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Advances in chromosomal microarray analysis: Transforming neurology and neurosurgery

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ABSTRACT

Over the past two decades, genomics has transformed our understanding of various clinical conditions, with Chromosomal Microarray Analysis (CMA) standing out as a key technique. Offering unparalleled sensitivity, CMA detects submicroscopic chromosomal imbalances, enabling the examination of DNA for copy number variations, deletions, duplications, and other structural differences. In neurology, CMA has revolutionised diagnoses, personalised treatment plans, and patient outcomes. By identifying genetic anomalies linked to neurological conditions, CMA allows clinicians to tailor treatments based on individual genetic profiles, enhancing precision medicine. CMA's clinical utility spans numerous neurological conditions, providing crucial insights into neurodevelopmental disorders, CNS tumours, neurodegenerative diseases, cerebrovascular diseases, and epilepsy. In neurodevelopmental disorders, CMA aids in diagnosing autism and intellectual disabilities, facilitating early interventions that improve long-term outcomes. In epilepsy, CMA helps identify genetic causes of drug-resistant seizures, enabling more targeted therapies and reducing adverse reactions. CMA also aids in stratifying risk for cerebrovascular diseases, enabling preventive interventions that improve patient prognosis. Despite its potential, challenges remain, such as interpreting variants of uncertain significance (VOUS), the lack of standardised testing guidelines, and issues of cost and accessibility. Addressing these challenges will optimise CMA's impact, advancing personalised medicine and reshaping neurology. This review discusses CMA's pivotal role in bridging the gap between genomics and clinical practice, underscoring its potential to transform neurogenetics and ultimately improve patient care.

1. Introduction

Neurological conditions, encompassing a broad spectrum of conditions affecting the brain, spinal cord, and peripheral nerves, are now the leading cause of ill health and disability, affecting more than 3 billion people worldwide (Huang et al., 2023). Due to their heterogeneous manifestations, multifactorial aetiology, and varying degrees of severity, they present a significant challenge for researchers and clinicians. Moreover, neurological conditions have profound societal implications,

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Abbreviations

CMA	Chromosomal microarray analysis
CNV	Copy number variations
CGH	Comparative genomic hybridization
SNP	single nucleotide polymorphism
aCGH	array-comparative genomic hybridization
CNS	Central nervous system
ASD	autism spectrum disorder
DD/ID	developmental delay/intellectual disability
MCA	Multiple congenital anomalies
WES	Whole exome sequencing
GBM	Glioblastoma multiformes
PD	Parkinson's disease
ICAM1	Intercellular Adhesion Molecule
AD	Alzheimer's disease
SVD	small vessel disease
SNVs	single-nucleotide variants
VRFs	Vascular risk factors
CAD	Coronary artery disease
PCR	polymerase chain reaction
MMPs	matrix metalloproteinases
TIMP-3	Tissue inhibitor of matrix metalloproteinases 3
iNOS	Nitric oxide synthase
JME	juvenile myoclonic epilepsy
CAE	childhood absence epilepsy
FISH	Fluorescence in Situ Hybridization
VOUS	Variants of Uncertain Clinical Significance

contributing substantially to the global burden of disease (Ningrum and Kung, 2023).

Over the last two decades, chromosomal microarray analysis (CMA) stands out as a powerful advancement in genomic technology that has revolutionised our knowledge of clinical conditions, allowing researchers to identify the genes implicated in the pathogenesis and progression of these conditions (Ningrum and Kung, 2023). By enabling the identification of genetic abnormalities with unprecedented resolution, CMA has reshaped the diagnostic landscape for neurological conditions, allowing for earlier, more accurate diagnoses and tailored therapeutic strategies that directly benefit patients.

The two fundamental techniques employed in CMA, comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) arrays, enable the detection, visualisation, and analysis of copy number variations (CNVs) and variations in single nucleotides across the genome, offering high-resolution insights into the genetic anomalies associated with these conditions. Unlike conventional cytogenetic methods, which are labour-intensive with a relatively low yield due to restraints in their capacity to identify small genetic alterations, CMA offers exceptional sensitivity and specificity. By studying DNA samples extracted from patient tissues, CMA can perceive CNVs, deletions, and duplications as small as 10 kb, up to 1000 times higher than that of conventional karyotyping (Batzir et al., 2015). This high-resolution capability ensures that genetic causes of neurological conditions are identified more quickly, allowing for faster and more precise itnerventions that can dramatically improve patient outcomes.

CMA has also proven to be exceedingly capable of identifying new microdeletions, microduplications, and new loci for novel candidate genes in patients with neurological conditions (Ceylan et al., 2018). Studies investigating the clinical application of CMA in neurology have demonstrated a high diagnostic yield, customised treatment strategies, and better patient outcomes (Miller et al., 2010). Additionally, CMA is pivotal in guiding therapeutic interventions for patients with complex neurological conditions. By identifying genetic drivers of disease progression and susceptibility, CMA provides clinicians with critical insights that shape therapeutic decisions (Adam et al., 2009). In neurodegenerative diseases (NDs), CMA's ability to elucidating the molecular pathways and significant genetic risk factors associated with disease progression allows for the early introduction of disease-modifying treatments (Madrid et al., 2021). This precision in treatment planning not only helps delay the onset of symptoms but also improves long-term quality of life for patients. The identification of specific biomarkers has been instrumental in the development of targeted therapies, offering patients treatments that are tailored to their genetic make-up, leading to more effective and less invasive therapeutic approaches.

Despite its transformative impact, CMA also faces several challenges in the context of neurological research and clinical practice (Coughlin et al., 2012). One major challenge is interpreting the large volume of data and distinguishing clinically significant genetic variations from those of uncertain significance (Miller et al., 2010). The absence of standardised guidelines for CMA testing in neurology results in variability between laboratories, leading to inconsistent interpretations of the data. (Muys et al., 2020; Liu et al., 2022). The high cost and need for specialised expertise also limit its widespread use, especially in resource-limited settings (Miller et al., 2010). These issues highlight the need for continued refinement and integration of CMA with other genomic tools. The aim of this review is to comprehensively discuss the neurological applications of CMA, explore its use across a diverse range of medical conditions, and elucidate its ability to reshape the landscape of neurogenetics. Furthermore, this paper aims to establish the position of CMA as a cornerstone technology in bridging the gap between genomics and clinical practice, offering new avenues for understanding, diagnosing, and targeting therapies for neurological and neurosurgical conditions.

2. Methodology

This narrative review seeks to comprehensively assess the role of CMA in neurology and neurosurgery, employing specific inclusion and exclusion criteria to ensure a thorough analysis. Inclusion criteria encompassed full-text articles in English published between 2000 and 2025, chosen to allow a comprehensive evaluation of established practices and capture significant advancements over an extended period. Multiple databases, including PubMed, EMBASE, the Cochrane Library, and Scopus, underwent comprehensive searches to establish an extensive literature base.

Utilising key search terms such as "CMA" in conjunction with "chromosomal microarray analysis," "neurology," "neurosurgery," and "neuroscience" ensured the inclusion of pertinent articles. In addition to the systematic database search, a manual examination of references cited in recent CMA-related reviews identified supplementary sources. Exclusion criteria were applied to exclude standalone abstracts, case reports, narrative reviews, editorials, books, posters, and unpublished or non-peer-reviewed studies, prioritizing high-quality, reliable evidence.

The review's scope did not impose restrictions on the number of included studies, aiming for a comprehensive understanding and encompassing diverse study designs. The review integrates descriptive studies, animal-model studies, cohort studies, and observational studies, providing a holistic perspective on the application of CMA. Both preclinical and clinical studies were incorporated to broaden the scope of knowledge covered in this review. A summary of the review's methodology is depicted in Table 1.

Table 1
Summary of Methodology for this Review.

Methodology Steps	Description
Literature Search	PubMed, EMBASE, Google Scholar, the Cochrane Library, and Scopus
Inclusion Criteria	- Full-text articles published in English - Publication date range: 2000–2024 - Focus on Chromosomal microarray analysis encompassing study designs: ● Descriptive studies ● Animal-model studies ● Cohort studies ● Observational studies - Including investigations in both pre-clinical and clinical settings
Exclusion Criteria	- Standalone abstracts - Case reports - Posters - Unpublished or non-peer-reviewed studies - Narrative Reviews - Editorials/commentaries - Books and book chapters
Search Terms	Key search terms such as "CMA" were used alongside "chromosomal microarray", "Neurology", "Neurosurgery", and "Neuroscience"
Additional Search	- Manual examination of references cited in recent disease-specific systematic reviews and meta-analysis - No predetermined limit on the number of studies

3. Types and functional process of CMA

CMA is a molecular technique that is increasingly used in the prenatal diagnosis of chromosomal abnormalities, which can include abnormalities in chromosomal numbers (aneuploidies or polyploidies) or smaller insertions and deletions, such as CNVs. The technique is reported to be highly sensitive by identifying most abnormalities detected by other cytogenetic tests while having a high resolution.

There are two main types of CMA: (i) CGH and (ii) SNP (Levy and Wapner, 2018). CGH arrays involve cutting the DNA samples from patients and controls into smaller fragments. These fragments are then incubated with different fluorescent dyes. These fluorescent dye-incorporated samples are then mixed in equal proportions. This specimen is then introduced onto a glass slide (array) with probes that have a complementary sequence of different segments across the human genome. The introduced sample binds to the probe on the microarray, with which it has high sequence complementarity. Since the samples are labelled with fluorescent dyes, the fluorescent intensity of every probe can be detected using imaging software (Redon et al., 2009). The ratio of fluorescence intensities between a test sample and a control sample is then compared. Where the ratio is greater than 1, indicating a greater amount of a particular sequence in the test sample than the control sample, it could indicate a possible duplication of genetic material. Conversely, where the ratio is less than one, it could indicate a potential deletion of genetic material (Levy and Wapner, 2018). Comparing the ratio of genetic material across the whole human genome, it is possible to deduce if whole chromosomes are duplicated or lost (as in aneuploidies), particular segments of chromosomes are duplicated or deleted, or chromosomal translocation has occurred. Resultantly, CGH arrays can be particularly impactful in diagnosing genetic causes of developmental delays, intellectual disabilities, autism spectrum disorders, and congenital anomalies.

Another form of CMA is the SNP microarray. With this particular type, instead of using probes across any part of the human genome as in the CGH form of CMA, specific probes from DNA loci that are known to vary across individuals are used (Beaudet and Belmont, 2008). Considering that the human genome is 99.9% identical across any two individuals, SNP microarrays use a subset of possible probes (Collins and Mansoura, 2001). In this method, only the DNA from the test patient sample is labelled with fluorescent markers and hybridised to probes on the array. By comparing the fluorescence intensity of the patient's sample upon hybridization on the array compared to normalised samples, changes in copy number can be identified. SNP microarrays can also aid in the identification of uniparental disomy, consanguinity, mosaicism, and triploidy (Levy and Wapner, 2018). For example, identifying uniparental disomy (UPD) can uncover imprinting disorders such as Prader-Willi syndrome or Angelman syndrome.

4. The application of CMA in neurological and neurosurgical diseases management

4.1. Neurodevelopmental disorders

CMA, including array-comparative genomic hybridisation (aCGH) and SNP-array, has become the gold standard for detecting CNVs in clinical settings, providing significant translational benefits for patients. It offers a substantially higher diagnostic yield (15–20%) compared to traditional G-banded karyotype (~3%) and is recommended as the first-tier cytogenetic test for patients with unexplained neurodevelopmental delays/intellectual disability, autism spectrum disorders, or multiple congenital anomalies (Miller et al., 2010). For autism, a study conducted over four years with CMA testing underscores its critical role in diagnosing neurodevelopmental disorders. Specifically, the study reported a CNV detection rate of 28.1% across 10,351 patients, which increased to 33% in those with developmental delay/intellectual disability (DD/ID) and/or multiple congenital anomalies (MCA). The rate for ASD patients stood at 24.4%, indicating the substantial role CNVs play in its aetiology and providing insights into ASD's genetic landscape, which can directly inform patient management strategies (Ho et al., 2016).

Furthermore, CMA has proven its utility in diagnosing patients with cerebral palsy (CP), revealing pathogenic CNVs in a significant proportion of cases, emphasising genetic factors in CP aetiology. This enables clinicians to offer more accurate diagnoses and personalised management plans, improving the quality of care for affected patients (Vanzo et al., 2019). However, the modest 5% diagnostic yield in a meta-analysis on CP indicates the limitations of CMA in this context (Srivastava et al., 2022), which can be addressed by incorporating complementary technologies like trio whole exome sequencing (WES).

Combined CMA and WES have shown a diagnostic success rate of 58%, highlighting the potential for more precise genetic diagnoses in cryptogenic CP cases and enabling the development of personalised treatment approaches (Yechieli et al., 2022). The diagnostic yield was significantly higher in CP patients with additional comorbidities (69%) compared to those with only motor symptoms (31%), indicating greater genetic complexity in the former group. This enhanced yield in patients with comorbidities and congenital anomalies further emphasises the importance of CMA in guiding anticipatory care, allowing for more personalised genetic counseling and management strategies that can improve patient outcomes. The higher yield in CP patients with comorbidities and congenital anomalies further underscores CMA's role in guiding anticipatory care and improving patient outcomes through tailored genetic counseling and management strategies (Yechieli et al., 2022). This direct application of CMA in clinical practice not only enhances diagnostic accuracy but also provides patients and their families with better-informed decisions, ultimately contributing to improved long-term health outcomes. Fig. 1 illustrates a graphical representation of the role of CMA in neurodevelopmental disorders such as ASD and CP.

4.2. CNS tumours

CMA significantly contributes to both the diagnosis and management of CNS tumours, offering a comprehensive understanding of genetic abnormalities that directly impact patient care. In diagnosing CNS tumours, CMA allows for the identification of genetic alterations such as gene amplifications, deletions, and chromosomal gains or losses, which

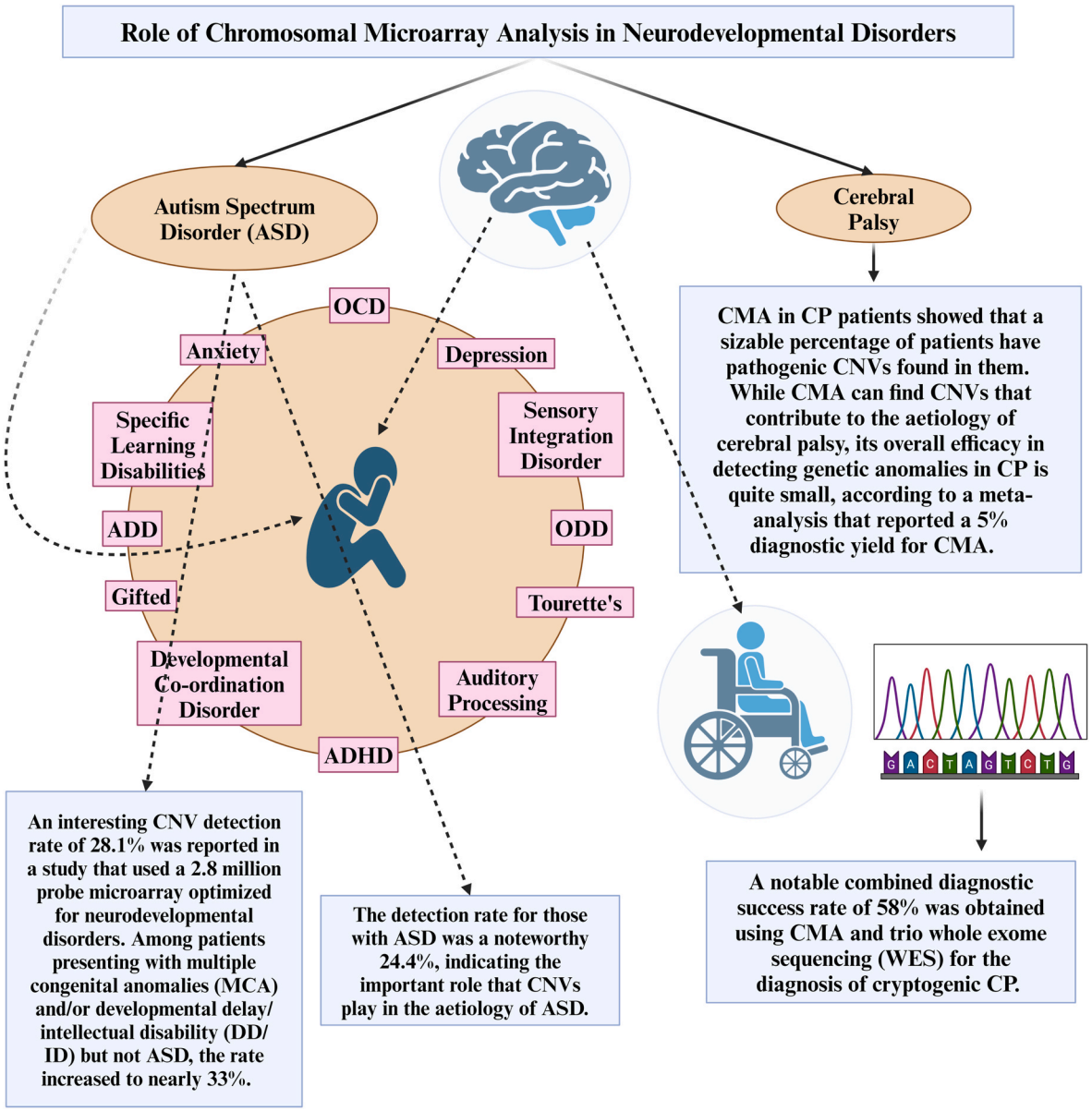

Fig. 1. The role of Chromosomal microarray analysis in neurodevelopmental disorders
Abbreviations: ASD: Autism Spectrum Disorder; OCD: Obsessive-compulsive Disorder; ADD: Attention Deficit Disorder; ODD: Oppositional Defiant Disorder; ADHD: Attention Deficit Hyperactivity Disorder; CMA: Chromosomal Microarray Analysis; CP: Cerebral Palsy; CNVs: Copy Number Variations; DD/ID: Developmental Delay/Intellectual Disability; WES: Whole Exome Sequencing.

are crucial for determining the tumour's genetic profile. For instance, amplifications of *RFC2* and *CYLN2* in glioblastoma multiformes (GBMs) and deletions of *FGFR2* have been identified through CMA, facilitating more accurate diagnoses and guiding treatment strategies tailored to each patient's unique tumour biology (Suzuki et al., 2004).

CMA has proven instrumental in uncovering unique genetic differences that distinguish between tumour types, improving diagnostic precision and guiding management decisions. For example, in spinal and intracranial meningiomas, CMA identified 1555 genes with differential expression, of which 35 genes exhibited distinct profiles, enabling clear differentiation between these tumour types and providing novel insights into their clinical and histological features (Sayagués et al., 2006). Additionally, CMA identified homozygous deletions in chromosome 22 linked to spinal cord tumours, highlighting pathways that contribute to tumour development and potentially offering new therapeutic targets. These findings directly inform clinical practices, such as refining surgical approaches or selecting targeted therapies, to optimise patient outcomes.

In ependymomas, CMA has revealed specific chromosomal aberrations correlated with location, histological subtype, and tumour grade, significantly enhancing diagnostic capabilities (Rousseau et al., 2010). By providing a molecular profile of these tumours, CMA enables clinicians to implement personalised treatments, including the potential use of targeted therapies under development for specific molecular subtypes. A recent study showcased a combination of radiation and chemotherapy specifically designed for posterior fossa group A ependymomas with gains in chromosome 1, underscoring CMA's role in driving subtype-specific therapies (Griesinger et al., 2024). Furthermore, studies argue for additional trials on management strategies, such as therapy de-escalation based on molecular subtypes identified through CMA, to reduce treatment-related morbidity while maintaining efficacy (Routman et al., 2019).

CMA has also advanced therapeutic interventions in other CNS tumours. For GBMs, CMA has not only validated previously recognised

chromosomal regions but also revealed novel loci implicated in disease pathogenesis, contributing to our understanding of underlying mechanisms (Sayagués et al., 2006; Persson et al., 2007). The identification of molecular subsets with varying survival rates supports the development of gene-based predictors that help clinicians administer targeted therapies and monitor therapeutic response more effectively (Mischel et al., 2004). CMA-assisted research has highlighted genetic pathways and protein networks, such as those involving Wnt/APC and Shh/PTCH in medulloblastomas, which pave the way for innovative treatments (Kagawa et al., 2006; Wang et al., 2020).

Risk stratification in medulloblastomas, enabled by CMA, has been instrumental in personalising patient care. Studies like the SJMB03 trial and "Head Start" 4 have used CMA to classify subtypes, guiding therapeutic decisions that reduce treatment toxicity while improving survival rates (Gajjar et al., 2021; Dhall et al., 2021). CMA's identification of chromosomal abnormalities, such as the 1q/19q co-deletion in oligodendrogliomas, has also provided clinicians with robust prognostic markers, enabling predictions of treatment response and long-term outcomes (Turkheimer et al., 2006). Technological advancements in CMA, such as high-density arrays and SNP arrays, have further improved its resolution and sensitivity, enabling the detection of smaller genetic alterations and mosaicism within tumours. This increased precision allows for earlier diagnoses, timely intervention, and more effective monitoring of therapeutic outcomes. The ability to detect tumour-related genetic alterations at earlier stages significantly enhances patient prognosis by enabling interventions before the disease progresses.

Moreover, CMA has proven valuable in identifying genetic profiles in rare CNS tumours such as spinal meningiomas and ependymomas. For instance, studies have demonstrated how CMA's detection of specific chromosomal alterations, such as loss of chromosome 22q and amplification of MSH2, informs not only diagnosis but also the identification of dysregulated pathways that could be therapeutically targeted (Wada et al., 2005). These molecular insights allow for more precise therapeutic interventions, improving patient care across a spectrum of CNS tumours.

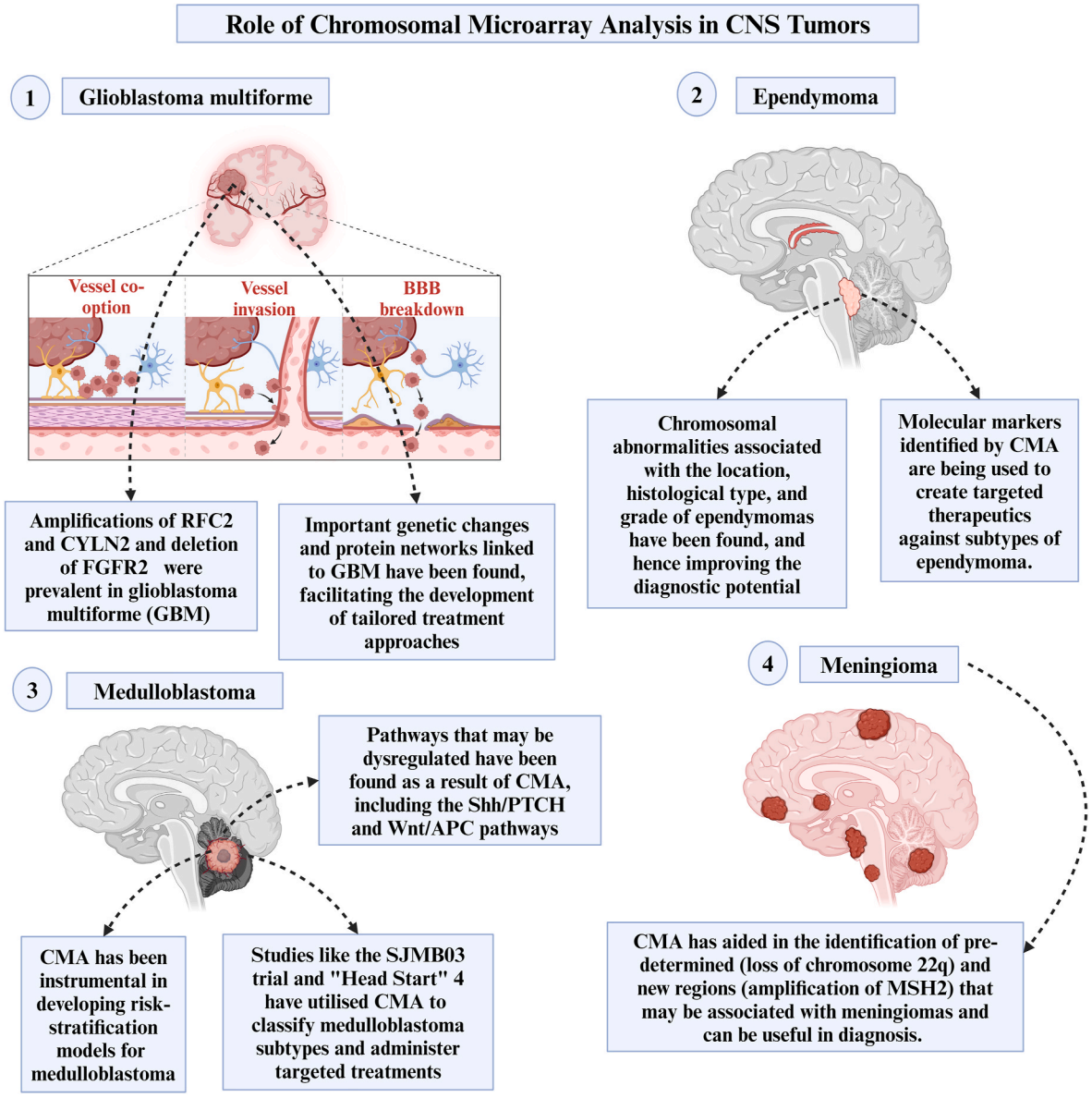

Fig. 2. The role of Chromosomal microarray analysis in CNS tumours.
Abbreviations: BBB: Blood-Brain Barrier; CNS: Central Nervous System; Blood-Brain Barrier; GBM: Glioblastoma Multiformes; CMA: Chromosomal Microarray Analysis.

In summary, CMA bridges the gap between research and patient care by identifying actionable genetic alterations that redefine the clinical management of CNS tumours. It empowers clinicians to make data-driven decisions, ranging from precise diagnostics to personalised treatment strategies and the development of targeted therapies. These advances translate directly into improved survival rates, reduced treatment-related toxicity, and better overall patient outcomes, establishing CMA as an indispensable tool in modern neuro-oncology. Fig. 2 portrays a graphical representation of the role of CMA in CNS tumours.

4.3. Neurodegenerative diseases

CMA has revolutionised our comprehension of the genetic complexities underlying NDs, surpassing the capabilities of traditional methods and offering profound insights. By enabling precise detection of CNVs and structural alterations, CMA has illuminated the intricate genetic landscape of these conditions, leading to actionable clinical advancements.

In Parkinson's disease (PD), CMA-based SNP analysis has uncovered 819 differentially expressed genes, shedding light on both upregulated and downregulated genes. Further investigation has pinpointed specific microRNAs and Intercellular Adhesion Molecule 1 (*ICAM1*) as contributors to PD pathogenesis, elucidating key pathways and potential therapeutic targets (Tan et al., 2018). These findings enable the identification of biomarkers for early diagnosis and pave the way for therapies targeting *ICAM1* or microRNAs to modify disease progression. Additionally, a meta-analysis of genome-wide association studies (GWAS) identified significant SNPs associated with PD susceptibility, such as those in the *SCNA* gene, which is crucial for synaptic function, neuronal development, and mitochondrial biology (Nalls et al., 2014). Clinically, these discoveries enhance diagnostic precision, allowing for earlier intervention and the development of gene-targeted therapies aimed at mitigating synaptic dysfunction and mitochondrial damage.

For Alzheimer's disease (AD), comparative microarray technology has unveiled deregulated pathways related to RNA splicing and chromatin remodelling in AD patients' brains compared to healthy individuals. This analysis also highlighted altered expression patterns of genes associated with AD's pathological hallmarks, such as tau, β-amyloid, and oxidative stress, deepening our understanding of the disease's pathogenesis (Ricciarelli et al., 2004). Translationally, these discoveries provide a foundation for developing therapies aimed at modulating RNA splicing or chromatin remodelling pathways to delay disease onset or progression. Genetic studies exploring interactions between genetic loci and the *APOE ε4* genotype in AD have significant therapeutic implications. For example, targeting *APOE ε4*-modulated pathways could yield interventions capable of showing neurodegeneration, directly benefiting patients by preserving cognitive function and delaying the transition to advanced stages of the disease (Serrano-Pozo et al., 2021).

In Huntington's disease (HD), GWAS have identified genetic modifiers influencing disease onset and progression, particularly DNA maintenance gene loci. This research provides crucial insights into the genetic factors contributing to clinical variability in HD, supporting personalised medicine approaches that account for individual genetic backgrounds (Genetic Modifiers of Huntington's Disease Consortium, 2015; Bettencourt et al., 2016). Additionally, the investigation of rare CNVs in ALS patients via CMA has uncovered several CNVs significantly associated with ALS, implicating them in disease susceptibility or progression. Notably, mutations in key ALS-associated genes such as *C9orf72*, *SOD1*, *TARDBP*, and *FUS* have been identified, elucidating the multistep nature of ALS and underlying pathogenic mechanisms (Chiò et al., 2018). These discoveries enable earlier and more precise genetic testing for both HD and ALS, allowing clinicians to identify patients who may benefit from specific interventions, such as emerging antisense oligonucleotide therapies targeting C9orf72 repeat expansions in ALS or modulators of DNA repair pathways in HD (Chiò et al., 2018). Furthermore, these genetic insights support risk stratification in clinical trials, ensuring patients most likely to benefit from experimental therapies are included, thereby accelerating the development of targeted treatments. Fig. 3 presents a graphical representation of the role of CMA in neurodegenerative diseases.

4.4. Cerebrovascular diseases

Microarray technology has revolutionised our understanding of cerebrovascular diseases (CVDs) by providing a comprehensive view of gene expression patterns and chromosomal aberrations associated with conditions such as stroke, intracerebral haemorrhage (ICH), and cerebral aneurysms (Grond-Ginsbach et al., 2018; Pfeiffer et al., 2019). By uncovering molecular mechanisms through the analysis of gene expression profiles and chromosomal variations, microarray studies have paved the way for identifying therapeutic targets, enabling early interventions, and personalising treatment approaches tailored to individual patients (Szuhai and Vermeer, 2015; Onda et al., 2001).

One of the pivotal revelations from microarray analysis is the identification of genetic factors linked to stroke, particularly in the context of cerebral infarction (Ritz et al., 2016). Ritz's study aimed to investigate the cellular pathways underlying cerebral small vessel disease (SVD) through gene expression microarray analysis of postmortem brain tissues. The study discovered significant expression changes, with over 228 differentially expressed genes in the cortex of which 89 were upregulated and 139 down regulated (Ritz et al., 2016). The down regulated genes were associated with principal neuronal functions which contributed to understanding the pathogenesis of the condition. Furthermore, the study identified 555 differentially expressed genes in the white matter, with alterations including 223 upregulated genes associated with inflammation and apoptosis in white matter, alongside 332 downregulated genes indicative of coagulation and metabolic process disturbances (Ritz et al., 2016). These findings suggest the potential for targeted therapies that mitigate inflammation or restore neuronal function, with applications in slowing disease progression or improving outcomes in patients with ischaemic stroke.

Further studies have outlined the genetic predisposition to intracranial atherosclerotic disease (ICAD), especially among East Asian populations. Through genome sequencing of symptomatic ICAD patients, researchers have identified rare and potentially deleterious single-nucleotide variants (SNVs) and small insertions and deletions (InDels) correlated with genes related to vascular risk factors (VRFs) and other stroke subtypes (Shi et al., 2022). Among 92 patients, likely ICAD-associated rare genomic variants were found in 54.3%, with 48 patients having 59 rare SNVs/InDels in genes related to VRFs and/or other stroke subtypes. None of these variants were identified in local subjects without ICAD. Furthermore, the study identified the CNS and chromosomal structural rearrangements potentially contributing to ICAD in 8.7% of patients (Shi et al., 2022). Gene enrichment analysis also highlighted that candidate genes were significantly enriched in pathways related to lipoprotein metabolism and cellular lipid catabolic processes. These findings have implications for precision medicine: screening individuals with identified variants may allow for earlier diagnosis, personalised risk assessment, and preemptive lifestyle or pharmacological interventions to reduce stroke incidence.

An integrated genomic-transcriptomic approach has also been employed to unravel genetic signatures associated with atherosclerosis, a major stroke risk factor. This innovative method has highlighted the differential expression of genes such as *BCL3*, *PVRL2*, and *ABCA1*, with the *BCL3* rs2965169 G allele showing an independent association with coronary artery disease (CAD) after adjustment for traditional cardiovascular risk factors (Marchetti et al., 2015). The up-regulation of *BCL3* mRNA levels in atherosclerotic tissue samples further supports its role in cardiovascular diseases, including stroke.

CMA has equally advanced our understanding of intracranial aneurysms, pinpointing specific chromosomal regions linked to aneurysm formation. Studies utilising aCGH have identified chromosomal gains

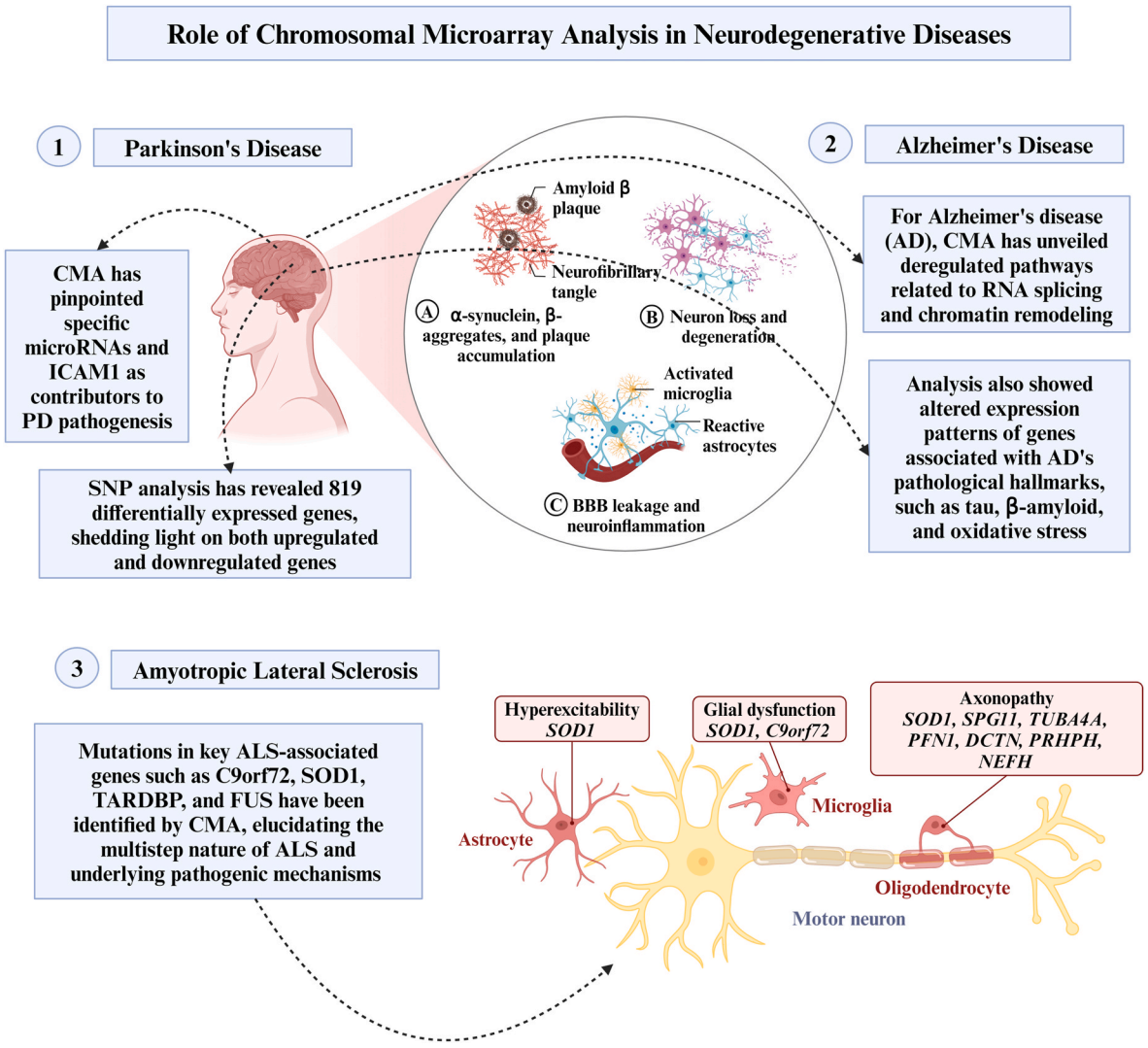

Fig. 3. The role of Chromosomal microarray analysis in neurodegenerative diseases.
Abbreviations: ICAM1: Intercellular Adhesion Molecule; PD: Parkinson's Disease; SNP:Single Nucleotide Polymorphism; AD: Alzheimer's Disease; RNA: Ribonucleic Acid.

and losses in patients with ruptured intracranial aneurysms, validating the involvement of certain genes in aneurysm pathogenesis. Findings from one such study revealed chromosomal gains in several regions, including 1p12, 4q24, 5p15.31, and 6p12.2, among others, as well as losses at 15q11.2 and 22q11.21 (Choi et al., 2009). Real-time polymerase chain reaction (PCR) further validated these results, confirming the involvement of genes such as *COL6A2*, *GRIN3B*, *MUC17*, and *PRODH* in IA pathogenesis. (Choi et al., 2009). These discoveries directly benefit patients by guiding risk stratification in individuals with a family history of aneurysms or chromosomal aberrations. High-risk individuals could undergo early screening, such as advanced imaging, enabling timely interventions to prevent rupture and its catastrophic consequences.

Differential gene expression analyses between ruptured and unruptured aneurysms have further delineated molecular mechanisms of aneurysm progression. The upregulation of matrix metalloproteinases (e.g., *MMP-2, MMP-9*) and pro-apoptotic genes, alongside downregulated anti-apoptotic pathways, provides actionable targets for pharmacological interventions aimed at stabilising aneurysms and reducing rupture risk (Marchese et al., 2010).

In the context of ICH, circRNA expression studies have identified novel therapeutic strategies. For instance, targeting miR-466b in haemorrhagic stroke models improved neuronal survival and recovery outcomes (Kim et al., 2024). These findings suggest that circRNA-miRNA interactions could be harnessed for therapies aimed at mitigating neuronal damage in ICH, potentially leading to better functional recovery and reduced long-term disability. Collectively, these studies underscore the importance of CMA in elucidating the genetic and molecular mechanisms underlying CVDs. By identifying chromosomal aberrations and gene expression profiles, these findings offer valuable insights into potential therapeutic targets and avenues for further research in this field. Fig. 4 demonstrates a graphical representation of the role of CMA in CVDs.

4.5. Epilepsy and seizure

CMA offers valuable insights into the genetic contributions to various disorders, including epilepsy and seizure disorders, by providing a comprehensive assessment of CNVs and other chromosomal abnormalities (Yamanouchi et al., 2005). Research indicates that over half of all epilepsies have a genetic basis, with mutations, chromosomal abnormalities, and inherited predispositions playing critical roles in the disorder's development (Pal et al., 2010). By identifying these genetic contributors, CMA has the potential to transform the diagnosis, management, and treatment of epilepsy, addressing the clinical challenges

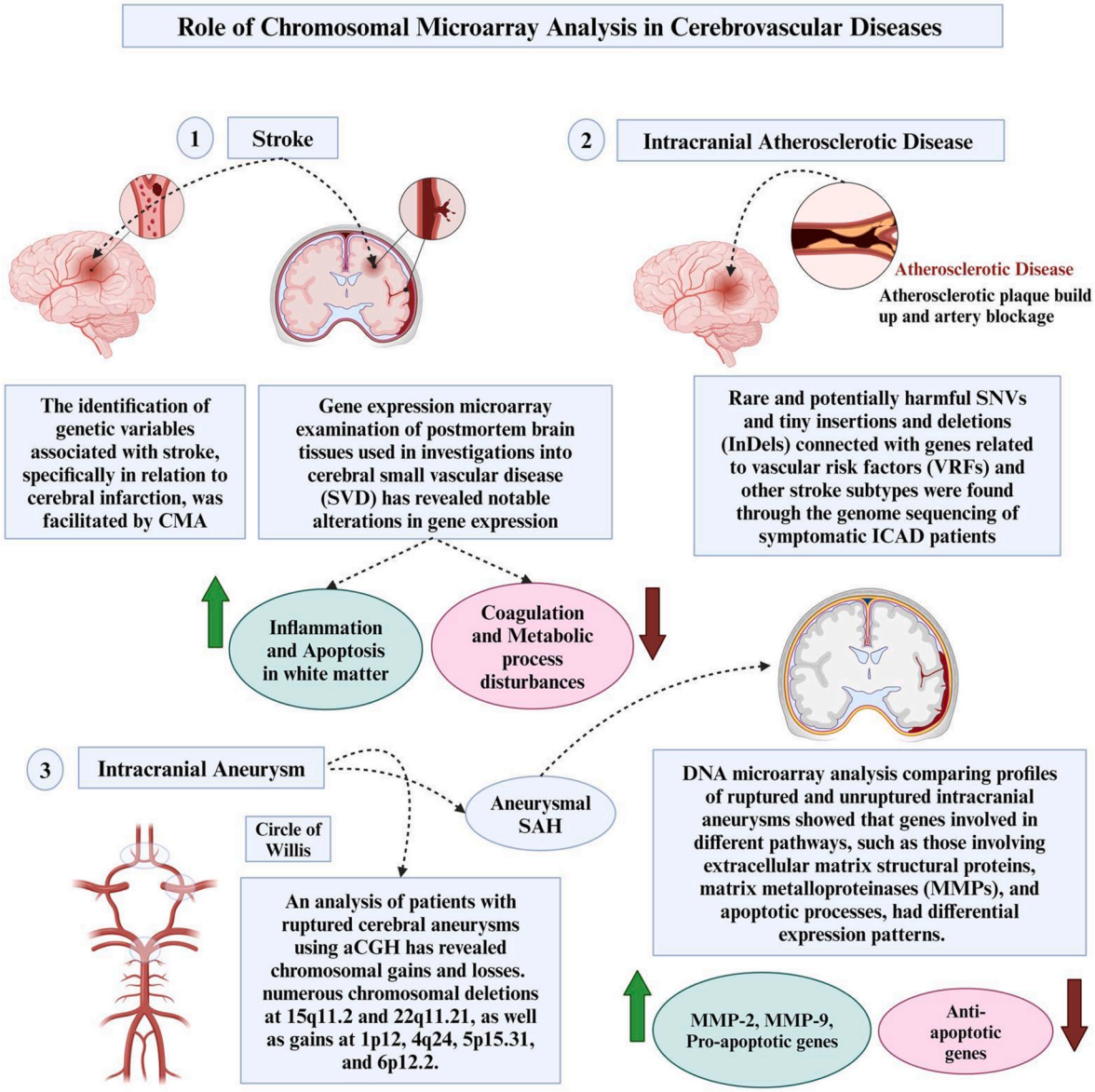

Fig. 4. The role Chromosomal microarray analysis of in cerebrovascular diseases
Abbreviations: CMA: Chromosomal Microarray Analysis; SVD: Small Vascular Disease; SNVs: Single-Nucleotide Variants; InDels: Insertions and Deletions; VRFs: Vascular Risk Factors; ICAD: Intracranial Atherosclerotic Disease; SAH: Subarachnoid Haemorrhage; aCGH: Array-Comparative Genomic Hybridization; DNA: Deoxyribonucleic Acid; MMPs: Matrix Metalloproteinases.

faced by patients and clinicians.

One of the most significant translational benefits of CMA is its enhanced diagnostic accuracy, particularly in cases of idiopathic epilepsy and drug-resistant epilepsy. For instance, aCGH has proven highly effective in detecting microdeletions and microduplications associated with epilepsy, offering a higher diagnostic yield compared to traditional methods (Coe et al., 2007). This is particularly relevant for patients with complex presentations, where identifying pathogenic CNVs can clarify the underlying cause and guide targeted therapeutic decisions. For example, adults with drug-resistant epilepsy and comorbidities have shown a significant proportion of pathogenic CNVs (Galizia et al., 2012). Incorporating CMA into routine diagnostic workflows allows for earlier identification of genetic abnormalities, enabling timely and individualised interventions.

Focused studies on specific forms of epilepsy have further delineated the genetic landscape of these disorders, leading to direct patient benefits. In juvenile myoclonic epilepsy (JME), the identification of the *Myoclonin1/EFHC1* gene on chromosome 6p11–p12 has opened avenues for precision medicine approaches, such as using EFHC1 mutations to stratify patients and personalise their management plans (Suzuki et al., 2006). Similarly, research into childhood absence epilepsy (CAE) has revealed significant associations with markers on chromosome 8q, narrowing the causative region to a 3.2-cM interval (Chen et al., 2017). These findings have implications for genetic counseling, risk assessment in affected families, and the development of targeted therapeutic strategies.

Overall, CMA, particularly aCGH, stands out as a valuable tool in clinical practice due to its ability to enhance diagnostic accuracy, personalise treatment approaches, and improve prognostic counseling. By bridging the gap between genetic insights and clinical care, CMA has the potential to transform epilepsy management, offering tangible benefits to patients and their families. Fig. 5 exhibits a graphical representation of the role of CMA in epilepsy/seizures. Fig. 5 exhibits a graphical representation of the role of CMA in epilepsy/seizures.

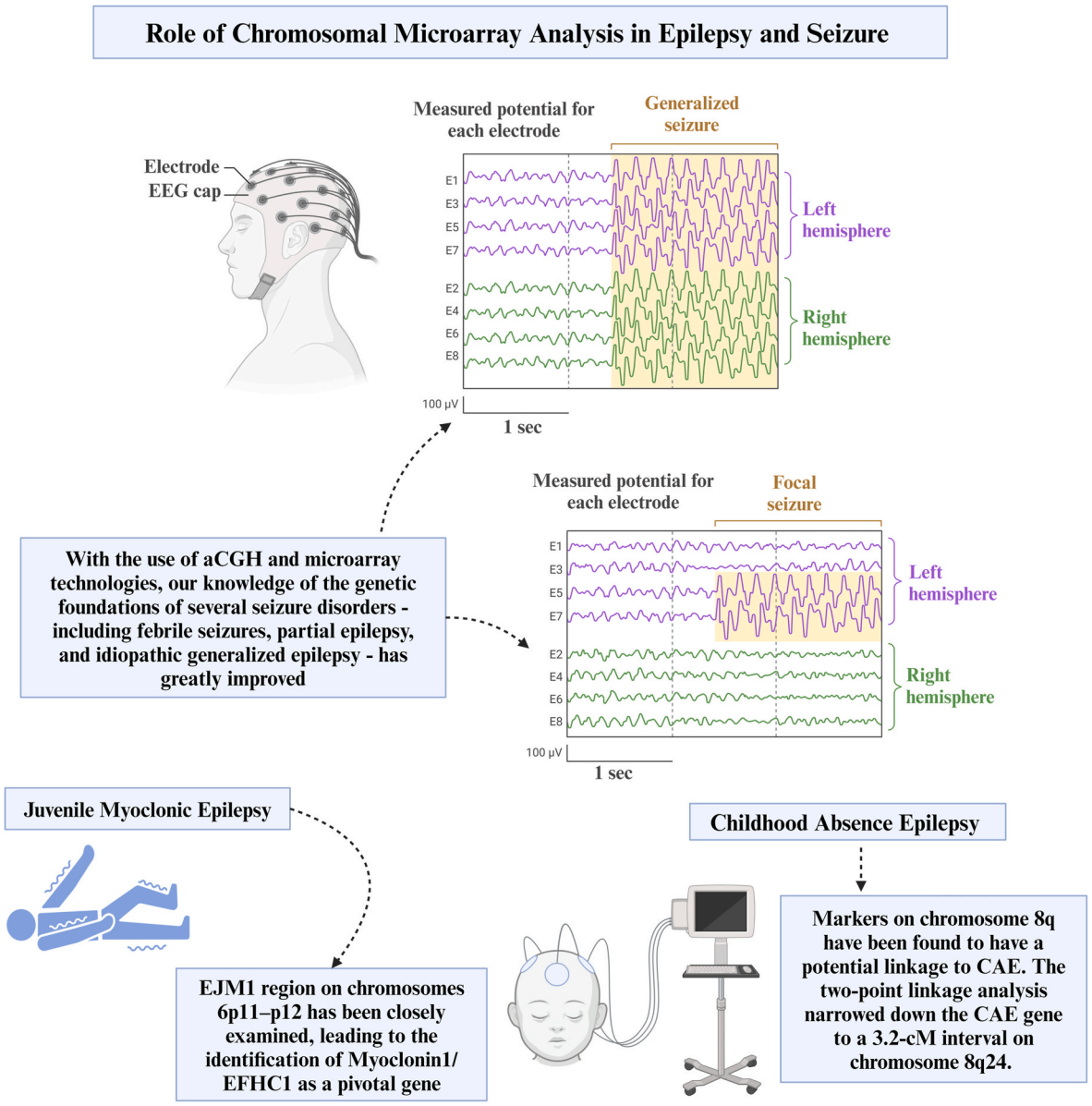

Fig. 5. The role of Chromosomal microarray analysis in epilepsy/seizures.
Abbreviations: EEG:Electroencephalogram; aCGH: Array-Comparative Genomic Hybridization; CAE: Childhood Absence Epilepsy.

5. Advantages of CMA over other cytogenetic techniques

CMA represents a significant leap over other cytogenetic techniques, delivering an enhanced diagnostic yield for conditions like unexplained DD/ID, ASD, and MCA. Compared to conventional karyotyping, CMA provides a superior resolution, enabling the detection of small submicroscopic deletions and duplications known as CNVs, further cementing its utility in genetic diagnostics (Dugoff et al., 2016). Its ability to detect submicroscopic deletions and duplications has been estimated to increase diagnostic yield to 15%–20%, compared to the approximately 3% yield from traditional G-banded karyotyping, which excludes known chromosomal syndromes (Miller et al., 2010). This advancement underscores the critical role of CMA in uncovering subtle genetic variations that contribute to complex conditions.

Furthermore, with prenatal diagnosis, CMA has proven its efficacy by uncovering clinically significant cytogenetic information that karyotyping cannot, despite its limitations in identifying balanced translocations and triploidies. CMA's effectiveness in identifying aneuploidies and unbalanced rearrangements, along with its added advantage of detecting other significant genomic imbalances in cases with structural anomalies, advanced maternal age, or positive screening results, is particularly noteworthy (Dugoff et al., 2016; Wapner et al., 2012). This analytical power of CMA is consistent with prior cytogenetic technique findings, reinforcing its reliability and accuracy in genetic diagnostics (Cheung et al., 2005).

Another cytogenetic technique that CMA has presented a distinct advantage over is FISH, particularly in other fields of clinical diagnostics. Unlike FISH, which is constrained by the finite number of probes that can be concurrently utilised, CMA has the capacity for coordinated and comprehensive analysis of DNA copy changes across multiple loci within the genome (Bejjani and Shaffer, 2006). CMA also offers a broader spectrum of detection, encompassing deletions, duplications, and amplifications at any probed locus, whereas FISH may overlook duplications(Bejjani and Shaffer, 2006). CMA does not require prior clinical suspicion to guide probe selection, unlike FISH, which further highlights the tool's advantage in revealing clinically relevant deletions or duplications in a significant percentage of cases, thereby enriching our understanding of various congenital and neurological

disorders.

Additionally, CMA has demonstrated versatility and enhanced resolution in diagnosing hematologic neoplasms by identifying copy number aberrations and copy-neutral loss of heterozygosity (Peterson et al., 2018). While cytogenetic techniques such as Q-PCR are sensitive and specific for targeted CNV detection, CMA offers a broader, genome-wide assessment of CNVs by analysing thousands of loci simultaneously. This high-throughput capability of CMA is particularly advantageous for identifying chromosomal abnormalities in diverse clinical scenarios, like developmental disorders and cancer (Manning and Hudgins, 2010). These contributions collectively underscore CMA's comprehensive genomic analysis capabilities, establishing it as an invaluable diagnostic tool despite its inability to detect balanced rearrangements and low-level mosaicism. The broad utility of CMA in revealing the genetic basis of a wide range of disorders provides essential insights for clinical management and genetic counseling, making it an indispensable asset in the landscape of genetic diagnostics. Table 2 encapsulates the key advancements and utilities of CMA over other cytogenetic techniques.

6. Limitations of CMA in neurological applications

Despite CMA's significant advancement over other cytogenetic techniques, its application comes with its own set of challenges and limitations. One of the primary hurdles is the interpretation of VOUS (Miller et al., 2010). The vast majority of copy-number variation detected by CMA is not recurrent, complicating the task of determining its clinical significance. This uncertainty presents difficulties for both clinicians and laboratories in interpreting these variants.

Another significant challenge is the absence of uniform guidelines for CMA testing in neurology, including expectations around clinical yield in terms of resolution and coverage. This lack of standardisation hampers the establishment of consistent clinical practices for CMA testing, and the opposite can be determined for prenatal diagnosis where guidelines have been established (Muys et al., 2020). The technology is performed using a variety of platforms and array designs across different laboratories, leading to variability in interpretations of clinical laboratories. Efforts to promote uniform array content and rational variant interpretation approaches are needed, along with initiatives to enhance data sharing among laboratories. Furthermore, obtaining appropriate tissue samples, such as brain or amniotic tissue, for CMA poses a significant challenge due to the risks involved (Liu et al., 2022).

Lastly, cost and accessibility also pose significant barriers to widespread CMA testing, with financial constraints preventing some patients from accessing this technology (Miller et al., 2010). In addition, ensuring the accuracy and reliability of CMA results demands stringent quality control measures and continuous technological updates. Specifically, the implementation of CMA in low and middle income countries (LMICs) faces particular challenges. Foremost among these is the cost barrier. The average expense for CMA testing is approximately $1, 500, which is considerably higher than the $800 typically required for routine karyotype analysis (Martin and Ledbetter, 2017). This elevated cost can be prohibitive in LMICs, where healthcare budgets are often constrained, and patients may lack sufficient insurance coverage or financial means to afford such tests.

Furthermore, ensuring the accuracy and reliability of CMA results necessitates stringent quality control measures. Laboratories must adhere to established guidelines, such as those provided by the Canadian College of Medical Geneticists (CCMG), which outline comprehensive protocols for quality assurance in genomic microarray testing (CCMG Guidelines for Genetic Modifiers of Huntington's Disease Consortium, 2015). However, maintaining these standards can be challenging in LMICs due to limited resources, lack of trained personnel, and the need for continuous technological updates.

The challenges and limitations of CMA in clinical practice have been summarised in Table 3.

7. Discussions and future perspectives

7.1. Integration of CMA into routine clinical practice

The integration of CMA into routine clinical practice has significantly enhanced the diagnostic process for neurological disorders. CMA's incredible specificity and sensitivity, along with its ability to detect

Table 2
Summary of Chromosomal Microarray Analysis Advantages Over Other Cytogenetic Techniques.
Abbreviations: CMA: Chromosomal Microarray Analysis, CNV: Copy number variations.

Advantage	Summary
Diagnostic Yield (Miller et al., 2010).	CMA offers a significant increase in diagnostic yield (15%–20%) over traditional cytogenetic techniques (3% from G-banded karyotyping), particularly for complex conditions.
Prenatal Diagnosis (Dugoff et al., 2016; Wapner et al., 2012).	CMA outperforms karyotyping in prenatal diagnosis, detecting clinically significant cytogenetic information, including aneuploidies and unbalanced rearrangements.
Clinical Relevance (Bejjani and Shaffer, 2006).	CMA reveals clinically relevant deletions or duplications in cases of structural anomalies, advanced maternal age, or positive screening results, enriching understanding.
Detection of CNVs (Dugoff et al., 2016).	CMA's superior resolution enables the detection of small submicroscopic deletions and duplications known as CNVs, enhancing genetic diagnostics.
Versatility in Hematologic Neoplasm (Peterson et al., 2018).	CMA demonstrates versatility in diagnosing hematologic neoplasms by identifying copy number aberrations and copy-neutral loss of heterozygosity.
Comprehensive Genomic Analysis Capabilities (Bejjani and Shaffer, 2006; Manning and Hudgins, 2010).	Despite limitations in detecting balanced rearrangements and low-level mosaicism, CMA provides comprehensive genomic analysis, essential for clinical management and counseling.

Table 3
Challenges and summary of chromosomal microarray analysis in neurology and Neurosurgery
Abbreviations: CMA: Chromosomal microarray analysis, VOUS: Variants of uncertain clinical significance.

Challenges and Limitations of CMA in Clinical Practice	Summary
Interpretation of VOUS presents a significant hurdle (Miller et al., 2010).	Difficulty in determining clinical significance due to non-recurrent copy-number variations detected by CMA.
Lack of uniform guidelines for CMA testing in neurology leads to variability across laboratories (Muys et al., 2020).	Variability in CMA testing practices due to the absence of standardised guidelines in neurology.
Variability in platforms and array designs used for CMA across laboratories leads to inconsistent interpretations (Liu et al., 2022).	Inconsistent interpretations of CMA results due to variability in platforms and array designs across laboratories.
Difficulty in obtaining appropriate tissue samples, such as brain tissue, for CMA in neurodegenerative diseases (Liu et al., 2022).	Challenges in acquiring suitable tissue samples, particularly brain tissue, for CMA due to high risks involved.
Cost and accessibility pose significant barriers to widespread CMA testing (Miller et al., 2010).	Financial constraints, limited accessibility, and the need for stringent quality control and technological updates in CMA testing to ensure accuracy and reliability of results.

unbalanced chromosomal abnormalities, including submicroscopic deletions and duplications, up to 1000 times higher than traditional karyotyping methods, offer a profound advantage in clinical practice (Batzir et al., 2015). The implementation of CMA in clinical settings underscores the shift towards precision medicine, allowing clinicians to have a more comprehensive understanding of genetic conditions and facilitating targeted interventions tailored to the individual's genetic makeup (Miller et al., 2010).

Moreover, the use of CMA complements traditional chromosome analysis by filling in the gaps left by the latter's limitations. While chromosome analysis can detect balanced translocations and inversions, CMA provides a detailed view of the genome, identifying abnormalities that are beyond the resolution of conventional methods. This complementary relationship between CMA and chromosome analysis ensures a more thorough and accurate genetic evaluation, enhancing the diagnostic yield and offering critical information for managing genetic disorders. This approach highlights the evolving landscape of genetic diagnostics, where integrating multiple methodologies enhances patient outcomes. Not only this, but the utility of CMA in diagnosing conditions such as nonimmune hydrops fetalis (NIHF) underscores its value in prenatal diagnosis, facilitating early intervention strategies (Mardy et al., 2020). Furthermore, the analysis of microarray data has extended into the investigation of brain ageing, highlighting its potential in unravelling the molecular mechanisms of age-related NDs (Sanfilippo and Di Rosa, 2021).

The clinical utility of CMA extends beyond diagnosis to include prognostic and therapeutic implications. By identifying specific genetic anomalies, clinicians can better predict disease progression and tailor therapeutic strategies accordingly. This level of genomic insight is crucial in neurodevelopmental disorders and congenital anomalies, where genetic heterogeneity can complicate clinical management. The challenge now lies in addressing the technical and ethical considerations that accompany the broader adoption of CMA in clinical practice, including the interpretation of variants of uncertain significance and the management of incidental findings. These considerations necessitate ongoing education, ethical deliberation, and policy development to maximise the benefits of CMA while safeguarding patient interests.

7.2. Personalised medicine and targeted therapies

Personalised medicine, which tailors medical treatment to the individual characteristics of each patient, has been significantly advanced by CMA's ability to provide comprehensive genetic insights. CMA facilitates a nuanced understanding of the genetic basis of diseases, particularly those with complex etiologies such as cancer, neurodevelopmental disorders, and congenital anomalies, by uncovering potential genetic variants underlying disease predisposition (Lam et al., 2010). For patients, this means that CMA enables early and precise diagnosis, often revealing the underlying genetic causes of conditions that would otherwise remain unexplained. This early detection allows for targeted interventions, improving clinical outcomes and quality of life.

In the realm of pharmacogenomics, CMA plays a pivotal role in optimising therapy. By identifying genetic variants that affect drug metabolism, efficacy, and toxicity, CMA empowers clinicians to predict which medications and dosages are most likely to be effective and safe for individual patients (Shao et al., 2021). This is particularly crucial for conditions like epilepsy, where treatment response can vary widely. For example, identifying CNVs associated with drug resistance would enable a shift to alternative therapies sooner, sparing patients from ineffective treatments and reducing the risk of adverse reactions. In oncology, CMA helps stratify patients based on their tumour's genetic profile, guiding the choice of targeted therapies and immunotherapies. This predictive capability exemplifies how CMA directly enhances patient outcomes while minimising adverse effects.

The diagnostic power of CMA is another key translational benefit. Recent studies demonstrate CMA's capability to identify pathogenic CNVs with greater sensitivity than traditional cytogenetic techniques, thereby enhancing diagnostic yield. For instance, the application of CMA in children with DD/ID revealed significantly higher number of genes implicated in the pathogenesis of the condition compared to conventional methods (Yang et al., 2021). This has a direct impact on families, as a precise genetic diagnosis provides clarity, reduces diagnostic trajectories, and enables access to condition-specific support, resources, and, where available, targeted therapies. CMA is now recognised as a first-tier test for evaluating chromosomal imbalances across both constitutional and neoplastic disorders (Shao et al., 2021). Its application in cancer has transformed patient care by identifying somatic CNVs that inform prognosis, guide treatment choices, and predict therapy response.

By integrating CMA into routine clinical practice, clinicians can bridge the gap between genetic discoveries and tangible patient benefits. This includes earlier diagnoses, reduced trial-and-error in treatment, and better prognostic predictions, which collectively enhance the efficiency and effectiveness of medical care. These advancements underscore CMA's transformative potential to drive personalised medicine and improve outcomes across a broad spectrum of diseases.

7.3. Collaboration between institutions and data sharing

Institutions around the globe are increasingly recognising the value of pooling genomic data. This collaborative approach not only accelerates the pace of genetic research but also broadens the scope of potential discoveries (Matar et al., 2023). By sharing CMA results and clinical outcomes, researchers and clinicians can identify patterns and correlations across larger populations, leading to more robust conclusions and potentially unravelling novel genetic markers of diseases. This vast repository of shared data becomes a powerful tool in the quest to understand the genetic basis of disease, thereby informing the development of new targeted therapies and improving diagnostic accuracy.

Furthermore, initiatives such as the International Nucleotide Sequence Database Collaboration (INSDC) and proposals for international codes of conduct for data sharing in genomics play a crucial role in this collaborative effort (Arita et al., 2021). These databases, often supported by consortia that include research institutions, hospitals, and sometimes even pharmaceutical companies, serve as central repositories of genetic data. They not only facilitate the sharing of information but also ensure that data is standardised, making it easier for researchers worldwide to access and analyse genetic information in a consistent manner (Arita et al., 2021). This level of international cooperation and data sharing is essential for advancing personalised medicine, as it enables the scientific community to draw from a diverse and comprehensive genetic dataset, reflecting the variability seen in the global population.

7.4. Addressing technical challenges and ethical issues

As CMA technology becomes more integrated into clinical practice, its potential to revolutionise patient care must be balanced with considerations for privacy, consent, and the interpretation of complex genetic data. One of the primary technical challenges lies in the interpretation of VOUS. These genetic variants, detected by CMA, lack clear evidence regarding their impact on health, posing dilemmas for clinicians and patients. To address this, continuous efforts in research are necessary to elucidate the clinical relevance of VOUS. Collaborative studies and data sharing among institutions can accelerate the classification of these variants, enhancing the predictive power of CMA (Burke et al., 2022). Moreover, developing standardised guidelines for reporting and communicating VOUS to patients is essential, ensuring that individuals understand the implications of their test results without undue anxiety or confusion (Alduaiji et al., 2023).

Ethical considerations are equally paramount, particularly in the

domain of patient consent and data privacy. The comprehensive nature of CMA raises the potential for incidental findings—genetic information unrelated to the initial reason for testing but which may have significant health implications. This possibility necessitates a robust informed consent process, wherein patients are made aware of the potential for incidental findings and can choose how much information they wish to receive. Additionally, the ethical management of genetic data, with respect to both privacy and access, is a critical concern. Ensuring data security while facilitating the sharing of genetic information for research purposes requires careful policy planning and the implementation of strict data governance protocols (Makhnoon et al., 2019).

Furthermore, CMA is being increasingly preferred due to its more cost-effective benefits compared to other cytogenetic techniques such as karyotyping (Chung et al., 2020). However, accessibility, particularly in low-income countries, remains an important ethical concern. The high initial investment and ongoing maintenance costs associated with CMA make it unattainable for healthcare systems of low-income countries with limited resources (Tsiplova et al., 2017). Consequently, only high-income healthcare nations can afford CMA, exacerbating healthcare disparities and widening the gap in access to advanced diagnostic services for neurological conditions. Addressing the accessibility challenges of CMA is crucial for reducing healthcare disparities and ensuring equitable access to diagnostic services worldwide.

Lastly, the integration of CMA into healthcare systems introduces the need for interdisciplinary collaboration among geneticists, ethicists, clinicians, and IT professionals. This team-based approach can help develop solutions that respect patient autonomy and confidentiality while leveraging CMA's full potential to improve health outcomes. Education and ongoing dialogue with patients and the public about the benefits and limitations of genetic testing will be key to navigating the ethical landscape of personalised medicine.

7.5. Balancing costs, accessibility and economic sustainability in genetic testing

While CMA offers significant diagnostic advantages, its broader implementation depends on addressing challenges related to cost, accessibility, and overall health economic impact. As previously highlighted, genetic testing for conditions such as GDD, ID, and congenital anomalies has expanded due to advances in technologies like CMA, NGS, and Exome Sequencing (ES). Although these methods offer essential insights into the genetic causes of these conditions, their cost-effectiveness and accessibility must be carefully considered to ensure their widespread adoption.

A growing body of research demonstrates that CMA is a cost-effective first-tier diagnostic tool, particularly when compared to traditional karyotyping. For instance, Li et al. (2018) showed that CMA is considerably more cost-effective for diagnosing GDD/ID in the U.S (Li et al., 2018). Their analysis revealed that CMA identifies more genetic diagnoses at a significantly lower incremental cost per diagnosis ($2692) compared to karyotyping ($11,033). This positions CMA as a clinically informative and economically viable first-line test. Furthermore, when CMA reveals VOUS, testing both parents has been shown to add diagnostic value, albeit at an additional cost, reinforcing the importance of using CMA as an initial approach in the diagnostic pathway (Li et al., 2018).

This cost-effectiveness extends beyond just genetic diagnoses. In prenatal genetic diagnosis, aCGH, a form of CMA, could replace karyotyping, even in settings where karyotyping is provided free of charge (Chung et al., 2020). The new algorithm combining aCGH with QF-PCR was found to be more effective and less costly than the current approach, underscoring the potential for cost savings without compromising diagnostic accuracy. Such findings suggest that policies supporting subsidised genetic testing—similar to those proposed in Hong Kong—could enhance access to vital diagnostic tools, particularly for patients with rare or undiagnosed neurological conditions (Chung et al., 2020).

However, the economic viability of CMA is not always straightforward. The combination of CMA with chromosomal analysis has shown limited additional diagnostic value in many cases. While chromosomal analysis can provide further insights, its cost-effectiveness is only favorable when CMA findings are clinically significant (Su et al., 2022). In cases where CMA results are inconclusive, combining the tests leads to a much higher incremental cost-effectiveness ratio. As such, a stepwise approach—starting with CMA and reserving chromosomal analysis for cases with significant CMA findings—has been recommended. This strategy not only maximises diagnostic efficiency but also ensures that resources are allocated effectively. (Su et al., 2022).

Similarly, as the use of ES becomes more prominent, particularly in cases where CMA fails to yield a diagnosis, its cost-effectiveness must be carefully weighed. The addition of ES to CMA in low-risk pregnancies revealed that while ES provides valuable diagnostic insights, it significantly increases costs ($3108 compared to $1348 for CMA alone) with only a marginal increase in quality-adjusted life years (14.19 vs. 14.15) (Friedman et al., 2024). The incremental cost-effectiveness ratio for ES was $46,383 per quality-adjusted life year. Sensitivity analyses indicated that factors such as the time horizon and the disutility of moderate or severe disability affected the cost-effectiveness of ES, suggesting that ES may be a viable option depending on the healthcare setting and budget (Friedman et al., 2024). This raises important questions about the cost-effectiveness of ES in clinical practice, particularly in neurology and neurosurgery, where complex cases may warrant its use. Although ES may be beneficial in certain contexts, its high cost and limited improvement in patient outcomes suggest that it should be considered only when the clinical benefit justifies the expense.

Collectively, these studies emphasise that while CMA is a cost-effective and clinically informative tool for genetic disorders, the broader implementation of genetic testing must balance the benefits of more advanced techniques like ES and chromosomal analysis with their economic impact. Policies that facilitate access to genetic testing and optimise the use of these technologies across healthcare systems are crucial for maximising their clinical benefit. The evidence collectively supports the need for a stepwise, tailored approach to genetic testing, ensuring that the diagnostic pathway remains both clinically effective and economically sustainable.

Table 4 encapsulates the discussion on the pivotal role of CMA in revolutionising genetic diagnostics, emphasising its integration into clinical practice, its contributions to personalised medicine, collaboration initiatives, and the challenges posed by technical and ethical considerations.

8. Conclusion

In conclusion, CMA represents a significant leap forward in neurogenetics, enhancing our understanding of neurological disorders and paving the way for personalised medicine. It has proven to be a crucial tool for identifying genetic variations, enabling targeted treatment approaches that promise improved patient outcomes. CMA allows for earlier, more accurate diagnoses, leading to tailored interventions that reduce trial-and-error prescribing and minimise adverse drug reactions, particularly in conditions like epilepsy and neurodevelopmental disorders. Additionally, it enables risk stratification, allowing for preventive measures and timely interventions. However, integrating CMA into clinical practice presents challenges, including the interpretation of complex genetic data and ethical concerns related to patient privacy. Addressing these requires ongoing research, ethical diligence, and collaboration. The future of CMA in neurology will depend on both technological advancements and careful consideration of its ethical implications. Through continued innovation, CMA will enhance patient care by providing treatments based on individual genetic profiles, ultimately improving clinical outcomes.

Table 4
Summary of Discussions on the Role of Chromosomal Microarray Analysis in Neurology and Neurosurgery
Abbreviations: CMA: Chromosomal Microarray Analysis, LMIC: Low and middle income country, GDD: Global Developmental Delay, ID: Intellectual Disability.

Discussion Points	Summary
Integration of CMA into Routine Clinical Practice (Batzir et al., 2015; Miller et al., 2010; Mardy et al., 2020; Sanfilippo and Di Rosa, 2021)	● Enhancing genetic disorder diagnostic yield by detecting unbalanced chromosomal abnormalities with high precision, surpassing traditional methods. CMA chromosome analysis by providing a detailed genomic view, improving the potential of therapeutic interventions and facilitating personalised patient care. ● Additionally, CMA's utility extends to prenatal diagnosis and investigating brain ageing, presenting opportunities for early interventions and understanding disease mechanisms. Technical and ethical challenges, including interpreting variants of uncertain significance, must be addressed to maximise CMA's benefits while safeguarding patient interests.
Personalised Medicine and Targeted Therapies (Lam et al., 2010; Shao et al., 2021; Yang et al., 2021)	● Playing a pivotal role in personalised medicine by providing genetic insights crucial for tailoring treatments to individual patients. It aids in predicting drug responses, guiding therapeutic decisions, and minimising adverse reactions, particularly in conditions like epilepsy and cancer. ● Recent studies underscore CMA's sensitivity in identifying pathogenic chromosomal imbalances, supporting its broad applicability across various disorders.
Collaboration Between Institutions and Data Sharing (Matar et al., 2023; Arita et al., 2021)	● Collaborative efforts and data sharing initiatives accelerate genetic research, broaden the scope of discoveries, and enhance diagnostic accuracy. International databases and codes of conduct facilitate standardised data sharing, enabling the global scientific community to access comprehensive genetic datasets. This international cooperation is vital for advancing personalised medicine and developing new therapies.
Addressing Technical Challenges and Ethical Issues (Burke et al., 2022; Alduaiji et al., 2023; Makhnoon et al., 2019; Chung et al., 2020; Tsiplova et al., 2017)	● Technical challenges in interpreting variants of uncertain significance and ethical considerations regarding patient consent, data privacy, and incidental findings must be addressed as CMA integrates into clinical practice. ● Accessibility of CMA remains limited to high-income healthcare nations, posing ethical and social challenges for equitable access to advanced diagnostic services worldwide. ● Research collaboration, standardised reporting guidelines, and interdisciplinary teamwork are essential for overcoming these challenges and navigating the ethical landscape of personalised medicine.
Balancing Costs, Accessibility and Economic Sustainability in Genetic Testing (Li et al., 2018; Chung et al., 2020; Su et al., 2022; Friedman et al., 2024)	● CMA is more cost-effective than traditional karyotyping for diagnosing conditions like GDD/ID, reducing incremental diagnostic costs. ● Accessibility challenges in LMICs hinder widespread use; subsidies and policy support are needed to improve affordability. ● Stepwise approaches, like prioritizing CMA before additional tests (e.g., chromosome analysis or exome sequencing), optimise cost-effectiveness. ● While exome sequencing can provide additional insights, its high cost and marginal clinical benefit require careful evaluation in different healthcare systems.

Consent for publication

Consent for publication is not applicable.

Ethics approval

Ethics approval is not applicable.

Consent to participate

No original data from new patients were collected, consent to participate is not applicable.

Availability of data and material

Not Applicable.

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Conflict of interests

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