W23: Incidence and inheritance of hyperphosphorylated paratarg-7 in patients with Waldenstrom's Macroglobulinemia from Sweden

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Background: Genetic factors play an important rote in the development of Waldenstrom's Macroglobulinemia (WM) and Multiple Myeloma (MM). Both these diseases are characterized by a monoclonal immunoglobulin (paraprotein). The antigenic target of the paraprotein might play a role in the pathogenesis. Paratarg-7 (P-7) has been identified as a paraprotein target of 15% of monoclonal immunoglobulin A (IgA) or lgG (IgG) both in monoclonal gammopathy of undetermined significance (MGUS) and MM and in 11% of monoclonal lgM in WM and MGUS of lgM type. In these patients, P-7 was hyperphosphorylated (pP-7) and the carrier state was inherited in an autosomal dominant fashion. pP-7 carrier state has been associated with an increased risk of developing MM, MGUS, and WM.[1-3] The incidence of WM, MM, and MGUS has geographical and ethnic differences. In Sweden, the incidence of WM/LPL is high, especially in the northern part.[4]

Aim: This study investigates pP-7 in WM patients in Sweden and the heredity of the carrier state of the paratarg protein.

Methods: Blood samples were analysed from 42 patients with non-familial WM, 15 families with two or more cases of WM, IgM MGUS, and/or MM from two Swedish counties; Norrbotten and Vasterbotten , and 57 Swedish patients with WM from other parts of the country participating in The Scandinavian Lymphoma Aetiology study (SCALE) (control group). For two non-familial WM patients, we also analysed pre-diagnostic samples from the biobank at Umea University.

The analyses for P-7 and pP-7were performed at José Carreras Centre for lmmuno and Gene Therapy, Saarland University Medical School, Germany.

Results: Reactivity against pP-7 was found in 3/42 (7.1%) non-familial WM patients, 2/15 (13.3%) index patients and two affected relatives in the families, and 2/57 (3.5 %) patients in the SCALE study. In the family cohorts, also 4/8 (50%) healthy first-degree relatives showed reactivity against pP-7.

Two patients with non-familial WM carrying pP-7 with pre-diagnostic blood samples are described in Figures 1 and 2. One patient was diagnosed with WM in July 2001 with a pre-diagnostic blood sample, collected 6.5 years earlier, showing no paraprotein or reactivity against P-7/pP-7, but the patient was a carrier of pP-7. Another patient diagnosed with WM in April 2007, and with a pre- diagnostic blood sample collected in January 1997, showing a paraprotein of lgM type of 14g/L and a low titre against P-7/pP-7 detectable at a dilution of 1:100.

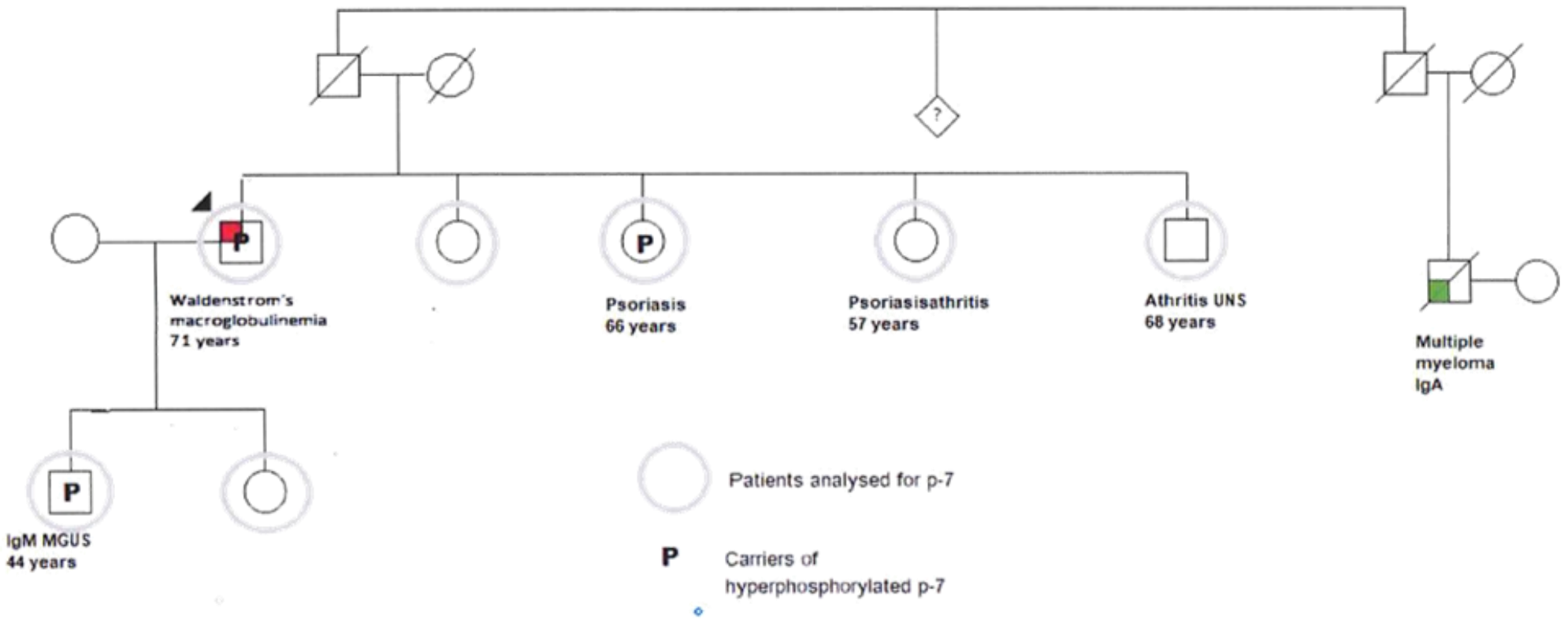
Conclusion: pP-7 carrier state is a strong risk factor for developing WM/MGUS and MM. The prevalence of pP-7 is of the same level in non-familial WM in Sweden as in other parts of Europe, but with a tendency for higher prevalence in familial WM. pP-7 was shown up to 10 years before diagnosis of WM, but antibody titres against P-7/pP-7 are built up with progressing disease and increasing paraprotein. In families with aggregation of WM, IgM MGUS, and/or MM, the pP-7 is inherited in an autosomal dominant fashion and enables the identification of family members at increased risk.

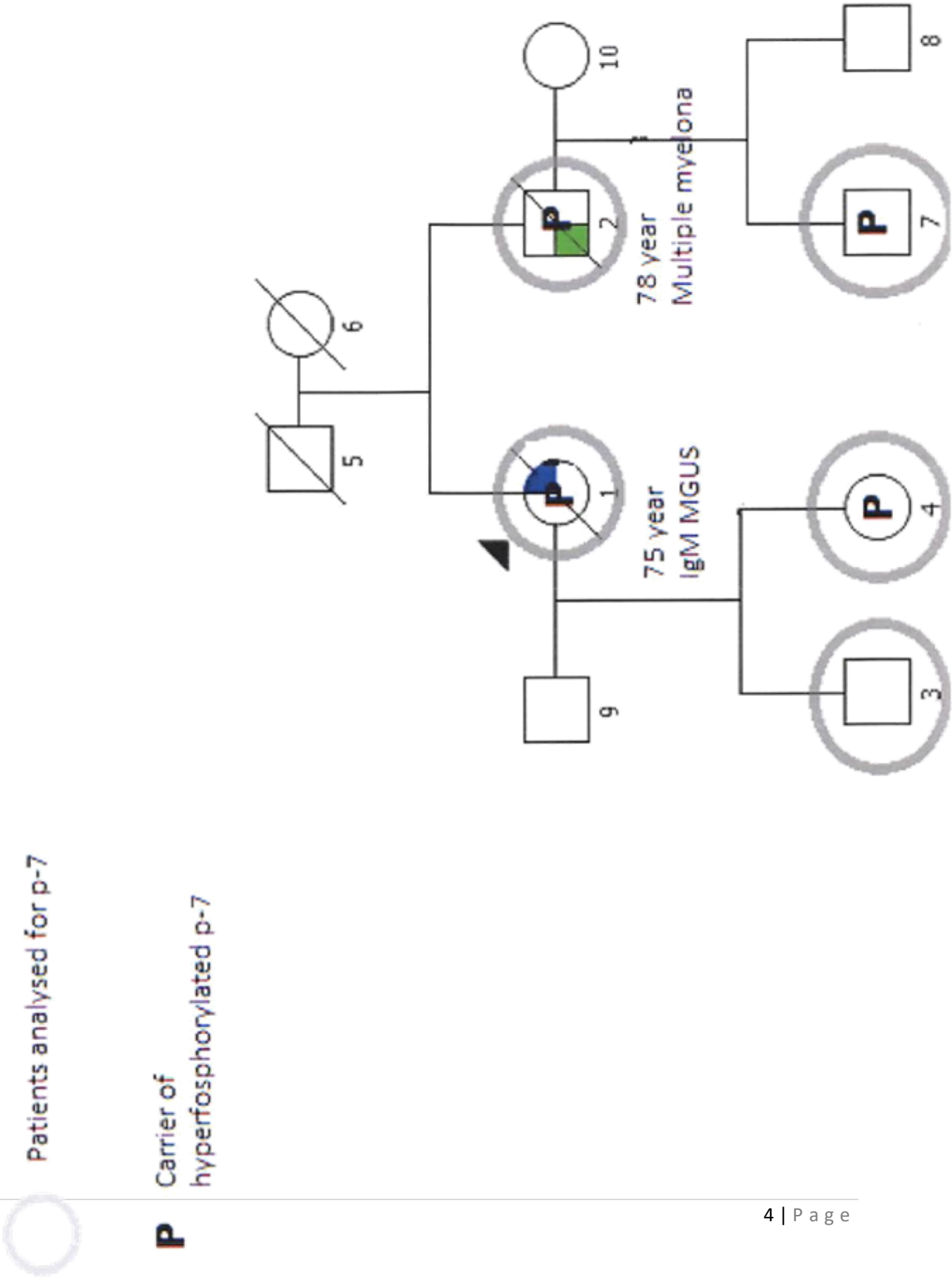
1. Grass S, Preuss KD, Ahlgrimm M, et at. Association of a dominantly inherited hyperphosphorylated paraprotein target with sporadic and familial multiple myeloma and monoclonal gammopathy of un- determined significance: A case-control study. *Lancet Oncol.* 2009;10(10):950-9S6.

2. Grass S, Preuss KD, Pfreundschuh M. Autosomal-dominant inheritance of hyperphosphorylated paratarg-7. *Lancet Oncol.* 2010;11(1):12-2045(09)70331-6.

3. Grass S, Preuss KD, Wikowicz A, et at. Hyperphosphorylated paratarg-7: A new molecularly defined risk factor for monoclonal gammopathy of undetermined significance of the IgM type and walden- strom macroglobulinemia. *Blood.* 2011;117(10):2918-2923.

4. Brandefors L, Kimby E, Lundqvist K, Melin B, Lindh J. Familial waldenstrom's macroglobulinemia and relation to immune defects, autoimmune diseases, and haematological malignancies - A population-based study from northern sweden. *Acta Oncol.*2016;55(1):91-98


?
P
Waldenstrom's
macroglobulinemia
71 years
P
Psoriasis
66 years
Psoriasisathritis
57 years
Athritis UNS
68 years
Multiple
myeloma
IgA
P
IgM MGUS
44 years
Patients analysed for p-7
P
Carriers of
hyperphosphorylated p-7


Patients analysed for p-7
P
Carrier of
hyperfosphorylated p-7
75 year
IgM MGUS
78 year
Multiple myeloma
1
2
3
4
5
6
7
8
9
10