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Patterns, Indications, and Outcomes of Genetic Testing Among Pediatric Patients

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ABSTRACT

Background: Genetic disorders contribute substantially to childhood morbidity, yet access to genetic testing in Nepal is limited by cost, availability, and a shortage of expertise. Evidence on testing practices and outcomes is scarce. This study aimed to describe the patterns, clinical indications, and outcomes of genetic testing among pediatric patients in a tertiary care hospital in Nepal.

Methods: This retrospective study was conducted at the Department of Pediatrics, Tribhuvan University Teaching Hospital from February 2024 to July 2025. We included all patients from birth to 18 years who underwent genetic testing for diagnostic purpose along with parents or siblings tested for segregation analysis. Data including the genetic reports were extracted from the investigator records and analyzed using SPSS.

Results: A total of 194 cases were included. Median age was three years (IQR 6.25) with males comprising 60.3%. Consanguinity was reported in 2.1%. Whole exome sequencing (WES) was the most commonly performed test (43.8%), followed by single-gene testing (20.1%) and karyotyping (15.9%). Neurodevelopmental disorders (18.0%) and congenital anomalies (15.0%) were the most frequent clinical indications. Overall diagnostic yield was 53.8%. Pathogenic or likely pathogenic variants were identified in 53.47% of WES/CES cases, while 31.7% yielded variants of uncertain significance. Down syndrome (7.7%), Duchenne muscular dystrophy (5.1%), and Lysosomal storage disorders (3.6%) were the most common diagnoses.

Conclusions: WES emerged as the most effective diagnostic tool in this cohort. Over half of cases achieved a genetic diagnosis, with neurodevelopmental disorders and congenital anomalies as the leading indications. A range of genetic disorders was identified, with Down syndrome and Duchenne muscular dystrophy being more prevalent.

Keywords: Diagnostic yield; genetic testing, Nepal; pediatrics; whole exome sequencing.

INTRODUCTION

Genetic disorders, including both single gene and chromosomal disorders contribute substantially to childhood morbidity and mortality worldwide. Around 80% of rare diseases have a genetic basis and 50-75% of these affect child.[1] A 2016-2017 U.S. survey reported genetic conditions in 3.9% of children.[2]

The integration of genetic tests into pediatric care is slowly increasing and is now a standard component of diagnostic workup in high income countries. In low and middle income countries like Nepal, the use of genetic testing remains limited because of high cost, restricted accessibility and a shortage of trained expertise. As a result, clinicians often rely on clinical judgement and basic investigations, leading to under diagnosis or delayed diagnosis of genetic condition which directly affects prognosis, management and family counseling.

Nepal lacks the population based data on the prevalence and burden of genetic disease. Hospital-based studies can however provide valuable insights into current genetic testing practice in children and helps identify service gaps thereby informing policy and training priorities.

We therefore conducted a retrospective descriptive study to examine the pattern, clinical indications and the outcomes of genetic testing among children who underwent testing at our center.

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METHODS

This was a retrospective study conducted at the Department of Pediatrics, Tribhuvan University Teaching Hospital, Kathmandu from February 2024 to July 2025.

Data were extracted from the investigator's clinical database which included genetic test reports obtained from patients attending the general pediatric and genetic outpatient department, as well as those admitted to the inpatient services during the study period. Tests were outsourced to internationally accredited laboratories owing to the lack of accredited genetic testing facilities within Nepal. Patients aged 0–18 years who underwent genetic testing for diagnostic purposes, along with any genetic tests performed on their parents or siblings as a part of segregation analysis to confirm or clarify the child's genetic findings were included in the study. Products of conception (POC) from spontaneous or elective pregnancy losses were included because many genetic disorders in live-born children also present as pregnancy loss, and the genetic findings from POC provide critical information for recurrence-risk counseling and family planning. Cases referred for prenatal or pre-pregnancy genetic counseling including carrier screening, without evaluation of a postnatal pediatric proband, patients above 18 years of age at the time of evaluation, unless tested as part of segregation analysis for a pediatric proband, cases with incomplete clinical information or unavailable genetic test reports and children who previously underwent genetic testing at other facilities and presented only with external reports, without tests ordered or processed through the study hospital were excluded from the study. Whole exome sequencing(WES) provided a comprehensive analysis of the entire exome, while Clinical exome sequencing (CES) focused on a targeted set of genes associated with the clinical indications of the patients. WES/ CES was performed on an Illumina next generation sequencing platform with mean coverage of >80-100X. Data were aligned to the GRCh38 reference genome and processed using standard bioinformatics pipelines for variant calling, annotation and interpretation. Variants were classified according to established guidelines.

Non random sampling technique was used during data collection in which consecutive cases with genetic reports were included in the study. The Institutional Review Committee of the institute approved ethical clearance (Reference Number: 101/082/083) Data were recorded in a semi-structured proforma, verified for completeness, and analyzed using SPSS version 30 .

RESULTS

Out of total 478 cases identified for genetic evaluation based on clinical indication, 240(50%) cases agreed and underwent genetic testing during the study period (February 2024 to July 2025). After applying exclusion and inclusion criteria, N= 194 cases were included in final analysis. Reasons for exclusion included prenatal cases (n = 12), prepregnancy testing (n = 12), index cases aged >18 years (n = 2), previous genetic testing performed at other facilities (n = 16), and unavailability of genetic test reports by the end of the study period (n = 4) Among the 194 cases, 174 represented the pediatric probands, 16 parental segregation analyses and 6 products of conception. The majority of the children belonged to age group of one to five years with median age of three years (IQR 6.25). Male comprised majority (60.31%) of the cohort (n=117). Parental consanguinity was reported in 4 children(2.06 %) (Table 1)

Table 1. Demographic Profile of Patients Undergoing Genetic Testing. (n=194)

Demographic category	Variable	Frequency	Percent
Age	0-28 days	20	10.31
	29 days-11 months	27	13.92
	1-5 years	68	35.05
	6-10 years	33	17.01
	11-18 years	24	12.37
	>18 years*	16	8.25
	Product of conception	6	3.09
Gender	Male	117	60.31
	Female	71	36.60
	Unindentified	6	3.09
Consanguinity	Yes	4	2.06
	No	190	97.94

* Included parents tested for segregation analysis

The most commonly performed test was Whole exome sequencing (WES), accounting for 85 cases(43.81%) followed by Single-gene testing in 39 cases (20.1%) using methods such as Sanger sequencing, Multiplex ligation probe amplificaton (MLPA), and Fragile X testing(FMR1 CGG repeat). Karyotyping was done in 31 cases(15.99%).Other tests included Fluorescent in situ hybridization(FISH) in 7(3.61%), Clinical exome

sequencing in 15(7.73%), Chromosomal microarray in 2(1.03%), low pass whole genome sequencing for chromosomal abnormalities in 11(5.67%) and combined WES with mitochondrial genome sequencing in 4 cases(2.06%). (Figure 1)

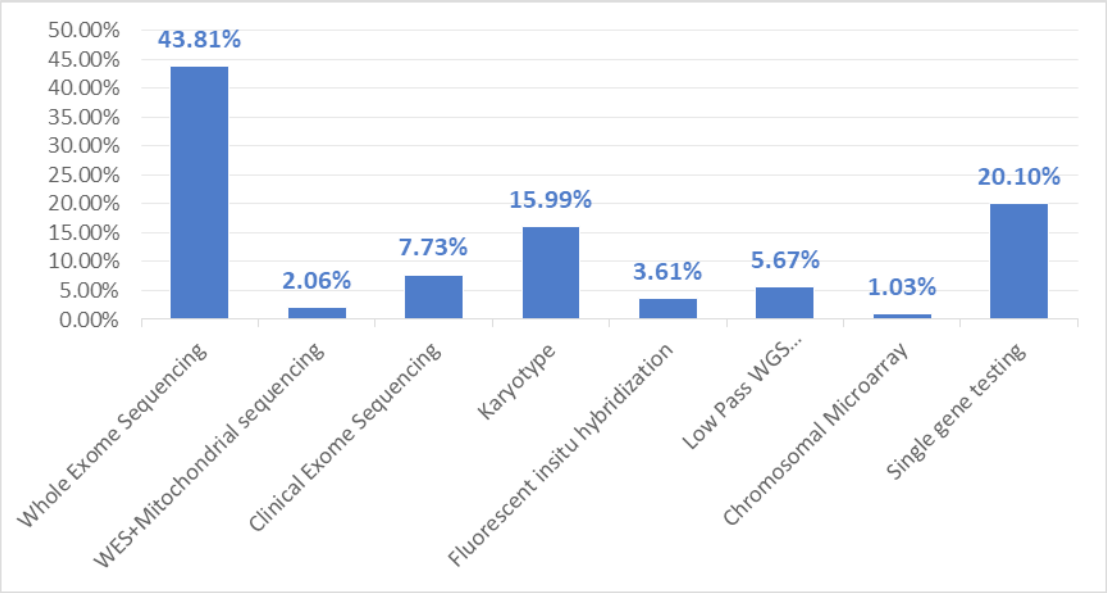

Figure 1.Types of Genetic Tests Performed.

A total of 33 (31.73%) pathogenic variant, 22 (21.15%) likely pathogenic variant and 33(31.73%) variant of uncertain significance were identified through whole exome sequencing and clinical exome sequencing. WES was performed in 3 product of conception out of which likely pathogenic variant was identified in one case. In 16 cases, no pathogenic/likely pathogenic variant related to clinical indications were identified (Figure 2)

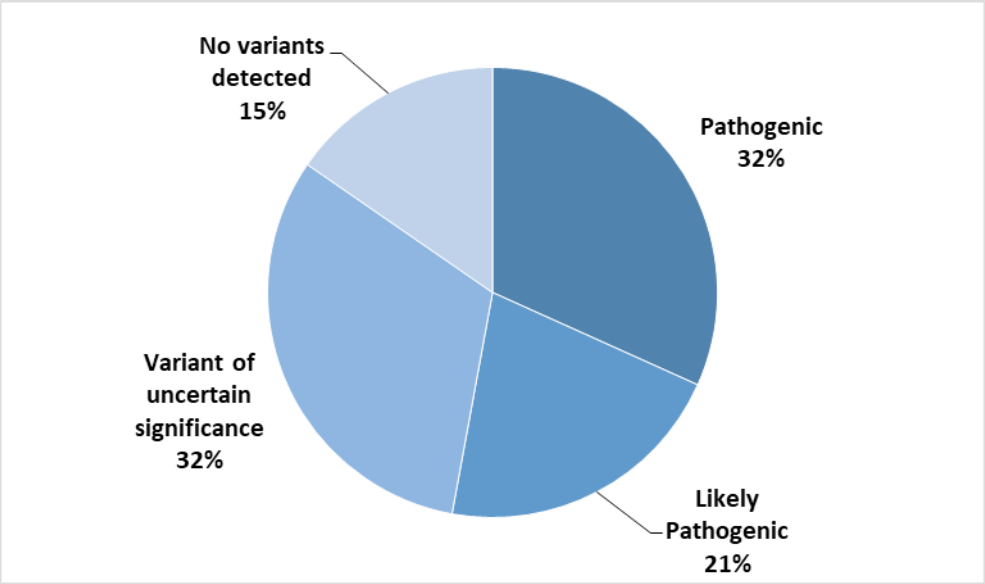

Figure2. Classification of variants in WES/CES.

The average turnaround time (TAT) for genetic tests varied depending on the test type. The fastest test was FISH, with median TAT of 5.5 (5-7.5) days while the slowest was Whole exome sequencing with median of 31 (27-34) days (Table 2)

Table 2. Average turnaround time(TAT) for various genetic tests.

Test	Median (IQR)
WES/ WES+ mitochondrial genome sequencing	31(27-34)
Clinical exome sequencing	27(26-28)
Karyotype	13 (12-15)
Fluorescent in situ hybridization	5.5 (5-7.5)
Chromosomal microarray *	12 (11-13)
MLPA DMD	20 (20-21)
Methylation Specific MLPA for imprinting disorders(MS-MLPA)	22.5 (20-25)
Low pass WGS for chromosomal abnormality	15 (14-16)
Sanger sequencing	27 (22-34)

* Turnaround time for chromosomal microarray is based on two observations (n = 2).

The primary clinical indications for genetic testing were categorized based on the affected system. The most common primary indication was neurodevelopmental disorders which accounted for 18.04 % of cases, followed by Dysmorphology/congenital anomalies(14.95 %).(Figure 3) Parental segregation analysis was done in 14 cases.

The diagnostic yield differed considerably among the various genetic tests performed, with highest diagnostic yield of MS-MLPA for imprinting disorders (100%) and MLPA for DMD (81.8%), followed by Karyotype (64.52%) and WES/ CES (53.47%). The overall diagnostic yield of all the genetic tests was 53.75%. The diagnostic yield for product of conception (POC)analysis was 16.6% (1/6 cases).

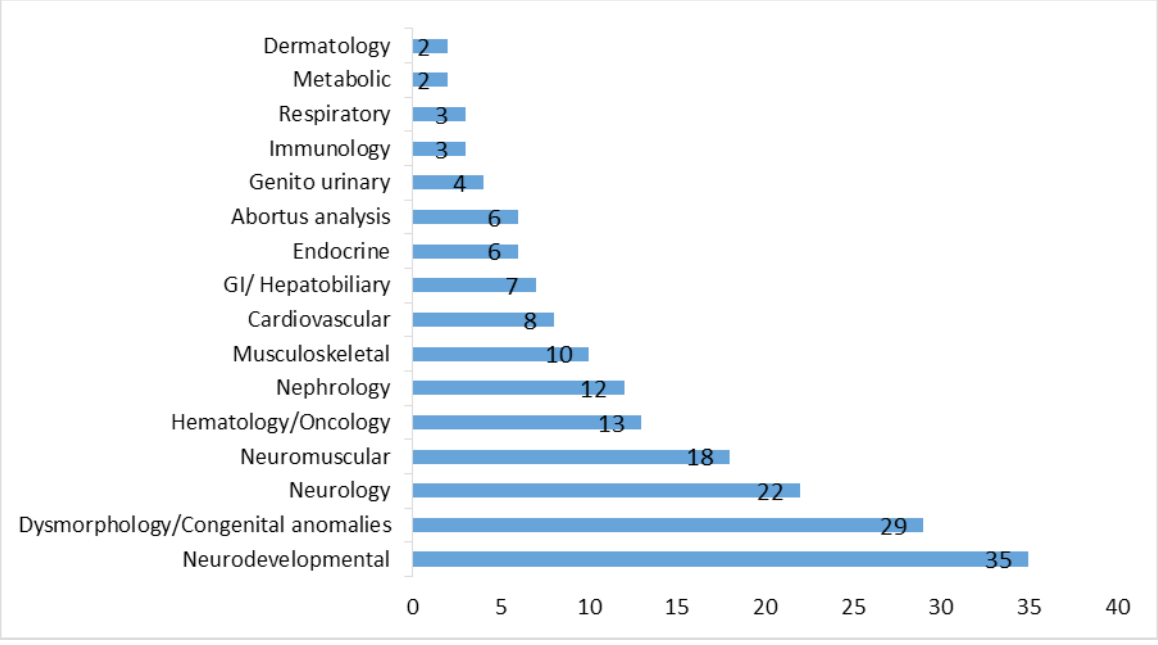

Figure 3. Primary clinical indications for genetic testing.

The genetic disorders in this study were classified into three main types: monogenic disorders (n=62, 66.6%), chromosomal disorders (n=30,32.26%), and imprinting disorders (n=1, 1.07%).

Among the monogenic disorders, the majority followed an autosomal recessive inheritance pattern (n=29, 46.77%), followed by autosomal dominant disorders(n=18, 29.03%) and X-linked disorders (n=15 ,24.19%). Among the

chromosomal disorders (n = 30), there were equal number of cases with numerical abnormalities(50%) and structural abnormalities (50%) as shown in Figure 4. The most common diagnosis was Down Syndrome (n=15, 7.7%) followed by Duchenne muscular dystrophy (n=10, 5.1%) and Lysosomal storage disorders (n=7, 3.6%).

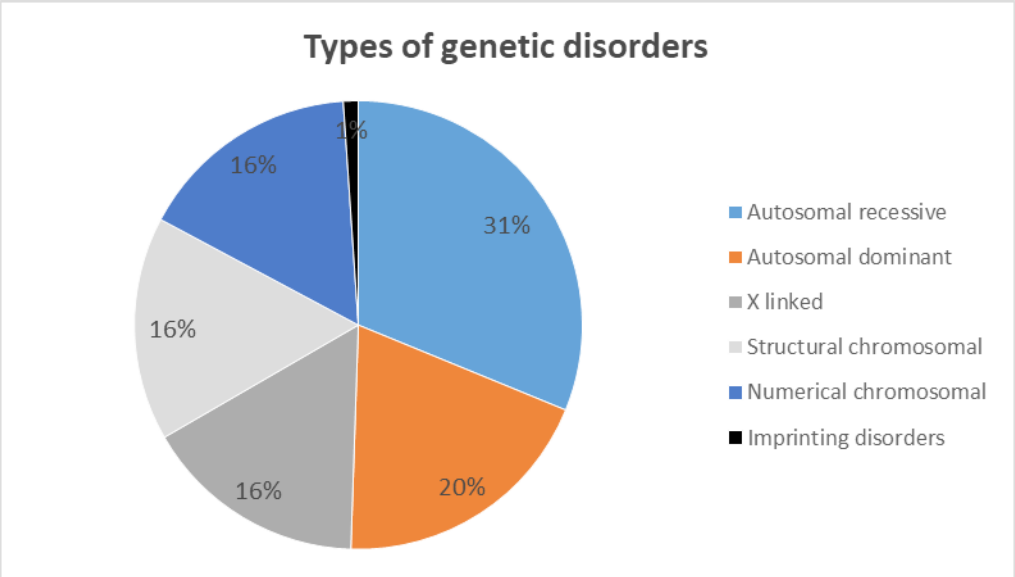

Figure 4. Types of Genetic Disorders.

DISCUSSION

This study provides a comprehensive overview of the genetic testing landscape in pediatric population at a tertiary hospital in Nepal. It describes the patterns of genetic testing including types of tests performed, the clinical indications, turn over time of various tests, types of genetic diseases and diagnostic yield of the tests.

The majority of the cases were in the age group less than five years reflecting early manifestation of genetic disorders. The male predominance in this study is consistent with the study by Sheth et al in India where 65% male were diagnosed with rare genetic disease.[3] This shows a possible higher health seeking behaviour for males in South Asian context.

Parental consanguinity was reported in only 2.06% which is lower than figures reported in other Asian countries, where consanguinity has been reported upto 50%[4]. This may reflect underreporting due to social desirability bias.

In Nepal, consanguinity in the form of close-relative marriages is not very common compared to other South Asian countries. However, autosomal recessive conditions remain prevalent; around half of the monogenic disorder in our cohort. This may be partly explained by the cultural tendency for marriages to occur within the same community or caste. This endogamous practice increases the likelihood of shared ancestry and genetic homogeneity, which can result in a higher frequency of certain pathogenic variants due to a possible founder effect.

Whole exome sequencing was the commonly ordered test underscoring the fact that there is a growing preference for comprehensive genetic test with wide phenotype, particularly in resource limited settings where sequential single gene testing may be time consuming and cost ineffective. Bastarache et al did a single centre analysis to describe the trends in clinical genetic testing over two decades and identified that there is a shift towards more comprehesive genetic testing in comparison to single gene test.[5] However more comprehensive test is associated with increased uncertainty with variant of uncertain significance(VOUS) identified in this study to be 31.73%. This result is consistent with the study by Bastarache et al where highest rate of inconclusive result (29.8%) was seen in Exome/Genome sequencing.[5] This high VOUS likely reflects the underrepresentation of South Asian populations in international variant databases such as ClinVar and gnomAD. In this study, due to financial constraints, segregation studies could not be performed in majority of VOUS, which further limits a definitive

diagnosis.

The diagnostic yield of Whole exome sequence in this study (53.47%) is comparable to study done by Seo et al in South Korea (42.7%) and Styoyanova et al in Bulgaria (51.3%).[6,7] The diagnostic yield of WES ranges between 25% to 60% in various international studies, depending upon indication and testing strategy.[8,9,10] The relatively high yield observed in this cohort may be attributed to careful clinical selection of patients for genetic testing. In resource limited setting, genetic testing is reserved for patients with strong clinical suspicion based on detailed phenotyping, family history and prior investigations. This targeted referral pattern increases the probability of detecting molecular diagnosis and may partly explain the higher observed yield. MLPA for DMD and and MS-MLPA for imprinting disorders showed high diagnostic yield highlighting the importance of targeted molecular testing in specific clinical conditions such as Duchenne muscular dystrophy or Prader Willi Syndrome. Karyotyping, though more conventional , demonstrated a notable yield (64.52%) in children with dysmorphic features or multiple congenital anomalies, underscoring its continued relevance in low resource settings. Numerical chromosomal abnormalities are generally more common than structural abnornalities in pediatric cohorts, however in this study. the distribution of chromosomal abnormalities showed a relatively equal proportion of numerical and structural abnormalities. This may be influenced by the use of both karyotyping and low pass whole genome sequencing, which improves the detection of structural chromosomal abnormalities in addition to aneuploidies.

The most common clinical indication in our study was neurodevelopmental disorders. Global evidences shows that a substantial proportion of children with neurodevelopmental disorder especially global developmental delay and intellectual disability have an underlying genetic cause and genetic test is a part of diagnostic evaluation in such conditions.[11] Quaio et al reviewed the clinical indications of patients who had undergone molecular genetic testing and found that 10.8% cases were of neurodevelopmental disorder and diagnostic yield of exome sequencing was 35% in such cases.[12] Our cohort also included children with wide range of clinical features such as dysmorphism, suspected inborn error of metabolism, neuromuscular disorders, and other multi-system involvement. This reflects the broad applicability of genetic testing across pediatric subspecialities.

Despite the increasing use of genetic test as a diagnostic modality, there are several challenges such as high cost and delay in report. The average turn around time for WES was 30 days. Factors contributing to this delay include time required for international transport and customs clearance, batching of samples at reference laboratories, the greater analytic complexity of exome sequencing, and the need for bioinformatic analysis and expert variant interpretation before result release. Although testing is performed outside the country, the TAT in our setting has not been further prolonged and remains comparable to that reported in other studies.[13.]

The absence of population based data on prevalence of genetic diseases in Nepal makes it challenging to interpret test results in a broader context. While this study is hospital based and may not reflect the entire population, it offers important baseline data in pediatric population that can help to expand genetic services in Nepal. In addition, only a proportion of eligible patients underwent genetic testing due to financial and access constraints, which may have introduced selection bias. Families who underwent testing may therefore differ from those who did not in terms of socioeconomic background and access to healthcare, which may have influenced the observed diagnostic yield and limits its generalizability to all suspected genetic cases in Nepal. Establishing and maintaining a national genetic registry would further strengthen genetic services in Nepal by enabling systematic data collection, monitoring of disease trends, and informed planning of genetic health services. Such initiatives will ultimately benefit future generations by supporting early diagnosis, informed reproductive choices, and improved genetic health outcomes across the population.

CONCLUSIONS

Over half of tested cases received a definitive or likely diagnosis, with whole exome sequencing contributing most results while conventional tests such as karyotyping and MLPA remained valuable in targeted settings. Monogenic disorders were the most common type of genetic condition identified. Neurodevelopmental disorders emerged as the most frequent indication for testing, followed by dysmorphism and congenital anomalies.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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