Rare Genetic Syndromes Associated with Autism

Subjects: Neurosciences

Contributor: Olga Sysoeva , Anastasia K Neklyudova , Kirill Smirnov , Anna B. Rebreikina , Olga Martynova

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social and communicative skills, behavioral stereotypes, and sensory abnormalities. Its prevalence is one in 54 children, with the number of identified cases rising annually. Atypical sensory processing is one of the key characteristics of autistic people that can have a cascading influence on higher-level functions, such as language or social inference. Behaviorally, sensory abnormalities can present as hypo- and hyperresponsiveness (or hypo- and hyperreactivity). One of potential reasons for this multidirectional deficit is the high heterogeneity of idiopathic ASD (the form of autism where the biological cause of the disease is not identified).

Fragile X syndrome | Angelman syndrome | Phelan–McDermid syndrome | Rett syndrome | autism spectrum disorder (ASD)

1. Hypersensitive Syndromes

1.1. Fragile X Syndrome

Fragile X syndrome (FXS) is a neurodevelopmental disorder associated with intellectual disability, social deficits, hypotonia, and anxiety. Its prevalence varies from approximately 1:4000 in males to 1:8000 in females [1], making it the second most common chromosome abnormality that leads to intellectual disability after Down's syndrome [2]. Intellectual disability is mild or moderate in this syndrome [3]. FXS has a strong comorbidity with ASD, with a prevalence of 22% for both sexes [1][4]. Another frequently associated condition is attention deficit and hyperactivity disorder (ADHD), which occurs in 60–84% of cases [5][6]. FXS patients display weaknesses across all language and literacy domains compared to peers, with particular noticeable impairment being the higher occurrence of word repetition in these patients [7]

Fragile X syndrome is caused by *FMR1* gene disruption on the X chromosome that prevents the expression of FMRP, which is involved in synaptic development and plasticity [8]. The disruption of this mechanism affects multiple neurotransmission neuromediator systems, including GABAergic. Studies have found a reduction in the expression of several GABA-A receptor subunits (namely α1,3, 4, β1,2, and γ1,2), suggesting a decrease in phasic inhibition in FXS [9]. Later experiments have reported a decrease in the number of δ subunits, which are located extra-synaptically [10] and are involved in tonic inhibition and the general level of excitability of neural networks [11]. Thus, both phasic and tonic inhibition systems are affected in FXS [12].

Studies of FXS consistently reflect hyperexcitation and hyperresponsiveness of the auditory system in patients and animal studies on both behavioral and electrophysiological levels, suggesting a neurophysiological pathway into the origin of these autistic symptoms. Of note, the neurophysiological hypersensitivity and decreased habituation that led to an increased response to the repetitive stimulation in the case of FXS (probably in both visual and auditory modality) might lead to decreased sensitivity to changes and inattention symptoms, as reflected in attenuated MMN and P3a components. This pattern of results might be linked to the decreased tonic and phasic inhibition found in this syndrome.

1.2. Angelman Syndrome

Angelman syndrome is a genetic neurodevelopmental disorder with a prevalence rate of 1:10,000–20,000 births [13]. The clinical phenotype includes intellectual disability that ranges from moderate to severe and is present almost in 100% of patients, microcephaly, and impairments in motor development, i.e., abnormal gait and coordination difficulties and hypotonia [14][15]. Language development in individuals with AS is severely impaired, from entirely non-verbal behavior to speaking a few words or phrases [16]. Hyperactivity is present in AS, though it decreases with age [17][18]. Autistic-like characteristics are a common symptom and affect 36% of AS patients [1].

Two main genetic causes lead to AS. The first one (nondeletion type) is connected with the *UBE3A* gene de novo mutations, imprinting defects, and paternal uniparental disomy and account for 25–30% of all cases. Paternal copies of *UBE3A* are epigenetically silenced in the brain; therefore, the maternal inactivation of *UBE3A* causes a nearly complete loss of UBE3A selectively in the brain [19]. *UBE3A* encodes ubiquitin-protein ligase E3A, which is involved in targeting proteins for subsequent degradation by proteasome [20], and is also involved in the regulation of the cell cycle, synaptic plasticity, and cellular protein quality control [21]. The second cause is deletion at the 15q11-q13 locus, which contains *UBE3A* and in several cases other genes, including those coding different GABA receptors subunits—*GABRB3*, *GABRA5*, and *GABRG3* [22]. Individuals with deletion AS have a more severe clinical phenotype [15][23].

Even among the patients with similar genetic etiology and relatively homogeneous symptoms that lead to diagnosis of AS, it can be seen that heterogeneity in the sensory processing with both hypo- and hyperresponsiveness reported at the behavioral level. This heterogeneity might be partly caused by the number of genetic abnormalities involved and the implication of additional genes (such as those related to GABA activity) that should be taken into consideration. On the electrophysiological level, it can be seen that hypersensitive patterns, such as frequently occurring seizures, prolonged components of somatosensory ERPs, and generally decreased neuronal noise that can be suggested from elevated slower rhythms (θ and Δ) over the higher ones (β) [24] reported for a subpopulation of AS with the deletion phenotype. Combining these findings with animal models, it can be assumed that the impairment in tonic inhibition leads to the hypersensitive phenotype in patients with AS.

2. Hyposensitive Syndromes

2.1. Phelan–McDermid Syndrome

22q13 deletion syndrome, also known as Phelan–McDermid syndrome (PMS), is a neurodevelopmental disorder characterized by hypotonia, intellectual disability of varying degrees (from severe in a majority of cases to mild in some patients), delayed or absent expressive speech, and dysmorphia [25][26]. Its prevalence according to approximate estimates is between 1:8000–15,000 and the rate of autism in PMS is very high and varies from 50 to 75% [25][27]. It is supposed that 1% of people with autism have Phelan–McDermid Syndrome [28].

PMS is caused by de novo or inherited impairments at the 22q13 locus with the *SHANK3* gene as the major candidate gene. The severity of symptoms positively correlates with deletion sizes [29]. The protein product of *SHANK3* (it has the same name) is a scaffolding protein in postsynaptic glutamate receptors, including NMDA, mGluRs, and AMPA receptors [30][31]. *SHANK3* knockout mice demonstrate a reduction in the expression of parvalbumin (PV), while the amount of GABAergic PV+ interneurons does not change [32]. As decreases in PV leads to increased facilitation of GABA release, the inhibition is increased [33]. A series of animal studies demonstrated that *SHANK3* deletion only in the GABAergic interneurons is enough to reproduce the phenotype [34] [35], supporting the crucial role of inhibition in the development of PMS.

PMS individuals showed a decreased amplitude of the P50 and P2 auditory components [36][37]. It was reported that weaker γ-band ASSR in patients with PMS as well as with idiopathic ASD [38]. However, data on 40-Hz ASSR in idiopathic ASD is inconsistent as no difference in this response was also reported [39][40], suggesting that atypical γ-band ASSR might be associated with a subgroup of ASD, probably those with abnormalities within a *SHANK3*-related pathway. This idea has been supported by a high-functioning girl with mild intellectual disability, attenuated language skills, and slightly atypical social and communication functions. She had a drastic reduction of 40-Hz ASSR and *SHANK3* microduplication [41], again linking γ-band ASSR with *SHANK3* abnormalities. As 40-Hz ASSR reflects the functioning of NMDA receptors on GABAergic interneurons [42][43], its reduction supports the link between the abnormal functioning of local inhibitory connections in PMS patients and potentially in a subgroup of idiopathic ASD.

2.2. Rett Syndrome

Rett syndrome (RS) is a severe neurodevelopmental disorder generally characterized by normal development during the first 6–18 months, followed by a stagnation and a loss of acquired motor and language skills. RS is frequently associated with autistic traits which occur in approximately 60% of cases [1]. Other common symptoms are breath irregularities, abnormal gait, and hand wringing [44][45]. Its prevalence varies from 1:10,000 to 1:20,000 [46]. RS patients are suggested to have severe intellectual disabilities [47], while adequate assessment of cognitive functions are challenging due to severe motor problems and the absence of necessary language skills.

The majority of Rett syndrome cases come from different types of *MECP2* gene mutations. Its protein product—*MECP2* protein—interacts with a regressor complex of HDACs and SIN3A proteins to repress gene transcription [48][49] and also plays the role of a transcriptional activator [50]. *MECP2* affects the activity of more than 60 different molecular pathways, including those involved in spine morphology, dendritic complexity, and mTOR signaling vital

for cell growth and metabolism [51]. Of note, *MECP2* disruption only in GABAergic neurons seemed to be enough to cause symptoms in mice models [52], pointing to the crucial role of inhibition in the development of RS.

Electrophysiological and phenotypical data concerning sensory deficit in Rett syndrome is inconsistent, suggesting discrepancies between modalities. ERPs studies of auditory and visual modalities suggested hyposensitivity (delayed and decreased amplitudes of P2 and MMN in the auditory modality and reduced N1-P2 and N2 components in the visual modality), whereas somatosensory studies pointed to hypersensitivity. Attenuated and delayed ERPs, as well as steeper 1/f slope of resting EEG with predominance of low-frequency over the high-frequency activity, might be linked to increased tonic inhibition suggested in RS. One possible mechanism of this imbalance in RS is based on increased GABA spillover beyond the synapse [53].

2.3. Tuberous Sclerosis

Tuberous sclerosis complex (TSC) is a genetic disorder with the prevalence of 1:5,500–10,000 live births in the population. It is characterized by benign tumors in multiple organs, epilepsy, attention deficit and hyperactivity disorder, anxiety, sleep disorders, and other behavioral problems [54]. Severe intellectual disability is present in more than half of patients [55]. ASD criteria meet around 25–40% of patients [56][57].

TSC is caused by a mutation in the *TSC1* (encodes hamaritine protein) or the *TSC2* (encodes tuberine protein) genes. Tuberine and hamaritine act as a complex and inhibit the RHEB protein, which activates mTORC1, a crucial protein for many neurodevelopmental processes, such as the initiation of protein translation and cell growth control [58].

Little is known about hypo- or hypersensitivity tendencies in sensory processing in TSC patients; however, in a case study, sensory dysregulation in daily activities was reported [59].

Electrophysiological evidence suggested hyposensitivity in patients with TSC (delayed visual components and decreased and delayed ERPs in auditory modality). Interestingly, despite downregulated inhibitory currents [60], this syndrome remains mostly hyposensitive. One possible explanation for this was provided from a magnetic resonance spectroscopy (MRS) study, where a decreased number of GABA-A receptors was found in patients with TSC, accompanied by elevated GABA concentration [61]. Authors suggested the elevation of GABA is a compensation mechanism for decreased inhibition. Possibly, the molecular impairments associated with TSC lead to overcompensation and result in a hyposensitive phenotype.

2.4. Neurofibromatosis Type 1

Neurofibromatosis type 1 (*NF1*) is the most common inherited disorder of the central nervous system with a prevalence that varies from 1:2,000 to 1:5,000 subjects [62]. Phenotypically, *NF1* is characterized by multiple cafe-au-lait spots (flat dark patches on the skin), axillary and inguinal freckling, and various and multiple benign tumors in the central nervous system. Patients with neurofibromatosis type 1 are likely to have ASD and its prevalence varies from 10 to 40% [63][64]. Moreover, ADHD is very common in this disorder, being a major contributor to

academic underachievement in this population [65]. Intellectual disabilities are not very common in *NF1*; however, it occurs in a mild degree in 5–30% of patients [66][67].

NF1 is caused by mutations in the *NF1* gene located at chromosome 17q11.2; they can be either inherited or de novo [68]. This gene encodes a neurofibromin protein, reduces cell proliferation, and is involved in the development and growth of a variety of tissues [69]. An animal model of *NF1* is characterized by an increased activity-dependent release of GABA, suggesting increased phasic inhibition in *NF1* [70].

Increased latencies of brainstem auditory evoked potential (bAEP) were found in 15–28% of *NF1* patients [71][72]. Findings suggested that abnormalities in auditory processing in the early stages of development can cause the occurrence of ASD symptoms in *NF1* [73]. Authors investigated ERPs to repetitive auditory stimuli in infants with *NF1* at the age of 5 and 10 months and found decreased age-related changes in the scalp profile of neural responses.

In addition to delayed and decreased early components in different modalities, especially in the visual modality, research focuses on impaired attention in neurofibromatosis type 1. A deficit of attention-related component P3 was reported and the possible cause for that is a reduced sensitivity to sensory stimuli that significantly impact the bottom-up attention switch; however, it failed to be proven experimentally. Interestingly, a later component N450 was shown to be enhanced, which probably corresponds with a compensation mechanism. Taken together, the increased phasic inhibition might be related to attenuated early ERP components, while lower inhibition in the frontal cortex might cause the quicker and smaller attention-related ERPs.

4. Conclusion

To conclude, it is important to say that based on electrophysiological findings it can be subdivided syndromes into two groups with hyper- and hyposensitivity phenotypes. Several indicators that would be useful for assessing sensory impairments in both research and clinical practice were identified. First, it is components of event-related potentials that might point to shifts towards hypo- or hypersensitivity at different stages of information processing. Second, resting state EEG can provide information about tendencies towards inhibition or excitation in the neuronal network, e.g., via such promising parameters as 1/f slope, and evoked and induced γ and α rhythms. The above-mentioned EEG/ERP parameters can be a good candidate for translational biomarkers between animal and patient studies that allow one to capitalize on the more precise understanding of mechanisms and the underlying molecular paths to sensory deficit in syndromic forms of ASD that is possible only in animal studies.

References

1. Richards, C.; Jones, C.; Groves, L.; Moss, J.; Oliver, C. Prevalence of autism spectrum disorder phenomenology in genetic disorders: A systematic review and meta-analysis. Lancet Psychiatry 2015, 2, 909–916.

2. Butler, M.G. Fragile X syndrome: A major cause of x-linked mental retardation. Compr. Ther. 1988, 14, 3–7.
3. Rousseau, F.; Heitz, D.; Biancalana, V.; Blumenfeld, S.; Kretz, C.; Boué, J.; Tommerup, N.; Hagen, C.V.D.; DeLozier-Blanchet, C.; Croquette, M.-F.; et al. Direct diagnosis by DNA analysis of the fragile X syndrome of mental retardation. N. Engl. J. Med. 1991, 325, 1673–1681.
4. Rotschafer, S.; Razak, K. Auditory processing in fragile X syndrome. Front. Cell. Neurosci. 2014, 8, 19.
5. Bailey, D.B.; Raspa, M.; Olmsted, M.; Holiday, D.B. Co-occurring conditions associated with FMR1 gene variations: Findings from a national parent survey. Am. J. Med. Genet. A 2008, 146, 2060–2069.
6. Sullivan, K.; Hatton, D.; Hammer, J.; Sideris, J.; Hooper, S.; Ornstein, P.; Bailey, D. ADHD symptoms in children with FXS. Am. J. Med Genet. 2006, 140, 2275–2288.
7. Finestack, L.H.; Richmond, E.K.; Abbeduto, L. Language development in individuals with fragile X syndrome. Top. Lang. Disord. 2009, 29, 133–148.
8. Huber, K.M.; Gallagher, S.M.; Warren, S.T.; Bear, M.F. Altered synaptic plasticity in a mouse model of fragile x mental retardation. Proc. Natl. Acad. Sci. USA 2002, 99, 7746–7750.
9. D'Hulst, C.; De Geest, N.; Reeve, S.P.; Van Dam, D.; De Deyn, P.P.; Hassan, B.A.; Kooy, R.F. Decreased expression of the GABAA receptor in fragile X syndrome. Brain Res. 2006, 1121, 238–245.
10. Chuang, S.-H.; Reddy, D.S. Genetic and molecular regulation of extrasynaptic GABA-A receptors in the brain: Therapeutic insights for epilepsy. J. Pharmacol. Exp. Ther. 2018, 364, 180–197.
11. Zhang, N.; Peng, Z.; Tong, X.; Lindemeyer, A.K.; Cetina, Y.; Huang, C.S.; Olsen, R.W.; Otis, T.S.; Houser, C.R. Decreased surface expression of the δ subunit of the GABA a receptor contributes to reduced tonic inhibition in dentate granule cells in a mouse model of fragile X syndrome. Exp. Neurol. 2017, 297, 168–178.
12. Paluszkiewicz, S.M.; Martin, B.S.; Huntsman, M.M. Fragile X syndrome: The GABAergic system and circuit dysfunction. Dev. Neurosci. 2011, 33, 349–364.
13. Cassidy, S.B.; Schwartz, S. Prader-willi and angelman syndromes. disorders of genomic imprinting. Medicine 1998, 77, 140–151.
14. Buiting, K.; Williams, C.; Horsthemke, B. Angelman syndrome—Insights into a rare neurogenetic disorder. Nat. Rev. Neurol. 2016, 12, 584–593.
15. Gentile, J.K.; Tan, W.-H.; Horowitz, L.T.; Bacino, C.A.; Skinner, S.A.; Barbieri-Welge, R.; Bauer-Carlin, A.; Beaudet, A.L.; Bichell, T.J.; Lee, H.-S.; et al. A neurodevelopmental survey of angelman

syndrome with genotype-phenotype correlations. J. Dev. Behav. Pediatr. JDBP 2010, 31, 592–601.

16. Kalsner, L.; Chamberlain, S.J. Prader-willi, angelman, and 15q11-Q13 duplication syndromes. Pediatr. Clin. N. Am. 2015, 62, 587–606.
17. Clarke, D.J.; Marston, G. Problem behaviors associated with 15q- angelman syndrome. Am. J. Ment. Retard. AJMR 2000, 105, 25–31.
18. Barry, R.J.; Berry, R.J.; Leitner, R.P.; Clarke, A.R.; Einfeld, S.L. Behavioral aspects of angelman syndrome: A case control study. Am. J. Med. Genet. A 2005, 132, 8–12.
19. Mabb, A.M.; Judson, M.C.; Zylka, M.J.; Philpot, B.D. Angelman syndrome: Insights into genomic imprinting and neurodevelopmental phenotypes. Trends Neurosci. 2011, 34, 293–303.
20. Hochstrasser, M. Evolution and function of ubiquitin-like protein-conjugation systems. Nat. Cell Biol. 2000, 2, E153–E157.
21. Vatsa, N.; Jana, N.R. UBE3A and its link with autism. Front. Mol. Neurosci. 2018, 11, 448.
22. Lossie, A.C.; Whitney, M.M.; Amidon, D.; Dong, H.J.; Chen, P.; Theriaque, D.; Hutson, A.; Nicholls, R.D.; Zori, R.T.; Williams, C.A.; et al. Distinct phenotypes distinguish the molecular classes of angelman syndrome. J. Med. Genet. 2001, 38, 834–845.
23. Keute, M.; Miller, M.T.; Krishnan, M.L.; Sadhwani, A.; Chamberlain, S.; Thibert, R.L.; Tan, W.-H.; Bird, L.M.; Hipp, J.F. Angelman syndrome genotypes manifest varying degrees of clinical severity and developmental impairment. Mol. Psychiatry 2021, 26, 3625–3633.
24. Voytek, B.; Kramer, M.A.; Case, J.; Lepage, K.Q.; Tempesta, Z.R.; Knight, R.T.; Gazzaley, A. Age-related changes in 1/f neural electrophysiological noise. J. Neurosci. 2015, 35, 13257–13265.
25. Soorya, L.; Kolevzon, A.; Zweifach, J.; Lim, T.; Dobry, Y.; Schwartz, L.; Frank, Y.; Wang, A.T.; Cai, G.; Parkhomenko, E.; et al. Prospective investigation of autism and genotype-phenotype correlations in 22q13 deletion syndrome and SHANK3 deficiency. Mol. Autism 2013, 4, 18.
26. Srivastava, S.; Condy, E.; Carmody, E.; Filip-Dhima, R.; Kapur, K.; Bernstein, J.A.; Berry-Kravis, E.; Powell, C.M.; Soorya, L.; Thurm, A.; et al. Parent-reported measure of repetitive behavior in phelan-mcdermid syndrome. J. Neurodev. Disord. 2021, 13, 53.
27. Sarasua, S.M.; Boccuto, L.; Sharp, J.L.; Dwivedi, A.; Chen, C.-F.; Rollins, J.D.; Rogers, R.C.; Phelan, K.; DuPont, B.R. Clinical and genomic evaluation of 201 patients with phelan–mcdermid syndrome. Hum. Genet. 2014, 133, 847–859.
28. Phelan, K.; McDermid, H.E. The 22q13.3 deletion syndrome (Phelan-mcdermid syndrome). Mol. Syndromol. 2012, 2, 186–201.

29. Sarasua, S.M.; Dwivedi, A.; Boccuto, L.; Rollins, J.D.; Chen, C.-F.; Rogers, R.C.; Phelan, K.; DuPont, B.R.; Collins, J.S. Association between deletion size and important phenotypes expands the genomic region of interest in phelan-mcdermid syndrome (22q13 deletion syndrome). J. Med. Genet. 2011, 48, 761–766.
30. Boeckers, T.M.; Bockmann, J.; Kreutz, M.R.; Gundelfinger, E.D. ProSAP/shank proteins—A family of higher order organizing molecules of the postsynaptic density with an emerging role in human neurological disease. J. Neurochem. 2002, 81, 903–910.
31. Sheng, M.; Kim, E. The shank family of scaffold proteins. J. Cell Sci. 2000, 113 Pt 11, 1851–1856.
32. Filice, F.; Vörckel, K.J.; Sungur, A.Ö.; Wöhr, M.; Schwaller, B. Reduction in parvalbumin expression not loss of the parvalbumin-expressing GABA interneuron subpopulation in genetic parvalbumin and shank mouse models of autism. Mol. Brain 2016, 9, 10.
33. Vreugdenhil, M.; Jefferys, J.G.R.; Celio, M.R.; Schwaller, B. Parvalbumin-deficiency facilitates repetitive ipscs and gamma oscillations in the hippocampus. J. Neurophysiol. 2003, 89, 1414–1422.
34. Chen, Q.; Deister, C.A.; Gao, X.; Guo, B.; Lynn-Jones, T.; Chen, N.; Wells, M.F.; Liu, R.; Goard, M.J.; Dimidschstein, J.; et al. Dysfunction of cortical GABAergic neurons leads to sensory hyper-reactivity in a shank3 mouse model of ASD. Nat. Neurosci. 2020, 23, 520–532.
35. Yoo, T.; Cho, H.; Lee, J.; Park, H.; Yoo, Y.-E.; Yang, E.; Kim, J.Y.; Kim, H.; Kim, E. GABA neuronal deletion of shank3 exons 14-16 in mice suppresses striatal excitatory synaptic input and induces social and locomotor abnormalities. Front. Cell. Neurosci. 2018, 12, 341.
36. Isenstein, E.; Durkin, A.; Zhang, Y.; Feldman, E.; Servedio, N.; Harony-nicolas, H.; Buxbaum, J.; Kolevzon, A.; Siper, P.; Foss-Feig, J. Electrophysiological evidence of auditory habituation abnormalities in young adults with phelan-mcdermid syndrome. Biol. Psychiatry 2018, 83, S200.
37. Reese, M. Effects of Age, Gender, and Genotype on Auditory Processing in Phelan-Mcdermid Syndrome. Master Dissertation, University of Oklahoma, Norman, Oklahoma, 2019.
38. Grosman, H.; Guillory, S.; McLaughlin, C.; Britvan, B.; Isenstein, E.; Keller, K.; Jones, O.; Siper, P.M.; Kolevzon, A.; Foss-Feig, J.H. Examining Gamma Oscillatory Response as a Marker of Disrupted Excitatory/Inhibitory Balance in Autism Spectrum Disorder and Phelan-Mcdermid Syndrome; INSAR: Kansas, MO, USA, 2020.
39. Ono, Y.; Kudoh, K.; Ikeda, T.; Takahashi, T.; Yoshimura, Y.; Minabe, Y.; Kikuchi, M. Auditory steady-state response at 20 Hz and 40 Hz in young typically developing children and children with autism spectrum disorder. Psychiatry Clin. Neurosci. 2020, 74, 354–361.
40. Stroganova, T.; Komarov, K.; Goiaeva, D.; Obukhova, T.; Ovsiannikova, T.; Prokofiev, A.; Orekhova, E. Left hemispheric deficit in the sustained neuromagnetic response to periodic click trains in children with ASD. Mol. Autism 2020, 11, 100.

41. Neklyudova, A.K.; Portnova, G.V.; Rebreikina, A.B.; Voinova, V.Y.; Vorsanova, S.G.; Iourov, I.Y.; Sysoeva, O.V. 40-Hz auditory steady-state response (ASSR) as a biomarker of genetic defects in the SHANK3 gene: A case report of 15-year-old girl with a rare partial SHANK3 Duplication. Int. J. Mol. Sci. 2021, 22, 1898.

42. Koshiyama, D.; Kirihara, K.; Tada, M.; Nagai, T.; Fujioka, M.; Ichikawa, E.; Ohta, K.; Tani, M.; Tsuchiya, M.; Kanehara, A.; et al. Electrophysiological evidence for abnormal glutamate-GABA association following psychosis onset. Transl. Psychiatry 2018, 8, 211.

43. Sivarao, D.V.; Chen, P.; Senapati, A.; Yang, Y.; Fernandes, A.; Benitex, Y.; Whiterock, V.; Li, Y.-W.; Ahlijanian, M.K. 40 Hz auditory steady-state response is a pharmacodynamic biomarker for cortical NMDA receptors. Neuropsychopharmacology 2016, 41, 2232–2240.

44. Neul, J.L.; Kaufmann, W.E.; Glaze, D.G.; Christodoulou, J.; Clarke, A.J.; Bahi-Buisson, N.; Leonard, H.; Bailey, M.E.S.; Schanen, N.C.; Zappella, M.; et al. Rett syndrome: Revised diagnostic criteria and nomenclature. Ann. Neurol. 2010, 68, 944–950.

45. Moretti, P.; Zoghbi, H.Y. MeCP2 dysfunction in rett syndrome and related disorders. Curr. Opin. Genet. Dev. 2006, 16, 276–281.

46. Sarajlija, A.; Kisic-Tepavcevic, D.; Nikolic, Z.; Pavicevic, D.S.; Obradovic, S.; Djuric, M.; Pekmezovic, T. Epidemiology of rett syndrome in serbia: Prevalence, incidence and survival. Neuroepidemiology 2015, 44, 1–5.

47. Friez, M.J.; Jones, J.R.; Clarkson, K.; Lubs, H.; Abuelo, D.; Bier, J.-A.B.; Pai, S.; Simensen, R.; Williams, C.; Giampietro, P.F.; et al. Recurrent infections, hypotonia, and mental retardation caused by duplication of MECP2 and adjacent region in Xq28. Pediatrics 2006, 118, e1687–e1695.

48. Nan, X.; Ng, H.H.; Johnson, C.A.; Laherty, C.D.; Turner, B.M.; Eisenman, R.N.; Bird, A. Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. Nature 1998, 393, 386–389.

49. Jones, P.L.; Veenstra, G.J.; Wade, P.A.; Vermaak, D.; Kass, S.U.; Landsberger, N.; Strouboulis, J.; Wolffe, A.P. Methylated DNA and MeCP2 recruit histone deacetylase to repress transcription. Nat. Genet. 1998, 19, 187–191.

50. Chahrour, M.; Jung, S.Y.; Shaw, C.; Zhou, X.; Wong, S.T.C.; Qin, J.; Zoghbi, H.Y. MeCP2, a key contributor to neurological disease, Activates and represses transcription. Science 2008, 320, 1224–1229.

51. Erhardt, E.B.; Rachakonda, S.; Bedrick, E.J.; Allen, E.A.; Adali, T.; Calhoun, V.D. Comparison of multi-subject ICA methods for analysis of FMRI data. Hum. Brain Mapp. 2011, 32, 2075–2095.

52. Chao, H.-T.; Chen, H.; Samaco, R.C.; Xue, M.; Chahrour, M.; Yoo, J.; Neul, J.L.; Gong, S.; Lu, H.-C.; Heintz, N.; et al. Dysfunction in GABA signalling mediates autism-like stereotypies and rett

syndrome phenotypes. Nature 2010, 468, 263–269.

53. Smirnov, K.; Stroganova, T.; Molholm, S.; Sysoeva, O. Reviewing evidence for the relationship of EEG abnormalities and RTT phenotype paralleled by insights from animal studies. Int. J. Mol. Sci. 2021, 22, 5308.
54. Prather, P.; de Vries, P.J. Behavioral and cognitive aspects of tuberous sclerosis complex. J. Child Neurol. 2004, 19, 666–674.
55. Goh, S.; Kwiatkowski, D.J.; Dorer, D.J.; Thiele, E.A. Infantile spasms and intellectual outcomes in children with tuberous sclerosis complex. Neurology 2005, 65, 235–238.
56. Numis, A.L.; Major, P.; Montenegro, M.A.; Muzykewicz, D.A.; Pulsifer, M.B.; Thiele, E.A. Identification of risk factors for autism spectrum disorders in tuberous sclerosis complex. Neurology 2011, 76, 981–987.
57. Smalley, S.L. Autism and tuberous sclerosis. J. Autism Dev. Disord. 1998, 28, 407–414.
58. Annear, N.M.P.; Appleton, R.E.; Bassi, Z.; Bhatt, R.; Bolton, P.F.; Crawford, P.; Crowe, A.; Tossi, M.; Elmslie, F.; Finlay, E.; et al. Tuberous sclerosis complex (TSC): Expert recommendations for provision of coordinated care. Front. Neurol. 2019, 10, 1116.
59. Brió, M.C.; Fazzina, M.; Chindi, M. Tuberous sclerosis complex associated with autism spectrum features and bumetanide as a pharmacological indication: A case report. Open, J. Psychiatry 2021, 11, 202–213.
60. Bateup, H.S.; Johnson, C.A.; Denefrio, C.L.; Saulnier, J.L.; Kornacker, K.; Sabatini, B.L. Excitatory/inhibitory synaptic imbalance leads to hippocampal hyperexcitability in mouse models of tuberous sclerosis. Neuron 2013, 78, 510–522.
61. Mori, K.; Mori, T.; Toda, Y.; Fujii, E.; Miyazaki, M.; Harada, M.; Kagami, S. Decreased benzodiazepine receptor and increased GABA level in cortical tubers in tuberous sclerosis complex. Brain Dev. 2012, 34, 478–486.
62. Kallionpää, R.A.; Uusitalo, E.; Leppävirta, J.; Pöyhönen, M.; Peltonen, S.; Peltonen, J. Prevalence of neurofibromatosis type 1 in the finnish population. Genet. Med. 2018, 20, 1082–1086.
63. Rasmussen, S.A.; Friedman, J.M. NF1 gene and neurofibromatosis 1. Am. J. Epidemiol. 2000, 151, 33–40.
64. Eijk, S.; Mous, S.E.; Dieleman, G.C.; Dierckx, B.; Rietman, A.B.; de Nijs, P.F.A.; ten Hoopen, L.W.; van Minkelen, R.; Elgersma, Y.; Catsman-Berrevoets, C.E.; et al. Autism spectrum disorder in an unselected cohort of children with neurofibromatosis type 1 (NF1). J. Autism Dev. Disord. 2018, 48, 2278–2285.
65. Hyman, S.L.; Shores, A.; North, K.N. The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. Neurology 2005, 65, 1037–1044.

66. Jett, K.; Friedman, J.M. Clinical and genetic aspects of neurofibromatosis 1. Genet. Med. Off. J. Am. Coll. Med. Genet. 2010, 12, 1–11.
67. Legius, E.; Descheemaeker, M.J.; Spaepen, A.; Casaer, P.; Fryns, J.P. Neurofibromatosis type 1 in childhood: A study of the neuropsychological profile in 45 children. Genet. Couns. Geneva Switz. 1994, 5, 51–60.
68. Curatolo, P.; Cusmai, R.; Cortesi, F.; Chiron, C.; Jambaque, I.; Dulac, O. Neuropsychiatric aspects of tuberous sclerosis. Ann. N. Y. Acad. Sci. 1991, 615, 8–16.
69. Ferner, R.E. Neurofibromatosis 1 and neurofibromatosis 2: A twenty first century perspective. Lancet Neurol. 2007, 6, 340–351.
70. Cui, Y.; Costa, R.M.; Murphy, G.G.; Elgersma, Y.; Zhu, Y.; Gutmann, D.H.; Parada, L.F.; Mody, I.; Silva, A.J. Neurofibromin regulation of ERK signaling modulates GABA release and learning. Cell 2008, 135, 549–560.
71. Ammendola, A.; Ciccone, G.; Ammendola, E. Utility of multimodal evoked potentials study in neurofibromatosis type 1 of childhood. Pediatr. Neurol. 2006, 34, 276–280.
72. Yerdelen, D.; Koc, F.; Durdu, M.; Karakas, M. Electrophysiological findings in neurofibromatosis type 1. J. Neurol. Sci. 2011, 306, 42–48.
73. Begum-Ali, J.; Kolesnik-Taylor, A.; Quiroz, I.; Mason, L.; Garg, S.; Green, J.; Johnson, M.H.; Jones, E.J.H.; Holman, R.; Kalwarowsky, S.; et al. Early differences in auditory processing relate to autism spectrum disorder traits in infants with neurofibromatosis type I. J. Neurodev. Disord. 2021, 13, 22.