable genomic regions. This mechanism explains that recurrent CNVs in two unrelated individuals with the same disorder have nearly identical breakpoints [9]. The occurrence of recurrent CNVs was initially noted in ID syndromes, such as Prader-Willi and Angelman syndromes. However, on proximal 15q, deletions and duplications involving various combinations of five BPs are associated not only with these syndromes but also with idiopatic genetic generalized (**Figure 1**) [10]. A selection of microdeletions and duplications identified as risk factors for neurodevelopmental disorders and epilepsy were summarized by Carvill and Mefford [11] (**Table 1**). With their study they highlighted that these microdeletions are associated with diverse phenotypes, including epilepsy as well as intellectual disability, autism and neuropsychiatric disorders [11].

For example, deletions and duplications of 16p11.2 have been shown to be associated with autism, ID, schizophrenia, but also epilepsy, as reviewed in a recent large case series. These patients presented a rather specific neurological phenotype as both, individuals with 16p11.2. microdeletion or duplication were found to have rather highly prevalent speech articulation abnormalities, hypotonia, abnormal agility, sacral dimples besides epilepsy. However, reciprocal phenotypic characteristics such as predominant hypo- versus hyperreflexia and macro- versus microcephaly may reflect opposite neurobiological abnormalities causing the functional impairments shared between 16p11.2 deletion and duplication carriers [12]. To make things even more complicated it has been shown, that the identical deletion on chromosome 16p11.2 (from genomic coordinates 29.5 Mb to 30.1 Mb) was found in children with developmental delay, mental retardation, or suspected ASD, as well as individuals with autism [13].

Rare, non-recurrent CNVs in epilepsy "plus"

There are several mechanisms for the generation of non-recurrent breakpoints that have been described; however, they seem to be often errors of replication. Non-recurrent CNVs with identical breakpoints are rare, but comparison of overlapping CNVs in similar phenotypes could reveal the "smallest region of overlap" that can highlight one or a few genes as primarily responsible for the phenotype. The technique of CGH array

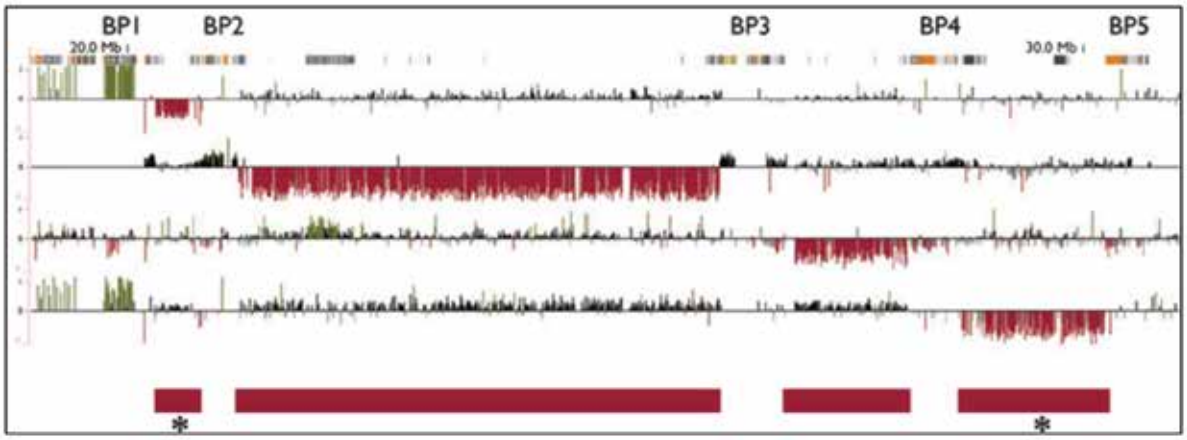

Figure 1. The current figure is taken from a publication by Mulley and Mefford, 2011. The authors demonstrated deletions and duplications involving various combinations of five BPs associated with Prader-Willi and Angleman syndromes (BP1–BP3 or BP2–BP3 deletions), autism (BP2–BP3 duplications), and genetic generalized epilepsy (BP1–BP2 and BP4–BP5 deletions) marked with an asterix. Blocks of segmental duplications, in which the BPs lie, are represented at the top by orange/yellow/gray blocks. Red bars represent the unique sequence deleted (or duplicated) between blocks of segmental duplications.

Table 1: Selected microdeletion and -duplication syndromes associated with phenotypic heterogeneity

Table adapted from Carvill and Mefford, Curr Opin Gen Dev 2013 [11]

Genomic location	Coordinates (hg19) for critical region (Mb)	Associated phenotypes, with focus on ID: Intellectual disability, EPI: epilepsy, ASD: Autism spectrum disorder, and MCA (multiple congenital anomalies
1q21.1	Chr1: 146.5–147.5	ID, EPI, MCA
3q29	Chr3: 195.8–197.4	ID, EPI
10q22q23	Chr10: 81.5–89.0	ID
15q11.2	Chr15: 22.8–23.1	ID, EPI, ASD
15q13.3	Chr15: 31.3–32.5	ID, EPI, ASD
15q24	Chr15: 74.4–75.5	ID, ASD
16p11.2	Chr16: 28.8–30.2	ID, ASD, specifically speech disorder
16p12.2	Chr16: 21.9–22.5	ID, EPI
16p13.11	Chr16: 15.0–16.3	ID, ASD, EPI
17q12	Chr17: 34.8–36.3	ID, ASD, EPI
17q21.3	Chr17: 43.7–44.3	ID
22q11.2 distal	Chr22: 21.8–23.7	ID, MCA
22q11.2 distal	Chr22: 21.8–23.7	ID, MCA

led to the detection of rare CNVs in 8.8 % (7/80) of the adults and children with ID or developmental delay, and childhood-onset epilepsy. The CNVs involved known microdeletion syndromes (16p11.2, 16p13.11 and 2q13) but also rare CNV encompassing known disease genes, such as SCN1A in four individuals. Such a finding is relevant, as deletions disrupting SCN1A might be associated with single gene abnormalities [14]. In the presence of SCN1A abnormalities certain anti-seizure medications should be avoided because they make seizures worse, and other medications or diet are more likely to be associated with improved seizure control.

As mentioned before, the importance of CGH array has been further increased through its role in the identification of disease-causing genes. The identification of regions of overlapping CNVs between patients with similar neurodevelopmental phenotypes and epilepsy, for example deletions of CDKL5 in girls with severe epilepsy and a Rett syndrome-like phenotype, might be a starting point toward identifying additional epilepsy genes [15]. The former only candidate epilepsy gene CHD2 was identified by being the only shared gene within several reported overlapping CNVs of the chromosome 15q26.1 region associated with complex

phenotypes including not only developmental delay but epilepsy with photosensitivity [16]. Another similar example is that of a de novo microdeletion at 9q33.3-q34.11 encompassing STXBP1 in a girl with mental retardation and Early Infantile Epileptic Encephalopathy (EIEE), characterized by tonic seizures, seizure intractability and characteristic suppression-burst pattern on EEG. After mutation analysis of the candidate gene STXBP1 four other unrelated EIEE patients revealed heterozygous missense mutations in the same gene [17].

Conclusion

CGH array is a method of genetic testing that has been shown to have a significant impact on epilepsy research and diagnosis, being that CNVs are an important genetic cause of epilepsy in children. Pathogenic CNVs are most likely to be found in cases where epilepsy is associated with developmental delay, intellectual disability or autism spectrum disorder, especially in the setting of dysmorphic features. CGH array testing to evaluate for potential pathogenic CNVs should be performed in patients with epilepsy "plus" (epilepsy combined with intellectual disability, malformations, dysmorphic stigmata, ASD or other features). However, evaluating the implications of a potentially pathogenic CNV for an individual patient can be challenging. To interpret the findings of a particular CNV and its possible degree of pathogenicity and the reproductive risk for the family the clinician should seek the assistance of a geneticist. Once a possibly disease causing or contributing CNV has been found the advantages to the patient and clinician include ending the often long diagnostic „odyssey", providing families with prognostic information and possible features of the syndrome that may be relevant for clinical management and in an increasing number of cases providing families access to syndrome-specific research or patient organizations.

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Seizures and Epilepsies due to Channelopathies and Neurotransmitter Receptor Dysfunction: A Parallel Between Genetic and Immune Aspects

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Key words: Ion channels, neurotransmitters, immunity, genetics

Introduction

The study of genetic and immune aspects in epilepsy has been increasing exponentially over the past decade. Both components have helped to better understand the pathophysiological mechanisms at the basis of seizure genesis. Hundreds of mutations in genes coding for ion channels, neurotransmitter receptors or synaptic proteins have been reported as causing variable types of epilepsies. During the same period, auto-antibodies targeting the very same molecules have been discovered and recognized as causing acute encephalitides with seizures. These parallel mechanisms at the basis of multiple situations in which seizures can be observed have been the object of an article we published in a recent issue of Molecular Syndromology [1]. We here summarize and update the illustrative examples described in this paper in order to draw attention of the readers on this fascinating topic.

NMDA-receptor, NR1 subunit

The *NMDA* receptor is an ion channel permeable to sodium, potassium, and calcium. It is found at excitatory synapses throughout the brain, and is composed of four subunits. Two of them are of the NR1 glycine-binding subtype and are ubiquitous. The two other subunits are glutamate-binding and of variable subtypes (NR2A, NR2B, NR2C, NR2D, NR3A or NR3B). The gene that encodes NR1 is *GRIN1* (OMIM : 138249); it is located at 9q34.3. GRIN1 mutations that generate protein loss-of-function have been recently related to an encephalopathy characterized by profound and early-onset developmental delay, seizures of variable types (including infantile spasms, tonic and atonic seizures, hypermotor seizures, focal dyscognitive seizures, febrile seizures, generalized seizures, and status epilepticus), abnormal movements, autistic features and sleep difficulties [2].

This phenotype is very similar to that reported earlier in association with auto-antibodies directed against the same subunit. After an initial report published in 2007, 100 patients aged 5 to 76 years were reported as having a homogeneous association of symptoms related to the presence of circulating anti-NMDA receptor antibodies [3]. Symptoms included in the majority of patients acute- or subacute-onset psychiatric troubles, seizures, abnormal movements and dysautonomic features. Severe sleep disorders have also been reported later. Immunohistochemical analyses from all patients' sera and cerebrospinal fluid samples showed that NR1 was the precise target against which these antibodies reacted. Up to now, the pathophysiology of these antibodies is explained by internalization and reduction of the number of synaptic NMDA receptors. The prognosis of this encephalitis is considered as rather favorable, as most patients will respond to promptly initiated immunomodulatory or immunosuppressive therapies. A certain number of women present an underlying ovarian tumor at the basis of the auto-immune reaction, whose removal usually allows complete recovery.

LGI

Leucin-rich glioma-inactivated 1 (LGI1) is a synaptic protein dimer that binds to the presynaptic and post-synaptic metalloproteinases ADAM22 and 23. This complex regulates the function of AMPA glutamatergic receptors and voltage-gated potassium channels [4]. *LGI1* (OMIM : 604619), also called epitempin, is the gene that encodes LGI1. It is located at 10q23.33.

LGI1 mutations have been associated with autosomal dominant partial epilepsy with auditory features (ADPEAF) (or autosomal dominant lateral temporal lobe epilepsy (ADLTLE)). This epilepsy is characterized by variable ictal auditory symptoms, which include unformed simple sounds, including humming, buzzing, or ringing, distortions, such as volume changes,

or complex sounds, such as specific songs or voices, or a receptive aphasia [5]. Convulsions may follow these initial features. The course of the epilepsy is usually favorable with excellent response to antiepileptic drugs. Sporadic cases have been described, but inherited mutations represent the vast majority of all those reported. All known mutations seem to induce a loss of function of LGI1, be it by loss of expression, loss of synaptic secretion, or loss of interaction with its main receptor, ADAM22.

Auto-antibodies against LGI1 have been reported in 2010 as being responsible for a form of limbic encephalitis previously attributed to potassium channels [6]. This encephalitis is characterized by acute onset of seizures (often, but not exclusively, facio-brachial and dystonic), cognitive decline involving memory and behavior, and sleep disturbance. Abnormal MRI signals are often noted in the mesiotemporal regions, and hyponatremia is frequently diagnosed.

In presence of these antibodies, the interaction between LGI1 and ADAM22/ADAM23 is inhibited (i.e., the ligand-receptor interaction is blocked). It is thought that consequently, the reduced AMPA receptor function on inhibitory interneurons could cause disinhibition of excitatory neurons, at the basis of seizures and cognitive symptoms observed in these patients. A loss of maturation of synapses through dysfunctional NMDA receptors and AMPA receptors is also suspected [7]. The course of the disease is usually favorable with a rapid response to immunomodulatory or immunosuppressive therapies. Cognitive sequelae may persist.

Conclusion

Genetic or dysimmune causes are at the basis of certain epilepsies involving ion channels, neurotransmitters, or their receptors. For unknown reasons, the clinical presentation associated with certain mutations or circulating auto-antibodies targeting their product may either be similar, or very different. Thus, the basic mechanisms at the basis of such diseases remain to be fully understood.

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Seizures and Epilepsies due to Channelopathies and Neurotransmitter Receptor Dysfunction: A Parallel between Genetic and Immune Aspects

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Schlüsselwörter: Ionenkanäle, Neurotransmitter, Immunität, Genetik

Einleitung

Das Forschungsaufkommen zu genetischen und immunologischen Aspekten der Epilepsie ist innerhalb der letzten zehn Jahre exponentiell gestiegen. Beide Komponenten haben zu einem besseren Verständnis der pathophysiologischen Mechanismen der Anfallsgenese beigetragen. Für Hunderte von Mutationen in Genen, die für Ionenkanäle, Neurotransmitter-Rezeptoren oder synaptische Proteine kodieren, wurde eine ursächliche Beteiligung an unterschiedlichen Epilepsieformen beschrieben. Im selben Zeitraum wurden Autoantikörper gegen ebendiese Moleküle entdeckt und als Ursache für akute Enzephalitiden mit Anfällen identifiziert. Diese parallelen ursächlichen Mechanismen der vielfältigen Anfallssituationen waren Gegenstand eines Artikels, den wir in einer der letzten Ausgaben von *Molecular Syndromology* veröffentlicht haben [1]. Im Vorliegenden werden die zur Veranschaulichung dienenden Beispiele aus diesem Fachartikel zusammengefasst und aktualisiert, um dem Leser diese faszinierende Thematik nahezubringen.

NMDA-Rezeptor, NR1-Untereinheit

Der NMDA-Rezeptor ist ein für Natrium, Kalium und Kalzium durchlässiger Ionenkanal. Er kommt an erregenden Synapsen im gesamten Gehirn vor und besteht aus vier Untereinheiten. Zwei dieser Untereinheiten gehören zum Glycin-bindenden NR1-Subtyp und sind ubiquitär. Zwei weitere Untereinheiten binden Glutamat und gehören unterschiedlichen Subtypen an (NR2A, NR2B, NR2C, NR2D, NR3A oder NR3B). Für NR1 kodiert das auf 9q34.3 lokalisierte Gen *GRIN1* (OMIM: 138249). *GRIN1*-Mutationen, die mit einem Protein-Funktionsverlust einhergehen, wurden in jüngerer Zeit mit einer Enzephalopathie in Zusammenhang gebracht, die durch eine tiefgreifende und früh einsetzende Entwicklungsverzögerung, Anfälle unterschiedlicher Art (zum Beispiel infantile Spamen, tonische und atonische Anfälle, hypermotorische Anfälle, fokale dyskognitive Anfälle, febrile Anfälle, generalisierte Anfälle und Status epilepticus), abnorme Bewegungen, autistische Merkmale und Schlafprobleme gekennzeichnet ist [2].

Dieser Phänotyp weist grosse Ähnlichkeit auf mit dem Phänotyp, der bereits im Zusammenhang mit gegen dieselbe Untereinheit gerichteten Autoantikörpern beschrieben wurde. Nach einem ersten, 2007 veröffentlichten Bericht wiesen 100 Patienten im Alter zwischen 5 und 76 Jahren einen einheitlichen Symptomenkomplex auf, der durch zirkulierende Antikörper gegen den NMDA-Rezeptor bedingt war [3]. Zu den Symptomen gehörten bei der Mehrzahl dieser Patienten akute oder subakute psychiatrische Störungen, Anfälle, abnorme Bewegungen und Merkmale einer dysautonomen Störung. Später wurde ausserdem über schwere Schlafstörungen berichtet. Immunhistochemische Serum- und Liquoranalysen aller Patienten zeigten, dass sich diese Antikörper gezielt gegen NR1 richteten. Bislang erklärt man sich die Pathophysiologie dieser Antikörper durch die Internalisierung und zahlenmässige Verminderung der synaptischen NMDA-Rezeptoren. Die Prognose gilt bei dieser Enzephalitis als relativ günstig, da die meisten Patienten auf zeitnah eingeleitete immunmodulatorische oder immunsuppressive Therapien ansprechen. Bei manchen Frauen bildet ein zugrundeliegendes Ovarialkarzinom den Ausgangspunkt der Autoimmunreaktion; nach dessen Entfernung ist in der Regel eine vollständige Genesung möglich.

LGI

Das Leucin-rich glioma-inactivated 1 (LGI1) ist ein dimeres synaptisches Protein, das an die prä- und postsynaptischen Metalloproteasen ADAM22 und 23 bindet. Dieser Komplex reguliert die Funktion von glutamatergen AMPA-Rezeptoren und spannungsabhängigen Kaliumkanälen [4]. Für LGI1 kodiert das Gen LGI1 (OMIM: 604619), das auch als Epitempin bezeichnet wird. Genort ist 10q23.33.

LGI1-Mutationen sind mit autosomal-dominanter partieller Epilepsie mit auditorischen Auren (ADPEAF, auch autosomal-dominante laterale Temporallappen-Epilepsie (ADLTLE) assoziiert. Diese Epilepsie ist gekennzeichnet durch unterschiedliche iktale auditorische Symptome, darunter einfache ungeformte Geräusche (z. B. Summen, Brummen oder Klingeln), Verzerrungen (z. B. Lautstärkenänderungen), komplexe Geräusche (z. B. bestimmte Lieder oder Stimmen) oder rezeptive Aphasie [5]. An diese anfänglichen Störungen können sich Konvulsionen schliessen. Die Epilepsie zeigt in der Regel einen günstigen Verlauf und spricht hervorragend auf Antiepileptika an. Zwar wurden sporadische Fälle beschrieben, doch beruhen die weitaus meisten berichteten Fälle auf vererbten Mutationen. Alle bekannten Mutationen scheinen einen Funktionsverlust von LGI1 zu induzieren – sei es durch einen Expressionsausfall, einen Verlust der synaptischen Sekretion oder den Interaktionsverlust mit seinem wichtigsten Rezeptor, ADAM22.

Autoantikörper gegen LGI1 sind laut einem Bericht aus dem Jahr 2010 verantwortlich für eine Form der limbischen Enzephalitis, die bis dahin auf Kaliumkanäle zurückgeführt worden war [6]. Diese Enzephalitis ist charakterisiert durch das akute Einsetzen von Anfällen (häufig, aber nicht ausschliesslich faziobrachial und dystonisch), eine Verschlechterung der gedächtnis- und verhaltensbezogenen kognitiven Funktionen sowie Schlafstörungen. Oft werden abnorme MRT-Signale in den mesiotemporalen Regionen beobachtet, und häufig wird eine Hyponatriämie diagnostiziert.

In Gegenwart dieser Antikörper ist die Wechselwirkung zwischen LGI1 und ADAM22/ADAM23 gehemmt (d. h., die Ligand-Rezeptor-Interaktion ist blockiert). Man geht davon aus, dass die infolgedessen verminderte Funktion der AMPA-Rezeptoren auf inhibitorischen Interneuronen eine Disinhibition exzitatorischer Neuronen hervorruft, die wiederum für die bei diesen Patienten beobachteten Anfälle und kognitiven Ausfälle verantwortlich ist. Eine Beeinträchtigung der Synapsenreifung durch dysfunktionelle NMDA- und AMPA-Rezeptoren wird ebenfalls vermutet [7]. Die Erkrankung zeigt in der Regel einen günstigen Verlauf und spricht rasch auf immunmodulatorische oder immunsuppressive Therapien an. Die kognitiven Folgeerscheinungen können fortbestehen.

Schlussfolgerung

Bestimmte Epilepsien mit Beteiligung von Ionenkanälen, Neurotransmittern oder deren Rezeptoren haben genetische oder immunologische Ursachen. Aus unbekannten Gründen kann das jeweilige klinische Bild, das mit bestimmten Mutationen oder zirkulierenden Autoantikörpern gegen deren Produkte einhergeht, entweder einheitlich oder sehr unterschiedlich sein. Zur vollständigen Aufklärung der Mechanismen, die derartigen Erkrankungen zugrunde liegen, sind daher weitere Untersuchungen erforderlich.

Danksagungen

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Seizures and Epilepsies due to Channelopathies and Neurotransmitter Receptor Dysfunction: A Parallel between Genetic and Immune Aspects

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Mots clés : Canaux ioniques, neurotransmitter, immunité, génétique

Introduction

L'étude des aspects génétiques et immunologiques de l'épilepsie a connu un développement exponentiel ces dix dernières années. Ces deux composantes ont permis de mieux comprendre les mécanismes physiopathologiques à l'origine des crises. Des centaines de mutations observées dans des gènes codant des canaux ioniques, des récepteurs de neurotransmetteurs ou des protéines synaptiques ont été recensées pour leur rôle dans des formes variables d'épilepsie. Durant la même période, des auto-anticorps dirigés contre ces mêmes molécules ont été découverts et identifiés comme la cause d'encéphalites aiguës accompagnées de crises. Ces mécanismes parallèles à l'origine de diverses situations de crises ont fait l'objet d'un article que nous avons publié dans un récent numéro de *Molecular Syndromology* [1]. Nous résumons et actualisons ici les exemples illustratifs décrits dans cet article afin d'attirer l'attention du lecteur sur cette thématique fascinante.

Récepteur NMDA, sous-unité NR1

Le récepteur NMDA est un canal ionique perméable au sodium, au potassium et au calcium. Localisé sur les synapses excitatrices dans tout le cerveau, il est composé de quatre sous-unités. Deux d'entre elles font partie du sous-type NR1 liant la glycine et sont obligatoires. Les deux autres sous-unités lient le glutamate et sont de sous-types variables (NR2A, NR2B, NR2C, NR2D, NR3A ou NR3B). Le gène qui code NR1 est *GRIN1* (OMIM : 138249) localisé sur le chromosome 9q34.3. Les mutations du gène *GRIN1* qui génèrent une perte de fonction des protéines ont été récemment mises en lien avec une encéphalopathie caractérisée par un retard de développement profond et précoce, des crises de différents types (notamment des spasmes infantiles, des crises toniques et atoniques, des crises hypermotrices, des crises dyscognitives focales, des convulsions fébriles, des crises généralisées et un état de mal épileptique), des mouvements anormaux, des caractéristiques autistiques et des troubles du sommeil [2].

Ce phénotype est très similaire à celui déjà rapporté en lien avec des auto-anticorps dirigés contre la même sous-unité. Après un premier rapport publié en 2007, les cas de 100 patients âgés de 5 à 76 ans ont été rapportés comme présentant un ensemble homogène de symptômes lié à la présence d'anticorps circulants dirigés contre le récepteur NMDA [3]. Chez la majorité des patients, les symptômes incluaient des troubles psychiatriques d'apparition aiguë ou subaiguë, des crises, des mouvements anormaux et des caractéristiques dysautonomiques. Des troubles sévères du sommeil ont également été rapportés ultérieurement. Les analyses immunohistochimiques des échantillons de liquide céphalorachidien et de sérum de tous les patients ont montré que ces anticorps étaient précisément dirigés contre le gène NR1. Jusqu'à présent, la physiopathologie de ces anticorps s'explique par l'internalisation et la réduction du nombre de récepteurs NMDA synaptiques. Le pronostic de cette encéphalite est considéré comme plutôt favorable, car la plupart des patients répondent aux thérapies immunomodulatrices ou immunosuppressives initiées rapidement. Un certain nombre de femmes présentent une tumeur ovarienne sous-jacente à l'origine de la réaction auto-immune. L'ablation de cette tumeur permet généralement une guérison complète.

LGI

LGI1 (Leucin-rich glioma-inactivated 1) est une protéine synaptique dimère qui se lie aux métalloprotéinases présynaptiques et postsynaptiques ADAM22 et 23. Ce complexe régule la fonction des récepteurs glutamatergiques AMPA et des canaux potassiques voltage-dépendants [4]. LGI1 (OMIM : 604619), également appelé épitempine, est le gène qui code LGI1. Il est localisé sur le chromosome 10q23.33.

Les mutations de *LGI1* sont associées à une épilepsie partielle autosomique dominante avec des signes auditifs (ADPEAF) (ou épilepsie du lobe temporal latéral autosomique dominante (ADLTLE)). Cette épilepsie est caractérisée par des symptômes auditifs ictaux variables, parmi lesquels des sons simples informes (notamment des fredonnements, bourdonnements, tintements), des distorsions (telles que des changements de volume), des sons complexes (tels que des chansons ou voix spécifiques) ou une aphasie réceptive [5]. Ces caractéristiques initiales peuvent être suivies de convulsions. L'évolution de cette épilepsie est généralement favorable, avec une excellente réponse aux médicaments antiépileptiques. Si des cas sporadiques ont été décrits, la très grande majorité des cas rapportés repose néanmoins sur des mutations héréditaires. Toutes les mutations connues semblent induire une perte de fonction de LGI1, que ce soit par perte d'expression, perte de sécrétion synaptique ou perte d'interaction avec son récepteur principal, ADAM22.

Selon un rapport de 2010, des auto-anticorps dirigés contre LGI1 sont responsables d'une forme d'encéphalite limbique jusque-là attribuée aux canaux potassiques. [6]. Cette encéphalite se caractérise par une apparition aiguë des crises (souvent, mais pas exclusivement, faciobrachiales et dystoniques), un déclin cognitif touchant la mémoire et le comportement, et des troubles du sommeil. Des signaux anormaux sont souvent observés à l'IRM dans les régions mésiotemporales et une hyponatrémie est fréquemment diagnostiquée.

En présence de ces anticorps, l'interaction entre LGI1 et ADAM22/ADAM23 est inhibée (l'interaction ligand/récepteur est bloquée). On suppose qu'en conséquence, la réduction de la fonction des récepteurs AMPA sur les interneurones inhibiteurs provoque une désinhibition de neurones excitateurs à son tour responsable des crises et des symptômes cognitifs observés chez ces patients. On suspecte également une perte de maturation des synapses due à un dysfonctionnement des récepteurs NMDA et AMPA [7]. Cette maladie connaît généralement une évolution favorable avec une réponse rapide aux thérapies immunomodulatrices ou immunosuppressives. Des séquelles cognitives peuvent subsister.

Conclusion

Certaines formes d'épilepsie impliquant des canaux ioniques, des neurotransmetteurs ou leurs récepteurs ont des causes génétiques ou immunologiques. Pour des raisons inconnues, la présentation clinique associée à certaines mutations ou certains auto-anticorps circulants ciblant leurs produits peut être soit similaire, soit très différente. Par conséquent, les mécanismes fondamentaux à la base de ces maladies sont encore entièrement à élucider.

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Genetic Testing for Epilepsy Surgery

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Summary

Dozens of novel epilepsy genes have been discovered at a very fast pace in the past decade. This progress improved understanding and management of epilepsy; however, this has not systematically been evaluated for the focal epilepsies that can be cured by epilepsy surgery. In this report we discus the impact and possible application of genetic diagnostics in epilepsy surgery evaluation. A review of the available data suggests that epilepsy gene mutations can be useful biomarkers for surgery. These may be negative predictors, such as mutations in genes encoding ion-channels or involved in synaptic function. The association of mutations in mTOR pathway genes with lesional focal epilepsy suggest that such mutations may be positive predictors that can improve selection of surgical cases, especially in the MRI-negative cases. However, it is clear that larger studies are needed to collect more detailed imaging and to interpret the link between surgery outcome, observational data, knowledge of disease aetiology, and genetics.

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Key words: Epilepsy surgery, genetics, DNA-diagnostics, prognosis

Gentests für die Epilepsiechirurgie

In den letzten zehn Jahren wurden in äusserst rascher Folge Dutzende neuer Epilepsie-Gene entdeckt. Dieser Fortschritt hat zu einem besseren Verständnis und Management der Epilepsie geführt; allerdings wurde dies für die epilepsiechirurgisch heilbaren fokalen Epilepsien nicht systematisch beurteilt. Der vorliegende Bericht erörtert die Auswirkungen und die mögliche Anwendung der Gendiagnostik bei der epilepsiechirurgischen Beurteilung. Eine Übersicht der verfügbaren Daten legt nahe, dass Mutationen in Epilepsie-Genen hilfreiche Biomarker im Hinblick auf chirurgische Optionen sein können. Dabei kann es sich um negative Prädiktoren handeln, z. B. Mutationen in Genen, die für Ionenkanäle kodieren oder an synaptischen Funktionen beteiligt sind. Der Zusammenhang zwischen Mutationen im mTOR-Signalweg und läsionsbedingten fokalen Epilepsien lässt vermuten, dass derartige Mutationen positive Prädiktoren darstellen, die eine bessere Selektion chirurgisch therapierbarer Fälle ermöglichen, insbesondere bei MRT-negativen Patienten. Allerdings steht ausser Zweifel, dass zur Erfassung detaillierterer Bildgebungsdaten und zur Klärung des Zusammenhangs zwischen chirurgischem Behandlungsergebnis, Beobachtungsdaten, Wissen um die Krankheitsätiologie und Genetik umfassendere Studien erforderlich sind.

Schlüsselwörter: Epilepsiechirurgie, Genetik, DNA-Diagnostik, Prognose

Tests génétiques pour la chirurgie épileptique

Ces dix dernières années, des douzaines de nouveaux gènes associés à l'épilepsie ont été découverts à une cadence particulièrement rapide. Si cette avancée a permis une meilleure compréhension et prise en charge de l'épilepsie, elle n'a pas systématiquement été évaluée pour les formes focales d'épilepsie pouvant être traitées par chirurgie épileptique. Le présent rapport s'intéresse à l'impact et à l'application potentielle des diagnostics génétiques dans l'évaluation de la chirurgie épileptique. Une analyse des données disponibles suggère que les mutations observées dans les gènes associés à l'épilepsie peuvent être des biomarqueurs utiles pour la chirurgie. Il peut s'agir de facteurs prédictifs négatifs, par exemple dans le cas des mutations de gènes codant des canaux ioniques ou impliqués dans une fonction synaptique. Le lien entre les mutations dans des gènes de la voie mTOR et l'épilepsie focale lésionnelle laisse penser que les mutations de ce type

peuvent être des facteurs prédictifs positifs susceptibles d'améliorer la sélection des cas pour la chirurgie, en particulier chez les patients dont l'IRM est négative. Cependant, il est certain que de plus amples études sont nécessaires pour collecter des données d'imagerie plus détaillées et pour interpréter le lien entre les résultats des traitements chirurgicaux, les données observationnelles, les connaissances sur l'étiologie de la maladie et la génétique.

Mots clés : chirurgie épileptique, génétique, diagnostic génétique, pronostic

Introduction

It stands without a doubt that genetic discoveries have progressed our understanding and management of the epilepsies. Dozens of novel epilepsy genes have been discovered in the past decades, largely as a result of inexpensive and readily available next generation sequencing. These discoveries have set several new paradigms. First, de novo mutations in various epilepsy genes are now seen as the major cause of sporadic epileptic encephalopathy. Second, the importance of genetic causes in focal epilepsy was established by the observation that inherited or de novo mutation in multiple genes, in particular genes involved in the mTOR pathway, can cause focal epilepsy.

Finally, it remains remarkable that for many, if not all epilepsy genes, a wide spectrum of clinical phenotypes, varying in type of epilepsy and severity of disease, are associated with mutations in the same gene. On the one hand, these genetic discoveries have enabled precision medicine, in which the DNA diagnosis limits the diagnostic odyssey and guides disease treatment and management. On the other hand, the variable clinical expression raises many questions on how to predict the clinical course of disease, and causes doubt whether genetics alone should determine clinical care.

From this perspective, we discuss the case of epilepsy surgery, for which the impact and importance of genetic diagnostics have not been explored substantially yet. Several studies have now reported on people with epilepsy that carry a presumed causal mutation in a known epilepsy gene and who are potentially eligible for, or have undergone, surgery. These reports suggest that genetics should play a role in the diagnostic strategy and therapeutic approach in people with epilepsy that are considered candidates for epilepsy surgery.

Monogenic causes of epilepsy

Next generation sequencing technology (NGS), in particular whole exome sequencing (WES), through which the coding sequence of all genes in the human genome can be scanned for putative disease-causing sequence variation, accelerated discovery of novel epilepsy genes in the past decade [1]. Major discoveries have been made in epileptic encephalopathy (EE) where many de novo mutations have recently been identified as causative. These include de novo mutations in *KCNQ2*, a gene that was already known for several decades, in which inherited mutations cause benign familial neonatal convulsions (BFNC) [2]. De novo missense mutations detected in severe childhood EE cluster in four hotspots of the gene that are important for essential channel properties, namely: the S4 voltage-sensor, the pore, the proximal C-terminal domain that binds phosphatidylinositol 4,5-bisphosphate (PIP2) and calmodulin (CaM A), and the more distal calmodulin binding (CaM B) domains [3, 4]. It is therefore assumed that these missense mutations cause EE through a dominant-negative effect on channel function, in contrast to the more variable effects of the mutations underlying BFNC that also include complete loss of function mutations, such as deletions. These observations illustrate the phenomena of variable clinical expression that is observed for many epilepsy genes. Like in *KCNQ2*, the type or location of the mutation can often explain the variable expression. However, this is not the case for all epilepsy genes, and for all mutations. The compelling example is *SCN1A*, a major epilepsy gene that is associated with a wide spectrum of different disease severities, and is currently associated with both common and rare, benign and severe disease. Mutations in SCN1A were reported as a major cause for severe myoclonic epilepsy of infancy (SMEI), also known as Dravet syndrome [5]. It is known as the most common genetic cause of severe epilepsy in infancy. In contrast, segregating mutations have been detected in families affected by generalized epilepsy and febrile seizure "plus" syndrome (GEFS+), a relative benign form of epilepsy with a favourable prognosis [6]. For a significant part, the difference in phenotype can be explained by the type of mutation, where complete loss of function mutations – such as non-sense mutations that result in a truncated protein that is vulnerable to nonsense mediated decay – are underlying the severe Dravet syndrome. On the other hand, GEFS+ is associated with missense SCN1A mutations specifically, that have a milder loss of function effect on the protein [7]. This clear association between variants and the two phenotypes demonstrates that rare coding variants of the gene with high to absolute risk for disease, are the main cause for these types of epilepsy. Finally, focal seizures may also be part of the semiology in Dravet syndrome, and as is discussed below, a few reports describe Dravet syndrome patients that also had a malformation of cortical development (MCD) [8, 9]. Furthermore, some families have been described in which a segregating *SCN1A* mutation was detected in family members that shared the same inherited mutation but showed clinical heterogeneous expression of disease, ranging from febrile seizures (FS), GEFS+, to Dravet syndrome and focal seizures [10, 11].

On the other side of the genetic spectrum of aetiologies of epilepsy are common variants that confer very low risk for disease that are typically detected through genome-wide association studies (GWAS). Such studies have now been performed using reasonably sized samples that detected variants in or around *SCN1A* that are associated with FS alone, focal epilepsy (in particular mesial temporal lobe epilepsy with hippocampal sclerosis and febrile seizures (mTLE-HS-FS)), and – remarkably – with all types of common epilepsy, including focal and genetic generalized epilepsy [12 - 16]. Recent large scale WES studies of common familial generalized and focal non-acquired epilepsy, showed a remarkable enrichment of ultra-rare coding variation in known epilepsy genes including *SCN1A*. This suggests that rare coding variants with a low risk of disease also increase susceptibility to epilepsy [17]. Finally, a few reports and unpublished observations described patients with focal epilepsy who were considered for epilepsy surgery and were found to be carriers of a likely pathogenic *SCN1A* mutation [8, 9]. Taken together, the genetic evidence for *SCN1A* shows a remarkable spectrum of disease associated *SCN1A* variants and their risk for disease, ranging from common low risk factors and rare inherited or de novo mutations with absolute risk for disease, to very rare relatively low risk factors. The clinical spectrum is equally broad, ranging from common benign to severe and very rare syndromes. This broad geno- and phenotypic spectrum associated with *SCN1A* must be taken into account when clinical decisions are made, especially in the case of surgical evaluation.

Even though the first gene for focal epilepsy, CHRNA4 causing autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), was found in 1995, it has only recently been demonstrated that genetic mutations are not only associated with generalized or multifocal epilepsies, but also underlie a broad range of focal epilepsies. The most notable novel gene discoveries have been made in the mTOR-family of genes, with a clinical spectrum of focal epilepsy that ranges from MCD to familial non-lesional focal epilepsy [18 - 22]. Causal mutations underlying these epilepsies have been found to be inherited, occurred de novo in sporadic cases, and have been detected as somatic mutations in resected brain tissue, which calls for comprehensive genetic testing and careful clinical genetic counselling. Mutations in DEPDC5, a gene that functions in the GATOR1 complex that inhibits the mTORC1 pathway, are now considered to be among the most common genetic causes of focal epilepsies, including familial focal epilepsy with variable foci (FFEVF), and have been reported in 13% of autosomal dominant sleep-related hypermotor epilepsy (ADSHE or ADNFLE) families [23]. A full overview of these genes and their implication in focal epilepsy is presented in the accompanying article in this issue. The importance of DEPDC5 and related genes in (familial) non-lesional focal epilepsy (FE) and in lesional epilepsies with MCD, in particular focal cortical dysplasia (FCD), may imply that searching for causal germline and somatic gene mutations underlying sporadic FE has consequences for surgical decision making. How the detection of such gene mutations should influence the decision to accept or reject a patient for surgery remains to be established.

Goals of epilepsy surgery

Epilepsy surgery is currently the only available curative treatment for pharmacoresistant focal epilepsy. However, it is clear that surgery is an invasive and irreversible procedure, and several restrictions apply, making it a safe procedure that is only performed on individuals that have a high probability of becoming seizure-free following surgery without unacceptable deficits that are the direct result of surgery. To accomplish this, a careful set of diagnostic procedures precedes any successful epilepsy surgery, aimed to accurately localize and delineate the epileptogenic zone and possible overlap with eloquent regions.

Presurgical evaluation procedures are complex, and have been outlined and standardized. Until recently, genetic screening was not part of the standard epilepsy surgery evaluation, although it has been mentioned as an important factor to consider in a perspective by Guerrini et al., that included genetic screening in the algorithm for diagnostic strategies and therapeutic approaches in patients with FCD [24].

Although the general aim of epilepsy surgery is to completely remove the epileptogenic focus, surgery is sometimes considered in patients for palliative treatment, aiming to reduce seizure load or cure the patient from just one, most burdensome, seizure type when there is a multifocal epilepsy syndrome. Whereas in the past only patients with clear structural MRI-visible lesions were considered surgical candidates, an increasing number of people with refractory epilepsy and normal imaging undergo evaluation, under the assumption that their focal epilepsy is caused by a MR-invisible, structural lesion, in particular FCD. The number of MRI-negative patients will decrease with improved imaging techniques, such as higher-field MRI or MRI post-processing [25, 26]. Currently 60 - 70% of these MRI-negative (but presumed lesional) patients are rejected for surgery, often after extensive and invasive intracranial electrode monitoring. Operated MRI-negative patients have a lower chance of reaching seizure freedom [27]. Furthermore, the absence of a histopathological abnormality occurs in ~8% of all operated patients and is a major predictor of poor outcome [28].

MRI-negative patients with refractory focal seizures can either have an 'invisible' structural lesion – such as a developmental abnormality – or an underlying genetic syndrome, not associated with a lesional source, or a combination of the two (e.g. tuberous sclerosis). We can assume that the lesional MRI-negative patients

have a higher chance of reaching seizure-freedom after epilepsy surgery than the non-lesional MRI-negative patients with a presumed genetic underlying cause. Therefore, we hypothesize that the crucial differentiation between people with operable and non-operable epilepsy (i.e. between a presumed lesional and non-lesional cause of seizures) requires new and reliable biomarkers.

Mutations in novel epilepsy genes are such biomarkers that are currently not routinely implemented in presurgical evaluation. Below we will summarize the current experience with genetic evaluation in patients who were considered surgical candidates, and discuss how preoperative genetic screening may differentiate between eligible and non-eligible surgical candidates. The discussion may be centralized around three crucial questions regarding the utility of genetic testing for presurgical evaluation.

The first question is to what extent can a genetic mutation be a negative predictor for postoperative seizure outcome and may be used to reject patients for surgery even in the presence of an operable lesion. With this question, the distinction must be made between palliative surgery and surgery with the aim to completely cure the patient from all seizures. The second question is whether mutations in genes can predict seizure freedom in people that have MRI-negative, but presumed lesional FE.

The final question is whether genetic mutations that predict lesional and operable epilepsy (for example the genes associated with FCD) have any additional and useful predictive value next to the current evaluation procedures.

The precise localization of the seizure-onset zone and eloquent cortical regions is challenging in FCD, as predictions of their anatomic locations may not conform to traditional models utilized for other pathologic substrates. These limitations must be appreciated fully to achieve higher rates of postoperative seizure freedom. Completeness of resection is an important determinant of outcome. Colocalization of the seizure onset zone with eloquentcortex is a major contributor to incom plete resection and surgical failure. The precise localization of the seizure-onset zone and eloquent cortical regions is challenging in FCD, as predictions of their anatomic locations may not conform to traditional models utilized for other pathologic substrates.

These limitations must be appreciated fully to achieve higher rates of postoperative seizure freedom. Completeness of resection is an important determinant of outcome. Colocalization of the seizure onset zone with eloquent cortex is a major contributor to incomplete resection and surgical failure. The precise localization of the seizure-onset zone and eloquent cortical regions is challenging in FCD, as predictions of their anatomic locations may not conform to traditional models utilized for other pathologic substrates. These limitations must be appreciated fully to achieve higher rates of postoperative seizure freedom. Completeness of resection is an important determinant of outcome. Colocalization of the seizure onset zone with eloquent cortex is a major contributor to incomplete resection and surgical failure.

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The published experience with epilepsy surgery in patients with genetic causes of epilepsy

There are relatively few reports on surgery cases that also carry a pathogenic mutation in an epilepsy gene. We recently reviewed the literature (until January 2017) on surgical outcome in different genetic causes of refractory epilepsy [29]. Only 24 eligible articles were found that described a total of 82 patients who underwent surgery for refractory epilepsy due to 15 different underlying genetic causes. The most frequent genetic abnormalities were mutations in *SCN1A* (8 cases), *DEPDC5* (9 cases), *NF1* (21 cases), and microdeletions (12 cases). We subdivided all cases in three broad categories including: “gene mutations involved with channelopathies and disorders of synaptic transmission”, “mTOR pathway gene mutations”, and “other genetic causes of epilepsy”. The most striking finding was the difference between the low rate of seizure-freedom in the germline mutations in genes associated with channelopathies and synaptic transmission disorders (2 out of 14 cases, 14%), versus the high rate of seizure freedom in the germline mTOR pathway gene mutations (6 out of 11, 55%) and the group of other genetic causes (24 out of 38, 63%, see **Table 1**).

These observations suggest that channelopathy and synaptic disorder genes are strong negative predictors for surgical candidacy, however, more observations for each gene, and type of mutation is clearly needed to come to definite conclusions.

The observations for the individual genes illustrate this point. For *SCN1A*, 8 cases have been described in two main papers. Barba et al. reported 4 patients who were found to have a MCD out of a series of 120 patients with *SCN1A* mutations, and two additional cases with MCD and SCN1A mutations that they included through U-task (the European taskforce for epilepsy surgery in children, [8]). All patients showed a phenotype consistent with Dravet syndrome, yet brain MRI showed periventricular nodular heterotopia (PNH) in 2, and FCD in 3 cases. Two of these FCD cases were oper-

Table 1: Success rates of epilepsy surgery for patients with different genetic causes – germline mutations – of epilepsy

Genetic Cause	MRI lesional Engel I	MRI non-lesional Engel I	all Engel I
Chanelopathies and disorders of synaptic transmission	1/9 (11%)	1/5 (20%)	2/14 (14%)
mTOR pathway mutation	4/7 (57%)	2/4 (50%)	6/11 (55%)
chromosomal other	23/35 (66%)	1/3 (33%)	24/38 (63%)
TOTAL	28/51 (55%)	4/12 (33%)	32/63 (51%)

ated after the partial seizure onset region was identified. This region was resected, but the authors report that same seizure types recurred after surgery without any reduction in seizure frequency. This report demonstrates that MCD and *SCN1A* mutations can co-occur, seemingly at a higher frequency than would be expected on the basis of the Dravet syndrome incidence of 1 in 20,000 - 40,000 births. It remains unclear whether the particular mutation had any effect on the occurrence of the MCD.

A second report described the clinical and histopathological outcome of 6 patients carrying a *SCN1A* mutation [9]. The phenotype was considered to be consistent with Dravet syndrome in 5 of these 6 patients, and one showed GEFS+. All developed focal seizures next to the generalized seizures. The patients underwent epilepsy surgery for their intractable focal seizures, and although some initial improvement was reported after surgery, recurrence of focal seizures occurred in 5 cases with an outcome classified as ILAE class 5, and one patient showed ILAE class 4.

Taken together, none of the reported 8 patients with *SCN1A* mutations seemed to benefit from epilepsy surgery with seizure reduction or reported improvement of quality of life, suggesting that surgery is unlikely to be beneficial in these children. However, larger series are needed to fully evaluate the predictive effect. It cannot be ruled out that palliative surgery can benefit some selected cases, by healing them from specific and targeted focal seizures, originating from an associated lesion, such as FCD or hippocampal sclerosis.

One report describes a family with segregating mutations in *SCN1B*, which encodes the beta-1-subunit that together with the alpha-subunit encoded by *SCN1A*, forms the voltage gated sodium channel [30]. It is described that the beta-1-subunit modulates the gating, inactivation kinetics, and localization of the ion-channel pore. Mutations in *SCN1B* are mainly detected in GEFS+ families, such as described in this paper. The family members showed variable phenotypes including febrile seizures alone, FS-plus, and 5 individuals presented TLE. Two of these patients underwent temporal lobectomy, that was successful in both. It can be hypothesized that these *SCN1B* mutations are causal for the febrile seizures that in turn may indirectly lead to the development of hippocampal sclerosis and TLE. Therefore, the effect of gene mutations on epilepsy surgery outcome must be evaluated for each gene separately and in the context of the presence of a clearly detectable focal brain lesion, that may be held responsible for at least part of the seizures.

In contrast to *SCN1A*, patients carrying mutations in genes associated with mTOR pathways appear to have better probability to become seizure free, which is in line with their association with focal epilepsy and FCD in particular. A detailed review of patients with *DEPDC5* mutation showed that for all these patients, the surgical approach was guided by a visible MRI lesion and/or by a circumscribed epileptogenic zone during invasive recordings (stereo-EEG). However, extensive presurgical imaging was performed and some patients were subjected to multiple interventions and had a wide resection including eloquent cortex, with post-surgical deficits. The main question to evaluate in such patients is whether subtle dysplastic lesions went undetected on imaging. Furthermore, in the patients with poor surgical outcome, a more complex epileptogenic network could not be excluded. A recent paper described a detailed analysis of a single patient with a *DEPDC5* mutation and sleep-related hypermotor epilepsy (SHE) who underwent a SEEG, but was rejected for surgery due to the lack of a clearly localised epileptogenic zone [31]. The authors also concluded that more tailored imaging procedures aimed at identifying a wider epileptogenic network may be essential to discriminate between *DEPDC5* patients who will benefit for surgery, irrespective of the presence of a MR visible circumvent lesion such as a FCD.

Our literature review identified 21 surgical cases with a mutation in NF1, the gene linked to neurofibromatosis type 1. The disease is associated with neurofibromatosis that may lead to epileptogenic lesions such as hippocampal sclerosis or low-grade tumours. Nevertheless, not all patients with epilepsy presented a single delineated epileptogenic zone, which is reflected by the reported seizure freedom rate of 57% (12/21). Only one MRI-negative case with NF1 was reported, who turned out to become seizure free after surgery.

A recent publication added *PCDH19* to the list of monogenic disorders that can be associated with focal seizures caused by a structural lesion [32]. The paper reports on five children with refractory epilepsy that was associated to *PCDH19* variants that underwent presurgical evaluation. *PCDH19* variants were confirmed to be de novo in three-, and FCD was reported in four out of the five children that were all girls. Interestingly, two patients underwent epilepsy surgery that resulted in a clear improvement of seizure control. On the other hand, one patient showed improvement at age 11 years without surgery, illustrating the previous observations that show seizure reduction over time and seizure freedom in some patients. Mutations in *PCDH19* are associated with early infantile epilepsy encephalopathy type 9 [33, 34]. In some cases, the phenotype resembles that of Dravet syndrome. Similarly, it is associated with a wide range of disease severity. *PCDH19* is located on the X-chromosome and heterozygous females are mostly affected, whereas males tend to show no symptoms unless they are mosaic for the mutation. This X-linked clinical expression pattern has been contributed to a phenomenon called "cellular interference" [35]. Seizure types observed in affected females include generalized tonic, clonic or tonic-clonic, and/or focal seizures, and most females have mental retardation, developmental problems, and psychiatric comorbidities [36, 37]. These observations, and the report of the *PCDH19* patients that underwent surgery, further underline the need to carefully investigate the benefit of epilepsy surgery for each epilepsy gene separately.

A growing body of evidence show that somatic mutations of several genes involved in the PI3K-AKT-mTOR pathway can also underlie MCD [38]. For example, low-level mosaic mutations of *mTOR* have been reported in the brain tissue of patients presenting with FCD type 2a [39]. Furthermore, another study showed mosaic *AKT3* mutations in brain tissue of patients presenting with focal brain malformations such as hemimegalencephaly and polymicrogyria, whereas germline or constitutional mutations presented in patients with diffuse bilateral cortical malformations, megalencephaly and heterotopia [40]. An important study of 118 children with bilateral perisylvian polymicrogyria (BPP) also showed a mixture of germline and mosaic mutations with some variability in phenotype [41]. The estimated degree of mosaicism varied widely between 5 - 73% of cells analysed. Furthermore, important for our question on the utility of genetic screening before epilepsy surgery, the authors showed that mosaic mutations can be easily missed when testing blood-derived DNA, but can be detected in saliva-derived DNA.

These observations have implications for genetic testing, suggesting that patients presenting with these MCD types must be tested using a deep sequencing technology that is able to detect low percentage of mosaic mutations, preferably using DNA derived from saliva. The importance for epilepsy surgery evaluation and prediction of post-surgery outcome needs further study, especially as somatic mutations are also reported in FCD.

Perspective for genetic testing in epilepsy surgery evaluation

Evidently, there is an urgent need for larger series of patients carrying mutations in the same epilepsy genes who are evaluated for, or have undergone epilepsy surgery. This data, ideally collected prospectively would allow clear quantification of the impact of a genetic diagnosis on presurgical selection and on its predictive capacity regarding outcome. As outlined above, several questions should be evaluated. First, the available data already suggest that genetic mutations are suitable biomarkers for selection or rejection of putative surgical candidates. This is illustrated by the data for the patients carrying pathogenic *SCN1A* mutations, who most likely do not benefit from surgery.

The second question is whether genetic testing can improve presurgical evaluation in MRI-negative patients. The data for the mTOR pathway genes seem to suggest that this would be possible, but clearly need more in-depth analysis of the clinical and imaging data.

Third, the broad phenotypes associated with *DEPDC5* mutations point to the question whether the presence of such mutations should indicate tailored, more detailed imaging prior to invasive recordings to evaluate the presence of a difficult to detect FCD, or, possibly, more widespread epileptogenic networks, even in the presence of a visible FCD. Such strategies should be evaluated for improved rate of post-surgery seizure freedom also in the mTOR pathway MRI-positive group, in which surgical outcome was only marginally better than in the mTOR pathway MRI-negative group.

Furthermore, the presence of mutations in genes encoding ion-channels or genes associated with synaptic function that are implicated in autosomal dominant forms of focal epilepsy – such as ADNFLE, or ADLTLE (autosomal dominant lateral temporal lobe epilepsy) – in MRI-negative patients, may exclude them from further evaluation. This would argue for early genetic testing prior to any invasive procedure. Finally, it is clear that recommendations should be based on both observational data and knowledge on disease aetiology. For example, in the case of *SCN1B* the occurrence of TLE – which may be operable – is probably not directly related to the mutation, but is likely secondary to the early occurrence of febrile seizures. Surgery in this case is directed to cure seizures originating from the abnormal tissue in the temporal lobe, and not to the febrile seizures.

The existence of international multi-centre collaborations, such as U-task, provides the ability to collect sufficient number of cases needed for meaningful analysis. The increase in genetic diagnostic screening of focal epilepsies, preferably with WES, will not only provide the opportunity for novel gene discovery, but will also clarify the promise of precision medicine for these patients.

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Somatic Mosaicism in Epilepsy with Focal Cortical Dysplasia

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Summary

Brain somatic variants are increasingly recognized as important causes of neurodevelopmental diseases, particularly in the pathogenesis of malformations of cortical development (MCDs), such as focal cortical dysplasia (FCD) and hemimegalencephaly. Therefore, the capability to detect such variants is critical to make genetic diagnosis in MCDs cases. Thanks to recent genomic technical improvements, multiple studies have implicated mTOR pathway brain somatic variants in various MCDs. The present review will show the main current approaches adopted to detect brain somatic variants, the role of mTOR signaling cascade in the pathogenesis of epilepsy with FCD and the therapeutic choices available at this time.

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Key words: Somatic mosaicism, focal cortical dysplasia, mTOR pathway

Mosaïcisme somatique dans l'épilepsie associée à une dysplasie corticale focale

Les mutations somatiques cérébrales sont de plus en plus reconnues comme des causes importantes de maladies neurodéveloppementales, en particulier dans la pathogenèse des malformations du développement cortical (MCD), telles que la dysplasie corticale focale (FCD) et l'hémimégalencéphalie. Par conséquent, la détection de telles mutations est essentielle pour le diagnostic génétique de ces pathologies. Grâce à de récentes techniques génomiques, plusieurs études ont impliqué des variants somatiques dans des gènes de la voie mTOR dans diverses MCD. La revue présente les principales approches actuelles adoptées pour détecter les variants somatiques du cerveau, le rôle de la cascade de signalisation mTOR dans la pathogenèse de l'épilepsie avec FCD et les choix thérapeutiques disponibles à ce jour.

Mots clés : Mosaïcisme somatique, dysplasie corticale focale, voie mTOR

Somatischer Mosaizismus bei Epilepsie mit fokaler kortikaler Dysplasie

Hirnsomatische Varianten werden zunehmend als wichtige Ursachen neurologischer Entwicklungsstörungen anerkannt, insbesondere hinsichtlich der Pathogenese von Fehlbildungen der Kortexentwicklung (MCDs), z. B. der fokalen kortikalen Dysplasie (FCD) und der Hemimegalenzephalie. Aus diesem Grund ist die Möglichkeit, derartige Varianten nachzuweisen, entscheidend für die Erstellung einer genetischen Diagnose bei MCD-Fällen. Dank neuerer technischer Fortschritte in der Genomik haben mehrere Studien eine Beteiligung hirnsomatischer Varianten des mTOR-Signalwegs an unterschiedlichen MCDs festgestellt. Die vorliegende Übersichtsarbeit fasst die wichtigsten aktuellen Ansätze zum Nachweis hirnsomatischer Varianten, die Rolle der mTOR-Signalkaskade bei der Pathogenese der FCD-Epilepsie und die derzeit verfügbaren Therapieoptionen zusammen.

Schlüsselwörter: Somatischer Mosaizismus, fokale kortikale Dysplasie, mTOR-Signalweg

Introduction

A postzygotic variant occurring during development can originate distinct populations of cells within an individual: this condition is referred to as mosaicism. If the variant occurs in the germline, it is indicated as "germline mosaicism", and the new variant can be transmitted to the progeny. Otherwise, we talk about "somatic mosaicism" if the variant arises in a cell that will develop in the soma, and therefore will not be transmitted to the descendants. Somatic variants may occur in both dividing and non-dividing cells and can be

due to an error during DNA replication (only in dividing cells) or to environmental factors (the most remarkable are UV light and carcinogens) [1].

The frequency of such variants in a cell population depends on different factors: the timing during development when they occurred; whether they affect patterns or rates of cellular proliferation and if a selective pressure is applied to the cells carrying the variant.

This review will summarize the current methodologies and techniques to detect somatic variants, and their role in brain development, with a focus on focal cortical dysplasia (FCD) and epilepsy.

Mosaicism discovery strategies

Somatic variants can be characterized by alterations of the DNA sequence (single nucleotide variants and small insertions/deletions) or by genomic structural variations (mobile element insertions, copy number variants, loss of heterozygosity, inversions, translocations, chromosomal aneuploidies/multiploidies), both in nuclear and mitochondrial DNA [2]. Most of the applied techniques can detect only a subset of these variants.

Another important factor influencing the detection of a somatic variant is its frequency in the examined tissue. Rare variants (i.e. with a low alternative allele frequency, < 10%) are harder to detect, regardless of the strategy and experimental technique used. Bulk tissue analysis and single-cell analysis are two major strategies applied in the discovery of somatic variants. Bulk tissue analysis is applied when the genomic DNA is extracted directly from a primary tissue, where cells carrying the variant can be present together with cells without the variant (wild-type). The tissue can be subjected to the sorting of certain cell fractions (e.g. specific neuronal cells by fluorescence activated cell sorting [FACS] of NeuN-positive cells), to analyze a more homogenous sample and to increase the percentage of cells carrying the variant. In the case of single-cell analysis, the genomic DNA of an individual cell is extracted, amplified and sequenced in a single experiment.

Experimental techniques usually applied to bulk tissue analyses during the variant discovery phase are whole exome sequencing (WES), whole genome sequencing (WGS), SNP (single nucleotide polymorphism) arrays, array-CGH (comparative genomic hybridization) and targeted high-coverage sequencing. Standard PCR (polymerase chain reaction), Sanger sequencing and digital droplet PCR are mostly applied as validation methods.

The bulk tissue approach is preferably chosen than the single-cell analysis because (i) it allows to obtain a greater amount of DNA, (ii) the preparation and handling of the sample is easier, (iii) it is less time consuming and less expensive and (iv) the technical validation of the identified variant in the original sample is equivalent to a biological duplicate. However, its main disadvantage consists in the fact that it can only detect variants at a relatively high allele frequency rate (~10%), unless a targeted high-depth sequencing is applied: in this case the detection has been proven to be as low as 0.1% [3]. The ability to detect these low frequency variants is important because evidence exists that these can lead to strong phenotypic effects. In the single-cell analysis, the genome of a single nucleus is sequenced in a unique experiment, and multiple cells are usually analyzed in parallel to obtain statistically significant findings. The main advantage of using the single-cell strategy is that it allows to discover variants present in the analyzed cell, regardless of its frequency in the tissue. However, for very rare variants, the analysis of a great number of individual cells would be necessary and the biological validation in the primary bulk tissue or in additional selected cells can be difficult. Therefore, the techniques applied to these studies must be robust. The first step in single-cell sequencing approaches consists in the whole genomic DNA amplification (WGA), during which cytosine deamination may occur resulting in common artifacts (artificial CG->TA transitions) [4]. Therefore, an error introduced during this phase will be propagated in the following sequencing steps, leading to a false positive call. An implementation of the currently used experimental procedures has been recently published, increasing the capability to detect somatic variants reducing false positive calls [5]. This will provide a greater insight into the pathogenic role of somatic variants in human disease. Lastly, the genomic sequence obtained by a single-cell analysis has always to be compared to the genome of a reference tissue to exclude germline variants: in single-cell sequencing, mosaic variants would appear at an alternative allele frequency of 50%, the same as germline heterozygous variants.

The technical and biological validation of an identified somatic variant is a crucial step. Depending on the discovery approach used, there are various recommended validation strategies, based on methods which differ for sensitivity, throughput and cost. If a bulk tissue analysis has been performed, the confirmation of the somatic call in the original sample is usually achieved using a technique more sensitive than the one used for the discovery phase, with a consequent biological and technical validation. For this reason, a targeted high-deep sequencing or digital droplet PCR are commonly adopted. If the mosaic variant has been identified through a single-cell sequencing approach, the biological confirmation, although very important, may not be achieved in the original bulk tissue, because the variant can be present at a frequency too low to be detected by any technique. Consequently, the technical validation is fundamental in these cases, though a variant artificially introduced during the DNA amplification phase of the single-cell sequencing approach will be validated anyway, leading to a false call. A comprehensive description of the cited techniques can be found in [6].

Specific bioinformatic tools are required for the analysis of next generation sequencing (NGS) data with the aim to detect somatic variants. The Broad Institute has suggested a workflow for the preprocessing of NGS data, consisting in the alignment of the raw files to the reference human genome, using Burrows-Wheeler Aligner (BWA) [7] and the Genome Analysis Toolkit (GATK) [8]. Subsequently, in the so-called variant discovery phase, different algorithms have been developed, e.g. Virmid [9] and MuTect [10], to generate a list of variants, that will be then annotated with different programs, e.g. SnpEff [11] or Variant Effect Predictor [12]. Optimized pipelines for the detection of mosaic SNVs in WES data have been recently presented [13, 14].

Brain somatic mosaicism and epilepsy with FCD

Mosaicism in the brain

The mutational burden in proliferating somatic cells is estimated to be very high: hypothetically, at each cell division a genetic variation can occur, with possible effects on cellular functions [15]. The role of somatic variants in the pathogenesis of most cancers is well known, but several studies have also demonstrated that somatic variants can lead to non-neoplastic diseases as well (e.g. Proteus syndrome, McCune-Albright syndrome and Sturge-Weber syndrome, which are skin disorders caused by somatic mutations in AKT1, GNAS1 and GNAQ genes respectively), and a small number of mutated cells can be sufficient to cause important structural/functional effects [15 - 19].

Most neurons do not face cell divisions during adult life; however, the cellular proliferation rate in the brain during the first half of the gestation period in animals is higher than in any other organ at any developmental phase. At the fourth week of gestation a limited number of neuronal progenitors are found in the developing brain, but at 24 gestation weeks 10^10 neurons will develop from these progenitors, with a 10^5 cell division rate per minute (higher than that of any cancerous or other somatic cell) [19]. The brain is therefore the organ with the highest risk of accumulating somatic variations during development, which could be linked to various neurodevelopmental disorders [19]. The development of the cerebral cortex involves different complex processes, including the proliferation of progenitor cells, migration and neuronal organization. Each of these steps may be affected by the occurrence of somatic variants in the DNA of subgroups of cells, causing phenotypes with different degrees of severity, from functional alteration of few neurons to malformations of cortical development (MCDs, including cortical layer disruption or enlarged brain) [20, 21].

Focal Cortical Dysplasia (FCD): definition and classification

MCDs are an important cause of pediatric and adult refractory epilepsy associated with developmental delay, in which seizures arise as a consequence of defective positioning of normal cortical neurons or due to abnormal cortical neurons leading to altered cortical circuitry [21 - 23]. A subgroup of MCDs include focal cortical dysplasia (FCD) and hemimegalencephaly (HME), cortical malformations limited to a portion or one entire brain hemisphere which can be identified by neuroimaging techniques (e.g. magnetic resonance imaging, MRI, and positron emission tomography, PET). The incidence and prevalence of FCD in the population is unknown; however, it is thought to account for most refractory epilepsy cases in childhood, and the proportion of FCD in surgical series is 9% [24]. Moreover, many cases of the so called non-lesional refractory focal epilepsy, undergoing surgical resection of the epileptogenic focus, result from small FCDs undetectable with standard MRI techniques, but which are confirmed by the histopathological analysis of the resected tissue.

Since its first description by Taylor and colleagues in 1971, several efforts for FCD classification have been made [25]. The last scheme was released by the International League Against Epilepsy (ILAE) in 2011, providing evidence for differences in morphology and protein expression among the different types and subtypes of FCD (**Figure 1**) [26].

It is to be noted that in the context of the same lesion, multiple FCD subtypes can coexist, as well as different severity grades are recognized among different tissue samples of the same FCD type, suggesting a common molecular mechanism that can have a graded effect with a spatial spectrum [27]. Nevertheless, the present classification is based on histopathological findings, without any correlation with genetic etiologies, which have been recently identified (see below). These findings may lead to another revision of the current classification [28].

FCDs share certain pathological phenotypes with HME: disorganized/absent cortical lamination, loss of radial neuronal orientation, and abnormal neuronal differentiation and maturation [13]. However, while HME leads to gross cortex malformation with the enlargement of an entire brain hemisphere, FCD is not always visible on MRI imaging, but may often be confirmed by histopathological examination of resected brain tissues from patients subjected to surgical removal of the epileptogenic focus. This finding together with the fact that most FCD and HME occur sporadically, suggests that somatic variants in genes involved in main brain developmental processes, as neuronal cell growth and migration, may be the leading cause.

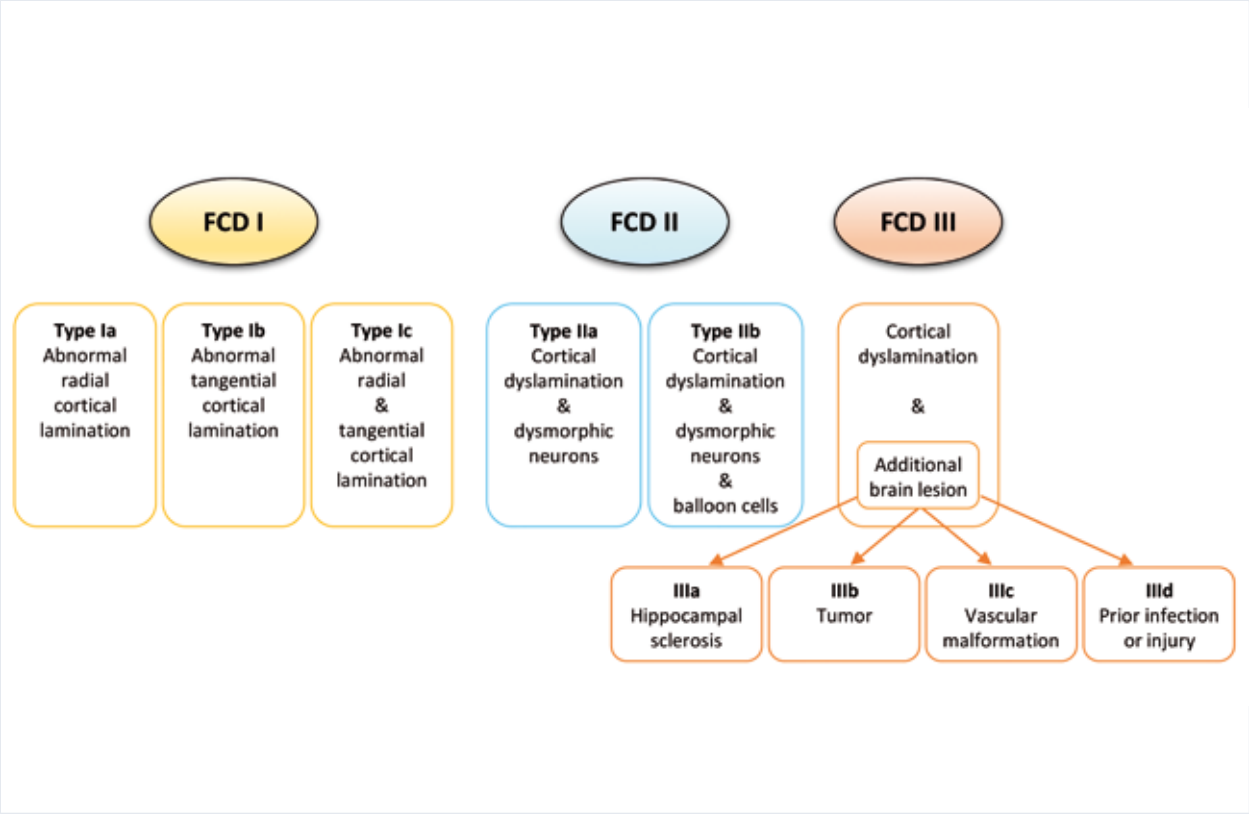

Figure 1. FCD classification, adapted from Blümcke et al. (2011) [26].

FCD and mTOR signaling

The first suspicions about the pathogenic mechanisms leading to the development of FCD came in 2004, only 30 years after its first report, when Babys et al. and Miyata et al. described the hyperactivation of the mechanistic target of rapamycin (mTOR) pathway in human FCD and cortical tuber samples [29, 30]. Subsequently, this was also demonstrated in HME brain specimens [31, 32]. mTOR is a serine/threonine kinase expressed ubiquitously in mammalian tissues. Its signaling pathway has important roles in different cellular functions: protein synthesis and transcription regulation, cell growth and proliferation, metabolism, cell motility and death [33]. In the brain, mTOR signaling has been implicated in synaptic plasticity and learning, neurogenesis and dendritic/axonal morphology [34, 35]. Therefore, the involvement of mTOR signaling alteration was in line with the pathological findings of FCD and HME, in particular cytomegaly. However, the hyperphosphorylation of mTOR targets was only confirmed in a subset of cells in the brain lesions, suggesting that the molecular cause of this cellular phenotype would have been present in the same cells and not in the entire lesion. This led to hypothesize that a somatic variant could be the cause of FCD or HME. Thanks to technical sequencing advancements, brain somatic variants in mTOR pathway genes PIK3CA, AKT3 and MTOR itself have been firstly identified in HME patients [36] and more recently MTOR brain variants have been detected in about 15 - 46% of FCD patients [37, 38]. In these cases, the mosaic variant allele frequency rate can be as low as about 1%, further underlining that low level somatic variants can cause neurodevelopmental disorders (as also shown by in vivo mouse model of FCD) [37]. After these first reports, many others have involved mTOR pathway genes in the pathogenesis of FCD, further confirming that FCD belongs to the so-called “mTORopathies”. Moreover, variants in MTOR are associated with a spectrum of brain malformations phenotypes that seem to be correlated with the levels of mosaicism [39, 40]. Not only somatic but also germline variants, and both gain of function as well as loss of function variants have been described. To date, FCD-associated gain of function variants in mTOR signaling have been reported in MTOR gene itself and PIK3CA, while variants with a loss of function effect (both null and missense variants) have been identified in inhibitors of the same signaling cascade (TSC1, TSC2, DEPDC5, NPRL2 and NPRL3), all leading to mTORC1 activation [41 - 43, 27, 44, 37, 45, 38, 46 - 49, 39] (**Figure 2**). The proteins encoded by DEPDC5, NPRL2 and NPRL3 genes constitute the GATOR1 complex, a negative regulator of mTORC1 complex, belonging to the amino acid sensing branch of the signaling. Several reports have underlined the role of loss of function GATOR1 variants in the pathogenesis

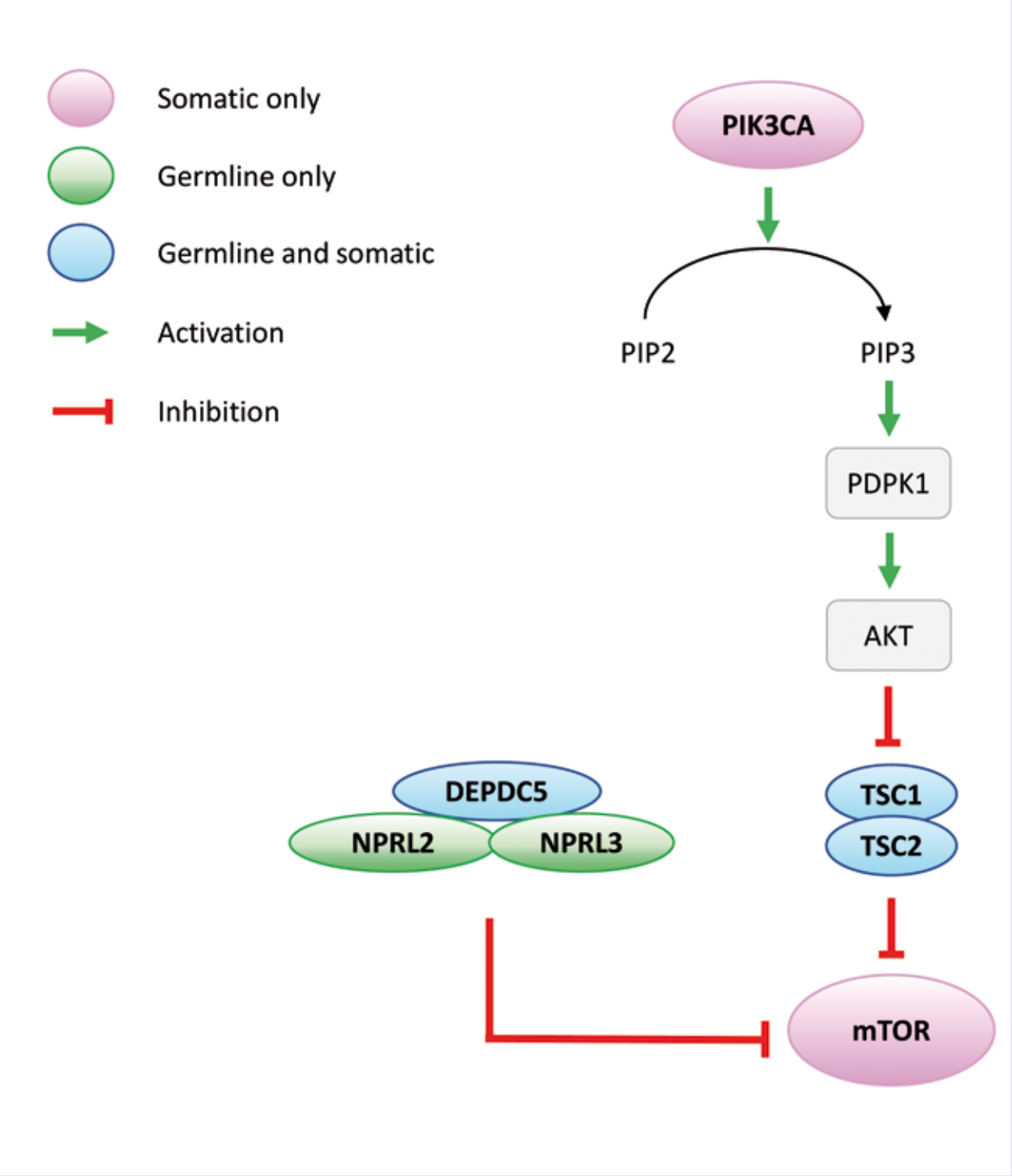

Figure 2. Schematic showing mTOR pathway main actors currently involved in the pathogenesis of epilepsy with FCD. Somatic and germline refer to the type of variant reported so far.

of focal epilepsy with MCDs, despite not all patients display MRI abnormalities. This has suggested that a second somatic hit (leading to the complete removal of inhibition of mTOR signaling) could be necessary for the MCD to occur: intriguingly, a second somatic nonsense variant was identified in the resected brain tissue of a patient with FCD carrying a germline nonsense variant of DEPDC5 [41]. This mechanism could also explain the differences seen among the brain lesions found in patients with FCD: the identification of the developmental time points at which the somatic variant occurs and of the progenitor cells involved may help to clarify how the same variant can lead to different histopathology features.

Epilepsy with FCD: Therapeutic strategies

A large spectrum of epileptic conditions characterizes the clinical manifestations of FCDs and depends on the age of seizures onset and on the extent and localization of the dysplasia. Despite the progresses made in the diagnosis of FCD-associated epilepsies, most cases are drug-resistant [50]. The standard treatment in cases of refractory epilepsy is the surgical resection of the lesion [22], with a fluctuating seizure freedom rate after the surgery. In fact, long term seizure outcome is influenced by diverse factors, such as the identification of the lesion on MRI and its complete removal, the localization and the extension of the lesion, histological findings, and the age at which the epilepsy surgery was conducted [51]. Recent publications have also highlighted that the seizure outcome in FCD patients is also related to the type of FCD diagnosed: in a long-term analysis of 211 FCD patients, Fauser and colleagues (2015) highlighted that FCD types I, II and IIIa have similar postoperative outcomes, with Engel class I at last follow-up (> 5 years) reported in 56% of FCD type I, 61% of FCD type II and 64% of FCD type III cases, and that a complete withdrawal of anticonvulsant drugs was significantly higher in FCD II patients [52]. However, in a more recent work, a significant difference among FCD IIa and IIb subtypes was reported, with a better outcome in FCD IIb (88% Engel Ia after 5 years) compared to FCD IIa (57% Engel Ia after 5 years) [51]. Interestingly, FCD type I resulted to be the one with the lower surgery success rate, with seizure freedom achieved in 21% of the patients (at 5 years from the surgery, Engel Ia) [51]. This finding is consistent with the fact that FCD type I lesions are often difficult to see on MRI [53], which is one of the factors mostly impacting the surgery outcome, possibly due to incomplete resection of the abnormal tissue.

Due to the high percentage of refractory seizures in FCD patients, alternative therapeutic approaches (e.g. ketogenic diet and vagus nerve stimulation) could also be considered in combination with surgical resection of the lesion, or alone in those cases not suitable for surgery [54]. However, the identification of variants in mTOR pathway genes in surgically resected FCD tissues shows that mTOR inhibitors, such as rapamycin analogs or ATP-competitive mTOR inhibitors, could be considered as possible alternative antiepileptic drugs, as already done for TSC patients [55]. The development of novel molecules targeting specifically other mTOR pathway components such as GATOR1 complex could lead to a more specific anti-epileptogenic effect, in contrast to the systemic effect of rapamycin, with possible fewer side effects for the patients [55].

Our present inability to adequately treat many patients with refractory epilepsy caused by FCD is a significant clinical problem.

Conclusions

The present review has highlighted the established role of brain somatic variants in neurodevelopmental diseases, and FCD in particular. Advancements in DNA sequencing techniques have allowed to sequence DNA extracted from FCD tissues, leading to the discovery of brain mosaic variants in mTOR pathway genes, at allele frequencies as low as 1%. Moreover, as FCD is characterized by a mosaic pattern of abnormal cells, the single-cell sequencing approach seems to be very promising for FCD genetic diagnosis. The molecular mechanisms leading to the development of these malformations of cortical development are not yet well understood; further efforts will be needed to elucidate how an altered mTOR signaling drives the development of FCD and other MCDs, ultimately leading to epilepsy. The epileptic phenotypes associated with these malformations can be severe and are often drug-resistant. The current strategies to face these conditions include the combination of multiple antiepileptic drugs and surgical resection of the epileptogenic zone, but seizure outcome depends on multiple factors and the anticipation of a long-term outcome is still difficult to achieve.

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Webcast Epilepsiebehandlung

Mit welchen neuen Medikamenten können wir in den nächsten Jahren rechnen? Wann lohnt sich eine Operation, wann eine ketogene Diät? Wer unsere Veranstaltung vom November 2017 in Basel verpasst hat, kann drei Vorträge auch im Nachhinein sehen und hören, ja sogar gezielt nach Begriffen suchen.

Fachveranstaltung: www.epi.ch/basel
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☐	☐	☐	.....	Häufigste Ursachen von Epilepsien
☐	☐	☐	.....	Medikamentöse Behandlung
☐	☐	☐	.....	Reisen und Epilepsie
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☐	☐	☐	.....	Arbeit und Epilepsie
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* Flyer auch auf Portugiesisch und Albanisch verfügbar.

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Ich (wir) möchte(n):

☐ Einzelmitglied der Epilepsie-Liga werden (50 Franken jährlich).
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Ligue Suisse contre l'Epilepsie
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Save the dates: Two ILAE congresses in Switzerland

We have started preparations to host the 2019 "Jahrestagung der Deutschen und Österreichischen Gesellschaften für Epileptologie und der Schweizerischen Epilepsie-Liga" (Annual Meeting of the Austrian and German Societies for Epileptology and the Swiss Epilepsy League), also known as the **"Dreiländertagung", in Basel**. Please block out **8 – 11 May 2019** on your calendar.

In addition, we are pleased to announce that the 14th European Congress on Epileptology will take place in **Geneva on 4 – 8 July 2020**. This biennial meeting is a collaboration of the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). We expect around 2,000 participants from all across Europe.

And for all those who have not registered yet: this year's annual conference takes place in Aarau on **30 – 31 May 2018**: www.sgkn-congress.ch

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Förderung der wissenschaftlichen Forschung im Bereich der Epilepsie (vorwiegend Starthilfen) durch die Schweizerische Epilepsie-Liga

Die Epilepsie-Liga unterstützt wissenschaftliche Projekte im Bereich der Epileptologie im Gesamtbetrag von

CHF 25'000.—

pro Jahr. Insbesondere soll die Erforschung von Ursachen und Behandlungen der Epilepsie gefördert werden.

Stipendien für Aus- oder Weiterbildung oder Auslandaufenthalte werden nicht ausgerichtet. Hingegen können Reise- und Aufenthaltskosten (ohne Salär) für Kurzaufenthalte (maximal einige Wochen) finanziert werden, sofern sie dem Erlernen von Methoden dienen, welche im Rahmen eines unterstützten Projektes in der Schweiz eingesetzt werden.

Falls der Antragsteller/die Antragstellerin bereits anderswo Anträge für Unterstützung gestellt hat, ist offen zu legen, bei wem und mit welchem Ergebnis.

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Bitte vormerken:

Die nächste Mitgliederversammlung findet am 30. Mai 2018 um 18.30 Uhr in Aarau statt.

Vorschau Epileptologie 2 | 2018

Die Ausgabe 2/2018 ist das 60. Heft der 2003 mit neuem Design gestalteten Fachzeitschrift „Epileptologie" der Schweizerischen Epilepsie-Liga (SEL). Dies wollen wir zum Anlass nehmen, das umfangreiche Angebot für Menschen mit Epilepsie vorzustellen. Schon aus Platzgründen müssen wir uns dabei auf die Kliniken beschränken, dabei aber sowohl mit ihrem stationären als auch ambulanten Leistungsspektrum. Jede Klinik hat die Gelegenheit sich vorzustellen.

Promotionspreis

Die Schweizerische Epilepsie-Liga vergibt alle 3 Jahre einen Preis in Höhe von

CHF 1'000.—

für die beste Dissertation an einer Schweizer Hochschule auf dem Gebiet der Epileptologie.

Bewerbungen sind aus allen Fachbereichen und Berufsgruppen möglich und erwünscht, sowohl aus Grundlagen- als auch klinischen Fächern. Eine Altersbeschränkung erfolgt nicht.

Preisrichterkollegium ist die Forschungskommission der Epilepsie-Liga, die bei Bedarf zusätzlich externe Gutachter hinzuziehen kann. Es trifft seine Entscheidung in geheimer Wahl.

Falls der Antragsteller/die Antragstellerin bereits anderswo Anträge für Unterstützung gestellt hat, ist offen zu legen, bei wem und mit welchem Ergebnis.

Die Preisverleihung erfolgt jeweils im darauf folgenden Jahr anlässlich der Jahrestagung oder Mitgliederversammlung der Epilepsie-Liga. Bewerbungen sind elektronisch oder in fünf Exemplaren bis zum **31.12.2018**

an die Geschäftsstelle der Epilepsie-Liga (Seefeldstrasse 84, 8008 Zürich, info@epi.ch) einzureichen und müssen beinhalten:

- die abgeschlossene und beim Dekanat eingereichte Dissertation
- und die Stellungnahme des Doktorvaters (dabei kann es sich auch um das entsprechende Gutachten für die Dissertation handeln).

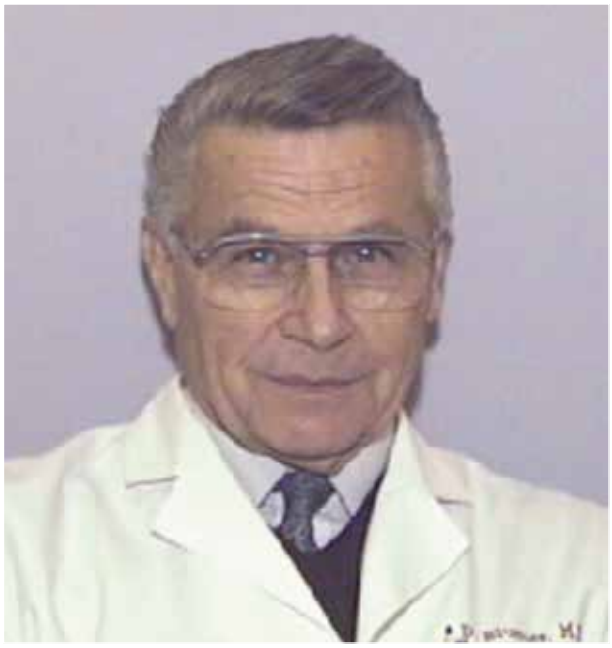
Nachruf Dietrich Blumer (1929 – 2017)

Am 29. September 2017 ist unser korrespondierendes Mitglied Dietrich Peter Blumer im Alter von 88 Jahren in Memphis, Tennessee, verstorben. Er wurde am 20. Juli 1929 in Luzern geboren. Studium, Promotion und Beginn der psychiatrischen Facharztweiterbildung erfolgten in Zürich. Von 1948 bis 1956 absolvierte er seinen Dienst in der Schweizer Armee. 1957 wechselte er in die USA, wo er 1962 eingebürgert wurde.

In den USA schloss er seine Weiterbildung an der Universität von Washington in Saint Louis, Missouri, und am Sheppard & Enoch Pratt Hospital in Towson, Maryland, bis 1961 ab. Von 1962 bis 1972 war er zunächst Instructor und dann Associate Professor für Psychiatrie am Johns Hopkins Hospital in Baltimore, Maryland, wo er u.a. mit dem Neurochirurgen A. Earl Walker kooperierte. Nach dessen Emeritierung wechselte er von 1972-77 als Associate Professor an die Harvard Medical School in Boston, Massachusetts, wo er u.a. mit den Neuropsychologen und Neurologen Norman Geschwind und Frank Benson zusammenarbeitete. Von 1977 bis 1987 war er Chairman für Psychiatrie sowie Abteilungsleiter für Neuropsychiatrie und Forschung am Henry Ford Hospital in Detroit, Michigan, sowie Klinischer Professor für Psychiatrie an der Universität von Michigan in Ann Arbor, Michigan. Während dieser Zeit war er u.a. betreuender Psychiater der „Detroit Tigers", dem lokalen Major-League-Baseball-Team.

1987 wechselte er schliesslich nach Memphis, Tennessee, an das dortige Epilepsie-Zentrum (Epi-Care Center), wo er eine Professur für Psychiatrie innehatte und Abteilungsleiter für Neuropsychiatrie am Health Science Center der Universität von Tennessee war, zuletzt war er dort Professor Emeritus.

Blumer prägte u.a. erstmals 1995 in Fortführung von Beschreibungen von Emil Kraepelin und Eugen Bleuler die Bezeichnung „interiktale dysphorische Störung" für periodisch auftretende interiktale Verstimmungszustände bei Epilepsie [1 - 3]. Für diese von ihm detailliert beschriebene pleomorphe affektive Störung bei Epilepsie, die neben einer labil-depressiven Stimmung, Anergie, Schmerz, und Insomnie auch durch affektive Symptome (Angst, Furcht) sowie die als „spezifisch" postulierten Symptome einer paroxysmalen Reizbarkeit und zeitweise euphorischen Stimmung charakterisiert ist, wurde auch die Bezeichnung Blumer-Syndrom vorgeschlagen [4].



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Günter Krämer, Neurozentrum Bellevue, Zürich

Prix d'encouragement de la recherche

Promotion de la recherche scientifique dans le domaine de l'épilepsie (surtout sous forme d'aide initiale) par la Ligue Suisse contre l'Epilepsie (Ligue contre l'Epilepsie)

La Ligue contre l'Epilepsie soutient les projets scientifiques dans le domaine de l'épileptologie par un montant total de

CHF 25'000.—

par an, la priorité étant accordée aux projets cherchant à élucider les causes et à mettre au point des traitements de l'épilepsie.

Aucune bourse ne sera octroyée pour la formation de base ou continue ou pour des séjours à l'étranger. En revanche, la prise en charge de frais de voyage et de séjour (sans salaire) est possible pour les séjours de courte durée (quelques semaines au maximum) lorsque ces séjours servent à apprendre des méthodes appliquées dans le cadre d'un projet bénéficiant de soutien en Suisse.

Si le requérant a déjà fait une demande de soutien ailleurs, il faut nous en informer en spécifiant où et avec quel résultat.

Délai de remise des demandes :

31 décembre 2018

Les demandes sont à adresser par voie électronique à info@epi.ch.

Voir instructions : www.epi.ch/soutien_recherche

Ligue Suisse contre l'Epilepsie
Seefeldstrasse 84
8008 Zurich
Tél. 043 488 67 77
Fax 043 488 67 78
info@epi.ch

Prix de la meilleure thèse

La Ligue Suisse contre l'Epilepsie (Ligue contre l'Epilepsie) décerne tous les 3 ans un prix d'un montant de

CHF 1'000.—

pour la meilleure thèse de doctorat à une université suisse dans le domaine de l'épileptologie.

Tous les domaines spécialisés et tous les groupes professionnels couvrant les disciplines fondamentales ou cliniques sont invités à soumettre leur candidature. Aucune limite d'âge n'a été fixée.

Le jury décernant le prix se compose de la Commission de la recherche de la Ligue contre l'Epilepsie. Il peut être complété au besoin par des experts externes. La décision est prise par vote secret.

Si le requérant a déjà fait une demande de soutien ailleurs, il faut nous en informer en spécifiant où et avec quel résultat.

Le prix est toujours décerné l'année suivante dans le cadre de l'assemblée annuelle ou générale de la Ligue contre l'Epilepsie.

Les dossiers de candidature doivent parvenir au Secrétariat général de la Ligue contre l'Epilepsie (Seefeldstrasse 84, 8008 Zurich, info@epi.ch), sous forme électronique ou en cinq exemplaires, jusqu'au

31 décembre 2018

et comporter les pièces suivantes :

- la dissertation achevée et remise au décanat,
- une prise de position du directeur de thèse (il peut par exemple s'agir de l'expertise concernant la thèse).

A noter s.v.p. (en langue allemande)

La prochaine assemblée générale aura lieu à Aarau le 30 mai 2018 à 18h30.

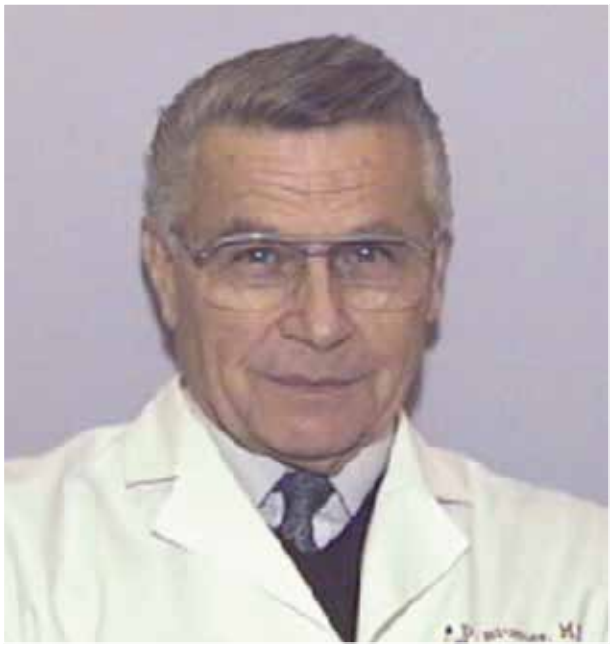
Eloge funèbre de Dietrich Blumer (1929 – 2017)

Notre membre correspondant Dietrich Peter Blumer est décédé à l'âge de 88 ans le 29 septembre 2017 à Memphis, Tennessee. Né le 20 juillet 1929 à Lucerne, il suit ses études, obtient son doctorat et se spécialise en psychiatrie à Zurich. Il officie de 1948 à 1956 dans l'armée suisse, avant de rejoindre les Etats-Unis en 1957, où il est naturalisé en 1962.

Aux Etats-Unis, il termine sa formation à l'université de Washington à Saint-Louis, Missouri, et au Sheppard & Enoch Pratt Hospital à Towson, Maryland, jusqu'en 1961. De 1962 à 1972, il occupe tout d'abord la fonction d'Instructor puis d'Associate Professor en psychiatrie au Johns Hopkins Hospital à Baltimore, Maryland, où il collabore notamment avec le neurochirurgien A. Earl Walker. Après le départ à la retraite de ce dernier en 1972, il devient jusqu'en 1977 Associate Professor à la Harvard Medical School à Boston, Massachusetts, où il travaille entre autres avec les neuropsychologues et neurologues Norman Geschwind et Frank Benson. De 1977 à 1987, il est Chairman en psychiatrie et directeur du service de neuropsychiatrie et de recherche du Henry Ford Hospital à Detroit, Michigan, ainsi que Professeur clinicien en psychiatrie à l'université du Michigan à Ann Arbor, Michigan. Pendant cette période, il est notamment le psychiatre qui suit l'équipe locale de la Ligue majeure de baseball, les « Detroit Tigers ».

En 1987, il s'installe finalement à Memphis, Tennessee, pour rejoindre le centre de l'épilepsie local (EpiCare Center), où il occupe une chaire de psychiatrie et la fonction de directeur du service de neuropsychiatrie au Health Science Center de l'université du Tennessee, où il est en dernier lieu professeur émérite.

On doit notamment à Dietrich Blumer la désignation « trouble dysphorique interictal » qu'il a utilisée pour la première fois en 1995, à la suite des descriptions d'Emil Kraepelin et Eugen Bleuler, pour qualifier les troubles interictaux de l'humeur survenant périodiquement chez les patients épileptiques [1 - 3]. La désignation de syndrome de Blumer a également été proposée pour ce trouble affectif pléomorphe de l'épilepsie qu'il avait décrit en détail et qui, outre l'humeur dépressive instable, l'anergie, la douleur et l'insomnie auxquelles il est associé, se caractérise également par des symptômes affectifs (anxiété, peur) ainsi que par les symptômes supposés « spécifiques » d'une irritabilité paroxystique et d'une humeur euphorique intermittente [4].



Quelle: www.memorialparkfuneralandcemetery.com

1. *Blumer D, Montouris G, Hermann B. Psychiatric morbidity in seizure patients on a neurodiagnostic monitoring unit. J Neuropsychiatry Clin Neurosci 1995; 7: 445-456*
2. *Blumer D. Dysphoric disorders and paroxysmal affects: recognition and treatment of epilepsy-related psychiatric disorders. Harvard Rev Psychiatry 2000; 8: 8-17*
3. *Blumer D, Montouris G, Davies K. The interictal dysphoric disorder: recognition, pathogenesis, and treatment of the major psychiatric disorder of epilepsy. Epilepsy Behav 2004; 5: 826-840*
4. *Schmitz B. Depression and mania in patients with epilepsy. Epilepsia (fourth series) 2005; 46: 45-49*

Günter Krämer, Neurozentrum Bellevue, Zürich

The MICHAEL PRIZE 2019

Awarded for the first time in 1963 to encourage epilepsy research in Germany, to date the MICHAEL PRIZE is one of the most highly regarded international awards for the best contributions to clinical and experimental research which promote further developments in epileptology. It is awarded biennially and is specifically addressed to younger researchers not older than 45 years of age. The prize money is 20.000 Euro.

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- Clinical neurophysiology
- Neuropsychology, Psychology and Psychiatry
- Epilepsy Genetics

The applicants may submit up to three scientific papers in English language, already published or submitted for publication; at least one of the papers, already published or not, must be from the period 2017 / 2018. The papers (publications or manuscripts) must be submitted to STIFTUNG MICHAEL before December 31, 2018 together with a curriculum vitae and with an indication which of the three eligible fields the applicant's research is referring to.

For entry form and upload, please consult:
www.michael-foundation.de/michaelpreis

The applications submitted will be rated by an independent jury consisting of:

Heidrun Potschka, Munich Germany;
Yushi Inoue, Shizuoka /Japan;
Jean Gotman, Montreal / Canada

The final decision will be taken by the Board of Trustees of the Michael Foundation.

The MICHAEL PRIZE 2019 is kindly sponsored by UCB International

For information:
Stiftung Michael
Alsstr. 12
D – 53227 Bonn / Germany
E-Mail: post@stiftung-michael.de
Website: www.stiftung-michael.de or
www.michael-foundation.de

2018

18.4.2018 I Genève, 17 h
Colloque pour médecins: L'épilepsie pour les généralistes et les neurologues
Information :
Ligue Suisse contre l'Epilepsie, Seefeldstrasse 84, 8008 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch, www.epi.ch

21.-27.4.2018 I Los Angeles, CA, USA
70th American Academy Of Neurology (AAN) Annual Meeting 2018
Information : American Academy of Neurology, 201 Chicago Avenue, Minneapolis, MN 55415,
Tel: 001 / 612 / 9286000,
Fax: 001 / 612 / 4542746,
e-mail: memberservices@aan.com,
https://www.aan.com/conferences/annual-meeting/

1.-6.5.2018 | Washington, D.C., USA
31st International Congress of Clinical Neurophysiology (ICCN) of the International Federation of Clinical Neurophysiology (IFCN)
Information: International Congress of Clinical Neurophysiology, 555 E. Wells St., Suite 1100, Milwaukee,
WI 53202-3823, USA,
Tel. 001 / 414 / 9189803,
Fax 001 / 414 / 2763349,
e-mail: ICCN2018@acns.org,
http://iccn2018.acns.org/

30.-31.5.2018 I Aarau, Kongresshaus
37. Jahrestagung der Schweiz. Gesellschaft für klinische Neurophysiologie zusammen mit der Schweizerischen Epilepsie-Liga
Information: Epilepsie-Liga, Seefeldstrasse 84, 8008 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch, www.epi.ch

13.-16.6.2018 | Fürth, Deutschland
54. Jahrestagung der Deutschen Gesellschaft für Epileptologie e.V.
Information: Conventus Congressmanagement & Marketing GmbH, Juliane Schönau, Carl-Pulfrich-Strasse 1, 07745 Jena, Deutschland,
Tel. 0049 / 3641 / 31 / 16347,
Fax 0049 / 3641 / 31 / 16243,
e-mail: juliane.schoenau@conventus.de,
www.conventus.de, www.epilepsie-tagung.de

16.-19.6.2018 I Lissabon, Portugal
4th Congress of the European Academy of Neurology
Information: European Academy of Neurology, Breite Gasse 4/7, 1070 Wien, Österreich,
Tel. 0043 / 1 / 889 / 0503,
Fax 0043 / 1 / 889 / 05 03 13,
e-mail: headoffice@ean.org,
www.ean.org/lisbon2018/

28.6.-1.7.2018 | Bali, Indonesien
12th Asian & Oceanian Epilepsy Congress
Information: ILAE/IBE Congress Secretariat, 7 Priory Office Park, Stillorgan Road, Blackrock, Co. Dublin, A94 FN26, Irland,
Tel. 00353 / 1 / 2056720,
Fax 00353 / 1 / 2056156,
e-mail: bali@epilepsycongress.org,
www.epilepsybali2018.org/

7.-11.7.2018 | Berlin, Deutschland
11th Forum of Neuroscience (FENS)
Information: Kenes International Organizers of Congresses S.A., rue François-Versonnex 7, 1207 Genf,
Tel. 0041 / 22 / 908 0488,
Fax 0041 / 22 / 9089140,
www.forum2018.fens.org/

16.8.2018 I Basel, 9.30 - 18.00 h
Basler Epilepsie-Tag: Epilepsy mimics – ist es wirklich Epilepsie?
Information: stephan.rueegg@usb.ch

26.-30.8.2018 | Wien, Österreich
13th European Congress on Epileptology
Information: ILAE/IBE Congress Secretariat,
7 Priory Office Park, Stillorgan Road, Blackrock,
Co. Dublin, A94 FN26, Ireland,
Tel. 00353 / 1 / 2056720,
Fax 00353 / 1 / 2056156,
email: vienna@epilepsycongress.org,
www.epilepsyvienna2018.org

13.9.2018 I Bürgerspital Solothurn, 14.15 h
Fachveranstaltung: Besser mit Epilepsie leben
Information: Epilepsie-Liga, Seefeldstrasse 84,
8008 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch, www.epi.ch

29.9.-2.10.2018 I San José, Costa Rica
10th Latin American Congress on Epilepsy
http://www.epilepsycongress.org/10th-latin-american-congress-on-epilepsy-2018/

4.10.2018 I Lugano, 16 h
Epilessia e psiche
Information: Lega contro l'Epilessia,
Seefeldstrasse 84, 8008 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch, www.epi.ch

30.11.-4.12.2018 I New Orleans, Louisiana, USA
72nd Annual Meeting of the American Epilepsy Society (AES)
e-mail: aes@experient-inc.com,
www.aesnet.org/annual_meeting

2019

4.-11.5.2019 I Philadelphia, PA, USA
71st American Academy of Neurology (AAN) Annual Meeting 2019
Information: American Academy of Neurology,
201 Chicago Avenue, Minneapolis, MN 55415,
Tel: 001 / 612 / 9286000,
Fax: 001 / 612 / 4542746,
e-mail: memberservices@aan.com,
https://www.aan.com/conferences/annual-meeting/

8.-11.5.2019 I Basel
11. Dreiländertagung der Schweizerischen Epilepsie-Liga und der Deutschen und Österreichischen Gesellschaften für Epileptologie
Information: Epilepsie-Liga
Seefeldstrasse 84, 8008 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 488 6778,
e-mail: info@epi.ch,
www.epi.ch

22.-26.6.2019 I Bangkok, Thailand
33. Internationaler Epilepsie-Kongress (IEC)
www.epilepsybangkok2019.org

2020

25.4.-2.5.2020 I Toronto, Ontario, Canada
72nd American Academy of Neurology (AAN) Annual Meeting 2020
Information: American Academy of Neurology,
201 Chicago Avenue, Minneapolis, MN 55415,
Tel: 001 / 612 / 9286000,
Fax: 001 / 612 / 4542746,
e-mail: memberservices@aan.com,
https://www.aan.com/conferences/annual-meeting/

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Bleulerstrasse 72, 8008 Zürich

Das Original

Lamotrigin

Lamictal®

Die bewährte Therapie bei Epilepsie*,1,2

* Zur Behandlung von partieller Epilepsie mit oder ohne sekundär generalisierte tonisch-klonische Anfälle und von primär generalisierten tonisch-klonischen Anfällen.
- Monotherapie oder Zusatztherapie bei Erwachsenen und Jugendlichen ab 12 Jahren.
- Zusatztherapie bei Kindern von 2–12 Jahren. Nicht als initiale Monotherapie.

Weiterhin nur 10% Selbstbehalt für Patienten[3]

Lamictal®. W: Lamotrigin. **I:** Epilepsie (partielle und generalisierte tonisch-klonische Anfälle), als Monotherapie ab 12 Jahren, als Add-on-Therapie ab 2 Jahren. **D:** *Monotherapie:* Übliche Erhaltungsdosis: 100–200 mg/Tag in 1–2 Dosen. *Add-on-Therapie:* Übliche Erhaltungsdosis: Erwachsene und Jugendliche ab 12 J.: 100–400 mg/Tag je nach Begleitmedikation; Kinder von 2–12 J.: 1–15 mg/kg/Tag je nach Begleitmedikation. Details wie Eindosierungsschemata, Dosisanpassung bei mässiger bis schwerer Leberinsuffizienz und bei Änderungen der Begleitmedikation: siehe Fachinformation. **KI:** Überempfindlichkeit gegenüber einem der Inhaltsstoffe, schwere Niereninsuffizienz. **W/V:** Vorsicht bei leichter bis mässiger Niereninsuffizienz. (Dosisabhängiges) Risiko schwerer Hautreaktionen: alle Patienten mit Hautausschlag umgehend untersuchen und Lamictal® sofort absetzen, sofern Kausalzusammenhang nicht sicher ausschliessbar. Risiko eines Überempfindlichkeitssyndroms (u.a. Kontrolle der Leberfunktionsparameter). Risiko einer aseptischen Meningitis. Rebound-Anfälle bei plötzlichem Absetzen von Lamictal®. Erhöhtes Risiko für Suizidalität. **IA:** Glukuronidierung-induzierende Medikamente (z.B. Carbamazepin, Phenytoin, Primidon, Phenobarbital, Rifampicin, gewisse HIV-Medikamente, Ethinylestradiol/Levonorgestrel) verkürzen Eliminationshalbwertszeit von Lamictal®, Glukuronidierung-inhibierende Medikamente (z.B. Valproat) verlängern diese. Lamotrigin hemmt die renale tubuläre Sekretion über OCT2-Proteine. Wirkung von Lamotrigin auf die Pharmakokinetik hormonaler Kontrazeptiva: Eine verminderte Wirksamkeit der Kontrazeptiva kann nicht mit Sicherheit ausgeschlossen werden. **S:** Lamictal® soll während der Schwangerschaft nicht angewendet werden, es sei denn, dies ist eindeutig erforderlich (tiefst mögliche therapeutische Dosis verwenden). Die physiologischen Veränderungen während der Schwangerschaft können Lamotriginspiegel und/oder Wirkung beeinflussen. **UW:** *Sehr häufig:* Exanthem, Schwindel, Kopfschmerzen, Ataxie, Schläfrigkeit, Diplopie, Verschwommensehen, Übelkeit, Erbrechen, Durchfall, Müdigkeit. *Häufig:* Aggressivität, Reizbarkeit, Schlaflosigkeit, Tremor, Nystagmus. *Selten oder sehr selten:* u.a. Stevens-Johnson-Syndrom, toxische epidermale Nekrolyse (Lyell-Syndrom), Lupus-ähnliche Reaktionen, Alopezie, aseptische Meningitis, Leberversagen, Angioödem, Überempfindlichkeitssyndrom, hämatologische Auffälligkeiten (u.a. aplastische Anämie), Halluzinationen, Albträume, Bewegungsstörungen, extrapyramidale Effekte, Zunahme der Anfallshäufigkeit. **P:** Tabletten zu 2 mg, 30 Stk. Tabletten zu 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 56 Stk. **AK:** B. **Stand der Information:** Oktober 2016. GlaxoSmithKline AG. Ausführliche Angaben finden Sie unter www.swissmedicinfo.ch. Unerwünschte Arzneimittelwirkungen melden Sie bitte unter pv.swiss@gsk.com.

Referenzen:
1. Marson AG et al. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. Lancet 2007; 369: 1000-1015.
2. Fachinformation Lamictal®, www.swissmedicinfo.ch
3. www.spezialitaetenliste.ch, 01.02.2017; Der reguläre Selbstbehalt von 10% ist für alle GSK-Medikamente gewährleistet.

GlaxoSmithKline AG, Talstrasse 3–5, CH-3053 Münchenbuchsee, www.glaxosmithkline.ch

CH-LTS-0006133/22.02.2017/02.2017/Ca

Gemeinsame Jahrestagung der SGKN und der Epilepsie-Liga

Mittwoch | Wednesday
Donnerstag | Thursday

30. und 31. Mai 2018

Kultur & Kongresshaus Aarau

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Informationen & Registration | www.sgkn-congress.ch