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Genotype-Phenotype Correlation in Idiopathic Cerebral Palsy

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ABSTRACT

Genetic etiology is an important cause of idiopathic cerebral palsy, especially in consanguineous populations. **Objectives:** To determine the genotype-phenotype correlation in idiopathic cerebral palsy at a tertiary care hospital in Lahore, Pakistan. **Methods:** This retrospective descriptive cross-sectional study was conducted in the Department of Developmental and Behavioral Pediatrics, University of Child Health Sciences, Lahore. The data on cerebral palsy children with Whole Exome Sequencing was collected from January 2022 to January 2025. The study duration for all patients with reports available from March to August 2025 was included using nonprobability consecutive sampling. **Results:** Eighty-two patients were included after receiving their whole exome sequencing reports, and 35 genes were identified in 58 patients, showing a diagnostic yield of WES as 70.2%. There were 52 (63.4%) males. The average age was 8.3 ± 4.1 years (SD). The phenotype of positive patients showed spastic cerebral palsy to be the most common (79%), with a predominant quadriplegic subtype (55%). Seventeen genes (SYNE 1, PYCR2, PTS, SEPSECS, MOCS1, SERAC1, DEGS1, ECHS1, HPDL, ALS2, BLM, ITPA, PARD3, RIF1, CHD2, RAB3GAP1, ADAD2, WDR62) were associated with quadriplegic type, five (TBC1D14, CENPJ, ADAMDEC1, AMPD2 and TKTL1) with spastic diplegic, five (BICRA, ADGRG, CENPF, MAGEL2, TXNDC11) with hemiplegic, five (MIX23, EXOSC8, METTL5, GNG7, EZH1) with dyskinetic and two (SLC25A12, LPIN1) with mixed type. **Conclusions:** Epilepsy was present in 69%, feeding issues in 84%, drooling in 74%, recurrent chest infections in 60%, sleep issues in 60%, and constipation in 79%. GMFCS level V and MACS level V were the most common. Genotype–phenotype correlations in idiopathic cerebral palsy will help in comorbidity management and prognosis.

INTRODUCTION

Cerebral palsy (CP) is characterized by permanent, non-progressive problems with movement, posture, and motor function of variable extent due to an insult in growing brain. It may be associated with intellectual disability, feeding difficulties, constipation, drooling, epilepsy, sleep issues, and visual and hearing impairment [1]. Cerebral palsy has been divided into multiple types, such as spastic, dyskinetic, and mixed [2]. It is a leading cause of childhood disability worldwide. The prevalence of cerebral palsy is 3.4 per 1000 live births in low- and middle-income countries, while it is 1.6 per 1000 live births in high-income countries [3]. The prevalence has decreased from 2.2-2.5 to 1.6 per thousand in developed countries (high-income countries). A small study in Swabi showed the prevalence of cerebral palsy in Pakistan to be around 2.2/1000. However, the exact prevalence is unknown due to the lack of a national registry [4]. Risk factors of cerebral palsy include prematurity, hypoxic ischemic encephalopathy, maternal infections, kernicterus, neonatal brain infections, and others [5]. However, no risk factors can be defined in many children with cerebral palsy, and they fall under the umbrella of CP mimics. It is proposed that such children need to be investigated for inborn errors of metabolism and genetic disorders so that they can benefit from specific disease-modifying therapeutic options [6]. The existing literature on genetic studies showed that as many as one third cases

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of cerebral palsy are thought to have an underlying genetic cause [7]. A study carried out by May HJ at New York Presbyterian Hospital included 20 patients with idiopathic cerebral palsy, who showed that 11 (55%) had genetic mutations on whole exome sequencing. The incidence of epilepsy and severity of motor impairment were found to be higher in children with cerebral palsy with underlying genetic mutations [8]. In another multicenter study conducted in China by Wang et.al., including 1578 children with cerebral palsy, researchers utilized whole exome sequencing to successfully identify genetic causes in 24.5% (n=387) of the participants. A total of 219 genes were isolated [9]. Another US study by Chopra et.al. with 50 patients shows that a high number of patients diagnosed with CP possess single-gene mutations on whole exome sequencing, with 13 children (26%) having a positive result [10]. Consanguinity is one of the major factors in gene-related disorders, including disabilities like developmental delay, cerebral palsy, spasticity, and epilepsy [11].

Pakistan is a highly consanguineous population, and there is limited data on genetics with respect to cerebral palsy mimics and genetic etiology. As per the researcher's knowledge, very few studies have been done in Pakistan to identify the genetic makeup and severity of symptoms in cerebral palsy. This study aims to fill the gap in knowledge of genetic heterogeneity in cerebral palsy. To determine the genotype-phenotype correlation in idiopathic cerebral palsy at a tertiary care hospital in Lahore, Pakistan.

METHODS

The Retrospective descriptive cross-sectional study was carried out on children with cerebral palsy in the Department of Developmental and Behavioral Pediatrics, University of Child Health Sciences and Children's Hospital, Lahore, whose samples for genetic analysis by whole exome sequencing were sent to UCL, London. The data were collected from January 2022 to January 2025. Eighty-two children had reports available during the study period from March 2025 to August 2025. Certificate of ethical approval (No.1076/CH-UCHS) for this research was taken from the IRB Committee of the University of Child Health Sciences, Children's Hospital, Lahore. Children were enrolled by non-probability consecutive sampling. Informed written consent was taken from parents, and confidentiality was ensured. Children with cerebral palsy having positive genetic reports of both genders born to consanguineous parents with a family history of developmental delay or miscarriage/ intrauterine death of a sibling were included. Children with identifiable known syndromes were excluded. Data was entered using a well-designed questionnaire. Demographic information was collected, including age and gender. A developmental behavioral pediatrician examined and classified each patient with cerebral palsy according to the Rosenbaum criteria. The phenotype of children with positive reports was studied in detail. ICD-11 classification of cerebral palsy was used to classify children into spastic (its subtypes), dyskinetic, and mixed forms of cerebral palsy based on clinical examination. Comorbidities like the presence of epilepsy, feeding difficulty, drooling, sleep issues, constipation, and behaviour issues were also documented. Severity of participants' disability was assessed by GMFCS (Gross Motor Function Classification System), MACS (Manual Ability Classification System), and BMFM (Bimanual Fine Motor Function) scale from level 1 to level V. Data was entered & analyzed by using SPSS version 25.0. Quantitative variable (age) was calculated as Mean ± SD. The diagnostic yield of whole-exome sequencing was calculated as a percentage of children with positive genetic reports. Qualitative variables like gender, type of cerebral palsy, presence of comorbidities, and levels of GMFCS, MACS, and BMFM were calculated as frequency and percentage. The association of comorbidities was compared between different types of cerebral palsy by using the chi-square test, and a p-value≤0.05 was taken as significant. Genomic DNA was extracted from peripheral blood samples according to standard procedures of phenol-chloroform extraction and enriched according to the Agilent Sure Select Target Enrichment Kit V7. Libraries were sequenced with the HiSeq or MiSeq sequencer (Illumina) with 50x coverage. Quality assessment of the sequence reads was performed by generating QC statistics with Fast QC. Priority was given to rare variants (<0.01% in public databases, including 1000 Genomes project, NHLBI Exome Variant Server, Complete Genomics 69, and Exome Aggregation Consortium) that were fitting dominant or a de novo model or variants in genes previously linked to neurological disorders. Variants of interest were confirmed with Sanger sequencing. For Sanger sequencing validation, genomic DNA was amplified by PCR using gene-specific primers designed with Primer3 software. Primer sequences, annealing temperatures, and expected amplicon sizes were carefully selected. PCR amplification was performed using FastStart PCR Master mix (Roche), and PCR products were purified using Exo-SAP (Exonuclease I and Shrimp Alkaline Phosphatase). Sequencing PCR was performed bi-directionally using an ABI 3730xl DNA Analyzer, and chromatograms were analysed using Geneious. The significance of the identified variant was classified according to American College of Medical Genetics and Genomics (ACMG) criteria using the Varsome tool [10].

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RESULTS

Positive gene mutation was seen in 58 out of 82 children with cerebral palsy, showing 70% diagnostic yield of the whole exome sequencing. Among 58 children with positive gene reports, 35 unique genes were identified. Mean age of presentation for children with positive reports was 6.9 years ± 4.2 SD. The most common age group of presentation was 10 years and above (34.5%), and 69%(n=40) of children were male (Table 1).

Table 1: Age Groups of Children With Positive Genetic Reports

Age Groups	Spastic Quadriplegic	Spastic Diplegic	Spastic Hemiplegic	Dyskinetic	Mixed	Total
0-1 Year 11 Months	4	1	0	0	1	6 (10.3%)
2 -4 Years 11 Months	9	0	2	2	1	13 (22.4%)
5 Years-9 Years 11 Months	11	3	0	0	2	19 (31.8%)
10 Years and Above	8	4	6	6	0	20 (34.5%)

The most common type of CP (phenotype) among the children with positive genetic etiology is spastic CP (79%, n=46), with quadriplegic cerebral palsy (55%, n=32) being the predominant subtype. Seventeen genes (SYNE 1, PYCR2, PTS, SEPSECS, MOCS1, SERAC1, DEGS1, ECHS1, HPDL, ALS2, BLM, ITPA, PARD3, RIF1, CHD2, RAB3GAP1, ADAD2, WDR62) were associated with this phenotype. Five genes (TBC1D14, CENPJ, ADAMDEC1, AMPD2, and TKTL1) were associated with spastic diplegic cerebral palsy, five (BICRA, ADGRG, CENPF, MAGEL2, TXNDC11) with spastic hemiplegic type, five (MIX23, EXOSC8, METTL5, GNG7, EZH1) with dyskinetic, and two (SLC25A12, LPIN1) with mixed form of cerebral palsy (Table 2).

Table 2: Genes and Their Type of CP (Phenotype)

Spastic Quadriplegic	Spastic Diplegic	Spastic Hemiplegic	Dyskinetic	Mixed
SYNE 1, PYCR2, PTS, SEPSECS, MOCS1, SERAC1, DEGS1, ECHS1, HPDL, ALS2, BLM, ITPA, PARD3, RIF1, CHD2, RAB3GAP1, ADAD2, WDR62)	TBC1D14, CENPJ, ADAMDEC1, AMPD2 and TKTL1	BICRA, ADGRG, CENPF, MAGEL2, TXNDC11	MIX23, EXOSC8, METTL5, GNG7, EZH1	SLC25A12, LPIN1

Novel genes (ADGRG, PTS, METTL5, and SLC25A12) had been reconfirmed by Sanger sequencing. All genes had an autosomal recessive pattern of inheritance except MAGEL2 and CHD2, which were autosomal dominant. The EZH1 gene had both dominant and recessive inheritance (Figure 1).

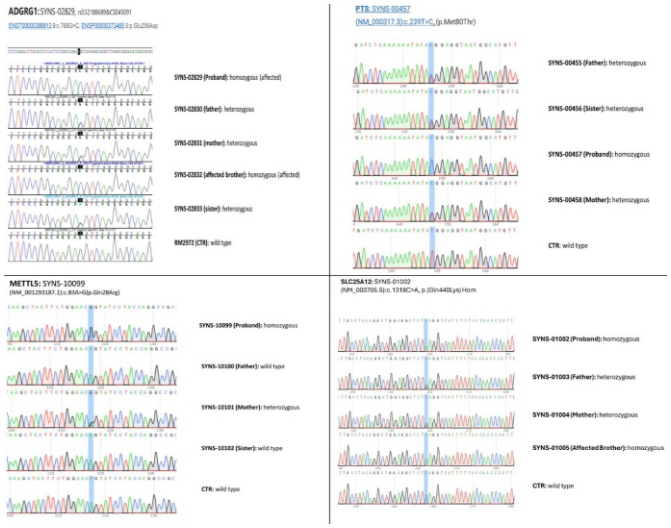

Figure 1: Sanger Sequence Images of Genes PTS, ADGRG, METTL5, and SLC25A12

Overall, epilepsy was present in 69%(n=40) feeding issues in 84%(n=49), sleep issues in 60%(n=35), recurrent chest infections in 60%(n=35), drooling in 74%(n=43), constipation in 79%(n=46) and behavior issues in 39%(n=23) of children. The highest percentage of comorbidities was seen in children with spastic quadriplegic cerebral palsy. Co-morbidities like feeding issues, drooling, sleep disturbance, recurrent chest infections, and constipation had a statistically significant association ($p<0.05$) with subtypes of CP (phenotype) except epilepsy and behavioural issues (Table 3).

Table 3: Association of Co-Morbidities with Subtypes of CP

Type of Cerebral Palsy	No. of Patients	Epilepsy	Feeding Issues	Drooling	Sleep Disturbance	Chest Infections	Constipation	Behavior Issues
p-values	–	0.510	<0.001	<0.001	<0.001	<0.001	<0.001	0.247
Spastic Quadriplegic	32	22 (69%)	32 (100%)	30 (94%)	27 (84%)	25 (78%)	31 (96%)	14 (44%)
Spastic Hemiplegic	6	4 (66%)	3 (50%)	1 (17%)	2 (33.3%)	0 (0%)	4 (67%)	4 (67%)
Spastic Diplegic	8	4 (50%)	7 (87%)	4 (50%)	0 (0%)	4 (50%)	4 (50%)	1 (12%)
Dyskinetic	8	6 (75%)	3 (38%)	4 (50%)	2 (25%)	2 (25%)	3 (38%)	2 (25%)
Mixed	4	4 (100%)	4 (100%)	4 (100%)	4 (100%)	4 (100%)	4 (100%)	2 (50%)
Total Patients In Each Column	58 (100%)	40 (69%)	49 (84%)	43 (73%)	35 (60%)	35 (60%)	46 (79%)	23 (39%)

Among 58 children with positive reports, most had a high level of motor impairment, showing GMFCS level V in 42 patients

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(72.4%), MACS level V in 38 patients (65.5%), and BMFM level V in 40 patients (69%) (Table 4).

Table 4: Level of Severity of Motor Impairment

Scales	Level I	Level II	Level III	Level IV	Level V
GMFCS	0 (0%)	10 (17.2%)	5 (8.6%)	1 (1.7%)	42 (72.4%)
MACS	0 (0%)	9 (15.5%)	4 (6.9%)	7 (12.1%)	38 (65.5%)
BMFM	0 (0%)	4 (6.9%)	7 (12.1%)	7 (12.1%)	40 (69%)

DISCUSSION

Cerebral palsy is a clinical diagnosis for a nonprogressive disorder of motor impairment. According to Van-Eyk *et al.* around one-third of the cases have an underlying genetic etiology [12]. A meta-analysis study done by Romeo *et al.* showed male predominance in all 57 articles included in the study [13]. Al-Sowi *et al.* found spastic cerebral palsy to be the most common type [14]. Studies have shown that there are multiple underlying etiologies in children presented with clinical signs of cerebral palsy. Numerous inborn errors of metabolism, CNS malformations, leukodystrophies, developmental epileptic encephalopathies, and rare syndromes with developmental delay can be diagnosed as cerebral palsy on clinical grounds [6]. Some children having genes for inborn errors of metabolism like Hyperphenylalaninemia (PTS), Molybdenum cofactor synthetase deficiency (MOCS1), and 3-methylglutaconic aciduria (SERAC1) presented with a clinical picture suggestive of quadriplegic cerebral palsy [15]. It has been observed that early detection and identification of genetic mutations in children with inborn errors of metabolism can change their prognosis. Infantile-onset leukodystrophies can also overlap in clinical picture with cryptogenic cerebral palsy. Discovery of leukodystrophy-related genes in our study (PYCR2 and DEGS1 gene) in the quadriplegic cerebral palsy group is consistent with previous literature reporting onset in infancy, developmental delay, and spasticity [16]. A neurodegenerative disorder of Developmental and epileptic encephalopathy (DEE), which presents with seizures in early infancy and developmental delay, mimics spastic cerebral palsy on clinical examination. DEE may be a result of both genetic and other causes. The ITPA gene has been associated with DEE and mimics spastic cerebral palsy when assessed clinically [17]. Similarly, CHD2 and SLC25A12 genes have been listed as pathogenic genes for DEE [18]. CNS malformation-related genes were another significant group we came across in our study. Pontocerebellar hypoplasia-related genes were more common (AMPD2, SEPSECS, and EXOSC8) as compared to genes related to cortical malformation (ADGRG, WDR62). Early detection of pathogenic/likely pathogenic genes. help in the genetic counselling of families [19, 20]. Epilepsy was present in 69% of our patients, with the highest prevalence in mixed type, followed by spastic quadriplegic CP. Bertoncelli *et al.* postulated that spastic quadriparesis is associated with the highest incidence of epilepsy and functional impairment [21]. A systematic review of literature on feeding difficulties in cerebral palsy by Calderone *et al.* highlighted that oropharyngeal dysphagia was more prevalent (81.5%) in children with cerebral palsy. Other significant feeding difficulties in cerebral palsy are problems with mastication and spasticity of muscles around the mouth [22]. Hassanein *et al.* state that three-fourths of all cerebral palsy children have constipation and may benefit from oral magnesium therapy, stretching exercises, and use of lactulose [23]. According to Spoto *et al.* recurrent chest infections in CP children leading to multiple admissions and hospital visits pose a significant burden on healthcare systems as well as the family of the patient [24]. Functional ability and severity of motor impairment of children with cerebral palsy are assessed by standardized scales like GMFCS, MACS, and BMFM. In our study, most of the children with CP had Level V in all scales, which signifies complete dependence. In a study conducted in South India by Brien *et al.* GMFCS level V is the most encountered class in lower-middle-income countries [25].

Limitations of the study includes retrospective cross-sectional study design, which can lead to data loss. More robust prospective study designs can shed more light on patients' prognosis. Selection bias among children with cerebral palsy due to inclusion criteria with affected sibling or intrauterine demise is also a limitation and might not represent the true proportion of genetic causality in cerebral palsy mimics. More resources need to be employed to ensure genetic testing for a wider group of patients and ideally for all patients with cerebral palsy, with or without a predisposing risk factor [26]. Significant work still needs to be done on understanding the genetic etiology of developmental delay, and not just cerebral palsy. Further studies can be carried out on comorbidities and functional impairment associated with each gene. Data is still insufficient even in high-resource setups, regarding exploring genetic causes in cerebral palsy, and it is being proposed that genetic testing should be done in every child with cerebral palsy.

CONCLUSIONS

Genetic etiology should be considered in idiopathic cerebral palsy to identify CP mimics, especially in consanguineous populations. Correlating genotype with phenotype will help in management options of comorbidities and prognosis in these children. Significant work still needs to be done to understand the genetic etiology of idiopathic cerebral palsy in resource-limited settings like Pakistan.

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Authors' Contribution

Conceptualization: MS, AF, SM, FR, SE, HH
Methodology: MS, AF, FR, SE, HH
Formal analysis: MS, SE, HH
Writing and Drafting: MS, AF, SM, FR, SE, HH
Review and Editing: MS, AF, SM, FR, SE, HH

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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