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Genetic dissection of Chiari malformation type 1 using endophenotypes and stratification

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ABSTRACT

Chiari malformation type 1 is a heterogeneous disease characterized by cerebellar tonsillar herniation through the foramen magnum. Symptomatology is diverse, and diagnosis and treatment are controversial. Some evidence suggests the presence of a genetic component to the disease. However, the specific genetic factors involved remain relatively unknown. Previous reviews have broadly addressed different aspects (clinical manifestations, anatomical trails, treatment) of CM-1 by itself or compared it with other types of Chiari malformation. In this mini-review, we focus our attention on the heterogeneity of this disease and its impact on the study of the genetic etiology of classic CM-1. Patient stratification strategies and endophenotypes definitions are offered to help overcome the heterogeneity.

Chiari malformation type 1

Chiari malformation type 1 (CM-1) is the most prevalent form of the "Chiari malformations", and is characterized by a downward herniation of the caudal part of the cerebellum through the foramen magnum into the upper cervical region (Figure 1). It is a very heterogeneous disease whose current diagnosis relies on an imaging observation of cerebellar tonsil herniation (TH) of at least 3-5mm below the foramen magnum[1,2]. This TH is usually attributed to a reduced size of the posterior cranial fossa (PCF) (classic CM-1), although other mechanisms may be involved (see below). That is, the subsequent smaller cranial space leads to overcrowded neural structures and the herniation of the cerebellum through the foramen magnum. This results in a direct compression of the neural tissue at the craniovertebral junction and, often, cerebrospinal fluid (CSF) disturbances (decreased velocity and elevated impedance), that can cause other related conditions such as syringomyelia or secondary hydrocephalus[3,4].

CM-1 is quite heterogeneous with respect to symptomatology, epidemiology and treatment. The symptomatology presented by CM-1 patients is diverse, and its severity does not correlate with the degree of TH, with some asymptomatic cases presenting with prominent TH[3,5]. The onset of symptoms generally develops gradually, however, trauma, coughing/sneezing or pregnancy can also precipitate the event[3,6,7]. The incidence, prevalence and distribution of CM-1 is still unclear, and estimations vary depending on the criteria used to characterize the disease: TH criterion alone, TH criterion accompanied by symptomatology or a defining

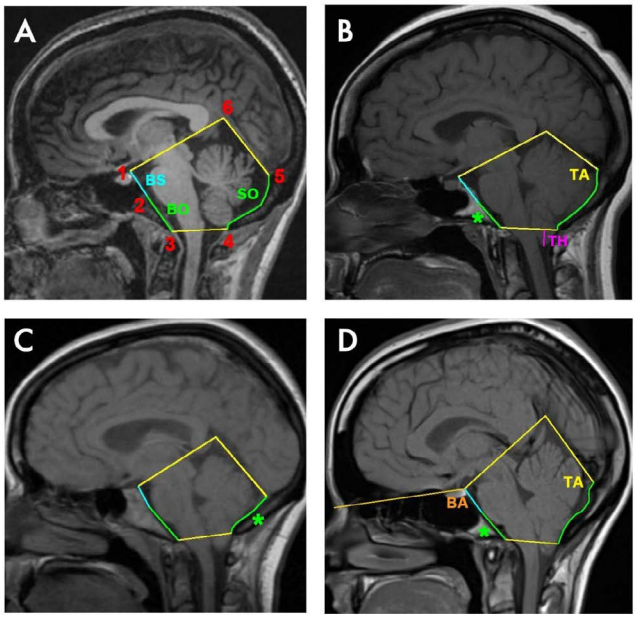

Figure 1: Sagittal T1W1 MRI showing the PCF in four different adult women. In A) Control, B) Classic CM-1 patient with a short basioccipital bone, reduced clivus slope and smaller tentorium angle, C) Classic CM-1 patient with a short supraoccipital bone and smaller tentorium angle, and D) Classic CM-1 patient with a short basioccipital bone, reduced clivus slope and larger tentorium angle. Cerebellum tonsillar herniation (TH) is showed in magenta in B. The occipital bone is shown in green: basioccipital (BO, from 2 to 3) and supraoccipital (SO, from 4 to 5). Basisphenoid (BS, from 1 to 2) with basioccipital results in the clivus (from 1 to 3). The asterisk shows the shorter occipital part in each patient. Tentorium angle (TA) is given by the tentorium cerebelli (from 5 to 6) and supraoccipital bone. Basal angle (BA) > 143º is considered platybasia.

mechanism of the TH. For example, in the United States (US), almost 1 % of normal adults undergoing MRI scanning have at least 5mm of TH but only about 0.01–0.04 % of adults demonstrate symptoms of CM-1[8]. Epidemiological data from other countries is generally missing. Moreover, in the US, estimates of the prevalence based on specific subtypes and/or comorbid conditions are scarce. Thus, the true prevalence of the condition, with respect to all forms of clinical heterogeneity is unknown. The treatment varies depending on the etiology of the TH. Indeed, in classic CM-1 it also depends on the severity of symptoms, the degree of TH and the presence of other conditions (i.e. syringomyelia or scoliosis). The most common treatment for these patients is surgical PCF decompression (alone or with duraplasty), although cerebellar tonsillectomy, cervical laminectomy, suboccipital cranioplasty are also applied[9,10]. The goal of these surgical procedures is to decompress the foramen magnum and increase the subarachnoid space in order to avoid the impaction of the cerebellar tonsils, reestablish the CSF flow and reverse the symptoms. However, there is still not a consensus about the best procedure to follow, since not all surgeries result in improvement of symptoms and often more than one surgery is required[8].

The presence of multiplex families with several CM-1 cases, the co-occurrence of CM-1 in monozygotic twins and the co-inheritance with known genetic syndromes (Table 1) strongly argue for a genetic contribution to CM-1 pathogenicity[11]. Despite this evidence, the precise genetic variants causative of the disease remain elusive in most cases. Several genetic studies, using different approaches (mutational analysis, whole genome linkage analysis, genetic association, expression analysis) have been performed in order to attempt to identify the genetic traits underlying this disease[11-16]. This work has resulted in the implication of several chromosomal regions and a number of candidate genes (Table 2). However, it is important to highlight that the major findings were achieved when the CM-1 population was stratified and analyzed in more homogenous clinical groups.

Strategies to consider in future genetic studies of CM-1

In a heterogeneous condition like CM-1, it is essential to properly characterize the patients, not only to establish a good diagnosis, but also to decide the best treatment to follow and to perform studies that help to improve the etiologic knowledge of the disease. Although TH is widely used in the diagnosis of CM-1, it is not heritable or completely correlated with symptomatic disease[12,16]. Since TH seems to be secondary in CM-1, other factors should be considered in order to successfully identify the genetic etiology of CM-1.

TH mechanism

As mentioned above, it has been generally assumed that TH was a consequence of a hypoplasic PCF due to a shortening of the occipital bone caused by an insufficiency during paraxial mesoderm development[17]. However, other cranial constriction mechanisms, such as premature closure of the cranial sutures (craniosynostosis), can also produce a reduced PCF with a smaller occipital bone; in addition, the reduced PCF is not the only explanation for the origin of TH. Other mechanisms such as cranial settling, occipitoatlantoaxial joint instability, spinal cord tethering, intracranial hypertension and intraspinal hypotension, can lead to TH[18]. For some of these mechanisms, different causal genetic pathways have been described. For example, craniosynostosis with TH (OMIM: #101200, #304110, #123500, #101600, #182212) can be produced by mutations in the *FGFR1*, *FGFR2*, *EFNB1* and *SKI* genes; and connective tissue disorders with TH (OMIM: #601776, #615539, #609192, #610168, #613795, #615582, #154700) have been associated with mutations in the *DSE, CHST14, TGFBR1, TGFBR2, SMAD3, TGFB3* and *FBN1* genes.

Table 1: Genetic disorders which can co-occur with CM-1.

Disorder or Syndrome	Associated clinical anomalies	Chromosome location (gene)	OMIM	Inheritance model	Reference
Achondroplasia	Skeletal	4p16.3 (*FGFR3*)	#100800	AD & sporadic	35
Acromegaly	Endocrine	20q13.32 (*GNAS*)	#102200	unknown	36-38
Blepharophimosis	Ophthalmic	3q23 (*FOXL2*)	#110100	AD	39
Bone marrow failure syndrome 1	Hematologic	4q12 (*SRP72*), 9q22 (*ERCC6L2*)	#614675 #615715	AD & AR	40
Cleidocranial dysplasia	Skeletal	6p21.1 (*RUNX2*)	#119600	AD	41
Craniometaphyseal dysplasia	Skeletal	5p15.2 (*ANKH*), 6q22.31 (*GJA1*)	#123000, #218400	AD & AR	42
Cystic fibrosis	Exocrine	7q31.2 (*CFTR*)	#219700	AR	43-45
Epilepsy	Neurologic	8q24	%600131	AD	46
Fanconi anemia	Hematologic	16q24.3 (*FANCA*)	#227650	AR	47
Furhmann syndrome	Skeletal, dermatologic & endocrine	3p25.1 (*WNT7A*)	#228930	AR	48
Goldenhar syndrome	Skeletal	14q32	%164210	AD	49
Growth hormone deficiency	Endocrine	17q23.3 (*GH1*) Xq22.1 (*BTK*)	#262400 #173100 #307200	AD, AR & X-linked	50-54
Hajdu–Cheney syndrome	Skeletal	1p12 (*NOTCH2*)	#102500	AD	55
Hyper IgE syndrome	Immune	17q21.2 (*STAT3*)	#147060	AD	56
Hypophosphatemic rickets	Skeletal	Xp22.2-p22.1 (*PHEX*)	#307800	X-linked	57, 58
Kabuki syndrome	Miscellaneous (FF, ID, skeletal, etc.)	12q13.12 (*KMT2D*)	#147920	AD	59, 60
Klippel-Feil syndrome	Skeletal	8q22.1 (*GDF6*), 17q21.31 (*MEOX1*), 12p13.31 (*GDF3*)	#118100 #214300 #613702	AD, AR & sporadic	3, 24, 61
Leopard syndrome	Miscellaneous (dermatologic, etc.)	12q24.13 (*PTPN11*)	#151100	AD	62, 63
Neurofibromatosis type I	Dermatologic	17q11.2 (*NF1*)	#162200	AD	64-70
Noonan syndrome	Miscellaneous (skeletal, FF, etc.)	12q24.13 (*PTPN11*)	#163950	AD	71
Osteopetrosis	Skeletal	11q13.2 (*LRP5*), 13q14.11 (*TNFS11*), 16p13.3 (*CLCN7*)	#166600, #611490 #607634	AD, AR & X-linked	72-74
Paget disease of bone	Skeletal	18q22.1 (*TNFRSF11A*), 5q35 (*SQSTM1*), 5q31 (*PDB4*) 8q24.12 (*TNFRSF11B*) 1q21.3 (*ZNF687*)	#602080 #167250 %606263 #239000 #616833	AD & AR	75, 76
Pseudohypoparathyroidism type 1A	Endocrine	20q13.32 (*GNAS*)	#103580	AD	77
Renal-coloboma syndrome	Ophthalmic & renal	10q24.3-q25.1 (*PAX-2*)	#120330	AD	78
Rubenstein-Taybi syndrome	Miscellaneous (ID, skeletal, FF, etc.)	16p13.3 (*CREBBP*), 22q13.2 (*EP300*)	#180849, #613684	AD & sporadic	53, 79, 80
Scoliosis	Skeletal	19p13.3, 17p11.2 8q12 9q31.2-q34.2	%181800 %607354 %608765 %612238	AD	81-85
Severe combined pituitary hormone deficiency	Endocrine	3p11.2 (*POU1F1*), 5q35.3 (*PROP1*), 9q34.3 (*LHX3*), 1q25.2 (*LHX4*)	#613038 #262600 #221750 #262700	AD & AR	53
Spondylo-epiphyseal dysplasia tarda	Skeletal	unknown	#271600	AD, AR & X-linked	86
Townes-Brocks syndrome	Skeletal & gastrointestinal	16q12.1 (*SALL1*)	#107480	AD	87
Velocardiofacial syndrome	Miscellaneous (skeletal, neurologic, etc.)	22q11(*TBX1*)	#192430	AD	88
William's syndrome	Miscellaneous (ID, FF, cardiovascular, etc.)	7q11.2 (Deletion of aprox 28 genes including: *LIMK1*, *RFC2*, *WBSCR1, WBSCR2*)	#194050	AD	89, 90

AD: autosomal dominant inheritance, AR: autosomal recessive inheritance, FF: facial features, ID: intellectual disability

Table 2: List of the candidate genes suggested for CM-1 from genetic studies performed.

Chromosome location	Gene	OMIM	Encodes for / Involved in	Type of study	Reference
1p36	*RUNX3*	*600210	Transcription factor / Segmentation body in Drosophila	Expression	16
1q25.2	*LHX4*	*602146	Transcription factor / Differentiation & development of pituitary gland	Linkage analysis	20
3p21.31	*PTH1R*	*168468	Receptor parathyroid hormone & parathyroid hormone / Chondrodysplasias & enchodromatosis	Expression	16
3p22	*TGFBR2*	*190182	Transmembrane protein / Transcription genes related cell proliferation	Expression	16
3p22-p21.2	*RPL14*		Ribosomal protein	eQTL	15
3q26.2	*RPL22L1*		Ribosomal protein	eQTL	15
5q14.2	*RPS23*	*603683	Ribosomal protein	eQTL	15
5q32	*CDX1*	*600746	Transcription factor / Anterior-posterior regional identify	Association	13
6p21	*RUNX2*	*600211	Transcription factor / Osteoblastic differentiation & skeletal morphogenesis	Expression	16
6p21.3	*NOTCH4*	*164951	Transmembrane protein / Chondrocyte Proliferation & maduration	Expression	16
8q12	*RPS20*	*603682	Ribosomal protein	eQTL	15
8q22.1	*GDF6*	*601147	Member of BMP family and the TGF-beta superfamily/ Bone formation	Linkage analysis	14
9q34.3	*NOTCH1*	*190198	Transmembrane protein / Proliferation & maduration of chondrocytes	Expression	16
11q23.3	*ETS1*	*164720	Transcription factor / Osteoblast differentiation & bone formation	Expression	16
12p11.21	*IPO8*	*605600	Ras-related small GTP-binding protein / Osteoblast differentiation	eQTL	15
12p13.31	*GDF3*	*606522	Ligand of TGF-beta protein / Ocular & skeletal development	Linkage analysis	14
12q13	*RPS26*	*603701	Ribosomal protein	eQTL	15
12q13.11	*COL2A1*	+120140	Collagen / Cartilage & the vitreous humor of the eye	Expression	16
13q12	*FLT1*	*165070	Receptor tyrosine kinases / Angiogenesis & vasculogenesis	Association	13
14q21	*RPL36AL*	*180469	Ribosomal protein L36A-like	eQTL	15
15q21.3	*ALDH1A2*	*603687	Aldehyde dehydrogenase protein / Mesoderm differentiation & somitogenesis	Association	13
15q21.1	*FBN1*	*134797	Mature extracellular matrix glycoprotein / Connective tissue	Linkage analysis	12
16p12.3	*XYLT1*	*608124	Xylosyltransferase enzyme / Ossification	eQTL	15
17q24.2	*PRKAR1A*	*188830	Protein kinase / Associated with genetic disorder of bone growth	eQTL	15
21q22.2	*ETS2*	*164740	Transcription factor / Osteoblast differentiation & bone formation	Expression	16
22q13.1	*ATF4*	*604064	Transcription factor / Osteoblast differentiation	Linkage analysis	20
22q13.2	*EP300*	*602700	Histone acetyltransferase / Cell proliferation & differentiation	Linkage analysis	20

In classic CM-1, most candidate genes have been related to the different stages of occipital bone development, including the paraxial mesoderm development, somite and sclerotome formation, chondrogenesis and osteogenesis (Table 2)[13,15,16,19,20].

Stratifying according to the TH mechanism (presence or absence of history of connective tissue disorders), Markunas *et al.* observed that the evidence for genetic linkage in several chromosomal regions increased significantly and led to the identification of two missense mutations with incomplete penetrance in the *GDF6* gene in two independent classic CM-1 families[14] (Table 2).

PCF MRI-morphometric traits as endophenotypes

Although TH herniation is not heritable[12,16], other PCF traits are, and the use of these heritable traits are more likely to aid in the identification of the underlying genes.

PCF morphometric characteristics are different in CM-1 patients according to the mechanism of TH[18]. In addition, although a hyploplastic PCF is a common trait for classic CM-1 patients, the regions of the PCF are not equally affected[16,13,20]. Usually the PCF is shallower, as a result of the shorter occipital bone, and often the slope of the clivus is reduced, resulting in a predisposition to platybasia. Most studies demonstrated the basilar part of the occipital bone (basioccipital) or clivus (when the sphenoccipital synchondrosis is not visible) is significantly reduced[6,21,22]. However, for some cohorts this reduction seems to be more significant in the supraoccipital part[23,24], or present for both regions[4]. There are also conflicting reports about the magnitude of the tentorium angle in patients compared to control cohorts[3,22] (Figure 1).

Since the formation and development of the occipital bone is intricate, a morphometric analysis of the PCF based on MRI is essential in classic CM-1 patients. Depending on which part of the occipital bone is abnormal (shorter and/or present with different slope), the genes involved may be different. The occipital bone is formed from the fusion of the first four somites. However, the parts of these somites that resegment to form the sclerotomes are different for each part

of the bone[25]. The basilar part fuses with the basisphenoid bone at the sphenoocipital synchondrosis (which derives from neural crests cells and the mesoderm, and its closure finishes at the age of 20 years)[8]; but the boundaries of the supraoccipital part are given by the interparietal-supraoccipital, lamboid and occipito-mastoid sutures[8,26]. In addition, the occipital bone has both membranous and cartilaginous types of ossification, and the number of ossification centers for each part is different[8,26].

After considering the PCF traits presented in CM-1 patients, Urbizu *et al.* identified four genetic variants (located in the genes *ALDH1A2*, *CDX1* and *FLT1*) to be associated with adult classic CM-1, and two of them also associated with the slope of the clivus[31] (Table 2). Using MRI endophenotypes defining two different "shapes" of PCF, Markunas *et al.* identified different levels of expression in genes related with dorso-ventral axis formation (*ETS1*, *ETS2, NOTCH4*), ribosome, spliceosome and proteasome in pediatric classic CM-1 patients[16] (Table 2). These initial findings support the complex genetic basis of the PCF development, and the genetic heterogeneity of CM-1.

Co-occurrence with other genetic disorders

Another approach to identifying genes for CM-1 is to stratify CM-1 according to co-occurring genetic disorders, either by syndrome or according to the associated clinical anomalies (skeletal, hematologic, ophthalmic, endocrine, exocrine, dermatologic, neurologic or immune) (Table 1). Importantly, some of these different disorders may be related since: 1) they are caused by the same gene/*locus* (i.e. mutations in *GNAS* gene have been identified in patients with acromegaly and Pseudohypoparathyroidism type 1A), 2) some of these genes interact (i.e. *CREBBP* and *EP300* are genes that cause Rubenstein-Taybi syndrome, and are involved in chondrocyte differentiation; they interact with *LHX4* which is associated with severe combined pituitary hormone deficiency, also described in CM-1 patients), and 3) some of these genes are in the same pathway (i.e. Noonan syndrome and Neurofibromatosis type 1 are caused by alterations in Ras pathway genes).

Familial or sporadic forms of CM-1

The majority of CM-1 cases are believed to be sporadic. However, familial cases (presenting autosomal recessive and autosomal dominant inheritance with incomplete penetrance) have also been reported[12]. Thus, it is possible that the presence or absence of family history is associated with different genes and disease pathogenesis. For example, in some diseases such as Fronto Temporal Dementia or Amyothropic Lateral Sclerosis, different genes, and even different pathways, are affected depending if the cases are familial or sporadic[27]. The fact that some CM-1 families present different inheritance patterns also suggests that there is more than one gene involved in the disease.

Age of symptom onset

Traditionally, CM-1 has been considered an adult form of the Chiari malformations since the onset of the symptoms usually occurs during the second or third decade of life. More recently, because of the increased use of MRI diagnosis and clinical awareness, this perception is changing, with an increasing number of pediatric cases being reported[10,28,29] . Both pediatric and adult CM-1 patients have TH in common. However, the symptomatology, comorbidities and gender proportion are not exactly the same. For example, and although the precise estimate is still unknown, in adults a higher incidence is generally observed for females, while in pediatric cases this incidence is more evenly distributed among sexes[3,10,13,18, 19,30].These differences could indicate that pediatric and adult onset cases are different forms of the disease. There are many examples of other diseases where age of onset is important. In Alzheimer disease, different genetic variants are involved in the early (younger than 65 years old) and late onset forms of the disease[31].

Gender

The fact that in CM-1 adult form is more common in females, suggests the possibility of sexual-dimorphism. Gender effects can manifest in the presentation of the disease, associated symptoms, prevalence, or age of onset. These differences are also seen in CM-1 as we have described above. Sexual-dimorphism has been observed in other complex human diseases such as cardiovascular disease, asthma, autoimmune diseases, some neurological and psychiatric disorders, as well as some common birth defects and cancers[32]. Many complex human diseases exhibit sex and age differences in gene expression where common variants may alter gene expression and influence disease susceptibility or its progression[33]. For CM-1, the alteration in the occipital bone could be produced at different developmental time points, from embryonic stages until the completion of bone development. Importantly, hormones (parathyroid hormone, growth hormone), including sexual hormones (estrogen, testosterone), are involved in bone growth[34]. Interestingly, some disorders that co-occur with CM-1 are caused by endocrine alterations (Table 1).

Conclusion

In conclusion, there remains little known about the genetic component involved in the etiology of CM-1. There is a tremendous need to replicate the published studies and validate the findings in independent cohorts, as well as to consider the effect of these stratification strategies on proposed candidate genes. We also cannot discard other genomic mechanisms, such as regulatory variation and epigenetic modifications, as additional contributors to disease etiology.

Thus, other genomic approaches may be needed, such as

epigenetic analyses and next generation sequencing, which have not yet been applied to CM-1. Ultimately, however, a better understanding of meaningful clinical stratifications will be required to identify more genetically homogeneous subsets in order to find the causative genetic variants.

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