# A genetic hypothesis for Chiari I malformation with or without syringomyelia

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In several reports the authors have suggested occasional familial aggregation of syringomyelia and/or Chiari 1 malformation (CM1). Familial aggregation is one characteristic of traits that have an underlying genetic basis. The authors provide evidence for familial aggregation of CM1 and syringomyelia (CM1/S) in a large series of families, establishing that there may be a genetic component to CM1/S in at least a subset of families. The authors observed no cases of isolated familial syringomyelia in their family studies, suggesting that familial syringomyelia is more accurately classified as familial CM1 with associated syringomyelia.

These data, together with the cosegregation of the trait with known genetic syndromes, support the authors' hypothesis of a genetic basis for some CM1/S cases.

**KEY WORDS • Chiari 1 malformation • syringomyelia • genetic basis • familial aggregation**

Syringomyelia is a condition that typically occurs as the sequela of either spinal cord injury, a primary tumor of the spinal cord, or an associated hindbrain anomaly such as CM1. It is uncommon for syringomelia to be idiopathic. Fundamental questions concerning the incidence, natural history, and pathogenesis of syringomyelia, especially idiopathic, are currently being investigated. For instance, although population-based studies of the incidence or prevalence of CM1/S have yet to be performed, findings from clinical series suggest that the prevalence is no greater than 0.24%.[8] The literature includes several case reports of familial aggregation of CM1 and CM1/S.[3,6,9,10,16,18,20,22]

Documenting familial aggregation or clustering is often the first step in characterizing the genetic basis for a trait. Other evidence supporting a genetic hypothesis for a trait is derived from twin studies, statistical segregation analysis, an increased risk to relatives of affected individuals as compared with the risk to the general population, and the cosegregation of the condition with known genetic traits. We report our expanded family studies of CM1/S in which we characterize the clustering of CM1/S in families, and we review the genetic syndromes associated with CM1/S. Both lines of evidence support a genetic basis for a subset of patients with CM1/S. We suggest that in at least one subset of patients with CM1/S genetic factors are responsible for the development of the condition. The immediate relevance of these data to clinical practice is that relatives of patients with CM1/S may be at higher risk for the condition than previously recognized.

*Abbreviations used in this paper:* CM1 = Chiari 1 malformation; CM1/S = CM1 with associated syringomyelia; MR = magnetic resonance.

## CLINICAL MATERIAL AND METHODS

### *Establishment of Familial Clustering in CM1/S*

Families were recruited for this study through a proband in whom CM1/S had been documented on $T_1$-weighted MR imaging. Detailed, standardized family histories were obtained. The proband's medical records and original MR image films were collected, as were those obtained in any other relative reported to be affected; these were reviewed as previously described.[16] A subset of these families—all first-degree relatives of affected individuals, regardless of symptom status—had been recruited to undergo imaging studies. Blood samples were collected and stored for DNA extraction and eventual genetic analysis. This study was approved by the Duke University Medical Center Institutional Review Board.

TABLE 1
*Characteristics obtained in 31 multiplex families with CM1/S*

| Diagnosed W/ CM1/S | No. of Individuals |
|---|---|
| females | 53 |
| males | 25 |
| mother–child pairs | 21 |
| father–child pairs (father–son pairs) | 8 (7) |
| pedigrees consistent w/ vertical "transmission" | 18 |
| sibling pairs | 28 |
| avuncular pairs (aunt/uncle & niece/nephew) | 8 |
| cousin pairs | 3 |

Families were excluded from the study if they had evidence of acquired CM1 due to presence of a supratentorial mass, hydrocephalus, history of cervical or cranial surgery unrelated to the CM1, or development of symptom following placement of a lumbar shunt. In addition, any syndromic cases (for example, those with Klippel–Feil syndrome or achondroplasia) were excluded to minimize inherent diagnostic heterogeneity.

### *Association of CM1/S With Known Syndromes*

The On-Line Mendelian Inheritance in Man database (http://www3.ncbi.nlm.nih.gov/Omim) was searched to determine the incidence of Chiari malformations and was augmented with a medical literature search.

## RESULTS

We identified 31 pedigrees in which two or more individuals are affected with CM1/S ("multiplex pedigrees"). Details on a subset of these pedigrees have been previously published.[16]an unreduced T-10 compression fracture *(arrow)* Characteristics of these families are presented in Table 1. In some of these families evidence consistent with parent-to-child transmission of the CM1/S trait was revealed (including apparent male-to-male transmission, consistent with autosomal dominant inheritance). There is a preponderance of affected women in these families, although full MR imaging assessment needs to be performed in all members of these families to determine whether this apparent preponderance is caused by ascertainment bias. In no case was syringomyelia identified without attendant CM1. To date, of the series of asymptomatic first-degree relatives of affected patients in whom imaging studies were obtained, 21% were diagnosed as having CM1/S.

Chari 1 malformation with syringomyelia co-occurs with a variety of syndromes of established inheritance patterns. These data are summarized in Table 2.

## DISCUSSION

A variety of sources is used to establish a genetic component for a condition such as CM1/S. One line of evidence can be derived from the cosegregation of CM1/S with known genetic conditions, under the hypothesis that a common genetic basis is responsible for the range of abnormal phenotypes within the syndrome. Some syndromes of which CM1 can be a feature include achondroplasia, hypophosphatemic rickets, Albright's hereditary osteodystrophy (pseudohypoparathyroidism), and Williams syndrome. Identification of CM1/S cases that are syndromic has been shown to be clinically relevant and therefore to impact clinical decision making. For instance, recognition of vertebral fusion anomalies in the Klippel–Feil syndrome may require that the surgical approach be altered or may additionally necessitate a cervical fusion procedure.[15] Furthermore, vertebral fusion anomalies, such as Klippel–Feil syndrome, have been suggested to result from abnormal vertebral segmentation that is characteristic of mutations in homeobox genes.[7]

Analyzing familial clustering of a trait is another mechanism method by which to provide support for a genetic hypothesis. Results of our studies, coupled with those found in reports the literature, demonstrate clear evidence for familial clustering of CM1/S. By itself, familial clustering does not establish a genetic basis for a condition because clustering can be caused by nongenetic causes, such as an environmental exposure common to affected family members. However, when familial clustering is combined with other lines of evidence including cosegregation of CM1/S in which there are known genetic conditions as well as cytogenetic abnormalities, the evidence in favor of a genetic contribution to at least a subset of CM1/S is compelling. These data are useful in the clinical characterization of patients and families and, ultimately, for identification of potential candidate genes and/or regions of interest in the genome. Interestingly, that we did not identify any cases of isolated syringomyelia in these families suggests that "familial syringomyelia" is more appropriately classified as familial CM1 with (or without) associated syringomyelia. Previously reported cases of familial "isolated" syringomyelia may in fact have involved a volumetrically small posterior fossa without hindbrain herniation,[11] and thus these cases would fall within the rubric of a more broadly defined CM1.[16]

Chiari 1 malformation with associated syringomyelia may have a basis as a primary mesodermal disorder involving the somitic mesoderm at the basicranium and craniovertebral junction.[13] The development of the basicranium (the clivus, occipital condyles, and occipital squama) and craniovertebral junction (the axis and atlas) is quite a complex process. Contributions from the four caudal occipital somites form the basicranium. The sclerotomal regions of the C-1 and C-2 somites are precursors for the axis and atlas. Dorsal portions of C-1 somite contribute to the lamina and pedicle, and ventral portions separate to form the ring of the axis and the odontoid process of the atlas, instead of the body for C-1. The C-2 somite forms the remainder of the atlas. Furthermore, the tip of the odontoid process is formed from the last occipital somite.

Proper segmentation and positional identity of these sclerotomal cells is vital for normal development and appears to be regulated by early developmental genes.[5] One gene in particular, *Pax-1*, has been shown to be important in somitic segmentation and proper sclerotomal differentiation.[1,4] Expression of the *Pax-1* gene is regulated by a complex inductive signaling balance from ventral notochord and dorsal nonneural inductive signals.[14] Perturbations of *Pax-1* function lead to vertebral fusions and missegmentation anomalies.[1] Furthermore, disturbance of *Pax-1* function appears to be the target in teratogenic models of vertebral malformations in which heat shock[1]

TABLE 2

*Compendium of genetic disorders in which CM1/S is a feature**

| Disorder or Syndrome (OMIM no.) | Clinical Features | Genetic Characteristics |
|---|---|---|
| achondroplasia (100800) | most common form of dwarfism | autosomal dominant & sporadic; mutations in fibroblast growth factor receptor on 4p16.3 are causative |
| Albright's hereditary osteodystrophy (psuedohypoparathyroidism type 1A) (103580, 139320) | short stature, short fingers, low serum calcium & high parathyroid levels | autosomal dominant; mutations in guanine nucleotide-binding protein on 20q13.2 are causative |
| aqueductal stenosis (307000) | congenital stenosis of the sylvian aqueduct; basilar impression, hypoplastic thumbs, & spastic paraplegia | x-linked inheritance; region of localization reported for for Xq28 |
| Carpenter's syndrome (acrocephalo-polysyndactyly type II) (201000) | brachycephaly w/ variable synostosis of coronal, sagittal, & lambdoid sutures; polydactyl & syndactyl | autosomal recessive inheritance reported; no causative gene identified |
| cleidocranial dysplasia (119600, 600211) | short stature, brachycephaly, "Arnold head," midface hypoplasia, delayed eruption of primary & secondary teeth | autosomal dominant inheritance; mutations in core binding factor, runt domain, a-subunit 1 |
| empty sella turcica, primary, w/ generalized dysplasia (130720) | osteosclerosis w/ abnormalities of the nervous system & meninges | x-linked inheritance reported; duplication of Xq identified, but no causative gene identified |
| familial osteosclerosis (166740) | ichythyosis & increased risk of fractures; cortical thickening of the diaphyses of long bones; bowed femurs & tibias | autosomal dominant inheritance reported; no causative gene identified |
| Furhmann syndrome (fibular aplasia) (228930) | aplasia or hypoplasia of the fibula, along w/ bowing of femurs, polydactyly, & syndactyly | autosomal recessive inheritance reported; no causative gene identified |
| Hadju–Cheney syndrome (102500) | osteoporosis, loose jointedness, dislocations of patella, hernias, early loss of teeth | autosomal dominant inheritance reported; no causative gene identified |
| hypophosphatemic rickets | different vague symptoms: joint pain, tooth abscesses | x-linked dominant; mutations in *PEX* gene are causative |
| Klippel–Feil syndrome (148900) | 3 different clinical types, generally characterized by vertebral fusion | sporadic & autosomal dominant cases reported; no causative gene identified |
| Paget's disease of the skull (239000) | remodeling of skull base secondary to excess production of growth hormone | autosomal recessive inheritence reported; no causative gene identified |
| primary basilar impression (109500) | isolated primary basilar impression | autosomal dominant inheritance reported; no causative gene identified |
| spondyloepiphyseal dysplasia tarda (271600) | short stature, platyspondyly, severe osteo arthritis of hip joints; deficiency of β-2-globulin reported w/ several forms | autosomal recessive; autosomal dominant and x-linked forms of inheritance are reported |
| Freeman–Sheldon syndrome (whistling face) (193700) | skeletal malformations & associated facial characteristics; considered a form of distal arthogryposis | primarily autosomal dominant forms; some sporadic cases have been reported; mutations in *DA2B* gene are causative |
| renal-coloboma syndrome (120330) | colobomatous eye defects, vesicoureteral reflux, & abnormal kidneys | autosomal dominant inheritance; mutations in *PAX2* gene are causative in one family |

* OMIM = On-line Mendelian Inheritance in Man database (http://www3.ncibi.nlm.gov/Omim).

and valproic acid[2] are used. Additonally, sister genes to *Pax-1*, such as *Pax-2*, *Pax-3*, and *Pax-6*, have been implicated in human developmental anomalies.[12] These data would suggest that a mutation in a gene such as *Pax-1* would be a reasonable candidate responsible for an anomaly such as CM1.

Clinically, over two thirds of the patients with CM1 have extensive bone abnormalities of the base and posterior aspect of the skull,[6,17,19] and they often harbor craniovertebral anomalies. These bony abnormalities include a shorter clivus, larger basal angles, basiliar impression, platybasia,[21] axis assimilation, and cervical vertebral fusion anomalies. Regardless of whether these bony abnormalities occur separately or in combination, their presence usually results in a smaller-sized posterior fossa and potentially, in craniovertebral anomalies.

Given the extent of familial clustering and the other lines of evidence that support a genetic involvement in the development of CM1/S, we anticipate that identifying a region of interest in the genome by using a narrow phenotypic definition will be successful. To date, genes for several syndromes in which CM1/S is associated have been identified, including genes for renal–coloboma syndrome and achondroplasia, among others. We hypothesize that the underlying gene or genes involved in CM1/S will have pleiotropic effects that influence the extent of cerebellar tonsillar herniation, posterior fossa volume, and/or other variables such as bone abnormalities in the skull base or syringomyelia. Such pleiotropic manifestations may or may not be clinically relevant. One possible condition within such a pleiotropic spectrum may be the "Chiari 0 malformation,"[11] which is found in individuals with volumetrically small posterior fossa and syringomyelia, who have been shown to respond to decompressive surgery. The next challenge will be to model exactly what biological effects of a gene are involved in the abnormal developmental processes leading to CM1/S. Clinically, elucidation of the genetic contribution to CM1/S will undoubtedly aid in diagnostic evaluation and surgical planning, and it will allow more accurate genetic counseling regarding risk of recurrence to relatives in the immediate future. Because it is currently assumed that CM1/S is an

isolated, nonfamilial occurrence, putatively symptomatic relatives of patients known to have CM1/S may not routinely undergo diagnostic MR studies, thereby delaying intervention. The promise of genetic research, however, is that it will allow us to identify at-risk individuals prior to the onset symptoms, intervene when necessary and appropriate, and provide a better understanding of the basic biological mechanisms underlying this early developmental process.

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Manuscript received January 21, 2000.

Accepted in final form February 9, 2000.

The authors received support of the American Syringomyelia Alliance Project (http://www.asap4sm.com/), the Bobby Jones Open Fund, and a grant from the National Institutes of Health (No. NS26630). Additional information regarding the collaborative study to characterize the genetic basis of Chari 1 malformation with or without syringomyelia is available at http://www2.mc.duke.edu/depts/medicine/medgen.

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