



The Genetic Nature of Osteochondritis Dissecans: A Systematic Review and Call for Improved Studies

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Introduction

Osteochondritis dissecans (OCD) is a focal, idiopathic, alteration of subchondral bone structure with risk for secondary damage to adjacent articular cartilage and premature osteoarthritis. These changes can manifest as early articular cartilage separation, partial detachment of an articular lesion, and osteochondral separation with loose bodies.¹⁻⁸

OCD is a relatively common cause of knee pain and dysfunction in adolescents, with a predominance of cases in adolescent males.² The incidence of OCD has been estimated at 1.2% of the population based on knee arthroscopy.⁹ OCD of the knee is subcategorized into a juvenile form and an adult form, depending on the status of the distal femoral physis. Juvenile OCD has a much better prognosis than adult OCD, with greater than 50% of cases showing healing within six to 18 months from non-operative treatment. The other 50% of patients with juvenile OCD, and most patients with adult OCD, frequently require operative intervention to achieve healing.⁸

The etiology of OCD remains unclear, and no theory regarding the cause of OCD is universally accepted.⁹ Leading thoughts on the cause of OCD include repetitive microtrauma, secondary effects associated with vascular insufficiency, avascular necrosis, inherited factors, and genetic predisposition.⁹ While a genetic factors have been proposed to play a role in OCD, surprisingly few genetic studies have been carried out to determine the underlying etiology. The purpose of this systematic review was to evaluate the present evidence supporting a genetic predisposition to OCD.

Methods

We searched the Medline and EMBASE computerized literature databases for articles from January 1946 to September 2012 satisfying the following logic: "osteochondritis dissecans" OR "OCD" AND "genetic" OR "genetics" OR "family" OR "families" OR "familial" OR "twin" OR "triplet". Reference lists from the articles retrieved were further scrutinized to identify any additional studies of interest. All studies

from the above-mentioned searches were then reviewed. Studies were included if they met the following criteria: 1) the language was English; 2) the main subjects were human. Studies were excluded if: 1) the above inclusion criteria were not met; 2) they were a review, editorial, or commentary. One author (I.G.) performed the initial search; another author (T.G.) then independently reviewed the results and selected the appropriate studies on the basis of the above criteria. Details of the search are highlighted in Figure 1.

We reviewed 35 studies that reported on a total of 232 patients with OCD: 8 familial series with at least 5 subjects,¹⁰⁻¹⁷ 2 genetic linkage studies,^{18,19} 18 familial case series with less than 5 subjects,²⁰⁻³⁷ 5 monozygotic twin reports,³⁸⁻⁴² and 1 dizygotic twin report.⁴³ None of the data was extractable in a usable form to be compared or combined with other studies for further meta-analysis.

Results

Alongside theories that OCD was caused by repetitive trauma and avascular necrosis, theories regarding the genetic nature of OCD were first proposed in the early 20th century. Bernstein³³ was the first to describe OCD lesions in multiple members of a family and to suggest a genetic component to its etiology.

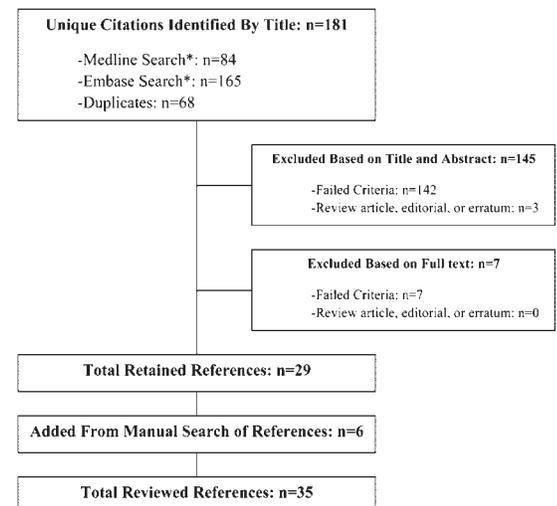


Figure 1. Details of the search methodology.

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Shortly thereafter, Wagoner and Cohn³⁷ described OCD in a son, father, and paternal uncle as well as in two brothers. In a series of 1,000 radiographs of asymptomatic men, Nielsen⁴⁴ noted an incidence of OCD of 4.1%. Interestingly, 14.6% of the male relatives of affected men also showed unmistakable radiographic evidence of OCD, thus strengthening the argument for a genetic predisposition to OCD.

In addition, multiple case reports and series have been published discussing findings of OCD in multiple members of a family. Novotny³⁴ and Livesly²⁶ each described families with two siblings affected by OCD, and Gardiner²³ described a family with three affected siblings. Additionally, Fonseca²² reported a family with two siblings and a maternal cousin affected with OCD. Pick²⁹ described a family in which a mother and three of four children were affected, and Tobin³¹ described a family in which a father and all three children were affected by OCD. Hammett³⁸, Mackie³⁹, Mei-Dan⁴⁰, and Onoda⁴¹, Woods⁴², and Kenniston⁴³ all described families with twins both affected by OCD, often in the same location, and usually unrelated to repeated stress, implying a genetic component to the development of OCD.

Contrary to the above reports, in 1977, Petrie¹⁷ conducted a study in 34 patients with OCD to establish if symptomatic first degree relatives were affected. Of 86 first degree relatives analyzed clinically and radiographically, only one was affected. The authors concluded that OCD is not a familial disease.

There have been multiple reports of syndromic OCD, in which patients are affected by other disease processes, indicating a genetic predisposition that the two diseases occur together. Stickler's syndrome, an autosomal dominant disease linked to mutations in both type II and XI collagen, has been reported in multiple cases to be associated with OCD.^{20,35,45} In a series looking at patients with Stickler syndrome, 30% of patients have been shown to present with polyarticular OCD.⁴⁰ Dwarfism, or short stature < 5th percentile for age, has been reported to be associated with the development of multiple OCD lesions implying a genetic component.^{11,12,14,28,29,32,46,47} Additionally, some endocrine factors, including thyroid disorders and cryptorchidism, have been postulated to have a genetic linkage to OCD based on familial occurrence.^{1,24,36}

Atypical familial OCD lesions also increase support for a genetic component to OCD. Numerous reports of simultaneous polyarticular OCD lesions exist.^{24,25,27,28,48} Repetitive trauma is intuitively thought to be less of a contributing factor to the occurrence of such lesions. Additionally, Anderson and Lyne²¹ and Woods and Harris⁴² described sisters and monozygotic twins, respectively, with lesions of the medial talus. While lesions of the lateral talus are often seen when a history of trauma is reported, medial talar OCD is typically not associated with trauma,⁴⁹ implying a possible genetic component to this lesion pattern. Lee *et al*¹³ reported ten cases of bilateral femoral head OCD within a three generation family, unrelated to trauma. Since this rare diagnosis occurred in multiple members of the same family, the authors concluded that a genetic influence was likely.

While small case series have been at the forefront of the published literature, large family reports of OCD have also been

well documented. Lee *et al*¹³ and Stougaard¹⁶ each reported on 3 generation families, Andrew *et al*¹¹ and Mubarak and Carroll¹⁴ each reported on 4 generation families, and Andren *et al*¹⁰ and Stattin *et al*¹⁵ each reported on five generation families with OCD. Each author presented a pedigree, and in all cases, the pedigree was consistent with an autosomal dominant mode of inheritance, usually with fairly high penetrance.

More recently, genetic linkage assays have revealed loci associated with the development of OCD. Jackson *et al*¹⁸ identified a mutation in *COL9A2*, located in an exon splice site which was associated with OCD lesions in two unrelated families with autosomal dominant multiple epiphyseal dysplasia. In 2010, Stattin *et al*¹⁹ conducted a genome wide linkage study in the same series of patients they described in their 2008 family study¹⁵ and identified the aggrecan (*ACAN*) gene as a prime candidate locus for OCD.

Discussion

The wide disparity in the literature regarding the cause of OCD suggests a poor understanding of its pathophysiology. While in 1979 Petrie¹⁷ concluded that OCD was not caused by genetic predisposition, it is important to remember that many cases of OCD are asymptomatic, and that asymptomatic relatives who may have had OCD were not examined in this study.

We reviewed 35 research articles related to the genetics of OCD; however, 34 were of a low level of evidence (≤ 4). The genome wide linkage study conducted by Stattin *et al*¹⁹ was the only high quality study that we found in our systematic search of the literature. In this study, the authors identified one candidate gene, *ACAN*, linked to the development of OCD.

Conclusion

The evidence in the literature for a genetic nature of OCD is predominantly of low quality. One candidate gene has been identified in a single genome wide linkage study, though the majority of published findings are inconclusive. Future studies of higher quality must be conducted to determine the genetic nature of OCD.

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