INTRODUCTION

Psoriasis is a common skin disease characterized by an inflamed, red scaly skin that affects 2–4% of the world’s population. Psoriasis involves a dysregulated immune system and is regarded as a T cell-mediated immune disease with a mixed upregulation of T helper type 1/17 (Th1/Th17) cytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL)-12, IL-23, interferon-γ (IFN-γ) and IL-17A. Biological drugs targeting TNF-α (infliximab, adalimumab, etanercept) and the p40 subunit of IL12 and IL23 (ustekinumab) are essential for treatment of patients with severe psoriasis. However, approximately one-third of the patients do not respond to a specific treatment and require a change in treatment. The consequences of this ‘trial and error’ policy results in periods of nonoptimal treatment for the patient and increased treatment costs, thus calling for ways of identifying the best treatment for each patient. Pharmacogenetics might be a way of predicting treatment response. However, little is known regarding the interaction between genetics and biological drugs in relation to psoriasis. Pharmacogenetics has been more thoroughly investigated in inflammatory bowel disease and rheumatoid arthritis, where polymorphisms in genes encoding Toll-like receptors (TLRs) and NOD-like receptors have been found to be associated with response to anti-TNF drugs. Nuclear factor-κB plays a major role in controlling inflammation and is an important regulator of pathways leading to expression of cytokines in psoriasis, including IL-1B. Nuclear factor-κB can be activated by TLRs and NOD-like receptors. The objective of this study was to determine whether variants in genes involved in nuclear factor-κB, TNF-α and pattern recognition (TLRs and NOD-like receptors) pathways could be used to predict response and nonresponse in patients with psoriasis who are treated either with anti-TNF or ustekinumab.

MATERIALS AND METHODS

Cohort

Blood clot samples, sent for Mycobacterium tuberculosis screening, were obtained from Statens Serum Institut (Copenhagen, Denmark); the Department of Respiratory Diseases B and the Department of Clinical Microbiology, Aarhus University Hospital (Aarhus, Denmark); the Department of Biochemistry, Hospital of Lillebaelt (Veje, Denmark); the Department of Clinical Biochemistry, Herlev and Gentofte Hospital (Hellerup, Denmark); and the Department of Biochemistry, Hospital of Slagelse (Slagelse, Denmark) from September 2009 through July 2015 as described earlier. Screening for Mycobacterium tuberculosis before initiation of treatment with biological drugs is generally performed in Denmark. Patients were identified by linking the unique personal identification number of Danish citizens (CPR number) from each blood
sample with the Danish national database DERMBIO (Figure 1). DERMBIO is a nationwide registry including all biological administered treatments for psoriasis in Denmark, with a 100% coverage of treatments administered in academic hospitals (88% of treatments) and an estimated coverage of >80% for private clinics (12% of treatments). Prospective data were collected from DERMBIO and were supplemented with and validated by information from patient records. If a patient had been given more than one anti-TNF treatment, only the first treatment was included. If a patient had been treated with both anti-TNF and ustekinumab, then both treatment series were included (Figure 1). Patient data included gender; body mass index; age at baseline and at diagnosis; Psoriasis Area Severity Index (PASI) and dermatology life quality index scores at baseline, 3 months and 6 months after initiation of the biological drug; side effects; psoriatic arthritis; concomitant methotrexate treatment; drug name; and

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Figure 1. Selection of patients included in the study.
treatment number. The baseline was defined as day of start of treatment (±14 days), the 3-month visit as 90 days (±45 days) and the 6-month visit as 180 days (±45 days). If more visits were recorded within the periods, the ones closest to the baseline and 3- and 6-month marks were chosen.

Ethical considerations
The study was conducted in accordance with the Declaration of Helsinki and was approved by the local regional ethics committees (M-20100153 and S-20120113) and the Danish Data Protection Agency (J. 2010-61-4719 and 2008-58-035). The regional ethics committees gave exemption from obtaining informed consent because information had no health-related impact on subjects.

Response criteria
We chose drug survival (the period of time that a patient receives biological treatment) to be our primary response criterion. Patients treated for 225 days (equivalent to 6 months+45 days) or more were categorized as responders. Patients who stopped treatment before 225 days were categorized as either primary nonresponders or secondary nonresponders. Patients who initially had a response (a relative reduction in PASI of at least 75%—or information from the doctor/health personnel in the patient record that a beneficial effect had been achieved), but where the response diminished over time or treatment was stopped for other reasons (for example, side effects), were categorized as secondary nonresponders, and those who never responded to treatment were categorized as primary nonresponders. Patients who stopped treatment before 225 days for other reasons than lack of effect, and where no information of response was available, were excluded from further analysis.

As our secondary response criteria, we evaluated response based on relative reduction in PASI score after 3 months. Patients who achieved reduction of <50% were categorized as being nonresponders, those with a reduction of between 50 and 75% were categorized as being intermediate responders and those with a reduction of ≥75% were categorized as being good responders. Patients with missing baseline PASI but a PASI score of 0 after 3 months (equivalent to a PASI reduction of 100%) were categorized as good responders.

Genotyping
We selected genes involved in nuclear factor-κB, TNF-α and pattern recognition pathways as described by Bank et al. and Sode et al. Briefly, candidates were found by searching for ‘polymorphism AND Gene name AND (reporter gene OR luciferase OR ELISA OR RT-PCR OR flow cytometry OR EMSA)’ and the single-nucleotide polymorphism (SNP) candidates were chosen based on the reported functionality, association with autoimmune disease, or association with response.1-4 A list of all SNPs studied is presented in Supplementary Table 1a. DNA extraction (Maxwell 16 LEV Blood DNA Kit; Promega, Madison, WI, USA) was performed as described by Bank et al.13

The polymorphisms were genotyped with PCR-based KASP genotyping assays by LGC Genomics (LGC Genomics, Hoddesdon, UK, http://www.lgcgenomics.com/). FGF2 (rs308379) and TLR10 (rs11096957) were only genotyped in 376 patients; the rest of the SNPs were genotyped in all patients. Linking disequilibrium was calculated using SNAP (http://archive.broad institute.org/mpg/snap/) using as reference the Central Europeans in the 1000 Genomes.14 As a quality control, all SNPs were replicated in 94 randomly selected samples, yielding >99% identical genotypes. The average call rate for all SNPs was >97%. None of the patients had the minor allele of IL-12RB2 (rs11810249). IL-18 (rs1827238) and IL-18 (rs360719) were in complete linking disequilibrium (r² = 1.00), and rs360719 was therefore excluded from further analysis.

Power analysis
At the 5% significance level and a minor allele frequency of 0.05, 0.25 and 0.45, we had >80% power of detecting a dominant effect with an odds ratio (OR) of 2.0, 1.8 and 2.2, respectively, for the anti-TNF cohort and an OR of 2.3, 2.2 and 3.3, respectively, for the ustekinumab cohort. The Genetic Power Calculator15 was used for power calculations, setting ‘prevalence’ to 0.33, df 1, type 1 error rate to 0.05 and number of cases and control/case ratio was based on data described in Supplementary Table 2a.

Statistical analysis
Under a dominant model logistic regression analysis was used to compare genotypes in responders against those in primary nonresponders (R vs PN), and genotypes in responders and secondary nonresponders combined against those in primary nonresponders (R+S vs PN), as genetics may not have main effects on secondary nonresponse. For our second outcome, we compared good responders against nonresponders (G vs N) and good and intermediate responders against nonresponders (G+I vs N) under a dominant model. Crude ORs and ORs adjusted for gender, age, psoriatic arthritis and previous biological treatment are reported (Supplementary Tables 3). Genotype distributions for all patients and for each outcome tested are presented in Supplementary Table 1b. We corrected for multiple testing by controlling the overall false discovery rate (FDR) at 20%,16 with computation of FDR-adjusted p-values (referred to as q-values) based on all p-values presented in Supplementary Tables 3. The q-value describes the expected proportion of false positives among all associations at least as extreme as the observed association. The χ² test was used to compare differences in categorical outcomes of clinical and demographic characteristics, and for continuous outcomes a one-way analysis of variance was used. Statistical analyses were performed using Stata version 14 (StataCorp LP, College Station, TX, USA). Computation of q-values was performed using the inbuilt p-adjust function in R (Vienna, Austria) using the Benjamini–Hochberg method.

RESULTS
Study population
A total of 480 patients with blood clot samples available were registered in DERMBIO as having psoriasis. Two patients were excluded because of participation in blinded clinical trials, leaving 478 patients with 631 treatment series. These treatment series involved 395 patients treated with anti-TNF and 236 patients treated with ustekinumab. Nineteen of the patients treated with anti-TNF were excluded from analysis because of inconclusive responses, resulting in a cohort of 376 patients treated with anti-TNF. Six of the patients treated with ustekinumab were excluded from analysis because of inconclusive responses, resulting in a cohort of 230 patients treated with ustekinumab (Figure 1). The clinical and demographic characteristics of all patients are given in Table 1, including stratification for treatment. Characteristics of all patients registered in DERMBIO are presented in Supplementary Table 2c.

Patients treated with anti-TNF
Looking at primary outcome of the 376 patients treated with anti-TNF, 294 (78%) were responders, 30 (8%) were secondary nonresponders and 52 (14%) were primary nonresponders (Supplementary Table 2a). Statistically fewer females than males responded when treated with anti-TNF (P < 0.001). Regarding secondary outcome, among patients treated with anti-TNF, 250 had PASI scores available at baseline and after 3 months. Of these, 163 (65%) were good responders, 41 (16%) were intermediate responders and 46 (18%) were nonresponders (Supplementary Table 2b). Previous treatment with ustekinumab was associated with nonresponse (P = 0.02).

Polymorphisms associated with anti-TNF treatment
Associations of each SNP and response to anti-TNF therapy were evaluated using drug survival as outcome, comparing genotypes of responders with those of primary nonresponders under a dominant model. Four of the analyzed SNPs showed nominal statistical significance (P < 0.05) for both crude and adjusted ORs (Supplementary Table 3). After controlling for the FDR, only TLR9 (rs352139) (OR: 2.42, P = 0.0044, q = 0.19) remained significant (Table 2). Associations of each SNP and response to anti-TNF therapy were then evaluated using PASI reduction as outcome, comparing genotypes of good responders with those of nonresponders under a dominant model. Six of the analyzed SNPs

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Five of the analyzed SNPs showed nominal statistical significance ($P < 0.05$) for both crude and adjusted ORs (Supplementary Table 4). After controlling for the FDR, 5 of the SNPs remained significant, whereas of the variant alleles of \textit{IL1B} (rs1143623) (OR: 0.35, $P = 0.0041$, $q = 0.19$), \textit{IL1B} (rs11436267; $r^2 = 0.83$) (OR: 0.28, $P = 0.0016$, $q = 0.19$), \textit{LY96} (rs11465996) (OR: 0.33, $P = 0.0044$, $q = 0.19$), \textit{TLR2} (rs119383228) (OR: 0.30, $P = 0.0019$, $q = 0.19$) and \textit{TLR2} (rs4696480; $r^2 = 0.48$) (OR: 0.22, $P = 0.0032$, $q = 0.19$) were all associated with nonresponse to treatment (Table 2).

Patients treated with ustekinumab
Looking at primary \textit{outcome} of the 230 patients treated with ustekinumab, 201 (87%) were responders, 2 (1%) were secondary nonresponders and 27 (12%) were primary nonresponders (Supplementary Table 2a). Previous treatment with anti-TNF was associated with nonresponse ($P = 0.02$). Regarding secondary \textit{outcome}, of the patients treated with ustekinumab, 143 had PASI scores available at baseline and after 3 months. Of these, 80 (56%) were good responders, 29 (20%) were intermediate responders and 34 (24%) were nonresponders (Supplementary Table 2b). Previous treatment with anti-TNF was associated with nonresponse ($P = 0.005$).

Polymorphisms associated with ustekinumab treatment
We then evaluated associations between SNPs and response to ustekinumab therapy using drug survival as outcome, comparing genotypes of responders with those of primary nonresponders. Five of the analyzed SNPs showed nominal statistical significance ($P < 0.05$) for both crude and adjusted ORs (Supplementary Table 5), none of which remained significant after controlling for FDR. Next, associations of each SNP and response to ustekinumab therapy were evaluated using PASI reduction as outcome, comparing genotypes of good responders with those of nonresponders under a dominant model. Six of the analyzed SNPs showed nominal statistical significance ($P < 0.05$) for both crude and adjusted ORs (Supplementary Table 6). Four associations remained significant after controlling for FDR, the variant alleles of \textit{TIRAP} (rs8177374) (OR: 9.42, $P = 0.0051$, $q = 0.19$) and \textit{TLR5} (rs5744174) (OR: 5.26, $P = 0.0012$, $q = 0.19$) were associated with beneficial response and the variant alleles of \textit{IL1B} (rs1143623) (OR: 0.22, $P = 0.0049$) and \textit{IL1B} (rs1143627; $r^2 = 0.83$) (OR: 0.24, $P = 0.0042$, $q = 0.19$) were associated with nonresponse (Table 2).

Haplotype analysis for both treatments
Polymorphisms in the \textit{IL1B} gene were associated with response to both treatments when we looked at the secondary \textit{outcome}. To assess whether any haplotypes could explain these associations, we performed haplotype analysis with PASI reduction as the response criterion (Supplementary Tables 7 and 8). Four haplotypes described all of the observed genotypes in both groups, excluding five patients who were treated with anti-TNF and four patients who were treated with ustekinumab because of missing genotypic data. With haplotype combination 11 (rs4884306AA, rs1143623GG and rs1143627TT) as reference, the haplotype combinations 22 (rs4884306GG, rs1143623CC and rs1143627CC) (OR: 0.22, 95% confidence interval: 0.05–0.95, $P = 0.043$) and 12 (rs4884306AG, rs1143623GC and rs1143627TC) (OR: 0.28, 95% confidence interval: 0.09–0.84, $P = 0.023$) were associated with nonresponse to anti-TNF (Supplementary Table 7). Haplotype combination 12 (OR: 0.12, 95% confidence interval: 0.03–0.54, $P = 0.006$) was associated with nonresponse to ustekinumab (Supplementary Table 8).

### Table 1. Clinical and demographic characters for all the patients included, the anti-TNF cohort and the ustekinumab cohort

|                          | All patients | Anti-TNF cohort | Ustekinumab cohort |
|--------------------------|-------------|-----------------|---------------------|
| **Patients, no.**        | 478         | 376             | 230                 |
| Female, no. (%)          | 193 (40)    | 145 (39)        | 107 (46)            |
| **Age, years**           |             |                 |                     |
| Age at baseline, mean (s.d.) | 44 (14)    | 43 (14)         | 44 (14)             |
| **Disease duration, years** |           |                 |                     |
| Duration at baseline, mean (s.d.) | 20 (13)   | 20 (13)         | 21 (13)             |
| BMI at baseline, mean (s.d.) | A = 295 (62%) | A = 248 (66%) | A = 133 (58%)       |
| Psoriatic arthritis, no. (%) | A = 177 (37%) | A = 146 (39%) | A = 102 (44%)       |
| Concomitant methotrexate, no. (%) | 148 (31)  | 126 (34)       | 50 (22)             |
|                          | 67 (16)     | 55 (16)         | 28 (13)             |
|                          | A = 432 (90%) | A = 340 (90%) | A = 220 (96%)       |
| **Biological treatment, no. (%)** |            |                 |                     |
| Adalimumab               | 216 (45.19) | 218 (57.98)     | —                   |
| Etanercept               | 106 (22.18) | 103 (27.39)     | —                   |
| Infliximab               | 55 (11.51)  | 55 (14.61)      | —                   |
| Ustekinumab              | 97 (20.29)  | —               | 230 (100)           |
| Efalizumab               | 4 (0.84)    | —               | —                   |
| Biological naive         | —           | —               | 358 (95)            |
|                          | —           | —               | 95 (41)             |
| **PASI scores, mean (s.d.)** |           |                 |                     |
| PASI at baseline         | 13.2 (7.8)  | 13.5 (7.8)      | 9.9 (7.2)           |
|                          | A = 365 (76%) | A = 297 (79%) | A = 185 (80%)       |
| PASI at 3 months         | 3.0 (4.0)   | 3.2 (4.2)       | 2.9 (3.6)           |
|                          | A = 329 (69%) | A = 269 (72%) | A = 165 (72%)       |
| PASI at 6 months         | 2.3 (3.5)   | 2.2 (3.1)       | 2.4 (3.4)           |
|                          | A = 291 (61%) | A = 233 (62%) | A = 146 (63%)       |

Abbreviations: A, available observations; BMI, body mass index; PASI, Psoriasis Area and Severity Index; TNF, tumor necrosis factor.
transcription of IL-1β in Caucasians, the variant alleles of these two SNPs led to increased haplotype context, which is the dominating haplotype in the results differing treatment, although the unknown function of the two SNPs makes it difficult to interpret. The same associations for IL1B (rs1143623 and rs1143627) were seen, and the same haplotype conveying increased IL-1β transcription was associated with nonresponse. The variant allele of TLR5 (rs5744174), which is related to decreased IL-1β and IL-6 mRNA, and increased levels of CCL20 (ref. 24) and INF-γ (ref. 25) were associated with beneficial response to ustekinumab, again indicating that an increased IL-1β level may be unfavorable when treating psoriasis with ustekinumab. However, the variant allele of TLR2 (rs3804099), which is related to high levels of TNF-α, IL-1β and IL-6 and a reduced MYD88 level, was nominally associated with a beneficial response, and this might indicate that not only the level of IL-1β but also the relative abundance of cytokines is crucial for response to ustekinumab treatment.

For patients treated with ustekinumab, variants related to an increased level of IFN-γ (TLR5 (rs5744174) and TIRAP (rs8177374)) appears to be associated with a beneficial response. Moreover, the variant allele of IFNG (rs2430561)—conveying high levels of IFN-γ (ref. 28,29) —was found to be nominally associated with a beneficial response to ustekinumab. Furthermore, when we adjusted for gender, age, psoriatic arthritis and previous treatments, the variant allele of TBX21 (rs17250932), which is related to decreased IFN-γ level, was nominally associated with nonresponse. IFN-γ is highly upregulated in psoriasis and is one of the genes most frequently associated with nonresponse to anti-TNF therapy.
key cytokines. A decrease in IFN-γ levels has been shown to be correlated with a decrease in PASI scores. By blocking IL-12p40, ustekinumab blocks the IL-12-dependent Th1 production of IFN-γ that could explain why a genetically determined elevated level of IFN-γ is associated with a beneficial response. However, we cannot exclude the possibility that the associations observed are because of factors other than the increased IFN-γ. Moreover, our results are supported by a Dutch pilot study in which patients who responded to ustekinumab had a strong IFN signature compared with that of nonresponders.

In order to increase the statistical power, we analyzed all anti-TNF treatments as one, a commonly used strategy. For all significant associations, except TLR9 (rs352139) and LY96 (rs11465996), similar tendencies were observed for ORs for each of the anti-TNF agents (data available on request). To our knowledge, this is one of the largest cohorts for evaluation of response in patients treated with ustekinumab and the second largest for evaluation of anti-TNF; only a Canadian study (also involving treatment primarily for psoriatic arthritis) had more patients. In the present study, some of the patients were included in both the ustekinumab cohort and the anti-TNF cohort; however, as the treatments target different pathways, including previously treated patients is a commonly used approach. Efficacy of treatments was evaluated based on both drug survival of 6 months and relative PASI reduction after 3 months. We cannot exclude that categorization of response for some of the patients may be influenced by other factors, for example, comedication, patients’ preferences or dose changes, although this is highly unlikely as these factors primarily affect the overall long-term drug survival and not the short-term response. Even though drug survival was our primary outcome, the majority of the associations were observed evaluating treatment based on PASI that could indicate outcomes based on PASI scores to be more suitable in future studies.

With increasing number of test performed, the risk of false positive associations similarly increases. To take this into account, we corrected for multiple testing by controlling the false discovery rate at 0.20. By doing so we found that eight of the SNPs evaluated were associated with response to one or both treatments and the majority were functionally and biologically plausible according to current knowledge and previous findings. Given the number of significant associations and the selected FDR of 0.20, approximately two of the reported associations would be expected to be false positives. However, by choosing functional polymorphisms possibly involved in the pathogenesis and treatment of psoriasis, we increased the a priori likelihood of true associations. The SNPs were evaluated for genotyping errors by assessing Hardy–Weinberg equilibrium. This was performed in a control group of healthy Danish blood donors as Hardy–Weinberg equilibrium cannot be assessed in the current highly selected study group of patients with psoriasis selected for treatment with biological therapy. The control group was genotyped by the same method at the same laboratory. All SNPs were in Hardy–Weinberg equilibrium. The overall characteristics of the current group resample that of the entire DERMBOI database, apart from a slightly higher proportion of female patients in the current study.

In conclusion, we have shown that genetic variants in genes that regulate cytokines involved in psoriasis are associated with response when psoriasis is treated with either anti-TNF or ustekinumab. Genetic variants related to elevated levels of IL-18 appear to be unfavorable when treating psoriasis with either anti-TNF or ustekinumab, whereas patients with genetic variants related to a high level of IFN-γ appear to be more likely to respond when being treated with ustekinumab. As none of our results have been associated with response to biological treatment of psoriasis previously, they should be validated in independent cohorts.

CONFLICT OF INTEREST
Dr Skov has received consultancy and/or speaker honoraria from Abbvie, Pfizer, Janssen-Cilag, Merck Sharp & Dohme (MSD) and LEO Pharma and is a member of the advisory boards of Abbvie, Pfizer, Janssen-Cilag, MSD, Eli Lilly, Celgene and Novartis. Dr Iversen has been a paid speaker for MSD, Pfizer, AbbVie, Almirall, Janssen-Cilag, Eli Lilly, Novartis and LEO Pharma. He has been consulting or serving on expert/advisory boards with Pfizer, AbbVie, Almirall, BMS, Janssen-Cilag, Novartis, Eli Lilly, LEO Pharma and MSD. He has served as investigator for MSD, Pfizer, AbbVie, Janssen-Cilag, Eli Lilly, Novartis, Amgen and LEO Pharma and has received research and educational grant from Pfizer, AbbVie, Novartis, MSD and LEO Pharma. Dr Gniadecki has received consultancy and speaker honoraria from Abbvie, Janssen-Cilag and Novartis and is a member of the advisory boards of Abbvie, Amgen, Janssen-Cilag, Eli Lilly, Celgen, Novartis and Therakos. Dr Dam has received compensation as a speaker and member of an advisory board for Janssen-Cilag and Abbvie. Dr Andersen has received compensation as a consultant and member of an advisory board for MSD and Janssen-Cilag.

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