Biological Psychiatry: Celebrating 50 Years

Measuring Electroencephalography: The Ups and Downs of Delta and Beta Bands as Biomarkers for 15q11-q13–Related Disorders

Geeske M. van Woerden

Human chromosome region 15q11-q13 is one of the genomic regions known to be susceptible to duplications, deletions, and mutations resulting in neurodevelopmental disorders. Some of the genes located in this chromosomal region are subject to genomic imprinting resulting in sole paternal or maternal expression, whereas other genes are biallelically expressed. Consequently, depending on whether the maternal or paternal allele is affected, disruptions in this region will result in Angelman syndrome (AS) (maternal allele disruption), Prader–Willi syndrome (PWS) (paternal allele disruption), or 15q11-q13 duplication syndrome (dup15q) (most often maternal allele duplication), each of which has its own distinct clinical features [as reviewed by Kalsner and Chamberlain (1)]. The causative genes for these 15q11-q13 disorders are *UBE3A* for AS and most likely dup15q syndrome and *MKRN3*, *MAGEL2*, *NDN*, *NPAP1*, *SNRPN*, and the small nucleolar RNA genes for PWS; in most cases, however, the biallelically expressed genes on this 15q11-q13 locus—specifically those encoding the gamma-aminobutyric acid A receptor ($GABA_AR$) subunits *GABRB3*, *GABRA5*, and *GABRG3*—are also thought to play a role in the phenotypic expression of these disorders. Indeed, individuals carrying a deletion of the 15q11-q13 locus in general show more severe clinical features compared with individuals in whom uniparental disomy or point mutations in the imprinted genes or imprinting region are causing the disorder. Regardless, there has not been a reliable measure to assess the precise role of the $GABA_AR$ subunits in the phenotypes seen in the 15q11-q13 syndromes. In the current issue of *Biological Psychiatry*, Frohlich *et al.* (2) introduce a tool for genotype–phenotype correlations in 15q11-q13 syndromes and offer a set of biomarkers to assess the involvement of the $GABA_AR$ subunits in these syndromes, focusing specifically on AS.

AS is caused by either deletions or mutations in the maternal allele that result in the loss of function of the UBE3A gene. Seventy percent of individuals with AS carry a deletion of the maternal allele at 15q11-q13, encompassing several genes, including *UBE3A*, *GABRB3*, *GABRA5*, and *GABRG3* (here referred to as AS deletion), but 20% to 25% of individuals with AS only carry a loss of function of the maternally inherited *UBE3A* gene either through point mutations or paternal uniparental disomy (here referred to as AS nondeletion). All individuals with AS irrespective of the genotype show clear abnormal electroencephalography (EEG) patterns, a clinical characteristic that has been proposed to be used as a biomarker (3,4). It was more recently proposed that specifically the rhythmic delta activity serves as a highly reliable preclinical as well as clinical biomarker for AS (5). However, this was again irrespective of genotype.

Frohlich *et al.* (2) used a large cohort of individuals with deletion and nondeletion AS to measure and quantitatively analyze EEG activity. In their analysis of the EEG measurements, they corroborate the findings of Sidorov *et al.* (5), showing increased delta power in the total AS cohort compared with typically developing (control) children. Further comparison between deletion with nondeletion AS reveals that at a younger age the increase in delta power is more pronounced in the deletion cohort, but this difference in delta power between deletion and nondeletion AS disappears when the children are older. Having the increased delta band in both AS cohorts makes it likely that this phenotype is caused by loss of function of *UBE3A*. Frohlich *et al.* (2) go one step further by comparing the presence and abundance of other frequency bands between deletion and nondeletion AS. They show that there are clear differences in the theta and the beta band oscillations between deletion and nondeletion AS. Beta bands are shown to be weaker in the deletion AS compared with the nondeletion AS cohort, whereas theta bands show a clear oscillation in deletion AS that is absent in the nondeletion AS cohort. These results indicate involvement of other genes besides the *UBE3A* gene in the deletion AS group causing these EEG patterns, for which the $GABA_AR$ subunit genes are the most likely candidate.

Changes in the beta and delta band activity have also been shown for dup15q syndrome (6,7). Most cases of dup15q are caused by duplication of the maternal allele [as reviewed by Adam *et al.* (8)], resulting in duplication of the *UBE3A* as well as the $GABA_AR$ subunit genes. Thus, the finding that these band frequencies in dup15q syndrome are changed in the opposite direction (i.e., increased beta power and decreased delta power) compared with deletion AS further supports the idea that differences in expression level of UBE3A and the $GABA_AR$ subunits are responsible for the differences in EEG patterns specifically in these frequency bands. In addition, the abnormal beta band activity seen in children with dup15q syndrome is similar to the pattern observed after injection with benzodiazepine and other positive $GABA_AR$ modulators, further narrowing down the specific beta band power changes in EEG measurements to the $GABA_AR$ subunit genes. Previously, Frohlich *et al.* (7) compared the dup15q syndrome group with children with nonsyndromic autism spectrum disorder and a group of typically developing control subjects and showed that

SEE CORRESPONDING ARTICLE ON PAGE 752

https://doi.org/10.1016/j.biopsych.2019.03.002
ISSN: 0006-3223

specifically the beta band increased in the dup15q group compared with both the autism spectrum disorder and the control subject groups. Unfortunately, in the current Frohlich *et al.* study (2), the beta band was not compared between the individuals with nondeletion AS and the control subjects, nor between the individuals with deletion AS and the control subjects. Considering that this specific EEG pattern is thought to derive from the hemizygosity of the $GABA_AR$ subunit genes, individuals with nondeletion AS would be expected to show no difference in the beta band compared with the control subjects. This would be further evidence that this frequency band would be a powerful biomarker when medically targeting the $GABA_AR$ subunit specifically. Moreover, it would be interesting to see whether individuals with PWS— also hemizygous for the $GABA_AR$ subunits—show similar changes in the beta band. Changes in EEG activity are not a characteristic clinical feature of PWS; thorough studies of EEG activity patterns, such as those done by Frohlich *et al.* (2), have not yet been performed in PWS.

There is need for some caution in interpreting the results put forward by Frohlich *et al.* (2). First, the average age of the different cohorts is quite different, with the deletion AS group (showing the biggest differences) being the youngest and the control subject group being the oldest. In early childhood, slow wave bands such as the delta frequency contribute significantly to EEG patterns during wakefulness, but this declines as the brain matures (9). Thus, as Frohlich *et al.* (2) also indicate, a larger cohort with better age-matched control subjects is required to further support their findings. In addition, because delta phenotypes are stronger in children with AS at younger ages and decrease with age (4,5), using the delta band frequency as a biomarker (as opted by many different studies) would be optimal during early childhood. Some caution is warranted, however, because brain activity measured with EEG is undergoing significant changes at this time point because of brain maturation (as mentioned above). This could make it difficult to interpret EEG measurements before and after a certain treatment—depending, of course, on the time course of the treatment.

Finally, as Frohlich *et al.* (2) mention, some patients were taking medication during the EEG recordings, and some medications act on the central nervous system. Frohlich *et al.* do not find significant difference between the deletion and nondeletion AS groups in the use of each type of medication, indicating that this is not a confounding factor in their data. I agree with that statement, but it would be interesting to see whether there is a correlation with the type of medication and EEG pattern in general in their data. In addition to this, in general it would be interesting to see a phenotype–EEG correlogram. How much of the differences in EEG patterns are correlated with the severity of the phenotypes seen in children with AS? Do the children with the most severe changes in EEG pattern in the cohort used by Frohlich *et al.* (2) also have the most severe clinical features? Previous studies have shown that epilepsy severity did not correlate with EEG pattern (10). How about correlation with other clinical features? Frohlich *et al.* (2) have a beautiful data set to make a first attempt to find such correlations, which possibly would open doors to other potential biomarkers.

In conclusion, the work by Frohlich *et al.* (2) is an important in-depth study showing the involvement of specific genes with specific EEG brain activity patterns (a genotype–EEG correlation) that sheds new light on the difference in phenotypes between individuals carrying deletions or duplications in 15q11-q13 region compared with those in whom only the imprinted genes are affected. This study has important implications for therapy possibilities as well as potential biomarkers for not only AS, but the whole spectrum of 15q11-q13 region syndromes.

Acknowledgments and Disclosures

Early Career Investigator Commentaries are solicited in partnership with the Education Committee of the Society of Biological Psychiatry. As part of the educational mission of the Society, all authors of such commentaries are mentored by a senior investigator. This work was mentored by Ype Elgersma, Ph.D.

I thank M.C.Y. de Wit, M.D., Ph.D., for her fruitful discussion and helpful comments.

The author reports no biomedical financial interests or potential conflicts of interest.

Article Information

From the Department of Neuroscience and the ENCORE Expertise Center for Neurodevelopmental Disorders, Erasmus Medical Center, Rotterdam, The Netherlands.

Address correspondence to Geeske Marieke van Woerden, Ph.D., Erasmus Medical Center, Neuroscience, Wytemaweg 80, Rotterdam, Zuid-Holland 3015CN, The Netherlands; E-mail: g.vanwoerden@erasmusmc.nl.

Received Mar 1, 2019; accepted Mar 5, 2019.

References

1. Kalsner L, Chamberlain SJ (2015): Prader-Willi, Angelman, and 15q11-q13 duplication syndromes. Pediatr Clin North Am 62:587–606.
2. Frohlich J, Miller MT, Bird LM, Garces P, Purtell H, Hoener MC, *et al.* (2019): Electrophysiological phenotype in Angelman syndrome differs between genotypes. Biol Psychiatry 85:752–759.
3. Korff CM, Kelley KR, Nordli DR (2005): Notched delta, phenotype, and Angelman syndrome. J Clin Neurophysiol 22:238–243.
4. Vendrame M, Loddenkemper T, Zarowski M, Gregas M, Shuhaiber H, Sarco DP, *et al.* (2012): Analysis of EEG patterns and genotypes in patients with Angelman syndrome. Epilepsy Behav 23:261–265.
5. Sidorov MS, Deck GM, Dolatshahi M, Thibert RL, Bird LM, Chu CJ, Philpot BD (2017): Delta rhythmicity is a reliable EEG biomarker in Angelman syndrome: A parallel mouse and human analysis. J Neurodev Disord 9:17.
6. Urraca N, Cleary J, Brewer V, Pivnick EK, McVicar K, Thibert RL, *et al.* (2013): The interstitial duplication 15q11.2-q13 syndrome includes autism, mild facial anomalies and a characteristic EEG signature. Autism Res 6:268–279.
7. Frohlich J, Senturk D, Saravanapandian V, Golshani P, Reiter LT, Sankar R, *et al.* (2016): A quantitative electrophysiological biomarker of duplication 15q11.2-q13.1 syndrome. PLoS One 11:e0167179.
8. Finucane BM, Lusk L, Arkilo D, Chamberlain S, Devinsky O, Dindot S, *et al.* (2016): 15q duplication syndrome and related disorders. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Stephens K, *et al.*, editors. GeneReviews. Seattle (WA): University of Washington.
9. Eisermann M, Kaminska A, Moutard ML, Soufflet C, Plouin P (2013): Normal EEG in childhood: From neonates to adolescents. Neurophysiol Clin 43:35–65.
10. Valente KD, Varela MC, Koiffmann CP, Andrade JQ, Grossmann R, Kok F, Marques-Dias MJ (2013): Angelman syndrome caused by deletion: A genotype-phenotype correlation determined by breakpoint. Epilepsy Res 105:234–239.