Introduction

Osteochondritis Dissecans (OCD) is a focal, idiopathic alteration of subchondral bone or epiphyseal cartilage with risk for instability and disruption of adjacent articular cartilage that may result in premature osteoarthritis. Prevalence has been estimated at 15 to 29 cases per 100,000 individuals and most commonly affects males between the ages of 10 to 20 years old. OCD can be separated into juvenile and adult forms based on skeletal maturity. The juvenile form of OCD occurs in patients with open growth plates while the adult form refers to cases diagnosed after growth plate closure. While originally described by König in 1887, the pathogenesis of OCD has yet to be fully explained. Current theories provide support for repetitive microtraumas, focal ischemic insults to the subchondral bone, and genetics. Mechanical factors, such as repetitive microtraumas, are an intuitive theory behind the etiology of OCD as the most common lesion site, the medial femoral condyle, lends itself to impingement by the tibial eminence during internal rotation with extension. In fact, the Wilson test, a provocative maneuver where the knee is extended from a flexed position and internally rotated, impinges the tibial eminence into the medial femoral condyle and elicits pain if medial femoral condyle OCD is present. However, other factors are likely at play given OCD lesions in other locations, the numerous cases of near identical OCD in monozygotic twins, familial cases of OCD, and reports of syndromic OCD cases associated with ACAN and COL9A2 mutations.

One of the last comprehensive reviews on the role of genetics in human OCD was performed in 2012. The group reported on numerous twin and familial studies that established a genetic basis for OCD. However, literature describing specific gene involvement was at its infancy. They did report on the isolation of a COL9A2 mutation and identification of ACAN mutations, both thought to be involved in OCD pathogenesis. The goal of this systematic review was to identify new literature published on the role of genetics in OCD pathogenesis since 2012.

Methods

Two computer databases were utilized to identify pertinent articles. Medline and EMBASE were queried for the terms “osteochondritis dissecans” AND “genetics” OR “genetic” OR “family” OR “familial” OR “twin” OR “twins” OR “triplet” OR “triplets” OR “heritable”. Additionally, reference lists were cross-referenced to ensure no additional articles were missed. Only articles written or translated into English that were published from 2012 to 2021 were included. Animal studies, in-vitro studies, reviews, opinions, and editorial articles were excluded.

A total of 48 unique articles were identified by title between EMBASE and Medline. Of these, 12 met full inclusion/exclusion criteria. A manual search of references of the reviewed articles did not reveal any additional papers. Of the original 48 articles, 30 were eliminated based on title. The remaining 18 articles were all read in full. After full text analysis 12 articles remained (Figure 1) detailing 35 unique patients. Studies were predominantly level 4.

Results

Since the last systematic review in human subjects, the literature has continued to produce case series highlighting twin and familial cases of OCD. One group identified two cases of bilateral OCD of the capitellum in fraternal twins. No known trauma was reported prior to the cases and the bilateral disease progression, right worse than left, was near identical in each brother. Another study identified 3 incidences of OCD occurring in the bilateral femoral heads of 3 family members. The three cases occurred in a father, a nephew, and the father’s son at 11, 9, and 9 years of age, respectively. There were no histories of significant trauma in these cases either. Similarly, a case series of a mother and daughter with identical, bilateral medial femoral condyle OCD lesions was published in 2015. The mother’s monozygotic twin sister was also found to have a unilateral medial femoral condyle OCD lesion. A separate group identified two pairs of monozygotic twins each presenting with nearly identical clinical courses. Both pairs suffered from unilateral dominant knee...
OCD with overlapping time periods providing further support of a genetic component to OCD. A 2013 study identified another incidence of near identical OCD lesions occurring in monozygotic twins.\(^\text{16}\) Again, there was no known history of trauma, their clinical courses had near identical timelines, and both lesions were located in the lateral trochlea of the same knee. Lastly, one final incidence of familial OCD in the proband as well as the father and paternal uncle.\(^\text{23}\) In addition, 15 other probands were found with ACAN variants. All suffered from short stature and brachydactyly, but only the aforementioned variant was associated with OCD. Similarly, a 2017 study found early onset osteoarthritis in 12 out of 20 families with heterozygous ACAN mutations.\(^\text{30}\) Three of these families exhibited mutations related specifically to OCD. The mutations included two c.7429G>A substitutions and a c.7064T>C substitution in another family. The two c.7429G>A mutations were located within the C-type lectin binding domain which is thought to be an integral component of the core protein structure.

To further elucidate the molecular and genetic etiology of OCD, a 2016 study isolated bone marrow mesenchymal stromal cells (BM-MSCs) and cartilage derived from induced pluripotent stem cells (iPSCs) from patients with known familial OCD.\(^\text{21}\) Their work shed light on the molecular phenotype of C-type lectin binding domain mutations in OCD patients. The mutations resulted in poor structural integrity of the induced chondrocytes, increased aggrecan protein build up within the endoplasmic reticulum opposed to the extracellular matrix, and overall cellular matrix dysregulation.

In addition to focusing on the role of the ACAN, a 2017 study published the first genome wide association study (GWAS) identifying candidate loci for juvenile osteochondritis dissecans.\(^\text{22}\) While no single nucleotide polymorphism (SNP) reached the threshold for genome-wide significance, one SNP, rs1464500, lies within the coding region of a known transcription factor important for cartilage development, SOX5. This makes rs1464500 a SNP of interest for future studies.

**Discussion**

Significant findings regarding the role of ACAN mutations have been reported since the last major review on topic.\(^\text{7}\) Most interesting are the group of mutations located within the C-terminal of the C-type lectin domain of the protein, which were also supported by earlier authors’ work.\(^\text{10}\) While the ACAN codes for aggrecan, a proteoglycan core protein that is ubiquitous in cartilage, the protein is also responsible for cartilage structure and growth.\(^\text{24}\) The molecular analysis of chondrocytes derived from patients with familial OCD determined that mutations in this specific coding region, while predominantly missense mutations, have serious effects on chondrocyte integrity and extracellular matrix regulation.\(^\text{21}\) Lastly, the significant population of twins and familial cases of OCD without syndromic features continues to be noteworthy. While most of these studies have lacked genetic analysis, identification of rs1464500 as a SNP of interest supports the idea of alternative genetic pathways in the development of OCD.\(^\text{22}\) Of note, a 2014 review article highlighted several GWAS studies on osteochondrosis in horse and swine populations and how identifying these candidate genes in the animal population can improve our understanding of OCD in humans.\(^\text{25}\) In agreement with the aforementioned review, further GWAS analyses of human patients are needed.
Conclusion

Overall, the vast majority of the literature consisted of small case series, and thus, the quality of evidence remains low. This is likely due to the rarity of OCD and the difficulty of performing large genome wide studies. However, significant expansion of the literature detailing the pathogenesis of ACAN mutations has further solidified the role of a genetic basis in familial and syndromic cases of OCD.

References