# Genetics of Chiari Malformation and Syringomyelia

5

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## Contents



## 5.1 Introduction

Chiari malformations are among the most common congenital abnormalities of the craniovertebral junction (Tubbs et al. 2008b). They encompass various degrees of herniation of inferior cerebellar structures, resulting in an overcrowding at the foramen magnum and altered cerebrospinal flow across the craniovertebral junction. Classification is based on the location and degree of herniation of the cerebellar tonsils and adjacent structures. Type I is the most common form of Chiari malformation and consists of a caudal descent of the cerebellar tonsils through the foramen magnum into the vertebral canal. It is a leading cause of syringomyelia and occurs in association with bony abnormalities at the craniovertebral junction. The most common of these is a small and shallow posterior fossa, with flattening of the squamous occipital bone (Tubbs et al. 2008b). Other associated abnormalities include kinking and inferior displacement of the medulla, angulation of the cervicomedullary junction and ventriculomegaly. Chiari malformation type II typically occurs in conjunction with myelomeningocoele and hydrocephalus. In addition to herniation of the cerebellar tonsils, the cerebellar vermis, fourth ventricle and medulla also protrude through the foramen magnum. Chiari malformations types III and IV are very rare conditions. Type III is structurally similar to type II malformation but with a coexistent low occipital or high cervical encephalocoele. Type IV is characterised by cerebellar

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hypoplasia with no hindbrain herniation (Hurlbert and Fehlings 1998).

Chiari types II, III and IV are very different from Chiari I embryologically, and little is known, at present, about the genetics of these forms of hindbrain hernia. The following discussions, therefore, relate in the main to the Chiari type I malformation.

## 5.2 Epidemiology and Clinical Presentation

If we accept that the diagnosis of Chiari type I malformation can only be confirmed by magnetic resonance imaging, then our best estimates of the prevalence of the condition, or at least the underlying anatomical abnormality, are likely to be given by reviews of MRI scans (Hurlbert and Fehlings 1998). Not surprisingly, estimated numbers have increased significantly with advances in MRI technology, and a review of all brain images in one hospital, over a 43-month period (22,591 individuals in total), produced a figure of 0.77 % (Meadows et al. 2000). This figure could be an overestimate since the study was conducted in a hospital population that is biased towards symptomatic patients with an increased incidence of anatomical abnormalities. Alternatively, this figure still could be an underestimate because of the under-diagnosed asymptomatic individuals in the normal population (Speer et al. 2003). Chiari type I malformation has a higher incidence in females than males (3:2) (Hurlbert and Fehlings 1998).

Nearly a third of patients with Chiari type I malformation become symptomatic (Hurlbert and Fehlings 1998). Initial presentation can occur in the paediatric population but is usually delayed until the third, fourth or fifth decade (Tubbs et al. 2007). Patients with Chiari type I may present with a variety of symptoms and signs, ranging from slight headache to severe neurological deficits and permanent nervous system damage, depending upon whether or not there is an associated syringomyelia. The most common symptom of Chiari is pain (60–70 %), usually occipital and upper cervical in location and often induced or exacerbated by Valsalva manoeuvres such as laughing, sneezing and coughing. Other common features are visual disturbances (78 %) and otoneurological symptoms (74 %), as well as those arising from an associated syringomyelia (Speer et al. 2003).

## 5.3 Aetiology and Pathogenesis

Whilst tonsillar herniation can be produced by pathologies causing increased intracranial pressure, including trauma, hydrocephalus, intracranial masses and benign intracranial hypertension, most cases of Chiari malformation are congenital in nature. The aetiology of congenital hindbrain hernias is probably multifactorial and almost certainly involves some genetic determinants. The majority of cases of Chiari that we regard as being congenital in origin is sporadic with no family history. Only about 1 % of the total number of Chiari type I malformations occur as part of a genetic syndrome (Speer et al. 2003; Tubbs et al. 2008b).

Several theories have been put forward to explain the embryological basis of Chiari type I malformation but with no single hypothesis being able to account for all aspects of the condition (Tubbs et al. 2008b; Sarnat 2007). Clearly, molecular studies are required and will be important, if we are to gain a better understanding of the underlying pathogenic mechanisms. The most widely accepted explanation, currently, is the ‘crowding theory’. This proposes that a small posterior fossa volume, relative to the total cranial volume, results in herniation of the cerebellar tonsils into the vertebral canal. Essentially, we have a volume discrepancy between the posterior fossa of the cranium and the neural tissue residing within it. This explanation implies that the primary developmental defect is mesodermal, involving the cranial base, rather than being a primary disorder of the neuroectodermal tissue (Sarnat 2007). Morphometric studies in human patients certainly indicate that the posterior fossa is small and shallow in Chiari type I patients, compared to the normal population, while the total cranial volume is not reduced. These studies also suggest that the fundamental defect may involve underdevelopment of the occipital somites, originating from the paraxial mesoderm (Nishikawa et al. 1997; Karagöz et al. 2002; Aydin et al. 2005; Sekula et al. 2005; Trigylidas et al. 2008). In hamsters,

Chiari type I malformation can be induced experimentally by administration of a single dose of vitamin A, a substance known to affect mesodermal development, on day 8 of embryonic life. These laboratory studies suggest that the defect of Chiari type I malformation involves the somitic mesoderm at the basicranium and craniovertebral junction. An insufficiency of the paraxial mesoderm after the closure of the neural folds could lead to underdevelopment of the basichondrocranium, resulting in a posterior fossa that is too small and shallow (Marin-Padilla and Marin-Padilla 1980). Another study demonstrated that the structures affected in both Chiari type I and type II malformations are neural crest derived, and hence the defect could be neuroectodermal in origin (Matsuoka et al. 2005).

Syringomyelia is encountered in anywhere between 30 and 85 % of patients with Chiari type I malformation (Speer et al. 2003). It is possible that some or all of these cases are simply another consequence of a single developmental defect involving posterior fossa size. If so, they would share the same underlying genetic lesions. Alternatively, the development of syringomyelia could be determined by a different set of genetic modifiers that modulate the Chiari type I genetic background.

## 5.4 Genetic Influences

A genetic basis for Chiari type I malformation is supported by three major lines of evidence: (1) familial aggregation, (2) twin studies and (3) association with other genetic conditions.

### 5.4.1 Familial Aggregation and Clustering

A number of case studies have reported familial aggregation and clustering of Chiari type I malformation, suggesting a genetic basis to the pathogenesis of this condition in at least a proportion of patients (Table 5.1). A large study of 364 patients with Chiari type I malformation found that 12 % had a close relative with Chiari (Milhorat et al. 1999). Another large retrospective institutional study, looking at 500 surgically treated paediatric Chiari type I malformations, reported a positive family history of approximately 3 % (Tubbs et al. 2011). Familial Chiari malformation is probably under-diagnosed because many affected relatives may be asymptomatic. Indeed, about one in five asymptomatic first-degree relatives of Chiari type I patients were also found to have Chiari malformations on MRI (Speer et al. 2000).

Families with Chiari type I malformation showed both vertical (mother-to-child) and male-to-male (father-to-son) transmission[1] consistent with an autosomal dominant mode of inheritance. Since the disease frequency in these affected families is less than what would be expected from pure Mendelian inheritance, Chiari type I malformation is thought to be incompletely penetrant.[2] Other pedigree studies, however, have implicated autosomal recessive mode of inheritance for Chiari type I malformation (Table 5.1). Most likely, the pattern of inheritance is oligogenic, i.e. determined by the cumulative effect of variants in several genes, albeit with variable penetrance.

A few cases have been reported of familial syringomyelia without an associated Chiari type I malformation (Robenek et al. 2006; Koç et al. 2007), although another study found no cases of familial syringomyelia in the absence of Chiari type I malformation, in a cohort of over 150 families (Speer et al. 2003). It may be that cases of 'isolated' familial syringomyelia have a volumetrically small posterior fossa without overt tonsillar herniation (Mavinkurve et al. 2005).

### 5.4.2 Twin Studies

Classical twin studies compare the occurrence of the same trait or disease in monozygotic and dizygotic twins. Monozygotic twins develop from a single fertilised egg and therefore have identical genetic material. Dizygotic twins derive

[1] Father-to-son transmission of a trait usually indicates that this trait is transmitted in a dominant fashion on an autosomal chromosome and not on the X chromosome.

[2] Penetrance is the proportion of individuals carrying a particular variant of a gene that also express an associated trait (phenotype). Penetrance is said to be incomplete or reduced when some individuals fail to express the trait, even though they carry the disease-causing mutation.

**Table 5.1** Studies of families affected with Chiari type I malformation, with or without syringomyelia

| Proposed inheritance | Number of families | Affected members | Reference study |
|---|---|---|---|
| Autosomal dominant with reduced penetrance | 21 families | Parent–child, siblings, avuncular pairs[a], cousins | Milhorat et al. (1999) |
| | 23 families | Parent–child, siblings, avuncular pairs, cousins | Boyles et al. (2006) |
| | 1 family | Two brothers | Robenek et al. (2006) |
| | 31 families | Parent–child, siblings, avuncular pairs, cousins | Speer et al. (2000) |
| | 1 family | 2 monozygotic twins and first-degree relatives | Stovner et al. (1992) |
| | 1 family | 3 generations | Coria et al. (1983) |
| | 1 family | 3 affected members | Giménez-Roldán et al. (1978) |
| Autosomal recessive | 21 families | Siblings, avuncular pairs, cousins | Milhorat et al. (1999) |
| Multifactorial | 3 families | Parent–child, monozygotic twins, avuncular pairs and cousins | Szewka et al. (2006) |
| Undetermined | 3 families | 2 mother–daughter pairs and 1 father–daughter pair | Schanker et al. (2011) |
| | 15 families | 15 surgically treated cases with positive family history including 3 pairs of affected siblings | Tubbs et al. (2011) |
| | 1 family | 4 generations | Tubbs et al. (2004a) |
| | 1 family | 3 sisters | Weisfeld-Adams et al. (2007) |
| | 31 families | Parent–child, siblings, avuncular pairs, cousins | Speer et al. (2000) |
| | 1 family | 2 sisters | Mavinkurve et al. (2005) |
| | 1 family | Monozygotic twin sisters and the daughter of one sister | Atkinson et al. (1998) |
| | 1 family | 2 siblings | Stovner and Sjaastad (1995) |
| | 1 family | 2 siblings | Herman et al. (1990) |

[a]An avuncular relationship describes that between uncles and their nieces and nephews

from two eggs that were fertilised independently from two different sperm cells at the same time. These twins, like any other siblings, share 50 % of their genes.

Comparing the concordance[3] of monozygotic twins for a trait or disease with that of dizygotic twins provides an estimate of the extent to which genetic variation contributes to that trait or disease. A higher concordance in monozygotic as opposed to dizygotic twins indicates a genetic contribution to the trait under study (Boomsma et al. 2002). Several twin studies of Chiari type I malformation have reported an almost 100 % concordance in monozygotic twins (Stovner et al. 1992; Iwasaki et al. 2000; Szewka et al. 2006; Miller et al. 2008; Tubbs et al. 2008a; Solth et al. 2010). Only five studies were examined for an associated syringomyelia, and three sets of twins were found to be discordant for this phenotype (Stovner et al. 1992; Iwasaki et al. 2000; Tubbs et al. 2008a), whilst two other sets were concordant for the absence of syringomyelia (Miller et al. 2008; Solth et al. 2010). Another report described syringomyelia in monozygotic twin brothers who were discordant for Chiari type I malformation (Tubbs et al. 2004b). A unique report of a monozygotic triplets described differing degrees of tonsillar descent; one triplet was affected by Chiari type I malformation and syringomyelia, whilst the other two asymptomatic siblings had tonsillar descent of 4 and 2.5 mm, respectively (Cavender and Schmidt 1995). A study of three pairs of dizygotic twins revealed that one pair of sisters was

[3]Concordance refers to the occurrence of the same trait in both members of a pair of twins.

concordant for Chiari type I malformation with syringomyelia. A second pair of sisters had Chiari type I malformation but only one of them had syringomyelia. In a third pair, one sister had Chiari type I malformation with syringomyelia while the female co-twin had neither (Speer et al. 2003). Collectively, these studies indicate a higher concordance of Chiari type I malformation between monozygotic than dizygotic twins, further supporting a genetic basis for Chiari type I malformation. Clearly, additional, larger twin studies are needed to confirm these findings and to investigate further twin concordance for syringomyelia associated with Chiari type I malformation.

### 5.4.3 Association with Known Genetic Syndromes

Co-segregation[4] of one condition, with one or more other known genetic conditions, suggests a genetic basis for the first condition. The assumption is that a common genetic defect is responsible for the various abnormal phenotypes within the complete syndrome. Chiari type I has been associated with several known genetic disorders or syndromes (Table 5.2). The majority of these disorders affect bone structures, for example, achondroplasia and Crouzon syndrome, or pathways involved in axial mesodermal growth and differentiation, for example, Williams syndrome and Shprintzen–Goldberg syndrome. The causative genes have been identified for some of these conditions and are mainly regulators of signalling pathways or transcription factors.[5] A few are implicated in essential cellular functions, such as chromatin methylation and proteolysis. DNA methylation plays an important role in regulation of gene expression during development and differentiation (Qureshi and Mehler 2011). Proteolysis is the process by which proteins are hydrolysed into small peptides and removed or cleaved for cell signalling (Maupin-Furlow 2011). The genes are hypothesised to have pleiotropic effects[6] on the manifestation of cerebellar tonsil herniation, occipital hypoplasia, syringomyelia and other phenotypes.

Alternatively, Chiari type I malformation could be acquired secondarily in some of these diseases, for example, in cystic fibrosis, consequent upon constant Valsalva, from recurrent coughing or wheezing or as a result of metabolic and electrolyte imbalances (Patel et al. 2011).

Genomic deletions or duplications, on chromosome 7q and chromosome 16p, have been associated with Chiari type I malformation (Pober and Filiano 1995; Mercuri et al. 1997; Ferrero et al. 2007; Schaaf et al. 2011). These rearranged chromosomal regions contain a large number of biologically plausible candidate genes for Chiari type I, including *TBX6*, on chromosome 16p, that encodes a transcription factor important in establishing mesodermal identity and which can have a role in the aetiology of congenital spinal anomalies (Schaaf et al. 2011). A more comprehensive and systematic research of these regions is needed to identify the underlying genetic lesions and to understand their pathogenic role in the development of Chiari type I malformation.

## 5.5 Molecular Studies of Chiari in Humans

While Chiari type I malformation has a tendency to aggregate in families, it is rarely segregating in a classical Mendelian fashion. It is believed to be a complex trait that could be either oligogenic or polygenic, i.e. resulting from a large number of genetic variants, each contributing small effects. One cannot exclude the possibility of unknown environmental or nongenetic influences that may interact with these predisposing genetic factors to modulate the incidence of the Chiari type I with or without syringomyelia phenotype.

Studies of alleles[7] that influence other complex diseases could provide some indication of

[4] Co-segregation is the tendency for closely linked genes or traits to segregate or be inherited together.

[5] A transcription factor is a protein that binds to specific DNA sequences and controls the transcription or flow of genetic information from DNA to mRNA.

[6] Pleiotropy is a phenomenon in which one gene can influence two or more phenotypic traits.

[7] Different alleles of a gene refer to alternative forms of the gene; usually they are only very minor sequence differences between different alleles of any gene.

**Table 5.2** Summary of genetic diseases and syndromes that can be associated with Chiari type I malformation

| Syndrome (phenotype MIM#[a]) | Locus | Gene | Gene function | References |
|---|---|---|---|---|
| *Signalling transducers* | | | | |
| Achondroplasia (MIM# 100800) | 4p16.3 | *FGFR3* (fibroblast growth factor receptor 3) | Transmembrane growth factor receptor that mediates FGF signalling during development | Nakai et al. (1995), Bauer et al. (2005), Caldarelli et al. (2007), Richette et al. (2008) |
| Costello syndrome (MIM# 218040) | 11p15.5 | *HRAS* (v-Ha-ras Harvey rat sarcoma viral oncogene homologue) | Member of the Ras oncogene family that functions in signal transduction pathways | Gripp et al. (2010), White et al. (2005) |
| Crouzon syndrome (MIM# 123500)<br>Apert's syndrome (MIM#101200) | 10q26.13 | *FGFR2* (fibroblast growth factor receptor-2) | Transmembrane growth factor receptor that mediates FGF signalling during development | Cinalli et al. (1995), Park et al. (1995), Reardon et al. (1994) |
| Hajdu–Cheney syndrome (MIM# 102500) | 1p12-p11 | *NOTCH2* (Notch gene homologue 2) | Notch type 1 transmembrane protein that plays a role in bone metabolism | Di Rocco and Oi (2005), Simpson et al. (2011) |
| Klippel–Feil syndrome (MIM# 118100) | 8q22.1 | *GDF6* (growth/differentiation factor 6) | Bone morphogenetic protein that regulates the formation of skeletal joints in the limbs, skull and axial skeleton | Tubbs et al. (2003), Tassabehji et al. (2008) |
| Loeys–Dietz syndrome type 1 (MIM# 609192) | 9q22.33 | *TGFBR1* (transforming growth factor, beta receptor 1) | Serine/threonine protein kinase that functions in TGF-beta signalling | Loeys et al. (2005) |
| Neurofibromatosis type I (MIM# 162200) | 17q11.2 | *NF1* (neurofibromin) | Negative regulator of the Ras signal transduction pathway | Tubbs et al. (2003), (2004a), Yohay (2006) |
| Noonan syndrome-1 (MIM# 163950) | 12q24.13, | *PTPN11* (protein tyrosine phosphatase, non-receptor type 11) | Protein tyrosine kinase that plays a role in signalling via the RAS-mitogen activated protein kinase (MAPK) pathway | Croonen et al. (2008), Holder-Espinasse and Winter (2003) |
| Paget's disease of bone (MIM# 602080) | Genetically heterogeneous | *PDB4* (Paget's disease of bone 4) | *PDB4*: undetermined function | Otsuka et al. (2004), Richards et al. (2001) |
| | 5q31 | *SQSTM1* (sequestosome 1) | SQSTM1: binds ubiquitin and regulates activation of the nuclear factor kappa-B (NF-kB) signalling pathway | |
| | 5q35.3 | *TNFRSF11A* (tumour necrosis factor receptor super family, member 11a) | *TNFRSF11A*: member of the TNF-receptor super family, an essential mediator for osteoclast and lymph node development | |
| | 18q21.33 | | | |
| *Transcription factors* | | | | |
| Chromosome 1p32-p31 deletion syndrome (MIM# 613735) | 1p32-p31 | *NF1A* (nuclear factor 1) | CAAT box transcription factor, plays a major role in development | Lu et al. (2007) |

| Syndrome (phenotype MIM#[a]) | Locus | Gene | Gene function | References |
|---|---|---|---|---|
| Cleidocranial dysplasia (MIM#600211) | 6p21.1 | *RNX2* (runt-related transcription factor 2) | Transcription factor, a key modulator of osteoblast differentiation | Vari et al. (1996), Ziros et al. (2008) |
| Combined pituitary hormone deficiency-4 (MIM#262700) | 1q25.2 | *LHX4* (LIM-homeobox 4) | Transcription factor, functions during the development of the mammalian pituitary gland and the nervous system | Machinis et al. (2001), Tajima et al. (2007) |
| Type II blepharophimosis–ptosis–epicanthus inversus syndrome (BPES) (MIM# #110100) | 3q22.3 | *FOXL2* (Forkhead box L2) | Forkhead transcription factor important in ovarian development | Paquis et al. (1998), Crisponi et al. (2001) |
| Velocardiofacial syndrome (MIM#192430) | 1.5–3.0-Mb hemizygous deletion of 22q11.2 | Some cases are caused by mutations in *TBX1* (T-box 1) | *TBX1*: transcription factor with a conserved DNA-binding domain, the T-box | Hultman et al. (2000), Yagi et al. (2003) |
| *Miscellaneous functions* | | | | |
| Cystic fibrosis (MIM# 219700) | 7q31.2 | *CFTR* (cystic fibrosis transmembrane conductance regulator) | Member of the ATP-binding cassette (ABC) transporter super family, functions as a chloride channel | Bobadilla et al. (2002), Patel et al. (2011) |
| Hypophosphatemic rickets (MIM# 307800) | Xp22.11 | *PHEX* (phosphate-regulating endopeptidase homologue, X-linked) | Zinc-dependent metalloprotease, found in the cell-surface membrane of osteoblasts, osteocytes and odontoblasts | Caldemeyer et al. (1995) The HYP Consortium (1995) |
| Idiopathic growth hormone deficiency (MIM# 173100) | 17q23.3 | *GH1* (growth hormone) | Growth hormone | Tubbs et al. (2003), Alatzoglou and Dattani (2010) |
| Kabuki syndrome (MIM# 147920) | 12q12-q14 | *MLL2* (myeloid/lymphoid or mixed-lineage leukaemia 2) | Trithorax-group histone methyltransferase, important in the epigenetic control of active chromatin states | Ciprero et al. (2005), Ng et al. (2010) |
| Miller–Dieker lissencephaly syndrome (MIM#247200) | 17p13.3 | *PAFAH1B1* (platelet-activating factor acetylhydrolase, isoform Ib) | Inactivating enzyme for platelet-activating factor, important for neuronal migration | Nagamani et al. (2009) |
| Shprintzen–Goldberg syndrome (MIM# 182212) | 15q21.1 | *FBN1* (fibrillin 1) in some cases | Extracellular matrix glycoprotein that serves as a structural component of 10–12 nm calcium-binding microfibrils | Sood et al. (1996), Greally (2006) |
| *Associated genes unknown* | | | | |
| Macrocephaly–capillary malformation (MIM# 602501) | Unknown | | Unknown | Garavelli et al. (2005),Conway et al. (2007) |

(continued)

**Table 5.2** (continued)

| Syndrome (phenotype MIM#[a]) | Locus | Gene | Gene function | References |
|---|---|---|---|---|
| Primary basilar impression (MIM#109500) | Unknown | | Unknown | Bentley et al. (1975) |
| Chromosome 16p11.2 rearrangements | Unknown | | Unknown | Schaaf et al. (2011) |
| William's syndrome or chromosome 7q11.23 deletion syndrome (MIM#194050) | Hemizygous deletion of 1.5–1.8 Mb on chromosome 7q11.23 | | Unknown | Ferrero et al. (2007), Mercuri et al. (1997), Pober and Filiano (1995) |

[a]MIM: Mendelian Inheritance in Man is a catalogue of human genes and genetic disorders (http://www.ncbi.nlm.nih.gov/omim/)

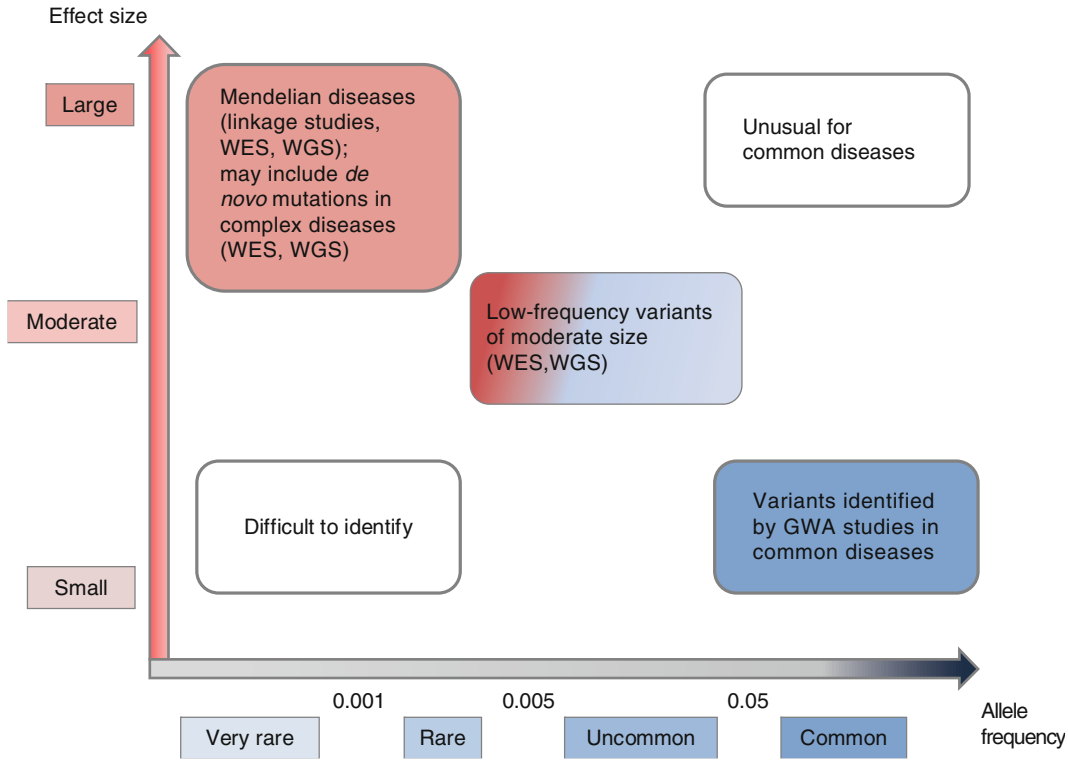


**Fig. 5.1** Feasibility of gene identification studies by allele frequency and effect size in Mendelian and complex human diseases. Rare variants that have a large effect on the phenotype in Mendelian diseases can be identified in linkage studies where one investigates the segregation of a genetic marker with the disease phenotype in large multiple families affected with the disease. Very rare Mendelian diseases that are present in few small families are not amenable to this kind of linkage analysis and can only be identified if one sequences the whole exome (WES) or the whole genome (WGS) of the few affected individuals in order to identify the mutation specific to the phenotype. Recent genomics studies have implicated the presence of de novo (new) mutations in complex diseases that can only be identified by WES and/or WGS to identify the new mutation present in the affected individual and absent in parents. On the other end of the spectrum, common variants that have a small effect on the phenotype in complex diseases are identified by genome-wide association studies where one determines the association of a marker allele with the phenotype in a large cohort of cases and controls. *Abbreviations*: *WES* whole exome sequencing, *WGS* whole genome sequencing, *GWA* genome wide association

what might be taking place with Chiari type I malformation and syringomyelia. There is considerable heterogeneity both as regards the frequency and as regards the strength of effect of the alleles described to date (Fig. 5.1). At one end of the spectrum are high risk alleles, segregating in large families affected with Mendelian diseases. These can be identified easily by family-based linkage studies that aim at identifying a polymorphic genetic marker allele[8] that segregates strongly with the disease phenotype in a family.[9] At the other extreme, gene identification in complex traits remains a challenge. A number of common alleles have been found to be associated with common phenotypes, as predicted from the common disease/common variant hypothesis.

[8] A genetic marker refers to a short sequence of DNA with a known location on a chromosome. This marker is polymorphic when there are two or more allelic forms in the same population and the most common allele has a frequency of 0.99 or less.

[9] The principle of a linkage study is the following: if a disease runs in a family, one could look for genetic markers that run exactly the same way as the disease in the family. A marker allele that segregates with the disease is said to be linked to the disease. In this case, we assume that the gene that causes the disease and the marker allele are in the same area of the genome. Since we know the location of the genetic marker in the genome, we can deduce the location of the disease gene.

These common variants are usually identified by genetic association studies that investigate the association between common genetic variation and disease in a large numbers of study subjects. This type of analysis requires a dense set of polymorphic markers that capture a substantial proportion of common variation across the genome (for genome-wide association studies or GWAS[10]) or across a set of biologically plausible candidate genes (for candidate gene association studies) (Frazer et al. 2009). Common variants seem to have modest effect sizes.[11] Even when combined, their impact on overall population variance and predictive power[12] is limited. For many traits, associated variants have explained only a small proportion of estimated heritability.[13] A significant proportion of this undetermined heritability, known as 'missing heritability', may be attributable to variants that are of low frequency (<0.01 in frequency) with intermediate penetrance effects, which cannot be detected by conventional gene-discovery approaches mentioned above (Manolio et al. 2009). Recently, a role for rare de novo mutations is emerging in the genetic architecture of some of the complex traits, particularly those that decrease the reproductive fitness and incur a large degree of selection against the phenotype (Gillis and Rouleau 2011).

Gene identification studies of Chiari type I malformation and syringomyelia have been hindered by their complex aetiologies and inheritance patterns. Two approaches have been adopted or suggested in an attempt to identify the responsible genes and the underlying molecular pathogenic mechanisms. These are candidate gene studies and genome-wide linkage studies.

### 5.5.1 Candidate Genes Studies

A number of biologically plausible candidate genes, derived from mouse models, have been proposed for Chiari type I malformation, including the *Hox* genes, *Pax* genes, *FGFR2* and *Noggin*. The *Hox* gene family controls the development of the occipital bone and ectopic expression[14] of *Hox-2.3* results in dysplasia or deficiency of occipital, basisphenoid and atlas bones in transgenic[15] mice (McLain et al. 1992). The *Pax* group of genes codes for transcription factors with a conserved DNA-binding domain that have important roles in mesodermal segmentation and vertebral development. In particular, *Pax1* plays an important role in somitic segmentation and proper sclerotomal differentiation in the cervico-occipital transitional zone (Chi and Epstein 2002). *FGFR2* is transmembrane protein conserved across evolution and known to be critical for the normal development of multiple organ systems, including the craniofacial skeleton. The most common cause of Crouzon syndrome, a well-known craniosynostosis, is a mutation in *FGFR2*, *and* Chiari type I malformation is a common feature of Crouzon syndrome (Park et al. 1995). *Noggin* is required for growth and differentiation of the somites of the paraxial mesoderm (see Chap. 4). Noggin knockout mice show various defects, affecting neural and axial skeletal defects (McMahon et al. 1998). *Noggin* was analysed in 33 cases of Chiari type I malformation but no variant was identified, which suggests that this gene is not a common genetic factor involved in Chiari type I malformation (Speer et al. 2003).

[10] GWAS (genome-wide association studies) involve scanning hundreds to thousands of samples, either as case–control cohorts or in family trios, utilising hundreds of thousands of genetic markers located throughout the genome. This analysis identifies regions with statistically significant differences in allele frequencies between cases and controls, pointing to their role in disease.

[11] Effect size measures the strength of the relationship between the variant and the phenotype in a study population.

[12] Variants identified through association studies as significantly associated with disease susceptibility may be used in a *genetic predictive test* to classify disease risk in individual.

[13] Heritability is a measure of how much variation of a trait within a population is due to genes compared to variation due to environment.

[14] Ectopic expression is the expression of a gene in an abnormal place in an organism.

[15] A transgenic mouse contains additional, artificially introduced genetic material in every cell. This can confer a gain of function if the mouse produces a new protein or a loss of function if the integrated DNA interrupts another gene.

### 5.5.2 Linkage Studies

To date, only one linkage study[16] of human Chiari type I malformation has been conducted in a collection of 23 families with 71 affected individuals. This detected significant linkage of Chiari type I malformation to two genomic regions, on chromosomes 9q21.33–33.1 (31.3 Mb) and 15q21.1–22.3 (12.3 Mb) (Boyles et al. 2006). These two regions were too large for positional candidate gene cloning efforts whereby disease genes are identified using only knowledge of their approximate chromosomal location. A large candidate region identified by a linkage or an association study will most likely contain a large number of genes to be analysed, hence making this cloning procedure long and tedious. Interestingly, the region on chromosome 15 harbours a biologically plausible gene for Chiari type I malformation, fibrillin 1. This has been linked to a human syndrome called Shprintzen–Goldberg syndrome, which has Chiari type I malformation as a distinguishing characteristic (Boyles et al. 2006). These studies also demonstrated significant heritability of posterior fossa volume, supporting the presence of a genetic basis for this condition. Results from both studies should be interpreted cautiously as they are complicated by probable genetic heterogeneity[17] and the multifactorial aetiology of Chiari type I malformation.

## 5.6 Canine Models for Chiari and Syringomyelia

Chiari type I malformation in humans is similar to a condition called Chiari-like malformation that is common in several toy breed dogs including two genetically related dog breeds, the Cavalier King Charles Spaniels and Griffon Bruxellois (Rusbridge and Knowler 2003; Rusbridge et al. 2009). Chiari-like malformation is present in almost 100 % of Cavalier King Charles Spaniels (Cerda-Gonzalez et al. 2009), and in a recent study of 56 Griffon Bruxellois dogs, the condition was found at a frequency of 6 in 10 (Rusbridge et al. 2009). Canine Chiari-like malformation therefore provides a spontaneously occurring, natural model of Chiari type I malformation in humans. In affected dogs, the caudal fossa is small relative to the entire cranial cavity (Cerda-Gonzalez and Dewey 2010), and the cerebellum is disproportionally large especially with dogs with early-onset syringomyelia (Shaw et al. 2012). As with humans, Chiari-like malformation in the dog is thought to involve an insufficiency of the occipital bones, producing a small caudal fossa (Rusbridge et al. 2009). The bony changes consist of a shortening of the basicranium, a shorter and vertical supraoccipital bone and a compensatory lengthening of the parietal bone. The latter characteristic does allow for accommodation of the forebrain, but there is insufficient room for the hindbrain, resulting in displacement of the neural structures into and through the foramen magnum (Rusbridge et al. 2009).

There is also a strong association between Chiari-like malformation and syringomyelia in dogs, which is thought to be related to obstruction of cerebrospinal fluid (CSF) movement across the craniovertebral junction (Rusbridge and Knowler 2003).

The high incidence of Chiari-like malformation in the Cavalier King Charles Spaniel and Griffon Bruxellois, as compared to other breeds, suggests the involvement of genetic factors in the aetiology of this disease (Rusbridge and Knowler 2003, 2004). Canine Chiari-like malformation does not segregate in Mendelian fashion in affected families, suggesting that this condition is oligogenic, polygenic or complex in origin, which could implicate environmental factors as well. The heritability of syringomyelia was estimated to be 0.37 (±0.15 standard error), indicating a moderate genetic effect on susceptibility to development of syringomyelia (Lewis et al. 2010). This heritability estimate implies that ~37 % of the trait is due to genetic factors.

[16] A genome-wide linkage scan refers to a screen of the whole genome for segregation of a marker allele with the phenotype.

[17] Genetic heterogeneity is a phenomenon in which many alleles of the same gene or of different genes cause the same phenotype.

Purebred dogs represent an invaluable tool for mapping and cloning genes affecting human health (Karlsson and Lindblad-Toh 2008). More than 450 diseases have been identified in dogs, and of these around 360 are homologues of common human disorders. These conditions can be studied and traced more easily when large dog pedigrees are available in established registries. The dog population has a unique history that is characterised by founder effects[18] and periodic population bottlenecks.[19] This, along with stringent breeding programmes, led to a closed genetic pool among dogs of each breed (Ostrander et al. 2000; Sutter and Ostrander 2004). There are some 350 breeds of dogs, and the high prevalence of specific diseases in many of these genetically homogeneous breeds suggests that a limited number of genes underlie each disease (Shearin and Ostrander 2010). These circumstances are mirrored, in part, in isolated human populations, such as the Finns and Icelanders. This situation can be used advantageously in genetic mapping studies, as such populations have limited variation in their gene pools, which reduces the chances of disease heterogeneity (Varilo and Peltonen 2004).

Most dog breeds are less than 200 years old and thus have long linkage disequilibrium[20] blocks, making them particularly amenable to linkage disequilibrium mapping with fewer markers and fewer dogs as compared to humans (Hyun et al. 2003; Sutter et al. 2004). This approach has been successful in mapping and identifying many genes predisposing to Mendelian as well as complex traits in the dog (Karlsson et al. 2007; Karlsson and Lindblad-Toh 2008; Patterson et al. 2008; Wilbe et al. 2010). Notably, a genome-wide association study in 81 affected dogs and 57 controls, from the Nova Scotia Duck Tolling Retriever breed, identified five loci associated with a systemic lupus erythematosus-related disease. This demonstrated the power of linkage disequilibrium mapping in the dog, even in a small cohort of less than 100 cases and 100 controls, to identify pathways involved in human complex diseases (Wilbe et al. 2010).

The dog model is the only known naturally occurring animal model for Chiari type I malformation and syringomyelia. The high prevalence of Chiari-like malformation in the Cavalier King Charles Spaniel and Griffon Bruxellois breeds, along with the genetic homogeneity within these breeds, should help identify the defective gene(s) in the dog and then provide an entry point for a parallel search for mutations in the human orthologue(s)[21] in Chiari type I and syringomyelia. We can hope to identify key genes, proteins and molecular pathways involved in normal and abnormal development of structures of the human craniovertebral junction.

## 5.7 Future Studies

To date, no genetic factor predisposing to Chiari type I malformation and syringomyelia has been identified in humans. Identification of such genes by classical linkage analysis, association studies and positional cloning strategies is hindered by the complex nature of the inheritance of the disease along with its multifactorial aetiology. The candidate gene approach where one investigates genes that are biologically plausible (e.g. genes that are important for development of the craniovertebral junction) has not been successful so far because little is known about the molecular mechanisms underlying the pathogenesis of Chiari type I and syringomyelia. Identification of the Chiari gene(s), as for all other complex diseases, faces other major difficulties. These include epistasis, which is the effect that genetic variants have on each other,

[18] Founder effect occurs when a small group of individuals from a genetically diverse population migrates away and forms a new colony. Because the new colony will be composed only of genes from those few individuals, its genetic diversity will be reduced compared to the parent population.

[19] Population bottleneck is an evolutionary event characterised by a marked reduction in population size followed by the survival and expansion of a small random sample of the original population.

[20] Linkage disequilibrium is the nonrandom association of alleles at two or more loci. The strength of LD depends on many factors including the number of founders and the number of generations over which recombination has driven the decay of LD.

[21] Orthologues are genes in different species that originated from a single gene of the last common ancestor.

genetic alterations that occur during gametogenesis or after fertilisation and imprinting, which is the phenomenon in which only one of the two alleles of a gene may be expressed (Dean 2003). Finally, we always have to take into account the influence of various unknown environmental factors.

Powerful advances in genomics technologies have the potential, in the future, to revolutionise the exploration of the molecular genetics of Chiari I and syringomyelia. We are entering an exciting era, when we can sequence the 'whole genome' of an individual, in a cost-effective manner and in a short period. The next generation sequencing technologies will allow whole genome mutation analysis, with no prior assumptions regarding gene function and identification of low-frequency variants that increase disease susceptibility in affected individuals. A similar approach can focus on sequencing only protein-coding exons,[22] which comprise about 1 % of the human genome sequence. Exon-containing genomic fragments are isolated using oligonucleotide capture libraries,[23] followed by next generation sequencing.[24] A major challenge remains, however, with such innovative technologies, as regards the management and analysis of the massive data sets that will be generated (Majewski et al. 2011).

Genetic defects other than point mutations[25] could be involved in the pathogenesis of Chiari type I and syringomyelia. Data have emerged on the role of DNA copy number variants[26] as an important cause of neurodevelopmental conditions and birth defects. The novel technology of array comparative genomic hybridisation can survey the whole genome and detect large segments of genomic imbalance that are usually detectable by karyotyping,[27] as well as smaller copy number variants (Vissers et al. 2005). Using whole genome array comparative genomic hybridisation, several groups have shown that pathogenic copy number variants are a frequent cause of structural malformations in foetuses and newborns (Choy et al. 2010).

Epigenetic modifications[28] including DNA methylation could play an important role in the development of Chiari malformation. Assays that interrogate the whole genome for epigenetic regulatory modifications, for example, chromatin immunoprecipitation combined with DNA microarrays,[29] will enable us to explore the epigenomic influences on Chiari malformations (Schones and Zhao 2008). Another key regulator of gene expression is the recently discovered class of small RNA molecules, known as microRNAs. These play important regulatory roles in developmental timing and patterning, cellular differentiation, organogenesis and apoptosis (Chang et al. 2008). Several methodologies, including cloning, northern blotting, real-time RT-PCR and in situ hybridisation, have been developed and applied successfully in microRNA profiling (Li and Ruan 2009).

## Conclusions

Chiari type I malformation, with or without syringomyelia, is a complex trait, with predisposing genetic influences. We are still in the early stages of identifying these genetic factors, and progress is hampered by the complexity of this trait. We are, however, witnessing a rapid expansion of high resolution technologies which, when coupled with the canine Chiari-like malformation model, will help us define these genetic factors and

[22] An exon is a sequence of DNA that codes information for protein synthesis that is transcribed to messenger RNA.

[23] Oligonucleotide capture libraries are pooled libraries of thousands of probes that will hybridise against and capture the coding exons.

[24] Next generation sequencing is the most recently developed high-throughput sequencing method that produces thousands or millions of sequences at once.

[25] A point mutation is when a single base pair is altered.

[26] A copy number variant is a segment of DNA ranging from 1 kb to several megabases in size that is caused by deletions, duplications, triplications, insertions or translocations.

[27] Karyotyping is a laboratory test that provides a picture of all the chromosomes from an individual's cells.

[28] Epigenetics is the study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in the DNA sequence.

[29] A DNA microarray or a DNA chip is a collection of microscopic DNA spots attached to a solid surface.

better understand the pathophysiology of human Chiari malformations. We may then be in a better position to advise affected patients about any likely inheritance of their condition.

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