The genetic variations associated with time to aseptic loosening after total joint arthroplasty

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Abstract

Background

Total joint arthroplasty (TJA) is one of the most frequent surgical procedures performed in modern hospitals, and aseptic loosening is the most common indication for revision surgeries. We conducted a systemic exploration of potential genetic determinants for early aseptic loosening.

Methods

Data from 423 patients undergoing TJA were collected and analysed. Three analytical groups were formed based on joint replacement status. Group 1 were TJA patients without symptoms of aseptic loosening of at least one year, group 2 were patients with primary TJA and group 3 were patients receiving revision surgery because of aseptic loosening. Genome-wide genotyping comparing genotype frequencies between patients with and without aseptic loosening (group 3 versus groups 1 and 2) was conducted. A case-control association analysis and linear modelling was applied to identify the impact of the identified genes on implant survival with time to the revision as an outcome measure.

Results

We identified 52 SNPs with a genome-wide suggestive p-value less than 10^{-5} to be associated with the implant loosening. The most remarkable odds ratios were found with the variations in the *IFIT2/IFIT3* (OR 21.6), *CERK* (OR 12.6) and *PAPPA* (OR 14.0) genes. Variations in the genotypes of four SNPs - rs115871127, rs16823835, rs13275667 and rs2514486 - predicted variability in the time to aseptic loosening. The time to aseptic loosening varied from 8 to 16 years depending on the genotype, indicating a substantial effect of genetic variance.

Conclusion

Development of the aseptic loosening is associated with several genetic variations and we identified at least four SNPs with a significant effect on the time for loosening. These data could help to develop a personalised approach for TJA and loosening management.

Keywords: arthroplasty, replacement, osteoarthritis, joint prosthesis, aseptic loosening, GWAS

Introduction

Aseptic loosening is a significant complication following prosthetic arthroplasty, which reduces implant survival and is a leading cause of revision surgery [1]. Aseptic loosening, or adverse immune reaction (AIR), is a complex reaction thought to be driven by a chronic immune activation that leads to osteolysis [2]. The probability of developing an osteolytic response is likely to be a combination of environmental and genetic factors, since susceptibility to osteolysis is variable between individuals with identical implant types [3]. Environmental factors (such as implant material), in combination with genetic susceptibility, may trigger an immune response to the implant, resulting in implant-induced osteolysis.

The mechanism of immune system activation and osteolysis appears to differ depending on the implant material. Metal-on-metal (MoM) constructs are thought to generate small metallic wear debris, which typically triggers a lymphocyte-mediated immunological response [4, 5], although activation of innate immunity that involves Toll-like receptors has also been demonstrated [6]. Metal-on-polymer (MoP) devices generate both small and sizeable polymeric wear debris that triggers an innate immune response through the Toll-like receptor pathway and periprosthetic tissue activation [4, 7].

In particular, the level of polyethylene (PE) wear particles correlates strongly with the degree of osteolysis [7].Although the cross-linked bearing surface of MoP implants was designed to reduce the amount of wear debris, and are generally better tolerated than MoM implants, PE particles are still capable of stimulating an inflammatory, pro-catabolic phenotype that can result in the development of osteolysis in a similar manner to MoM implants [7, 8].

Therefore, according to our present understanding, wear debris from any type of implant induces a multifaceted immune response with the generation of osteolysis that leads to aseptic loosening [9]. This simplistic model does not account for genetic susceptibility and does not explain the individual differences between patients in their risk of developing aseptic loosening.

Only a few studies have addressed the role of genetic variability in the development of aseptic loosening. In one of the early studies, SNPs in the *OPG* and *RANK* genes were found to have a positive association [3]. Subsequent research also identified the positive associations with *MBL*, *MMP-1* and *VDR* genes [10, 11]. Significant associations with *GNAS1* and *TNF* genes were initially described [12, 13], although additional analyses found no association between aseptic loosening and *GNAS1*, or with *BCL2*, *CALCA* and *P2RX7* genes [14-16]. These studies indicate that a genetic influence for aseptic loosening exists, but the results are not yet convincing.

Taken together, the role of genetic susceptibility and detailed mechanisms of aseptic loosening are still unclear. The HypOrth consortium, consisting of 8 partners from 6 different EU member states and Switzerland, was established to develop a better understanding of the mechanisms underlying aseptic loosening and the development of predictive biomarkers. The present study is a part of the HypOrth project and aims to identify genetic markers associated with aseptic loosening.

Material and methods

Study design and participants

Ethical Review boards at the University of Magdeburg and the University of Tartu approved the study protocols (IRB No 150/12 and Tartu No 227/T-14). Subjects participating in this study provided informed consent and 423 patients were recruited between September of 2013 and December of 2015. General epidemiological data for the patient cohorts are presented in Table 1. Participants were divided into three groups: patients with no symptoms of aseptic loosening who received an endoprosthesis at least one year previously (Group 1 n=156); patients undergoing primary endoprosthesis surgery (Group 2 n=163); and patients receiving revision surgery because of aseptic loosening (Group 3 n=104).

After quality control and data filtering, analysis was performed on the remaining 156 subjects in Group 1, 133 subjects in Group 2 and 97 subjects in Group 3. Blood samples were collected from each patient before surgery. Study data was collected and managed using the REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Tartu [17]. REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Sample preparation and genotyping

DNA was purified from the blood samples at the University of Tartu and the University of Magdeburg using standard protocols. Genotyping was performed with an Illumina Infinium

PsychArray v 1.3 array at the Genomics & Biomarker Core Facility at the Institute of Psychiatry, Maudsley Biomedical Research Centre. This array contains around 600,000 markers to provide high-throughput genotyping. After quality control, the association analysis was performed.

Genome-wide association analysis

A genome-wide association study of 97 cases and 289 controls was carried out using PLINK software. Survival analysis and Cow regression was performed with statistical environment R (https://www.r-project.org). Linear modelling was performed using SPSS. After quality control, a statistical analysis was performed in two stages: the association analysis was performed first, followed by linear modelling of implant survival. During the association analysis, Group 3 was tested against Groups 1 and 2, which were used as controls. In linear modelling of implant survival, only Group 3 data were used.

Survival analysis for the time from primary surgery until revision surgery was applied. Kaplan-Meier survival curves were used to compare genotype effects on survival differences. Cox proportional hazard model was used for genotype-related regression analysis of the implant survival.

Results

We initially identified 52 SNPs to be associated with aseptic loosening with at least a suggestive genome-wide significance (p-value below 10^{-5}; Table 1 and Figure 1). Several hot spots are visible on the Manhattan plot on chromosomes 2, 9, 14 and 22. The majority of SNPs were intergenic or from genes with no known function. However, several SNPs were identified in genes related to bone remodelling and inflammation. The highest odds ratio (OR) was for interferon-induced protein with tetratricopeptide repeats 2 (*IFIT2*) and 3 (*IFIT3*) genes (OR 21.6), followed by pappalysin 1 (*PAPPA*: OR 14.01) and ceramide kinase (*CERK*: OR 12.64).

We next analysed whether the identified SNPs were associated with implant survival. We identified 32 SNPs related to time to revision surgery (Table 2). We used regression modelling and survival analysis to determine the impact of genotype on time to revision surgery. Statistically significant differences between genotype and time to revision were found for SNPs rs115871127, rs16823835, rs13275667 and rs2514486 (Table 3, Figure 2). The period of implant survival between genotypes AA and AG for SNP rs115871127 differed by approximately ten years. For SNP rs16823835, the AA genotype was associated with an average implant survival of 8.3 years, the AG genotype with a survival of 12.2 years and the GG genotype with a survival of 15.5 years from primary surgery to revision, indicating a clear linear increment in the survival of the implant. Implant survival times for SNP rs13275667 genotype AA was 13.2 years, genotype AG was 8.4 years and genotype GG was 8 years from primary surgery. Finally, for SNP rs2514486, the implant lasted for 13 years in patients with a GG genotype, 9 years with a GA genotype and 7 years for AA genotypes.

The statistically significant differences were also evident in the Kaplan-Meier survival analysis, indicating the involvement of these four SNPs in implant survival (Figure 3). Cox regression confirmed statistically significant differences in survival times were related to the

166 difference in the genotypes of the four SNPs with significantly different hazard ratios (HRs)
167 (Figure 4). Rs115871127, located on chromosome 4, has a HR of 19.8, indicating its potential
168 influence on development of aseptic loosening. The other three SNPs had lower, although still
169 statistically significant, HRs from 3.8 to 4.3.
170

Discussion

Aseptic loosening is the most common reason for the failure of an artificial joint prosthesis and as such is a significant factor for requirement of revision surgery [18]. Different pathogenetic models exist, indicating that autoimmunity, particle material and size, and bone remodelling all play a role. Autoimmune responses to the implants have been found to be strongly associated with genetic variations that can explain the TJA outcome differences between patients [3]. However, whether a potential genetic predisposition to aseptic loosening exists has not been well studied. Only a few studies have addressed the problem, and these studies have only analysed associations with selected genes [12-15, 19].

In the present study, we performed a genome-wide association study to find genes and SNPs that may be associated with the development of aseptic loosening. We identified 52 SNPs with a suggestive genome-wide significance. Using linear modelling and survival analysis, we identified four SNPs with a highly significant effect on time to revision surgery. These four SNPs may be useful in the future as predictive genetic markers to identify patients with an increased risk for aseptic loosening after TJA.

The identification of several SNPs with high odds ratios related to aseptic loosening is one of our main findings. While the function of the most of these genes is not known, the finding itself is remarkable. These SNPs designate regions in the human genome that confer susceptibility to aseptic loosening. The Manhattan plot (Figure 1) suggests the presence of clusters of aseptic loosening susceptibility regions. The most prominent region seems to be on chromosome 9 (6 SNPs), followed by chromosome 14 (at least 2 associated SNPs). Clustering of these SNPs is indirect evidence that the genetic association with aseptic loosening has a functional consequence.

194 Of the genes with a known function, *CERK* encodes ceramide kinase, an enzyme that
195 is involved in ceramide metabolism and inflammation [20]. The CERK protein is involved in a
196 newly identified pathway regulating the anti-proliferative action of vitamin D3 [21]. *PAPPA*
197 encodes pappalysin 1, a metalloprotease involved in the homeostasis of insulin-like growth
198 factors [22]. Pappalysin 1 is involved in bone formation and has been implicated in the
199 pathogenesis of Ewing sarcoma [23, 24]. The list of the most significant GWAS hits also
200 included the *IFIT2* and *IFIT3* genes that are involved in the regulation of innate immune
201 response and inflammation [25]. While there is no direct evidence that the genes identified
202 in this study have a role in the development of aseptic loosening, these genes do have a
203 function in bone remodelling and immune regulation and deserve attention as indicators of
204 potentially significant and undiscovered pathways that may be future targets for therapeutic
205 intervention.
206 Previous studies have identified associations with genetic variations in *TGFB1*, *TNF*,
207 *BCL2*, *GNAS1*, *CALCA* and other genes with pre-existing molecular evidence in bone
208 metabolism or immune regulation [14, 15, 19]. These studies tested the hypothesis that
209 particular genes are involved in aseptic loosening and focused on the selected list of genes
210 based on existing information of their role in the regulation of osteogenesis [26, 27]. Selected
211 molecular targets are involved in the balance between osteolytic and osteogenic processes.
212 For instance, loss-of-function polymorphisms in the *P2RX7* gene could impair osteogenesis,
213 and a significant association between genetic variation in *P2RX7* and THA failure has been
214 found [16]. *BCL2* regulates proliferation and apoptosis in normal tissues, but it is also involved
215 in osteolysis induced by wear particles [28]. The promoter of *BCL2* has polymorphisms
216 regulating gene activity, and these polymorphisms have been studied in the context of aseptic
217 loosening [15, 29].

Similarly, *CALCA* encodes alpha-CGRP and calcitonin, which are involved in bone remodelling and particle-induced osteolysis [26, 30]. A previous study that tested whether both of these genes were associated with aseptic loosening did not find an association [15]. A more recent study identified a significant connection between *BCL2* polymorphisms and time to aseptic loosening [19]. *CALCA* and *BCL2* are good examples that even functionally-justified genes do not provide unambiguous associations in genetic association paradigms, illustrating the complexity of genome function.

The second main finding of our study was the identification of statistically significant SNPs that have an impact on the time to revision surgery, or survival of the implant. The survival differences were remarkable, with differences of between 5 and 10 years. All these SNPs had very high hazard ratios (HR). Three SNPs had HRs of approximately 4, and the fourth SNP had a HR of 19. These numbers are indicative of the enormous impact that given SNPs have on the risk of development of aseptic loosening.

The present study has several limitations. One of the limitations is the small sample size, which is not sufficiently powered to identify SNPs with smaller effects. Nevertheless, larger genetic effects on aseptic loosening were still evident, with several SNPs identified that were associated with a higher risk for the loss of implant. An additional study, with a larger sample size and additional international partners, is necessary. A new study would also serve as an independent validation of the findings presented here. The other limitation is the lack of the functional validation of the results. SNPs with statistically significant effects should have an apparent functional role, but a functional analysis was outside the scope of this study. Finally, the small sample size did not allow stratification by implant material or by any other clinically relevant characteristics that could be important in predicting implant survival.

Conclusions

In conclusion, in the current genome-wide association analysis, several genes were found to be significantly associated with aseptic loosening, with the SNPs identified in these genes showing a significant impact on implant survival. The results presented here suggest that genetic susceptibility may have a significant impact on the outcomes of the TJA and provide clear evidence for the existence of genotypes that could be utilised as markers for personalised management of TJA. However, further validation studies with independent samples are needed.

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Contribution of authors

SK performed analysis and wrote manuscript; DW helped with drafting of manuscript, FA helped to perform analysis; CHL conceived the study, organized clinical sampling in Germany, discussed results, helped with writing; JB helped with samples and analysis, discussed results; EP organised sample collection and purification, laboratory analysis; ER helped with laboratory analysis and sample collection; KM helped with clinical sampling; AM conceived the study and organised clinical sampling in Estonia

Data availability statement

Original data are available on request.

Competing interests

Authors do not have competing interests related to the present study.

Table 1. Demographics of the study groups.

Male : Female ratio	167 : 256
Group 1 : Group 2 : Group 3 ratio before QC	156 : 163 : 104
Group 1 : Group 2 : Group 3 ratio after QC	156 : 133 : 97
Magdeburg : Tartu sites	220 : 203
Mean age during revision ± SD	68.9 ± 10.3
Mean age during primary surgery ± SD	58.9 ± 11.9
Mean age during inclusion to study ± SD	68.16 ± 8.9
Mean duration to revision ± SD, years	10.1 ± 6.55

Table 2. Association with the aseptic loosening for 52 SNPs with suggestive p-values

SNP	Chromosome	Position	Major/Minor Allele	Gene	Minor Allele Frequency	P-Value	Odds Ratio
rs10131142	14	21231661	C/A	LOC107984671	0.09	4.08E-07	6.47
exm1619312	22	47108189	G/A	CERK	0.06	7.51E-07	12.64
rs10813300	9	30567014	A/C		0.44	1.53E-06	2.27
rs1885318	14	21244696	A/C	LOC107984671	0.29	2.00E-06	2.53
psy_rs72739140	9	85363649	G/A		0.08	2.32E-06	6.84
rs10969796	9	30619070	A/G		0.27	2.49E-06	2.57
1KG_2_39262640	2	39262640	D/I	SOS1	0.04	4.48E-06	NA
exm2259311	9	30647718	C/A		0.40	5.54E-06	2.21
rs1033216	9	30647718	C/A		0.40	5.54E-06	2.21
rs10962594	9	16791743	A/G	BNC2	0.21	6.97E-06	2.74
rs4699193	4	106601989	A/G	ARHGEF38	0.14	1.25E-05	3.30
psy_rs149989188	9	118954442	A/G	PAPPA	0.05	1.27E-05	14.01
rs13185834	5	10857683	C/A		0.42	1.43E-05	2.11
rs1538294	1	246146328	G/A	SMYD3	0.32	1.72E-05	2.22
rs10813260	9	30467975	G/A		0.35	1.94E-05	2.17
rs2687386	4	33288145	C/A		0.28	1.97E-05	2.30
rs2488552	9	136669004	A/G	VAV2	0.44	2.07E-05	2.06
rs3849892	9	30679704	A/G		0.25	2.33E-05	2.39
psy_rs72797226	5	151974836	C/A		0.34	3.59E-05	2.12
psy_rs72739291	9	101937605	G/A		0.06	3.94E-05	6.29
rs2377092	12	7960723	G/A		0.11	4.16E-05	3.57
exm840504	10	91066446	G/C	IFIT2	0.04	4.35E-05	21.60
exm840569	10	91099466	G/C	IFIT3	0.04	4.35E-05	21.60
rs7027645	9	30698142	G/A		0.24	4.66E-05	2.32
rs2795050	1	230504875	C/A	PGBD5	0.31	5.09E-05	2.14
rs2687463	4	33240041	A/G		0.29	5.15E-05	2.17
rs338935	1	58853893	A/C		0.25	5.55E-05	2.27
exm1387498	18	50683727	A/T	DCC	0.05	5.57E-05	7.80
kgp5187881	5	166543705	A/C		0.14	5.77E-05	2.95
rs9634217	12	95823231	A/C		0.22	5.79E-05	2.37
exm534227	6	32036788	G/A	TNXB	0.05	5.97E-05	9.32
exm2260300	14	25977770	C/A		0.05	5.97E-05	9.32
rs2280302	9	97349520	A/G	FBP2	0.07	6.03E-05	4.92
psy_rs182382303	19	29695986	A/G		0.07	6.03E-05	4.92
rs12486758	3	20907259	G/A		0.12	6.07E-05	3.25
rs4396955	4	169845720	G/A	PALLD	0.04	6.09E-05	0.24
kgp10945711	4	169850155	A/C		0.04	6.09E-05	0.24
rs17054604	4	169909593	G/A	CBR4	0.04	6.09E-05	0.24
rs6940071	6	22404476	A/G		0.31	6.12E-05	0.50
rs2059764	12	11503205	G/A		0.51	6.75E-05	1.94
kgp11611891	12	87552248	A/G		0.15	6.87E-05	2.75
rs7223173	17	18805887	G/A	PRPSAP2	0.30	7.11E-05	0.50
kgp971099	12	86996435	A/C	MGAT4C	0.18	7.33E-05	2.55
rs7966441	12	41981726	A/C		0.18	7.36E-05	2.58
rs562445	1	166730812	G/A		0.09	7.50E-05	0.36
exm2262088	6	165493183	A/G		0.20	7.52E-05	0.46
psy_rs13095942	3	65278571	A/G		0.11	7.56E-05	3.39
rs9671539	14	21203159	G/A		0.11	7.56E-05	3.39
rs920233	3	127295084	G/A	TPRA1	0.37	8.56E-05	2.01
rs16924281	8	59845715	G/A	TOX	0.11	8.98E-05	3.23
rs1029723	17	54767548	A/G		0.44	9.03E-05	1.94
rs9509986	13	22630930	C/A		0.26	9.20E-05	2.19

Table 3. SNPs predicting implant survival in linear model.

SNP	Chromosome	Position	Gene	Beta	R^2	T	P-Value
rs115871127	4	34860320		12.09	0.22	5.24	9.83E-07
rs16823835	2	145288341	LOC101928455	3.99	0.20	4.93	3.48E-06
rs13275667	8	5092970		-3.07	0.19	-4.69	9.19E-06
rs2514486	11	80975989		-3.01	0.19	-4.68	9.35E-06
rs10859419	12	93452175	LOC643339	4.82	0.18	4.59	1.37E-05
rs7190447	16	16289126	ABCC6	5.32	0.18	4.58	1.43E-05
rs6894296	5	179532944	RASGEF1C	3.53	0.18	4.55	1.58E-05
rs1393097	5	28286502		3.31	0.17	4.46	2.26E-05
rs6798584	3	8548827	LMCD1	3.12	0.17	4.42	2.64E-05
exm567347	6	97414949	KLHL32	7.21	0.17	4.40	2.84E-05
exm1066643	13	44411432	CCDC122	4.62	0.17	4.40	2.84E-05
rs7043949	9	2651809	VLDLR	9.42	0.17	4.38	3.04E-05
rs2063572	9	2663639		9.42	0.17	4.38	3.04E-05
rs6540172	16	88151971		3.37	0.17	4.37	3.13E-05
rs11126167	2	68115179		-3.22	0.16	-4.33	3.70E-05
rs1503236	2	68138786		-3.04	0.16	-4.29	4.27E-05
rs6704741	2	68149455		-3.08	0.16	-4.28	4.40E-05
rs429963	12	117170989	C12orf49	-3.01	0.16	-4.22	5.62E-05
rs4798656	18	8579817		2.93	0.16	4.21	5.71E-05
rs4959299	6	4492079		-3.39	0.16	-4.21	5.73E-05
rs9392718	6	5831567		-2.82	0.16	-4.21	5.86E-05
rs7203013	16	6964963	RBFOX1	3.50	0.16	4.20	6.10E-05
rs797827	7	83583757		2.83	0.16	4.19	6.33E-05
rs10515721	5	154527802		6.89	0.15	4.17	6.71E-05
rs67411719	19	3052907	AES	5.54	0.15	4.15	7.20E-05
rs2012125	19	1630341	TCF3	3.36	0.15	4.12	7.99E-05
rs768082	11	29037522		3.27	0.15	4.12	8.10E-05
exm1100436	14	50788213	ATP5S	-2.93	0.15	-4.10	8.82E-05
rs2275592	14	50788213	ATP5S	-2.93	0.15	-4.10	8.82E-05
exm1100483	14	50799126	CDKL1	-2.93	0.15	-4.10	8.82E-05
rs13282938	8	3196760	CSMD1	3.71	0.15	4.10	8.83E-05
rs1052651	12	96052721	NTN4	2.87	0.15	4.07	9.74E-05

Legends to the figures

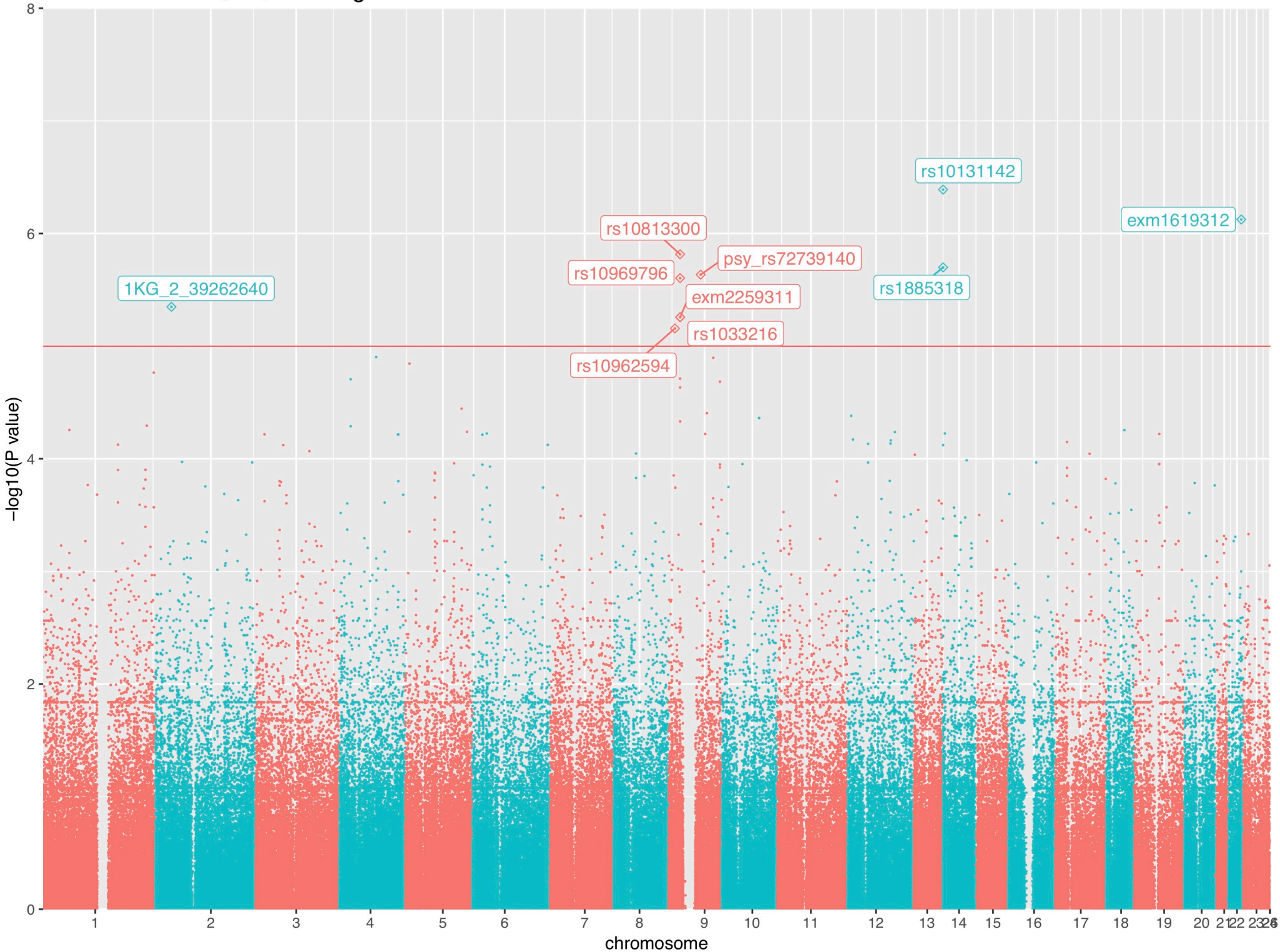
Figure 1. Manhattan plot of the GWAS results. Ten of the most significant SNPs are labelled. The majority of SNPs are in the chromosome 9.

Figure 2. Time to revision surgery (implant survival) in years, in relation to the genotypes of SNPs rs16823835, rs2514486, rs13275667 and rs115871127. A clear linear relationship is evident, and all SNPs had a statistically significant effect over the implant survival.

Figure 3. Kaplan-Meier survival graphs indicating relationship between genotype and time to develop aseptic loosening.

Figure 4. The Cox regression modelling identified significant hazard ratios in development of aseptic loosening related to the genotypes of four SNPs.

Manhattan Plot for group 3 Figure 1




Implant survival and rs16823835 genotype
Implant survival, years
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12
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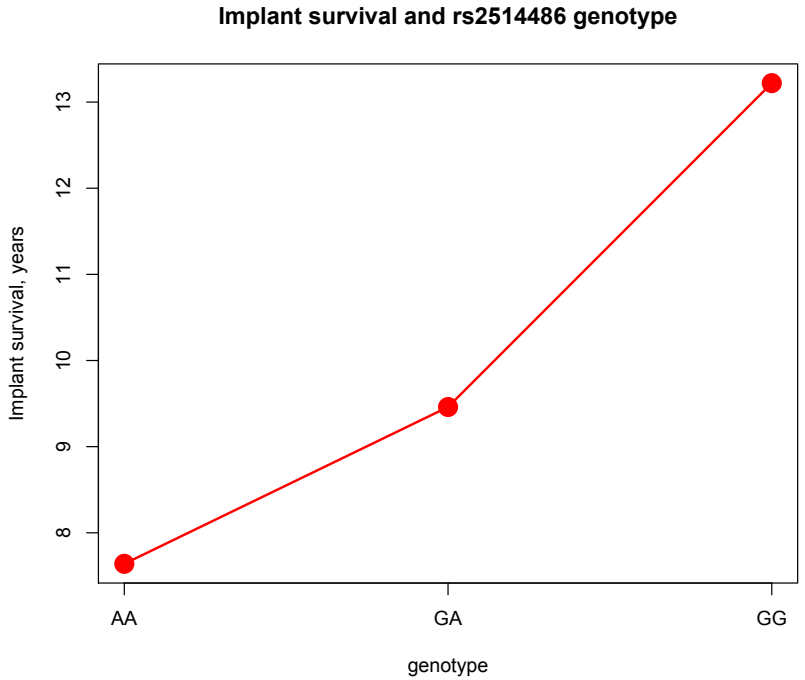
GG
genotype


Implant survival and rs2514486 genotype
Implant survival, years
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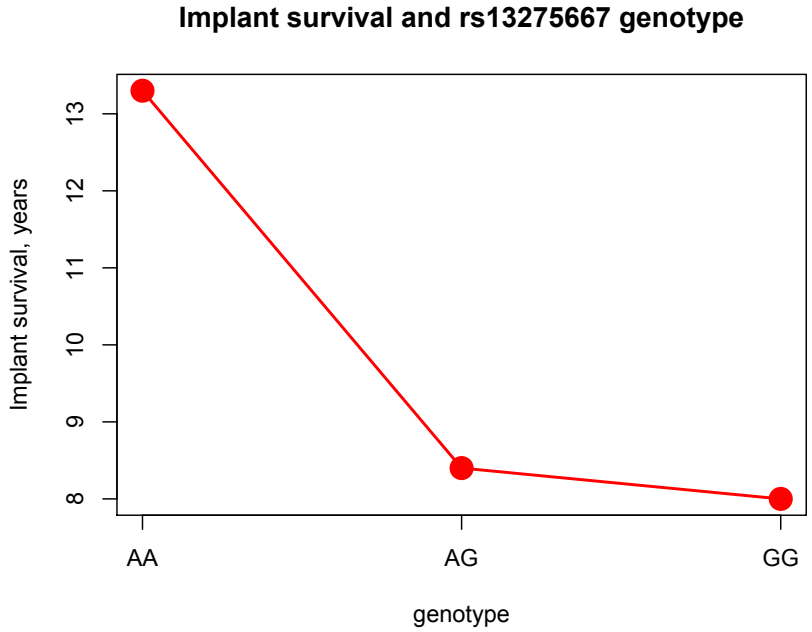
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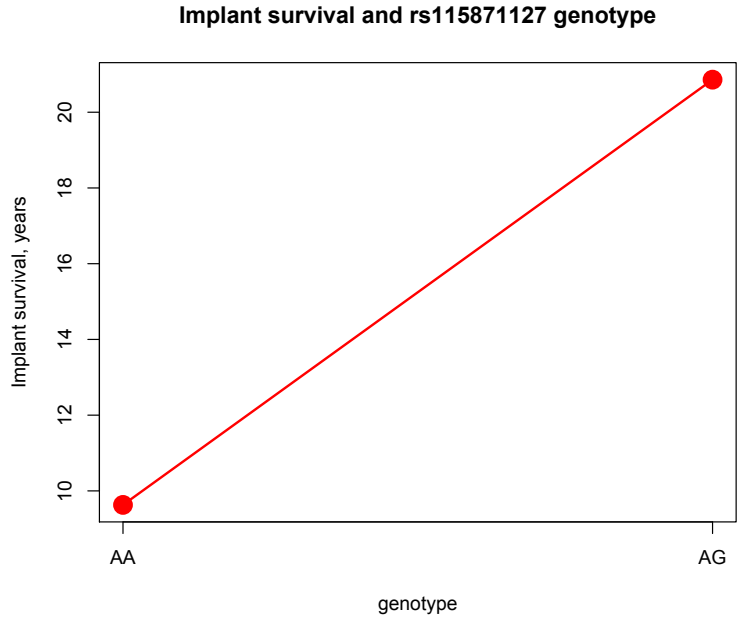
Implant survival and rs115871127 genotype
Implant survival, years
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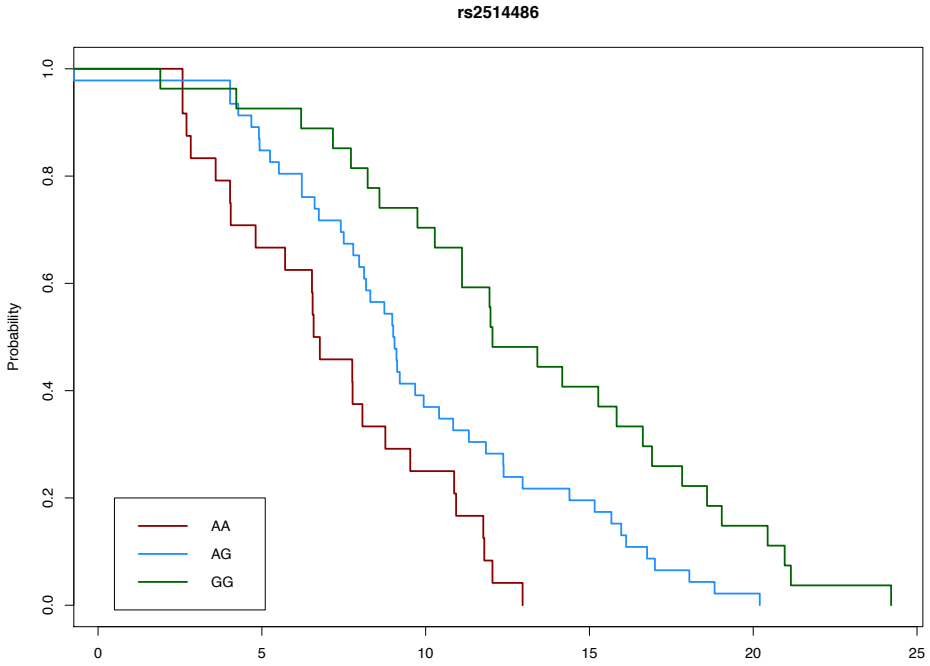
16
18
20
AA
AG
genotype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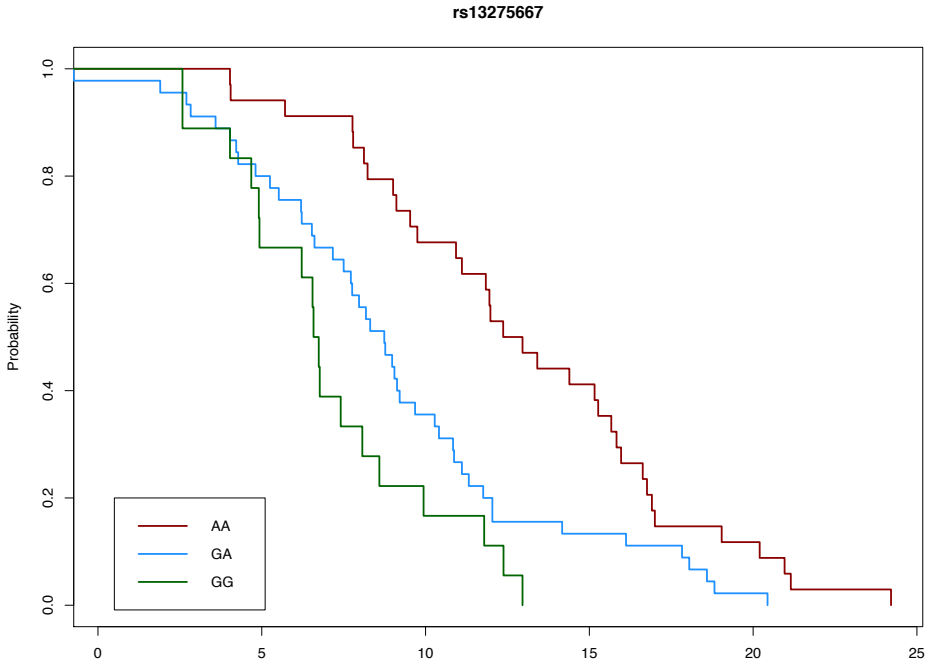
Probability
AA
AG
GG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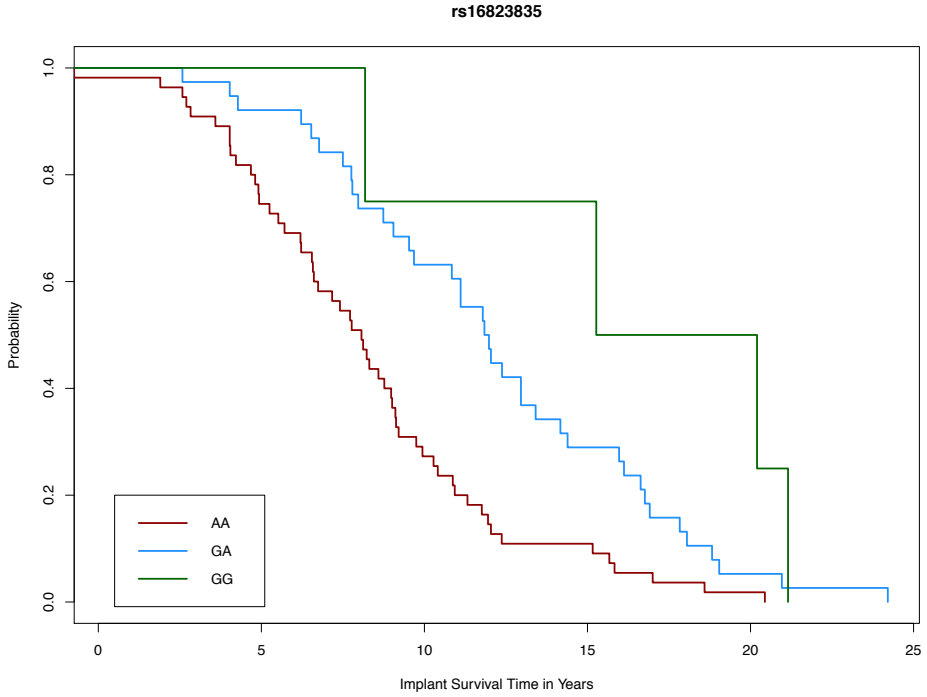
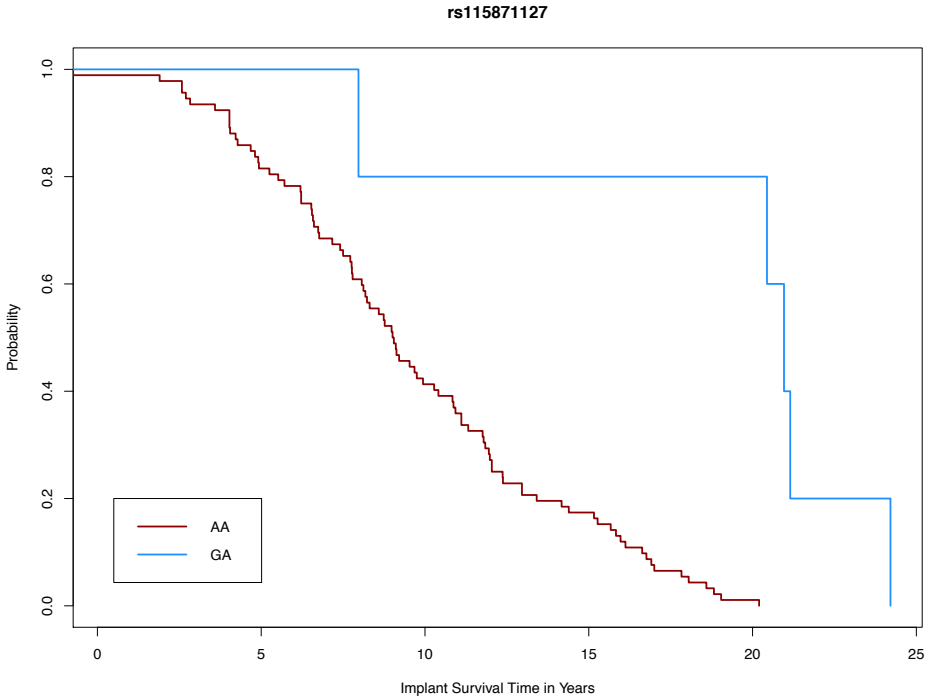
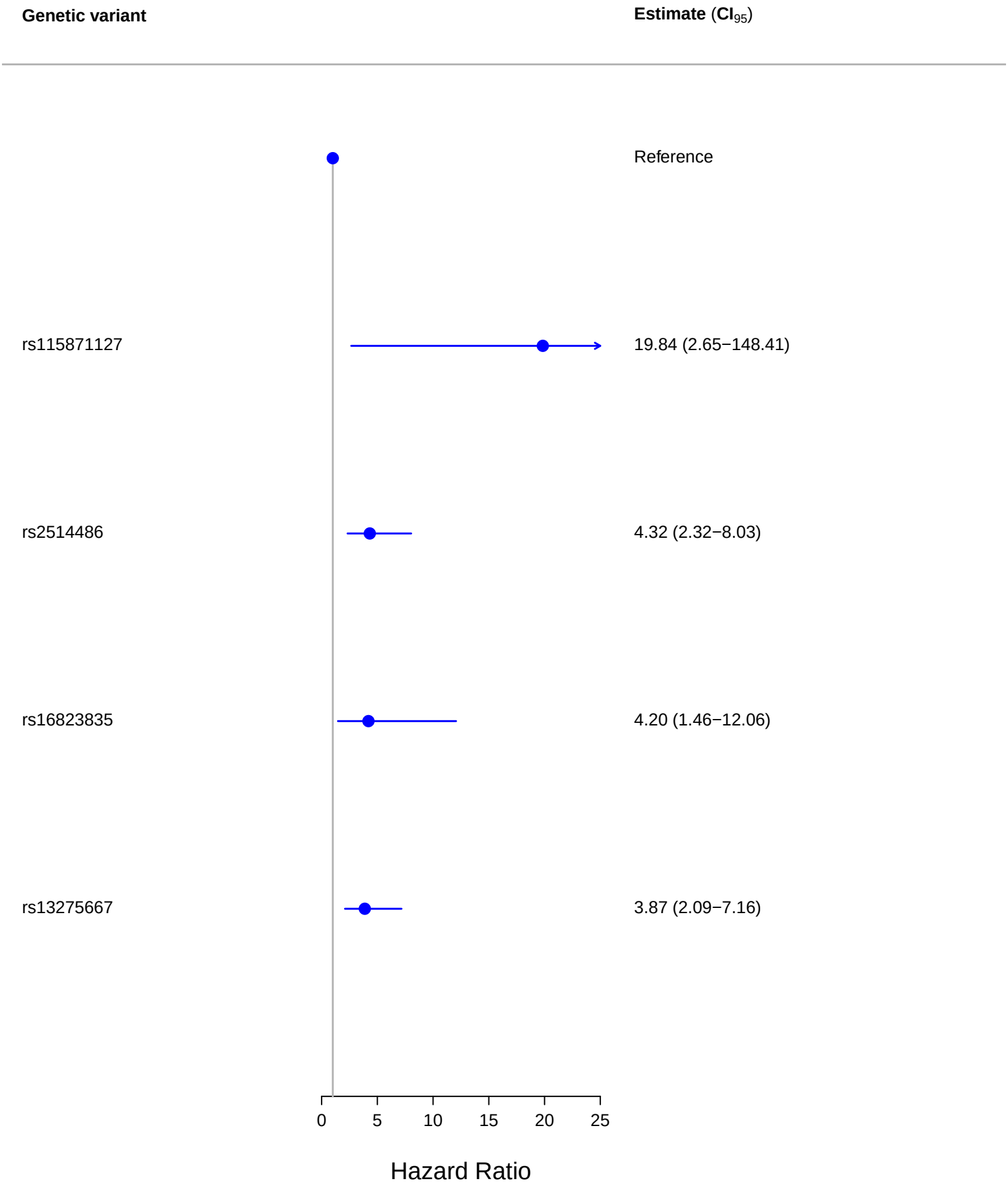
Probability
AA
GA
GG


rs16823835
Probability
AA
GA
GG
Implant Survival Time in Years


rs115871127
Probability
AA
GA
Implant Survival Time in Years


Genetic variant
Estimate (CI95)
Reference
rs115871127
19.84 (2.65−148.41)
rs2514486
4.32 (2.32−8.03)
rs16823835
4.20 (1.46−12.06)
rs13275667
3.87 (2.09−7.16)
0
5
10
15
20
25
Hazard Ratio

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