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Molecular Genetics of Inherited Neurodevelopmental and Neurodegenerative Brain Disorders in Pakistan: Genomic Landscape, Genotype–Phenotype Correlations, Diagnostic Challenges and Precision Medicine Perspectives

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Abstract

Neurological disorders with inherited causes encompass a diverse range of conditions, including intellectual disability, autism spectrum disorders, epilepsy, hereditary spastic paraplegia, and progressive neurodegenerative disorders. In Pakistan, factors such as high rates of consanguineous marriages, large multi-generational families, geographical isolation and unique population structures have intensified the prevalence of autosomal recessive neurological disorders, leading to an accumulation of rare homozygous pathogenic variants. This review consolidates contemporary insights into the genetic architecture, genotype-phenotype correlations, and clinical challenges related to inherited brain disorders in Pakistani families. A strong emphasis is placed on advanced techniques such as homozygosity mapping, targeted gene panels, and various sequencing methods including whole-exome and whole-genome sequencing, alongside copy-number-variation analysis and functional validation. These genomic approaches have identified pathogenic variants in genes involved in neuronal processes, including migration, cortical development, synaptic signaling and mitochondrial metabolism. Despite extensive research in neurological genetics globally, Pakistan faces significant obstacles to translating genomic discoveries clinically. These challenges include a lack of diagnostic facilities, high sequencing costs, insufficient trained genetic professionals, limited bioinformatics resources and the absence of population-specific genomic databases and national rare disease registers. To overcome these hurdles, it is essential to integrate genomics with advancements in Artificial Intelligence, multi-omics technologies, detailed clinical phenotyping, functional studies and culturally sensitive genetic counseling. The implementation of national genomic initiatives, establishment of multidisciplinary precision-neurology centers and provision of equitable diagnostic services stand to enhance early diagnosis, variant interpretation, reproductive counseling and the development of personalized therapeutic strategies for inherited neurological disorders in Pakistan.

Introduction

Inherited neurological disorders are part of a broad spectrum of genetic disorders that are high in clinical and molecular heterogeneity and have altered brain development pathways, neuronal signaling, and neurodegeneration. The disorders are intellectual disability (ID), developmental delay, autism spectrum disorder (ASD), epilepsy, hereditary movement disorders, hereditary ataxias, hereditary spastic paraplegias, leukodystrophies and neurodegenerative disorders that progress. These are rare diseases individually but may be a substantial burden of disease collectively on a global scale with genetic variants being a key part of susceptibility to disease and phenotypic variation (Boycott et al., 2019).

Many inherited brain disorders are transmitted in a number of different ways such as autosomal recessive, autosomal dominant, X linked, mitochondrial and de novo variants. Next generation sequencing (NGS) and in particular whole-exome sequencing (WES) and whole genome sequencing (WGS) has revolutionised the diagnosis of rare neurological diseases making it possible to identify the vast majority of variants and discover new disease-associated genes (Turro et al., 2020; Afzal et al., 2025). Consanguinity is common in Pakistan and there is a high prevalence of consanguineous

marriages making it an important aspect of the study of inherited neurological disorders as this causes more homozygosity and simplifies identification of recessive disease causing variants.

Pathogenic variants contributing to intellectual disability, epilepsy, neurodevelopmental and progressive neurological disease have been identified in Pakistani families through genomic investigations and the genomic data would be correlated with clinical phenotype in these families (Riazuddin et al., 2021; Khan et al., 2022). However, the clinical use of sequencing is hampered by significant challenges including low genomic infrastructure and resources lack of genetic counselling, cost of sequencing and the absence of population-specific reference databases. The review is focused on molecular genetics, genotype-phenotype correlations, recent advances in diagnostics, challenges and future prospects of precision medicine in inherited brain disorders of neurodevelopmental and neurodegenerative origins in Pakistan.

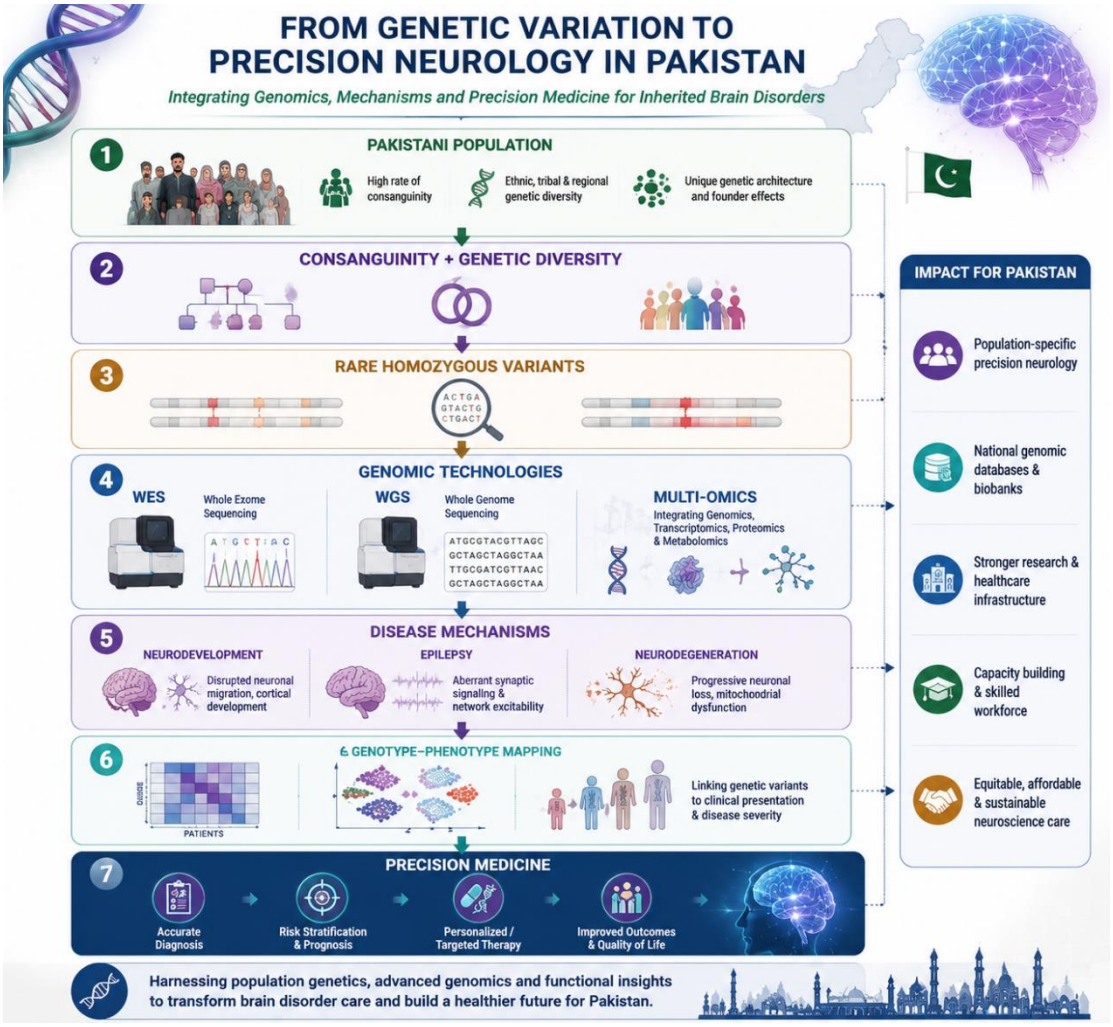

Figure 1. Conceptual framework linking Pakistan's population genetics and rare homozygous variants with genomic technologies, disease mechanisms, genotype–phenotype mapping, and precision neurology

Genetic Architecture of Inherited Brain Disorders in Pakistan

Inherited brain disorders are genetically and clinically heterogeneous brain disorders due to pathogenic variants and inheritance, population history and environment. This is because of the vast consanguinity, geographical isolation and population structure in Pakistan, which has resulted in the enrichment of rare recessive variants and a high level of homozygosity, making this a significant population model to study these disorders. These features have also enabled the discovery of new disease-related genes via genomic analysis approaches and have been critical in understanding molecular

mechanisms underlying intellectual disabilities, epilepsy, neurodevelopmental disorders and neurodegenerative diseases (Khan et al., 2022).

Burden of inherited neurological diseases in Pakistan is greatly influenced by consanguinity. Increased relatedness of parents with homozygous regions of the genome is associated with longer homozygous regions and increased expression of autosomal recessive disorders. These genomic features have allowed the discovery of new genes in families with ID and developmental disorders (Blackstone, 2018), including through homozygosity mapping and sequencing. In the families of Pakistan, it has been found that there are many pathogenic variants of neuronal development, synaptic function, intracellular signaling and metabolic pathways. Consanguinity helps in revealing the prevalence of recessive disease genes but also contributes to the higher prevalence of inherited neurological disorders (Harripaul et al., 2018; Paracha et al., 2024).

The most common mode of inheritance in inherited neurological disorders in Pakistan is the autosomal recessive inheritance. The occurrence of affected siblings with consanguineous families is common due to pathogenic variants in both alleles, which is often passed on from asymptomatic parents (Ahmad & Naeem, 2025). Genomic studies have identified recessive variants in genes involved in differentiating neurons, guiding the development and growth of their axons, transmitting information between neurons, regulating the production of energy within the mitochondria and creating the brain. The research done in Pakistan has therefore helped to increase the understanding of intellectual disability and epilepsy including discovery of molecular basis of otherwise indistinguishable clinical conditions (Bibi et al., 2024).

Pathogenic variants of genes related to neuronal maintenance, migration and organization of the cortex have been identified in hereditary spastic paraplegia, intellectual disability and cortical developmental disorders such as FA2H, SPG11, SACS, WDR62 and ADGRG1 (Azeem et al., 2024; Sawal et al., 2018). Though most neurological disorders are recessive; inherited neurological disorders in Pakistan are highly genetically and clinically heterogeneous. Variants of similar type in different genes can lead to similar phenotypes (e.g. developmental delay, epilepsy, intellectual disability) and variants of the same type in the same gene can have different clinical presentations (Vissers et al., 2016).

The complexity of this makes phenotype diagnosis difficult and highlights the importance of genomic sequencing as well as careful clinical examination. There is genotype/phenotype variation in Pakistani families indicating the importance of having a complete molecular and clinical evaluation for the accurate diagnosis of the disease (Usmani et al., 2024; Boycott et al., 2019). The Pakistani families have been a missing link in the world in neurological genetics due to their large size, high consanguinity and multiple affected members in pedigrees. These have led to the discovery and characterization of genes involved in intellectual disability, epilepsy and neurodegenerative disorders (Rafiullah et al., 2016).

The studies in Pakistani populations, in addition to the discovery of the genes, have resulted in a better understanding of molecular pathways involved in brain development, neuronal survival and disease progression. The study emphasized the importance of the representation diversity of underrepresented populations in global genome studies for the equitable precision medicine (Saadi et al., 2023).

Table 1. Representative genomic studies of inherited neurodevelopmental and neurodegenerative disorders in Pakistani families

Disorder or spectrum	Gene(s) identified	Inheritance / variant pattern	Major phenotype	Genomic approach	Principal contribution	Reference
Autosomal recessive intellectual disability	Thirty established ID genes and 30 candidate genes	Mainly homozygous or compound-heterozygous variants	Variable intellectual disability, developmental delay, speech impairment, and neurological abnormalities	Exome sequencing with segregation analysis	Analysis of 60 families expanded the candidate-gene landscape of recessive intellectual disability.	Riazuddin et al. (2017)
Intellectual disability with infantile epilepsy	LMAN2L	Homozygous missense variant	Severe intellectual disability and infantile epilepsy	Homozygosity mapping, exome sequencing, and segregation analysis	Established recessive LMAN2L-related intellectual disability in a large Pakistani family.	Rafiullah et al. (2016)
Bilateral frontoparietal polymicrogyria	ADGRG1/ GPR56	Homozygous recessive variants	Moderate-to-severe intellectual disability, seizures, motor impairment, and abnormal cortical lamination	Genetic mapping and sequencing	Expanded the ADGRG1 mutation spectrum in Pakistani intellectual-disability families.	Sawal et al. (2018)

Disorder or spectrum	Gene(s) identified	Inheritance / variant pattern	Major phenotype	Genomic approach	Principal contribution	Reference
Neurodevelopmental disorders	ABAT, SLC12A6, SHANK3, BCKDK, DDHD2, ERCC2, and additional established genes	Predominantly homozygous variants	Microcephaly, developmental delay, intellectual disability, movement abnormalities, and syndromic NDDs	WES, Sanger validation, segregation analysis, and selected protein modelling	Identified likely molecular diagnoses in 30 unrelated consanguineous families, including newly reported variants.	Paracha et al. (2024)
Neurodevelopmental and neuromuscular disorders	ADGRG1, METTL23, SPG11, GPAA1, MFN2, SGSH, AP4M1, and FAM126A	Homozygous pathogenic, likely pathogenic, or candidate variants	NDDs, spasticity, neuropathy, neuromuscular impairment, and developmental abnormalities	Exome sequencing and family segregation analysis	Demonstrated extensive genetic heterogeneity and identified several previously unreported variants.	Bibi et al. (2024)
Primary microcephaly	WDR62	Novel and recurrent recessive variants	Reduced head circumference, developmental delay, intellectual disability, and cortical abnormalities	Molecular sequencing, neuroimaging, and structural analysis	Connected WDR62 variation with neuroimaging findings and predicted structural effects in two families.	Aslam et al. (2024)

Disorder or spectrum	Gene(s) identified	Inheritance / variant pattern	Major phenotype	Genomic approach	Principal contribution	Reference
Intellectual disability with epilepsy and spasticity	HACE1	Homozygous missense variant	Intellectual disability, epilepsy, spasticity, and psychomotor impairment	Exome sequencing, segregation analysis, computational prediction, and expression analysis	Expanded the clinical spectrum of HACE1-associated neurodevelopmental disease.	Usmani et al. (2024)
Familial epilepsy and complex neurological disease	CNTN2, CARS2, ARSA, and CLCN4	Four homozygous variants and one X-linked variant	Epilepsy, cognitive decline, spasticity, sensory abnormalities, and progressive neurological manifestations	WES, Sanger validation, segregation analysis, and in-silico assessment	Showed that clinically overlapping epilepsy phenotypes could be molecularly distinguished using WES.	Abdulkareem et al. (2023)
Rare spinocerebellar disorders	ZFYVE26, SACS, BICD2, ALS2, B4GALNT1, FA2H, APTX, and SETX	Predominantly biallelic recessive variants	Ataxia, spasticity, cognitive impairment, muscular abnormalities, and ocular features	WES and segregation analysis	Demonstrated extensive locus heterogeneity and overlapping spinocerebellar phenotypes.	Saadi et al. (2023)

Disorder or spectrum	Gene(s) identified	Inheritance / variant pattern	Major phenotype	Genomic approach	Principal contribution	Reference
Hereditary spastic paraplegia and cerebellar ataxia	SACS, FA2H, ZFYVE26, and SPG11	Biallelic pathogenic variants	Progressive spasticity, ataxia, intellectual impairment, neuropathy, and white-matter abnormalities	WES, segregation analysis, and clinical phenotyping	Expanded the genotypic and phenotypic spectra of HSP and cerebellar ataxia in Pakistan.	Azeem et al. (2024)
Autosomal recessive spinocerebellar ataxia type 13	GRM1	Homozygous frameshift variant	Psychomotor delay, intellectual disability, poor or absent speech, nystagmus, and stance ataxia	Exome sequencing, segregation analysis, and functional prediction	Expanded the molecular landscape of ultra-rare GRM1-related spinocerebellar ataxia.	Ahmad et al. (2025)

Genomic Technologies Transforming Diagnosis of Inherited Brain Disorders in Pakistan

The idea of inherited brain disorders has changed in Pakistan with the advent of genomic technologies. The introduction of ‘genomic technologies' caused a paradigm shift in the inherited brain disorders in Pakistan. The introduction of ‘genomic technologies' brought about a paradigm shift in inherited brain disorders in Pakistan. With the development of genomic technologies and a shift towards a genome-based approach for diagnosis inherited neurological disorders has undergone a revolution, rather than the traditional phenotype-based approach.

Characterized by high genetic heterogeneity and overlapping clinical and laboratory features, standard diagnostic approaches often were inadequate. Due to the next generation sequencing (NGS) technologies (whole genome sequencing (WGS), whole-exome sequencing (WES), targeted gene panels and homozygosity mapping), a comprehensive identification of disease-causing variants is now possible. In Pakistan, these technologies have special significance as many neurological disorders are inherited and there are consanguineous families with more than one member affected with these disorders which are more likely to be homozygous.

Recent studies have confirmed the potential of genomic medicine in improving diagnosis and disease understanding through identification of pathogenic variants associated with intellectual disability, epilepsy, developmental and neurodegenerative

conditions using WES and segregation analysis (Ahmad & Naeem, 2025). The following methods were used for the diagnosis of inherited neurological disorders in the past: single gene testing, linkage analysis and chromosomal investigations. However, there was a large overlap between the clinical manifestations of the neurological disorders making it difficult to prioritize genes and frequently leading to delayed or not complete diagnosis.

The advantage of using a consanguineous population for recessive disease studies was the possibility to map those regions of the genome that were shared by common ancestors by homozygosity mapping. Among the Pakistani families who have Intellectual Disability, Epilepsy and Cortical abnormalities, this method was very helpful for Gene discovery (Lander & Botstein, 1987; Rafiullah et al., 2016). This new high throughput sequencing method called whole-exome sequencing can sequence thousands of coding regions simultaneously and could be a major diagnostic tool for inherited neurological diseases and is rapidly emerging as an important tool for the discovery of rare pathogenic variants. In Pakistani populations WES has been able to effectively prioritize variants associated with Intellectual disability, Epilepsy and Neurodevelopmental disorders in the homozygous state in consanguineous families (Yang et al., 2014).

The research on genes involved in neuronal migration, synaptic regulation, intracellular transports and brain development conducted by the scientists of WES in Pakistan has added to the knowledge. However, there are limitations to WES for the difficulty of detecting regulatory variants, structural abnormalities, mitochondrial variants and the difficulty in interpreting variants of uncertain significance (of uncertain effect), which may require clinical/functional evidence to be integrated into interpretation (Richards et al., 2015; Paracha et al., 2024). Whole genome sequencing (WGS) can be used to gain wider genomic information in the form of coding and non-coding variants, structural changes, repeat expansions and abnormalities of the mitochondria.

WGS has been introduced in a limited fashion in Pakistan but is a very important approach for future use in unsolved neurologic cases and for the discovery of the genome of a population. National WGS initiatives are available to improve the diagnostic rate and develop capacity in precision medicine (Turro et al., 2020; Smedley et al., 2022). Although the benefits of WGS have become clear, targeted gene panels are still valuable for well-defined neurological diseases due to the following reasons: they can be sequenced to high depths, are relatively inexpensive, and are easier to interpret. They have been found to be very useful in the treatment of certain nerve degenerative diseases, epilepsy and hereditary spastic paraplegia. Pathogenic variants in developmental epileptic encephalopathies and clinically overlapping syndromes (Ahsan et al., 2025; McKnight et al., 2021).

Table 2: The principal genotype–phenotype relationships and molecular pathways identified in Pakistani inherited neurological disorders.

Technology	**Variants detected**	**Major strengths**	**Major limitations**	**Best application in Pakistan**	**Supporting references**
Homozygosity mapping	Long runs of homozygosity and candidate recessive loci	Highly useful in large consanguineous pedigrees; narrows candidate regions	Does not independently identify the causal nucleotide change; limited in small families	Initial prioritization of recessive loci in multiplex consanguineous families	Riazuddin et al. (2017); Rafiullah et al. (2016)

Technology	Variants detected	Major strengths	Major limitations	Best application in Pakistan	Supporting references
Targeted gene panel	SNVs and small indels in selected disease genes; some panels include CNVs	High depth, lower analytical burden, and relatively affordable	Cannot detect genes absent from the panel; panels become outdated	Clinically recognizable epilepsy, HSP, ataxia, or leukodystrophy	Ahsan et al. (2025)
Whole-exome sequencing	Coding SNVs and small indels; selected CNVs	Broad gene coverage; effective for heterogeneous recessive disorders; supports novel-gene discovery	Limited detection of non-coding variants, repeat expansions, complex structural variants, and some CNVs	Preferred first-line test for unresolved familial NDDs, epilepsy, HSP, and ataxia	Paracha et al. (2024); Bibi et al. (2024); Abdulkareem et al. (2023)
Whole-genome sequencing	Coding and non-coding SNVs, indels, CNVs, structural variants, and some repeat expansions	Most comprehensive short-read test; improved uniformity and variant detection	Higher cost, storage requirements, interpretation burden, and incidental findings	WES-negative cases, suspected regulatory or structural disease, and national reference-genome initiatives	Turro et al. (2020); Smedley et al. (2022)
Chromosomal microarray / CNV analysis	Deletions, duplications, and regions of homozygosity	Established method for large CNVs and developmental disorders	Does not reliably detect sequence-level variants or balanced rearrangements	Syndromic developmental delay, ASD, congenital abnormalities, or negative WES with suspected dosage change	Miller et al. (2010)
Mitochondrial genome sequencing	Mitochondrial SNVs, indels, and heteroplasmy	Detects variants not adequately assessed by standard WES pipelines	Tissue heteroplasmy and nuclear mitochondrial genes complicate interpretation	Epilepsy, regression, ataxia, multisystem disease, and suspected mitochondrial dysfunction	Abdulkareem et al. (2023)

Technology	Variants detected	Major strengths	Major limitations	Best application in Pakistan	Supporting references
Long-read sequencing	Repeat expansions, complex structural variants, difficult genomic regions, and phasing	Resolves variants missed by short reads; supports haplotype and methylation analysis	High cost, specialized analysis, and limited routine availability	Unresolved familial disorders after WES/WGS and suspected repeat or structural disease	Proposed future platform
RNA sequencing and functional assays	Abnormal splicing, expression changes, transcript loss, and pathway dysfunction	Provides functional evidence for uncertain variants	Tissue availability and disease-relevant cellular models may be limited	Functional validation of VUS and candidate genes	Richards et al. (2015); Aslam et al. (2024)
AI-assisted phenotype and variant prioritization	Integrates genomic, phenotype, structural, and literature evidence	Reduces candidate burden and supports standardized prioritization	Risk of ancestry bias, opaque predictions, and dependence on training data	Local decision-support systems linked to Pakistani phenotype and allele-frequency databases	Smedley et al. (2022)

However, gene panels are only able to cover certain genes, which can result in the loss of coverage of new genes that lead to disease. Therefore, WES and WGS are gaining in popularity for genetically heterogeneous neurological disorders. Copy number variations (CNVs) are amplifications or deletions that play an important role in neurological disorders that are inherited. CNV analysis in addition with sequencing methods improves the diagnostic accuracy, particularly for ID and ASD.

The ability to find CNV will be improved in Pakistani laboratories which will help in the better diagnosis of complex genetic disorders and a decrease in the number of unresolved cases (Miller et al., 2010). The correct interpretation of the genetic variations is one of the most significant challenges of genomic medicine. With the increasing need for confirmation of disease causing mechanisms, functional approaches such as transcript analysis, protein studies, cellular models and computational prediction are increasingly gaining importance. Apart from sequencing studies alone, limited number of recent studies in Pakistan have used sequencing combined with functional validation to gain insights on genes implicated in microcephaly, intellectual disability or neurodegeneration (Landrum et al., 2018; Aslam et al., 2024).

The development of Pakistani-specific genomic databases of allele frequencies, clinical annotations and genotype-phenotype information is essential for improving variant interpretation and clinical diagnosis. There are advances in terms of genomics but there is not enough facilities for routine clinical sequencing, genetic specialists and counselling services and access to services in rurality. To ensure the successful

application of genomic medicine, it is crucial for neurologists, geneticists, molecular biologists and bioinformaticians to cooperate and collaborate. For the success of genomic research to bring readily available precision healthcare solutions to Pakistani patients, national rare disease programmes, genetic infrastructure and genetic counselling services will play an important role.

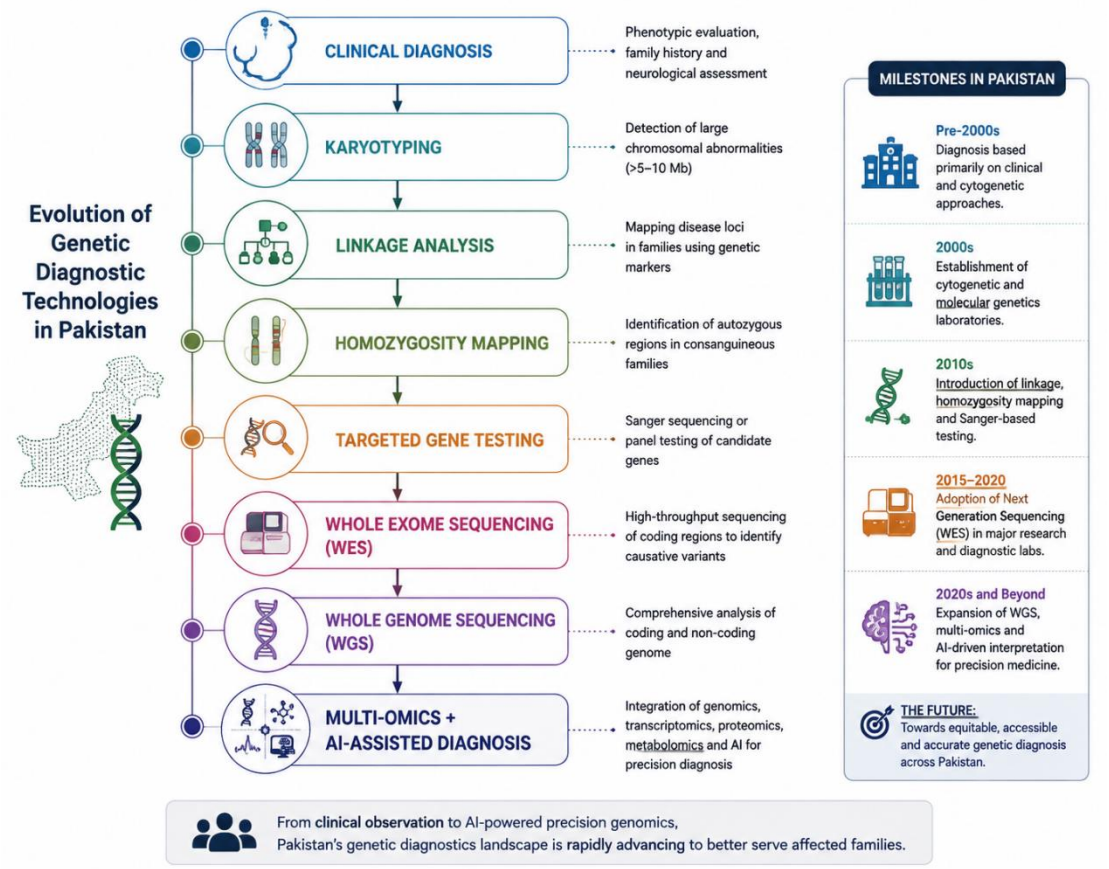

Figure 2. Evolution of genetic diagnostic technologies in Pakistan, progressing from clinical and cytogenetic methods to WES, WGS, multi-omics, and AI-assisted precision diagnosis

Neurodevelopmental Brain Disorders in Pakistan

Neurodevelopmental disorders are the most diverse and greatest family of inherited brain disorders in Pakistan. The abnormalities are seen when the synapses develop, move and form; when chromatin is regulated; and when intracellular pathways lead to intellectual disability, autism spectrum disorder, epilepsy, developmental delay, and abnormalities of brain structure. The genomic technologies have also identified considerable genetic similarity between clinically different disorders thus the need for molecular diagnosis is becoming important (Deciphering Developmental Disorders Study, 2017). In Pakistan homozygosity mapping and WES have been used to identify numerous recessive variants associated with cognitive defects and to provide insight into developmental programs (Vissers et al., 2016, Riazuddin et al., 2017).

In the past decade, however, molecular analysis of Pakistani ID patients has revealed the presence of substantial genomic variation in ID patients, which further supports the concept of cognitive impairment as a spectrum of genetically distinct disorders, and calls for a genomic approach to the evaluation of ID patients (Paracha et al., 2024). The key molecular features of ID are disruption of chromatin regulation, neuronal migration, transcriptional control and synaptic function. Defects in the migration pathways: disrupt brain organization and development of cortex Abnormalities in synapses: interfere communication and transport of information between neurons.

Genetic polymorphisms that affect the development of synapses and cortex have been found in Pakistan which further support knowledge on these mechanisms (Kaufman et al., 2022; Bibi et al., 2024). Autism spectrum disorder (ASD) is a de novo mutation, complex disorder with variants of inherited mutations and structural alterations of the genome influencing the functioning of synapses, neuronal connection and chromatin regulation (Satterstrom et al., 2020). While ASD research in Pakistan is still in its infancy, studies on genomes have suggested recessive, X-linked and de novo variants that are associated with autistic traits. This study highlights the need for representation and inclusion of South Asian populations in global genome studies and to understand how variants are interpreted and precision medicine approaches developed (Khan et al., 2024; Fatima et al., 2022).

Inherited Epileptic Disorders in Pakistan

Inherited epilepsy is a significant part of neurological genetic disease and different types of epilepsy are included such as isolated syndrome epilepsy and severe developmental epileptic encephalopathy. Abnormalities of ion channels, synaptic function, metabolic function and neural development are among the genetic abnormalities. In Pakistani genome-wide studies more genes are identified which are associated with epilepsy, especially consanguineous families (Scheffer et al, 2017; Ahsan et al, 2025). Epilepsy in Pakistan is a highly genetically heterogeneous disorder with the autosomal recessive forms being much more frequently seen than the other types due to the high level of consanguineous marriage.

Sequencing studies have revealed neuronal developmental, synaptic pathway, and metabolic variants, often associated with epilepsy and developmental delay and/or intellectual disability (Muhammad et al., 2025). DEEs are highly serious genetic epilepsy conditions that have an early onset of seizures and developmental problems. Variants in genes encoding ion channels, synaptic proteins and transcription regulators have been identified using genomic diagnosis, which has helped to better classify the disorder, and may help develop treatment strategies (Zuberi et al., 2022; McTague et al., 2016). It is believed that epilepsy occurs due to excessive or inadequate activity of the ionic channels of the brain, which are regulated by genes for ion channel proteins (such as SCN1A, CACNA1A, KCNQ2 and CLCN4).

In a Pakistani study more variant of ion regulation and synapse pathways were identified which further highlights the importance of molecular diagnosis in the management of epilepsy (Oyrer et al., 2018; Abdulkareem et al., 2023). Defects of mitochondrial, lysosomal and metabolic pathways can also be inherited and result in epilepsy. This indicates that there are molecular variants of epilepsy associated neurodegeneration (EAN), such as CLN5, ITPA, CARS2 and ARSA (Pearson et al., 2020; Muhammad et al., 2025). Pathogenic variations have been recently identified in the genome of patients with epilepsy syndromes such as Dravet syndrome, Rett syndrome, GEFS+ and Lafora disease. The findings of this study emphasize the importance of using sequencing for distinguishing clinically similar types of epilepsy and providing better counselling (Ahsan et al., 2025).

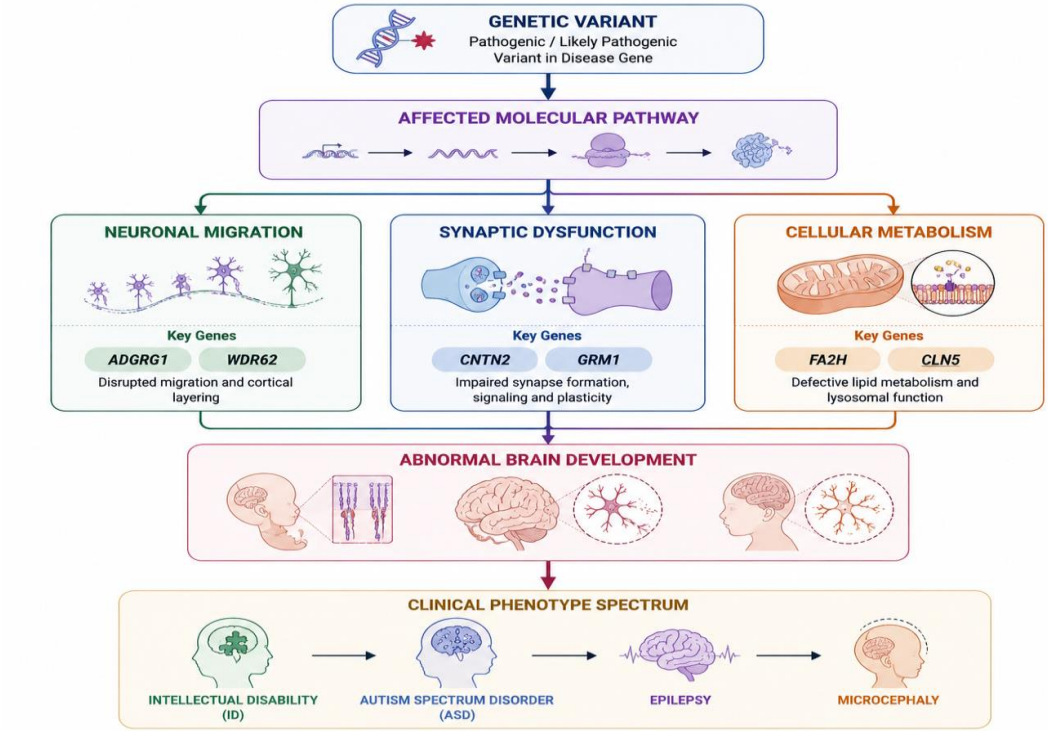

Figure 3. Pathogenic variant to genotype to phenotype framework: how pathogenic variants in the brain disrupt neuronal migration, synaptic function and brain cell metabolism resulting in abnormal brain development and diverse neurodevelopmental phenotypes.

Neurodegenerative Disorders, Hereditary Spastic Paraplegia and Cerebellar Ataxia in Pakistan

The Neurodegenerative Disorders, Hereditary Spastic Paraplegia and Cerebellar Ataxia in Pakistan is also present. There is also a presence of Neurodegenerative Disorders, Hereditary Spastic Paraplegia and Cerebellar Ataxia in Pakistan. Progressive loss of neurons due to disrupted mechanisms for maintaining neurons, protein degradation, axonal transport, lipid metabolism and mitochondrial dysfunction result in inherited neurodegenerative disorders. Due to high rate of consanguinity and large affected families in Pakistan, it is an important population for the study of these disorders where recessive disease-causing variants are easily identifiable. In recent years, the molecular genetic characterization of hereditary spastic paraplegia (HSP), spinocerebellar ataxias, and leukodystrophies and related neurological diseases (Klein & Mazzulli, 2019; Ahmad & Naeem, 2025). Hereditary spastic paraplegia (HSP) includes a clinically and genetically diverse group of disorders characterized by progressive weakness and spasticity involving the lower limbs, which occurs as a result of the degeneration of the corticospinal tract. The syndrome of HSP can be either simple or more complex, with intellectual disability, epilepsy, ataxia, and peripheral neuropathy included. More than 80 genetic loci have been identified as being involved in HSP, including those related to axonal transport, mitochondrial metabolism, membrane trafficking and lipid metabolism. Genetic diversity is quite large with genes found in Pakistani studies being SACS, SPG11, FA2H and ZFYVE26 (Blackstone, 2018; Azeem et al., 2024).

FA2H encodes fatty acid hydroxylase 2 (FA2H), a protein that is necessary for maintenance of myelin and for neuronal function. Pathogenic variants are the cause of FAHN, and these cause spastic paraplegia, cerebellar ataxia, cognitive decline, dystonia and white matter abnormalities. Families with FA2H variants from Pakistan helped to shed light on the mechanism of the disease and potential founder effect among certain communities. Genomic analysis may be combined with neuroimaging to complement diagnosis, clinical classification (Kruer et al., 2010; Azeem et al., 2024).

SPG11 is one of the most important genes implicated in the development of autosomal recessive HSP, and encodes a protein called “spatacsin” which is involved in the maintenance of neurons and their proper functioning, and also in autophagy. Thin corpus callosum, intellectual disability, neuropathy, involvement of the cerebellum with juvenile onset of spasticity are the most common features of disease related to SPG11. The variants in the SPG11 gene have been identified in Pakistan, and this has helped to better understand the genetic variation in this country and the contribution of these mutations to the genomic diagnosis of a condition of unexplained progressive spasticity (Stevanin et al., 2008; Azeem et al., 2024).

The GRM1 gene encodes a protein that plays a role in signalling and plasticity of the cerebellum. Pathogenic variants impair neuronal communication by disrupting glutamate signaling, and cause progressive cerebellar dysfunction. The need to investigate under-studied populations to reveal novel disease mechanisms and broaden neurological genetics knowledge worldwide (Ahmad et al., 2025). Mitochondrial defects are a significant part of inherited neurological diseases, and have been implicated in many different ways that can impact the cell's ability to generate energy, communicate with other cells and survive.

Epilepsy, developmental regression and neurodegeneration has been identified as a family disorder in Pakistani studies which led to finding mitochondrial associated variants. The knowledge of the mechanism of the mitochondria is critical because some disorders can be treated by a metabolic-specific treatment (Abdulkareem et al., 2023). Genotype–phenotype correlations in neurodegenerative disorders are complicated due to the fact that mutations in the same gene can lead to different severity, age of onset and clinical features. Overlapping clinical features of SACS, FA2H, SPG11 and ZFYVE26 patients such as ataxia, spasticity, white matter abnormalities and cognitive impairment are highlighted in studies of these groups of patients. A combination of genomics, imaging and functional studies is necessary for diagnosis (Saadi et al., 2023). While genomic progresses has enhanced disease identification and diagnostics of neurodegenerative disorders are still restricted in Pakistan, due to lack of adequate testing facilities, trained professionals and awareness. The genetic databases and access to the sequence will have to be broadened, as will as genetic counsellor services, to enable future targeted treatment and aid diagnosis.

Genotype–Phenotype Correlations and Molecular Pathways in Pakistani Inherited Brain Disorders

Patients with ADGRG1 mutations in Pakistan have contributed to understanding of the developmental mechanisms of the cortex and genotype–phenotype variability (Bae et al., 2014; Sawal et al., 2018). WDR62 is essential in the proliferation of neural progenitors and migration of neurons. Autosomal recessive primary microcephaly with cortical abnormalities and developmental impairment is caused by mutations. Sequencing, imaging and functional studies have been conducted simultaneously in Pakistan which has contributed to a better understanding of the mechanisms underlying the disease caused by the absence of WDR62 (Bilgüvar et al., 2010; Aslam et al., 2024). The mutations of FA2H result in lipid metabolism and myelin maintenance defects, and FAHN involves white matter abnormalities, ataxia, cognitive impairment, and spasticity. The identification of the variants of FA2H associated with HSP and neurodegeneration in progressive neurological diseases in Pakistan has been very few, so these variants are a need for genomic testing in progressive neurological diseases (Kruer et al., 2010; Azeem et al., 2024). Impairment of autophagy and neuronal maintenance is the cause of SPG11 related disease. The SPG11 variants have been found in Pakistani families with a variety of phenotypes such as spasticity, cognitive deficits, and progressive neurological deterioration. These findings agree with the role of genomic testing in the diagnosis of idiopathic juvenile onset spastic paraplegia (Stevanin et al., 2008).

The mutations of CLN5 result in a disorder called neuronal ceroid lipofuscinosis, which leads to epilepsy, mental retardation, visual problems and progressive degeneration of the nervous system. CLN5 variants have been identified in Pakistani families and extended knowledge of the mechanism of lysosomal pathology in inherited epilepsy and neurodegeneration has been gained (Mole et al., 2019; Muhammad et al., 2025). Homozygous variants have been reported to be associated with infantile epilepsy and intellectual disability. In Pakistan, family studies have shown the significance of WES to detect a rare recessive neurological disease (Rafiullah et al., 2016).

Table 3. Genotype–phenotype relationships and molecular pathways in inherited neurological disorders reported in Pakistani families

Gene or gene group	Normal biological role	Molecular consequence of pathogenic variation	Principal phenotype	Genotype-phenotype observation	Pakistani evidence
ADGRG1/GPR56	Neuronal migration, extracellular-matrix interaction, and cortical organization	Disrupted neuronal migration and abnormal cortical lamination	Bilateral frontoparietal polymicrogyria, intellectual disability, epilepsy, and motor impairment	Different recessive variants produce variable degrees of cortical malformation and neurological severity.	Sawal et al. (2018); Bibi et al. (2024)
WDR62	Mitotic-spindle organization, neural-progenitor proliferation, and neuronal migration	Reduced neuronal production and disrupted cortical development	Primary microcephaly, developmental delay, epilepsy, and cortical abnormalities	Phenotypic severity appears to depend on variant type and residual protein function.	Aslam et al. (2024)
LMAN2L	Endoplasmic-reticulum and Golgi protein trafficking	Abnormal glycoprotein processing and intracellular transport	Severe intellectual disability and infantile epilepsy	Recessive variation was associated with severe ID and early seizures in the reported family.	Rafiullah et al. (2016)

Gene or gene group	Normal biological role	Molecular consequence of pathogenic variation	Principal phenotype	Genotype-phenotype observation	Pakistani evidence
HACE1	Ubiquitination, protein quality control, oxidative-stress regulation, and cellular homeostasis	Disrupted protein degradation and neuronal stress responses	Intellectual disability, epilepsy, spasticity, and psychomotor impairment	The reported missense variant broadened the phenotype beyond isolated intellectual disability.	Usmani et al. (2024)
CNTN2 and CLCN4	Axonal organization, neuronal adhesion, and ion regulation	Disturbed neuronal communication and excitability	Epilepsy, intellectual disability, movement abnormalities, and sensory impairment	Variants may produce syndromic rather than isolated epilepsy.	Abdulkareem et al. (2023)
CARS2	Mitochondrial protein translation	Impaired mitochondrial protein synthesis and energy metabolism	Epilepsy, developmental impairment, spasticity, and progressive neurological dysfunction	Mitochondrial dysfunction may explain the multisystem and progressive phenotype.	Abdulkareem et al. (2023)
ARSA	Lysosomal sulfatide degradation and myelin maintenance	Sulfatide accumulation, demyelination, and neurodegeneration	Seizures, motor decline, cognitive impairment, and white-matter disease	Neurological progression may reflect the degree of residual enzyme activity.	Abdulkareem et al. (2023)
FA2H	Synthesis of hydroxylated fatty acids required for myelin integrity	Abnormal lipid metabolism and impaired myelin maintenance	Spastic paraplegia, ataxia, dystonia, cognitive decline, and white-matter abnormalities	Recurrent variation may indicate regional enrichment or founder effects.	Saadi et al. (2023); Azeem et al. (2024)

Gene or gene group	Normal biological role	Molecular consequence of pathogenic variation	Principal phenotype	Genotype-phenotype observation	Pakistani evidence
SPG11	Autophagic-lysosomal function and long-axon maintenance	Defective lysosomal recycling and progressive axonal degeneration	Juvenile spastic paraplegia, thin corpus callosum, cognitive impairment, and neuropathy	Variation produces substantial differences in onset and neurological complexity.	Bibi et al. (2024); Azeem et al. (2024)
SACS	Mitochondrial organization, cytoskeletal regulation, and neuronal maintenance	Progressive degeneration of cerebellar and peripheral neuronal systems	Ataxia, spasticity, neuropathy, and developmental impairment	Considerable overlap with HSP and other recessive ataxias complicates clinical diagnosis.	Saadi et al. (2023); Azeem et al. (2024)
GRM1	Metabotropic glutamate signalling and cerebellar synaptic plasticity	Impaired glutamate-mediated cerebellar signalling	Spinocerebellar ataxia, nystagmus, developmental delay, and intellectual disability	Frameshift variants causing major loss of function are associated with severe recessive phenotypes.	Ahmad et al. (2025)
NDD gene groups	Chromatin regulation, synaptic development, metabolism, neuronal migration, and intracellular transport	Pathway-specific disruption of brain development and neuronal connectivity	Broad developmental delay, intellectual disability, microcephaly, epilepsy, and movement disorders	Similar clinical phenotypes may result from genetically unrelated pathways.	Riazuddin et al. (2017); Paracha et al. (2024)

Diagnostic Challenges, Genetic Counselling, and Healthcare Limitations in Pakistan

While genomic research has seen great advances, in Pakistan today, precision medicine is not common. Some of the key challenges are limited molecular diagnostic facilities, high testing costs, a lack of genetic specialists, poor counselling services, a lack of

population-specific genomic databases, and a lack of healthcare coordination. The use of advanced genomic testing continues to be limited to a few research centers in cities. Poor laboratory infrastructure and capacity of bioinformatics cause long diagnostic journeys and late intervention. Many families unable to access molecular diagnosis due to high costs of sequencing, interpretation and follow-up testing.

There are also no reimbursement systems which further restrict access to genomic healthcare. Few trained genetic professionals to interpret and communicate the result of the genome. The demand for increase in genetic counselling services particularly in the communities of high consanguinity rate. Misrepresentation of populations in the global databases make the variants difficult to interpret. To improve the accuracy of the diagnosis, it is important to create Pakistani specific genomic resources. Ethical guidelines for privacy, informed consent, reproductive choices and responsible data usage are essential to the field of genomic medicine. Counselling is essential for effective implementation, and must be culturally sensitive. National registers for rare diseases and large-scale genomic networks need to be established to improve the epidemiological knowledge, patient referral networks and research potential.

Future Perspectives

In inherited neurological disorders the application of precision medicine provides new opportunities for earlier diagnoses improved prognosis and targeted treatment. In Pakistan, there is a need for the integration of genomic technologies, artificial intelligence, multi-omics and population-specific genomic resources to advance the country's growth and development. Genomic databases with allele frequency and clinical data as well as genotype–phenotype relationships from Pakistan are necessary in providing assistance in an interpretation of variants and uncertain diagnosis. AI-driven approaches can improve variant prioritisation through leveraging genomic, clinical and biological aspects.

The recruitment of computational genomic specialists in the local area will support the development of diagnostics. Better knowledge of disease mechanisms and discovery of therapeutic targets by the synergy of genomics and transcriptomics, proteomics, metabolomics and epigenomics. For genetically defined neurological disorders future treatment options exist, e.g. emerging gene replacement therapies, RNA-based therapies and genome editing. Early genetic diagnosis allows for possible treatment, particularly in severe neurologic conditions which can affect the child's development. More counseling will make families aware of inheritance patterns, recurrence risk and their options for reproduction. For sustainable genomic care, there must be a multidisciplinary precision neurology center where diagnosis, counseling, research and development of treatment meet. Responsible development of genomic medicine requires robust policies around privacy, consent and equitable access.

Research Priorities in Pakistan for the Future

Future work should be directed at national genomic sequencing projects to characterize the genetic diversity of Pakistanis and to identify disease variants unique to Pakistanis. Moreover, there is a need for more focus on functional validation of identified variants to understand their biological consequences and disease mechanisms. AI-driven diagnostic platforms can improve variant interpretation and help to make more accurate clinical decisions. Also, a national rare disease registry should be established to collect common clinical and genetic information from those individuals and families affected by rare diseases . Research in precision therapy needs to connect genetic discoveries with therapies such as gene-based, molecular and personalised therapies.

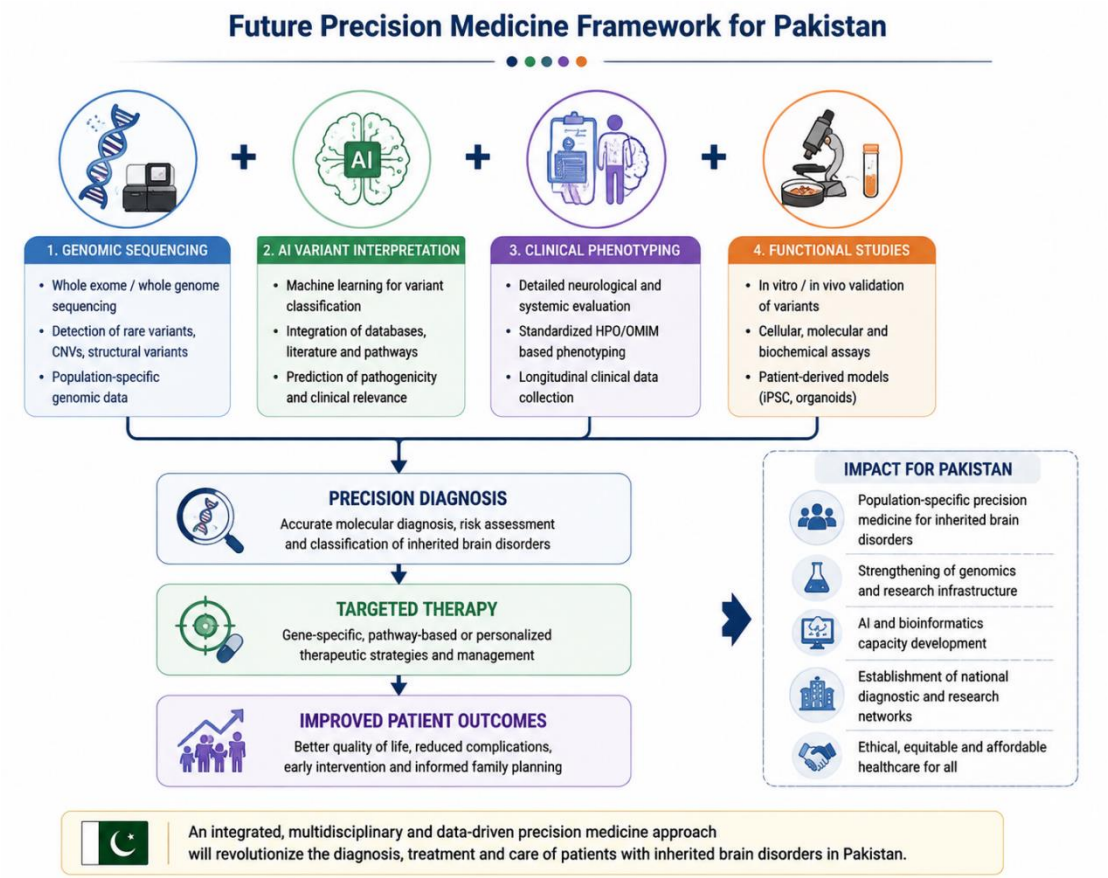

Figure 5. Future precision medicine framework for Pakistan integrating genomic sequencing, AI-assisted variant interpretation, clinical phenotyping, and functional validation to support precision diagnosis, targeted therapy, and improved patient outcomes.

Conclusion and Future Recommendations

Brain disorders are one of the major genetic and neurological problems in health care sector in Pakistan which are inherited. Next generation sequencing technologies revolutionized the knowledge of these diseases by identifying pathogenic variants, discovering new genes and genotype-phenotype correlation. The contribution of Pakistani families to the field of Global Neurological Genetics is significant due to the high prevalence of recessive disorders, unique population structure and large pedigrees. Additional barriers to translating genomic discovery into practice, however, include infrastructure, funding, lack of genetic professionals and inadequate genomic resources. Development of precision neurology in Pakistan requires the establishment of national genomic databases, rare disease registries, genetic counselling centers, multi-disciplinary centers and integration of AI and multi-omic technologies in the future. Future developments of precision neurology in Pakistan should include the development of national genomic databases, rare disease registries, genetic counselling services, multi-disciplinary centres and the integration of AI and multi-omic technologies. These approaches will be useful in helping to make diagnosis, allow individual treatment and will transform the inherited neurologic disease from unmanageable to clinically manageable.

References

Boycott, K. M., Ardigó, D., & others. (2019). International cooperation to enable the diagnosis of rare genetic diseases. *Nature Reviews Genetics*, *20*, 1–12.

Turro, E., Astle, W. J., Megy, K., Gräf, S., Greene, D., Shamardina, O., Ouwehand, W. H. (2020). Whole-genome sequencing of patients with rare diseases in a national healthcare system. *Nature*, *583*, 96–102.

Riazuddin, S., Hussain, M., Razzaq, A., Iqbal, Z., Shahzad, M., Polla, D. L., Riazuddin, S. (2017). Exome sequencing of Pakistani consanguineous families identifies 30 novel candidate genes for recessive intellectual disability. *Molecular Psychiatry*, *22*, 1604–1614.

Khan, A., Khan, S., Rehman, M. U., et al. (2022). NGS-driven molecular diagnosis of heterogeneous hereditary neurological disorders reveals novel and known variants in disease-causing genes. *Molecular Genetics and Genomics, 297*(6), 1601–1613.

Blackstone, C. (2018). Hereditary spastic paraplegia. *Handbook of Clinical Neurology*, *148*, 633–652.

Harripaul, R., Vasli, N., Mikhailov, A., Rafiq, M. A., Mittal, K., Windpassinger, C., Tzschach, A. (2018). Mapping autosomal recessive intellectual disability: Combined microarray and exome sequencing identifies 26 novel candidate genes in 192 consanguineous families. *Molecular Psychiatry*, *23*, 973–984.

Paracha, S. A., Nawaz, S., Tahir Sarwar, M., Shaheen, A., Zaman, G., Ahmed, J., Shah, F., Khwaja, S., Jan, A., Khan, N., Kamal, M. A., Alam, Q., Abbas, S., Farman, S., Waqas, A., Alkathiri, A., Hamadi, A., Santoni, F., Ullah, N., . . . Ansar, M. (2024). The genetic cause of neurodevelopmental disorders in 30 consanguineous families. Frontiers in Medicine, 11, 1424753.

Ahmad, R., & Naeem, M. (2025). A systematic review of hereditary neurological disorders diagnosed by whole exome sequencing in Pakistani population: Updates from 2014 to November 2024. *Neurogenetics*, *26*(1), Article 40.

Bibi, A., Ji, W., Jeffries, L., Zerillo, C., Konstantino, M., Mis, E. K., Khursheed, F., Khokha, M. K., Lakhani, S. A., & Malik, S. (2024). Exome sequencing reveals genetic heterogeneity in consanguineous Pakistani families with neurodevelopmental and neuromuscular disorders. American Journal of Medical Genetics Part C: Seminars in Medical Genetics, 196(4), e32103.

Azeem, A., Ahmed, A. N., Khan, N., Voutsina, N., Ullah, I., Ubeyratna, N., Yasin, M., Baple, E. L., Crosby, A. H., Rawlins, L. E., & Saleha, S. (2024). Investigating the genetic basis of hereditary spastic paraplegia and cerebellar ataxia in Pakistani families. BMC Neurology, 24, Article 354.

Sawal, H. A., Harripaul, R., Mikhailov, A., Vleuten, K., Naeem, F., Nasr, T., Hassan, M. J., Vincent, J. B., Ayub, M., & Rafiq, M. A. (2018). Three mutations in the bilateral frontoparietal polymicrogyria gene GPR56 in Pakistani intellectual disability families. Journal of Pediatric Genetics, 7(2), 60–66.

Vissers, L. E. L. M., Gilissen, C., & Veltman, J. A. (2016). Genetic studies in intellectual disability and related disorders. *Nature Reviews Genetics*, *17*, 9–18.

Usmani, M. A., Ghaffar, A., Shahzad, M., Akram, J., Majeed, A. I., Malik, K., Fatima, K., Khan, A. A., Ahmed, Z. M., Riazuddin, S., & Riazuddin, S. (2024). A missense variant in HACE1 is associated with intellectual disability, epilepsy, spasticity, and psychomotor impairment in a Pakistani kindred. Genes, 15(5), 580.

Rafiullah, R., Aslam, M., Kuss, A. W., Ishaq, M., Khan, F. S., Ali, G., Ahmad, W. (2016). Homozygous missense mutation in the LMAN2L gene segregates with intellectual disability in a large consanguineous Pakistani family. *Journal of Medical Genetics*, *53*(2), 138–144.

Saadi, S. M., Cali, E., Khalid, L. B., Yousaf, H., Zafar, G., Khan, H. N., Sher, M., Vona, B., Abdullah, U., Malik, N. A., Klar, J., Efthymiou, S., Dahl, N., Houlden, H., Toft, M., Baig, S. M., Fatima, A., & Iqbal, Z. (2023). Genetic investigation of consanguineous Pakistani families segregating rare spinocerebellar disorders. Genes, 14(7), 1404.

Ahmad, R., Sayyad, F., Naeem, M., & Houlden, H. (2025). Report of a novel missense TDP1 variant in a Pakistani family affected with congenital spinocerebellar ataxia with axonal neuropathy type 1 (SCAN1). *Molecular Biology Reports, 52*, Article 7.

Lander, E. S., & Botstein, D. (1987). Homozygosity mapping: A way to map human recessive traits with the DNA of inbred populations. *Science, 236*(4808), 1567–1570.

Yang, Y., Muzny, D. M., Xia, F., Niu, Z., Person, R., Ding, Y., Lupski, J. R. (2014). Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA, 312*(18), 1870–1879.

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Rehm, H. L. (2015). Standards and guidelines for the interpretation of sequence variants. *Genetics in Medicine, 17*, 405–424.

Smedley, D., Smith, K. R., Martin, A., Thomas, E. A., McDonagh, E. M., Cipriani, V., Wright, C. F. (2022). 100,000 Genomes Pilot on rare disease diagnosis: Applications of genome sequencing in clinical medicine. *Nature Genetics, 54*, 110–119.

Ahsan, N., Ahmad, A., Hussain, S., Fatima, N., Yousafzai, I. K., Kalsoom, U. E., Dad, R., & Hassan, M. J. (2025). Identification of mutations in five Pakistani families with epilepsy. Neurogenetics, 26(1), Article 44.

Afzal, M. A., Shahzadi, N., Saadat, S., Seemab, R., Sajjad, I., Tariq, N., Ashraf, S. R., Tahir, S., & Kharl, H. A. (2025). CRISPR-Cas9 genome-editing technology: A transformative tool for curing human disorders. *Journal of Medical & Health Sciences Review, 2*(3).

McKnight, D., Morales, A., & Muir, A. (2021). Genetic testing approaches for epilepsy diagnosis and precision treatment. *Epilepsy Research, 170*, 106560.

Miller, D. T., Adam, M. P., Aradhya, S., Biesecker, L. G., Brothman, A. R., Carter, N. P., Ledbetter, D. H. (2010). Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities. *American Journal of Human Genetics, 86*(5), 749–764.

Landrum, M. J., Lee, J. M., Benson, M., Brown, G., Chao, C., Chitipiralla, S., … Maglott, D. R. (2018). ClinVar: Improving access to variant interpretations and supporting evidence. *Nucleic Acids Research, 46*(D1), D1062–D1067.

Aslam, K., Saeed, A., Saeed, H. I., Bashir, R., Abid, H., Akhtar, R., Habib, N., Khan, R., Asif, R., Rafiq, S., Asif, M., Makhdoom, E. U. H., Hussain, M. S., Baig, S. M., & Anjum, I. (2024). Molecular genetics, neuroimaging outcomes, and structural analyses of novel and recurrent variants of WDR62 gene in two consanguineous Pakistani families with autosomal recessive primary microcephaly. Molecular Biology Reports, 51(1), Article 783.

Kaufman, L., Ayub, M., & Vincent, J. B. (2022). The genetic basis of intellectual disability: New insights from genomic sequencing. *Human Genetics, 141*, 1–18.

Satterstrom, F. K., Kosmicki, J. A., Wang, J., Breen, M. S., De Rubeis, S., An, J. Y., Buxbaum, J. D. (2020). Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. *Cell, 180*(3), 568–584.e23.

Fatima, S., Chikowore, T., Choudhury, A., Ayub, M., Martin, A. R., & Kuchenbaecker, K. (2022). A roadmap to increase diversity in genomic studies. Nature Medicine, 28(2), 243–250.

Scheffer, I. E., Berkovic, S., Capovilla, G., Connolly, M. B., French, J., Guilhoto, L., Zuberi, S. M. (2017). ILAE classification of the epilepsies: Position paper of the International League Against Epilepsy Commission for Classification and Terminology. *Epilepsia, 58*(4), 512–521.

Muhammad, A., Inayat, F., Sethi, B. A., Kashif, M., Khan, A. U., Ahmad, S., Atlas, A., Rehman, S. U., & Sarwar, M. T. (2025). Genomic insights into autosomal

recessive epilepsy: Novel pathogenic variants in ITPA and CLN5 identified in consanguineous families. Molecular Biology Reports, 52, Article 952.

Zuberi, S. M., Wirrell, E., Yozawitz, E., Wilmshurst, J. M., Specchio, N., Riney, K., Scheffer, I. E. (2022). ILAE classification and definition of developmental and epileptic encephalopathy with onset in infancy and childhood. *Epilepsia, 63*(6), 1349–1397.

McTague, A., Howell, K. B., Cross, J. H., Kurian, M. A., & Scheffer, I. E. (2016). The genetic landscape of the epileptic encephalopathies of infancy and childhood. *The Lancet Neurology, 15*(3), 304–316.

Oyrer, J., Maljevic, S., Scheffer, I. E., Berkovic, S. F., Petrou, S., & Mullen, S. A. (2018). Ion channels in genetic epilepsy: From genes and mechanisms to therapeutic targets. *Pharmacological Reviews, 70*(1), 142–173.

Abdulkareem, A. A., Zaman, Q., Khan, H., Khan, S., Rehman, G., Tariq, N., … Muthaffar, O. Y. (2023). Whole exome sequencing identified five novel variants in CNTN2, CARS2, ARSA, and CLCN4 leading to epilepsy in consanguineous families. *Frontiers in Genetics, 14*, 1185065.

Pearson, T. S., Akman, C., & Hacohen, Y. (2020). Inherited metabolic epilepsies: Clinical and genetic perspectives. *Neurology Genetics, 6*(3), e421.

Klein, C., & Mazzulli, J. R. (2019). Genetics of neurodegenerative disorders. *Current Opinion in Neurology, 32*(4), 1–8.

Fatima, T., Sajjad, I., Qamar, M., Afzal, M. A., Noor, N., Tariq, N., Yawar, A., Abbasi, A. J., Rahim, F., Farooq, M. U., Noor, M., & Zahid, I. (2026). The expanding role of artificial intelligence in health, life, and applied sciences: A multidisciplinary review. *Social Science Review Archives, 4*(2), 237–257.

Stevanin, G., Santorelli, F. M., Azzedine, H., Coutinho, P., Chomilier, J., Denora, P. S., Brice, A. (2008). Mutations in SPG11, encoding spatacsin, are a major cause of autosomal recessive spastic paraplegia with thin corpus callosum. *Nature Genetics, 39*, 366–372.

Bae, B. I., Tietjen, I., Atabay, K. D., Evrony, G. D., Johnson, M. B., Asare, E., … Walsh, C. A. (2014). Evolutionarily dynamic alternative splicing of GPR56 regulates human cortical development. *Science, 343*(6170), 764–768.

Bilgüvar, K., Oztürk, A. K., Louvi, A., Kwan, K. Y., Choi, M., Tatli, B., … Günel, M. (2010). Whole-exome sequencing identifies recessive WDR62 mutations in severe brain malformations. *Nature, 467*, 207–210.

Kruer, M. C., Paisán-Ruiz, C., Boddaert, N., Yoon, W., Hama, H., Gregory, A., Gitschier, J. (2010). Defective FA2H leads to a novel form of neurodegeneration with brain iron accumulation. *Brain, 133*(12), 3310–3319.

Mole, S. E., Williams, R. E., & Goebel, H. H. (2019). Correlations between genotype, phenotype, and disease progression in neuronal ceroid lipofuscinosis. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1865*(4), 113–125.