American Journal of Medical Genetics Part A 146A:2023–2037 (2008)

Research Review

Genetic Disorders Associated With Macrocephaly

Charles A. Williams,[1]* Aditi Dagli,[1] and Agatino Battaglia[2]

[1]Raymond C. Philips Research and Education Unit, Division of Genetics, Department of Pediatrics, University of Florida, Gainesville, Florida

[2]Stella Maris Clinical Research Institute for Child and Adolescent Neuropsychiatry, Calambrone, Pisa, Italy

Received 6 February 2008; Accepted 15 May 2008

Macrocephaly is associated with many genetic disorders and is a frequent cause of referral to the clinical geneticist. In this review we classify the commonly encountered macrocephaly disorders into useful categories and summarize recent genetic advances. Conditions where macrocephaly is a predominant aspect of the clinical presentation are discussed and a diagnostic approach to the common macrocephaly disorders is provided. Some emphasis is placed on familial macrocephaly (sometimes referred to as benign external hydrocephalus) and on the macrocephaly associated with autism spectrum disorders. The more recent conditions associated with the leukodystrophies and the organic acidurias are reviewed, but the well known conditions involving storage disorders and bone dysplasias are mentioned but not discussed. The genetic macrocephaly conditions cover a broad spectrum of gene disorders and their related proteins have diverse biological functions. As of yet it is not clear what precise biological pathways lead to generalized brain overgrowth. © 2008 Wiley-Liss, Inc.

Key words: macrocephaly syndromes; familial macrocephaly; autism; megalencephaly; genetics; macrocephaly

How to cite this article: Williams CA, Dagli A, Battaglia A. 2008. Genetic disorders associated with macrocephaly. Am J Med Genet Part A 146A:2023–2037.

INTRODUCTION

Macrocephaly is a common reason for a medical genetics referral. As there are many genetic conditions associated with macrocephaly, the diagnostic possibilities are numerous. An OMIM search for macrocephaly returned 175 entries, and a search for megalencephaly returned 21 listings [OMIM, 2008]. Eliminating duplicated entries, there were 164 conditions, including 17 metabolic disorders. Accordingly, any review of macrocephaly must acknowledge a broad group of genetic conditions.

The adult brain reaches a total volume of about 1,700 ml, composed of 80% parenchyma, 10% blood, and 10% cerebrospinal fluid [Blinkov and Glezer, 1968]. Brain parenchyma is composed mainly of neurons and glial cells, the total number of neurons is estimated at 100 billion in the adult. Glial cells (oligodendrocytes, astrocytes, ependymal cells, and microglia) may be 10–50 times more numerous than neurons [Williams and Herrup, 1988]. Additionally, water constitutes 77–78% of brain weight with most of the remaining due to lipids (10%) and proteins (8%) [McIlwain and Bachelard, 1985]. Given these aspects, a subtle increase in the number and/or the molecular–fluid environment of cells in the CNS could lead to significantly increased brain size. It is not surprising then that many conditions with brain overgrowth are not associated with obvious cytoarchitectual or other histological abnormalities.

Macrocephaly refers to an abnormally large head inclusive of the scalp, cranial bone and intracranial contents. Macrocephaly may be due to megalencephaly (true enlargement of the brain parenchyma) or due to other conditions such as hydrocephalus or cranial hyperostosis. In this review, we will use the term macrocephaly to include conditions of megalencephaly. The head circumference measurement, herein referred to as the occipital frontal circumference (OFC), extends from the most prominent part of the glabella to the most prominent posterior area of the occiput. The OFC can be affected by thick hair and cranial bone deformations or hypertrophies.

Grant sponsor: Raymond C. Philips Research and Education Contract, State of Florida, USA.

*Correspondence to: Charles A. Williams, M.D., Division of Genetics, Department of Pediatrics, University of Florida, P.O. Box 100296, Gainesville, FL 32610. E-mail: willicx@peds.ufl.edu

DOI 10.1002/ajmg.a.32434

Ethnicity and stature must also be considered when evaluating the OFC [DiLiberti, 1998]. Relative macrocephaly indicates that the OFC plots within 2.0 SD of the mean but plots disproportionately above that for stature. The measurement of cranial height in combination with the OFC, or the use of brain imaging, provide a more accurate determination of intracranial volume but these methods have mainly been used in the research setting [Gooskens et al., 1989]. The single OFC measurement however remains the customary method for identification of macrocephaly.

Non-syndromic macrocephaly refers to conditions in which the enlarged brain is the predominant abnormality, not associated with any other noteworthy physical trait or major malformation. Minor craniofacial changes can be present but they are due to the secondary effects of the enlarged cranial vault. These changes include a prominent or high forehead and a dolichocephalic head shape. Increased width of the cranial base can at times produce mild hypertelorism and down slanting palpebral fissures. Also, the facial area may be relatively small giving a triangular craniofacial appearance. Syndromic macrocephaly means that significant abnormalities (physical or behavioral) are associated with the generalized brain enlargement. The constellation of these abnormalities creates a recognizable pattern worthy of a syndromic designation. Syndromic macrocephaly conditions should be distinguished from other genetic syndromes in which macrocephaly is an occasional but not consistent, or clinically predominant, finding. Finally, the non-genetic macrocephalies are due to secondary effects of environmental events such as those related to neonatal intraventricular hemorrhage or infection.

CLASSIFICATION

The genetic and acquired types of macrocephaly can be categorized based on associated physical, metabolic, or brain imaging findings (Table I). This table resembles those of prior reviews [DeMyer, 1986; Bodensteiner and Chung, 1993] but is expanded to include newly recognized syndromic conditions. Table I is not a complete listing of the genetic disorders known to be associated with macrocephaly, but the listings are representative of the more common conditions that the clinician may encounter. Table II indicates the importance of macrocephaly as a predominant clinical feature of the given genetic condition; most of these entities are discussed in this review. This review does not discuss metabolic storage diseases or conditions associated with the osteochondrodysplasias (e.g., bone dysplasia and hyperplasia disorders). These general categories are however included in Table I and a few specific conditions are listed in Table II to illustrate their importance as a clinical grouping.

TABLE I. Classification of Macrocephaly Conditions

- I. Genetic types
  - Familial macrocephaly
    - Benign; symptomatic
  - Autism disorder
    - Multifactorial, non-syndromic type
  - Syndrome associations (many types)
    - With cutaneous findings
      - PTEN hamartoma syndromes
      - Neurofibromatosis, type 1
      - Hemimegalencephaly
    - With overgrowth
      - Sotos, Weaver
      - Macrocephaly cutis marmorata telangiectatica congenita
      - Simpson–Golabi–Behmel, Beckwith–Wiedemann syndrome
    - Neuro-cardio-facial-cutaneous syndromes
      - Noonan, Costello
      - Cardiofaciocutaneous (CFC)
      - LEOPARD
    - With mental retardation
      - Fragile X
  - Metabolic types
    - With leukodystrophy
      - Alexander; Canavan
      - Megalencephalic leukodystrophy
    - With organic acidurias
      - Glutaric aciduria, type 1
      - D-2-hydroxyglutaric aciduria
    - With storage
  - Bone dysplasia/hyperplasia
  - Hydrocephalus
    - Aqueductal stenosis types
    - Multifactorial, non-obstructive types
- II. Non-genetic types
  - Hydrocephalus
    - Hemorrhage
    - Infections; other causes
  - Subdural effusions
    - Post-traumatic and infectious
  - Arachnoid cysts

Familial Macrocephaly

The typical child with familial macrocephaly (FM) has a birth OFC in the higher normal percentiles that then increases to exceed 2.0 SD by one year of age. The growth rate may increase by 0.6–1.0 cm/week in the first months of life (exceeding the normal rate of 0.4 cm/week) [Lorber and Priestley, 1981]. During this period, the infant with FM has an enlarged, dolichocephalic-appearing cranium. Brain scans may show only prominent supratentorial CSF spaces, especially bifrontal widening of the subarachnoid space and a widened frontal interhemispheric fissure (Fig. 1) [Alvarez et al., 1986]. These findings have also been reported as "benign external hydrocephalus" of infancy [Alvarez et al., 1986; Odita, 1992]. More recently, it has been shown that this type of external hydrocephalus is a normal CSF variant that can be observed in both normocephalic and macrocephalic infants [Prassopoulos and Cavouras, 1994; Prassopoulos et al., 1995]. In FM, the CSF spaces become normal by 3–4 years of age, but the OFC continues to develop at or above 2 SD. By adulthood, the

TABLE II. Table of Macrocephaly Syndromes Summarizing Certain Clinical Aspects of Macrocephaly and Listing Causative Genes, if Known, and Inheritance Patterns

Syndrome/disease	↑OFC: major clinical finding	↑OFC: minor clinical finding	Absolute macrocephaly	Relative macrocephaly	Identified genes	Inheritance pattern
Familial macrocephaly						
Benign asymptomatic	+		+		—	?AD/MF
Autism disorder						
Multifactorial, non-syndromic		+	+		—	MF
Syndrome associations						
With cutaneous findings						
Bannayan–Riley–Ruvalcaba syndrome (BRRS)/ Cowden syndrome/Lhermitte–Duclos syndrome	+		+		*PTEN*	AD
Neurofibromatosis, type 1 (NF1)		+	+	+	*NF1*	AD
Linear Epidermal Nevus syndrome (LENS)		+	+		—	?AD
Klippel–Weber–Trenaunay syndrome (KTW)		+	+		*VG5Q*[a]	AD[a]
With overgrowth						
Sotos syndrome	+		+		*NSD1*	AD
Weaver syndrome	+		+		*NSD1*[b]	AD
Macrocephaly–Cutis–Marmorata telangiectatica congenita (M-CMCT)	+		+		—	?AD
Simpson–Golabi–Behmel syndrome	+		+		*GPC3*[c]	XLD
Beckwith–Wiedemann syndrome		+	+		*CDKN1C*[d]	AD
With neuro-cardio-facio-cutaneous syndromes						
Noonan syndrome		+		+	*PTPN11*, *KRAS*, *SOS1*, *RAF1*	AD
Costello syndrome		+		+	*HRAS*	AD
Cardiofaciocutaneous syndrome		+		+	*KRAS*, *BRAF*, *MEK1*, *MEK2*	AD
LEOPARD		+		+	*PTPN11*, *RAF1*	
With mental retardation						
Fragile X syndrome		+		+	*FMR1*	XLD
Metabolic types						
With organic aciduria						
Glutaric aciduria, type 1 (GA-1)	+		+		*GCDH*	AR
D-2-hydroxyglutaric aciduria	+		+		*D2HGD*	AR
With leukodystrophy						
Alexander disease	+		+		*GFAP*	AD
Canavan disease	+		+		*ASPA*	AR
Megalencephalic leukoencephalopathy with subcortical cysts (MLC)					*MLC1*	AR
With storage						
Hunter syndrome	+		+		*IDS*	XLD
Hurler syndrome	+		+		*IDUA*	AR
Tay–Sachs disease	+		+		*HEXA*	AR
Bone dysplasia/hyperplasia						
Achondroplasia	+		+	+	*FGFR3*	AD
Craniometadiaphyseal dysplasia	+		+	+		AR, AD
Osteopetrosis		+	+		*TCIRG1*, *CLCN7*, *OSTM1*, *TNFSF11*, *PLEKHM1*, *CA2*, *LRP5*	AR, AD
Hydrocephalus						
X-linked aqueductal stenosis/hydrocephalus	+		+		*L1CAM*	XLD
Congenital stenosis of aqueduct of Sylvius	+		+		—	AR

AD, autosomal dominant; AR, autosomal recessive; XLD, X-linked disorder; MF, multifactorial inheritance; OMIM, Online Mendelian Inheritance in Man.
[a]Some cases of KTW are caused by mutations in *VG5Q* [Tian et al., 2004].
[b]Some cases have *NSD1* mutations.
[c]Not all cases have *GPC3* mutations; a second locus is at Xp22.
[d]Also caused by abnormal methylation and segmental UPD events in the 11p15.5 region.

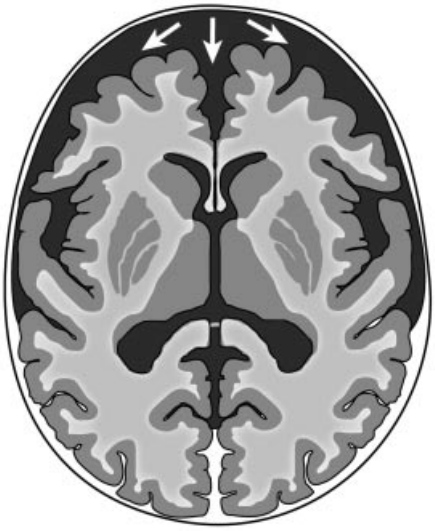

FIG. 1. Diagram illustrating the normal brain variants seen in familial macrocephaly. The subarachnoid compartments and the interhemispheric fissure width over the frontal regions are relatively enlarged (white arrows) and the frontal lobes appear atrophic.

craniofacial shape appears normal although the OFC remains >2 SD (Fig. 2B).

Criteria for the diagnosis of FM have been set forth by DeMyer: (1) absence of craniofacial, neurocutaneous or somatic anomalies that might identify a syndrome; (2) normal radiographic study of the brain; and (3) a parent or sibling with macrocephaly or macrocephaly that could be traced through several generations [DeMyer, 1986]. A small percentage of children with FM have developmental handicaps, suggesting that FM may be a risk factor for learning delay [Alvarez et al., 1986; DeMyer, 1986]. In addition, 7 of 109 (6.4%) children with apparent isolated macrocephaly were noted to be "retarded" on one study, and another found that, of 75 children in classroom for learning disability, 16% had macrocephaly compared to 4.1% in control children [Lorber and Priestley, 1981; Smith et al., 1984]. Accordingly, in a child with macrocephaly and learning disability when other normal family members have macrocephaly, it can be difficult to know if this familial trait is truly associated with the child's developmental problem.

Normally, the OFC measurement shows a continuous distribution in the population, as is also observed for stature and body mass. About 50% of OFC variance has been shown to be familial [Weaver and Christian, 1980] and the OFC trait has traditionally been understood as exhibiting multifactorial inheritance. Studies of affected family members and of children with macrocephaly show a 4:1 male to female predominance [Lorber and Priestley, 1981] consistent with ratios often observed in multifactorially inherited conditions. A multifactorial model of inheritance of FM has in fact been proposed based on a study of the distribution of head circumference measurements in 23 families in which one child from each family was clinically ascertained to have macrocephaly [Arbour et al., 1996]. However, the relatively common observation of macrocephaly in a sibling or in a parent, and the observation of extended families in which macrocephaly is apparently segregating as a dominant trait, appears to distinguish FM from other classical mutifactorial disorders in which dominant-like, extended pedigrees are not often observed. Several authors have thus proposed an autosomal dominant model of inheritance [Schreier et al., 1974; Asch and Myers, 1976; Alvarez et al., 1986; DeMyer, 1986]. This type of dominant inheritance might be due a single gene exhibiting a major effect as part of a multifactorial phenomenon in some families.

Autism

Autism spectrum disorders have received increased attention recently because of concerns about its apparent increasing prevalence, estimated as now occurring in one in 150 children in the United States [Anon., 2007]. Mental retardation is as well quite prevalent among individuals with autism and is estimated to occur in 40–55% [Chakrabarti and Fombonne, 2001; Newschaffer et al., 2007]. Autism is not a homogeneous diagnostic group but has etiologic heterogeneity with 10–15% of this group having identifiable genetic or metabolic disorders [Battaglia and Carey, 2006; Sebat et al., 2007; Schaefer and Mendelsohn, 2008]. However, there remains a group in whom extensive genetic testing reveals no known cause and these children appear to have autism consistent with multifactorial model of inheritance.

Macrocephaly occurs in about 15–35% of autistic children and can also be seen in other types of pervasive developmental disorders [Woodhouse et al., 1996; Stevenson et al., 1997; Courchesne et al., 2003; Dementieva et al., 2005]. Although minor physical anomalies have been noted among children with autism, it is clear that macrocephaly is the most prominent correlated physical abnormality. The prevalence of macrocephaly among autism cohorts is greater than that seen in children with learning delays, where the prevalence of macrocephaly can be up to 15% of children [Smith, 1981; Smith et al., 1984]. The increased prevalence is present across all types of autism spectrum children and is even present in those who have near-normal developmental quotients [Gillberg and de Souza, 2002].

The macrocephaly observed in autism becomes manifest around 1–3 years of age and is typically not present at birth (Fig. 2I). There is an apparent increased rate of brain growth in the first years of life that diminishes and becomes subnormal in later childhood; macrocephaly in adults with autism is less prevalent than in autistic children [Aylward et al., 2002]. Brain MRI studies have not found migrational

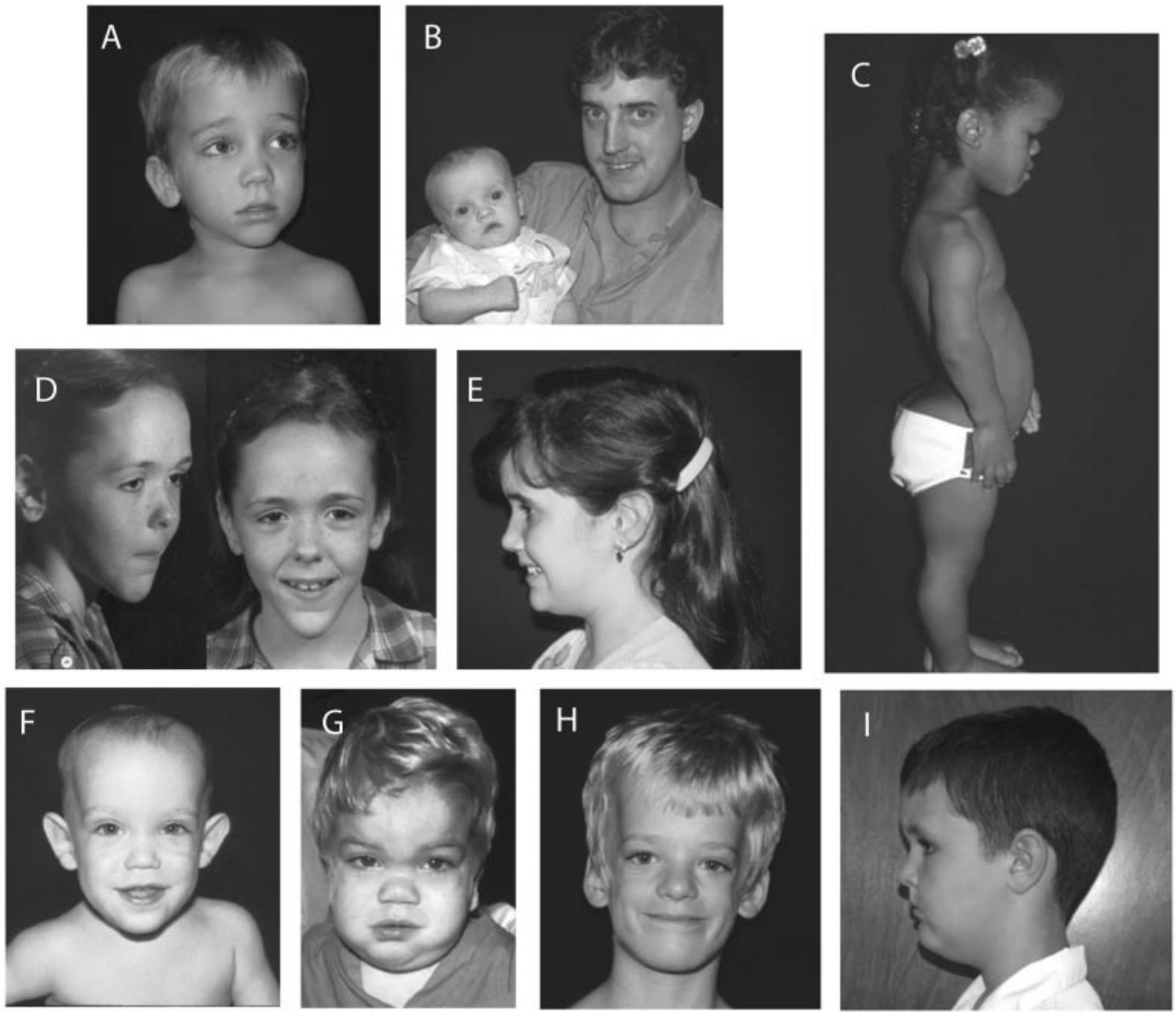

FIG. 2. Appearance of macrocephaly in different genetic conditions: (**A**) *PTEN* disorder; (**B**) father and child with benign familial macrocephaly; (**C**) Achondroplasia; (**D**) Sotos syndrome; (**E**) glutaric aciduria, type 1; (**F**) fragile X syndrome; (**G**) Hunter syndrome; (**H**) craniodiaphyseal-like bone dysplasia; (**I**) autism of unknown cause.

defects or other structural problems. Quantitative MRI studies, aimed at determining volume differences, find that most of the volume change is due to differential white matter increase [Courchesne and Pierce, 2005; Herbert, 2005]. Cytoarchitectural studies have found defects ranging from abnormal cell distributions in frontal and temporal lobe "minicolumns" to neuroimmune inflammatory reactions [Casanova et al., 2002; Vargas et al., 2005; Pardo and Eberhart, 2007]. Overall, no consistent brain pathology has been demonstrated [Casanova, 2007].

It is unclear whether macrocephaly is associated with an autism endophenotype; a recent report on quantitative trait locus analysis involving macrocephaly in sib pairs of autistic children found evidence of several genomic loci, including one near the *PTEN* gene region (10q25.2) [Spence et al., 2005]. Several cases have recently been reported where children with autism and macrocephaly, and autism with no other clinical features, have been found to have germline *PTEN* mutations, and it has been suggested that *PTEN* gene sequencing be included in the diagnostic work-up of these children [Herman et al., 2007]. The relationship between the macrocephaly and the autism disorder is confounded by the observation that first degree relatives of autism probands have an increased prevalence of macrocephaly [Fidler et al., 2000]. A recent report also showed that both normocephalic and macrocephalic autistic children were more likely to have parents who were macrocephalic [Keegan et al., 2007]. In these studies, the macrocephaly appeared to be segregating as an independent trait in the non-autistic family members. It is currently not only unclear how macrocephaly is related pathoetiologically to the autism problem, but it is also unclear how the heritable aspect of autism interplays with that of macrocephaly.

SYNDROMES WITH CUTANEOUS FINDINGS

PTEN Harmartoma-Tumor Syndromes

Bannayan–Riley–Ruvalcaba syndrome (OMIM 153480) encompasses the association of macrocephaly with various cutaneous findings (e.g., lipomas, hemangiomas, and pigmented macules) [DiLiberti, 1998, for review]. Macrocephaly has also been noted in Cowden (OMIM 158350) and Lhermitte–Duclos syndromes [Perez-Nunez et al., 2004]. These macrocephaly associated conditions are due to heterozygous mutations in the *P*hosphatase and tensin homolog deleted on chromosome *TEN* (*PTEN*) gene (10q23.31), hence the term *PTEN* harmartoma-tumor syndromes [Marsh et al., 1999]. They can be inherited as an autosomal dominant disorder with extremely variable expression.

It appears that most children with *PTEN* mutations are macrocephalic; in a study of *PTEN* cases, all 19 individuals, age 15 years or less, who had head circumference measurements, were macrocephalic [Tan et al., 2007]. Prevalence of macrocephaly in adults with Cowden syndrome has been noted as 80% in a study of 21 patients [Starink et al., 1986]. The macrocephaly, when present in childhood, can be impressive, sometimes >4–8 SD, and developmental delay and/or autism may be the only apparent clinical abnormalities (Fig. 2A) [Butler et al., 2005]. In such cases, closer clinical scrutiny may disclose a family history of cerebellar dysplastic gangliocytomas (Lhermitte–Duclos type) or thyroid cancers (as part of Cowden syndrome). Further physical examination may reveal unique pigmented macules on the glans of the penis or small otherwise unrecognized lipomas on the trunk or arms. Brain MRI has generally been reported as normal although recent reports suggest that prominent Virchow–Robin spaces, or vascular flow anomalies may be important indicators of *PTEN*-associated macrocephaly [Medne et al., 2007; Tan et al., 2007].

The *PTEN* gene encodes a putative tumor suppressor protein targeted to phosphoinositidie-3 kinase (PI3K) which is involved in cell-cycle regulation, angiogenesis, and cellular growth and proliferation [Sansal and Sellers, 2004; Hay, 2005]. As a tumor suppressor, the dysplastic cerebellar changes (e.g., gangliocytoma) associated with *PTEN* mutations could be explained by a 2-hit model but this model seems unlikely to account for generalized macrocephaly.

Neurofibromatosis Type 1 (NF1)

At least 20–30% of older children with NF1 (OMIM 162200) have macrocephaly and an even greater percentage have relative macrocephaly [Clementi et al., 1999; Szudek et al., 2000]. The macrocephaly occurs in otherwise normal NF1 children (i.e., without intracranial tumor or hydrocephalus) and, although learning deficits are common in NF1, they do not seem to be correlated with the presence of macrocephaly [Hyman et al., 2005].

Neurofibromin, the protein product of the *Neurofibromin* or *NF1* gene (17q11.2), is a GTP-ase activating protein that downregulates RAS signaling and this appears to keep in check the mTOR growth signaling system [Costa and Silva, 2003]. In the mouse, heterozygous *NF1* mutations can increase CNS progenitor cell pools, including oligodendrocytes, and astrogliosis has been observed in some but not all areas of the mouse brain [Bennett et al., 2003]. While astrogliosis has been reported in some parts of the human NF1 brain, only a few individuals have been reported [Nordlund et al., 1995]. Recently *SPRED 1* gene (15q13.2) mutations have been described in individuals with some clinical features of NF1 including macrocephaly, café au lait spots and axillary freckling. These individuals did not have neurofibromas. *SPRED 1* belongs to the SPROUTY/SPRED family of proteins that act as negative regulators of RAS/MAPK pathway [Brems et al., 2007]. Despite these advances, a molecular explanation of the macrocephaly in NF1 remains unknown.

The MRI has been used to study regional area and volume differences in NF1 and it appears that the macrocephaly is associated mainly with a relative increase in frontal and parietal white matter, but gray matter as well may be affected [Moore et al., 2000; Cutting et al., 2002]. Focal MRI intensity changes are well known in the midbrain, cerebellum or brainstem, a finding observed in both macrocephalic and normocephalic NF1 individuals [Feldmann et al., 2003]. Histological study of these areas reveals glial dysplasia and increased intercellular spaces, but these are not sufficient to account alone for the frontal-parietal white matter volume increases [DiPaolo et al., 1995]. More diffuse increases in presumed white matter water content can be demonstrated by MRI diffusion brain study and this theoretically could be a major contributor to the increased brain volume [Tognini et al., 2005].

Hemimegalencephaly

Hemimegalencephaly implies unilateral increased size of the entire cerebral hemisphere and should be distinguished from focal neuronal or glial dysplasias, although the histological findings may be similar [Mischel et al., 1995; Yasha et al., 1997]. Gross pathology can show areas of pachygyria and agyria with enlarged lateral ventricles, easily identified on MRI scans [Barkovich and Chuang, 1990; Broumandi et al., 2004]. Hemimegalencephaly has been observed in tuberous sclerosis (OMIM 191100), Neurofibromatosis-1, linear epidermal nevus syndrome (LENS), Klippel–Trenaunay–Weber syndrome (KTW) (OMIM 149000), Proteus syndrome (OMIM 176920) and macrocephaly cutis marmorota

telangiectatica congenita (M-CMCT) (OMIM 602501). LENS is probably the most frequent syndrome association, hemimegalencephaly was seen in 11/44 cases in one survey [Sasaki et al., 2005]. Most cases of hemimegalencephaly appear to be sporadic occurrences although one report found mutations in vascular growth factor (*VG5Q*) gene (5q13.3) in some cases of KTW [Tian et al., 2004].

SYNDROMES WITH OVERGROWTH

The overgrowth conditions are well represented in any differential listing of conditions associated with macrocephaly in combination with generalized somatic overgrowth, and include the syndromes of Sotos (OMIM 117550), Weaver (OMIM 277590), Simpson–Golabi (OMIM 312870), Beckwith–Wiedemann (OMIM 130650) and others [Cohen, 1999].

Sotos syndrome, initially reported as cerebral gigantism in childhood [Sotos et al., 1964], is the prototypical example of an overgrowth/macrocephaly syndrome. Individuals with Sotos syndrome have a distinctive facial appearance with macrocephaly, a high prominent forehead, downslanting palpebral fissures, long pointed chin, and high-arched palate. In childhood, the height is above average with an advanced bone-age and large hands and feet. Final adult height may not be increased [Agwu et al., 1999]. Brain MRI scans in a series of Sotos patients typically show no migrational or structural defects but only mild, generalized ventriculomegaly and enlarged supratentorial extracerebral fluid spaces. Thus, it is possible that the macrocephaly observed in childhood is attributable mainly to increased CSF spaces [Schaefer et al., 1997]. Aoki et al. [1998] however found macrocephaly due to parenchymal enlargement in two neonates with Sotos syndrome who then developed mild ventriculomegaly changes as children suggesting that true megalencephaly is initially present at birth. Sotos syndrome is caused by disruption of the *n*uclear receptor *S*ET-*d*omain-containing (*NSD1*) gene (5q35), which codes for a nuclear steroid receptor co-regulator protein [Wang et al., 2001]. The clinical aspects of Sotos have now been more accurately delineated in many patients with *NSD1* proven mutations and/or microdeletions [Cecconi et al., 2005; Faravelli, 2005]. Nuclear receptor genes control diverse roles in cell growth and differentiation via transcriptional modulation [Rayasam et al., 2003]. There does not appear to be any reports yet as to how *NSD1* function relates to brain overgrowth.

Weaver syndrome is characterized by accelerated growth of prenatal onset, advanced osseous maturation, unusual facial appearance, macrocephaly and camptodactyly. Loose skin may be observed [Weaver et al., 1974; Opitz et al., 1998]. Macrocephaly is present in 83% of the individuals [Jones, 2006]. CNS abnormalities reported include cysts of septum pellucidum, cerebral atrophy, localized hypervascularization, and pachygyria [Freeman et al., 1999]. Definite genetic etiology has not been identified but autosomal dominant inheritance is proposed. Some individuals with a clinical phenotype of Weaver syndrome have been found to have mutations in the *NSD1* gene [Douglas et al., 2003].

Simpson–Golabi–Behmel syndrome is associated with macrosomia of prenatal onset, distinctive facial appearance, developmental delay and other congenital anomalies. The craniofacial appearance is characterized by a large head with coarse features, thickened lips, wide mouth, large tongue, high-arched palate, malposition of the teeth, prominent jaw and short neck. Mutations in the glypican-3 (*GPC-3*) gene, at Xq26, are responsible for most cases. GPC-3 controls the growth of mesoderm tissues in the embryo [Pilia et al., 1996]. A more severe form of the disorder, Simpson–Golabi–Behmel syndrome, type II, maps to Xp22 [Brzustowicz et al., 1999]. Macrocephaly is commonly present at birth and is progressive through childhood. CNS abnormalities have been reported only in one case where Chiari malformation and corpus callosum agenesis were noted [Young et al., 2006].

The M-CMTC syndrome consists of congenital telangiectasias (sometimes localized to the face), macrosomia, macrocephaly, developmental delay and minor anomalies including syndactyly [Clayton-Smith et al., 1997; Moore et al., 1997]. The syndrome has been recently referred to as macrocephaly capillary malformation syndrome [Toriello and Mulliken, 2007]. Often, there is body asymmetry or hemihypertrophy. MRI scans may show generalized parenchymal enlargement, white matter irregularities, focal cortical dysplasia, polymicrogyria. Generalized ventriculomegaly, prominent Virchow–Robin spaces with dilated dural venous sinuses are seen in many affected patients [Conway et al., 2007]. Chiari I anomaly, cerebellar tonsillar herniation and hemimegalencephaly have been reported [Moore et al., 1997; Lapunzina et al., 2004; Garavelli et al., 2005]. The genetic cause of M-CMTC has not yet been determined and neither parents nor siblings have been affected; sporadic autosomal dominant mutation is thus a possibility [Garavelli et al., 2005].

NEURO-CARDIO-FACIO-CUTANEOUS SYNDROMES

These conditions include Noonan (OMIM 163950), LEOPARD (OMIM 151100), Costello (OMIM 218040) and cardiofaciocutaneous (CFC) (OMIM 115150) syndromes and are associated with mutation the *RAS/MAP Kinase* signaling pathway genes [Denayer and Legius, 2007]. They are often associated with relative macrocephaly but in infancy this type of macrocephaly may be a striking component of the craniofacial phenotype. Macrocephaly in Noonan

syndrome may occasionally be associated with hydrocephalus or true megalencephaly. Noonan syndrome is characterized by short stature, congenital heart defects, webbed neck, abnormal chest, developmental delay, macrocephaly, characteristic facial features and varied coagulopathies [Allanson, 1987]. Noonan syndrome is caused by mutations in the *PTPN11* gene (12q24.1) in 50% [Tartaglia et al., 2001, 2002; Jongmans et al., 2004], *KRAS* gene (12p12.1) in less than 5% [Schubbert et al., 2006], *SOS1* gene (2p22-p21) in 10% [Roberts et al., 2007], and *RAF1* gene (3p25) in 3–17% of cases [Pandit et al., 2007; Razzaque et al., 2007]. CFC syndrome is characterized by cardiac abnormalities, distinctive craniofacial appearance including relative macrocephaly and cutaneous abnormalities. Cognitive delay is seen in all affected individuals [Rauen, 2-18-2007]. The four genes known to be associated with CFC syndrome are: *BRAF* (7q34) in 75–80% [Niihori et al., 2006; Rodriguez-Viciana et al., 2006], *MAP2K1* (15q21) and *MAP2K2* (7q32) in 10–15% [Rodriguez-Viciana et al., 2006], and *KRAS* in less than 5% [Niihori et al., 2006; Schubbert et al., 2006]. Costello syndrome is characterized by failure to thrive in infancy, short stature, developmental delay, coarse facial features, macrocephaly deep palmar and plantar creases, papillomata, cardiac abnormalities, and risk for tumors [Gripp et al., 2006b]. *HRAS* (11p15.5) missense mutations can be detected in 80–90% of individuals with this clinical diagnosis [Aoki et al., 2005; Estep et al., 2006; Gripp et al., 2006a,b; Kerr et al., 2006]. LEOPARD is an acronym for *l*entigines, *E*CG conduction abnormalities, *o*cular hypertelorism, *p*ulmonic stenosis, *a*bnormal genitalia, *r*etardation of growth, and *s*ensorineural deafness [Gorlin et al., 1969]. Additionally, LEOPARD syndrome is associated with learning difficulties, hypertrophic cardiomyopathy and abnormalities of the spine. Mutations in *PTPN11* are detected in about 90% of affected individuals [Digilio et al., 2002; Legius et al., 2002]. *RAF 1* mutations have recently been reported [Pandit et al., 2007].

SYNDROMES WITH MENTAL RETARDATION

Fragile X Syndrome

Fragile X syndrome (OMIM 300624) occurs when a trinucleotide expansion, usually more than 200 repeats, disrupts the function of the promoter region of the *FMR1* gene (Xq27.3). The protein product, FMRP, is important for synaptic maturation and pruning and might have a regulatory role in activity-dependant transcription at the synapse [Gatchel and Zoghbi, 2005; Dolen et al., 2007].

Fragile X syndrome is the most common genetic cause of mental retardation in males and should be considered in the differential diagnosis of males presenting with developmental delay. Affected young adults may have a long face, large ears and a prominent jaw, but these features may be mild or absent in children. Testicular size is increased in the post-pubertal period. Macrocephaly is not a primary identifying characteristic but relative macrocephaly may be present. In infancy, the OFC tends to be above the mean but occasionally absolute macrocephaly is identified (Fig. 2F). Hence, Fragile X syndrome should be considered in the differential diagnosis for infants with macrocephaly. Adults with Fragile X syndrome continue to have head circumferences above the mean [Partington, 1984; Chiu et al., 2007]. It is of interest that infants with Fragile X syndrome and autism have accelerated OFC growth rates that peak at age 30 months but return to a normal rate by age 60 months [Chiu et al., 2007]. MRI of the head demonstrates a diminished white to gray matter ratio and enlarged lateral and fourth ventricles [Cohen, 2003]. A recent study of 84 children and adolescents with full mutation Fragile X syndrome showed that a large caudate nucleus, small posterior cerebellar vermis, amygdala and superior temporal gyrus were distinguishing features from normal controls. The association between macrocephaly and the above findings was not clarified [Gothelf et al., 2008]. Routine brain scans however are usually normal although Moro et al. [2006] reported two unrelated cases with periventricular heterotopia.

METABOLIC, WITH LEUKODYSTROPHY

Of all the leukodystrophies, Alexander disease (OMIM 203450), Canavan disease (CD) (OMIM 271900) and megalencephalic leukoencephalopathy with subcortical cysts (OMIM 604004) are most clearly associated with macrocephaly. In Alexander disease, there are widespread astrocytic inclusions of dense protein aggregates (Rosenthal fibers) composed mainly of abnormal glial fibrillary acidic protein (GFAP) [Towfighi et al., 1983; Lake, 1997]. There is widespread axonal loss and diffuse demyelination especially prominent in the frontal lobes, associated with a distinctive MRI appearance (Fig. 3) [van der Knaap et al., 2001]. The most common presentation involves infants less than 2 years of age who have a severe regressive course associated with seizures, pyramidal spasticity, and feeding difficulties. Juvenile and adult forms are also described but all types are caused by heterozygous (autosomal dominant), gain of function mutations in the *GFAP* gene (17q21) [Rodriguez et al., 2001; Li et al., 2005]. In a recent report of 26 cases with mutation proven infantile presentation, only 62% had macrocephaly and macrocephaly did not appear to be a feature in the juvenile and adult onset type [Li et al., 2005].

CD has a higher incidence of associated macrocephaly as by 12 months of age, 54 of 59 affected children had head circumferences greater than the 90th centile [Traeger and Rapin, 1998]. In the typical

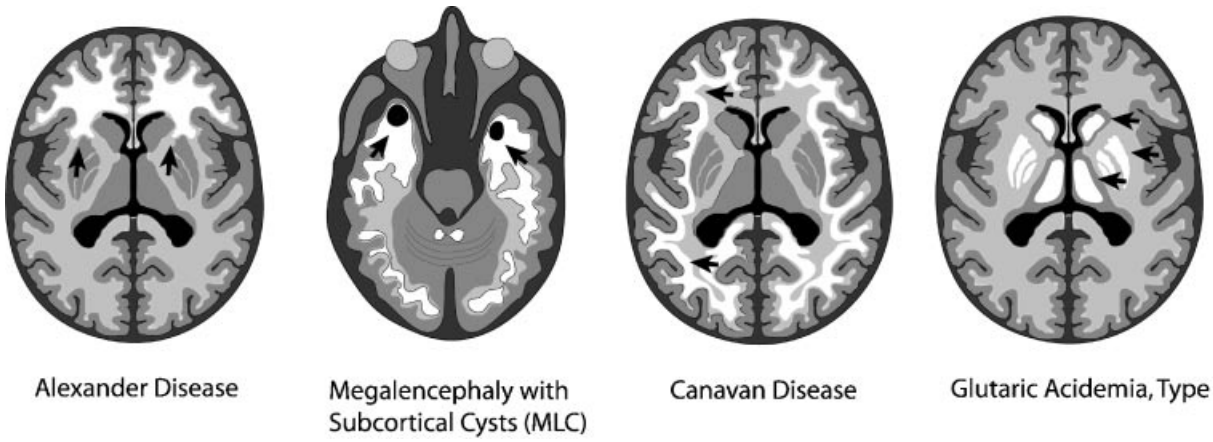

FIG. 3. Illustration of the pattern of brain abnormalities (black arrows) associated with certain metabolic disorders. The white areas represent the main changes that can occur in the white matter for the leukodystrophies and in the basal ganglia for glutaric aciduria, type 1.

form, symptoms develop between 2 and 4 months of life with onset of muscular hypotonia, cognitive delay, and vision impairment leading to blindness and optic atrophy but no evidence of retinopathy. Spongiform degeneration of the white matter is the classical histological picture. Astrocytes are swollen and vacuolated with apparent water spaces and there is diminished myelin [Lake, 1997]. On MRI these white matter changes are especially evident in the arcuate fibers of the frontal and parietal regions (Fig. 3) [Sener, 2003]. Deficiency of the enzyme, aspartoacylase (ASPA), causes CD [Kaul et al., 1993]. This enzyme is predominantly active in oligodendrocytes and hydrolyzes *N*-acetyl-L-aspartic acid (NAA) to aspartate and acetate [Kirmani et al., 2002]. Confirmation of CD can be ascertained by urinary determination of NAA, fibroblast enzyme analysis or by genotyping, demonstrating pathogenic homozygous or compound heterozygous mutations that disrupt function of the *ASPA* gene (17pter-p13).

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is associated often with pronounced infantile macrocephaly and leukodystrophy but lacks the rapid course of neurodeterioration typically seen in Alexander or CD [van der Knaap et al., 1995; Leegwater et al., 2001]. Over 100 clinical cases have been reported and macrocephaly is uniformly present by early childhood but it is unclear what proportion has congenital macrocephaly [Riel-Romero et al., 2005]. The macrocephaly can approach 4–6 SD above the mean. A distinctive feature of this entity is relatively large subcortical cysts, especially in the temporal lobes (Fig. 3). This is an autosomal recessive disorder that can be confirmed in most cases by genotyping the *MLC1* gene (22q13.33), although there may be some genetic heterogeneity [Leegwater et al., 2001]. The gene product is a novel transmembrane protein of unknown function. In the mouse, this protein is extensively expressed in astrocytes [Teijido et al., 2004].

METABOLIC, WITH ORGANIC ACIDURIAS

While there are a number of inborn errors of metabolism associated with neuronal or glial dysfunction, few appear to be associated with macrocephaly. Glutaric aciduria, type 1 (GA-1) (OMIM 231670), is an exception since macrocephaly is present in the neonate [Hoffmann and Zschocke, 1999; Horster et al., 2005] (Fig. 2E). Brain scans demonstrate apparent non-specific frontal and temporal lobe atrophy with prominent overlying subdural spaces. Bridging veins that traverse the subdural spaces appear at increased risk for subdural hemorrhage, and infants with GA-I have been erroneously diagnosed as abused or neglected children [Hartley et al., 2001]. In early infancy, there is usually no evidence of metabolic acidosis or episodic illness but, between 6 and 18 months of age, there is usually the onset of a movement disorder with progressive dystonia and, in some cases, rapid clinical deterioration due to acute injury to the basal ganglia area. At this time, the MRI scan can show distinctive bilateral striatal injury, apparently related to the excitatory effects of glutaric acid metabolites (Fig. 3) [Kolker et al., 2004]. The enzyme defect involves a mitochondrial flavoprotein, glutaryl-CoA dehydrogenase, with subsequent increased accumulation of 3-hydoxyglutaric and glutaconic acids. Diagnosis is usually confirmed by urine organic acid analysis or plasma acylcarnitine profiling. Molecular studies reveal mutations consistent with the known autosomal recessive mechanism of this disorder [Hoffmann and Zschocke, 1999].

Macrocephaly has also been noted in some patients with a recently delineated condition characterized by urine excretion of D-2-hydroxyglutaric aciduria (OMIM 600721). Over 35 cases have been reported and the clinical picture demonstrates both severe and mild types, with cardiomyopathy and severe developmental delay observed in infants with the severe type [van der Knaap et al., 1999]. Mutations

in D-2-dehydroxyglutaric dehydrogenase gene cause this autosomal recessive condition but it remains unclear what the biochemical neurotoxic mechanism is [Struys et al., 2005].

HYDROCEPHALUS

Congenital hydrocephalus, both obstructive (e.g., due to aqueductal stenosis) and non-obstructive type, often have a genetic basis albeit one that is often difficult to identify [Schrander-Stumpel and Fryns, 1998; Haverkamp et al., 1999]. Multifactorial inheritance is presumed for many cases of congenital hydrocephalus and thus confers an increased risk for recurrence. Aqueductal stenosis types, especially those occurring in an X-linked pattern of inheritance (OMIM 307000), can be due to mutations in the L1 cell adhesion molecule gene (*L1CAM*) (Xq28) [Weller and Gartner, 2001, for review]. Congenital aqueductal stenosis can also be caused by autosomal recessive mechanisms (OMIM 236635) [Lapunzina et al., 2002].

Macrocephaly due to acquired hydrocephalus is usually related to the complications of intracranial hemorrhage or infection [Bodensteiner and Chung, 1993]. Prematurity is a well known major risk factor. Macrocephaly may be due to subdural hematomas, most commonly due to child abuse or to birth-related trauma. Chronic subdural effusions (either sequelae of trauma or infection) can be associated with macrocephaly in later infancy. Chronic subdural hematoma with macrocephaly can rarely be due to bleeding due to a vascular malformation, inherited coagulopathy or metabolic derangement [Powers et al., 2007]. Patients below 2 years with arachnoids cysts can present with macrocephaly. Patients who present with macrocephaly are more likely to require shunts post-cyst fenestration compared to those who present with other features such as seizures or incidental lesions [Zada et al., 2007].

EVALUATION OF MACROCEPHALY

The evaluation approach is relatively straight forward and is summarized in Figure 4. Physical examination and history alone may identify a syndromic disorder that can then be confirmed by an appropriate test, for example *NSD1* gene analysis

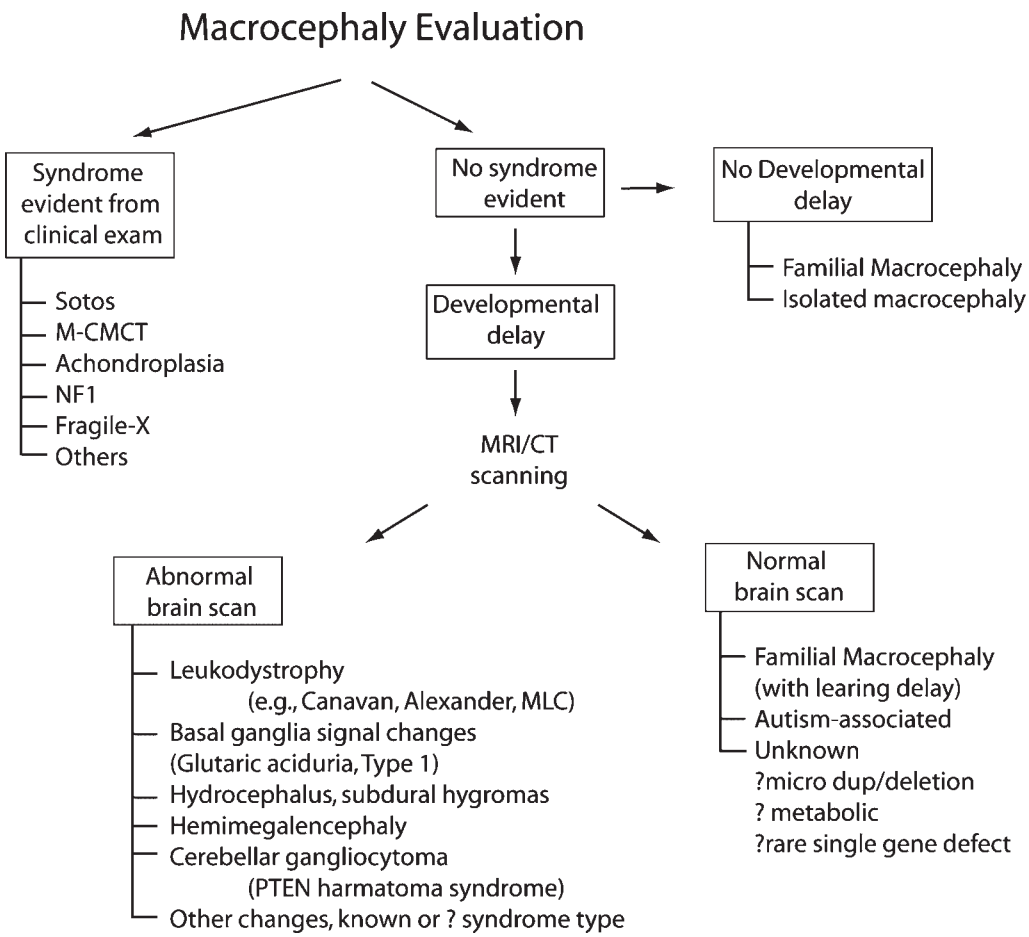

FIG. 4. Algorithm outlining a diagnostic approach to the evaluation of macrocephaly. Megalencephalic leukoencephalopathy with subcortical cysts (MLC); macrocephaly cutis marmorata telangiectatica congenital (M-CMTC); phosphatase and tensin homolog deleted on chromosome TEN.

in Sotos syndrome. If there is no neurological dysfunction, a brain imaging study may not be needed and the possibility of FM should be considered. When there are developmental concerns, a brain MRI is usually performed. In the absence of an informative MRI phenotype, tests such as chromosome study, array-CGH and fragile X molecular screening are often performed, not so much due to presence of macrocephaly, but related to assessment of concurrent developmental delay and/or dysmorphism. Metabolic screening with urine organic acids analysis and blood acylcarnitine profile may also be considered. Lysosomal enzyme screening is indicated if the clinical picture suggests a storage disorder like Tay–Sachs disease (OMIM 272800). An MRI phenotype showing a predominant leukodystrophy warrants specific diagnostic testing such as enzyme or gene analysis.

CONCLUSION

In this review, we have provided a limited discussion of genetic disorders known to be associated with macrocephaly. We have tried to emphasize the conditions where macrocephaly is likely to be one of the presenting clinical symptoms or a predominant aspect of the clinical presentation. Because identification of macrocephaly can lead to correct syndrome identification, the careful assessment of the OFC remains a crucial part of the clinical genetics evaluation.

Twenty years ago, DeMyer [1986] published a seminal review of macrocephaly and delineated the main criteria for diagnosis of familial macrocephaly. At that time, few of the genes responsible for macrocephaly had been identified. Now many genes are known but the basic cellular pathogenesis for macrocephaly is still unknown. While the genetic pathogenesis for the microcephaly disorders are better understood [Guerrini and Filippi, 2005; Leroy and Frias, 2005; Woods et al., 2005], such correlates are less evident for the genes known to be significantly associated with macrocephaly. Increasing societal attention on the problem of autism brings renewed interest in the study of macrocephaly since it is so prevalent among those with autism, and it is one of the few consistent physical abnormalities observed. An additional outcome of these studies related to autism has been a revisiting of the inheritance patterns, and the developmental outcomes, associated with FM. It is hoped that continued research in these arenas may shed additional light on the basic pathogenesis of macrocephaly.

ACKNOWLEDGMENTS

The authors declare that they have no competing or financial interests related to this scientific work. This study was funded in part by the Raymond C. Philips Research and Education Contract, State of Florida, USA.

REFERENCES

Agwu JC, Shaw NJ, Kirk J, Chapman S, Ravine D, Cole TR. 1999. Growth in Sotos syndrome. Arch Dis Child 80:339–342.

Allanson JE. 1987. Noonan syndrome. J Med Genet 24:9–13.

Alvarez LA, Maytal J, Shinnar S. 1986. Idiopathic external hydrocephalus: Natural history and relationship to benign familial macrocephaly. Pediatrics 77:901–907.

Anon., 2007. Prevalence of autism spectrum disorders—Autism and developmental disabilities monitoring network, 14 sites, United States, 2002. MMWR Surveill Summ 56:12–28.

Aoki N, Oikawa A, Sakai T. 1998. Serial neuroimaging studies in Sotos syndrome (cerebral gigantism syndrome). Neurol Res 20:149–152.

Aoki Y, Niihori T, Kawame H, Kurosawa K, Ohashi H, Tanaka Y, Filocamo M, Kato K, Suzuki Y, Kure S, et al. 2005. Germline mutations in HRAS proto-oncogene cause Costello syndrome. Nat Genet 37:1038–1040.

Arbour L, Watters GV, Hall JG, Fraser FC. 1996. Multifactorial inheritance of non-syndromic macrocephaly. Clin Genet 50: 57–62.

Asch AJ, Myers GJ. 1976. Benign familial macrocephaly: Report of a family and review of the literature. Pediatrics 57:535–539.

Aylward EH, Minshew NJ, Field K, Sparks BF, Singh N. 2002. Effects of age on brain volume and head circumference in autism. Neurology 59:175–183.

Barkovich AJ, Chuang SH. 1990. Unilateral megalencephaly: Correlation of MR imaging and pathologic characteristics. Am J Neuroradiol 11:523–531.

Battaglia A, Carey JC. 2006. Etiologic yield of autistic spectrum disorders: A prospective study. Am J Med Genet Part C Semin Med Genet 142C:3–7.

Bennett MR, Rizvi TA, Karyala S, McKinnon RD, Ratner N. 2003. Aberrant growth and differentiation of oligodendrocyte progenitors in neurofibromatosis type 1 mutants. J Neurosci 23:7207–7217.

Blinkov SM, Glezer II. 1968. The Human Brain in Figures and Tables. A Quantitative Handbook. New York: Plenum Press.

Bodensteiner JB, Chung EO. 1993. Macrocrania and megalencephaly in the neonate. Semin Neurol 13:84–91.

Brems H, Chmara M, Sahbatou M, Denayer E, Taniguchi K, Kato R, Somers R, Messiaen L, De Schepper S, Fryns JP, et al. 2007. Germline loss-of-function mutations in SPRED1 cause a neurofibromatosis 1-like phenotype. Nat Genet 39:1120–1126.

Broumandi DD, Hayward UM, Benzian JM, Gonzalez I, Nelson MD. 2004. Best cases from the AFIP: Hemimegalencephaly. Radiographics 24:843–848.

Brzustowicz LM, Farrell S, Khan MB, Weksberg R. 1999. Mapping of a new SGBS locus to chromosome Xp22 in a family with a severe form of Simpson-Golabi-Behmel syndrome. Am J Hum Genet 65:779–783.

Butler MG, Dasouki MJ, Zhou XP, Talebizadeh Z, Brown M, Takahashi TN, Miles JH, Wang CH, Stratton R, Pilarski R, et al. 2005. Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. J Med Genet 42:318–321.

Casanova MF. 2007. The neuropathology of autism. Brain Pathol 17:422–433.

Casanova MF, Buxhoeveden DP, Switala AE, Roy E. 2002. Minicolumnar pathology in autism. Neurology 58:428–432.

Cecconi M, Forzano F, Milani D, Cavani S, Baldo C, Selicorni A, Pantaleoni C, Silengo M, Ferrero GB, Scarano G, et al. 2005. Mutation analysis of the NSD1 gene in a group of 59 patients with congenital overgrowth. Am J Med Genet Part A 134A: 247–253.

Chakrabarti S, Fombonne E. 2001. Pervasive developmental disorders in preschool children. JAMA 285:3093–3099.

Chiu S, Wegelin JA, Blank J, Jenkins M, Day J, Hessl D, Tassone F, Hagerman R. 2007. Early acceleration of head circumference in children with fragile x syndrome and autism. J Dev Behav Pediatr 28:31–35.

Clayton-Smith J, Kerr B, Brunner H, Tranebjaerg L, Magee A, Hennekam RC, Mueller RF, Brueton L, Super M, Steen-Johnsen J, et al. 1997. Macrocephaly with cutis marmorata, haemangioma and syndactyly—A distinctive overgrowth syndrome. Clin Dysmorphol 6:291–302.

Clementi M, Milani S, Mammi I, Boni S, Monciotti C, Tenconi R. 1999. Neurofibromatosis type 1 growth charts. Am J Med Genet 87:317–323.

Cohen MM Jr. 1999. Overgrowth syndromes: An update. Adv Pediatr 46:441–491.

Cohen MM Jr. 2003. Mental deficiency, alterations in performance, and CNS abnormalities in overgrowth syndromes. Am J Med Genet Part C Semin Med Genet 117C:49–56.

Conway RL, Pressman BD, Dobyns WB, Butler MG, Zackai EH, Saitta SC, Campbell L, Clericuzio CL, Milunsky JM, Hoyme HE, et al. 2007. Neuroimaging findings in macrocephaly-cutis marmorata telangiectatica congenita. American Society of Human Genetics Annual Meeting, San Diego, CA, http://www.ashg.org/genetics/ashg07s/index.shtml, A558.

Costa RM, Silva AJ. 2003. Mouse models of neurofibromatosis type I: Bridging the GAP. Trends Mol Med 9:19–23.

Courchesne E, Pierce K. 2005. Brain overgrowth in autism during a critical time in development: Implications for frontal pyramidal neuron and interneuron development and connectivity. Int J Dev Neurosci 23:153–170.

Courchesne E, Carper R, Akshoomoff N. 2003. Evidence of brain overgrowth in the first year of life in autism. JAMA 290:337–344.

Cutting LE, Cooper KL, Koth CW, Mostofsky SH, Kates WR, Denckla MB, Kaufmann WE. 2002. Megalencephaly in NF1: Predominantly white matter contribution and mitigation by ADHD. Neurology 59:1388–1394.

Dementieva YA, Vance DD, Donnelly SL, Elston LA, Wolpert CM, Ravan SA, DeLong GR, Abramson RK, Wright HH, Cuccaro ML. 2005. Accelerated head growth in early development of individuals with autism. Pediatr Neurol 32:102–108.

DeMyer W. 1986. Megalencephaly: Types, clinical syndromes, and management. Pediatr Neurol 2:321–328.

Denayer E, Legius E. 2007. What's new in the neuro-cardio-facial-cutaneous syndromes? Eur J Pediatr 166:1091–1098.

Digilio MC, Conti E, Sarkozy A, Mingarelli R, Dottorini T, Marino B, Pizzuti A, Dallapiccola B. 2002. Grouping of multiple-lentigines/LEOPARD and Noonan syndromes on the PTPN11 gene. Am J Hum Genet 71:389–394.

DiLiberti JH. 1998. Inherited macrocephaly-hamartoma syndromes. Am J Med Genet 79:284–290.

DiPaolo DP, Zimmerman RA, Rorke LB, Zackai EH, Bilaniuk LT, Yachnis AT. 1995. Neurofibromatosis type 1: Pathologic substrate of high-signal-intensity foci in the brain. Radiology 195:721–724.

Dolen G, Osterweil E, Rao BS, Smith GB, Auerbach BD, Chattarji S, Bear MF. 2007. Correction of Fragile X syndrome in mice. Neuron 56:955–962.

Douglas J, Hanks S, Temple IK, Davies S, Murray A, Upadhyaya M, Tomkins S, Hughes HE, Cole TR, Rahman N. 2003. NSD1 mutations are the major cause of Sotos syndrome and occur in some cases of Weaver syndrome but are rare in other overgrowth phenotypes. Am J Hum Genet 72:132–143.

Estep AL, Tidyman WE, Teitell MA, Cotter PD, Rauen KA. 2006. HRAS mutations in Costello syndrome: Detection of constitutional activating mutations in codon 12 and 13 and loss of wild-type allele in malignancy. Am J Med Genet Part A 140A: 8–16.

Faravelli F. 2005. NSD1 mutations in Sotos syndrome. Am J Med Genet Part C Semin Med Genet 137C:24–31.

Feldmann R, Denecke J, Grenzebach M, Schuierer G, Weglage J. 2003. Neurofibromatosis type 1: Motor and cognitive function and T2-weighted MRI hyperintensities. Neurology 61:1725–1728.

Fidler DJ, Bailey JN, Smalley SL. 2000. Macrocephaly in autism and other pervasive developmental disorders. Dev Med Child Neurol 42:737–740.

Freeman BM, Hoon AH Jr, Breiter SN, Hamosh A. 1999. Pachygyria in Weaver syndrome. Am J Med Genet 86:395–397.

Garavelli L, Leask K, Zanacca C, Pedori S, Albertini G, Della Giustina E, Croci GF, Magnani C, Banchini G, Clayton-Smith J, Bocian M, Firth H, Gold JA, Hurst J. 2005. MRI and neurological findings in macrocephaly-cutis marmorata telangiectatica congenita syndrome: Report of ten cases and review of the literature. Genet Couns 16:117–128.

Gatchel JR, Zoghbi HY. 2005. Diseases of unstable repeat expansion: Mechanisms and common principles. Nat Rev Genet 6:743–755.

Gillberg C, de Souza L. 2002. Head circumference in autism, Asperger syndrome, and ADHD: A comparative study. Dev Med Child Neurol 44:296–300.

Gooskens RH, Willemse J, Faber JA, Verdonck AF. 1989. Macrocephalies—A differentiated approach. Neuropediatrics 20:164–169.

Gorlin RJ, Anderson RC, Blaw M. 1969. Multiple lentigenes syndrome. Am J Dis Child 117:652–662.

Gothelf D, Furfaro JA, Hoeft F, Eckert MA, Hall SS, O'Hara R, Erba HW, Ringel J, Hayashi KM, Patnaik S, et al. 2008. Neuroanatomy of fragile X syndrome is associated with aberrant behavior and the fragile X mental retardation protein (FMRP). Ann Neurol 63:40–51.

Gripp KW, Lin AE, Stabley DL, Nicholson L, Scott CI Jr, Doyle D, Aoki Y, Matsubara Y, Zackai EH, Lapunzina P, et al. 2006a. HRAS mutation analysis in Costello syndrome: Genotype and phenotype correlation. Am J Med Genet Part A 140A:1–7.

Gripp KW, Stabley DL, Nicholson L, Hoffman JD, Sol-Church K. 2006b. Somatic mosaicism for an HRAS mutation causes Costello syndrome. Am J Med Genet Part A 140A:2163–2169.

Guerrini R, Filippi T. 2005. Neuronal migration disorders, genetics, and epileptogenesis. J Child Neurol 20:287–299.

Hartley LM, Mrcp B, Khwaja OS, Verity CM, Frcpch B. 2001. Glutaric aciduria type 1 and nonaccidental head injury. Pediatrics 107:174–175.

Haverkamp F, Wolfle J, Aretz M, Kramer A, Hohmann B, Fahnenstich H, Zerres K. 1999. Congenital hydrocephalus internus and aqueduct stenosis: Aetiology and implications for genetic counselling. Eur J Pediatr 158:474–478.

Hay N. 2005. The Akt-mTOR tango and its relevance to cancer. Cancer Cell 8:179–183.

Herbert MR. 2005. Large brains in autism: The challenge of pervasive abnormality. Neuroscientist 11:417–440.

Herman GE, Butter E, Enrile B, Pastore M, Prior TW, Sommer A. 2007. Increasing knowledge of PTEN germline mutations: Two additional patients with autism and macrocephaly. Am J Med Genet Part A 143A:589–593.

Hoffmann GF, Zschocke J. 1999. Glutaric aciduria type I: From clinical, biochemical and molecular diversity to successful therapy. J Inherit Metab Dis 22:381–391.

Horster F, Surtees R, Hoffmann GF. 2005. Disorders of intermediary metabolism: Toxic leukoencephalopathies. J Inherit Metab Dis 28:345–356.

Hyman SL, Shores A, North KN. 2005. The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. Neurology 65:1037–1044.

Jones KL. 2006. Smiths's recognizable pattern of human malformation. Philadelphia: Elsevier Saunders.

Jongmans M, Otten B, Noordam K, van der Burgt I. 2004. Genetics and variation in phenotype in Noonan syndrome. Horm Res 62:56–59.

Kaul R, Gao GP, Balamurugan K, Matalon R. 1993. Cloning of the human aspartoacylase cDNA and a common missense mutation in Canavan disease. Nat Genet 5:118–123.

Keegan MM, Takahaski TN, Miles JH. 2007. Macrocephaly in autism is not a homogeneous marker phenotype. American Society of Human Genetics Annual Meeting, San Diego, A755.

Kerr B, Delrue MA, Sigaudy S, Perveen R, Marche M, Burgelin I, Stef M, Tang B, Eden OB, O'Sullivan J, et al. 2006. Genotype-phenotype correlation in Costello syndrome: HRAS mutation analysis in 43 cases. J Med Genet 43:401–405.

Kirmani BF, Jacobowitz DM, Kallarakal AT, Namboodiri MA. 2002. Aspartoacylase is restricted primarily to myelin synthesizing cells in the CNS: Therapeutic implications for Canavan disease. Brain Res Mol Brain Res 107:176–182.

Kolker S, Koeller DM, Okun JG, Hoffmann GF. 2004. Pathomechanisms of neurodegeneration in glutaryl-CoA dehydrogenase deficiency. Ann Neurol 55:7–12.

Lake B. 1997. Lysosomal and peroxisomal disorders. In: Graham DI, Lantos PL, editors. Greenfield's Neuropathology. 6th edition. London: Arnold Publications. p 657–753.

Lapunzina P, Delicado A, de Torres ML, Mor MA, Perez-Pacheco RF, Lopes PI. 2002. Autosomal recessive hydrocephalus due to aqueduct stenosis: Report of a further family and implications for genetic counselling. J Matern Fetal Neonatal Med 12:64–66.

Lapunzina P, Gairi A, Delicado A, Mori MA, Torres ML, Goma A, Navia M, Pajares IL. 2004. Macrocephaly-cutis marmorata telangiectatica congenita: Report of six new patients and a review. Am J Med Genet Part A 130A:45–51.

Leegwater PA, Yuan BQ, van der Steen J, Mulders J, Konst AA, Boor PK, Mejaski-Bosnjak V, van der Maarel SM, Frants RR, Oudejans CB, Schutgens RB, Pronk JC, van der Knaap MS. 2001. Mutations of MLC1 (KIAA0027), encoding a putative membrane protein, cause megalencephalic leukoencephalopathy with subcortical cysts. Am J Hum Genet 68:831–838.

Legius E, Schrander-Stumpel C, Schollen E, Pulles-Heintzberger C, Gewillig M, Fryns JP. 2002. PTPN11 mutations in LEOPARD syndrome. J Med Genet 39:571–574.

Leroy JG, Frias JL. 2005. Nonsyndromic microcephaly: An overview. Adv Pediatr 52:261–293.

Li R, Johnson AB, Salomons G, Goldman JE, Naidu S, Quinlan R, Cree B, Ruyle SZ, Banwell B, D'Hooghe M, Siebert JR, Rolf CM, Cox H, Reddy A, Gutierrez-Solana LG, Collins A, Weller RO, Messing A, van der Knaap MS, Brenner M. 2005. Glial fibrillary acidic protein mutations in infantile, juvenile, and adult forms of Alexander disease. Ann Neurol 57:310–326.

Lorber J, Priestley BL. 1981. Children with large heads: A practical approach to diagnosis in 557 children, with special reference to 109 children with megalencephaly. Dev Med Child Neurol 23:494–504.

Marsh DJ, Kum JB, Lunetta KL, Bennett MJ, Gorlin RJ, Ahmed SF, Bodurtha J, Crowe C, Curtis MA, Dasouki M, Dunn T, Feit H, Geraghty MT, Graham JM Jr, Hodgson SV, Hunter A, Korf BR, Manchester D, Miesfeldt S, Murday VA, Nathanson KL, Parisi M, Pober B, Romano C, Eng C. 1999. PTEN mutation spectrum and genotype-phenotype correlations in Bannayan-Riley-Ruvalcaba syndrome suggest a single entity with Cowden syndrome. Hum Mol Genet 8:1461–1472.

McIlwain H, Bachelard HS. 1985. Biochemistry and the central nervous system. Edinburgh: Churchill Livingstone.

Medne L, Waldman A, Bonnemann C. 2007. PTEN gene mutation causes megalencephaly with prominent Virchow-Robin spaces without cognitive delays or autism: New PTHS phenotype. American Society of Human Genetics Annual Meeting, San Diego, CA, A1890.

Mischel PS, Nguyen LP, Vinters HV. 1995. Cerebral cortical dysplasia associated with pediatric epilepsy. Review of neuropathologic features and proposal for a grading system. J Neuropathol Exp Neurol 54:137–153.

Moore CA, Toriello HV, Abuelo DN, Bull MJ, Curry CJ, Hall BD, Higgins JV, Stevens CA, Twersky S, Weksberg R, Dobyns WB. 1997. Macrocephaly-cutis marmorata telangiectatica congenita: A distinct disorder with developmental delay and connective tissue abnormalities. Am J Med Genet 70:67–73.

Moore BD III, Slopis JM, Jackson EF, De Winter AE, Leeds NE. 2000. Brain volume in children with neurofibromatosis type 1: Relation to neuropsychological status. Neurology 54:914–920.

Moro F, Pisano T, Bernardina BD, Polli R, Murgia A, Zoccante L, Darra F, Battaglia A, Pramparo T, Zuffardi O, Guerrini R. 2006. Periventricular heterotopia in fragile X syndrome. Neurology 67:713–715.

Newschaffer CJ, Croen LA, Daniels J, Giarelli E, Grether JK, Levy SE, Mandell DS, Miller LA, Pinto-Martin J, Reaven J, Reynolds AM, Rice CE, Schendel D, Windham GC. 2007. The epidemiology of autism spectrum disorders. Annu Rev Public Health 28:235–258.

Niihori T, Aoki Y, Narumi Y, Neri G, Cave H, Verloes A, Okamoto N, Hennekam RC, Gillessen-Kaesbach G, Wieczorek D, Kavamura MI, Kurosawa K, Ohashi H, Wilson L, Heron D, Bonneau D, Corona G, Kaname T, Naritomi K, Baumann C, Matsumoto N, Kato K, Kure S, Matsubara Y. 2006. Germline KRAS and BRAF mutations in cardio-facio-cutaneous syndrome. Nat Genet 38:294–296.

Nordlund ML, Rizvi TA, Brannan CI, Ratner N. 1995. Neurofibromin expression and astrogliosis in neurofibromatosis (type 1) brains. J Neuropathol Exp Neurol 54:588–600.

Odita JC. 1992. The widened frontal subarachnoid space. A CT comparative study between macrocephalic, microcephalic, and normocephalic infants and children. Childs Nerv Syst 8: 36–39.

Online Mendelian Inheritance in Man, OMIM (TM). McKusick Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), 5/1/2008. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/.

Opitz JM, Weaver DW, Reynolds JF Jr. 1998. The syndromes of Sotos and Weaver: Reports and review. Am J Med Genet 79:294–304.

Pandit B, Sarkozy A, Pennacchio LA, Carta C, Oishi K, Martinelli S, Pogna EA, Schackwitz W, Ustaszewska A, Landstrom A, Bos JM, Ommen SR, Esposito G, Lepri F, Faul C, Mundel P, Lopez Siguero JP, Tenconi R, Selicorni A, Rossi C, Mazzanti L, Torrente I, Marino B, Digilio MC, Zampino G, Ackerman MJ, Dallapiccola B, Tartaglia M, Gelb BD. 2007. Gain-of-function RAF1 mutations cause Noonan and LEOPARD syndromes with hypertrophic cardiomyopathy. Nat Genet 39:1007–1012.

Pardo CA, Eberhart CG. 2007. The neurobiology of autism. Brain Pathol 17:434–447.

Partington MW. 1984. The fragile X syndrome II: Preliminary data on growth and development in males. Am J Med Genet 17:175–194.

Perez-Nunez A, Lagares A, Benitez J, Urioste M, Lobato RD, Ricoy JR, Ramos A, Gonzalez P. 2004. Lhermitte-Duclos disease and Cowden disease: Clinical and genetic study in five patients with Lhermitte-Duclos disease and literature review. Acta Neurochir (Wien) 146:679–690.

Pilia G, Hughes-Benzie RM, MacKenzie A, Baybayan P, Chen EY, Huber R, Neri G, Cao A, Forabosco A, Schlessinger D. 1996. Mutations in GPC3, a glypican gene, cause the Simpson-Golabi-Behmel overgrowth syndrome. Nat Genet 12:241–247.

Powers CJ, Fuchs HE, George TM. 2007. Chronic subdural hematoma of the neonate: Report of two cases and literature review. Pediatr Neurosurg 43:25–28.

Prassopoulos P, Cavouras D. 1994. CT evaluation of normal CSF spaces in children: Relationship to age, gender and cranial size. Eur J Radiol 18:22–25.

Prassopoulos P, Cavouras D, Golfinopoulos S, Nezi M. 1995. The size of the intra- and extraventricular cerebrospinal fluid compartments in children with idiopathic benign widening of the frontal subarachnoid space. Neuroradiology 37:418–421.

Rauen KA. 2007. 2-18-2007. Cardiofaciocutaneous Syndrome. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online) Copyright, University of

Washington, Seattle 1997–2008 Available at http://wwwgenetestsorg Accessed [11-01-2007].

Rayasam GV, Wendling O, Angrand PO, Mark M, Niederreither K, Song L, Lerouge T, Hager GL, Chambon P, Losson R. 2003. NSD1 is essential for early post-implantation development and has a catalytically active SET domain. EMBO J 22:3153–3163.

Razzaque MA, Nishizawa T, Komoike Y, Yagi H, Furutani M, Amo R, Kamisago M, Momma K, Katayama H, Nakagawa M, Fujiwara Y, Matsushima M, Mizuno K, Tokuyama M, Hirota H, Muneuchi J, Higashinakagawa T, Matsuoka R. 2007. Germline gain-of-function mutations in RAF1 cause Noonan syndrome. Nat Genet 39:1013–1017.

Riel-Romero RM, Smith CD, Pettigrew AL. 2005. Megalencephalic leukoencephalopathy with subcortical cysts in two siblings owing to two novel mutations: Case reports and review of the literature. J Child Neurol 20:230–234.

Roberts AE, Araki T, Swanson KD, Montgomery KT, Schiripo TA, Joshi VA, Li L, Yassin Y, Tamburino AM, Neel BG, Bucherlapati RS. 2007. Germline gain-of-function mutations in SOS1 cause Noonan syndrome. Nat Genet 39:70–74.

Rodriguez D, Gauthier F, Bertini E, Bugiani M, Brenner M, N'Guyen S, Goizet C, Gelot A, Surtees R, Pedespan JM, Hernandorena X, Troncoso M, Uziel G, Messing A, Ponsot G, Pham-Dinh D, Dautigny A, Boespflug-Tanguy O. 2001. Infantile Alexander disease: Spectrum of GFAP mutations and genotype-phenotype correlation. Am J Hum Genet 69: 1134–1140.

Rodriguez-Viciana P, Tetsu O, Tidyman WE, Estep AL, Conger BA, Cruz MS, McCormick F, Rauen KA. 2006. Germline mutations in genes within the MAPK pathway cause cardio-facio-cutaneous syndrome. Science 311:1287–1290.

Sansal I, Sellers WR. 2004. The biology and clinical relevance of the PTEN tumor suppressor pathway. J Clin Oncol 22:2954–2963.

Sasaki M, Hashimoto T, Furushima W, Okada M, Kinoshita S, Fujikawa Y, Sugai K. 2005. Clinical aspects of hemimegalencephaly by means of a nationwide survey. J Child Neurol 20:337–341.

Schaefer GB, Mendelsohn NJ. 2008. Genetics evaluation for the etiologic diagnosis of autism spectrum disorders. Genet Med 10:4–12.

Schaefer GB, Bodensteiner JB, Buehler BA, Lin A, Cole TR. 1997. The neuroimaging findings in Sotos syndrome. Am J Med Genet 68:462–465.

Schrander-Stumpel C, Fryns JP. 1998. Congenital hydrocephalus: Nosology and guidelines for clinical approach and genetic counselling. Eur J Pediatr 157:355–362.

Schreier H, Rapin I, Davis J. 1974. Familial megalencephaly or hydrocephalus? Neurology 24:232–236.

Schubbert S, Zenker M, Rowe SL, Boll S, Klein C, Bollag G, van der Burgt I, Musante L, Kalscheuer V, Wehner LE, Nguyen H, West B, Zhang KY, Sistermans E, Rauch A, Niemeyer CM, Shannon K, Kratz CP. 2006. Germline KRAS mutations cause Noonan syndrome. Nat Genet 38:331–336.

Sebat J, Lakshmi B, Malhotra D, Troge J, Lese-Martin C, Walsh T, Yamrom B, Yoon S, Krasnitz A, Kendall J, Leotta A, Pai D, Zhang R, Lee YH, Hicks J, Spence SJ, Lee AT, Puura K, Lehtimaki T, Ledbetter D, Gregersen PK, Bregman J, Sutcliffe JS, Jobanputra V, Chung W, Warburton D, King MC, Skude D, Geschwind DH, Gilliam TC, Ye K, Wigler M. 2007. Strong association of de novo copy number mutations with autism. Science 316:445–449.

Sener RN. 2003. Canavan disease: Diffusion magnetic resonance imaging findings. J Comput Assist Tomogr 27:30–33.

Smith RD. 1981. Abnormal head circumference in learning-disabled children. Dev Med Child Neurol 23:626–632.

Smith RD, Ashley J, Hardesty RA, Tulley R, Hewitt J. 1984. Macrocephaly and minor congenital anomalies in children with learning problems. J Dev Behav Pediatr 5:231–236.

Sotos JF, Dodge PR, Muirhead D, Crawford JD, Talbot NB. 1964. Cerebral gigantism in childhood. A syndrome of excessively rapid growth and acromegalic features and a nonprogressive neurologic disorder. N Engl J Med 271:109–116.

Spence S, Kono N, Geschwind DH, Cantor RM. 2005. A QTL Analysis of Macrocephaly in Autism Families. American Society of Human Genetics Annual Meeting, Salt Lake City, UT. http://www.ashg.org/genetics/ashg05s/index.shtml A1652.

Starink TM, van der Veen JP, Arwert F, de Waal LP, de Lange GG, Gille JJ, Eriksson AW. 1986. The Cowden syndrome: A clinical and genetic study in 21 patients. Clin Genet 29:222–233.

Stevenson RE, Schroer RJ, Skinner C, Fender D, Simensen RJ. 1997. Autism and macrocephaly. Lancet 349:1744–1745.

Struys EA, Salomons GS, Achouri Y, Van Schaftingen E, Grosso S, Craigen WJ, Verhoeven NM, Jakobs C. 2005. Mutations in the D-2-hydroxyglutarate dehydrogenase gene cause D-2-hydroxyglutaric aciduria. Am J Hum Genet 76:358–360.

Szudek J, Birch P, Friedman JM. 2000. Growth charts for young children with neurofibromatosis 1 (NF1). Am J Med Genet 92: 224–228.

Tan WH, Baris HN, Burrows PE, Robson CD, Alomari AI, Mulliken JB, Fishman SJ, Irons MB. 2007. The spectrum of vascular anomalies in patients with PTEN mutations: Implications for diagnosis and management. J Med Genet 44:594–602.

Tartaglia M, Mehler EL, Goldberg R, Zampino G, Brunner HG, Kremer H, van der Burgt I, Crosby AH, Ion A, Jeffery S, Kalidas K, Patton MA, Kucherlapati RS, Gelb BD. 2001. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. Nat Genet 29:465–468.

Tartaglia M, Kalidas K, Shaw A, Song X, Musat DL, van der Burgt I, Brunner HG, Bertola DR, Crosby A, Ion A, Kucherlapati RS, Jeffery S, Patton MA, Gelb BD. 2002. PTPN11 mutations in Noonan syndrome: Molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. Am J Hum Genet 70:1555–1563.

Teijido O, Martinez A, Pusch M, Zorzano A, Soriano E, Del Rio JA, Palacin M, Estevez R. 2004. Localization and functional analyses of the MLC1 protein involved in megalencephalic leukoencephalopathy with subcortical cysts. Hum Mol Genet 13:2581–2594.

Tian XL, Kadaba R, You SA, Liu M, Timur AA, Yang L, Chen Q, Szafranski P, Rao S, Wu L, Housman DE, DiCorleto PE, Driscoll DJ, Borrow J, Wang Q. 2004. Identification of an angiogenic factor that when mutated causes susceptibility to Klippel-Trenaunay syndrome. Nature 427:640–645.

Tognini G, Ferrozzi F, Garlaschi G, Piazza P, Patti A, Virdis R, Bertolino C, Bertolino G, Manfredini D, Zompatori M, Crisi G. 2005. Brain apparent diffusion coefficient evaluation in pediatric patients with neurofibromatosis type 1. J Comput Assist Tomogr 29:298–304.

Toriello HV, Mulliken JB. 2007. Accurately renaming macrocephaly-cutis marmorata telangiectatica congenita (M-CMTC) as macrocephaly-capillary malformation (M-CM). Am J Med Genet Part A 143A:3009.

Towfighi J, Young R, Sassani J, Ramer J, Horoupian DS. 1983. Alexander's disease: Further light-, and electron-microscopic observations. Acta Neuropathol (Berl) 61:36–42.

Traeger EC, Rapin I. 1998. The clinical course of Canavan disease. Pediatr Neurol 18:207–212.

van der Knaap MS, Barth PG, Stroink H, van Nieuwenhuizen O, Arts WF, Hoogenraad F, Valk J. 1995. Leukoencephalopathy with swelling and a discrepantly mild clinical course in eight children. Ann Neurol 37:324–334.

van der Knaap MS, Jakobs C, Hoffmann GF, Duran M, Muntau AC, Schweitzer S, Kelley RI, Parrot-Roulaud F, Amiel J, De Lonlay P, Rabier D, Eeg-Olofsson O. 1999. D-2-hydroxyglutaric aciduria: Further clinical delineation. J Inherit Metab Dis 22: 404–413.

van der Knaap MS, Naidu S, Breiter SN, Blaser S, Stroink H, Springer S, Begeer JC, van Coster R, Barth PG, Thomas NH, Valk J, Powers JM. 2001. Alexander disease: Diagnosis with MR imaging. Am J Neuroradiol 22:541–552.

Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. 2005. Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol 57:67–81.

Wang X, Yeh S, Wu G, Hsu CL, Wang L, Chiang T, Yang Y, Guo Y, Chang C. 2001. Identification and characterization of a novel androgen receptor coregulator ARA267-alpha in prostate cancer cells. J Biol Chem 276:40417–40423.

Weaver DD, Christian JC. 1980. Familial variation of head size and adjustment for parental head circumference. J Pediatr 96:990–994.

Weaver DD, Graham CB, Thomas IT, Smith DW. 1974. A new overgrowth syndrome with accelerated skeletal maturation, unusual facies, and camptodactyly. J Pediatr 84:547–552.

Weller S, Gartner J. 2001. Genetic and clinical aspects of X-linked hydrocephalus (L1 disease): Mutations in the L1CAM gene. Hum Mutat 18:1–12.

Williams RW, Herrup K. 1988. The control of neuron number. Annu Rev Neurosci 11:423–453.

Woodhouse W, Bailey A, Rutter M, Bolton P, Baird G, Le Couteur A. 1996. Head circumference in autism and other pervasive developmental disorders. J Child Psychol Psychiatry 37:665–671.

Woods CG, Bond J, Enard W. 2005. Autosomal recessive primary microcephaly (MCPH): A review of clinical, molecular, and evolutionary findings. Am J Hum Genet 76:717–728.

Yasha TC, Santosh V, Das S, Shankar SK. 1997. Hemimegalencephaly–morphological and immunocytochemical study. Clin Neuropathol 16:17–22.

Young EL, Wishnow R, Nigro MA. 2006. Expanding the clinical picture of Simpson-Golabi-Behmel syndrome. Pediatr Neurol 34:139–142.

Zada G, Krieger MD, McNatt SA, Bowen I, McComb JG. 2007. Pathogenesis and treatment of intracranial arachnoid cysts in pediatric patients younger than 2 years of age. Neurosurg Focus 22:E1.