Studies into Structure and Inheritance of the Genetics Hp Ca-Variant

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Several theories exist on the nature of the Carlberg variant (Galatius-Jensen, 1958): Parker and Bearn (1963) assumed that possibly there was a gene complex consisting of a normal Hp*1-, a normal Hp*2- genes. According to studies by Giblett (1964), Hp Ca was characterised by reduced production of Hp 1-units. Henningsen and co-workers (1977) confirmed Giblett's assumption and produced evidence to the effect that reduced production applied exclusively to the gene product of the Hp*1S-gene. That phenomenon has been attributed to a mutated regulator gene that is closely linked to the Hp*1S-gene.

We received for paternity testing sera of individuals involved which were to be subtyped in the Hp system. The phenotype situation was favourable, according to the outcome of preparatory tests (Table 1). Diagnosis of the rare Carl-

Table 1.

	Starch gel electrophoresis	Isoelectric focusing	Gradient gel electrophoresis
Mother	Hp1-1	1 S	1-1
Child	Hp1-1	1 S	1-1
Defendant	Hp2-1?	(1 S)-2 FS	Ca

berg variant obviously failed for too low haptoglobin concentrations in the serum of the defendants, and the Carlberg variant, after all, is characterised by a complex and usually poor band pattern. A 2-1S-like pherogram, conspicuous for absence of the heterosis effect, was recorded from subtyping (Patzelt and Schröder, 1985). A "normal" α_2FS band was paralleled by a very poor α_1S line which, however, could not be overlooked (Fig. 1). For type identification we used high-resolution, concentrating polyacrylamide gradient gel electrophoresis, and we obtained a separation image close to the Carlberg variant, as repeatedly described in the literature (Prokop and Geserick, 1986).

The views of Giblett (1964) as well as of Henningsen and co-workers (1977) on the deficiency of the Hp 1S gene product of the Carlberg type have thus been confirmed by our own results which had been obtained from isoelectric focusing. Yet, we consider probable the existence of a gene Hp*1Ca, its product having an isoelectric spot almost or fully identical with that of α_1S-peptide. Such gene products result from point mutations which are accompanied by exchange of similar amino acids.

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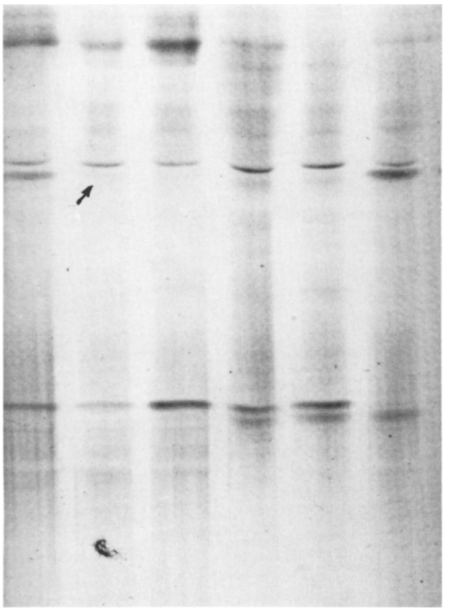

Fig. 1. Representation of Hp subtypes; types from left to right: Hp1S-2FS, 1Ca-2FS, 2FS, 1F-2FS, 1F-2FS, 1F-1S. The arrow points at the 1Ca band

Now, if one looks at the structure of haptoglobin polymers, the reduced offer of the Hp 1 component must have considerable consequeces for hybridisation of the Hp 2-1 molecule (Fig. 2).

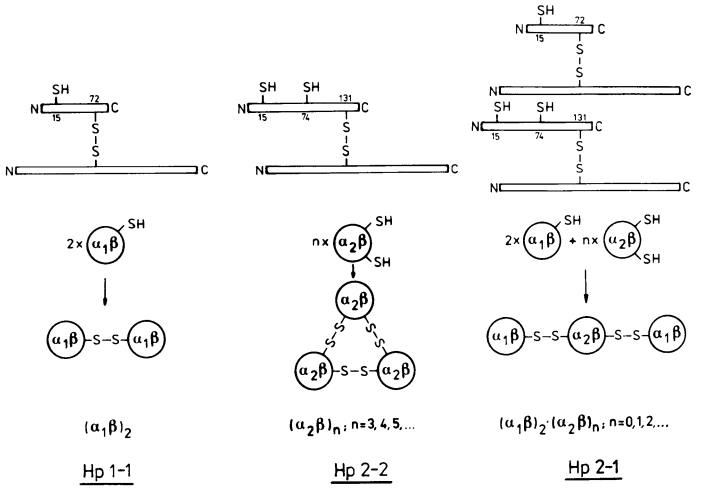

Fig. 2. Diagram of structure of haptoglobin polymers (modified after Bowman and Kurosky)

The primary gene products of Hp*1 and Hp*2 on a heterozygous basis are normally formed in identical quantity, which for higher 2-1 polymers results in a surplus

of Hp 1 molecules. This is reflected in the Hp 1 band of the 2-1 type. Hp 2 components, on the other hand, are fully hybridised in all cases, so that free Hp 2 molecules do not exist in the mixed type. However, ring closure of $\alpha_2\beta$ units resulting in the Hp 2 molecule cannot be fully avoided in the case of imbalance of gene products at the expense of Hp 1. Hence, Hp 2 molecules will have to be expected in addition to the hybrid molecules of the 2-1 type. An attempt was made by means of high-resolution polyacrylamide gradient gel electrophoresis to make comparisons between the Carlberg type and an artificial Hp 2/2-1 mixture, since the corresponding Hp 2-1 and Hp 2 polymers, such as $(\alpha_2\beta)_2$, $(\alpha_1\beta)_2$ or $(\alpha_2\beta)_4$, each exhibited a molecular weight difference of some 13,000 Dalton. The separation images thus obtained were absolutely identical, which confirmed the conceptual model. Amino acid analysis of the gene products

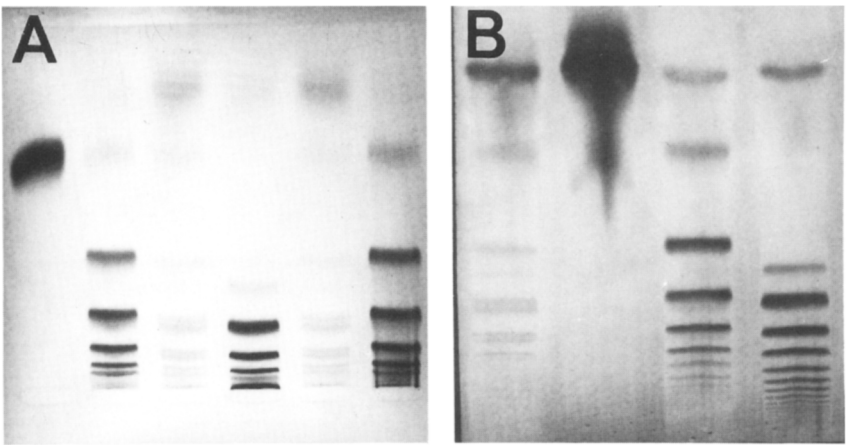

Fig. 3. Representation of Hp types in polyacrylamide gel electrophoresis (A) and polyacrylamide gradient gel electrophoresis (B). Types from left to right are A: Hp 1, 2-1, 2-1Ca, 2, 2-1Ca and B: Hp2/2-1 mixture, artifact, 2-1, 2

probably will be necessary to definitely clear up, if the Carlberg variant is an expression of point mutation with an amino acid sequence different from the α_1S-peptide or an expression of a mutated regulator gene (no segregation so far being observed).

Interesting enough, there are alleles also for the Hp 2 gene product which encode a α_2-peptide with reduced concentration: modified Hp 2 genes (Hp*2M). These genes possibly are recombination products of Hp*Ca genes with Hp*2FS genes. From the polymerisation diagram (Fig. 2) one can easily predict the Hp 2M-1 type which is characterised by a shortened polymer series.

So, the following concept should apply to the specific case of paternity assessment: No definite ruling can be made as to whether the child is homozygous Hp 1S or heterozygous Hp 1Ca-1S. The defendant's paternity, consequently, cannot be excluded in the Hp system.

The authors of this paper, on the basis of their own results, should like propose that the Hp Ca variant in future should be renamed more informatively Hp 2-1Ca.

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