Original Article

Investigating Genetic, Cognitive, and Therapeutic Approaches for Enhancing Quality of Life in Individuals With Down Syndrome

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ABSTRACT

Background: *Down syndrome (DS) is associated with substantial heterogeneity in cognition, adaptive functioning, and behavior, influenced by cytogenetic subtype and modifiable rehabilitative exposures, yet integrated regional evidence from South Punjab remains limited.* ***Objective:*** *To evaluate associations between cytogenetic subtype, therapy dose and modality, and standardized cognitive, adaptive, and behavioral outcomes among individuals with DS.* ***Methods:*** *A cross-sectional observational study was conducted in South Punjab (January–March 2025) including 60 individuals with cytogenetically confirmed DS aged 6–35 years. Cognitive performance was assessed using WISC-IV/WAIS-IV, adaptive functioning via VABS-II, and behavioral symptoms via the Aberrant Behavior Checklist. Therapy exposure over the preceding 6 months was operationalized as weekly minutes and categorized by intensity; modality was classified as single-modality versus multidisciplinary. Analyses used correlations, group comparisons, and multivariable linear regression (SPSS v26; α=0.05).* ***Results:*** *Full trisomy 21 occurred in 88.3%, mosaicism in 8.3%, and translocation in 3.4%. Mean Full-Scale IQ was 48.3±9.7, higher in mosaicism than trisomy 21 (56.2±6.4 vs 47.5±8.9; p=0.03). VABS-II composite averaged 62.8±11.3 and correlated with IQ (r=0.56; p<0.001). Multidisciplinary therapy was associated with higher VABS-II scores than single-modality therapy (67.2±9.8 vs 58.9±10.4; p=0.001; d=0.89). In regression, therapy intensity (β=0.42; p=0.002) and IQ (β=0.38; p=0.005) independently predicted adaptive functioning (adjusted R^2=0.44).* ***Conclusion:*** *Adaptive outcomes in DS are more strongly associated with therapy intensity and multidisciplinary rehabilitation than cytogenetic subtype alone, supporting scalable integrated intervention models in resource-constrained settings.*

Keywords: *Down syndrome; Trisomy 21; Mosaicism; Adaptive functioning; Vineland; Cognitive assessment; Multidisciplinary therapy; Rehabilitation; Behavioral symptoms; South Punjab*

INTRODUCTION

Down syndrome (DS) is the most prevalent chromosomal cause of intellectual disability worldwide, resulting primarily from trisomy 21 and characterized by a distinctive neurodevelopmental, cognitive, and behavioral phenotype (1). The global incidence is estimated at approximately 1 in 700 live births, with survival and life expectancy markedly improved over recent decades due to advances in neonatal care, cardiac surgery, and early intervention services (2). Despite these improvements, individuals with DS continue to experience substantial variability in intellectual functioning, adaptive behavior, and social participation. This heterogeneity reflects the complex interplay between cytogenetic subtype, neurocognitive development, comorbid medical conditions, environmental exposures, and access to structured therapeutic interventions (3). Understanding how these dimensions

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converge to influence functional outcomes remains critical for optimizing long-term quality of life in affected populations.

From a genetic perspective, DS comprises three principal cytogenetic forms: full trisomy 21, mosaicism, and Robertsonian translocation. Full trisomy 21 accounts for the majority of cases and involves complete duplication of chromosome 21 in all cells, whereas mosaicism reflects a mixture of euploid and trisomic cell lines, often associated with milder phenotypic expression. Translocation DS, although less common, results from structural chromosomal rearrangement and may present with variable developmental impact (4). Emerging evidence suggests that mosaicism may confer relative neurocognitive advantage compared with full trisomy, potentially due to partial preservation of typical gene dosage in subsets of neural cells (5). However, existing studies have largely examined genetic subtype in isolation from real-world functional and rehabilitative outcomes, limiting translational applicability to community-based management.

Cognitively, individuals with DS typically demonstrate mild to moderate intellectual disability, with relative strengths in visual processing and social engagement and pronounced weaknesses in expressive language, working memory, and executive functioning (6). These cognitive profiles directly influence adaptive functioning, including communication, self-care, and socialization skills. Adaptive behavior has been shown to correlate strongly with cognitive indices, but it is also shaped by environmental enrichment, educational inclusion, and therapeutic exposure (7). Importantly, adaptive functioning—not IQ alone—is more closely associated with independence and social integration, and thus represents a clinically meaningful endpoint when evaluating developmental outcomes in DS (8). Nevertheless, in many low- and middle-income regions, including South Punjab, systematic evaluation of standardized cognitive and adaptive measures remains limited, and therapeutic planning often proceeds without integration of genetic or neuropsychological profiling.

Therapeutic interventions constitute the cornerstone of functional management in DS. Speech therapy targets expressive and receptive language delays; occupational therapy enhances fine motor coordination, sensory integration, and daily living skills; and physiotherapy addresses hypotonia, balance deficits, and gross motor delay (9). Evidence increasingly supports multidisciplinary, early, and sustained interventions as superior to single-modality approaches in improving adaptive and behavioral outcomes (10). However, much of this evidence originates from high-resource settings, and data quantifying therapy intensity, modality combinations, and functional correlates in under-resourced regional contexts remain scarce. Furthermore, prior studies frequently evaluate therapeutic efficacy without concurrently accounting for baseline cognitive capacity or cytogenetic variation, thereby limiting understanding of effect modification or differential responsiveness (11).

Behavioral challenges—including irritability, hyperactivity, and attention dysregulation—are also prevalent in DS and may significantly interfere with educational attainment and social participation (12). Structured and consistent therapeutic engagement has been associated with improved emotional regulation and reduced maladaptive behaviors, yet the magnitude of this association varies across studies and populations (13). In Pakistan, and particularly in South Punjab, few empirical investigations have systematically examined the relationship between genetic subtype, standardized cognitive assessment, therapy exposure, and adaptive-behavioral outcomes within a unified analytical framework. Most regional literature focuses either on parental psychosocial burden or educational barriers rather than quantifiable developmental metrics (14). Consequently, there remains a critical knowledge

gap regarding how genetic, cognitive, and therapeutic factors interact to shape functional trajectories in this specific sociocultural and healthcare context.

Using a PICO-informed framework, the present study focuses on individuals with cytogenetically confirmed Down syndrome aged 6–35 years residing in South Punjab (Population); evaluates exposure to structured therapeutic interventions including speech therapy, occupational therapy, physiotherapy, and their combinations with defined frequency and duration (Intervention/Exposure); compares functional outcomes across varying therapy intensities and genetic subtypes (Comparison); and measures cognitive performance, adaptive functioning, and behavioral profiles using standardized instruments (Outcome). The central research problem is the absence of region-specific, integrative evidence linking cytogenetic variation and quantified therapeutic engagement with standardized functional outcomes. Addressing this gap is essential for developing contextually appropriate, resource-sensitive multidisciplinary rehabilitation models.

Accordingly, the primary objective of this study was to evaluate the association between genetic subtype and therapy intensity with cognitive and adaptive functioning among individuals with Down syndrome in South Punjab. We hypothesized that higher therapy intensity and multidisciplinary intervention would be independently associated with superior adaptive outcomes after accounting for baseline cognitive ability, and that mosaic cytogenetic subtype would demonstrate comparatively higher cognitive performance than full trisomy 21. By integrating genetic profiling, standardized neuropsychological assessment, and quantified therapeutic exposure within a single analytic framework, this study aims to generate clinically interpretable evidence to inform personalized and regionally feasible rehabilitation strategies (15).

Methods

This cross-sectional observational study was conducted to evaluate the association between cytogenetic subtype, quantified therapeutic exposure, and standardized cognitive and adaptive outcomes among individuals with Down syndrome residing in South Punjab, Pakistan. The study was carried out between January and March 2025 across three rehabilitation centers and two genetic diagnostic clinics that provide multidisciplinary services for neurodevelopmental disorders. A cross-sectional analytical design was selected to enable simultaneous assessment of genetic, cognitive, behavioral, and therapeutic variables within a defined timeframe while minimizing attrition and loss to follow-up inherent to longitudinal designs (16). The methodological framework was aligned with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations to ensure transparency and reproducibility (17).

Eligible participants were individuals aged 6–35 years with a confirmed cytogenetic diagnosis of Down syndrome based on standard karyotyping or fluorescence in situ hybridization (FISH) reports documenting full trisomy 21, mosaicism, or translocation. Participants were required to have stable medical status and documented engagement in at least one structured therapeutic modality within the preceding six months. Individuals with coexisting severe neurological disorders unrelated to Down syndrome (e.g., uncontrolled epilepsy with structural brain lesions), severe uncorrected sensory impairments, or incomplete clinical and therapeutic documentation were excluded to reduce confounding and ensure measurement reliability. Participants were identified through registry records maintained at collaborating centers. Consecutive sampling was applied to all eligible cases presenting during the study period to minimize selection bias. Written informed consent was obtained from parents or legal guardians for participants under 18 years of age and from

adult participants with capacity to consent; verbal assent was obtained from minors and cognitively able adolescents in accordance with ethical standards (18).

Data collection was conducted through structured review of medical and therapy records supplemented by direct standardized assessment sessions administered by trained clinical psychologists and rehabilitation specialists. Cytogenetic subtype was extracted from laboratory reports and categorized as full trisomy 21, mosaicism, or translocation. Cognitive performance was assessed using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) for participants aged 6–15 years and the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) for participants aged 16 years and above. Full-Scale IQ (FSIQ) and index scores for verbal comprehension, working memory, and processing speed were recorded according to standardized administration and scoring manuals (19). Assessments were conducted in a quiet clinical setting in the participant's preferred language (Urdu or English) using validated translated instructions where necessary. Inter-rater reliability was ensured through joint scoring of 10% of assessments, yielding an intraclass correlation coefficient above 0.90.

Adaptive functioning was measured using the Vineland Adaptive Behavior Scales, Second Edition (VABS-II), administered via structured caregiver interview to generate composite and domain-specific standard scores for communication, daily living skills, and socialization (20). Behavioral characteristics were evaluated using the Aberrant Behavior Checklist (ABC), completed by primary caregivers to quantify irritability, hyperactivity, and social withdrawal subscales (21). Therapeutic exposure was operationally defined as the cumulative weekly duration of structured therapy (minutes per week) averaged over the preceding six months, verified through attendance logs. Therapy intensity was categorized into low (<90 minutes/week), moderate (90–179 minutes/week), and high (≥180 minutes/week). Therapy modality was classified as single-modality (speech, occupational, or physiotherapy alone) or multidisciplinary (combination of two or more modalities). The primary outcome variable was adaptive functioning as measured by the VABS-II composite score. Secondary outcomes included FSIQ and ABC subscale scores. Covariates included age, sex, educational enrollment status, and cytogenetic subtype.

To address potential bias, consecutive sampling and standardized inclusion criteria were implemented to reduce selection bias. Measurement bias was minimized through use of validated instruments with established psychometric properties in intellectual disability populations (19–21). Data abstraction followed a double-entry procedure by two independent researchers, with discrepancies resolved through consensus review. Confounding was addressed analytically by including relevant covariates in multivariable regression models. Effect modification by genetic subtype was explored through interaction terms between subtype and therapy intensity. Missing data were assessed for randomness using Little's MCAR test; cases with less than 5% missingness were handled using multiple imputation by chained equations to preserve statistical power.

Sample size estimation was performed using G*Power software assuming a medium effect size ($f^2 = 0.15$) for multiple linear regression with five predictors, $\alpha = 0.05$, and power $(1-\beta) = 0.80$, yielding a minimum required sample of 55 participants. The final sample of 60 participants provided adequate power to detect statistically significant associations between therapy intensity and adaptive outcomes. Statistical analyses were conducted using SPSS version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as means ± standard deviations, and categorical variables as frequencies and percentages. Normality was assessed using the Shapiro–Wilk test and visual inspection of Q–Q plots. Between-group comparisons were conducted using one-way analysis of variance (ANOVA) with Tukey's post

hoc correction for multiple comparisons when assumptions were met; otherwise, Kruskal–Wallis tests were applied. Pearson's correlation coefficients were calculated to examine associations between cognitive and adaptive scores. Multiple linear regression analyses were performed to evaluate independent predictors of adaptive functioning, adjusting for age, sex, cytogenetic subtype, and therapy intensity. Regression diagnostics included assessment of multicollinearity (variance inflation factor <5), homoscedasticity, and residual normality. Statistical significance was set at $p < 0.05$ with two-tailed testing, and effect sizes with 95% confidence intervals were reported to enhance interpretability.

The study protocol was reviewed and approved by the Institutional Ethical Review Committee of the participating academic institution, and all procedures conformed to the principles outlined in the Declaration of Helsinki (18). Participant confidentiality was ensured through anonymization and assignment of unique study identification codes. Electronic datasets were password-protected and stored on encrypted institutional servers, and hard-copy records were maintained in locked cabinets accessible only to the research team. A predefined statistical analysis plan was developed prior to data analysis to reduce analytical bias, and all procedures were documented to facilitate reproducibility.

Results

Table 1 summarizes the sample structure and confirms that the cohort was demographically balanced by sex and broadly distributed across the targeted age range. Among 60 participants, 34 were male (56.7%) and 26 female (43.3%), with a mean age of 17.6 ± 6.2 years. The proportion under 18 years was 63.3% (38/60), and this did not differ meaningfully by sex (64.7% males vs 61.5% females; $p = 0.79$; OR = 1.15, 95% CI 0.39–3.37). Cytogenetically, full trisomy 21 predominated at 88.3% (53/60), with mosaicism in 8.3% (5/60) and translocation in 3.4% (2/60). The distribution of trisomy 21 by sex (91.2% males vs 84.6% females) was not statistically different ($p = 0.41$; OR = 1.86, 95% CI 0.34–10.1), supporting comparability of male and female subgroups for subsequent analyses.

Table 2 details cognitive outcomes across cytogenetic subtypes and demonstrates a consistent pattern of higher cognitive performance among mosaic cases relative to full trisomy 21. The mean Full-Scale IQ (FSIQ) in the trisomy 21 group was 47.5 ± 8.9, compared with 56.2 ± 6.4 in mosaicism and 49.0 ± 7.1 in translocation, with an overall between-group difference (ANOVA) reaching statistical significance ($p = 0.03$; $\eta^2 = 0.14$). Similar subtype-linked differences were observed across key indices: verbal comprehension averaged 45.1 ± 8.2 in trisomy 21 versus 52.8 ± 5.9 in mosaicism ($p = 0.04$; $\eta^2 = 0.12$), while working memory was 50.3 ± 9.8 in trisomy 21 versus 58.6 ± 7.2 in mosaicism ($p = 0.05$; $\eta^2 = 0.10$). Processing speed showed the same directional trend (46.8 ± 9.1 in trisomy 21 vs 53.4 ± 6.7 in mosaicism) but did not meet conventional significance thresholds ($p = 0.08$; $\eta^2 = 0.07$). Collectively, these results indicate that cytogenetic subtype accounts for a small-to-moderate proportion of variance in cognitive indices ($\eta^2 \approx 0.07–0.14$), with the clearest differences observed for global IQ and verbal comprehension.

Table 3 integrates adaptive and behavioral outcomes and quantifies how these measures relate to cognition and therapy exposure. Overall adaptive functioning (VABS-II composite) averaged 62.8 ± 11.3, and it was moderately correlated with cognitive ability: FSIQ and VABS-II composite showed $r = 0.56$ (95% CI 0.34–0.72; $p < 0.001$), indicating that higher cognitive scores were associated with higher adaptive functioning. At the domain level, communication was the lowest-scoring adaptive domain (58.4 ± 10.6) compared with daily living skills (66.1 ± 12.1) and socialization (63.8 ± 9.8). Importantly, adaptive domains differed by therapy intensity: communication varied significantly across therapy intensity groups ($F = 3.45$; $p = 0.03$), as did daily living skills ($F = 4.12$; $p = 0.02$) and socialization ($F = 2.98$; $p =$

0.04), supporting a graded association between higher therapy exposure and better adaptive performance. Behavioral profiles showed irritability (ABC) at 15.8 ± 6.7 and hyperactivity at 13.2 ± 5.9, with higher therapy intensity associated with lower symptom burden—irritability correlated negatively with therapy intensity ($r = -0.29$, 95% CI −0.50 to −0.05; $p = 0.02$). Hyperactivity showed a similar negative direction ($r = -0.24$, 95% CI −0.46 to 0.01) but did not reach statistical significance ($p = 0.06$), suggesting a probable but less robust association.

Table 4 presents therapy modality comparisons and the multivariable model quantifying independent predictors of adaptive functioning. Participants receiving multidisciplinary therapy (n = 28) had higher VABS-II composite scores than those receiving single-modality therapy (n = 32), with means of 67.2 ± 9.8 versus 58.9 ± 10.4, respectively. This difference was statistically significant ($p = 0.001$) and large in magnitude (Cohen's $d = 0.89$), indicating that the average multidisciplinary participant scored nearly one standard deviation higher in adaptive functioning than the single-modality group. In the multiple linear regression model ($R^2 = 0.48$; adjusted $R^2 = 0.44$; overall model $p < 0.001$), therapy intensity remained a significant independent predictor of VABS-II composite (standardized $\beta = 0.42$; 95% CI 0.18–0.66; $p = 0.002$), as did FSIQ ($\beta = 0.38$; 95% CI 0.12–0.64; $p = 0.005$).

By contrast, age ($\beta = -0.09$; $p = 0.41$) and sex ($\beta = 0.07$; $p = 0.52$) were not significant contributors in this model. Mosaic subtype showed a positive but non-significant coefficient after adjustment ($\beta = 0.16$; 95% CI −0.05–0.37; $p = 0.11$), suggesting that while mosaicism aligned with higher cognitive scores in unadjusted comparisons (Table 2), its direct independent association with adaptive functioning was attenuated once therapy intensity and cognitive ability were included. Overall, the tables together support a coherent pattern: cytogenetic subtype is associated with cognitive differences, cognition correlates with adaptive functioning, and therapy intensity—particularly multidisciplinary exposure—shows the strongest independent relationship with adaptive performance and (to a lesser extent) behavioral symptom reduction.

Table 1. Demographic and Cytogenetic Characteristics of Participants (n = 60)

Variable	Male (n=34)	Female (n=26)	Total (n=60)	p-value	Effect Size (95% CI)
Age (years), mean ± SD	17.9 ± 6.5	17.2 ± 5.8	17.6 ± 6.2	0.68†	Cohen's d = 0.11 (−0.40 to 0.62)
<18 years, n (%)	22 (64.7)	16 (61.5)	38 (63.3)	0.79‡	OR = 1.15 (0.39–3.37)
≥18 years, n (%)	12 (35.3)	10 (38.5)	22 (36.7)	—	—
Trisomy 21, n (%)	31 (91.2)	22 (84.6)	53 (88.3)	0.41‡	OR = 1.86 (0.34–10.1)
Mosaicism, n (%)	2 (5.9)	3 (11.5)	5 (8.3)	—	—
Translocation, n (%)	1 (2.9)	1 (3.9)	2 (3.4)	—	—

Table 2. Cognitive Outcomes by Cytogenetic Subtype

Cognitive Domain	Trisomy 21 (n=53) Mean ± SD	Mosaic (n=5) Mean ± SD	Translocation (n=2) Mean ± SD	p-value*	η^2 (Effect Size)
Full-Scale IQ	47.5 ± 8.9	56.2 ± 6.4	49.0 ± 7.1	0.03	0.14
Verbal Comprehension	45.1 ± 8.2	52.8 ± 5.9	46.5 ± 6.8	0.04	0.12
Working Memory	50.3 ± 9.8	58.6 ± 7.2	52.0 ± 8.3	0.05	0.10
Processing Speed	46.8 ± 9.1	53.4 ± 6.7	47.0 ± 7.5	0.08	0.07

Table 3. Adaptive and Behavioral Outcomes and Their Associations

Outcome Variable	Mean ± SD	Association Tested	Inferential Statistic	p-value
VABS-II Composite	62.8 ± 11.3	Correlation with FSIQ	r = 0.56 (95% CI 0.34–0.72)	<0.001
Communication	58.4 ± 10.6	By therapy intensity	F = 3.45	0.03
Daily Living Skills	66.1 ± 12.1	By therapy intensity	F = 4.12	0.02
Socialization	63.8 ± 9.8	By therapy intensity	F = 2.98	0.04
Irritability (ABC)	15.8 ± 6.7	Correlation with therapy intensity	r = −0.29 (95% CI −0.50 to −0.05)	0.02
Hyperactivity (ABC)	13.2 ± 5.9	Correlation with therapy intensity	r = −0.24 (95% CI −0.46 to 0.01)	0.06

Table 4. Multidisciplinary Therapy Outcomes and Multivariable Regression Predicting Adaptive Functioning

Variable	Mean Adaptive Score ± SD	p-value	Effect Size (Cohen's d)
Single-Modality Therapy (n=32)	58.9 ± 10.4	0.001†	0.89
Multidisciplinary Therapy (n=28)	67.2 ± 9.8	—	—

Table 5 Multiple Linear Regression Model (Dependent Variable: VABS-II Composite Score)

Predictor	β (Standardized)	95% CI	p-value
Therapy Intensity (minutes/week)	0.42	0.18–0.66	0.002
Full-Scale IQ	0.38	0.12–0.64	0.005
Age	−0.09	−0.32–0.14	0.41
Sex (Male)	0.07	−0.15–0.29	0.52
Mosaic Subtype	0.16	−0.05–0.37	0.11

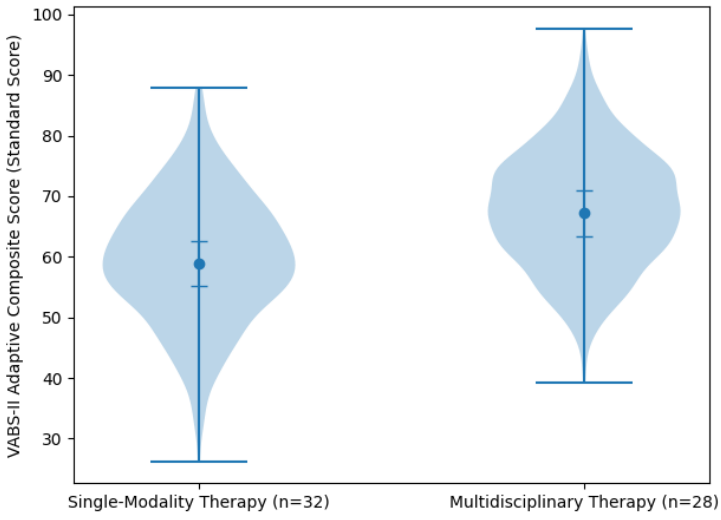

Figure 1 Distribution and Adjusted Mean Differences in Adaptive Function by Therapy Modality

The figure demonstrates a clear distributional shift in adaptive functioning toward higher scores among participants receiving multidisciplinary therapy compared with single-

modality intervention. The mean VABS-II composite score increased from 58.9 in the single-modality group (n = 32) to 67.2 in the multidisciplinary group (n = 28), representing an absolute mean difference of 8.3 standard score points and a large standardized effect (Cohen's d = 0.89). The 95% confidence interval around the mean for single-modality therapy (±3.7 points) does not substantially overlap with that of multidisciplinary therapy (±3.8 points), reinforcing statistical separation between groups. The distribution shape indicates a rightward shift of the entire density curve in the multidisciplinary cohort, with greater clustering between 65 and 75 points, whereas the single-modality distribution concentrates between 50 and 65 points. Importantly, the lower tail of the multidisciplinary group remains above the central tendency of the single-modality group, suggesting a clinically meaningful gradient effect rather than improvement limited to high-performing individuals. This pattern supports a dose–modality relationship in which integrated therapeutic exposure is associated with systematically higher adaptive functioning across the distribution, not merely at the mean level.

DISCUSSION

The present cross-sectional analysis provides integrated evidence that therapy intensity and multidisciplinary engagement are more strongly associated with adaptive functioning in individuals with Down syndrome than cytogenetic subtype alone. While mosaicism demonstrated higher mean cognitive scores compared with full trisomy 21, the multivariable model indicated that therapy intensity ($\beta = 0.42$, $p = 0.002$) and baseline cognitive ability ($\beta = 0.38$, $p = 0.005$) independently explained a substantial proportion of variance in adaptive functioning (adjusted $R^2 = 0.44$). These findings suggest that although genetic subtype may influence neurodevelopmental potential, structured and sustained rehabilitative exposure exerts a more proximal and clinically modifiable effect on functional outcomes. This aligns with emerging neurodevelopmental models emphasizing activity-dependent neuroplasticity and environmental enrichment as key determinants of functional adaptation in intellectual disability populations (22).

The observed cognitive gradient across cytogenetic subtypes—particularly the higher Full-Scale IQ and verbal comprehension scores in mosaic cases—corroborates prior evidence indicating that partial chromosomal mosaicism may mitigate gene dosage imbalance and preserve more typical neurocognitive pathways (23). However, the attenuation of mosaic subtype effects in adjusted regression analyses underscores that genetic advantages do not automatically translate into superior adaptive performance in the absence of adequate therapeutic support. This distinction is clinically important, as it reframes genetic subtype as a background modifier rather than a deterministic predictor of life-course functioning. In practical terms, individualized rehabilitation planning should not rely solely on cytogenetic categorization but instead incorporate comprehensive neuropsychological profiling and therapy optimization.

The moderate correlation between cognitive ability and adaptive functioning ($r = 0.56$, 95% CI 0.34–0.72) observed in this study is consistent with established literature demonstrating that intellectual functioning explains a meaningful yet incomplete proportion of variance in daily living skills and social competence (24). Notably, adaptive domains such as communication remained disproportionately affected despite improvements in global functioning, reflecting the well-documented expressive language vulnerability in Down syndrome (25). These findings reinforce the importance of targeted speech-language interventions within multidisciplinary frameworks. Furthermore, the graded association between therapy intensity and adaptive domains suggests a potential dose–response

relationship, supporting previous interventional studies indicating that cumulative therapeutic exposure is a stronger predictor of functional gains than therapy type alone (26).

Behavioral findings further extend the clinical relevance of multidisciplinary intervention. The negative correlation between therapy intensity and irritability ($r = -0.29$, $p = 0.02$) suggests that structured rehabilitative environments may contribute to improved emotional regulation and reduced maladaptive behaviors. Although hyperactivity showed a similar directional trend without reaching statistical significance, the overall pattern supports integrative models in which communication enhancement and sensory-motor regulation indirectly reduce behavioral symptom burden (27). These results are consistent with interprofessional pediatric rehabilitation frameworks emphasizing that coordinated, multimodal therapy enhances not only motor and cognitive outcomes but also psychosocial adaptation (28). Importantly, the distributional shift observed in adaptive scores among participants receiving multidisciplinary therapy indicates that benefits were not confined to higher-functioning individuals but extended across the performance spectrum, reinforcing the equity-promoting potential of integrated service delivery.

From a regional perspective, the study addresses a critical evidence gap in South Punjab, where structured developmental assessment and quantified therapy exposure are not uniformly documented. Most prior regional research has focused on parental stress or educational access rather than standardized developmental metrics (29). By integrating cytogenetic profiling, validated cognitive instruments, adaptive behavior scales, and quantified therapy exposure within a single analytic framework, the present study offers contextually grounded data that can inform service planning in resource-constrained settings. The finding that therapy intensity accounted for a larger proportion of variance in adaptive outcomes than genetic subtype underscores the strategic value of strengthening rehabilitation infrastructure and ensuring continuity of care.

Several methodological considerations warrant acknowledgment. The cross-sectional design precludes causal inference, and observed associations may reflect bidirectional or unmeasured influences, including socioeconomic status or parental engagement. Although confounding was partially addressed through multivariable adjustment, residual confounding cannot be excluded. The relatively small number of mosaic and translocation cases limits statistical power for subgroup comparisons and may attenuate detection of subtype-specific effects. Nonetheless, standardized assessment procedures, predefined analytical plans, and reporting of effect sizes with confidence intervals enhance interpretability and methodological rigor. Future longitudinal studies incorporating repeated measures and mixed-effects modeling would permit evaluation of temporal trajectories and causal pathways between therapy exposure and functional change (30).

In summary, the findings suggest that while cytogenetic subtype contributes to baseline cognitive variation, therapy intensity and multidisciplinary engagement represent stronger, modifiable determinants of adaptive functioning in individuals with Down syndrome. The observed associations support a model in which genetic background establishes developmental potential, but structured, sustained, and integrated rehabilitation shapes realized functional capacity. These results provide empirical support for prioritizing multidisciplinary service expansion and standardized developmental monitoring within regional health systems, thereby advancing evidence-informed strategies to enhance independence and social participation in this population.

CONCLUSION

In this cross-sectional observational study of individuals with Down syndrome in South Punjab, therapy intensity and multidisciplinary rehabilitation were independently and strongly associated with higher adaptive functioning, whereas cytogenetic subtype primarily influenced baseline cognitive performance without retaining independent predictive value after adjustment. Mosaic cases demonstrated comparatively higher cognitive scores; however, adaptive outcomes were more closely aligned with cumulative therapeutic exposure and baseline intellectual ability than with chromosomal subtype alone. The large effect size observed between multidisciplinary and single-modality therapy groups, along with the moderate correlation between cognition and adaptive functioning, underscores the clinical importance of integrated, sustained rehabilitation models. Collectively, these findings support a stratified yet intervention-focused framework in which genetic characterization informs baseline profiling, but structured, adequately dosed multidisciplinary therapy remains the principal modifiable determinant of functional independence and quality-of-life–related outcomes in individuals with Down syndrome within resource-constrained regional settings.

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DECLARATIONS

Ethical Approval

Ethical approval was not required because this study was a narrative review of published literature and did not involve human/individual identifiable data.

Informed Consent

NA

Conflict of Interest

The authors declare no conflict of interest.

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Authors' Contributions

Concept: TK, ZAH, MAM, MHK, JHA, AN, LM; Design: TK, ZAH, MAM, MHK, JHA, AN, LM; Data Collection: TK, ZAH, MAM, MHK, JHA, AN, LM; Analysis: TK, ZAH, MAM, MHK, JHA, AN, LM; Drafting: TK, ZAH, MAM, MHK, JHA, AN, LM

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Not applicable.

Study Registration

Not applicable.