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Etiology of Caudal Regression Syndrome

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Abstract

Caudal regression syndrome (CRS) is a rare congenital disorder in which lumbosacral anomalies are combined with anorectal and urogenital malformations. However, the molecular mechanisms of human CRS are not yet known. Trauma, nutritional problems, toxic agents, and genetics are suggested in the etiology of CRS. To the best of our knowledge, linkage studies of families affected exclusively by CRS or total sacral agenesis have not been conducted. In spite of the small number of familial cases reported, some specific genes have been shown to cause defined phenotypes. Environmental factors also may act as an enhancer in the etiology for CRS. There are several mutant mice that are considered as models for CRS, showing characteristic vertebral, anorectal, and urogenital abnormalities. Understanding the mechanisms for CRS development gives us valuable information to understand better what mutations may cause or contribute to CRS in humans. This review highlights the current evidence that pinpoints the link to the etiology of CRS.

Keywords: Caudal regression syndrome; Etiology; Mutation; Diabetes; Animal model

Introduction

Caudal regression syndrome (CRS) is characterized by sacrococcygeal or lumbosacrococcygeal agenesis, of variable extent, most often accompanied by multiple musculoskeletal abnormalities of the pelvis and legs. In addition, various other malformations, vertebral and non-vertebral, have occasionally been reported to be associated with the complex [1-5]. CRS occurs at a rate of approximately one per 25,000 live births [6,7]. The condition is caused by some factor or set of factors present during weeks 3-7 of fetal development. Formation of the sacrum/lower back and corresponding nervous system is usually nearing completion by week 4 of development. Owing to abnormal gastrulation, the mesoderm migration is disturbed. This disturbance results in symptoms varying from minor lesions of the lower vertebrae to more severe symptoms such as complete fusion of the lower limbs, also known as sirenomelia or mermaid syndrome. CRS is a heterogeneous disorder with respect to its etiology and developmental pathogenesis. In fact, caudal regression is caused by various gene mutations in mice (Table 1) [8-33]. In addition, it is clear that environmental factors and an underlying genetic predisposition are involved in CRS.

CRS and Associated Anomalies of Other Systems

CRS is a rare and usually sporadic disorder. It comprises developmental anomalies of the caudal vertebrae, neural tube, urogenital and digestive organs, and hindlimbs; the precursors of which are derived from the caudal eminence. This may result in various types of anorectal malformations (ARMs), agenesis of spinal segments (usually sacral or lumbosacral), and multiple visceral anomalies. In the most severe cases, the lower limbs are fused [1-5]. Diagnosis can be made in the first trimester by noting the short crown-rump length. Distal vertebral anomalies and fetal spinal anatomy may be seen by obstetric ultrasonography, and in the intrauterine period, amnioinfusion may be important, especially in cases associated with oligohydramnios. It may help in detecting associated genitourinary and gastrointestinal anomalies. The superiority of lumbosacral magnetic resonance imaging for diagnosis, both antenatal and postnatal, and for classification, is generally accepted today. It also readily detects various associated anomalies [34-46].

Phenotype	Gene symbol	Reference
CRS	*Cdx2*	[25]
CRS	*Cdx4*	[22]
CRS	*Brachyury*	[29]
CRS	*Wnt3a*	[11]
CRS	*Cyp26a1*	[16]
CRS	*Hoxb13*	[22]
CRS	*Hoxc13*	[22]
VACTER	*Shh*	[10]
CRS	*Ptf1a*	[32] [31] [30]
CRS	*Acd*	[18]
CRS	*Pcsk5*	[21]

Table 1: List of CRS model mutant mice.

The simple form of CRS is sacral agenesis. Renshaw classified the spectrum of sacral agenesis into five types based on type of defect and articulation between bones [47]. Type I has total or partial unilateral sacral agenesis; type II has variable lumbar and total sacral agenesis and the ilia articulate with the sides of the lowest vertebra; type III has variable lumbar and total sacral agenesis, and the caudal end plate of the lowest vertebra rests above fused ilia or an iliac amphiarthrosis; type IV has fusion of soft tissues in both lower limbs; and type V, also known as sirenomelia or mermaid syndrome, has a single femur and tibia.

Several associated anomalies of other systems are frequently present and complicate the picture of CRS. For example, CRS can be found in association with OEIS complex (omphalocele, exstrophy of the bladder, imperforate anus, and spinal defects) [48,49].

VATER association was originally named in the early 1970s with

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the description of seven patients who had at least three of the following features: vertebral defects, anal atresia, tracheoesophageal fistula, and radial and renal dysplasia [50]. Shortly thereafter, additional features, such as cardiac malformations and additional limb abnormalities, were added, and the condition was called VACTERL syndrome, which remains the more prevalent term according to our survey [50-56]. However, the precise definition has remained uncertain [57].

In 1981 Guido Currarino described the triad of hemisacrum, ARM (rectoperineal fistula, rectourethral fistula, rectovestibular fistula, or rectocloacal fistula) and presacral mass (teratoma, anterior meningocele, rectal duplication, or a combination of these). Currarino syndrome (CS) has great phenotype variability. Many cases present with asymptomatic hemisacrum without other anomalies, whereas others present with a complete spectrum of malformations and other associated anomalies [58-60].

Ocular findings can also be described together with CRS, including hypertelorism, epibulbar dermoid, anophthalmia infantile glaucoma, and punctal atresia [61].

Genetic basis for CRS

Three genetic and association studies on CRS suggested the involvement of genes such as *HOXD13* [62], *CYP26A1* [63], and *HLXB9* [64]. Although mutations in *SHH* and *GLI3* are associated with human syndromes that may include ARM as part of the phenotypic spectrum, such as holoprosencephaly type 3 (OMIM #142945) and Pallister-Hall syndrome (OMIM #146510), *SHH* and *GLI3* mutations have not been identified in CRS. However, mutations in the human *HOXD13* gene, which is an *SHH t*arget during gut morphogenesis, are associated with limb malformations, including synpolydactyly 1 (SPD1; OMIM #186000), brachydactyly types D (BDD; OMIM #113200) and E (BDE; OMIM #113300), syndactyly type V (OMIM #186300), and a novel brachydactyly-syndactyly syndrome [65]. Thus, *HOXD13* may not only be implicated in limb malformations, but also in the development of gut and genitourinary structures.

Retinoic acid (RA) is a key determinant of vertebrate embryo patterning and organogenesis [66,67]. The spatiotemporal distribution of embryonic RA results from regulated expression of RA-synthesizing enzymes (RALDH1, RALDH2, and RALDH3) [68] and RA-catabolizing enzymes (CYP26A1, CYP26B1, and CYP26C1) [69-72]. Differences in the genotype and allele frequency of each single nucleotide polymorphism (SNP) in 49 CRS patients and 132 controls were analyzed using 8 SNPs [63]. However, both single-locus and haplotype analyses revealed no association with increased risk for CRS, although two intronic polymorphisms affected the intron splicing efficiency. The relationship between CRS risk and *CYP26A1* genotype requires further study with a larger number of genotyped subjects.

Three previous reports have shown *HLXB9* to be a major causative gene for CS [73-75]. *HLXB9* has three exons and encodes a protein of 403 amino acids. A polymorphic GCC repeat coding for a polyalanine stretch occurs in exon 1 of *HLXB9*. To date, no gene other than *HLXB9* has been shown to be involved in sacral malformations. Several studies reaffirm the lack of associations between *HLXB9* mutations and several caudal regression variants. Thus, many other genes will be involved in CRS. In contrast to humans, a null mouse mutation of the *HLXB9* gene showed agenesis of the dorsal pancreas but no skeletal truncation [76]. It is possible that gain of function, but not loss of function, may induce CRS-like disease with sacral malformations.

In addition, three studies have shown an association between chromosomal abnormalities 18p11.2 deletion and micro duplication at 22q11.21 and CRS, and between duplication-deletion of distal 7q and CS (Table 2) [77-79]. In the 18p11.2 region, several genes such as *CDH2, TTR, SMAD2, SMAD7, SMAD4, DCC, TCF4, FECH, NEDD4L, MC4R*, and *TNFRSF* are found. In 22q11.21, genes such as *SMARCB1, MIF, GSTT1, ADORA2A, CHEK2, NF2, TIMP3, HMOX1, MYH9, LGALS1, APOBEC3G, PDGFB, EP300, XRCC6, CYP2D6*, and *PPARA* are found. It may be that a gene dosage effect involving the 22q11.2 region is involved in predisposition to association with VACTERL, but it is not clear whether these genes are directly involved in CRS. In the third case, there is a *de novo* 10.3-Mb duplication of 7q34-q35 (chromosome 7: 138,293,371-148,443,994) as well as an 8.8-Mb deletion on 7q36 (chromosome 7: 148,472,027-157,265,994) [79]. The deleted region contains 70 RefSeq genes including *HLXB9*, *SHH* and *EN2*, while the duplication contains82 genes (Table 2). Loss of *HLXB9* may account for the CS phenotype.

Disease	Gene or genetic position	Association or evidence	Reference
CS	*HLXB9*	yes	[73]
CS	*HLXB9*	yes	[74]
CS	*HLXB9*	yes	[75]
CRS	*CYP26A1*	no	[63]
CRS	*HLXB9*	no	[64]
CRS	*18p11.2*	yes	[77]
VACTER	*HOXD13*	yes	[62]
CS	*7q*	yes	[79]
VACTER	*22q11.21*	yes	[78]

Table 2: Genetic research list for diseases related and similar to caudal regression syndrome.

Pathogenesis of human CRS is still unknown. Further investigations are warranted to determine the genetic causes of this complex malformation.

CRS caused by Environmental Factors

Overt type 1 diabetes around conception carries a marked risk of embryopathy (neural tube defects, cardiac defects, and CRS), whereas later in gestation, severe and unstable type 1 maternal diabetes carries a higher risk of intrauterine growth restriction, asphyxia, and fetal death. CRS is seen in 0.1-0.25:10,000 of normal pregnancies [6,7]. In contrast, about 1% of newborn infants born to diabetic mothers exhibit CRS, indicating a risk at least 250 times higher than that in the offspring of nondiabetic mothers [80]. As a result, 15-25% of mothers who have children with CRS have insulin-dependent diabetes mellitus [81-86].

The possible role of the prediabetic state in the etiology of CRS is obscure. Landauer et al. [87] demonstrated that defective development of the tail skeleton orits complete absence ("rumplessness") was induced inchickens by injection of insulin.

Apart from hyperglycemia, other environmental factors are presumably involved, as demonstrated by the rare incidence of CRS compared with that of diabetes. Certainly not all children born with CRS have diabetic mothers. However, it is not yet clear which other factors are involved. Further clinical investigations may clarify the relationship between maternal diabetes and CRS.

Animal Models of CRS caused by Gene Mutation

Various mouse mutants show that caudal agenesis occurs as a result of hypodevelopment of the anterior–posterior axis (Table 1) [8-33]. These mutant mice can be classified into four categories. Mutants

with CRS phenotypes can be caused by mutation in: (1) Shh-related related signaling molecules such as Hoxa13, Hoxd13 [88-90] and Bmp4 [10,11,17,19]; (2) Cdx2 and its downstream signaling molecules such as Cyp26a1 and T; (3) Wnt and its related genes such as *Wnt3a*, *Acd* and *Lrp6*; and (4) *Danforth's short tail* (*Sd*).

Shh protein is a regulator of mesodermal patterning during many aspects of development [91,92]. It acts locally on adjacent visceral mesoderm to induce expression of bone morphogenetic protein and the Hox genes [93]. Shh appears to signal an epithelial–mesenchymal interaction in the developing hindgut. Hoxd13 is an SHH target during gut morphogenesis. Hoxd13 natural mutant mice and mice with genetically engineered inactivation of the most 5' genes of the Hoxd cluster show disorganization of the anorectal region [94-96].

Cdx2 encodes homeodomain transcription factors related to the *Drosophila* gene *caudal*. Expression of *Cdx2* in the embryo proper initiates at E8.5 in all germ layers of the posterior embryo, extending caudally into the base of the allantois and rostrally into the posterior neural plate, hindgut endoderm and unsegmented paraxial mesoderm. Expression of *Cdx2* continues into the tail bud, the posterior neural plate and the endoderm, and is eventually confined to the hindgut endoderm located posterior to the foregut/midgut junction from E12.5 onwards, and perdures in the adult intestinal epithelium [97]. Deficiency in *Cdx* genes causes body truncations and malformations of the caudal spine and urorectal system, a phenotype reminiscent of CRS in humans [12,25].

Savory et al. [25] demonstrated that *T*, *Wnt3a* and *Cyp26a1* are direct Cdx2 targets. In accordance with this, mutant mice for these genes showed similar CRS phenotypes. T encodes a transcription factor, which was the first T-box gene to be molecularly characterized. Heterozygous T mutant mice exhibit a variably shortened tail, whereas homozygous T mutant mice die between E9.5 and E10.5. T-deficient embryos display an overall loss of mesoderm caused by failure of epiblast cells to ingress through the primitive streak. Consequently, embryos have impaired axial development and allantoic defects; the latter of which are thought to be the cause of death [98-100]. Homozygous T mutant mice die during early development; therefore, this T mutant cannot be used to analyze the effect of T on other tissues. Interestingly, the hypomorphic mutant was created using an inducible miRNA-based *in vivo* knockdown of *Brachyury*. These mice survive until birth and show skeletal defects as well as urorectal malformations resembling CRS [29].

Cyp26a1$^{-/-}$ mice showed caudal truncation, vertebra transformation, and hindbrain mis-patterning. Externally, *Cyp26a1*$^{-/-}$ mice exhibited a mermaid-like deformity (sirenomelia), with the caudal part of the body severely truncated and the anterior portion remaining relatively normal. The hindlimbs were typically fused at the midline and the tail was missing. Spina bifida was also apparent. Postmortem examination of abdominal organs of *Cyp26a1*$^{-/-}$ mice revealed aplasia or hypoplasia of the urogenital system, including the kidneys. The posterior end of the hindgut was often terminated as an appendix. Histological analysis of embryos confirmed the aplasia or hypoplasia of the urogenital system. The kidneys were often fused, resulting in the development of horseshoe kidney [16]. These phenotypes in *Cyp26a1*$^{-/-}$ mouse mimicked those generated by excess RA administration. As described before, further investigation is required to provide evidence that *CYP26A1* has implications for the pathogenesis of human CRS.

The *Wnt* family, which encodes cysteine-rich secreted glycoproteins,consists of at least 16 members in mice [101,102]. *Wnt-3a* expression is detected first at 7.5 days post-coitum (dpc), extending along much of the length of the streak. *Wnt-3a* null mutant embryos lack all but the first seven to nine somites, have a disrupted notochordand pronounced central nervous system dysmorphology, and most die before 12.5 dpc [103]. A mutation in the *Wnt3a* gene results in a lack of caudal somites, a disrupted notochord, and failure to form a tail bud [11,104]. Interestingly, *Wnt3a* mutants fail to express *T* [105] and *T* mutants fail to express *Shh* [29]. However, the downstream mechanisms via T are still not entirely clear.

Adrenocortical dysplasia (*acd*) is a spontaneous autosomal recessive mouse mutant with developmental defects in organs derived from the urogenital ridge. Keegan et al. [49] identified a splice donor mutationin a gene, which is the mouse ortholog of a newly discovered telomeric regulator. This gene, termed *Acd*, is a component of the TRF1 protein complex that controls telomereelongation by telomerase and is widely expressed in adult tissues and throughout embryonic development. On the DW/J background, a striking caudal regression and limb malformation phenotype is observed in mutant embryos, resembling CRS in humans. Interestingly, expression of *Wnt3a* and *Dll1* at E11.5 is reduced in the tip of the developing tail. The extent of reduction in expression of *Wnt3a* and *Dll1* correlates with severity of the abnormal morphology of the tail bud. This suggests that Acd functions upstream of *Wnt3a* and *Dll1* in the developing tail bud directly or indirectly. The caudal truncation observed in some *acd* homozygotes is similar to that observed in *Wnt3a*$^{-}$/*Wnt3a*^{vt} or *Wnt3a*^{vt}/*Wnt3a*^{vt} mice [11].

The *LRP6* gene encodes a member of the low-density lipoprotein receptor (LDLR) gene family [106] and *Lrp6* is required during *Wnt*/β-catenin signaling, acting as a co-receptor for *Wnt* molecules. *LRP6* is internalized with caveolin in human cell lines, and this endocytic pathway is required for WNT3A-induced internalization of *LRP6* and accumulation of β-catenin [107].Targeted disruption of *Lrp6* results in widespread developmental defects that include caudal truncation, limb defects and urogenital anomalies [108]. The specific developmental defects in homozygous embryos are remarkably similar to mice carrying mutations in the *Wnt3a* gene [11,103]. *LRP6* mutant mice do not exhibit all of the *Wnt* phenotypes reported, for example, the early embryonic lethality associated with *Wnt-3* mutants [109]. Therefore, LRP6 may be involved in signaling by only a subset of vertebrate *Wnts*. In any case, *LRP6* is required for efficient signaling by several *Wnt* proteins.

Finally, *Danforth's short tail* (*Sd*) mutant mice accurately model human caudal malformation and regression syndromes. In recent studies, three laboratories including our research group independently identified the *Sd* mutation as a ETn retrotransposon insertion upstream from the *Ptf1a* gene [30-33]. *Ptf1a* encodes a cell-type-restricted basic helix–loop–helix transcription factor required for development of the pancreas and cerebellum [110,111]. We demonstrated an insertion of one type of retrotransposon 12 kb upstream of the *Ptf1a* gene. This resulted in ectopic expression of *Ptf1a* gene in the caudal region of the embryo and downregulation of *Cdx2* and its downstream targets, *Cdx2*, *T*, *Cyp26a1* and *Wnt3a*, leading to characteristic phenotypes in *Sd* mouse. The shortened tail phenotype of the *Sd* mutant is similar to that of the *Cdx2*, *T*, *Cyp26a1*, *Wnt3a*, *Acd* and *Lrp6* mutants. Human CRS is a heterogeneous disorder with respect to its etiology and developmental pathogenesis, thus, *Sd* mutant mice are considered the best model for human CRS. In addition, *Sd* mutants show phenotypic similarity in terms of abnormalities in the spine, hindgut, and urogenital system. Taken together, these results suggest that the phenotypes observed in *Sd* mice are caused by combination of partial deficiency of *Cdx2* and its downstream target genes.

One puzzling question remains. As described before, a null mutation of the *Hlxb9* gene in mice showed agenesis of the dorsal pancreas but no skeletal truncation [76]. Various types of mutation, such as insertion, deletion or substitution, were found resulting in nonsense mutation, frame shift mutation, or abnormal splicing [73]. Thompson et al. showed that both *Ptf1a* and *Hlxb9* were expressed in the pancreas, and that *Ptf1a* was required for *Hlxb9* expression [112]. Although it is not clear whether *PTF1A* is involved in human CRS or CS, the evidence from this study implies that misexpression of *PTF1A* and possibly *HLXB9* in the caudal abnormalities may cause CRS. Further studies using *Sd* mice will provide insight into the development of human CRS.

Animal models of CRS caused by Environmental Factors

Animal experiments have shown that CRS-like syndrome could be induced by RA, adriamycin, and hyperglycemia [113-118]. However, the exact etiology is unknown. In this syndrome, chromosomal studies have been normal, with few exceptions. Similar to human CRS, the offspring of diabetic mice also exhibit poor development of the lower part of the body, including genitourinary dysmorphogenesis [83]. Vestigial tail (*Wnt3a*^{vt}) mutants provide evidence that *Wnt3a*, a gene that controls the development of the caudal region, is directly involved in the pathogenic pathway of RA-induced caudal regression. The mutants further show that the increased susceptibility of embryos of diabetic mice to RA involves enhanced down regulation of *Wnt3a*. This positive interaction between RA and maternal diabetes may have implications for humans in suggesting increased susceptibility to environmental teratogens during diabetic pregnancy [115].

Conclusion and Perspectives

As discussed above, CRS is a heterogeneous disorder with respect to its etiology and developmental pathogenesis. In addition, both an underlying genetic predisposition and environmental factors are involved in CRS. The etiological mechanisms can be summarized as follows. As shown in figure 1, at least 4 pathways seem to be involved in CRS. One is the *Shh* signaling pathway in which the *Shh* downstream target, Hoxd13, is involved in caudal formation. Second, the *Cdx2* pathway including T, *Cyp26a1*, and *Wnt3a*, plays an important role in caudal formation. Third, the Acd pathway involving also *Wnt3a* is responsible for caudal formation. Fourth, the *Lrp6* pathway is involved through regulation of *Wnt*/β-catenin signaling. At present, the pathway of *Hlxb9* is totally unknown. In any case, it is plausible that CRS is caused by a combination of partial deficiency of the molecules described in figure 1.

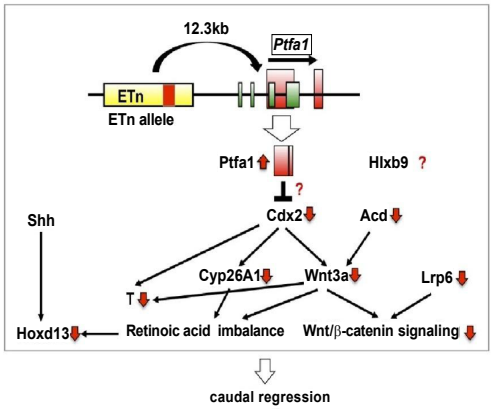

Figure 1: Pathogenetic mechanisms for CRS.

Recently, next-generation sequencing technology has advanced rapidly. Using the newest techniques, whole-genome sequencing from five persons can be done within 10 days. Thus, it is possible to sequence whole genomes from 100 CRS patients. However, it is difficult to assess whether variations found in patients are responsible for the development of CRS. Therefore, there will be a strong demand for production of genetically engineered mice with particular genetic alterations.

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