Genome-Guided Proteomic Analysis Identifies Biomarkers for the Progression from Psoriasis to Psoriatic Arthritis

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Background

Early diagnosis of psoriatic arthritis (PsA) is important for psoriasis (PsO) patient management. Bloodborne protein biomarkers of early PsA would be optimal. However, few studies have identified biomarkers specific to the progression of cutaneous-only psoriasis (PsC) to PsA.
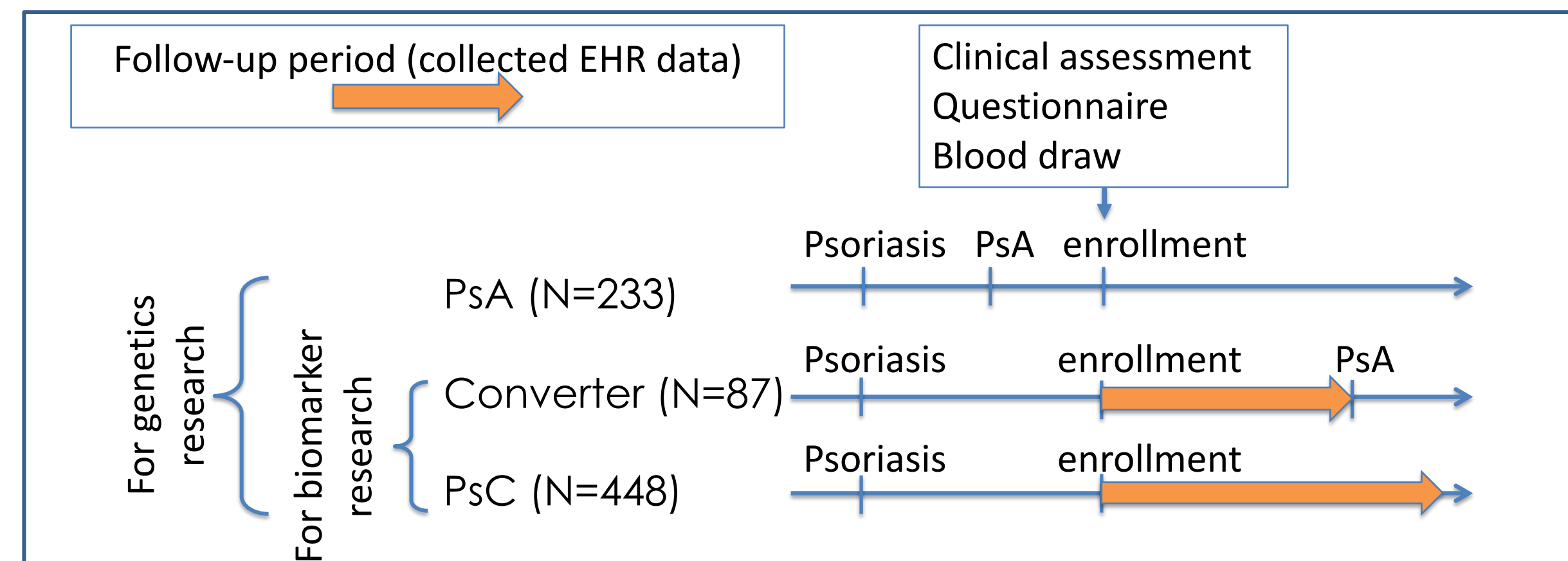
Methods

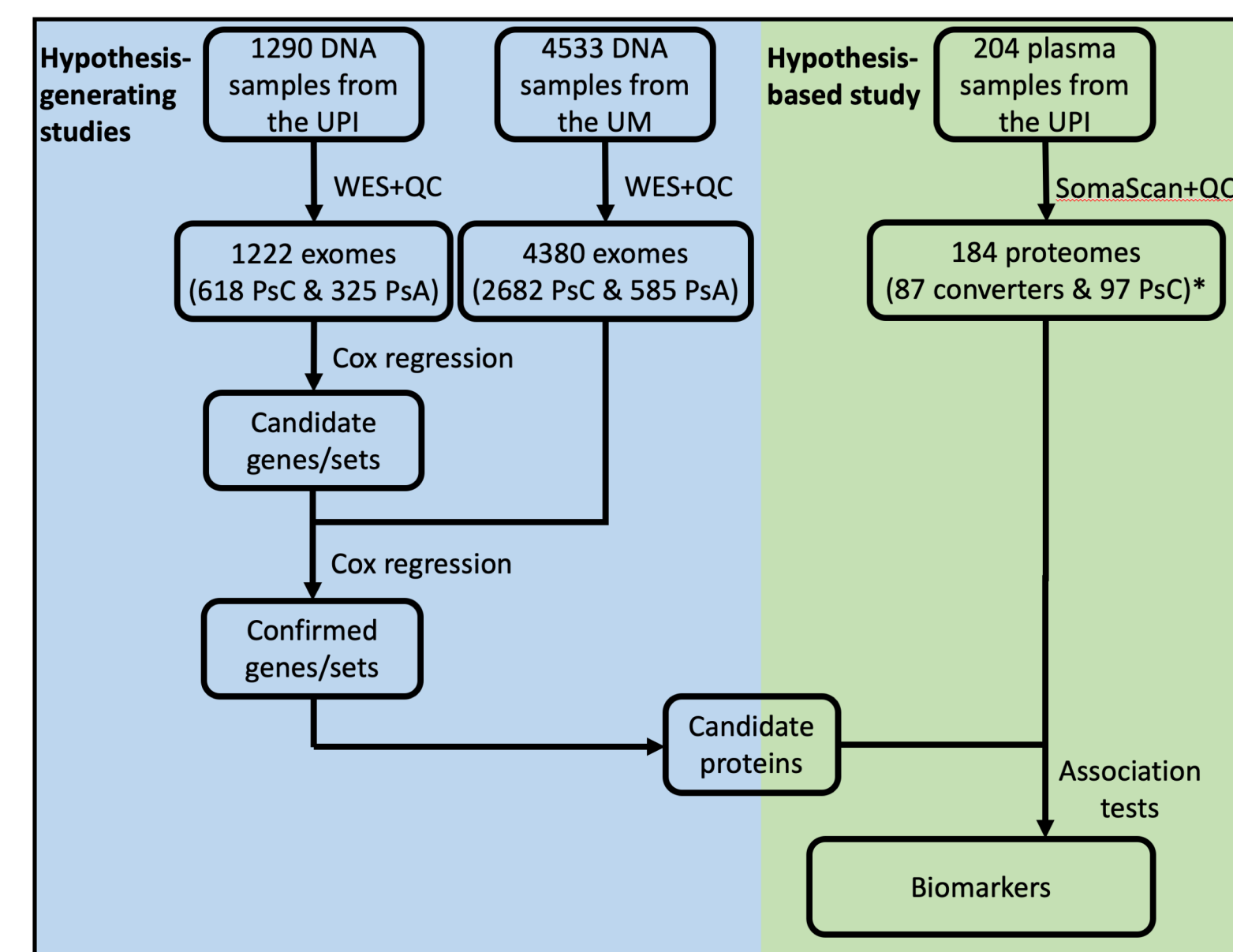**Figure 1**: The Utah Psoriasis Initiative (UPI).

Figure 2: Study design. WES, whole-exome sequencing; QC, quality control; UPI, Utah Psoriasis Initiative; UM, University of Michigan. * Converter: patients who initially enrolled as PsC and then subsequently diagnosed with PsA. PsC for proteomic analysis: PsC patients who had been followed for at least ten years without converting to PsA.

Results

1. Susceptibility genes and pathways identified through exome-wide Cox proportional hazards regression

- Association of *OSTF1* was genome-wide significant in the Utah cohort (p=0.0000043) and was confirmed in the Michigan cohort (p=0.040). A gene set called "Positive Regulation of Osteoclast Differentiation" was associated in the Michigan (p=0.000031, multiple-testing corrected p-value Pc=0.00046), further supporting the involvement of osteoclasts in the etiology of PsA.

- A gene set identified from the Utah cohort (p=0.000092), Cobalamin Binding, was confirmed in the Michigan cohort (p=0.006, Pc=0.041).

2. Biomarkers identified from protein candidates selected based on exome sequencing results

Table 1: Candidate selection

| Criterion	Selected candidates assayed by SomaScan
Confirmed susceptibility gene	OSTF1 (osteoclast stimulating factor 1)
Nominally associated genes in confirmed susceptibility pathways	TCN1, CD320, CBLIF (Cobalamin Binding) GPR68 (Osteoclast Differentiation)
Secreted proteins correlated with the above	TRAP (an osteoclast marker encoded by the ACP5 gene)[1]
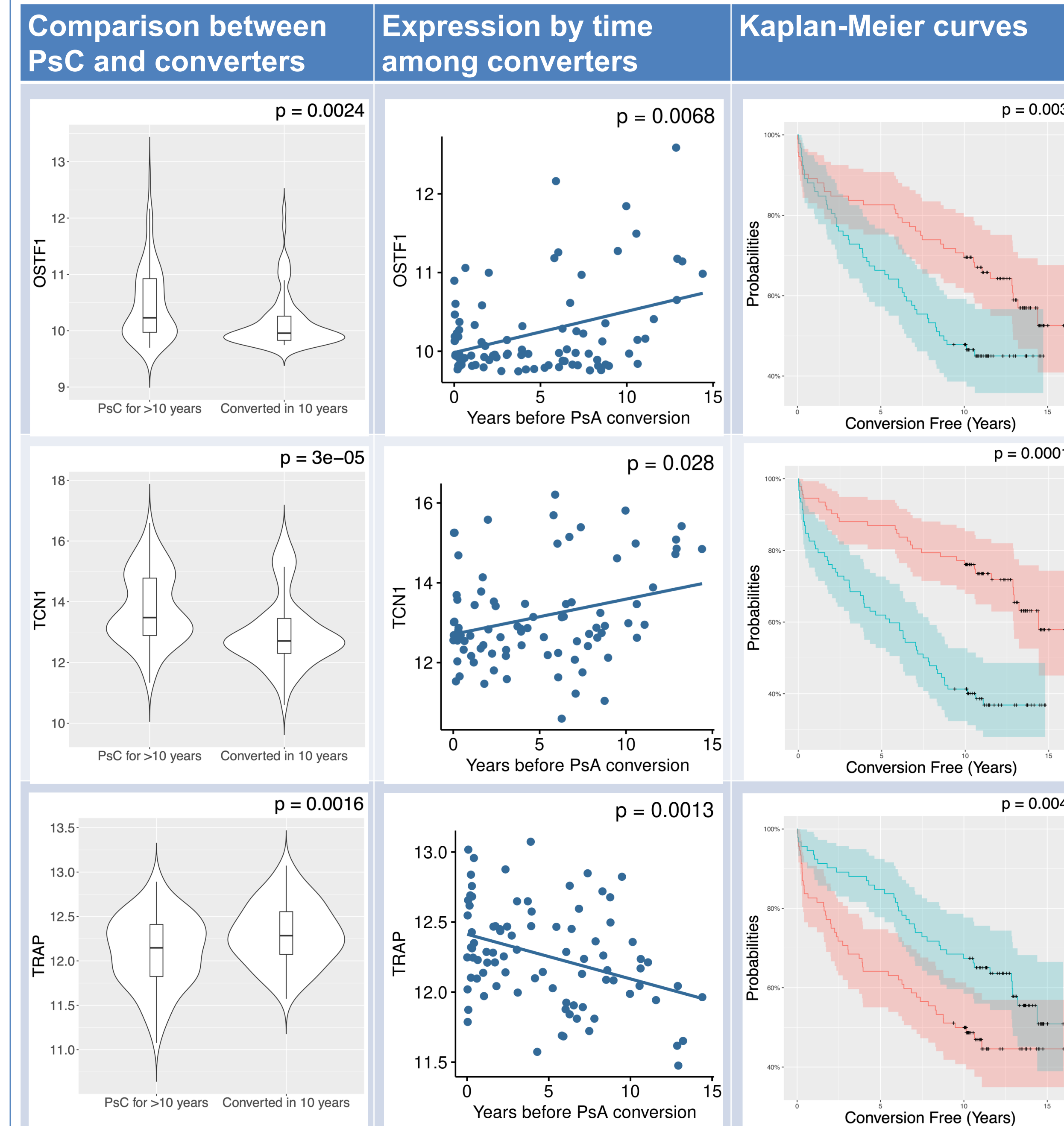
Figure 3: Association of plasma protein biomarkers with PsA.
In the Kaplan-Meier curves, blue is biomarker-low and red is biomarker-high separated by the median. Findings from these figures:
- OSTF1, TRAP, and TCN1 showed a significant corrected p-value.
- The direction of association was consistent across the following tests
  - Comparison of the mean concentration between PsC and converters
  - Testing for the linear trend of expression by time among converters
  - Cox regression comparing biomarker-low to biomarker-high patients
  - Cox regression comparing deleterious variant carriers to non-carriers

3. Predictive value of the biomarkers

In a previous study, we found that two clinical phenotypes (untreated psoriasis plaque thickness and history of fingernail psoriasis) were significantly associated with the conversion of PsC to PsA.[2] In this study, logistic regression suggested that ACP5 and TCN1 had additional predictive value beyond these clinical phenotypes (**Table 2**).

Table 2: Predictive value of biomarkers beyond clinical predictors.

Biomarker	Adjusted for untreated PsO thickness and history of fingernail PsO			
	Adjusted for symptoms		Excluded patients with symptoms	
	OR [95% CI]	p-value	OR [95% PI]	p-value
TCN1	0.41 [0.21,0.82]	**0.011**	0.32 [0.13,0.78]	**0.012**
TRAP	2.19 [1.08,4.44]	**0.029**	2.99 [1.21,7.42]	**0.018**
OSTF1	0.57 [0.28,1.16]	0.12	0.38 [0.14,1.02]	0.055

Note: All analyses were adjusted for age, sex, body mass index. Symptoms were morning stiffness >30 minutes, swelling, tenderness, deformity, or dactylitis.

4. Biomarker concentration as a function of time before PsA

Spline regression tests showed that OSTF1 was consistently low for up to 7.1 years before conversion to PsA, and TCN1 was consistently low for up to 8.9 years before conversion to PsA (**Figure 4**).
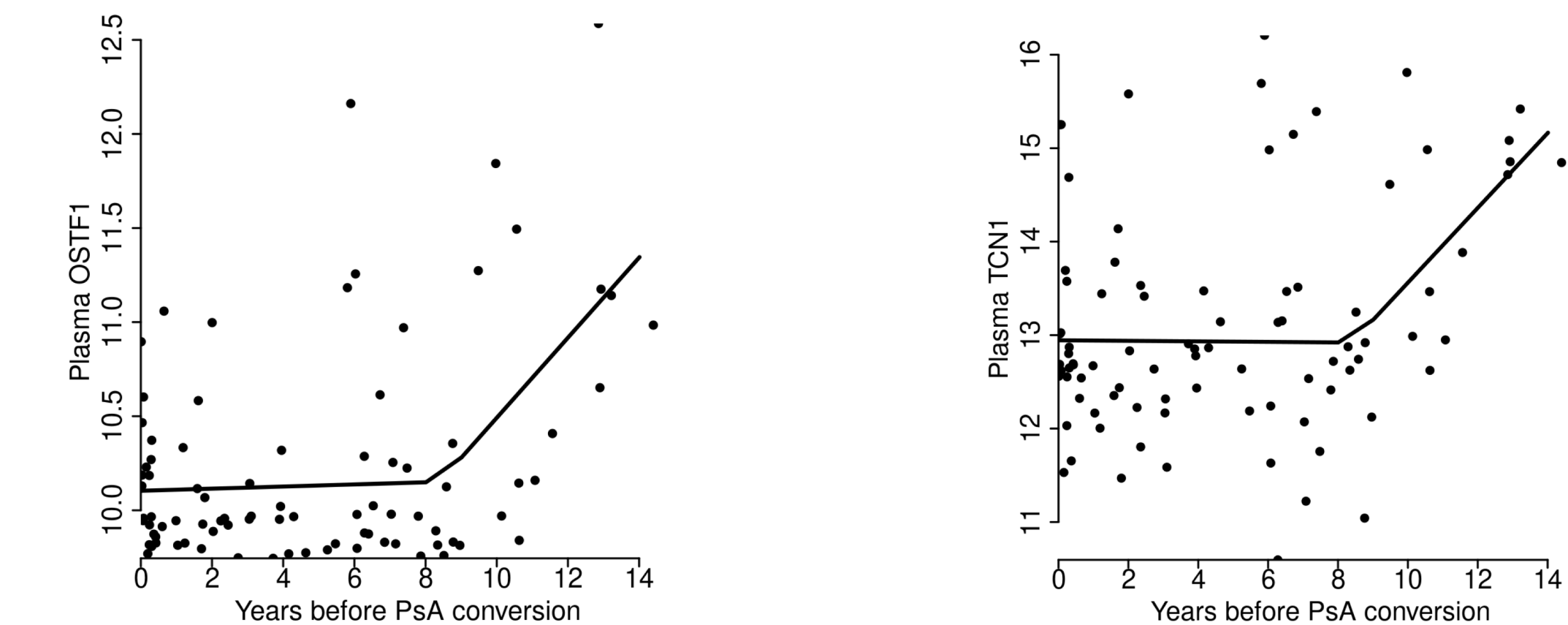

Figure 4: Scatter plots with spline regression model.
Time zero represents PsA conversion. The line represents output of a one-knot one-degree spline regression. Only biomarkers with a significant likelihood ratio test result comparing the best-fit spline regression to a linear regression model are shown in this figure. P-values from the likelihood ratio tests were 0.016 and 0.013 for OSTF1 and TCN1, respectively.

Conclusion

This study identified *OSTF1* as a PsA susceptibility gene, Osteoclast Differentiation and Cobalamin Binding as susceptibility pathways, and plasma protein concentration of OSTF1, TRAP, and TCN1 as biomarkers of early PsA. Biomarkers TCN1 and TRAP provided predictive information beyond what can be learned from clinical phenotype data.

Acknowledgements & Disclosures

References

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