Genetic insights into the causes and classification of the cerebral palsies

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Cerebral palsy—the most common physical disability of childhood—is a clinical diagnosis encompassing a heterogeneous group of neurodevelopmental disorders that cause impairments of movement and posture that persist throughout life. Despite being commonly attributed to a range of environmental factors, particularly birth asphyxia, the specific cause of cerebral palsy remains unknown in most individuals. A growing body of evidence suggests that cerebral palsy is probably caused by multiple genetic factors, similar to other neurodevelopmental disorders such as autism and intellectual disability. Recent advances in next-generation sequencing technologies have made possible rapid and cost-effective sequencing of the entire human genome. Novel cerebral palsy genes will probably be identified as more researchers and clinicians use this approach to study individuals with undiagnosed neurological disorders. As our knowledge of the underlying pathophysiological mechanisms of cerebral palsy increases, so will the possibility of developing genomically guided therapeutic interventions.

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Introduction

The first description of cerebral palsy as a clinical entity is attributed to William John Little, an eminent British orthopaedic surgeon. In 1861, he wrote a monograph in which he proposed for the first time an association between perinatal asphyxia and poor neurological outcomes later in life.[1] Three decades later, Sigmund Freud, a neurologist and founder of psychoanalysis, questioned Little's conclusions on the cause of cerebral palsy. On the basis of the observation that children with cerebral palsy had medical comorbidities, including intellectual disability, epilepsy, and visual disturbances, he proposed that cerebral palsy could begin earlier in life, during in-utero brain development.[2] Despite Freud's hypothesis, the notion that complications during labour and delivery are the leading cause of cerebral palsy was widely accepted by the medical, scientific, and lay communities. Not until almost one century later did large population-based studies show that only a minority of cerebral palsy cases result from birth asphyxia, thus providing support for Freud's hypothesis.[3–6]

Cerebral palsy is a clinical descriptive term applied to a heterogeneous group of neurodevelopmental disorders in which motor impairments often co-occur with a range of medical disorders. In 2004, the International Working Group on the Definition and Classification of Cerebral Palsy[7] defined cerebral palsy as "a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive 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 behaviour; by epilepsy, and by secondary musculoskeletal problems". Unfortunately, in some cases, once a child is given a clinical diagnosis of cerebral palsy, limited efforts, if any, are made to determine the underlying cause. However, identification of specific causes of the disorder would provide individuals with cerebral palsy and their families with numerous benefits, including a better understanding of the disorder, accurate assessment of recurrence risk, and early intervention; it would also encourage further research into the development of specific medical treatments and therapeutic interventions for cerebral palsy.

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

Epidemiology and classification

Cerebral palsy is the most common cause of physical disability in childhood.[8] The worldwide prevalence of cerebral palsy has remained stable at 2–3 per 1000 livebirths for more than four decades,[9] despite substantial improvements in obstetric and neonatal care. A recent report from the Centers for Disease Control and Prevention[8] noted a prevalence of 3·3 per 1000 8-year-old children from four areas of the USA. Moreover, up to an estimated 1 million children and adults in the USA live with a diagnosis of cerebral palsy, with an average lifetime cost per affected individual in 2003 of US$921 000.[10,11] Because of the increasing life expectancy of individuals with cerebral palsy, the number of adults with this disorder is increasing and their medical and social care needs are changing.[10]

Cerebral palsy can be classified on the basis of 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 can help to identify abnormal neuromuscular tone (hypotonia or hypertonia) and the predominant type of motor impairment, which can be spastic, ataxic, dyskinetic (dystonia or choreoathetosis), or mixed. The characteristics and severity of the motor impairments should be described for each limb and the trunk to differentiate unilateral from bilateral involvement and to establish an anatomical distribution (monoplegia, diplegia, triplegia, hemiplegia, and tetraplegia).[13] These classification systems, which are based on motor type and topography, are often used to infer which area of the brain might be affected (pyramidal or extrapyramidal systems); however, they have poor reliability, even among experienced clinicians.[14,15]

In an effort to establish an accurate, reliable, and standardised system to classify cerebral palsy, Palisano and colleagues[16] 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 range of settings including routine clinical management (mobility assessment, intervention planning, and prognosis), research (sample selection and stratification), and health-care administration.[17–19] A similar scale to assess bimanual fine motor function has been developed and validated as a complement to the GMFCS,[20,21] and a manual ability classification system has been designed to assess the ability of children with cerebral palsy to use their hands for routine activities.[22] Furthermore, the communication function classification system was recently developed in an effort to assess the functional communication competence of individuals with cerebral palsy in daily life situations.[23] The development of objective and valid functional classification systems has greatly improved health-care delivery and standardised research efforts.[16,18]

Although the hallmark feature of cerebral palsy is motor and posture deficit, patients often present with several other impairments and medical disorders. Commonly reported comorbidities include intellectual disabilities in 30–65%, seizure disorders in 30–50%, speech and language deficits in 40%, visual impairments in 40%, and hearing problems in 5–15% of patients.[24–28] Additional systems that might be affected include the somatosensory (deficits in stereognosis and proprioception),[29] genitourinary (enuresis, urinary infections, and voiding dysfunction),[30,31] gastrointestinal (dysphagia, gastroesophageal reflux disease, and constipation),[32] respiratory (recurrent pneumonia, atelectasis, bronchiectasis, and restrictive lung disease),[32] and endocrine systems (reduced growth and osteopenia).[33,34] Furthermore, 20% of individuals with cerebral palsy have psychosocial and behavioural problems and 9% have an autism spectrum disorder.[35] The severity of the motor impairment, along with the presence and extent of accompanying disorders, influences the functional ability of individuals with cerebral palsy and also affects the burden and challenges faced by caregivers and the health system.

Causes

The causes of cerebral palsy have been attributed to a wide range of prenatal, perinatal, and postnatal factors that can present as single, isolated factors or as a combination of multiple potential risk factors. The presence and contribution of individual events varies to some extent between gestational groups and cerebral palsy subtypes.[36] The most commonly reported risk factors include prematurity, low birthweight, birth asphyxia, fetal intrauterine exposure to maternal infection and inflammation, maternal fever during labour, multiple gestations, coagulation disorders and ischaemic stroke in the fetus or newborn, maternal thyroid disease, and placental pathology.[37–39] However, despite the large number of known and proposed causes, the specific causal mechanism remains elusive in most cases of cerebral palsy.

Perhaps the most studied, and still controversial, risk factor associated with cerebral palsy is birth asphyxia. Historically, and unfortunately still today in many groups (eg, researchers, clinicians, and the general public), inadequate oxygen delivery to the brain, caused by adverse intrapartum events, is assumed to be the leading cause of cerebral palsy.[40–42] On the basis of this hypothesis, detection and early intervention in episodes of acute birth asphyxia were proposed as ways to decrease the rate of cerebral palsy and improve long-term neurological outcomes of newborns at risk.[43,44] To that extent, technologies such as electronic fetal monitoring during birth were developed and rapidly introduced into clinical practice, without adequate supporting evidence from scientific studies.[43,44] Electronic fetal monitoring, considered a standard of care by many physicians and institutions, is now widely used to detect early fetal distress resulting from hypoxia during delivery, and despite a five-times increase in the rate of caesarean sections, driven partly by the use of electronic fetal monitoring,[8] the incidence of cerebral palsy has not decreased over time.[9,45,46] Moreover, large population-based, controlled studies, done in various countries, over different timeframes, and across different populations, have shown that birth asphyxia is an uncommon cause of neonatal encephalopathy and accounts for less than 10% of cerebral palsy cases.[3,5,47–50]

Even though most cases of cerebral palsy are not caused by birth asphyxia and those that are can rarely be prevented by obstetric intervention,[51] between 1999 and 2003 an estimated 76% of obstetricians in the USA faced medical malpractice litigation, most often for alleged birth mismanagement resulting in cerebral palsy.[44] A similar situation was reported in a 2002 study from Australia, which reported that 18% of the total medical indemnity claims were attributed to the 2% of physicians who practise obstetrics.[52]

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

An alternative hypothesis is that cerebral palsy is caused by many diverse and individually rare genomic abnormalities, as with 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 cerebral palsy has not been researched extensively, although in the authors' opinion it probably accounts for a substantial proportion of the 70–80% of cases that are attributed to prenatal causes. Furthermore, genomic abnormalities could also be the underlying cause in cases in which classic risk factors such as prematurity, coagulopathies, or difficult birth are identified.[57] Children with malformations of cortical development present with birth complications more frequently than those without these malformations, which often results in the misdiagnosis of intrapartum asphyxia.[58]

***Panel:* Criteria proposed by the International Cerebral Palsy Task Force to define an acute intrapartum hypoxic event**

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 nonspecific

4 A sentinel (signal) hypoxic event occurring immediately before or during labour
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 min
7 Early evidence of multisystem involvement
8 Early imaging evidence of acute cerebral abnormality

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Evidence for genetic factors in cerebral palsy

Several lines of evidence support the theory that multiple genetic factors contribute to the cause of cerebral palsy. First, mutations in multiple genes result in mendelian disorders that present with cerebral palsy-like features (as discussed below), and several single-gene mutations have been identified in idiopathic (ie, non-syndromic) cerebral palsy pedigrees.[59–63] Second, the prevalence of congenital anomalies in individuals with cerebral palsy (11–32%) is significantly higher than in the general population (2–3%).[64,65] Most malformations in children with cerebral palsy are cerebral (72%), of which microcephaly (26%) and hydrocephaly (19%) are the most common.[64] Among the non-cerebral malformations, the most frequent are cardiac (29%), musculoskeletal (14%), and urinary abnormalities (9%), and facial clefts (18%).[64,66,67] Third, register-based studies have reported a significantly higher concordance rate for cerebral palsy in monozygotic twins than in dizygotic twin pairs (p=0·0026).[68] Fourth, the risk of cerebral palsy in consanguineous families is about 2·5 times higher than the risk in outbred families.[69,70] Fifth, several studies have reported familial aggregation of cerebral palsy, including identical cerebral palsy syndromes in the same family.[71–75] Sixth, a paternal age effect has been described in some forms of cerebral palsy.[76] Furthermore, a quantitative analysis of risk factors in 681 individuals with congenital cerebral palsy, from the west Swedish population-based cerebral palsy study, estimated that 60% of hemiplegic cerebral palsy cases, 45% of spastic diplegic cases, and an estimated 100% of cases with isolated ataxia, were caused by genetic mutations.[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 for the study of individuals with intellectual disabilities.[78]

Despite the growing body of evidence for genomic causes of cerebral palsy, it has traditionally been proposed that genetic and metabolic abnormalities should be ruled out before a diagnosis of cerebral palsy is made.[79] However, comprehensive genetic testing is rarely, if ever, offered as part of the diagnostic workup of individuals with suspected cerebral palsy, which makes cerebral palsy gene discovery a challenging task. Furthermore, in several studies in which individuals with cerebral palsy were found to harbour genetic mutations, the diagnosis was often changed and cerebral palsy was regarded as an initial misdiagnosis.[80] At present, our knowledge of the genomic component of cerebral palsy lags behind that of other neurodevelopmental disorders, such as intellectual disabilities and autism spectrum disorders.

The cerebral palsy spectrum disorders

Cerebral palsy is a non-specific clinical diagnosis made on the basis of the presence of signs and symptoms, such as delayed motor development and abnormalities in posture, muscle tone, coordination, and reflexes. Thus, it is not uncommon for individuals with a wide range of neurodevelopmental conditions to be

diagnosed with cerebral palsy.[81] Several single-gene (mendelian) disorders, inherited as autosomal dominant, autosomal recessive, or X-linked, often present with clinical features similar to cerebral palsy (webappendix). In such cases, individuals might live with a diagnosis of cerebral palsy for several years before specific molecular or biochemical diagnostic testing is done. Some of these mendelian disorders are individually rare, but as a group they are not uncommon and should all be considered when assessing an individual with cerebral palsy. Moreover, the spectrum of cerebral palsy-like syndromes includes some genetic conditions that, once identified, can be successfully treated with available drugs.

See Online for webappendix

Of particular interest, because of 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 results in a dramatic and sustained improvement in symptoms, even in advanced cases.[83]

Recently, Lee and colleagues[84] reported the case of a severely disabled young woman who presented with bilateral club foot, stiffness of the trunk, neck, and arms, and an inability to walk. She had lived with a diagnosis of cerebral palsy 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 was made. Because of shared clinical features, up to 24% of patients with dopa-responsive dystonia are initially diagnosed with cerebral palsy.[85] Furthermore, a recent report by Bainbridge and colleagues[86] described a twin pair with dopa-responsive dystonia of unknown cause (previously diagnosed as cerebral palsy), whose genomes were sequenced and found to contain compound heterozygous mutations in the *SPR* gene. Because 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 (oxitriptan), which resulted in symptomatic improvement after 1 week of treatment. These examples show the importance of undertaking comprehensive genetic testing in individuals with disorders of the cerebral palsy spectrum, and provide compelling evidence for genomically oriented medical decision making.

Another group of genomic diseases that often presents as cerebral palsy is the hereditary spastic paraplegias (HSP). These disorders are characterised by leg weakness and spasticity arising from length-dependent, distal axonopathy of the corticospinal tract fibres.[87] More than 40 loci have been mapped for HSP, which can be inherited in an autosomal dominant, autosomal recessive, or X-linked fashion.[88] Rainier and colleagues[89] assessed a 34-year-old woman who had been diagnosed with spastic diplegic cerebral palsy in early childhood. When her 10-month-old child presented with similar symptoms, both mother and child were diagnosed with autosomal dominant, uncomplicated, early-onset HSP. Further genetic testing identified a heterozygous mutation in the *ATL1* (atlastin GTPase 1) gene, which is responsible for spastic paraplegia type 3A.

The webappendix summarises additional mendelian disorders that present with features of cerebral palsy, including recognisable genetic disorders such as Rett (*MECP2*)[90] and Angelman (*UBE3A*) syndromes;[91] metabolic disorders including Lesch-Nyhan syndrome (*HPRT*)[92] and glutaric acidemia type 1 (*GCDH*);[93] heritable thrombophilias, such as protein C deficiency (*PROC*);[57] and cerebral dysgenesis such as classic lissencephaly (*PAFAH1B1*)[94] and pontocerebellar hypoplasia type 1 (*VRK1*).[95]

Single-gene causes of idiopathic cerebral palsy

As described below, the identification of the first cerebral palsy genes was accomplished by 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 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 was 2687,[96] of which six are known to cause mendelian forms of cerebral palsy (table 1).[59–63] The list of monogenic causes of cerebral palsy will probably grow exponentially because of the increasing use of cutting-edge genomic technologies to assess individuals with undiagnosed disorders of brain development.

GAD1

In 2004, Lynex and colleagues[59] were the first group to identify a gene linked to a mendelian form of cerebral palsy. They reported two consanguineous families in which six individuals presented with congenital spastic cerebral palsy of unknown cause. All individuals had global developmental delay, moderate-to-severe intellectual disability, poor or absent speech, and spasticity with hypertonia and brisk reflexes predominantly in the legs. One family member also had microcephaly, contractures, and kyphoscoliosis, and another had bilaterally dislocated hips that needed surgical management. With 290 polymorphic DNA markers for linkage mapping, a 5 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, which encodes the brain-expressed isoform of glutamate decarboxylase, and

was considered a good candidate gene for cerebral palsy by Lynex and colleagues.[59] Direct sequencing of *GAD1* in affected and unaffected individuals from both families revealed a homozygous missense mutation segregating with the cerebral palsy phenotype. Glutamate decarboxylase is responsible for the production of GABA, the major inhibitory neurotransmitter, from its excitatory counterpart glutamate. Both molecules, and the balance between excitatory and inhibitory neurotransmission, which is modulated partly by *GAD1*, are crucial for normal brain development and synaptic plasticity.[97]

	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, μ1 subunit	612936	AR	Verkerk et al[61]
AP4E1	Adaptor-related protein complex 4, ε1 subunit	613744	AR	Moreno-De-Luca et al[62]
AP4B1	Adaptor-related protein complex 4, β1 subunit	614066	AR	Abou Jamra et al[63]
AP4S1	Adaptor-related protein complex 4, σ1 subunit	614067	AR	Abou Jamra et al[63]

OMIM=Online Mendelian Inheritance in Man. AR=autosomal recessive. AD=autosomal dominant.

Table 1: **Genes associated with cerebral palsy**

KANK1

1 year after the discovery of the first cerebral palsy gene, Lerer and colleagues[60] studied a large four-generation pedigree in which nine children had cerebral palsy. All affected individuals were born after normal pregnancies and showed congenital hypotonia that evolved to spastic tetraplegia within the first year of life. Additional features included moderate-to-severe intellectual disability, nystagmus, and brain atrophy with ventriculomegaly. Linkage analysis showed that a region on chromosome 9p24.3 seemed to harbour the causative gene. Further studies identified a 225 kb deletion on 9p24.3 involving one gene, *KANK1* (KN motif and ankyrin repeat domains 1, previously called *ANKRD15*), in affected individuals in the family, which was not identified in 210 control individuals. *KANK1* is expressed in the developing brain and is thought to play a part in protein–protein interactions and adhesion complexes.[60] Moreover, the KANK family of proteins regulates actin polymerisation and cell migration.[98]

The adaptor protein complex-4 deficiency syndrome: *AP4M1*, *AP4E1*, *AP4B1*, and *AP4S1*

In 2009, Verkerk and colleagues[61] reported data from a consanguineous Moroccan family in which five siblings had cerebral palsy. They presented with infantile hypotonia that progressed to spastic tetraplegia with hypertonia and hyper-reflexia, severe intellectual disability, absent speech, and absence of independent walking and sphincter control. Additional features included microcephaly, drooling, and stereotypical laughter. Neuroimaging studies showed diffuse white matter loss, ventriculomegaly, and cerebellar atrophy. Post-mortem neuropathological examination of a patient who died of aspiration pneumonia at 17 months revealed reduced myelin in cerebral white matter compared with normal brains and abnormal dendritic arborisation of cerebellar Purkinje cells compared with an age-matched control individual. 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.

After this report, our group[62] reported a Palestinian-Jordanian inbred kindred with two siblings affected by a type of cerebral palsy that resembled that of the individuals previously described.[61] Both patients presented at birth with microcephaly and hypotonia that progressed to spastic tetraplegia with hyper-reflexia and generalised hypertonia. They also had severe intellectual disability, generalised tonic-clonic seizures, absent speech, an inability to walk or to control sphincters, drooling, and outbursts of stereotypical laughter. Dysmorphic features included bitemporal narrowing, down-slanted palpebral fissures, a broad nasal bridge, and a short philtrum. Brain MRI showed ventriculomegaly, cerebellar atrophy, reduced hippocampal volume, and white matter loss. We did copy number array analyses and identified a homozygous deletion on chromosome 15q21.2 that included exons 1–11 of the *AP4E1* (ε subunit of AP-4) gene in both individuals.

On the basis of findings from these two unrelated cerebral palsy pedigrees, each of which had a homozygous mutation in a different subunit of AP-4 (*AP4E1*[62] and *AP4M1*[61]), along with previous findings that mutations in a third subunit (the β subunit) result in axonal abnormalities in mice,[99] 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 cerebral palsy disorder, which we defined as AP-4-deficiency syndrome.[62]

Our hypothesis was confirmed by a recent study of eight individuals, from three consanguineous families, who presented with a similar phenotype to that described in the previous patients (summarised in table 2).[63] In addition to sharing many neurodevelopmental features, these individuals had common dysmorphisms, including a wide nasal bridge, bulbous nose, and coarse features. By autozygosity mapping followed by either sequencing of candidate genes or whole-exome sequencing, mutations in *AP4E1*, *AP4B1* (β subunit of AP-4), and *AP4S1* (□ subunit of AP-4) were identified in affected individuals from each of the three pedigrees.[63] 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.[100]

These findings from 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.[61–63,100] Furthermore, because all affected individuals presented with a similar cerebral palsy phenotype, the existence of an AP-4-deficiency syndrome is confirmed, defining a clinically and genetically recognisable form of cerebral palsy.

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 part in vesicular trafficking of membrane proteins along the late secretory and endocytic pathways.[101] 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 high homology between the complexes (β1-4), one medium subunit (μ1-4), and one small subunit (□1-4).[102] Although all four AP complexes share a common structural pattern, each one targets 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 CNS throughout the embryologic and postnatal developmental stages.[61,103] 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.[104] Known cargo molecules sorted by AP-4 include AMPA and δ2 glutamate receptors, transmembrane AMPA receptor regulatory proteins, low-density lipoprotein receptors, and Alzheimer's disease amyloid precursor protein (APP).[99,103,105] Because AMPA receptors participate in excitatory synaptic transmission, adequate AP-4-mediated trafficking of these receptors to their target membrane is crucial 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.[105] Therefore, deficiency of AP-4 has the potential to disturb crucial neurophysiological processes, leading to increased amyloidogenic processing of APP and abnormal synaptic transmission due to deficient cycling of glutamate receptors.

In an effort to define the role of AP-4 in neurons, Matsuda and colleagues[99] disrupted the gene encoding the β subunit of the complex in mice, both in vitro and in vivo. AP-4-deficient mice showed no major brain anomalies but did less well on the rotorod test than wild-type mice. Furthermore, examination of cerebellar Purkinje cells and hippocampal neurons revealed axonal swelling and accumulation of AMPA, δ2, and low-density lipoprotein 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 mislocalisation 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 show how disturbances in different proteins along a shared biological pathway can lead to disorders with similar clinical phenotypes. Furthermore, these findings show that several genes and proteins involved in the AP-4-mediated vesicular trafficking pathway are strong candidate genes for cerebral palsy. Further studies are needed to establish the frequency of AP-4-deficiency syndrome and to explore the contribution of other genes in this pathway to the development of cerebral palsy.

	Frequency
Male:female ratio	1·1:1
Severe intellectual disability	15/15 (100%)
Hypotonia progressing to hypertonia	14/14 (100%)
Hyper-reflexia	11/11 (100%)
Short stature	8/8 (100%)
Absent speech	13/14 (93%)
Stereotypical 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%)
Overweight	2/8 (25%)
Epilepsy	3/15 (20%)
Ventriculomegaly	5/6 (83%)
Cerebellar atrophy	3/6 (50%)
Abnormal white matter	3/6 (50%)

Data are n/N (%), unless otherwise stated. Information on all the clinical features was not available for all 15 individuals. Data from Verkerk and colleagues,[61] Moreno-De-Luca and colleagues,[62] and Abou Jamra and colleagues.[63]

Table 2: **Summary of clinical findings in 15 individuals with AP-4-deficiency syndrome**

Genetic association studies

On the basis of the hypotheses that abnormalities in the inflammatory system and the coagulation cascade might contribute to the causal pathway of cerebral palsy, numerous studies have explored whether single nucleotide polymorphisms (SNPs) in a subset of genes involved in these processes confer an increased risk for cerebral palsy. 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, tumour

necrosis factor α, and lymphotoxin-α.[106] Despite more than 20 case-control studies focused on these candidate genes, the results are inconsistent and often conflicting. In an effort to increase the statistical power of individual studies, Wu and colleagues[107] undertook a meta-analysis exploring 17 polymorphisms in 2533 cases and 4432 control individuals from 11 studies and concluded that only one SNP in interleukin-6 (rs1800795) was significantly associated with cerebral palsy.[107]

In 2009, O'Callaghan and colleagues[108] applied the human genome epidemiology network (HuGENet) guidelines to undertake a systematic review of 22 targeted association studies in individuals with cerebral palsy. Multiple polymorphisms were analysed, including 18 SNPs in thrombophilic genes, eight in cytokine genes, *APOE* ε2, ε3, and ε4 alleles, and 23 polymorphisms in genes involved in other systems. The authors concluded that because of limited sample sizes, ethnically diverse cohorts, and inadequate control individuals in most studies, proposed associations of SNPs and cerebral palsy outcome remained controversial.[108] However, some candidate genes, including factor V Leiden, methylenetetrahydrofolate reductase, lymphotoxin-α, tumour necrosis factor-α, endothelial nitric oxide synthase, and mannose binding lectin, were more promising than the rest in O'Callaghan and colleagues' opinion. The most recent population-based, case-control study investigating genetic polymorphisms in cerebral palsy included 138 cases and 165 control individuals from 334 333 infants born at term or near term in a health-care organisation in California, USA.[106] In an effort to replicate previously proposed associations between genetic polymorphisms and cerebral palsy, 15 well studied SNPs were genotyped. After correcting for multiple comparisons, no statistically significant association between any SNP and cerebral palsy was identified.

Genetic association studies have failed to reach strong, replicable results when applied to complex, multifactorial, and highly heterogeneous groups of disorders, such as cerebral palsy. The genomic makeup of cerebral palsy probably resembles that of other developmental brain disorders that result from multiple rare, and often private (ie, mutations rare enough to be restricted to an individual or kindred), genetic variations that are infrequently detected in association studies.[55,109] Furthermore, because all cerebral palsy association studies so far have been hypothesis driven, only a limited number of polymorphisms within a small group of candidate genes have been assessed. At present, commercially available genotyping platforms feature more than 1·5 million markers that can be used simultaneously for genome-wide association studies and copy number variation analyses. The implementation of whole-genome scans, as an unbiased approach to study individuals with cerebral palsy, could enable discovery of novel cerebral palsy genes and biological pathways to further unravel the genomic underpinnings of this disorder.

Whole-exome and genome sequencing

The longstanding quest to find the cause of some of the most common neurodevelopmental disorders, as well as rare conditions with suspected genetic causes, has recently made rapid progress, with exciting new findings. A major factor in this 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 that includes all coding genes, referred to as the exome.[110] Exome sequencing has been successfully implemented to uncover the causative gene in a range of mendelian disorders, including *MLL2* in Kabuki syndrome,[111] *DHODH* in Miller syndrome,[112] and *KIF1A* in hereditary spastic paraparesis.[113] 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 genes for intellectual disability,[114] autism spectrum disorders,[115] and schizophrenia.[116] These findings support the notion that developmental brain disorders such as cerebral palsy are probably caused by hundreds of genes, and that systematic family-based exome or genome sequencing has the power to uncover them.

For **HuGENet** see http://www.cdc.gov/genomics/hugenet/

Conclusions

The field of cerebral palsy genetics is rapidly growing and has already changed our understanding of the underpinnings of this complex disorder. Multiple monogenic syndromes that present with cerebral palsy-like features (cerebral palsy spectrum disorders) should be considered as part of the diagnostic assessment of individuals with suspected cerebral palsy. Furthermore, we now know of six genes that can cause cerebral palsy when disrupted, and we estimate that many other developmental brain genes probably contribute to the genetic heterogeneity of this disorder. The availability of personal and family-based genome sequencing has made identification of rare or private mutations in cerebral palsy families feasible at a reasonable cost—at present for research and soon on a clinical diagnostic basis. Moreover, the continuous discovery of genes and molecular pathways that are

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" from inception to November, 2011. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

disrupted in cerebral palsy will increase the possibility of developing genomically guided pharmacological interventions for this disorder. 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, we will probably witness an increase in research efforts, a change in the diagnostic approach, and eventually novel therapies for cerebral palsy. This exciting new era of cerebral palsy genomics will unquestionably benefit this patient population.

Contributors

AM-D-L prepared the first draft of this Review. DHL and CLM revised the manuscript. All authors approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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References

1 Little WJ. On the influence of abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum, on the mental and physical condition of the child, especially in relation to deformities. *Trans Obstet Soc Lond* 1861; **62:** 293–344.

2 Freud S. Die infantile Cerebrallähmung. In: Nothnagel H, ed. Specielle Pathologie und Therapie. Wien, Austria: Alfred Hölder; 1897: 1–327.

3 Nelson KB, Ellenberg JH. Obstetric complications as risk factors for cerebral palsy or seizure disorders. *JAMA* 1984; **251:** 1843–48.

4 Grether JK, Nelson KB. Maternal infection and cerebral palsy in infants of normal birth weight. *JAMA* 1997; **278:** 207–11.

5 Torfs CP, van den Berg B, Oechsli FW, Cummins S. Prenatal and perinatal factors in the etiology of cerebral palsy. *J Pediatr* 1990; **116:** 615–19.

6 Badawi N, Kurinczuk JJ, Keogh JM, et al. Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ* 1998; **317:** 1554–58.

7 Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007; **109:** 8–14.

8 Kirby RS, Wingate MS, Van Naarden Braun K, et al. Prevalence and functioning of children with cerebral palsy in four areas of the United States in 2006: a report from the Autism and Developmental Disabilities Monitoring Network. *Res Dev Disabil* 2011; **32:** 462–69.

9 Clark SL, Hankins GD. Temporal and demographic trends in cerebral palsy—fact and fiction. *Am J Obstet Gynecol* 2003; **188:** 628–33.

10 Tosi LL, Maher N, Moore DW, Goldstein M, Aisen ML. Adults with cerebral palsy: a workshop to define the challenges of treating and preventing secondary musculoskeletal and neuromuscular complications in this rapidly growing population. *Dev Med Child Neurol* 2009; **51** (suppl 4)**:** 2–11.

11 Centers for Disease Control and Prevention. Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment—United States, 2003. *MMWR Morb Mortal Wkly Rep* 2004; **53:** 57–59.

12 Bax M, Goldstein M, Rosenbaum P, et al. Proposed definition and classification of cerebral palsy, April 2005. *Dev Med Child Neurol* 2005; **47:** 571–76.

13 Cans C. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). *Dev Med Child Neurol* 2000; **42:** 816–24.

14 Blair E, Stanley F. Interobserver agreement in the classification of cerebral palsy. *Dev Med Child Neurol* 1985; **27:** 615–22.

15 Howard J, Soo B, Graham HK, et al. Cerebral palsy in Victoria: motor types, topography and gross motor function. *J Paediatr Child Health* 2005; **41:** 479–83.

16 Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997; **39:** 214–23.

17 Shevell MI, Dagenais L, Hall N. Comorbidities in cerebral palsy and their relationship to neurologic subtype and GMFCS level. *Neurology* 2009; **72:** 2090–96.

18 Palisano RJ, Hanna SE, Rosenbaum PL, et al. Validation of a model of gross motor function for children with cerebral palsy. *Phys Ther* 2000; **80:** 974–85.

19 Rosenbaum PL, Walter SD, Hanna SE, et al. Prognosis for gross motor function in cerebral palsy: creation of motor development curves. *JAMA* 2002; **288:** 1357–63.

20 Beckung E, Hagberg G. Neuroimpairments, activity limitations, and participation restrictions in children with cerebral palsy. *Dev Med Child Neurol* 2002; **44:** 309–16.

21 Himmelmann K, Beckung E, Hagberg G, Uvebrant P. Gross and fine motor function and accompanying impairments in cerebral palsy. *Dev Med Child Neurol* 2006; **48:** 417–23.

22 Eliasson AC, Krumlinde-Sundholm L, Rosblad B, et al. The manual ability classification system (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. *Dev Med Child Neurol* 2006; **48:** 549–54.

23 Hidecker MJ, Paneth N, Rosenbaum PL, et al. Developing and validating the communication function classification system for individuals with cerebral palsy. *Dev Med Child Neurol* 2011; **53:** 704–10.

24 Parkes J, Dolk H, Hill N, Pattenden S. Cerebral palsy in Northern Ireland: 1981–93. *Paediatr Perinat Epidemiol* 2001; **15:** 278–86.

25 Murphy CC, Yeargin-Allsopp M, Decoufle P, Drews CD. Prevalence of cerebral palsy among ten-year-old children in metropolitan Atlanta, 1985 through 1987. *J Pediatr* 1993; **123:** S13–20.

26 Beckung E, White-Koning M, Marcelli M, et al. Health status of children with cerebral palsy living in Europe: a multi-centre study. *Child Care Health Dev* 2008; **34:** 806–14.

27 Andersen GL, Irgens LM, Haagaas I, Skranes JS, Meberg AE, Vik T. Cerebral palsy in Norway: prevalence, subtypes and severity. *Eur J Paediatr Neurol* 2008; **12:** 4–13.

28 Colver AF, Gibson M, Hey EN, Jarvis SN, Mackie PC, Richmond S. Increasing rates of cerebral palsy across the severity spectrum in north-east England 1964-1993. The North of England Collaborative Cerebral Palsy Survey. *Arch Dis Child Fetal Neonatal Ed* 2000; **83:** 7–12.

29 Yekutiel M, Jariwala M, Stretch P. Sensory deficit in the hands of children with cerebral palsy: a new look at assessment and prevalence. *Dev Med Child Neurol* 1994; **36:** 619–24.

30 Ozturk M, Oktem F, Kisioglu N, et al. Bladder and bowel control in children with cerebral palsy: case-control study. *Croat Med J* 2006; **47:** 264–70.

31 Karaman MI, Kaya C, Caskurlu T, Guney S, Ergenekon E. Urodynamic findings in children with cerebral palsy. *Int J Urol* 2005; **12:** 717–20.

32 Pruitt DW, Tsai T. Common medical comorbidities associated with cerebral palsy. *Phys Med Rehabil Clin N Am* 2009; **20:** 453–67.

33 Henderson RC, Gilbert SR, Clement ME, Abbas A, Worley G, Stevenson RD. Altered skeletal maturation in moderate to severe cerebral palsy. *Dev Med Child Neurol* 2005; **47:** 229–36.

34 Henderson RC, Kairalla JA, Barrington JW, Abbas A, Stevenson RD. Longitudinal changes in bone density in children and adolescents with moderate to severe cerebral palsy. *J Pediatr* 2005; **146:** 769–75.

35 Pakula AT, van Naarden Braun K, Yeargin-Allsopp M. Cerebral palsy: classification and epidemiology. *Phys Med Rehabil Clin N Am* 2009; **20:** 425–52.

36 Himmelmann K, Ahlin K, Jacobsson B, Cans C, Thorsen P. Risk factors for cerebral palsy in children born at term. *Acta Obstet Gynecol Scand* 2011; **90:** 1070–81.

37 Nelson KB. Causative factors in cerebral palsy. *Clin Obstet Gynecol* 2008; **51:** 749–62.

38 Keogh JM, Badawi N. The origins of cerebral palsy. *Curr Opin Neurol* 2006; **19:** 129–34.

39 Clark SM, Ghulmiyyah LM, Hankins GD. Antenatal antecedents and the impact of obstetric care in the etiology of cerebral palsy. *Clin Obstet Gynecol* 2008; **51:** 775–86.

40 Windle WF. Neurological and psychological deficits from asphyxia neonatorum. *Public Health Rep* 1957; **72:** 646–50.

41 O'Brien JR, Usher RH, Maughan GB. Causes of birth asphyxia and trauma. *Can Med Assoc J* 1966; **94:** 1077–85.

42 Windle WF. Brain damage at birth. Functional and structural modifications with time. *JAMA* 1968; **206:** 1967–72.

43 Greene MF. Obstetricians still await a deus ex machina. *N Engl J Med* 2006; **355:** 2247–48.

44 MacLennan A, Nelson KB, Hankins G, Speer M. Who will deliver our grandchildren? Implications of cerebral palsy litigation. *JAMA* 2005; **294:** 1688–90.

45 Natale R, Dodman N. Birth can be a hazardous journey: electronic fetal monitoring does not help. *J Obstet Gynaecol Can* 2003; **25:** 1007–09.

46 Freeman R. Intrapartum fetal monitoring—a disappointing story. *N Engl J Med* 1990; **322:** 624–26.

47 Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. Multivariate analysis of risk. *N Engl J Med* 1986; **315:** 81–86.

48 Blair E, Stanley FJ. Intrapartum asphyxia: a rare cause of cerebral palsy. *J Pediatr* 1988; **112:** 515–19.

49 Nelson KB. What proportion of cerebral palsy is related to birth asphyxia? *J Pediatr* 1988; **112:** 572–74.

50 Graham EM, Ruis KA, Hartman AL, Northington FJ, Fox HE. A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. *Am J Obstet Gynecol* 2008; **199:** 587–95.

51 Nelson KB. Can we prevent cerebral palsy? *N Engl J Med* 2003; **349:** 1765–69.

52 MacLennan AH, Spencer MK. Projections of Australian obstetricians ceasing practice and the reasons. *Med J Aust* 2002; **176:** 425–28.

53 MacLennan A. A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. *BMJ* 1999; **319:** 1054–59.

54 van Bokhoven H. Genetic and epigenetic networks in intellectual disabilities. *Annu Rev Genet* 2011; **45:** 81–104.

55 Miles JH. Autism spectrum disorders—a genetics review. *Genet Med* 2011; **13:** 278–94.

56 Mulley JC, Mefford HC. Epilepsy and the new cytogenetics. *Epilepsia* 2011; **52:** 423–32.

57 Fong CY, Mumford AD, Likeman MJ, Jardine PE. Cerebral palsy in siblings caused by compound heterozygous mutations in the gene encoding protein C. *Dev Med Child Neurol* 2010; **52:** 489–93.

58 Montenegro MA, Cendes F, Saito H, et al. Intrapartum complications associated with malformations of cortical development. *J Child Neurol* 2005; **20:** 675–78.

59 Lynex CN, Carr IM, Leek JP, et al. Homozygosity for a missense mutation in the 67 kDa isoform of glutamate decarboxylase in a family with autosomal recessive spastic cerebral palsy: parallels with stiff-person syndrome and other movement disorders. *BMC Neurol* 2004; **4:** 20.

60 Lerer I, Sagi M, Meiner V, Cohen T, Zlotogora J, Abeliovich D. Deletion of the *ANKRD15* gene at 9p24.3 causes parent-of-origin-dependent inheritance of familial cerebral palsy. *Hum Mol Genet* 2005; **14:** 3911–20.

61 Verkerk AJ, Schot R, Dumee B, et al. Mutation in the *AP4M1* gene provides a model for neuroaxonal injury in cerebral palsy. *Am J Hum Genet* 2009; **85:** 40–52.

62 Moreno-De-Luca A, Helmers SL, Mao H, et al. Adaptor protein complex-4 (AP-4) deficiency causes a novel autosomal recessive cerebral palsy syndrome with microcephaly and intellectual disability. *J Med Genet* 2011; **48:** 141–44.

63 Abou Jamra R, Philippe O, Raas-Rothschild A, et al. Adaptor protein complex 4 deficiency causes severe autosomal-recessive intellectual disability, progressive spastic paraplegia, shy character, and short stature. *Am J Hum Genet* 2011; **88:** 788–95.

64 Garne E, Dolk H, Krageloh-Mann I, Holst Ravn S, Cans C. Cerebral palsy and congenital malformations. *Eur J Paediatr Neurol* 2008; **12:** 82–88.

65 Blair E, Al Asedy F, Badawi N, Bower C. Is cerebral palsy associated with birth defects other than cerebral defects? *Dev Med Child Neurol* 2007; **49:** 252–58.

66 Croen LA, Grether JK, Curry CJ, Nelson KB. Congenital abnormalities among children with cerebral palsy: more evidence for prenatal antecedents. *J Pediatr* 2001; **138:** 804–10.

67 Rankin J, Cans C, Garne E, et al. Congenital anomalies in children with cerebral palsy: a population-based record linkage study. *Dev Med Child Neurol* 2010; **52:** 345–51.

68 Petterson B, Stanley F, Henderson D. Cerebral palsy in multiple births in Western Australia: genetic aspects. *Am J Med Genet* 1990; **37:** 346–51.

69 al-Rajeh S, Bademosi O, Awada A, Ismail H, al-Shammasi S, Dawodu A. Cerebral palsy in Saudi Arabia: a case-control study of risk factors. *Dev Med Child Neurol* 1991; **33:** 1048–52.

70 Erkin G, Delialioglu SU, Ozel S, Culha C, Sirzai H. Risk factors and clinical profiles in Turkish children with cerebral palsy: analysis of 625 cases. *Int J Rehabil Res* 2008; **31:** 89–91.

71 Hemminki K, Li X, Sundquist K, Sundquist J. High familial risks for cerebral palsy implicate partial heritable aetiology. *Paediatr Perinat Epidemiol* 2007; **21:** 235–41.

72 Palmer L, Petterson B, Blair E, Burton P. Family patterns of gestational age at delivery and growth in utero in moderate and severe cerebral palsy. *Dev Med Child Neurol* 1994; **36:** 1108–19.

73 Amor DJ, Craig JE, Delatycki MB, Reddihough D. Genetic factors in athetoid cerebral palsy. *J Child Neurol* 2001; **16:** 793–97.

74 Adler E. Familial cerebral palsy. *J Chronic Dis* 1961; **13:** 207–14.

75 Gustavson KH, Hagberg B, Sanner G. Identical syndromes of cerebral palsy in the same family. *Acta Paediatr Scand* 1969; **58:** 330–40.

76 Fletcher NA, Foley J. Parental age, genetic mutation, and cerebral palsy. *J Med Genet* 1993; **30:** 44–46.

77 Costeff H. Estimated frequency of genetic and nongenetic causes of congenital idiopathic cerebral palsy in west Sweden. *Ann Hum Genet* 2004; **68:** 515–20.

78 Costeff H, Cohen BE, Weller L. Relative importance of genetic and nongenetic etiologies in idiopathic mental retardation: estimates based on analysis of medical histories. *Ann Hum Genet* 1983; **47:** 83–93.

79 Paneth N. Establishing the diagnosis of cerebral palsy. *Clin Obstet Gynecol* 2008; **51:** 742–48.

80 Kurian MA, Li Y, Zhen J, et al. Clinical and molecular characterisation of hereditary dopamine transporter deficiency syndrome: an observational cohort and experimental study. *Lancet Neurol* 2011; **10:** 54–62.

81 Gupta R, Appleton RE. Cerebral palsy: not always what it seems. *Arch Dis Child* 2001; **85:** 356–60.

82 Neville B. Congenital dopa-responsive disorders: a diagnostic and therapeutic challenge to the cerebral palsies? *Dev Med Child Neurol* 2007; **49:** 85.

83 Nyraard TG, Waran SP, Levine RA, Naini AB, Chutorian AM. Dopa-responsive dystonia simulating cerebral palsy. *Pediatr Neurol* 1994; **11:** 236–40.

84 Lee JH, Ki CS, Kim DS, Cho JW, Park KP, Kim S. Dopa-responsive dystonia with a novel initiation codon mutation in the *GCH1* gene misdiagnosed as cerebral palsy. *J Korean Med Sci* 2011; **26:** 1244–46.

85 Nygaard TG, Marsden CD, Fahn S. Dopa-responsive dystonia: long-term treatment response and prognosis. *Neurology* 1991; **41:** 174–81.

86 Bainbridge MN, Wiszniewski W, Murdock DR, et al. Whole-genome sequencing for optimized patient management. *Sci Transl Med* 2011; **3:** 87re3.

87 Blackstone C, O'Kane CJ, Reid E. Hereditary spastic paraplegias: membrane traffic and the motor pathway. *Nat Rev Neurosci* 2011; **12:** 31–42.

88 Salinas S, Proukakis C, Crosby A, Warner TT. Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. *Lancet Neurol* 2008; **7:** 1127–38.

89 Rainier S, Sher C, Reish O, Thomas D, Fink JK. De novo occurrence of novel SPG3A/atlastin mutation presenting as cerebral palsy. *Arch Neurol* 2006; **63:** 445–47.

90 Kumar S, Alexander M, Gnanamuthu C. Recent experience with Rett syndrome at a tertiary care center. *Neurol India* 2004; **52:** 494–95.

91 Williams CA. Neurological aspects of the Angelman syndrome. *Brain Dev* 2005; **27:** 88–94.

92 Chiong MA, Marinaki A, Duley J, Bennetts B, Ouvrier R, Christodoulou J. Lesch-Nyhan disease in a 20-year-old man incorrectly described as developing 'cerebral palsy' after general anaesthesia in infancy. *J Inherit Metab Dis* 2006; **29:** 594.

93 Morton DH, Bennett MJ, Seargeant LE, Nichter CA, Kelley RI. Glutaric aciduria type I: a common cause of episodic encephalopathy and spastic paralysis in the Amish of Lancaster County, Pennsylvania. *Am J Med Genet* 1991; **41:** 89–95.

94 Cardoso C, Leventer RJ, Dowling JJ, et al. Clinical and molecular basis of classical lissencephaly: mutations in the *LIS1* gene (*PAFAH1B1*). *Hum Mutat* 2002; **19:** 4–15.

95 Salman MS, Blaser S, Buncic JR, Westall CA, Heon E, Becker L. Pontocerebellar hypoplasia type 1: new leads for an earlier diagnosis. *J Child Neurol* 2003; **18:** 220–25.

96 OMIM Gene Map Statistics. www.omim.org/statistics/geneMap (accessed Nov 1, 2011).

97 Hyde TM, Lipska BK, Ali T, et al. Expression of GABA signaling molecules KCC2, NKCC1, and GAD1 in cortical development and schizophrenia. *J Neurosci* 2011; **31:** 11088–95.

98 Kakinuma N, Zhu Y, Wang Y, Roy BC, Kiyama R. KANK proteins: structure, functions and diseases. *Cell Mol Life Sci* 2009; **66:** 2651–59.

99 Matsuda S, Miura E, Matsuda K, et al. Accumulation of AMPA receptors in autophagosomes in neuronal axons lacking adaptor protein AP-4. *Neuron* 2008; **57:** 730–45.

100 Najmabadi H, Hu H, Garshasbi M, et al. Deep sequencing reveals 50 novel genes for recessive cognitive disorders. *Nature* 2011; **478:** 57–63.

101 Robinson MS. Adaptable adaptors for coated vesicles. *Trends Cell Biol* 2004; **14:** 167–74.

102 Nakatsu F, Ohno H. Adaptor protein complexes as the key regulators of protein sorting in the post-Golgi network. *Cell Struct Funct* 2003; **28:** 419–29.

103 Yap CC, Murate M, Kishigami S, et al. Adaptor protein complex-4 (AP-4) is expressed in the central nervous system neurons and interacts with glutamate receptor delta2. *Mol Cell Neurosci* 2003; **24:** 283–95.

104 Matsuda S, Yuzaki M. Polarized sorting of AMPA receptors to the somatodendritic domain is regulated by adaptor protein AP-4. *Neurosci Res* 2009; **65:** 1–5.

105 Burgos PV, Mardones GA, Rojas AL, et al. Sorting of the Alzheimer's disease amyloid precursor protein mediated by the AP-4 complex. *Dev Cell* 2010; **18:** 425–36.

106 Wu YW, Croen LA, Vanderwerf A, Gelfand AA, Torres AR. Candidate genes and risk for cerebral palsy: a population-based study. *Pediatr Res* 2011; **70:** 642–46.

107 Wu D, Zou YF, Xu XY, et al. The association of genetic polymorphisms with cerebral palsy: a meta-analysis. *Dev Med Child Neurol* 2011; **53:** 217–25.

108 O'Callaghan ME, MacLennan AH, Haan EA, Dekker G. The genomic basis of cerebral palsy: a HuGE systematic literature review. *Hum Genet* 2009; **126:** 149–72.

109 Iyengar SK, Elston RC. The genetic basis of complex traits: rare variants or "common gene, common disease"? *Methods Mol Biol* 2007; **376:** 71–84.

110 Ku CS, Naidoo N, Pawitan Y. Revisiting mendelian disorders through exome sequencing. *Hum Genet* 2011; **129:** 351–70.

111 Ng SB, Bigham AW, Buckingham KJ, et al. Exome sequencing identifies *MLL2* mutations as a cause of Kabuki syndrome. *Nat Genet* 2010; **42:** 790–93.

112 Ng SB, Buckingham KJ, Lee C, et al. Exome sequencing identifies the cause of a mendelian disorder. *Nat Genet* 2010; **42:** 30–35.

113 Erlich Y, Edvardson S, Hodges E, et al. Exome sequencing and disease-network analysis of a single family implicate a mutation in *KIF1A* in hereditary spastic paraparesis. *Genome Res* 2011; **21:** 658–64.

114 Vissers LE, de Ligt J, Gilissen C, et al. A de novo paradigm for mental retardation. *Nat Genet* 2010; **42:** 1109–12.

115 O'Roak BJ, Deriziotis P, Lee C, et al. Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. *Nat Genet* 2011; **43:** 585–89.

116 Girard SL, Gauthier J, Noreau A, et al. Increased exonic de novo mutation rate in individuals with schizophrenia. *Nat Genet* 2011; **43:** 860–63.