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HIP

Identification of protective and 'at risk' HLA genotypes for the development of pseudotumours around metal-on-metal hip resurfacings

A CASE-CONTROL STUDY

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Aims

Hip resurfacing remains a potentially valuable surgical procedure for appropriately-selected patients with optimised implant choices. However, concern regarding high early failure rates continues to undermine confidence in use. A large contributor to failure is adverse local tissue reactions around metal-on-metal (MoM) bearing surfaces. Such phenomena have been well-explored around MoM total hip arthroplasties, but comparable data in equivalent hip resurfacing procedures is lacking. In order to define genetic predisposition, we performed a case-control study investigating the role of human leucocyte antigen (HLA) genotype in the development of pseudotumours around MoM hip resurfacings.

Methods

A matched case-control study was performed using the prospectively-collected database at the host institution. In all, 16 MoM hip resurfacing 'cases' were identified as having symptomatic periprosthetic pseudotumours on preoperative metal artefact reduction sequence (MARS) MRI, and were subsequently histologically confirmed as high-grade aseptic lymphocyte-dominated vasculitis-associated lesions (ALVALs) at revision surgery. 'Controls' were matched by implant type in the absence of evidence of pseudotumour. Blood samples from all cases and controls were collected prospectively for high resolution genetic a nalysis targeting 11 separate HLA loci. Statistical significance was set at 0.10 a priori to determine the association between HLA genotype and pseudotumour formation, given the small sample size.

Results

Using a previously-reported ALVAL classification, the majority of pseudotumour-positive caseswere found to have intermediate-grade group 2 (n = 10; 63%) or group 3 (n = 4; 25%) histological findings. Two further patients (13%) had high-grade group 4 lesions. HLA-DQB1*05:03:01 (p = 0.0676) and HLA-DRB1*14:54:01 (p = 0.0676) alleles were significantly associated with a higher risk of pseudotumour formation, while HLA-DQA1*03:01:01 (p = 0.0240), HLA-DRB1*04:04:01 (p = 0.0453), HLA-C*01:02:01 (p = 0.0453), and HLA-B*27:05:02 (p = 0.0855) were noted to confer risk reduction.

Conclusion

These findings confirm the association between specific HLA genotypes and the risk of pseudotumour development around MoM hip resurfacings. Specifically, the two 'at risk' alleles (DQB1*05:03:01 and DRB1*14:54:01) may hold clinical value in preoperative screening and prospective surgical decision-making.

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Introduction

With increasing accessibility to personal genetic information worldwide, we are likely to see a sharp rise in the application of patient-specific genomic data to various clinical settings. These data may be used for the purposes of understanding the aetiology, prognosis, and best management of an array of conditions.[1] Oncology routinely uses the concept of patient-specific genotyping to improve outcomes by genetically characterising specific tumour traits to improve survivorship.[2]

Emerging applications using personal genetic information are already occurring in several domains of orthopaedic surgery, including hip arthroplasty. A recent Norway- and UK-based study recently identified five independent genetic signals showing suggestive association with periprosthetic osteolysis using a robust case-control approach.[3] Similarly, Koks et al[4] identified at least four single-nucleotide polymorphisms (SNPs) with a significant negative effect on the time to implant loosening.[4] These were related to the specific IFIT2/IFIT3, CERK and PAPPA genes. Previous work by co-authors (DSG, BAM, and APK) have already demonstrated the utility of the HLA genotype assessment in metal-on-metal (MoM) conventional total hip arthroplasty (THA) applications.[5] The current manuscript addresses the related but distinct field of MoM hip resurfacing.

While the benefits of patient-specific genomic data are significant in the medical context, this technology is still in its infancy. As more data emerge, our understanding of the complex role of patient-specific genetic information as it relates to tailored patient healthcare provision will grow and develop. In a complex multifactorial condition, such as developmental dysplasia of the hip (DDH), and where there are both environmental and genetic factors at play, Kenanidis et al[6] demonstrated that studies from different populations often report conflicting results on the same single-nucleotide polymorphism. The same may be true of other conditions, such as hip resurfacing or hip arthroplasty, and so caution should be practiced when interpreting genetic results and applying this knowledge to inform decisions around patient management. For example, it is known that in the context of pseudotumour secondary to metal debris, high levels of local cytotoxic metal ions coordinate their effect through macrophages, whereas adverse reactions to metal debris in the context of lower metal ion levels are affected through T-lymphocytes in a process physiologically-akin to a hypersensitivity reaction.[7,8] This variation in cellular involvement, which is determined by specific genotypes at differing metal ion levels, may explain why pseudotumour formation is evident in some patients and not others. For this reason, the role of HLA genotype in pseudotumour formation due to metal debris should be further investigated.

In recent history, hip resurfacing has illustrated how new technology requires stringent clinical evaluation both at pre- and post-market phases.[9] Hip resurfacing may still, however, be useful as a surgical technique for appropriately-selected patients, using implants with evidence-supported superior performance records.[10] In order to establish a body of evidence in relation to genetic predisposition, we performed a case-controlled study investigating the association between HLA genotype and the development of periprosthetic pseudotumours around MoM hip resurfacings.

Table I. ALVAL histological classification.

Group	Description
1	Dendritic synovitis
2	Synovitis with metal, plastic, or cement debris or lymphocytes present
3	Metallosis and/or marked lymphocyte infiltration
4	High-grade ALVAL or pseudotumour

ALVAL, aseptic lymphocyte-dominated vasculitis-associated lesion.

Methods

A matched case-control study was performed using the prospectively-collected database at the host institution (National Orthopaedic Hospital Cappagh, Dublin, Ireland). All MoM hip resurfacings performed in the history of the institution were assessed. A total of 392 hip resurfacings were performed by 12 surgeons between 1 February 2005 and 31 October 2007, all with greater than ten years of follow-up. Similar to recent work published by Kilb et al,[5] and given that the current study is also hypothesis-generating in relation to hip resurfacing, no formal a priori sample size calculations were made.[5] Institutional review board (IRB) approval was attained prior to conducting this study.

Inclusion criteria. Cases were defined as those patients that underwent revision THA for pseudotumour as the primary indication. In all cases, pseudotumour presence was confirmed non-invasively in the preoperative setting using conventional metal artefact reduction sequence (MARS) MRI, as per the protocol of the host institution. During revision THA surgery, intraoperative samples were collected for pathological analysis and only those patients with pseudotumour confirmed on histology were included as cases. The histological classification system to describe aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL) defined by Kurmis et al[11] was used to describe our findings (Table I and Table II).

Controls were matched by index implant type. Two separate implants were used exclusively during the data collection time period and included the Articular Surface Arthroplasty (ASR; (DePuy, USA) and the Birmingham Hip Resurfacing (BHR; Smith & Nephew, USA). Previously published data using this same cohort confirmed superior outcomes using the BHR, and so this strategy of implant matching was considered a reasonable

Table II. Case-control baseline comparison.

Variable	Case	Control	p-value
Implants, %			**1.000***
ASR	55	55	
BHR	45	45	
Head size, mm, range	46 to 55	50 to 54	0.086‡
Sex, n			**< 0.001†**
Male	6	17	
Female	10	N/A	
Mean age, yrs (SD)	49.5 (9.558)	50.4 (9.314)	0.791‡
Mean BMI, kg/m^2 (SD)	30.8 (5.699)	28.1 (4.912)	0.337‡

*Fisher's exact test.
†Chi-squared test.
‡Two-sample *t*-test with equal variances.
ASR, Articular Surface Replacement (DePuy, USA); BHR, Birmingham Hip Resurfacing (Smith & Nephew, USA); SD, standard deviation.

approach for control selection.[12] For all controls, all implants remained in situ at the time of review, none were scheduled for revision for any reason, and all controls had undergone MARS MRI scans confirming no radiological evidence of pseudotumour.

In the absence of robust population data to guide sample size selection, we adopted an approach similar to that of Kilb et al,[5] with an a priori target of 20 cases and 20 matched controls. Due to difficulties associated with patient attendance in hospital and recruitment into research studies imposed by the COVID-19 pandemic, a final total sample size of 33 (16 cases and 17 controls) was achieved.

Genetic testing. Blood samples were referred to the National Histocompatibility and Immunogenetics Reference Laboratory (NHIRL) at the Irish Blood Transfusion Service for genetic testing. Using the MagNA Pure Compact System (Roche, Germany), DNA was extracted according to the manufacturer's instructions. All samples were genotyped at the 11 HLA loci (A, B, C, DRB1, DRB3/4/5, DQA1, DQB1, DPB1, DPA1) by Next Generation Sequencing (NGS) on the illumina MiSeq System (illumina, USA) using the AllType NGS 11-loci amplification kit (One Lambda, USA), according to the manufacturer's instructions. The final HLA genotypes were assigned using TypeStream Visual (TSV) NGS Analysis Software version 1.3 (One Lambda).

Statistical analysis. An odds ratio (OR) was intended to be used to quantify the clinical association between HLA genotype and the need for revision surgery due to pseudotumour. Statistical significance of the OR was set at 0.10 a priori and determined using Fisher's exact test or chi-squared test (if numbers per group were five or more) given the small sample size. Interval independent and categorical dependent variables were analyzed using a two-sample *t*-test with equal variances. Categorical independent and categorical dependent variables were assessed using Fisher's exact test or chi-squared test depending on whether there were five or more samples per group. Genotype data from all study participants were also compared with healthy, matched national population norms.[13] This comparison functioned as a population control reference for each allele. The level of statistical significance was set at $p < 0.05$ for all other analyses. The statistical software used was Stata (version 13.1; StataCorp, USA).

Results

Demographics. Both groups were precisely matched for implant type (55% ASR, 45% BHR) ($p = 1.000$). Mean age in the case group was 49.5 years (standarad deviation (SD) 9.5; 95%confdence interval (CI) 43.9 to 55.0) compared to 50.4 years (SD 9.3; 95% CI 45.6 to 55.2) in the control group ($p = 0.791$). Mean BMI in the case group was 30.8 kg/m^2 (SD 5.6; 95% CI 25.5 to 36.1) compared to 28.1 kg/m^2 (SD 4.9; 95% CI 24.0 to 32.2) in the control group ($p = 0.337$). The only significant difference noted between the two groups was sex, with the case group consisting of six males and ten females. The control group consisted of males only ($p < 0.001$) (Table II). This was an ethnically homogenous group with no notable difference in ethnic origin between both groups.

Metal ions. Pre-revision cobalt ion levels in the case group were recorded at a mean of 730 nmol/l (95% CI 231.5 to 1,230.2). The control group had a mean cobalt ion level of 31 nmol/l (95% CI 16.4 to 46.8) on the most recent review ($p = 0.0011$). Pre-revision chromium ion levels in the case group were recorded at a mean of 443 nmol/l (95% CI 134.0 to 753.2) compared to the control group which had a mean chromium ion level of 35 nmol/l (95% CI 16.7 to 54.0) on the most recent review ($p = 0.0016$).

Histological classification. According to the ALVAL histological classification described by Kurmis et al, [11] no cases were reported as having group 1 histological findings on intraoperative sampling.[11] The majority of cases were found to have intermediate-grade group 2 (n = 10; 63%) or group 3 (n = 4; 25%) histological findings. There were two patients (12%) with high-grade/group 4 features.

Genotype. From the 11 HLA loci analyzed, two alleles were significantly associated with a higher risk of pseudotumour formation (DQB1*05:03:01 and DRB1*14:54:01). Four separate alleles were associated with a decreased risk (i.e. protective against pseudotumour formation) - DQA1*03:01:01, DRB1*04:04:01, C*01:02:01, and B*27:05:02 (Table III). Because the relevant alleles were not detected in the comparison group in any case, it was not mathematically possible to calculate an OR. The p-values of the analysis are recorded here.

DQB1*05:03:01 (At risk). The DQB1*05:03:01 allele was detected in 9.3% (3/16) of cases and none of the 17 controls ($p = 0.0676$). The reference population normal DQB1*05:03:01 allele frequency is 2.6%.[13]

Table III. Human leucocyte antigen alleles associated with pseudotumour formation.

Allele	Case frequency, n (%)	Control frequency, n %)	p-value*
At risk			
DQB1*05:03:01	3/16 (9.3)	0/17 (0)	0.0676
DRB1*14:54:01	3/16 (9.3)	0/17 (0)	0.0676
Protective			
DQA1*03:01:01	0/16 (0)	5/17 (29.4)	0.0240
DRB1*04:04:01	0/16 (0)	4/17 (23.5)	0.0453
C*01:02:01	0/16 (0)	4/17 (23.5)	0.0453
B*27:05:02	0/16 (0)	3/17 (17.6)	0.0855

*Fisher's exact test.

DRB1*14:54:01 (At risk). The DRB1*14:54:01 allele was detected in 9.3% (3/16) of cases and none of the 17 controls (p = 0.0676). The reference population normal DRB1*14:54:01 allele frequency is 2.6%.[13]

DQA1*03:01:01 (Protective). The DQA1*03:01:01 allele was detected in 29.4% (5/17) of controls and none of the 16 cases (p = 0.0240). There is no population data available for this particular allele.

DRB1*04:04:01 (Protective). The DRB1*04:04:01 allele was detected in 23.5% (4/17) of controls and none of the 16 cases (p = 0.0453). The reference population normal DRB1*04:04:01 allele frequency is 7%.[13]

C*01:02:01 (Protective). The C*01:02:01 allele was detected in 23.5% (4/17) of controls and none of the 16 cases (p = 0.0453). The reference population normal C*01:02:01 allele frequency is 28%.[13]

B*27:05:02 (Protective). The B*27:05:02 allele was detected in 17.6% (3/17) of controls and none of the 16 cases (p = 0.0855). The reference population normal B*27:05:02 allele frequency is 4.2%.[13]

There were no other specific HLA alleles identified with significant risk-modifying effects (i.e. increased risk or protective effect) in relation to pseudotumour formation around MoM hip resurfacings.

Discussion

It is widely acknowledged that MoM hip resurfacings have historically been associated with some of the most catastrophic complications seen in modern orthopaedics. Such a significant implant failure rate had not previously been seen on such a large scale across the global orthopaedic community prior to the introduction of the ASR MoM resurfacing. A global recall of this implant type followed on 24 August 2010, but the ramifications of this problematic implant have been endured by many patients and orthopaedic surgeons across the world to this day.[14]

Many risk factors likely contributed to the high failure rates associated with these implants. Female sex, smaller head sizes, cup inclination angles of > 55˚, and predisposing hip disorders (e.g. DDH) were all associated with decreased implant survivorship.[15] Perhaps the largest contributor to metal ion release and pseudotumour formation was the specific implant design. High clearance designs, such as the ASR, were intended to increase the range of hip motion in a high demand cohort. Unknowingly, this subtle alteration in component design from the long-standing BHR to the new ASR lead to an increase in edge loading with accelerated release of metal ions and subsequent pseudotumour formation. For this reason, long-term survivorship analyses demonstrate grossly inferior results of the ASR when compared to hip resurfacing designs with slightly less radial clearance (such as the BHR).[16] In fact, the BHR, which was approved by the US Food and Drug Administration in 2006, continues to demonstrate only a 7.1% cumulative percentage revision rate (CPRR) for all hips at ten years, and an impressive 96% all-cause survivorship in male patients aged less than 65 years.[17] Excellent hip function remains possible with the BHR, and many surgeons continue to advocate for its use, despite the global controversy associated with MoM bearings.[18]

Many patients with high risk factors do not develop pseudotumours, and many patients without these risk factors may proceed to develop pseudotumours. We postulate that this is a complex multifactorial issue whereby the role of genetics is likely to play a very important role. The results presented herein go some way to supporting this thesis. We report on two specific 'at risk' HLA alleles (DQB1*05:03:01 and DRB1*14:54:01) that were deemed to confer a higher risk for pseudotumour development when compared to a baseline population. Both of these genotypes were greater than three-times more frequent in the case group than the disease-free control cohort.

There were also four 'protective' alleles identified. The strongest statistically significant association for a protective genotype was seen with HLA-DQA1*03:01:01. This allele was detected in five of the 17 controls, and none of the 16 cases. The strength of these findings lies in the fact that the case group and control group both had equal numbers of ASR and BHR implants. This further supports the argument that metal ion release and pseudotumour formation are not simply implant-related phenomena, but that they are likely to have a more complex process playing out at the cellular and genetic level.

From a cellular perspective, the Th-1 cell-mediated inflammatory pathway is known to play a key role in the development of pseudotumours.[7] Individual patient affinity for pseudotumour formation may be affected through this cellular mechanism based on specific patient genotypes. Paukkeri et al.[8] explored the adverse reaction to metal debris at the cellular level in failed MoM hip resurfacings.[8] While high levels of local cytotoxic metal ions coordinated their effect through macrophages, adverse reactions to metal debris in the context of lower metal ion levels were affected through T-lymphocytes in

a process physiologically-akin to a hypersensitivity reaction. This variation in cellular involvement, which is determined by specific genotypes at differing metal ion levels, may explain why pseudotumour formation is evident in some patients and not others. We foresee a time in the realistic future where the entire genome for each patient will be readily accessible to healthcare providers, allowing patient-specific decisions to be made based on tailored risk and complication profiles using this genetic information.

In light of current evidence, we are not blanketly condoning the continued use of MoM hip resurfacing. That is not to say, however, that lessons cannot be learned from the MoM disaster. The current study relates to the developing role of patient-specific genotypes and the ability to pre-empt and avoid specific surgical complications (i.e. pseudotumour) using this genetic data.[19] The interaction of patient genetic data within a wide range of medical fields seems to be inevitable for future practice. Continued increasingly robust and large-scale studies must be performed in order to create a scientific knowledge base that our patients will benefit from for years to come.

Although some meaningful results have been demonstrated in the current study, there are some acknowledged limitations. This is a small sample size due to the probing nature of this study into the relatively novel field of the role of HLA genotype in pseudotumour formation. The COVID-19 pandemic also hindered the effort to achieve a target of 20 patients per group. Recruitment of 17 controls and 16 cases was deemed to be a reasonable success given the difficulty with patient recruitment to scientific studies during the height of the pandemic. It should be noted, however, that our work represents the second largest periprosthetic ALVAL-associated study in the field of orthopaedics published to date.

In all cases, MARS MRI scanning was used to identify pseudotumours in the preoperative setting. There is evidence by Garbuz et al[20] to suggest that ultrasound has a superior sensitivity rate in the detection of pseudotumours and so it is possible that a false negative may have occurred in the control group.[20] All control group participants were also asymptomatic which further increases the likelihood that no pseudotumor was present in these cases. With a sensitivity of 92% and a specificity of 100%, and given the retrospective nature of this study, MARS MRI was considered a reasonable tool for pseudotumour detection, and one can be confident that there will likely be no false positive results given the excellent specificity of this test.

There were some imbalances in the sex characteristics of both groups. This discrepancy has occurred due to the small cohort size and retrospective nature of the study. This is an issue that can be addressed in future larger, prospective studies where all independent variables of importance can be controlled for between larger comparative groups.

In conclusion, these findings further contribute to the evolving knowledge base around specific HLA genotypes and their role in the development of periprosthetic pseudotumour formation around MoM hip resurfacings. Specifically, the two alleles at higher risk of pseudotumour formation (DQB1*05:03:01 and DRB1*14:54:01) in MoM hip resurfacing should be noted, particularly as patient-specific genotype-dependent surgical treatments continue to develop in the future. The influence of 'protective' genotypes is a relatively new extension of allele analysis in orthopaedics, and also presents an avenue for future targeted investigation.

Take home message

- There is an association between specific human leukocyte antigen (HLA) genotypes and the risk of pseudotumour development around metal-on-metal hip resurfacings.
- The two 'at risk' alleles (DQB1*05:03:01 and DRB1*14:54:01) may hold clinical value in preoperative screening and prospective surgical decision-making in future.

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- The datasets generated and analyzed in the current study are not publicly available due to data protection regulations. Access to data is limited to the researchers who have obtained permission for data processing. Further inquiries can be made to the corresponding author.

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