Taiwanese Journal of Obstetrics & Gynecology 57 (2018) 578–582

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Prenatal diagnosis of a 3.2-Mb 2p16.1-p15 duplication associated with familial intellectual disability

Chih-Ping Chen [a, b, c, d, e, f, *], Schu-Rern Chern [b], Peih-Shan Wu [g], Shin-Wen Chen [a], Shih-Ting Lai [a], Tzu-Yun Chuang [a], Wen-Lin Chen [a], Chien-Wen Yang [b], Wayseen Wang [b, h]

[a] Department of Obstetrics and Gynecology, MacKay Memorial Hospital, Taipei, Taiwan
[b] Department of Medical Research, MacKay Memorial Hospital, Taipei, Taiwan
[c] Department of Biotechnology, Asia University, Taichung, Taiwan
[d] School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan
[e] Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan
[f] Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[g] Gene Biodesign Co. Ltd., Taipei, Taiwan
[h] Department of Bioengineering, Tatung University, Taipei, Taiwan

ARTICLE INFO

Article history:
Accepted 8 May 2018

Keywords:
2p16.1-p15 duplication
BCL11A
Intellectual disability

ABSTRACT

Objective: We present prenatal diagnosis of a 2p16.1-p15 duplication associated with familial intellectual disability, and we discuss the genotype–phenotype correlation.

Case report: A 22-year-old, primigravid woman underwent amniocentesis at 22 weeks of gestation because of a family history of intellectual disability. The woman and her two sisters had intellectual disability but no behavioral disorders. The intellectual disability was noted in at least one paternal aunt and six paternal cousins of the woman. Cytogenetic analysis revealed the karyotype of 46,XX in the fetus and the two women. Array comparative genomic hybridization (aCGH) analysis on the DNAs extracted from cultured amniocytes and the bloods of the woman and the her sister revealed a 3.244-Mb duplication of 2p16.1-p15 or arr 2p16.1p15 (58,288,588–61,532,538) × 3.0 [GRCh37 (hg19)] encompassing eight Online Mendelian Inheritance in Man (OMIM) genes of *VRK2*, *FANCL*, *BCL11A*, *PAPOLG*, *REL*, *PUS10*, *PEX13* and *USP34* in the fetus and the two women. Prenatal ultrasound findings were unremarkable. The woman elected to continue the pregnancy. A 3244-g female baby was delivered at term with neither craniofacial dysmorphism nor structural abnormalities.

Conclusion: aCGH is useful in prenatal diagnosis of inherited subtle chromosome imbalance in pregnancy with familial intellectual disability. Chromosome 2p16.1-p15 duplication can be associated with intellectual disability.

Introduction

Chromosome 2p16-p15 deletion [Online Mendelian Inheritance in Man (OMIM) 612,513] is a well recognized neurodevelopmental syndrome characterized by delayed psychomotor development, intellectual disability, craniofacial dysmorphism of microcephaly, bitemporal narrowing, smooth and long philtrum, hypertelorism, downslanting palpebral fissures, broad nasal root, thin upper lip, and high palate, autistic behavior, short stature, pachygyria, hypoplastic corpus callosum and other brain malformations [1–10]. Various genes have been proposed for the association with the phenotypic features in chromosome 2p16.1-p15 deletion syndrome, *i.e.*, haploinsufficiency of *BCL11A* is responsible for neurodevelopmental disorders and dysmorphic facial features [8,9]. *VRK2* haploinsufficiency is responsible for autism and neuroectodermal developmental disorders [2], and *BCL11A* is responsible for language development [11]. Recently, Bagheri et al. [12] in a multifaceted analysis suggested that *XPO1*, *REL* and *BCL11A* are candidate genes for 2p16.1-p15 deletion syndrome.

Chromosome 2p16-p15 duplication, on the other hand, may present a less severe phenotype than chromosome 2p16-p15 deletion syndrome. Mimouni-Bloch et al. [13] previously reported a

* Corresponding author. Department of Obstetrics and Gynecology, MacKay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei 10449, Taiwan. Fax: +886 2 25433642, +886 2 25232448.
E-mail address: cpc_mmh@yahoo.com (C.-P. Chen).

https://doi.org/10.1016/j.tjog.2018.06.018

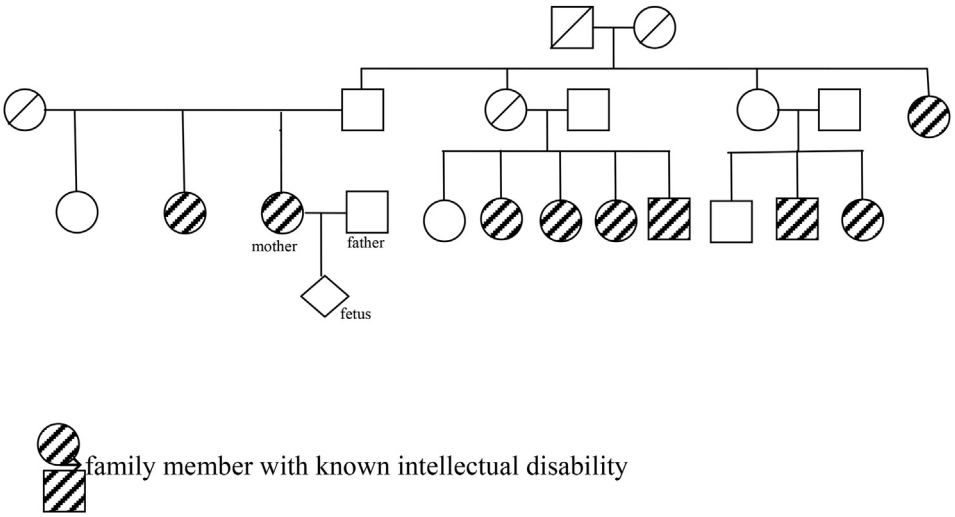

Fig. 1. A family pedigree of intellectual disability.

2p16.1-p15 duplication in a child with milder clinical phenotypes in comparison with the corresponding chromosome 2p16.1-p15 deletion syndrome. Here, we present prenatal diagnosis of a 2p16.1-p15 duplication associated with familial intellectual disability. Our presentation adds to the literature of 2p16.1-p15 duplication syndrome.

Case report

A 22-year-old, primigravid woman underwent amniocentesis at 22 weeks of gestation because of a family history of intellectual disability. The woman and her two sisters had intellectual disability but no behavioral disorders. The woman and her sister had

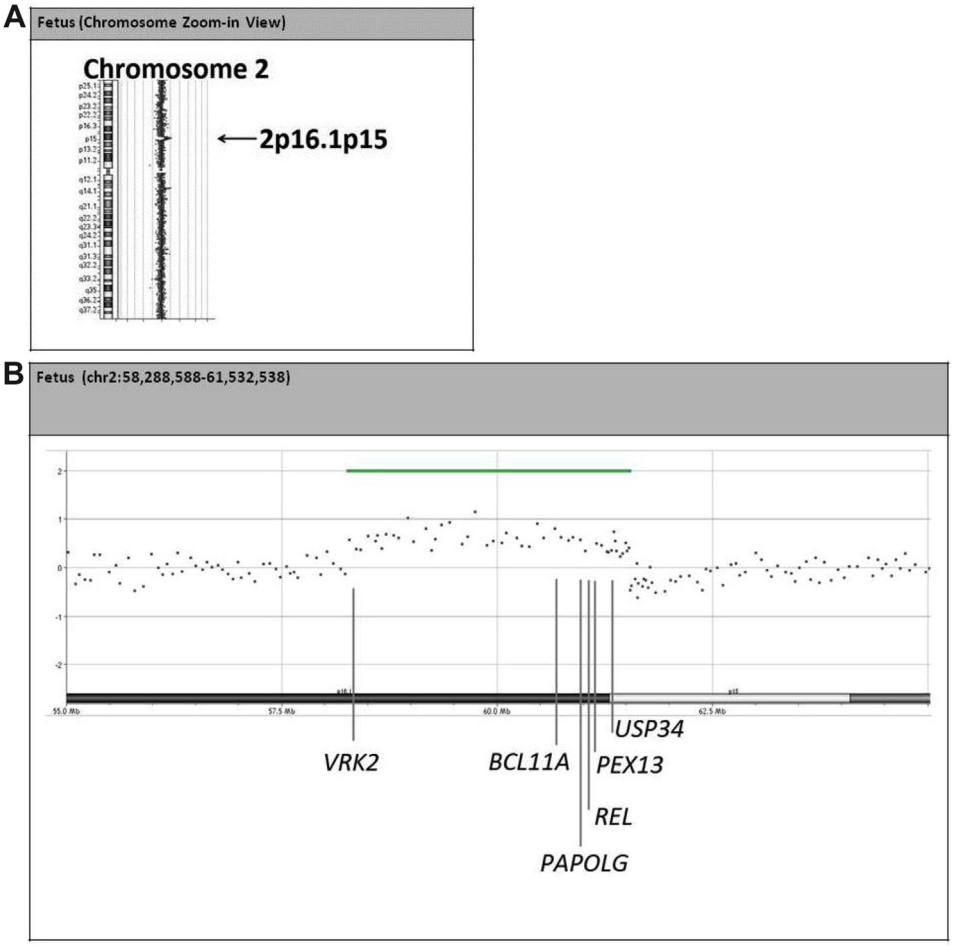

Fig. 2. Array comparative genomic hybridization (aCGH) on the DNA extracted from cultured amniocytes shows a 3.244-Mb duplication of 2p16.1-p15. (A) and (B) Chromosome zoom-in views.

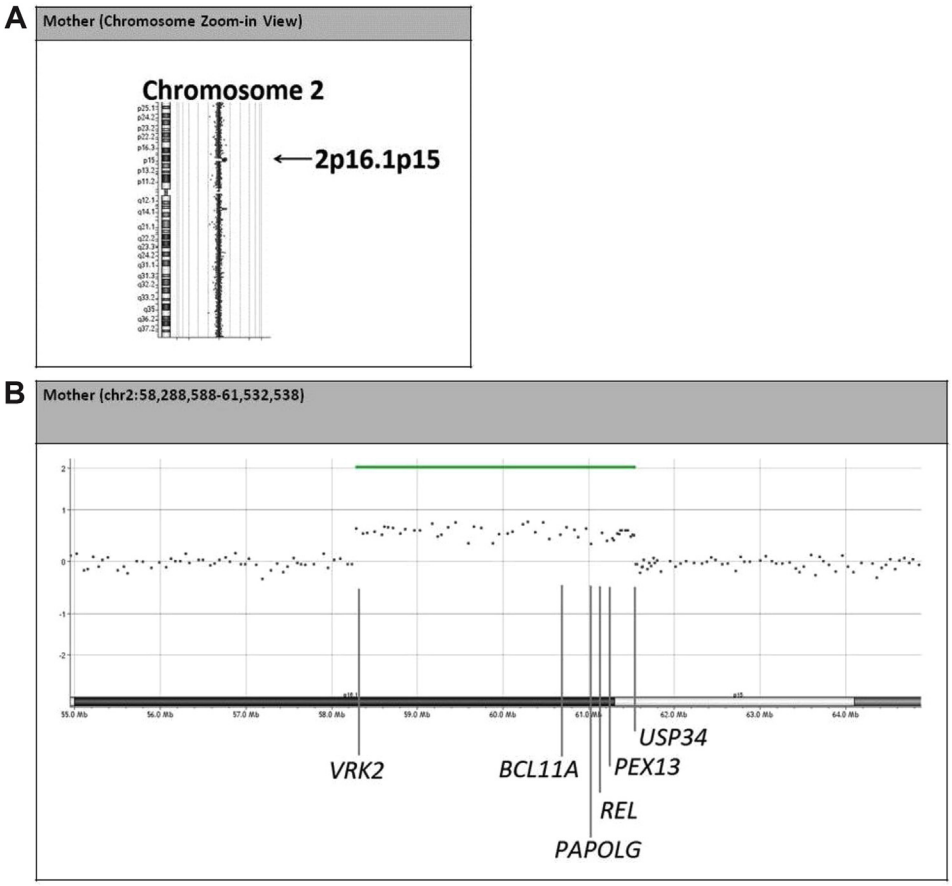

Fig. 3. aCGH on the DNA extracted from the peripheral blood of the mother with moderate intellectual disability shows a 3.244-Mb duplication of 2p16.1-p15. (A) and (B) Chromosome zoom-in views.

moderate intellectual disability, and her elder sister had mild intellectual disability. The intellectual disability of various degrees was noted in at least one paternal aunt and six paternal cousins of the woman (Fig. 1). All family members identified to have intellectual disability had received governmental handicap assistance. Those family members with governmental handicap assistance had low intellectual quotient (IQ) and had received middle school education for intellectual disability. Cytogenetic analysis revealed the karyotype of 46,XX in the fetus and the two women. Array comparative genomic hybridization (aCGH) analysis of the DNAs extracted from cultured amniocytes and the bloods of the woman and her sister using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K (Agilent Technologies, CA, USA) revealed a 3.244-Mb duplication of 2p16.1-p15 or arr 2p16.1p15 (58, 288, 588–61,532,538) × 3.0 [GRCh37 (hg19)] encompassing eight OMIM genes of *VRK2*, *FANCL*, *BCL11A*, *PAPOLG*, *REL*, *PUS10*, *PEX13* and *USP34* in the fetus and the two women (Figs. 2–4). Prenatal ultrasound findings were unremarkable. The woman elected to continue the pregnancy. A 3244-g female baby was delivered at term with a body length of 51 cm and manifested neither craniofacial dysmorphism nor structural abnormalities. When follow-up at 8 months of age, the infant had a head circumference of 44.5 cm (75th–85th centile), a body weight of 6.9 Kg (5th–15th centile) and a body length of 65.5 cm (5th–15th centile). There was no psychomotor developmental abnormality.

Discussion

Minouni-Bloch et al. [13] first reported intellectual developmental disorder in a 3-year-old boy with a 1.655-Mb 2p16.1-p15 duplication encompassing *BCL11A*, *PAPOLG*, *REL*, *PUS10*, *PEX13*, *USP34* and *XPO1* (Fig. 4B). The present family members had a 3.244-Mb 2p16.1-p15 duplication encompassing *VRK2*, *FANCL*, *BCL11A*, *PAPOLG*, *REL*, *PUS10*, *PEX13* and *USP34*. In the case reported by Mimouni-Bloch et al. [13], the proband had a normal head, mild intellectual disability, absence of autistic behavior, mild global developmental delay and mild dysmorphism. In the DECIPHER database [14], all the patients with 2p16.1-p15 duplication manifested an abnormal developmental phenotype. Our presentation provides evidence that patients with a 2p16.1-p15 duplication can be associated with intellectual disability.

VRK2 (OMIM 602169) encodes vaccinia-related kinase 2. Vrk2 has been found to be expressed in the developing cerebral cortex of the mice and is involved in regulating multipolar–bipolar transition and neural progenitor proliferation [15]. *VRK2* may play an important role in schizophrenia [15–22]. *VRK2* interacts with *JIP1* which is important in the neurite initiation and axon outgrowth in neuronal cells [23,24], and is involved in the JNK1 and MAPK signaling pathway which plays a role in axonal development in neuronal cells [23,25,26].

PAPOLG (OMIM 616865) encodes poly(A) polymerase γ, which is a protein responsible for the post-transcriptional 3′ polyadenylation of mRNA and small RNA precursors [27]. PAPOLG is expressed in the brain [28], and RNA processing is among the basic cellular processes involved in intellectual disability [29].

BCL11A (OMIM 606557) encodes B-cell CLL/lymphoma 11A which is a zinc finger protein that regulates transcription through interaction with COUP-TF proteins and direct sequence-dependent

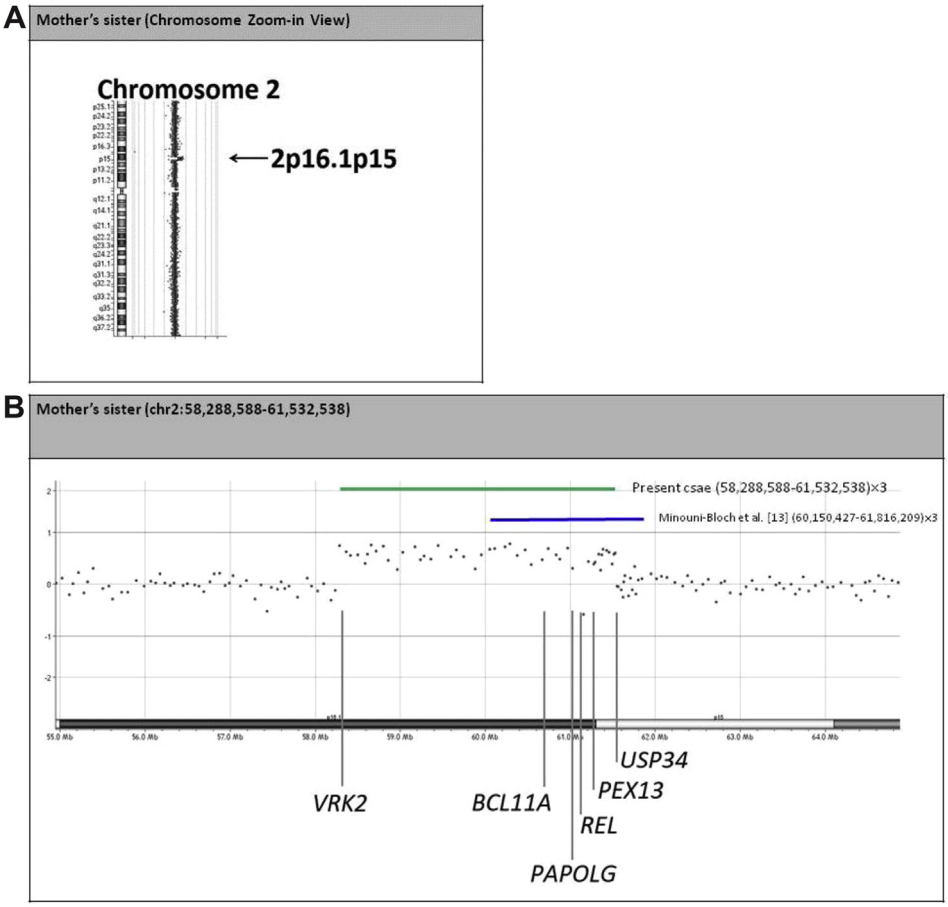

Fig. 4. aCGH on the DNA extracted from the peripheral blood of the mother's sister with mild intellectual disability shows a 3.244-Mb duplication of 2p16.1-p15. (A) and (B) Chromosome zoom-in views.

DNA binding [30], and is highly expressed in brain, B-lymphocytes and adult erythroid lineage [10]. *BCL11A* heterozygous mutation is associated with autosomal dominant Dias-Logan syndrome or intellectual developmental disorder with persistence of fetal hemoglobin (OMIM 617101). Kuo et al. [31] found that *BCL11A* regulates expression of DCC and MAP1b in control of axon branching and dendrite outgrowth. Kuo et al. [32] also found that *CASK*, a known X-linked intellectual disability gene, interacts with *BCL11A* and regulates axon branching and outgrowth. Peter et al. [11] reported the association of *BCL11A* deletion with severe speech sound disorder. Basak et al. [9] found that *BCL11A* deletions result in neurodevelopmental alterations such as schizophrenia and attention deficit hyperactivity disorder. Dias et al. [33] found that *BCL11A* haploinsufficiency causes neurodevelopmental deficits, developmental delay and intellectual disability. Bagheri et al. [12] found that knockdown of both *BCL11A* orthologs in zebrafish result in microcephaly. Cai et al. [34] identified *BCL11A* mutations in patients with autism and intelligence disabilities. Shimbo et al. [35] reported the association of *BCL11A* haploinsufficiency with cerebellar abnormalities. Soblet et al. [36] reported that *BCL11A* frameshift mutation causes dyspraxia and hypotonia. Yoshida et al. [37] identified *BCL11A* variants in patients with epileptic encephalopathy.

REL (OMIM 164910) encodes c-Rel which is a transcription factor that is a member of the Rel/NFKB family. *REL* is required for hippocampal long-term synaptic plasticity and memory function [38].

PEX13 (OMIM 601789) encodes peroxisome biogenesis factor 13 which is a peroxisomal membrane protein. Mutations in *PEX* genes such as *PEX2*, *PEX6*, *PEX10*, *PEX12* and *PEX13* can lead to peroxisomal biogenesis disorders including the Zellweger spectrum [39].

USP34 (OMIM 615295) encodes ubiquitin-specific protein 34. *USP34* regulates AXIN stability and Wnt/β-catenin signaling [40]. Wnt signaling pathway plays a role in central nervous system development, and disruption of Wnt will cause developmental delay and autism [41,42]. Deregulation of *USP34* has been found to prevent the correct forming of the corpus callosum by interfering with normal neuronal and glial cell proliferation, midline patterning, callosal neuron migration and specification [43–45].

In summary, we discuss the genotype–phenotype correlation in chromosome 2p16.1-p15 duplication. Our presentation shows that aCGH is useful in prenatal diagnosis of inherited subtle chromosome imbalance in pregnancy with familial intellectual disability, and chromosome 2p16.1-p15 duplication can be associated with intellectual disability.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

This work was supported by research grants MOST-105-2314-B-195-012 from the Ministry of Science and Technology and MMH-E-106-04 from MacKay Memorial Hospital, Taipei, Taiwan.

References

[1] Rajcan-Separovic E, Harvard C, Liu X, McGillivray B, Hall JG, Qiao Y, et al. Clinical and molecular cytogenetic characterisation of a newly recognised microdeletion syndrome involving 2p15-16.1. J Med Genet 2007;44:269–76.

[2] Chabchoub E, Vermeesch JR, de Ravel T, de Cock P, Fryns J-P. The facial dysmorphy in the newly recognised microdeletion 2p15-p16.1 refined to a 570 kb region in 2p15. J Med Genet 2008;45:189–92.

[3] De Leeuw N, Pfundt R, Koolen DA, Neefs I, Scheltinga I, Mieloo H, et al. A newly recognised microdeletion syndrome involving 2p15p16.1: narrowing down the critical region by adding another patient detected by genome wide tiling path array comparative genomic hybridisation analysis. J Med Genet 2008;45:122–4.

[4] Liang J-S, Shimojima K, Ohno K, Sugiura C, Une Y, Ohno K, et al. A newly recognised microdeletion syndrome of 2p15-16.1 manifesting moderate developmental delay, autistic behaviour, short stature, microcephaly, and dysmorphic features: a new patient with 3.2 Mb deletion. J Med Genet 2009;46:645–7.

[5] Félix TM, Petrin AL, Sanseverino MTV, Murray JC. Further characterization of microdeletion syndrome involving 2p15-p16.1. Am J Med Genet 2010;152A:2604–8.

[6] Prontera P, Bernardini L, Stangoni G, Capalbo A, Rogaia D, Romani R, et al. Deletion 2p15-16.1 syndrome: case report and review. Am J Med Genet 2011;155A:2473–8.

[7] Piccione M, Piro E, Serraino F, Cavani S, Ciccone R, Malacarne M, et al. Interstitial deletion of chromosome 2p15-16.1: report of two patients and critical review of current genotype-phenotype correlation. Eur J Med Genet 2012;55:238–44.

[8] Balci TB, Sawyer SL, Davila J, Humphreys P, Dyment DA. Brain malformations in a patient with deletion 2p16.1: a refinement of the phenotype to *BCL11A*. Eur J Med Genet 2015;58:351–4.

[9] Basak A, Hancarova M, Ulirsch JC, Balci TB, Trkova M, Pelisek M, et al. *BCL11A* deletions result in fetal hemoglobin persistence and neurodevelopmental alterations. J Clin Invest 2015;125:2363–8.

[10] Funnell APW, Prontera P, Ottaviani V, Piccione M, Giambona A, Maggio A, et al. 2p15-p16.1 microdeletions encompassing and proximal to *BCL11A* are associated with elevated HbF in addition to neurologic impairment. Blood 2015;126:89–93.

[11] Peter B, Matsushita M, Oda K, Raskind W. *De novo* microdeletion of *BCL11A* is associated with severe speech sound disorder. Am J Med Genet 2014;164A:2091–6.

[12] Bagheri H, Badduke C, Qiao Y, Colnaghi R, Abramowicz I, Alcantara D, et al. Identifying candidate genes for 2p15p16.1 microdeletion syndrome using clinical, genomic, and functional analysis. JCI Insight 2016;1:e85461.

[13] Mimouni-Bloch A, Yeshaya J, Kahana S, Maya I, Basel-Vanagaite L. A *de-novo* interstitial microduplication involving 2p16.1-p15 and mirroring 2p16.1-p15 microdeletion syndrome: clinical and molecular analysis. Eur J Paediatr Neurol 2015;19:711–5.

[14] DECIPHER database. Database of chromosomal imbalance and phenotype in humans using ensembl resources. 2017. Available at: http://decipher.sanger.ac.uk/. [Accessed 13 October 2017].

[15] Yu H, Yan H, Li J, Li Z, Zhang X, Ma Y, et al. Common variants on 2p16.1, 6p22.1 and 10q24.32 are associated with schizophrenia in Han Chinese population. Mol Psychiatry 2017;22:954–60.

[16] Steinberg S, de Jong S, Irish Schizophrenia Genomics Consortium, Andreassen OA, Werge T, Borglum AD, et al. Common variants at *VRK2* and *TCF4* conferring risk of schizophrenia. Hum Mol Genet 2011;20:4076–81.

[17] EPICURE Consortium, EMINet Consortium, Steffens M, Leu C, Ruppert A-K, Zara F, et al. Genome-wide association analysis of genetic generalized epilepsies implicates susceptibility loci at 1q43, 2p16.1, 2q22.3 and 17q21.32. Hum Mol Genet 2012;21:5359–72.

[18] Li M, Wang Y, Zheng X-B, Ikeda M, Iwata N, Luo X-J, et al. Meta-analysis and brain imaging data support the involvement of *VRK2* (rs2312147) in schizophrenia susceptibility. Schizophr Res 2012;142:200–5.

[19] Sohn H, Kim B, Kim KH, Kim M-K, Choi TK, Lee S-H. Effects of *VRK2* (rs2312147) on white matter connectivity in patients with schizophrenia. PLoS One 2014;9:e103519.

[20] Zhang B, Gao CY, Zhang HB, Yang B, Yin JF, Wei SG, et al. Association of the *VRK2* gene rs3732136 polymorphism with schizophrenia in a Northwest Chinese Han population. Genet Mol Res 2015;14:9404–11.

[21] Chang H, Zhang C, Xiao X, Pu X, Liu Z, Wu L, et al. Further evidence of *VRK2* rs2312147 associated with schizophrenia. World J Biol Psychiatry 2016;17:457–66.

[22] Tesli M, Wirgenes KV, Hughes T, Bettella F, Athanasiu L, Hoseth ES, et al. *VRK2* gene expression in schizophrenia, bipolar disorder and healthy controls. Br J Psychiatry 2016;209:114–20.

[23] Blanco S, Sanz-Garcia M, Santos CR, Lazo PA. Modulation of interleukin-1 transcriptional response by the interaction between VRK2 and the JIP1 scaffold protein. PLoS One 2008;3:e1660.

[24] Barnat M, Enslen H, Propst F, Davis RJ, Soares S, Nothias F. Distinct roles of c-Jun N-terminal kinase isoforms in neurite initiation and elongation during axonal regeneration. J Neurosci 2010;30:7804–16.

[25] Dajas-Bailador F, Jones EV, Whitmarsh AJ. The JIP1 scaffold protein regulates axonal development in cortical neurons. Curr Biol 2008;18:221–6.

[26] Fernández IF, Pérez-Rivas LG, Blanco S, Castillo-Dominguez AA, Lozano J, Lazo PA. VRK2 anchors KSR1-MEK1 to endoplasmic reticulum forming a macromolecular complex that compartmentalizes MAPK signaling. Cell Mol Life Sci 2012;69:3881–93.

[27] Kyriakopoulou CB, Nordvarg H, Virtanen A. A novel nuclear human poly(A) polymerase (PAP), PAP γ. J Biol Chem 2001;276:33504–11.

[28] Lein ES, Hawrylycz MJ, Ao N, Ayres M, Bensinger A, Bernard A, et al. Genome-wide atlas of gene expression in the adult mouse brain. Nature 2007;445:168–76.

[29] Najmabadi H, Hu H, Garshasbi M, Zemojtel T, Abedini SS, Chen W, et al. Deep sequencing reveals 50 novel genes for recessive cognitive disorders. Nature 2011;478:57–63.

[30] Wiegreffe C, Simon R, Peschkes K, Kling C, Strehle M, Cheng J, et al. Bcl11a (Ctip1) controls migration of cortical projection neurons through regulation of Sema3c. Neuron 2015;87:311–25.

[31] Kuo T-Y, Hong C-J, Hsueh Y-P. *Bcl11A*/*CTIP1* regulates expression of DCC and MAP1b in control of axon branching and dendrite outgrowth. Mol Cell Neurosci 2009;42:195–207.

[32] Kuo T-Y, Hong C-J, Chien H-L, Hsueh Y-P. X-linked mental retardation gene *CASK* interacts with *Bcl11A*/*CTIP1* and regulates axon branching and outgrowth. J Neurosci Res 2010;88:2364–73.

[33] Dias C, Estruch SB, Graham SA, McRae J, Sawiak SJ, Hurst JA, et al. *BCL11A* haploinsufficiency causes an intellectual disability syndrome and dysregulates transcription. Am J Hum Genet 2016;99:253–74.

[34] Cai T, Chen X, Li J, Xiang B, Yang L, Liu Y, et al. Identification of novel mutations in the HbF repressor gene *BCL11A* in patients with autism and intelligence disabilities. Am J Hematol 2017;92:E653–6.

[35] Shimbo H, Yokoi T, Aida N, Mizuno S, Suzumura H, Nagai J, et al. Haploinsufficiency of *BCL11A* associated with cerebellar abnormalities in 2p15p16.1 deletion syndrome. Mol Genet Genomic Med 2017;5:429–37.

[36] Soblet J, Dimov I, Graf von Kalckreuth C, Cano-Chervel J, Baijot S, Pelc K, et al. *BCL11A* frameshift mutation associated with dyspraxia and hypotonia affecting the fine, gross, oral, and speech motor systems. Am J Med Genet A 2018;176A:201–8.

[37] Yoshida M, Nakashima M, Okanishi T, Kanai S, Fujimoto A, Itomi K, et al. Identification of novel *BCL11A* variants in patients with epileptic encephalopathy: expanding the phenotypic spectrum. Clin Genet 2018;93:368–73.

[38] Ahn HJ, Hernandez CM, Levenson JM, Lubin FD, Liou H-C, Sweatt JD. c-Rel, an NF-κB family transcription factor, is required for hippocampal long-term synaptic plasticity and memory formation. Learn Mem 2008;15:539–49.

[39] Krause C, Rosewich H, Thanos M, Gartner J. Identification of novel mutations in *PEX2*, *PEX6*, *PEX10*, *PEX12*, and *PEX13* in Zellweger spectrum patients. Hum Mutat 2006;27:1157.

[40] Lui TTH, Lacroix C, Ahmed SM, Goldenberg SJ, Leach CA, Daulat AM, et al. The ubiquitin-specific protease USP34 regulates axin stability and Wnt/β-catenin signaling. Mol Cell Biol 2011;31:2053–65.

[41] Oliva CA, Vargas JY, Inestrosa NC. Wnts in adult brain: from synaptic plasticity to cognitive deficiencies. Front Cell Neurosci 2013;7:224.

[42] Sowers LP, Loo L, Wu Y, Campbell E, Ulrich JD, Wu S, et al. Disruption of the non-canonical Wnt gene *PRICKLE2* leads to autism-like behaviors with evidence for hippocampal synaptic dysfunction. Mol Psychiatry 2013;18:1077–89.

[43] Sajan SA, Fernandez L, Nieh SE, Rider E, Bukshpun P, Wakahiro M, et al. Both rare and *de novo* copy number variants are prevalent in agenesis of the corpus callosum but not in cerebellar hypoplasia or polymicrogyria. PLoS Genet 2013;9:e1003823.

[44] Edwards TJ, Sherr EH, Barkovich AJ, Richards LJ. Clinical, genetic and imaging findings identify new causes for corpus callosum development syndromes. Brain 2014;137:1579–613.

[45] Palmer EE, Mowat D. Agenesis of the corpus callosum: a clinical approach to diagnosis. Am J Med Genet C: Semin Med Genet 2014;166C:184–97.