Published in final edited form as:
Lancet Neurol. 2012 March ; 11(3): 283–292. doi:10.1016/S1474-4422(11)70287-3.

Genomic insights into the etiology and classification of the cerebral palsies

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Abstract

Cerebral palsy (CP), the most common physical disability of childhood, is a clinical diagnosis that encompasses a highly heterogeneous group of neurodevelopmental disorders resulting in movement and posture impairments that persist throughout life. Despite being commonly attributed to a variety of environmental factors, particularly to birth asphyxia, the specific cause remains unknown in the majority of individuals. Conversely, a growing body of evidence suggests that CP is likely caused by multiple genetic factors, similar to other neurodevelopmental disorders, such as autism and intellectual disability. Due to recent advances in next-generation sequencing technologies, it is now possible to sequence the entire human genome in a rapid and cost-effective way. It is likely that novel CP genes will be identified as more researchers and clinicians use this approach to study individuals with undiagnosed neurological disorders. As our knowledge of the underlying pathophysiologic mechanisms increases, so does the possibility of developing genomically-guided therapeutic interventions for CP.

Introduction

The first descriptions of cerebral palsy (CP) as a clinical entity are attributed to William John Little, an eminent British orthopedic surgeon. In 1861, he wrote a monograph, “On the influence of abnormal parturition, difficult labor, premature birth and asphyxia neonatorum on the mental and physical condition of the child”, proposing for the first time an association between perinatal asphyxia and poor neurological outcomes later in life.[1] Three decades later, Sigmund Freud, neurologist and founder of psychoanalysis, questioned Little’s conclusions on the etiology of CP. Based on the observation that children with CP had medical comorbidities, including intellectual disability, epilepsy, and visual disturbances, he proposed that CP could begin earlier in life, during *in utero* brain development.[2] Despite

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Authors’ contributions
AMD prepared the first draft of this review. DHL and CLM were involved in the writing and revision of the manuscript. All authors approved the final version.

Conflicts of interest
None declared.

Freud's premises, the notion that complications during labor and delivery were the leading cause of CP was widely accepted by the medical, scientific, and lay communities. In fact, it was almost one century later that large population-based studies showed that only a minority of CP cases result from birth asphyxia, thus providing support that Freud's hypothesis was indeed correct.[3–6]

CP is a clinical descriptive term applied to an exceedingly heterogeneous group of neurodevelopmental disorders that share the presence of motor impairments which often co-occur with a wide range of medical conditions. In 2004, the International Working Group on the Definition and Classification of Cerebral Palsy defined CP as "a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior; by epilepsy, and by secondary musculoskeletal problems".[7] Unfortunately, in some cases, once a child is given a clinical diagnosis of CP, very limited efforts, if any, are made to determine the underlying etiology. Alternatively, if specific causes were identified, individuals with CP and their families would have numerous benefits including a better understanding of the condition, accurate assessment of recurrence risk, early intervention, and more importantly, further research efforts to develop specific medical treatments and therapeutic interventions for CP.

Here, we review the growing body of evidence supporting the contribution of genetic abnormalities to the occurrence of CP. We discuss previously proposed environmental risk factors and their repercussion to obstetric management and medical malpractice litigation. We also present an overview of the rapidly changing field of CP genetics, from the initial targeted association studies with inconclusive results to the successful implementation of genome-wide, exon-level copy number array analyses and whole-exome sequencing to discover novel CP genes and syndromes. We also provide our perspective on current diagnostic challenges and directions for future research.

Epidemiology and classification

CP is the most common cause of physical disability in childhood. The worldwide prevalence of CP has remained stable at 2–3 per 1,000 live births for more than four decades, despite remarkable improvements in obstetric and neonatal care.[8] A recent report from the Centers for Disease Control and Prevention noted a prevalence of 3·3 per 1,000 eight-year-old children from four areas of the United States (US).[9] Moreover, up to an estimated one million children and adults in the US live with a diagnosis of CP, with an average lifetime cost per affected individual of $921,000 dollars (in 2003 dollars).[10,11] Due to the increasing life expectancy of individuals with CP, the number of adults with this disorder is increasing and their medical and social care needs are changing.[10]

CP can be classified based on four major components: type and severity of the motor abnormalities, anatomical distribution, associated impairments, and timing of the presumed causal event (prenatal, perinatal, or postnatal).[12] A thorough physical and neurological examination allows the identification of abnormal neuromuscular tone (hypotonia or hypertonia) as well as the predominant type of motor impairment, which can be spastic, ataxic, dyskinetic (dystonia or choreoathetosis), or mixed. The characteristics and severity of the motor manifestations should be described for each limb and the trunk, thus differentiating unilateral from bilateral involvement and establishing an anatomical distribution (monoplegia, diplegia, triplegia, hemiplegia, and tetraplegia).[13] These classification systems, based on motor type and topography, are often times used to infer

which area of the brain could be affected (pyramidal or extrapyramidal systems); however, they have poor reliability even between experienced clinicians.[14,15]

In an effort to establish an accurate, reliable, and standardized system to classify CP, Palisano et al. developed the Gross Motor Function Classification System (GMFCS), a five-level classification based on the child's gross motor abilities, functional limitations, and need for wheeled mobility or assistive devices.[16] The GMFCS has been successfully implemented worldwide in a variety of settings including routine clinical management (mobility assessment, intervention planning, and prognosis), research (sample selection and stratification), and healthcare administration.[17–19] A similar scale to assess Bimanual Fine Motor Function (BFMF) was developed and validated as a complement to the GMFCS,[20,21] whereas a Manual Ability Classification System (MACS) was designed to evaluate the ability of children with CP to use their hands for routine activities.[22] Furthermore, the Communication Function Classification System (CFCS) was recently developed in an effort to assess the functional communication competence of individuals with CP in daily life situations.[23] The development of objective and valid functional classification systems has greatly improved health care delivery and standardized research efforts.

Although the hallmark feature of CP is the motor and posture deficit, it is not uncommon for individuals with this disorder to present with several other impairments and medical conditions.

Commonly reported comorbidities include intellectual disabilities in 30–65% of the cases, seizure disorders in 30–50%, speech and language deficits in 40%, visual impairments in 40%, and hearing problems in 5–15%.[24–28] Additional systems that may be affected include the somatosensory (deficits in stereognosis and proprioception),[29] genitourinary (enuresis, urinary infections, and voiding dysfunction),[30,31] gastrointestinal (dysphagia, gastroesophageal reflux diease, constipation),[32] respiratory (recurrent pneumonia, atelectasis, bronchiectasis, restrictive lung disease),[32] and endocrine (reduced growth and osteopenia).[33,34] Furthermore, 20% of individuals with CP have psychosocial and behavioral problems, and 9% have an autism spectrum disorder.[35] The severity of the motor impairment, along with the presence and extent of accompanying disorders, determines the functional level of individuals with CP, as well as the burden and challenges posed on caregivers and ultimately on the health system.

Etiology

The etiology of CP has been attributed to a wide range of prenatal, perinatal, and postnatal factors that may present as single, isolated findings or as a combination of multiple potential risk factors. The presence and contribution of individual events varies to some extent between gestational groups and CP subtypes.[36] The most commonly reported risk factors include prematurity, low birth weight, birth asphyxia, infection, inflammation, maternal fever during labor, multiple gestations, coagulation disorders, ischemic stroke, maternal thyroid disease, and placental pathology.[37–39] However, despite the large number of known and proposed etiologies, the specific causal mechanism remains elusive in the majority of CP cases.

Perhaps the single, most studied, and still controversial, risk factor associated with CP is birth asphyxia. Historically, and unfortunately still today in many groups, it is assumed that inadequate oxygen delivery to the brain, caused by adverse intrapartum events, is the leading cause of CP.[40–42] Based on this hypothesis, it was proposed that detection and early intervention in episodes of acute birth asphyxia would decrease the rate of CP and improve long-term neurological outcomes of newborns at risk. To that extent, technologies such as electronic fetal monitoring (EFM) during birth were developed and rapidly introduced into

clinical practice, without adequate supporting evidence from scientific studies.[43,44] EFM, considered a standard of care, is now widely used to detect early fetal distress resulting from hypoxia during delivery, and despite a five-fold increase in the rate of Cesarean sections driven partly by the use of EFM, the rate of CP has not decreased over time.[8,45,46] Moreover, large population-based, controlled studies, conducted in various countries, in different time frames, and across different populations, have shown that birth asphyxia is an uncommon cause of neonatal encephalopathy and accounts for less than 10% of CP cases.[3,5,47–50]

Even though the vast majority of CP cases are not caused by birth asphyxia, and those that are can rarely be prevented by obstetric intervention,[51] an estimated 76% of obstetricians in the United States have faced medical malpractice litigation, most often for alleged birth mismanagement resulting in CP.[44] A similar situation occurs in Australia, where 18% of the total medical indemnity claims are attributed to the 2% of physicians that practice obstetrics.[52]

In an effort to help clinicians, researchers, and law courts to determine whether an acute intrapartum event was likely the cause of any particular case of CP, an objective template of evidence was published by the International Cerebral Palsy Task Force.[53] These guidelines, supported by multiple medical colleges and societies worldwide, provide three essential and five non-essential criteria to define an acute intrapartum hypoxic event (table 1). The absence of any of the essential criteria strongly suggests that intrapartum hypoxia was not the cause of CP.

An alternative hypothesis for the etiology of CP is that it is caused by many diverse and individually rare genomic abnormalities, just like other developmental brain disorders, such as intellectual disabilities,[54] autism spectrum disorders,[55] and epilepsy.[56] However, as opposed to other neurodevelopmental disabilities, the contribution of genomic abnormalities to the occurrence of CP has been scarcely explored and likely accounts for a significant proportion of the 70–80% of cases that are attributed to prenatal causes. Furthermore, genomic abnormalities could also be the underlying cause in cases where “classic” risk factors such as prematurity, coagulopathies, or difficult birth are identified.[57] Indeed, children with malformations of cortical development present with birth complications much more frequently than others, which often results in the misdiagnosis of intrapartum asphyxia.[58]

Evidence for genetic factors in CP

Several lines of evidence strongly support the contribution of multiple genetic factors to the etiology of CP, as follows: 1) Mutations in multiple genes result in Mendelian disorders that present with CP-like features (as discussed below) and several new single gene mutations have been identified in idiopathic (i.e., non-syndromic) CP pedigrees.[59–63] 2) The prevalence of congenital anomalies in individuals with CP (11–32%) is significantly higher than the rate in the general population (2–3%).[64,65] The majority of malformations in children with CP are cerebral, of which microcephaly and hydrocephaly are the most common. Among the non-cerebral malformations, the most frequent are cardiac, musculoskeletal, and urinary abnormalities, as well as facial clefts.[66,67] 3) Register-based studies have reported a significantly higher concordance rate for CP in monozygotic twins when compared to dizygotic twin pairs.[68] 4) The risk of CP in consanguineous families is approximately 2·5 times higher than the risk in outbred families.[69,70] 5) Familial aggregation of CP cases has been reported by several studies, including the identification of identical CP syndromes in the same family.[71–75] 6) A paternal age effect has been described in some forms of CP.[76] Furthermore, a quantitative analysis of risk factors conducted in 681

individuals with congenital CP, from the west Swedish population-based CP study, estimated that 60% of hemiplegic CP cases, 45% of spastic diplegics, and the majority of cases with isolated ataxia, are genetically caused.[77] The mathematical method used for this study, which was based on medical history analysis of prenatal and perinatal risk factors, has been previously validated and successfully applied to study individuals with intellectual disabilities.[78]

In spite of the growing body of evidence for genomic causes of CP, it has been traditionally proposed that genetic and metabolic abnormalities should be excluded before making a diagnosis of CP.[79] However, comprehensive genetic testing is rarely, if ever, offered as part of the diagnostic workup of affected individuals, thus making CP gene discovery a challenging task. Furthermore, in numerous studies where individuals with CP have been studied and found to harbor genetic mutations, the diagnosis is often changed and CP is regarded as an initial misdiagnosis.[80] Not surprisingly, our knowledge of the genomic component of CP lags behind that of other neurodevelopmental disorders.

The CP spectrum disorders: monogenic syndromes that often present as CP

Since CP is a nonspecific clinical diagnosis based on the observation of signs and symptoms, such as delayed motor milestones and abnormalities in posture, muscle tone, coordination, and reflexes, it is not uncommon for individuals with a wide range of neurodevelopmental conditions to be diagnosed as having CP.[81] There are several single-gene (Mendelian) disorders, inherited as autosomal dominant, autosomal recessive, or X-linked, that often present with clinical features similar to CP (supplementary table 1). In such cases, individuals may live with a diagnosis of CP for several years until specific molecular or biochemical diagnostic testing is performed. Some of these disorders are individually rare, but as a group they are not uncommon and should be considered when assessing an individual with CP. Moreover, the spectrum of CP-like syndromes includes some genetic conditions that, once identified, can be successfully treated with currently available medications.

Of particular interest, due to the potential for genomically-guided therapeutic interventions, is the group of dopa-responsive dystonic disorders caused by mutations in the *GCH1* (GTP cyclohydrolase 1), *SPR* (sepiapterin reductase), and *TH* (tyrosine hydroxylase) genes.[82] If untreated, individuals with these disorders can progress to a state of complete loss of ambulation, whereas appropriate management with levodopa leads to a dramatic and sustained improvement in symptoms, even in advanced cases.

Earlier this year, Lee et al. reported the case of a severely disabled young woman who presented with bilateral pes equinovarus, stiffness of the trunk, neck, and upper limbs, and inability to walk.[83] She lived with a diagnosis of CP for more than 10 years until a small dose of levodopa was prescribed and dramatically improved her condition prompting further genetic testing. Sequencing of the *GCH1* gene identified a pathogenic mutation and a diagnosis of Dopa-responsive dystonia (DRD) was made. Indeed, due to shared clinical features, up to 24% of patients with DRD are initially diagnosed with CP.[84] Furthermore, a recent report by Bainbridge et al. described a twin pair with DRD of unknown etiology (previously diagnosed as CP), whose genomes were completely sequenced identifying compound heterozygous mutations in the *SPR* gene.[85] Since disruption of this gene leads to a decrease in tetrahydrobiopterin (cofactor for the synthesis of dopamine and serotonin), their management with levodopa was supplemented with a serotonin precursor (5-hydroxytryptophan) resulting in symptomatic improvement after one week of treatment. These striking examples illustrate the importance of conducting comprehensive genetic

testing in individuals with disorders of the CP spectrum and provide compelling evidence for genomically-oriented medical decision making.

Another group of genomic diseases that often times present as CP is the hereditary spastic paraplegias (HSP). These disorders are characterized by lower limb weakness and spasticity arising from length-dependent, distal axonopathy of the corticospinal tract fibers.[86] More than 40 loci have been mapped for HSP, which can be inherited in an autosomal dominant, autosomal recessive, or X-linked fashion.[87] A notable example of the overlapping presentation of CP and HSP comes from a report by Rainier et al. who evaluated a 34-year-old woman diagnosed with spastic diplegic CP since early childhood. When her 10-month-old child presented with similar symptoms, the diagnosis was changed to autosomal dominant, uncomplicated, early-onset HSP. Further genetic testing identified a heterozygous mutation in the *ATL1* (atlastin GTPase 1) gene responsible for spastic paraplegia type 3A.[88]

Additional Mendelian conditions that present with features of CP are summarized in supplementary table 1 and include recognizable genetic disorders such as Rett (*MECP2*)[89] and Angelman (*UBE3A*) syndromes,[90] metabolic disorders including Lesch-Nyhan syndrome (*HPRT*)[91] and glutaric acidemia type 1(*GCDH*),[92] heritable thrombophilias, like protein C deficiency (*PROC*),[57] and cerebral dysgenesis such as classic lissencephaly (*PAFAH1B1*)[93] and pontocerebellar hypoplasia type 1 (*VRK1*).[94]

New single gene causes of idiopathic CP

As described below, the identification of the first CP genes was accomplished by means of positional cloning techniques, such as microsatellite-based linkage mapping, followed by conventional (Sanger) sequencing of candidate genes in large multi-generational families with multiple affected individuals.[59] More recent studies have relied on high-resolution copy number variation (CNV) analyses and next-generation sequencing technologies for gene discovery.[61–63] At the time of this review, the total number of genes with mutations causing human disease is 2,687 (www.omim.org/statistics/geneMap), of which six are known to cause Mendelian forms of CP (table 2). It is likely that the list of monogenic causes of CP will continue to grow exponentially due to the increasing use of cutting-edge genomic technologies to evaluate individuals with undiagnosed disorders of brain development.

GAD1

In 2004, Lynex et al. identified the first gene responsible for a Mendelian form of CP. They reported two consanguineous families in which six individuals presented with congenital spastic CP of unknown etiology.[59] All individuals had global developmental delay, moderate to severe ID, poor or absent speech, and spasticity with hypertonia and brisk reflexes predominantly in the lower limbs. One of them also had microcephaly, contractures, and kyphoscoliosis and another one bilaterally dislocated hips that required surgical management. Using 290 polymorphic DNA markers for linkage mapping, a 5 centimorgan (cM) region of homozygosity was identified on chromosome 2q24-q25 and subsequently refined to 0·5 cM by microsatellite typing. The region included the *GAD1* gene, encoding the brain-expressed isoform of glutamate decarboxylase, which was considered to be a good candidate gene for CP. Indeed, direct sequencing of *GAD1* in affected and unaffected individuals from both families revealed a homozygous missense mutation segregating with the CP phenotype. Glutamate decarboxylase is responsible for the production of γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter, from its excitatory counterpart glutamate. Both molecules, as well as the balance between excitatory and inhibitory neurotransmission modulated partly by *GAD1*, are known to be critical for normal brain development and synaptic plasticity.[95]

KANK1

One year after the discovery of the first CP gene, Lerer et al. studied a large four-generation pedigree in which nine children had CP.[60] All affected individuals were born after normal pregnancies and showed congenital hypotonia which evolved to spastic tetraplegia over the first year of life. Additional features included moderate to severe ID, nystagmus, and brain atrophy with ventriculomegaly. Using linkage analysis, a region in chromosome 9p24.3 was suggested to harbor the causative gene. Further studies identified a 225 kb deletion in 9p24.3 involving a single gene, *KANK1* (KN motif and ankyrin repeat domains 1, previously called *ANKRD15*), in affected individuals in the family which was not observed in 210 control individuals. *KANK1* is expressed in the developing brain and is thought to play a role in protein-protein interactions and adhesion complexes.[60] Moreover, the KANK family of proteins is known to regulate actin polymerization and cell migration.[96]

The AP-4 deficiency syndrome: *AP4M1, AP4E1, AP4B1*, and *AP4S1*

In 2009, Verkerk et al.[61] reported a consanguineous Moroccan family in which five siblings had CP. They presented with infantile hypotonia that progressed to spastic tetraplegia with hypertonia and hyperreflexia, severe ID, absent speech, and lack of independent walking and sphincter control. Additional features included microcephaly, drooling, and stereotypic laughter. Neuroimaging studies showed diffuse white matter loss, ventriculomegaly, and cerebellar atrophy. Postmortem neuropathologic examination of a patient who died at 17 months of aspiration pneumonia revealed reduced myelin in cerebral white matter and abnormal dendritic arborization of cerebellar Purkinje cells. Using homozygosity mapping followed by candidate gene sequencing, a homozygous mutation in the *AP4M1* gene, encoding the μ subunit of the adaptor protein complex-4 (AP-4), was identified in all affected individuals.

Following this report, our group reported a Palestinian-Jordanian inbred kindred with two siblings affected by a type of CP resembling that of the individuals previously described.[62] Both subjects presented at birth with microcephaly and hypotonia that progressed to spastic tetraplegia with hyperreflexia and generalized hypertonia. They also had severe ID, generalized tonic-clonic seizures, absent speech, inability to walk or to control sphincters, drooling, and outbursts of stereotypic laughter. Dysmorphic features included bitemporal narrowing, downslanted palpebral fissures, broad nasal bridge, and short philtrum. Brain imaging showed ventriculomegaly, cerebellar atrophy, reduced hippocampal volume, and white matter loss. We performed copy number array analyses and identified a homozygous deletion of chromosome 15q21.2 that includes exons 1–11 of the *AP4E1* (ε subunit of AP-4) gene in both individuals.

Based on these two unrelated CP pedigrees, each with a homozygous mutation in a different subunit of AP-4 (*AP4E1*[62] and *AP4M1*[61]), along with previous reports of mouse mutations in a third subunit resulting in axonal abnormalities,[97] we proposed that disruption of any one of the four subunits of AP-4 (*AP4E1, AP4M1, AP4B1*, and *AP4S1*) would result in dysfunction of the entire complex and lead to a distinct autosomal recessive CP disorder, which we designated as AP-4 deficiency syndrome.[62]

Indeed, our hypothesis was rapidly confirmed by a recent study of eight individuals, from three consanguineous families, that presented with a remarkably similar phenotype to that described in the previous patients (summarized in table 3).[63] In addition to sharing most of the neurodevelopmental features, they had common dysmorphisms including wide nasal bridge, bulbous nose, and coarse features. By means of autozygosity mapping followed by either sequencing of candidate genes or whole exome sequencing, mutations in *AP4E1*, *AP4B1* (β subunit of AP-4), and *AP4S1* (σ subunit of AP-4) were identified in affected

individuals from each of the three pedigrees. Furthermore, a recent study of 136 consanguineous families with autosomal recessive intellectual disability identified mutations in *AP4E1* and *AP4M1* in two unrelated families with five individuals affected by severe intellectual disability, microcephaly, and spastic paraplegia.[98]

Altogether, 20 affected individuals, from seven unrelated consanguineous families, provide compelling evidence for pathogenic mutations in each of the four genes encoding the AP-4 complex subunits.[61–63] Furthermore, since all affected individuals presented with a strikingly similar CP phenotype, the existence of an AP-4 deficiency syndrome is confirmed, defining a clinically and genetically recognizable form of CP.

The AP-4 complex

The adaptor protein complexes, AP-1, AP-2, AP-3, and AP-4 are ubiquitously expressed heterotetrameric structures that play a crucial role in vesicular trafficking of membrane proteins along the late secretory and endocytic pathways.[99] They create an interface between cargo molecules and an outer coat protein, thus promoting the assembly of coated vesicles. The AP-complexes are composed of four different subunits that come together to form a heterotetramer: one large variable subunit (γ in AP-1, α in AP-2, δ in AP-3, and ε in AP-4), one large subunit with higher homology between the complexes (β1–4), one medium subunit (μ1–4), and one small subunit (σ1–4).[100] Although all four AP-complexes share a common structural pattern, each one selects a different set of cargo proteins to be included into coated vesicles and sorted along a specific trafficking route.

The AP-4 complex is expressed in the central nervous system throughout the embryologic and postnatal developmental stages.[61,101] It selectively sorts proteins from the *trans*-Golgi network to the postsynaptic somatodendritic domain, avoiding the presynaptic axonal domain, thus helping to establish neuronal polarity.[102] Known cargo molecules sorted by AP-4 include α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and δ2 glutamate receptors, transmembrane AMPA receptor regulatory proteins, low density lipoprotein (LDL) receptors, and Alzheimer's disease amyloid precursor protein (APP).[97,101,103] Since AMPA receptors participate in excitatory synaptic transmission, adequate AP-4-mediated trafficking of these receptors to their target membrane is critical for neurotransmission and synaptic plasticity. Moreover, AP-4-dependent transport of APP reduces γ-secretase cleavage of the precursor protein to the pathogenic amyloid-β peptide.[103] Therefore, deficiency of AP-4 has the potential to disturb critical neurophysiologic processes leading to increased amyloidogenic processing of APP, as well as abnormal synaptic transmission due to deficient cycling of glutamate receptors.

In an effort to define the role of AP-4 in neurons, Matsuda et al. disrupted the gene encoding the β subunit of the complex.[97] AP-4 deficient mice showed no major brain anomalies, but performed poorer on the rotorod test when compared to wild type mice. Furthermore, examination of cerebellar Purkinje cells and hippocampal neurons revealed axonal swelling and accumulation of AMPA, δ2, and LDL receptors in autophagosomes near the axon terminals. These findings suggest that AP-4 deficiency results in loss of somatodendritic-specific sorting of cargo molecules, leading to mislocalization of such proteins to the axonal domain and further degradation via the autophagic pathway. Together, these findings highlight the crucial role of vesicular trafficking in brain development and function, and illustrate how disturbances in different proteins along a shared biological pathway can lead to disorders with similar clinical phenotypes. Furthermore, several other genes and proteins involved in the AP-4-mediated vesicular trafficking pathway instantly become strong candidate CP genes. Further studies are needed to establish the frequency of the AP-4

deficiency syndrome and to explore the contribution of other genes in this pathway to the etiology of CP.

Genetic association studies

Based on the hypotheses that abnormalities in the inflammatory system and the coagulation cascade may contribute to the causal pathway of CP, numerous studies have explored whether single nucleotide polymorphisms (SNPs), in a subset of genes involved in these processes, confer an increased risk for CP. Some of the most studied polymorphisms are located within genes that code for factor V Leiden, prothrombin, methylenetetrahydrofolate reductase, apolipoprotein E (*APOE*, ε2 and ε4 alleles), interleukins 6 and 8, nitric oxide synthase (endothelial and inducible), platelet activator inhibitor, endothelial protein C receptor, mannose binding lectin, tumor necorsis factor α, and lymphotoxin-α.[104] Despite more than 20 case-control studies focused on these candidate genes, the results have been inconsistent and often times conflicting. In an effort to increase the statistical power of individual studies, Wu et al. conducted a meta-analysis exploring 17 polymorphisms in 2533 cases and 4432 controls from 11 studies and concluded that only one SNP within interleukin-6 (rs1800795) had a significant association with CP.[105]

In 2009, O'Callaghan et al. applied the human genome epidemiology network (HuGENet) guidelines to conduct a systematic review of 22 targeted association studies in individuals with CP.[106] Multiple polymorphisms were analyzed including 18 SNPs in thrombophilic genes, eight in cytokine genes, *APOE*'s ε2, ε3, and ε4 alleles, and 23 polymorphisms in genes involved in other systems. The authors concluded that due to limited sample sizes, ethnically diverse cohorts, and inadequate controls in the majority of studies, proposed associations of SNPs and CP outcome remained controversial.[106] However, some candidate genes, including factor V Leiden, methylenetetrahydrofolate reductase, lymphotoxin-α, tumor necrosis factor-α, endothelial nitric oxide synthase, and mannose binding lectin, were more promising than the rest. The most recent population-based, case-control study exploring genetic polymorphisms in CP included 138 cases and 165 controls from 334,333 infants born at term or near-term in a health care organization in California.[104] In an effort to replicate previously proposed associations between genetic polymorphisms and CP, 15 well-studied SNPs were genotyped. After correcting for multiple comparisons, no statistically significant association between any SNP and CP was identified.

Not surprisingly, genetic association studies have failed to reach strong, replicable results when applied to complex, multifactorial, and highly heterogeneous groups of disorders, such as CP. The genomic architecture of CP likely resembles that of other developmental brain disorders resulting from multiple rare, and often times private, genetic variations that are infrequently detected by association studies.[55,107] Furthermore, since all CP association studies to date have been hypothesis-driven, only a limited number of polymorphisms within a small group of candidate genes have been explored. Currently, commercially available genotyping platforms feature more than 1·5 million markers that can be used simultaneously for genome-wide association studies and CNV analyses. The implementation of whole-genome scans, as an unbiased approach to study individuals with CP, has the potential to discover novel CP genes and biological pathways to further unravel the genomic underpinnings of this disorder.

Whole-exome and genome sequencing: new opportunities for CP research

The longstanding quest to find the cause of some of the most common neurodevelopmental disorders, as well as rare conditions with suspected genetic etiologies, has recently seen a surge in progress with exciting new results. A major factor in this tremendous success comes from recent advances in next-generation sequencing technologies, which have allowed rapid

and cost-effective sequencing of the entire human genome or a subset which includes all coding genes, referred to as the "exome".[108] Exome sequencing has been successfully implemented to uncover the causative gene in a wide range of Mendelian disorders, including *MLL2* in Kabuki syndrome,[109] *DHODH* in Miller syndrome,[110] and *KIF1A* in Hereditary Spastic Paraparesis.[111]

Furthermore, the widespread use of trio-based exome sequencing as the standard approach to study complex neurodevelopmental disorders has resulted in the discovery of pathogenic *de novo* mutations in multiple new genes for intellectual disability,[112] autism spectrum disorders,[113] and schizophrenia.[114] These findings support the notion that developmental brain disorders such as CP are likely caused by hundreds of genes, and that systematic family-based exome or genome sequencing has the power to uncover them.

Conclusions

The field of CP genetics is rapidly growing and has already changed our understanding of the underpinnings of this complex disorder. There are multiple monogenic syndromes that present with CP-like features (CP spectrum disorders) that should be considered as part of the diagnostic evaluation of affected individuals. Furthermore, we now know of six genes that can cause CP when disrupted and estimate that many other developmental brain genes are likely to contribute to the genetic heterogeneity of this disorder. The availability of personal and family-based genome sequencing has made it feasible to identify rare or private mutations in CP families at a reasonable cost, currently for research and soon on a clinical diagnostic basis. Moreover, the continuous discovery of genes and molecular pathways disrupted in CP will increase the possibility of developing genomically-guided pharmacological interventions for this condition. As the paradigm shift continues and more researchers, clinicians, and the general population start to consider the cerebral palsies as a group of neurogenetic disorders, it is likely that we will witness an increase in research efforts, a change in the diagnostic approach, and eventually novel therapies for CP. This exciting new era of CP genomics will unquestionably benefit this patient population.

Search strategy and selection criteria

References for this review were identified through searches of Pubmed with the search terms "neurogenetics", "genetics", "genomics", "genes", "mutations", "chromosomes", and "cerebral palsy" up to November, 2011. Articles were also identified through searches of the authors' own files. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Erin B. Kaminsky, Ph.D. and Daniel Moreno-De-Luca, M.D. for insightful comments and discussions.

Funding

This work was funded in part by grant MH074090 (to DHL and CLM) from the National Institutes of Health.

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Table 1

Criteria proposed by the International Cerebral Palsy Task Force to define an acute intrapartum hypoxic event.[53]

Essential criteria
1. Evidence of a metabolic acidosis in intrapartum fetal, umbilical arterial cord, or very early neonatal blood samples (pH < 7·00 and base deficit >12 mmol/l)
2. Early onset of severe or moderate neonatal encephalopathy in infants of >34 weeks' gestation
3. Cerebral palsy of the spastic quadriplegic or dyskinetic type
Criteria that together suggest an intrapartum timing but by themselves are non-specific
4. A sentinel (signal) hypoxic event occurring immediately before or during labor
5. A sudden, rapid, and sustained deterioration of the fetal heart rate pattern usually after the hypoxic sentinel event where the pattern was previously normal
6. Apgar scores of 0–6 for longer than 5 minutes
7. Early evidence of multisystem involvement
8. Early imaging evidence of acute cerebral abnormality

Table 2

Known cerebral palsy genes

Gene	Name	OMIM ID	Inheritance	Reference
GAD1	Glutamate decarboxylase 1	603513	AR	Lynex et al.[59]
KANK1	KN motif and ankyrin repeat domains 1	612900	AD	Lerer et al.[60]
AP4M1	Adaptor-related protein complex 4, mu 1 subunit	612936	AR	Verkerk et al.[61]
AP4E1	Adaptor-related protein complex 4, epsilon 1 subunit	613744	AR	Moreno-De-Luca et al.[62]
AP4B1	Adaptor-related protein complex 4, beta 1 subunit	614066	AR	Abou Jamra et al.[63]
AP4S1	Adaptor-related protein complex 4, sigma 1 subunit	614067	AR	Abou Jamra et al.[63]

OMIM, Online Mendelian Inheritance in Man; AR, autosomal recessive; AD, autosomal dominant

Table 3

Summary of clinical findings in 15 individuals with AP-4 deficiency syndrome

Clinical features	Frequency
Male/female ratio	1·1:1
Severe ID	15/15 (100%)
Hypotonia → hypertonia	14/14 (100%)
Hyperreflexia	11/11 (100%)
Short stature	8/8 (100%)
Absent speech	13/14 (93%)
Stereotypic laughter	13/14 (93%)
Spasticity	13/14 (93%)
Inability to walk	13/14 (93%)
Babinski sign	8/9 (89%)
Microcephaly	11/14 (79%)
Absent sphincter control	11/14 (79%)
Drooling	10/14 (71%)
Foot deformity	6/13 (46%)
Epilepsy	3/15 (20%)
Overweight	2/8 (25%)
Ventriculomegaly	5/6 (83%)
Cerebellar atrophy	3/6 (50%)
Abnormal white matter	3/6 (50%)