Case Report of Proliferative Peripheral Retinopathy in Two Familial Lissencephaly Infants with Miller–Dieker Syndrome

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J Pediatr Genet 2018;7:86–91.

Abstract

Keywords

- agyria
- LIS1 gene
- pediatric
- PDIA2
- retina
- SERPINF1

A complete ophthalmic examination is not routinely performed on infants with Miller–Dieker syndrome (MDS, chromosome 17p13.3 microdeletion). The authors present the cases of four cousins with MDS who also carried a 16p13.3 microduplication (not associated with Rubinstein–Taybi syndrome). Retinopathy of prematurity-like proliferative peripheral retinopathy (PPR) was detected in two male first cousins, but was not detected in the female half-cousins. PPR in the first infant resolved by 4 months, but the second infant's PPR progressed, requiring photocoagulation followed by lens-sparing vitrectomy. While ocular abnormalities are more prevalent and severe in other lissencephalopathies, the PPR in these MDS infants underscores the sight-saving potential of performing an ophthalmologic exam with early molecular testing for all lissencephaly infants.

Introduction

Lissencephalies are a group of rare brain malformations due to defective neuronal migration during the first 4 gestational months.^{1,2} Children with lissencephaly (“smooth brain”) commonly have intellectual disability, developmental delay, and seizures. They may also have facial dysmorphism, cerebral vision impairment (disorder in projection and/or interpretation of the visual input), and/or ocular abnormalities (dysfunctions or defects in anterior/posterior segments).^{3–7} Other symptoms may include difficulty swallowing and anomalies of the hands, fingers, or toes. Lissencephalies are histopathologically graded based on the absence (agyria) or extent (pachygyria) of brain folds (gyri) and grooves (sulci) distinguished by neuroradiological imaging.⁸ The two major types of lissencephaly are classic (type 1) and cobblestone (type 2).

Classic lissencephaly is the most common (~1/100,000 births).⁹ It is characterized by clinical features, agyria, and

abnormal cerebral cortex presenting as a “figure 8” or “hour-glass” due to cortical thickening and enlarged ventricles.^{2,3,10} Most classic lissencephaly children (80–90%) carry a mutation or deletion in chromosome 17p13.3 that encodes the platelet activating factor acetylhydrolase (*PAFAH1B1*, formerly *LIS1*) gene, while 10 to 20% inherit a deletion from a parent who carries a balanced chromosome rearrangement of the *LIS1* gene.^{11,12} Classic lissencephalies are subdivided into Miller–Dieker Syndrome (MDS; codeletion of *LIS1* and *YWHAE* genes),¹³ type 1 isolated lissencephaly (*LIS1* gene mutation), lissencephaly due to a X-linked doublecortin (*DCX*) gene (*LISX1*) mutation,¹⁴ and lissencephaly without the occurrence of a known genetic error.¹⁵ Notably, high-resolution genotyping is a prerequisite to ascribe brain neuroimage phenotypes to the heterogeneous findings of mental retardation, facial dysmorphism, and seizures in classic lissencephalies.^{13,16}

Ocular abnormalities of classic lissencephaly (not necessarily MDS) may include absent ocular fixation or tracking,

received

August 16, 2017

accepted after revision

November 15, 2017

published online

December 29, 2017

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Verlag KG, Stuttgart · New York

DOI <https://doi.org/10.1055/s-0037-1612638>.
ISSN 2146-4596.

Fig. 1 Family pedigree. The brother (III-2) and sister (III-6), parents of the two affected children (Case #1, IV-9; Case #2 IV-1) and a half-sister (III-9), also a parent of two affected children (Case #3, IV-12; Case #4, IV-10), are carriers of the chromosome 16p13.3;17p13.3 translocation in balanced form and are phenotypically normal. They inherited the translocation from a carrier parent (II-2). An additional affected child (III-15) died without an ophthalmic examination.

poor visual tracking, nystagmus, variable esotropia, oculomotor apraxia, microphthalmos, corneal clouding, cataracts, glaucoma, abnormal irides, tortuous fundal vessels, and delayed visual maturation.⁵ The visual dysfunctions without fundus anomalies reported for MDS are less severe than in cobblestone and other classic lissencephalies.^{3,5,17–19}

We report postpartum ophthalmic evaluations revealed retinal dysplasia consistent with peripheral proliferative retinopathy (PPR) in two of four cousins with the MDS lissencephaly phenotype (►Fig. 1). The retinopathy detected in the two MDS cases supports the importance of early ophthalmic evaluation in all lissencephaly children including those with MDS to detect sight-threatening ocular abnormalities and provide treatment to maintain visual function.

Case Presentations

Case #1 (►Fig. 1, IV-9): A full-term (39-week) African-American male weighing 2,041 g at birth was delivered at the Louisiana State University (LSU) Health, Shreveport. Multiple congenital

abnormalities were present including microcephaly, hypertelorism, down-slanting palpebral fissures, retrognathia, low set ears, webbed neck, camptodactyly of the third and fourth digits, hypospadias, and bilateral undescended testes (no oxygen therapy). Magnetic resonance imaging (MRI) scans of the head showed lissencephaly; absence of sulcation with a smooth cerebral cortex (agyria) and a gross brain “figure eight” structure (►Fig. 2). Comparative genomic hybridization (CGH; 180K oligonucleotide microarray; DNAarray-Oligo 180K, CombiMatrix Molecular Diagnostics, Inc., Irvine, California, United States) revealed an abnormal male genotype, a terminal 3.0 Mb microdeletion in short arm of chromosome 17 (17p13.3) encompassing the *PAFAH1B1* and *YWHAE* genes, a 2.0 Mb microduplication in chromosome 16p13.3, a common variant pericentric inversion in chromosome 9 (9p11q13), and several chromosomal polymorphisms (not shown). Fluorescence in situ hybridization (FISH) analysis on interphase cells confirmed the array findings. The bilateral dilated ocular exams at 12.5 weeks were significant for 1 to 2 hours of elevated retinal ridge of fibrovascular proliferation similar to retinopathy of prematurity (ROP) Stage 3.

Fig. 2 (A) Sagittal T1 MRI scan and selected image from axial (B) T1, (C) T2-weighted, and (D) T2-Flair MRI scans of Case #1's brain performed at 2 weeks of age. The anterior and posterior lobes of the brain show a paucity of cortical sulcation with broad, thickened gyri, and a near-smooth and thickened appearance of the surface of the cerebral cortex with an atrophic corpus callosum (Grade 1 lissencephaly). The brain acquires a figure eight configuration due to the narrowing of its middle portion by the Sylvian fissures (arrows). MRI, magnetic resonance imaging.

The PPR lesions regressed by 4 months without treatment. At 8 months, the ocular exam revealed clear corneas and lenses (both eyes, OU), ability to fix and follow, appropriate response to visual stimuli, 30 degrees (~52 prism diopters) of exotropia, small amplitude horizontal nystagmus, and hyperopia. His medical history prior to death at 18 months due to asphyxia was significant for heart murmur, seizures, hypotonia, quad-ruparesis, hypertension, and multiple infections.

Case #2 (►Fig. 1, IV-1): An African-American male first cousin of case #1 was delivered via cesarean section at 33 gestational weeks at the LSU Health. He weighed 1,700 g at birth with Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) scores of 1, 5, and 7. He was given oxygen using a Neopuff (Fisher & Paykel Healthcare, Ltd., East Tamaki, Auckland, Australia) in the delivery room, and then placed on bubble continuous positive airway pressure (CPAP) fraction of inspired oxygen (FiO_2) of 0.21 to 0.45 with oxygen saturation of 98%. Within 48 hours, he was on room air and off of all supplemental oxygen. Physical examination revealed retro-gnathia, natal teeth, smooth philtrum, low set ears, hypoplastic nails, simian crease, clinodactyly, heart murmur (no oxygen therapy), and early hypotonia. Cranial MRI scans revealed cranial abnormalities similar to case #1. CGH testing revealed a male with a chromosome 17p13.3 terminal microdeletion (►Fig. 3A) and a chromosome 16p13.3 terminal microduplication (CombiMATRIX Molecular Diagnostics, Inc.) (►Fig. 3B). An ophthalmic examination was requested due to the presence of facial anomalies. Fundus examination at age 9 days revealed an elevated ridge of proliferative retinopathy temporally in

zone 2 for 6 hours with dilated, tortuous vessels in the posterior pole of the right eye. Examination of the left eye showed an elevated ridge for 360 degrees in zone 2 with 2 hours of proliferative retinopathy temporally. The following day, the patient underwent bilateral laser photocoagulation to the avascular areas of the retinas. One week later, 2 hours of tractional retinal detachment were present temporally in the right eye. The area of retinal detachment increased to 4 hours temporally through the next week (►Fig. 4A), while the left eye showed signs of improvement postperipheral photocoagulation (►Fig. 4B). The patient was referred to a vitreoretinal specialist (W.R.S.) for lens-sparing vitrectomy of the right eye. The retinal detachment resolved 3 days following the right eye vitrectomy and the neovascular tissue was regressing in all of the avascular retina. The 9-month ocular exam revealed poor fixation, no afferent pupillary defect, full extraocular movements, and right exotropia (right eye, OD). Funduscopy exam showed central 360° of chorioretinal scarring OU peripherally in each eye, and a dragged disc OD with 2+ pallor. Patching of the left eye was recommended 2 hours/day. At age 2, the vision exam revealed fixation with intermittent following, bilateral intermittent nystagmus, exotropia, and -8.00 sphere OD and +1.50 sphere OS refractive errors. At age 3, the patient had a Teller cards visual acuity of 20/400 (both eyes open), -15.00 sphere OD and +3.25 sphere OS refractive errors, and intermittent vertical and horizontal nystagmus OU. Currently, the child is nonambulatory and nonverbal. His 5-year past medical history is significant for global developmental delay, amblyopia, and 35 to 40 degrees (60–70 prism diopters) exotropia,

Fig. 3 Case #2's CGH analysis (DNAarrayTM-Oligi-180) revealed (A) a single copy number decrease of 3.0 Mb of chromosome 17p13.3 region and (B) a single copy increase of 2.0 Mb of chromosome 16p13.3 region consistent with a 17p13.3 microdeletion and a 16p13.3 microduplication. The derivative chromosome likely represents a malsegregation of a paternal balanced chromosome 16;17 translocation. The 16p duplication does not encompass the *CREBBP* gene within the Rubenstein-Taybi critical region. CGH, comparative genomic hybridization; CREBBP, CREB binding protein (CREB, cAMP response element binding protein binding protein).

Fig. 4 Fundus photographs of Case #2's right and left eyes taken previtreotomy showing (A) retinal dysplasia (elevated ridge of proliferative neovascularization) in zone 2 of the right fundus and (B) the left eye fundus status 7 days postlaser photocoagulation for retinal dysplasia. Note the fibrovascularization in zone 3 of the left retina.

cataractous changes in the lens OD, myoclonic type seizures, possible infantile spasms, multiple respiratory tract infections, a gastrostomy tube at age 2, chronic encephalopathy, electroencephalogram significant for an hypsarrhythmic pattern, and five respiratory distress incidents due to aspiration pneumonia with recurrent intubations leading to tracheostomy.

Case #3 (→ **Fig. 1**, IV-12, a half first cousin of the affected males): The ophthalmic exam performed at 16 months postpartum on a full-term female with MDS phenotype (cytogenetically confirmed 17p13.3 microdeletion/16p13.3 microduplication) did not detect PPR. The concurrent physical examination showed a high forehead with frontal bossing, mild bifrontal narrowing, flat, wide nasal bridge, ocular hypertelorism, short nose with anteverted nares, long philtrum, protuberant upper lip, teeth not yet erupted, ears normally set and anteriorly rotated, simplified auricles, bilateral single palmar creases, and bilateral clinodactyly of the fifth finger. The patient has failed to thrive and has coexisting intellectual and developmental delay.

Case #4 (→ **Fig. 1**, IV-10, a half first cousin of the affected males): A full-term female, small for gestational age, showed at birth microcephaly, ocular hypertelorism, short columella, slightly low-set ears, and calcaneovalgus deformity of the right foot. Newborn screen was positive for hemoglobin Bart, and α thalassemia trait with deletion of an α globin gene haplotype was discovered. Subsequent course included feeding difficulties, failure to thrive, and developmental and intellectual delay. MRI showed no lissencephaly, but thin corpus callosum with incomplete formation of the splenium. The ophthalmic exam performed at 4 years of age noted amblyopia, strabismus, and high myopia. Cytogenetic analysis revealed duplication of 17p13.3 with deletion of a copy of 16p13.3, the patient having inherited the translocated chromosome 16 (with 16p13.3 material replaced by 17p13.3 material). CGH testing (CombiMATRIX Molecular Diagnostics, Inc.) confirmed the same breakpoints in 17p13.3 microdeletion and 16p13.3 microduplication as present in the other affected children causing the MDS (not shown).

Discussion

The clinical, neuroradiological, cytogenetic, and molecular genetic data of three of the affected children in the extended family were consistent with the MDS variant of classical lissencephaly. The second infant was born prematurely, but had supplemental oxygen for only 48 hours. In addition, the proliferative retinopathy was present at age 9 days, much too early for the development of ROP. Early ophthalmic examinations detected PPR in two familial MDS children. Hospital records show the retinal lesions were not due to oxygen-induced ROP. As for the inheritance pattern, the cousins likely inherited the identical rearrangement from parents who are sibs and carriers of a balanced translocation between 16p13.3 and 17p13.3. The affected children with the MDS phenotype inherited the *LIS1*-deleted chromosome in imbalanced form, with a partial monosomy (deletion) of a segment in 17p13.3 and a partial trisomy (duplication) of a segment in 16p13.3. The CombiMATRIX data, especially the sizes of the duplication/deletion, suggests a cryptic translocation between the distal parts of those two chromosome bands were inherited from a carrier parent. (The 16p13.3 microduplication did not encompass the cAMP response element binding (CREB) binding protein gene associated with the Rubinstein-Taybi syndrome.²⁰) A fourth child (→ **Fig. 1**, IV-4) was born with the reciprocal chromosomal imbalance, a duplication of 17p13.3 and deletion of 16p13.3 with no finding of PPR.

The visual anomalies seen in our cases were consistent with previously reported visual abnormalities in MDS children⁵ and were less severe than those observed in cobblestone lissencephaly children.⁷ A case review of postpartum fundus examinations revealed PPR is uncommon to MDS (17p13.3 microdeletion as the sole chromosomal abnormality). That is, no posterior segment abnormalities were noted in six (one retinal coloboma) of seven reported MDS children evaluated for ocular abnormalities.⁵ The PPR in our first infant resolved without treatment, but the PPR in the second child required indirect laser to the avascular area of each eye, with progression to

peripheral retinal detachment in the right eye requiring lens-sparing vitrectomy. Notably, the proliferative retinopathy was quite similar (in fact, identical) to the typical picture of ROP, but occurred in near full-term infants; ruling out classical ROP. Follow-up ophthalmic examinations of the infants revealed previously reported MDS-associated anomalies of poor fixation, exotropia, nystagmus, hyperopia, amblyopia, and cataractous changes in the lens (postvitrectomy).⁵

The first case died at 18 months and the second case is 5 years old. The two MDS female cousins (cases #3 and #4) are less than 5 years of age and have multiple health issues requiring continuous care, in addition to physical disabilities, delayed growth, and cognitive functions. An additional female child (►Fig. 1, III-15) died without an ophthalmic examination. The mortality rate for classic lissencephaly children is high with a reported 54% 5-year survival rate.^{21,22} However, there are a few accounts of MDS adults with survival apparently related to the severity of prominent abnormalities noted by neuroimaging.²²

The DNA microarray reports listed deleted 17p13.3 and duplicated 16p13.3 genes. At least two genes within the translocated chromosomes are candidates for contributing to the observed PPR. *SERPINF1* (a serine protease inhibitor) gene is present in only one copy in the children with the 17p13.3 MDS phenotype. Its protein product, PEDF (pigmented epithelium-derived factor, the epithelium being retinal), is multifunctional, reflecting the extraordinary pleiotropy of the gene. PEDF can be neurotrophic²³ and, significantly for our patients, inhibitory to neovascularization.^{24,25} The second gene is on 16p13.3, a protein disulfide-isomerase (*PDIA2*), and is present in three copies due to the translocation of 16p13.3 material into the abnormal chromosome 17. *PDIA2* has multiple functions, including assisting in protein folding and chaperoning proteins. Tissue factor (TF), one of the proteins it chaperones, reacts with Factor VII, a primary initiator of blood coagulation, and, in a different function, mobilizes vascular smooth muscle cell migration and formation.²⁶

The PPR detected by early ophthalmic exams in our MDS patients varied from serious in one patient to transient in another, and was not detected by ophthalmic exams performed over 1 year postpartum in the two female half-cousins. These findings may suggest a stage-specific (perinatal) phenomenon, potentially serious though otherwise transient. The PPR has not been observed previously in MDS cases, most likely due to the fact that ocular exams were not performed. Accordingly, publications describing adequate ophthalmologic exams of MDS patients are in the minority. Our cases introduce the possibility that some MDS children may have early sight-threatening retinal pathology, demonstrate the benefit of an early ophthalmic consultation in detection and treatment of PPR, and stress the importance of full ocular examination of newborn MDS infants who generally are not examined. Finally, early ophthalmic evaluation, neuroradiology, histopathology, and high-resolution molecular genetic analyses^{27,28} are obligatory for characterizing the chromosomal mutations and genes related to the retinopathies of the classic lissencephalies.

Conclusion

Our observations support the benefit of a complete ophthalmic examination in preserving useful vision in infants with lissencephalopathies. Additional molecular genetic and neuroimaging studies are needed to support the association of *SERPINF1* and *PDIA2* gene mutations in the development of proliferative retinopathy in MDS patients.

Availability of Data and Materials

All the data supporting the findings of this study are available from the LSU Health, Shreveport, but restrictions apply to the availability of these data, which were used under the Internal Review Board (IRB) approval for the current study, and so are not publicly available. However, data are available upon reasonable request from the author (s) and with permission of the LSU Health, Shreveport IRB.

Authors' Contributions

O.S.: Patient interaction, literature research, and initial drafting of the manuscript. A.B.R.: Patient interaction, patient diagnosis, literature research, critical revision, and language editing. L.A.P.: Literature research, evaluated the gene analysis, and made critical revision. J.H.: Patient interaction and patient diagnosis. W.R.S.: Operated on the patient, consented, and took the fundus photographs. M.P.L.: Literature research, critical revision, language editing, drafting, and submission of the manuscript. All authors have read and approved the final manuscript.

Conflict of Interest

None.

Note

Written informed consent was obtained from the parents for publication of the accompanying deidentified images.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the LSU Health Sciences Center, Shreveport (FWA 00000653), and adheres to the tenets of the Declaration of Helsinki.

Funding

None.

Acknowledgments

The authors acknowledge the contributions of Alex Anders, MD, Jonathan Carrere, MD, and Austin Lash, MD, who performed follow-up ophthalmic examinations on one or more of the patients. The authors thank Susonne Ursin, MD (Department of Pediatrics) for her invaluable genetic insight and discussion regarding MDS. The material of this manuscript was not previously presented at a meeting.

References

- Spalice A, Parisi P, Nicita F, Pizzardi G, Del Balzo F, Iannetti P. Neuronal migration disorders: clinical, neuroradiologic and genetics aspects. *Acta Paediatr* 2009;98(03):421–433

- 2 Banna M, Malabarey T. Lissencephaly and pachygyria. *Can Assoc Radiol J* 1989;40(03):156–158
- 3 Dobyns WB, Das S. LIS1-associated lissencephaly/subcortical band heterotopia. 2009 Mar 3. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. *GeneReviews®* [Internet]. Seattle, WA: University of Washington, Seattle; 1993–2014. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK5189/>. Accessed March 2015
- 4 De Wilde G, Hansens M, Govaert P. The Walker-Warburg syndrome. *Bull Soc Belge Ophtalmol* 1992;243:129–138
- 5 Nabi NU, Mezer E, Blaser SI, Levin AA, Buncic JR. Ocular findings in lissencephaly. *J AAPOS* 2003;7(03):178–184
- 6 Bosch DG, Boonstra FN, Reijnders MR, Pfundt R, Cremers FP, de Vries BB. Chromosomal aberrations in cerebral visual impairment. *Eur J Paediatr Neurol* 2014;18(06):677–684
- 7 Marqués-Fernández VE, Sánchez-Tocino H, Escudero-Caro MT, Cancho-Candela R, García-Zamora M. Visual impairment due to lissencephaly. *Neuroophthalmology* 2016;40(05):229–233
- 8 Di Donato N, Chiari S, Mirzaa GM, et al. Lissencephaly: expanded imaging and clinical classification. *Am J Med Genet A* 2017;173(06):1473–1488
- 9 Verloes A, Elmaleh M, Gonzales M, Laquerrière A, Gressens P. Genetic and clinical aspects of lissencephaly [in French]. *Rev Neurol (Paris)* 2007;163(05):533–547
- 10 Dobyns WB, McCluggage CW. Computed tomographic appearance of lissencephaly syndromes. *Am J Neuroradiol* 1985;6(04):545–550
- 11 Dobyns WB, Reiner O, Carrozzo R, Ledbetter DH. Lissencephaly. A human brain malformation associated with deletion of the LIS1 gene located at chromosome 17p13. *JAMA* 1993;270(23):2838–2842
- 12 Cardoso C, Leventer RJ, Dowling JJ, et al. Clinical and molecular basis of classical lissencephaly: mutations in the LIS1 gene (PAFAH1B1). *Hum Mutat* 2002;19(01):4–15
- 13 Noor A, Bogatan S, Watkins N, Meschino WS, Stavropoulos DJ. Disruption of YWHAE gene at 17p13.3 causes learning disabilities and brain abnormalities. *Clin Genet* 2018;93(02):365–367
- 14 Pilz DT, Matsumoto N, Minnerath S, et al. LIS1 and XLIS (DCX) mutations cause most classical lissencephaly, but different patterns of malformation. *Hum Mol Genet* 1998;7(13):2029–2037
- 15 Cardoso C, Leventer RJ, Ward HL, et al. Refinement of a 400-kb critical region allows genotypic differentiation between isolated lissencephaly, Miller-Dieker syndrome, and other phenotypes secondary to deletions of 17p13.3. *Am J Hum Genet* 2003;72(04):918–930
- 16 Kato M. Genotype-phenotype correlation in neuronal migration disorders and cortical dysplasias. *Front Neurosci* 2015;9:181
- 17 Dobyns WB, Truwit CL. Lissencephaly and other malformations of cortical development: 1995 update. *Neuropediatrics* 1995;26(03):132–147
- 18 Mano N, Mitsutsuji T, Yoshikawa Y, et al. Optical coherence tomography in an infant with Walker-Warburg Syndrome. *Case Rep Ophthalmol* 2015;6(02):210–215
- 19 Hodgkins PR, Kriss A, Boyd S, et al. A study of EEG, electroretinogram, visual evoked potential, and eye movements in classical lissencephaly. *Dev Med Child Neurol* 2000;42(01):48–52
- 20 Kim SR, Kim HJ, Kim YJ, Kwon JY, Kim JW, Kim SH. Cryptic microdeletion of the CREBBP gene from t(1;16) (p36.2;p13.3) as a novel genetic defect causing Rubinstein-Taybi syndrome. *Ann Clin Lab Sci* 2013;43(04):450–456
- 21 de Rijk-van Andel JF, Arts WF, Hofman A, Staal A, Niermeijer MF. Epidemiology of lissencephaly type I. *Neuroepidemiology* 1991;10(04):200–204
- 22 de Wit MC, de Rijk-van Andel J, Halley DJ, et al. Long-term follow-up of type 1 lissencephaly: survival is related to neuroimaging abnormalities. *Dev Med Child Neurol* 2011;53(05):417–421
- 23 Tombran-Tink J, Barnstable CJ. PEDF: a multifaceted neurotrophic factor. *Nat Rev Neurosci* 2003;4(08):628–636
- 24 Dawson DW, Volpert OV, Gillis P, et al. Pigment epithelium-derived factor: a potent inhibitor of angiogenesis. *Science* 1999;285(5425):245–248
- 25 Tombran-Tink J. PEDF in angiogenic eye diseases. *Curr Mol Med* 2010;10(03):267–278
- 26 Peña E, Arderiu G, Badimon L. Protein disulphide-isomerase A2 regulated intracellular tissue factor mobilisation in migrating human vascular smooth muscle cells. *Thromb Haemost* 2015;113(04):891–902
- 27 Civelek M, Lusi AJ. Systems genetics approaches to understand complex traits. *Nat Rev Genet* 2014;15(01):34–48
- 28 Rosenfeld JA, Patel A. Chromosomal microarrays: understanding genetics of neurodevelopmental disorders and congenital anomalies. *J Pediatr Genet* 2017;6(01):42–50