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Y.R. Grechanin[1], A.L. Fadieieva[2], D.V. Shkolnikova[3]

Molecular genetics of neurodevelopmental disorders in Ukrainian children

[1]Kharkiv National Medical University, Ukraine

[2]Mitochondrial and Epigenomic Medicine of Kharkiv National Medical University, Ukraine

[3]MNCE of Kharkiv Regional Council «Interregional Specialized Medical-Genetic Center for Rare (Orphan) Diseases», Ukraine

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Neurodevelopmental disorders make a significant contribution to pediatric pathologies. This group of diseases varies symptomatically and has various underlying molecular reasons, which result in the necessity of personalized diagnostic and treatment protocols.

Aim – to detect metabolic pathways and molecular markers potentially contributing to the development of the pathological phenotype in pediatric patients with neural pathology.

Materials and methods. Selection of the patient's cohort for the pilot study was done during consultations provided by pediatricians, geneticists, and neurologists following principles of an interdisciplinary approach in diagnostic and management of children with developmental abnormalities. Further analysis of detected DNA variations, along with structural and functional predictions, was done using the SNP-NEXUS tool.

Results. The work presented in this manuscript enabled the identification of all detected genomic variations that may be associated with the chosen clinical phenotype in the small cohort of patients. Further functional enrichment analysis allowed us to identify various biological cellular processes that may be affected by the identified genomic alterations. Particularly, we found metabolic pathways with high enrichment score for possibly pathogenic and probably pathogenic amino acid substitutions in proteins, with lipid metabolism having the highest enrichment score.

Conclusions. Predictive and functional enrichment analysis of SNV (Single Nucleotide Variation) patterns detected by DNA sequencing on a small cohort of pediatric patients with neurodevelopmental pathology allowed us to identify cellular processes and proteins that potentially play a role in neural pathology. Further investigation in a higher number of patients and search for statistically significant associations of the preselected targets with the phenotype may help to improve the diagnostic and treatment approach for the selected pathology.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Local Ethics Committee of the institution. Informed parental consent was obtained for participation in the study.

The authors declare no conflict of interest.

Keywords: neurodevelopmental disorders, pediatrics, molecular diagnostics, functional enrichment analysis, lipid metabolism.

Молекулярна генетика нейророзвиткових розладів у дітей України

Я.Р. Гречанін[1], А.Л. Фадєєва[2], Д.В. Школьнікова[3]

[1]Харківський національний медичний університет, Україна

[2]Український інститут мітохондріальної та епігеномної медицини Харківського національного медичного університету, Україна

[3]КНП Харківської обласної ради «Міжрегіональний спеціалізований медико-генетичний центр – центр рідкісних (орфанних) захворювань», Україна

Розлади нервового розвитку становлять значну частину дитячих захворювань. Ця група порушень має варіативні симптоматичні прояви та молекулярні основи, що формує необхідність у персоналізованій діагностиці та протоколах лікування.

Мета – виявити метаболічні шляхи та молекулярні маркери, що можуть відігравати роль у розвитку патологічних проявів у дітей із розладами нервового розвитку.

Матеріали та методи. Вибір пацієнтів для пілотного дослідження здійснено на медичних консультаціях за участю педіатрів, генетиків та невропатологів із дотриманням принципів міждисциплінарного підходу в діагностиці та медичного супроводу дітей із аномаліями розвитку. Подальший аналіз виявлених варіацій ДНК та структурні й функціональні передбачення виконано за допомогою ресурсу SNP-NEXUS.

Результати. Виявлено геномні варіації, що можуть бути асоційовані зі зазначеними клінічними розладами в невеликій групі пацієнтів. Подальший аналіз функціонального збагачення виявив різноманітні біологічні клітинні процеси з можливими порушеннями внаслідок знайдених геномних змін. Знайдено метаболічні шляхи з високим коефіцієнтом збагачення білками з можливо патогенними та вірогідно патогенними замінами амінокислот, серед яких метаболізм ліпідів мав найвищий коефіцієнт збагачення.

Висновки. Передбачувальний аналіз функціонального збагачення однонуклеотидних варіантів, що були знайдені секвенуванням ДНК у невеликій групі дітей із розладами нервового розвитку, дав змогу виявити клітинні процеси та білки, що, можливо, відіграють роль у розвитку нервових розладів. Подальше дослідження за участю більшої кількості пацієнтів та пошук статистично значущих асоціацій між попередньо виявленими молекулярними цілями та клінічними проявами можуть допомогти покращити підходи в діагностиці та лікуванні зазначеної патології.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом установи. На проведення досліджень отримано інформовану згоду батьків дітей.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: розлади нервового розвитку, педіатрія, молекулярна діагностика, аналіз функціонального збагачення, метаболізм ліпідів.

Introduction

Neurodevelopmental disorders represent a heterogeneous group with evolving diagnostic concepts and substantial genetic and biological complexity [2,18,20,25]. Neurodevelopmental outcomes may be shaped by social stressors, neglect, and early deprivation, with reported associations with executive function and brain deve-

lopment [10,12,14,16,17,22,24]. Post-infectious neurodevelopmental sequelae have also been reported after SARS-CoV-2 infection and long COVID-19 [5,13,15]. Genetic testing contributes to diagnostic yield in pediatric epilepsy and autism spectrum disorder cohorts [4,28]. Related neurodevelopmental conditions and neurodevelopmental impacts across the lifespan are actively studied, including ADHD (Attention Deficit Hyperactivity Disorder) in adults and learning/anxiety-related outcomes [3,6,9,23], as well as school-related mental health correlates in children [11].

At the same time, variability of SNPs (Single Nucleotide Polymorphisms) in various populations and further various outcomes on functionality of coding and non-coding transcripts, deoxyribonucleic acid (DNA) structure and epigenetics and functional uncertainty of amino acid substitutions in proteins complicate direct use of DNA sequencing results for personalized diagnosis and therapeutic approach in clinical settings. Recent developments in computational biology, such as GWAS (Genome-Wide Association Study) [26], PolyPhen-2 prediction [1] and functional enrichment analysis [7,19,29] are novel computing tools capable of linking structural DNA changes with clinical phenotype and underlying biological pathways.

Given the increasing prevalence and clinical significance of pediatric neural pathology, we conducted this study, which applies predictive computational tools to select from sequencing results additional Single Nucleotide Variations (SNVs) and associated molecular pathways and proteins with a potential role in neural pathology in pediatric patients.

The aim of the study was to preselect potentially pathogenic heterozygous and homozygous SNVs and metabolic pathways in a small group of children with neural pathology for further validation and association studies on a larger number of patients.

Materials and methods of the study

Patients for the pilot study were selected from a total of 174 patients from 1 to 8 years old who approached Kharkiv Specialized Medical Genetic Center in 2022–2025.

Children with clinical symptoms of neuropsychiatric developmental disorders, including defects in speech, cognitive functions, social adaptation, and behavioral abnormalities, were included in the study.

Inclusion criteria were: age 1 to 8 years, gestational age at birth ⩾37 weeks, absence of chronic somatic and neurological pathology, informed consent of the parents. *Exclusion criteria* were: inherited or inborn pathology, organic pathology of the central neural system, and chronic somatic pathology that may influence neurodevelopmental processes.

Clinical investigation of patients was done using the next assessment scores and criteria: aggression (0 – no, 1 – present); hyperactivity (0 – no, 1 – present); hypermobility (0 – no, 1 – present); hypertonus (0 – no 1 – present); hypotonia (0 – no, 1 – present); retarded speaking (0 – no, 1 – moderate, 2 – obvious); motor development retardation (0 – no, 1 – moderate, 2 – obvious); regress (0 – no, 1 – present); seizures (0 – no, 1 – present).

30 patients were included in the study based on the described clinical assessment criteria, with the following blood sampling for genetic analysis.

Molecular genetic studies were conducted to identify gene variants in early and preschool children with symptoms of neurodevelopmental disorders (NDDs). For molecular genetic analysis, 30 children aged 1 to 8 years were examined. Biological material was peripheral venous blood samples collected in sterile vacuum tubes with Ethylenediamine tetraacetic acid (EDTA) anticoagulant, as well as scrapings of buccal epithelium. Genetic testing was performed in certified specialized laboratories, Invitae (LabCorp Genetics, USA) and CENTOGENE (Germany).

The laboratories provided the results of the sequencing containing coordinates of SNV location on the genome, reference allele and observed allele, homo-, hetero-, or hemizygosity, corresponding gene names and laboratories' recommendations on clinical interpretation based on the American College of Medical Genetics and Genomics (ACMG) protocols [21]. We additionally analyzed the data using predictive tools to identify heterozygous and homozygous SNVs with predicted pathological effects on protein amino acid substitutions and potential epistatic interactions.

RSID annotations were retrieved using NCBI dbSNP, and SNVs were classified by transcript location. Amino acid substitutions' pathogenicity was predicted using PolyPhen-2 [1]. Functional enrichment analysis was performed using Reactome [8] and Fisher's Exact Test [27] via SNPnexus/SNP-NEXUS resource [7,19,29]. Linkage disequilibrium was tested using the Ensemble tool. The level of statistical significance was set at $p<0.05$.

Table 1

Frequency of neurodevelopmental symptoms in the pilot cohort

Symptom	Severity of the symptom	Severity of the symptom	Number of patients
Aggression	1 (3.33%)	NA	1
Hyperactivity	11 (33.33%)	NA	11
Hypermobility	3 (10.0%)	NA	3
Hypertonia	1 (3.33%)	NA	1
Hypotonia	11 (33.3%)	NA	11
Retarded speaking	12 (40.0%)	16 (53.3%)	28
Motor development retardment	17 (51.5%)	6 (20%)	23
Regress	2 (6.66%)	NA	2
Seizures	4 (13.33%)	NA	4

Results of the study and discussion

Patients having at least one symptom of a neurodevelopmental disorder were selected for further molecular diagnostics; symptom frequencies are summarized in Table 1.

Sequencing analysis revealed 337 different variations in 310 functional regions of the genome, including 280 annotated (rsid) and 57 novel variants, and a predominance of point mutations. Variants showed uneven chromosomal distribution, with the highest proportion on chromosomes 1, 2, 16, 11, 3, 12, 6, and 14 (Fig. 1). Structural annotation suggested 2,099 functional genome alterations, including coding variants with synonymous and non-synonymous changes.

Chromosome mapping showed that almost any chromosome could have a DNA variation in the selected patient group. The number of variations did not depend on the size of the chromosomes (Figure 1a). The majority of variations in the coding region were non-synonymous (Figure 1c, d, and e), forming a group that should be the focus of further studies, as those bringing changes in amino acid sequences and potential alterations of protein functionality that might lead to the development of the selected medical condition. However, the complexity and variability of the detected genomic variations affecting both coding and regulatory regions of the genome (Figure 1b) make it difficult to establish associations with the clinical symptoms. So, we applied additional functional analysis based on the PolyPhen prediction algorithm to narrow down the variations to those that result in possibly pathogenic and probably pathogenic transcripts and protein changes. PolyPhen-based prediction indicated that coding sequence changes may affect up to 920 transcripts (benign, possibly pathogenic, and probably pathogenic), and 247 proteins with predicted amino acid changes (109 benign, 61 possibly pathogenic, 78 probably pathogenic). To detect potentially affected molecular pathways, we then conducted functional enrichment analysis for the detected SNV's in the coding region.

Functional enrichment analysis (Reactome; $p \leqslant 0.05$) identified pathways with the highest enrichment score for Metabolism and Extracellular matrix organization (Fig. 2). Thus, Metabolism and Extracellular matrix organization may be in focus for further studies of the underlying reasons of neurodevelopmental pathology.

To narrow down further the selection of potential molecular targets, we quantified the proportion of patients with at least one possibly pathogenic or probably pathogenic amino acid alteration within selected pathways. The analysis revealed that Lipid metabolism had the highest enrichment score (Fig. 3).

Functional enrichment analysis combined with PolyPhen predictive structural analysis revealed that 73.33% (n=22) of patients had at least one DNA variation resulting in possibly or probably pathogenic amino acid replacement in proteins involved in

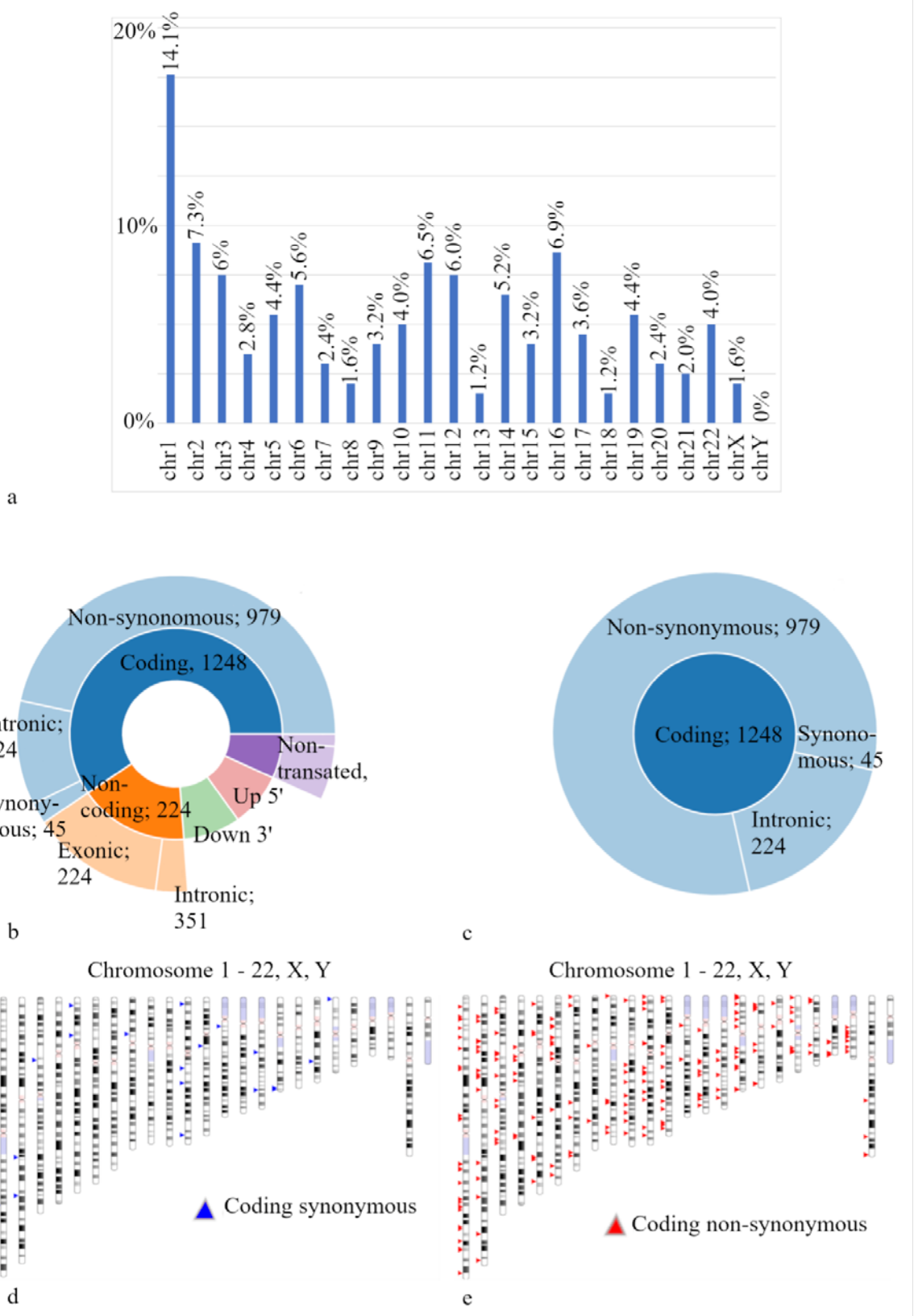

Fig. 1. Structural and functional distribution of detected DNA variations (chromosomal distribution and functional classes): a – numerical distribution of detected changes on chromosomes; b – structural distribution of detected changes between coding and non-coding regions, untranslated region, as well as above the 5′ end of genes and below the 3′ end of genes; c – distribution of detected changes according to the criterion of amino acid sequence substitution between synonymous mutations, non-synonymous mutations and intronic regions; d – arrangement of coding synonymous variations on chromosomes; e – placement of coding non-synonymous variations on chromosomes

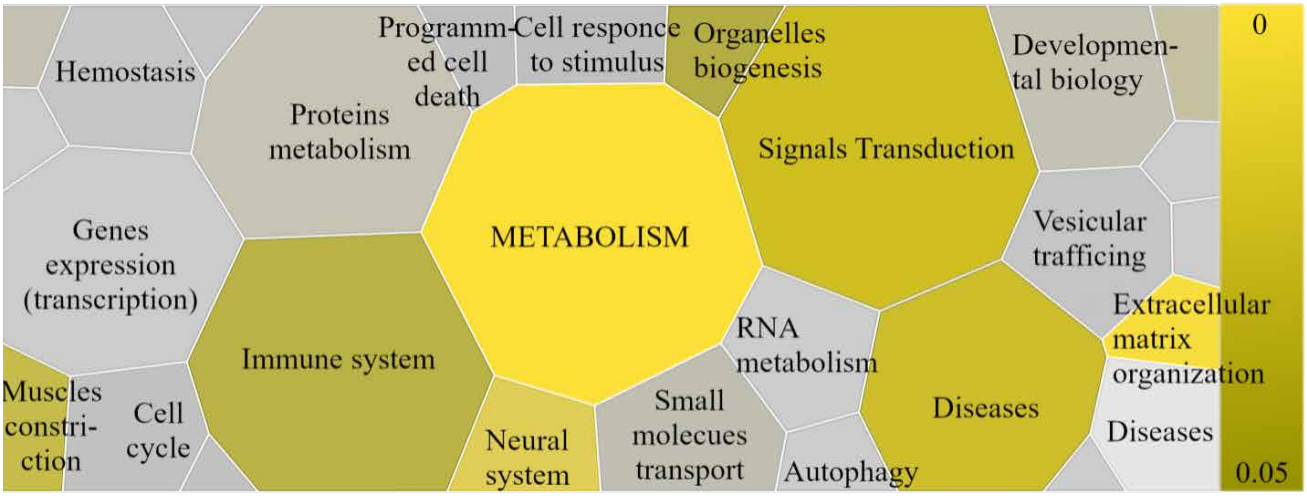

Fig. 2. Reactome pathway enrichment analysis results (top enriched pathways; p≤0.05)

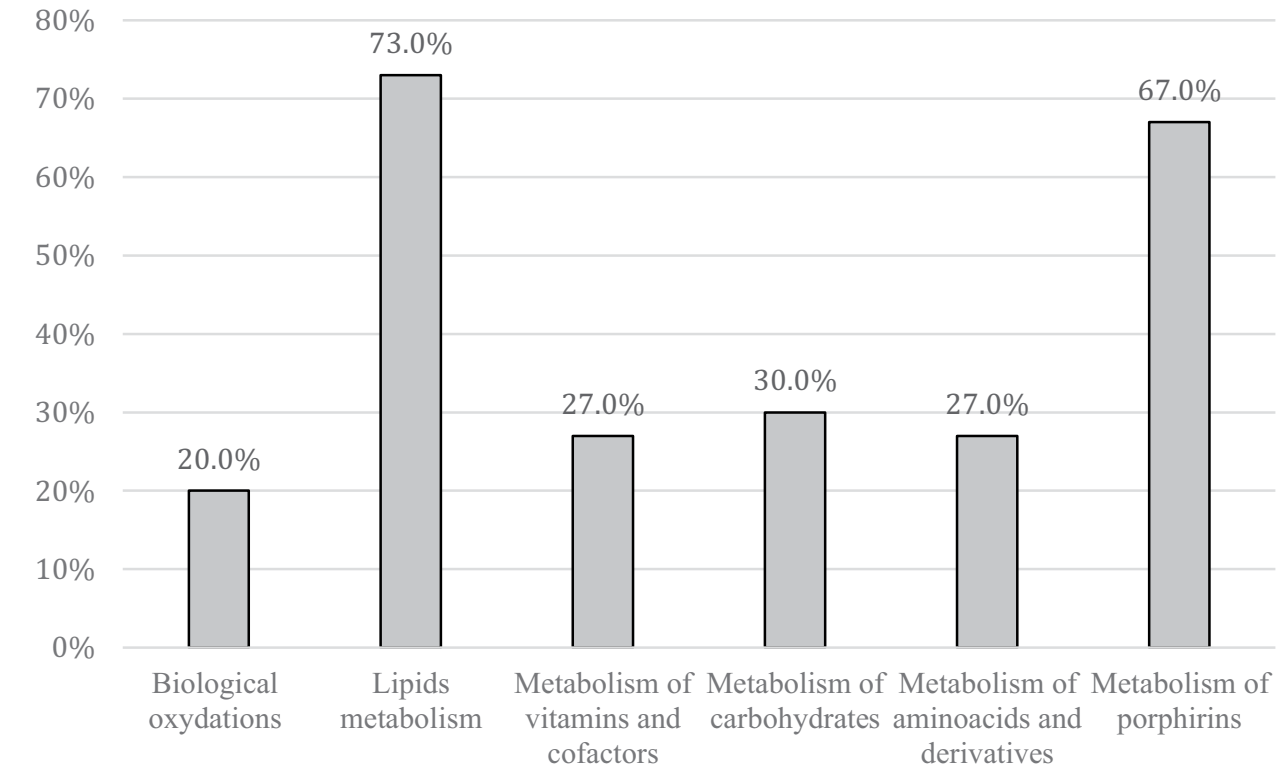

Fig. 3. Proportion of patients with at least one Possibly/Probably pathogenic variant in various metabolic pathways, %

lipid metabolism (Fig. 3). This makes lipids metabolism an interesting target in further research on the molecular underlying reasons of neural pathologies and potential therapeutic targets selection. To look in more details at identified SNV's potentially affecting lipid metabolism, we compared the frequencies of the detected variations with population frequencies (gnomAD Non-Finnish European) (Table 2).

The most frequently detected lipid metabolism variants in the selected group of patients were in Acyl-CoA dehydrogenase short chain (*ACADS*) (rs1799958) and Galactosylceramidase (*GALC*) (rs398607). While the *ACADS* variation frequency was significantly higher compared to the corresponding population number, SNV in *GALC* has similar frequencies with population. However, the pro-

Table 2

Most frequent variants of genes involved in lipid metabolism and corresponding gnomAD population frequencies

Protein name	Rsid of the detected SNV	Reference and alternate alleles	Frequencies of the detection in the research group, n (%)	gnomAD population frequency, %
ACADS	rs1799958	G>A	12 (40.0)	26.5
ACADVL	rs151254520	C>T	1 (3.3)	0.03
CREBBP	rs794727551	G>A	1 (3.3)	0.0015
CYP1B1	rs1800440	C>G	1 (3.3)	18.65
	rs1056836	A>G	1 (3.3)	44.14
GALC	rs398607	T>C	13 (43.33)	47.6642
	rs1805078	C>T	2 (6.67)	5.8165
	rs200378205	C>A	1 (3.3)	0.0033
	rs34362748	G>A	5 (16.67)	15.65
GBA	rs80356768	c.1265_1319del	1 (3.3)	not reported
	rs1064651	G>C	1 (3.3)	0.01
	rs421016	T>C	1 (3.3)	0
LBR	rs11551873	C>T	1 (3.3)	not reported
PLD3	rs373686736	C>T	1 (3.3)	0.009
SBF2	rs150028248	G>A	1 (3.3)	0.0002
SLC25A20	rs749507449	C>T	1 (3.3)	0.0039
UGT1A9	rs3064744	c.-41_-40dup	4 (13.3)	not reported
VDR	rs731236	T>C	1 (3.3)	40.10
	rs7975232	C>A	1 (3.3)	52.73
BTD	rs13078881	G>C	2 (6.7)	4.1975
MTRR	rs1801394	A>G	1 (3.3)	56.2208
	rs1802059	G>A	1 (3.3)	36.7668

portion of patients carrying an alternative allele in both genes was 53.3% (n=16) in the selected cohort, while these SNV's were not reported to be in linkage disequilibrium ($r_2 \geqslant 0.5$; 1000 Genomes).

Variability of the underlying reasons for the development of neurological pathology requires various diagnostic approaches. The DNA sequencing method can detect genetic variations and their further predictive bioinformatic analysis aimed to find corresponding transcriptomic, proteomic and functional consequences may help to preselect SNV's playing a role in neural system dysfunction. We have applied the described diagnostic pipeline to the small cohort of patients with neural pathology. The strategy allowed the detection of SNV's resulting in possibly pathogenic and probably pathogenic alterations in amino acid sequences of the corresponding proteins and selected the most affected molecular pathways (Lipid metabolism). Comparison with population frequencies of the most frequently detected SNV's and their combination additionally allowed for selecting a pair with a potential synergetic effect in the selected phenotype. Interestingly, both *ACADS* and *GALC* homozygous mutations were reported to cause neurological symptoms, while heterozygous SNV's in the genes were mostly reported as those not associated with clinical pathogenicity. Our data point on the potential synergetic effect of SNV's in these genes in neural pathology and the role of their heterozygous variations and potential synergy in neural pathology should be further validated on a larger number of patients.

Lipid metabolism is a well-established central player in neuronal functionality and its alterations in such neural pathologies as Alzheimer's disease, Huntington's disease, Parkinson's disease, diabetes-associated cognitive loss, etc. have been previously shown. In line with this, our data points on its central role in pediatric neurodevelopmental pathology highlight the importance of further studies of molecular players and reactions of lipid metabolism involved in neural functions. Overall, we believe that the presented pipeline allowed us to identify SNV's and pathways of interest for their potential role in neural pathology and can help in diagnostic and selection of therapeutic targets.

Conclusion

The work presented in this manuscript allowed us to select out of all detected genomic variations those that may be associated with the chosen clinical phenotype in the small cohort of patients. Further functional enrichment analysis allowed us to identify various biological cellular processes that may be affected by the identified genomic alterations. Particularly, we found metabolic pathways with high enrichment score for possibly pathogenic and probably pathogenic amino acid substitutions in proteins, with lipid metabolism having the highest enrichment score. Predictive and functional enrichment analysis of SNV patterns detected by DNA sequencing in a small cohort of pediatric patients with neurodevelopmental pathology allowed the identification of cellular processes and proteins that potentially play a role in neural pathology. Further investigation on a higher number of patients and search for statistically significant associations of the preselected targets with the phenotype may help to improve the diagnostic and treatment approach for the selected pathology.

The authors declare no conflict of interest.

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Відомості про авторів:
Гречанін Ярослав Русланович – аспірант каф. пропедевтики педіатрії ХНМУ. Адреса: м. Харків, просп.т Науки, 4. https://orcid.org/0000-0002-5987-2765.
Фадєєва Анастасія Леонідівна – ст.н.с. Українського інституту мітохондріальної та епігеномної медицини ХНМУ. Адреса: м. Харків, просп.т Науки, 4. https://orcid.org/0009-0001-9147-3107.
Школьнікова Дар'я Владиславівна – генетик КНП ХОР «Міжрегіональний спеціалізований медико-генетичний центр рідкісних (орфанних) захворювань». Адреса: м. Харків, просп. Незалежності, 13. https://orcid.org/0009-0002-1343-293X.
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