

A three generation family with low cortisol, CBG deficiency, chronic fatigue and pain, lipomatosis and behavioral alterations



S. Moia¹, G. E. Walker¹, M. Roccio¹, R. Ricotti¹, E. Giglione¹, S. Bellone¹, F. Fanelli², G. Bona¹ and F. Prodam¹

¹Dipartimento di Scienze della Salute, Università del Piemonte Orientale A. Avogadro - Novara

²Dipartimento Medicina Clinica U.O. Endocrinologia Policlinico S.Orsola Malpighi - Bologna

Background: Corticosteroid Binding Globulin (CBG) is a member of the serine protease inhibitor (SERPIN) family. Plasmatic CBG is synthesized by hepatocytes and its role is to transport and regulate the amount of free cortisol that is available to target tissues and cells. Inherited CBG deficiency (MIM 611489) is a rarely recessive disorder characterized by low cortisol levels, presence of normal ACTH, hypotension and fatigue, although the exact pathophysiological mechanisms involved remain uncertain.

Methods: Plasmatic concentration of CBG protein was quantified both in our family (n=9) than in a group of healthy controls (n=15) by using a commercial kit (Human Corticosteroid Binding Globulin ELISA, BioVendor). Molecular analysis of four coding exons (exons 2-5) of CBG gene was performed by direct sequencing. In the hypothesis of a recessive disorder, segregation analysis of parental alleles was performed through linkage analysis.

Results: A children was referred to our Pediatric Endocrinology Unit for an evaluation of chronic fatigue, low cortisol levels, persistent pain and hypotension detected after a viral infection. This phenotype suggested a CGB deficiency. His brother presented also diffuse abdominal lipomatosis (like the paternal grandfather), cryoglobulinemia, mild hyposmia and mild central hypoacusia. One year later, after a viral infection, the sister presented symptoms of CBG deficiency (pain, hypotension, fatigue and cryoglobulinemia). In addition, all the children had some behavioural alterations. Cortisol levels at baseline were reduced in the proband, his brother, sister, father and paternal grandfather. The ID-LC-MS/MS analysis identified very low free cortisol levels in two children (the proband and his brother) and in the father, despite normal ACTH levels. Cortisol levels were normal in the other kindreds (*Figure 1*).

Patient	Cortisol	21-deoxycortisol	Corticosterone	11-deoxycortisol	Aldosterone	11-deoxy corticosterone	Testosterone	17-Hydroxy progesterone	dehydro epiandrosterone	Progesterone
	ng/ml	ng/ml	ng/ml	ng/ml	ng/ml	ng/ml	ng/ml	ng/ml	ng/ml	ng/ml
III-1	22,6	<0.078	0,40	0,174	0,292	<0.078	2,301	0,422	2,17	<0.049
III-2	4,4	<0.078	<0.31	<0.078	0,178	<0.078	2,767	0,433	0,79	<0.049
III-3	86,6	<0.078	2,72	0,992	0,117	0,121	0,023	0,510	n.d.	0,058
II-1	54,4	<0.078	0,82	0,237	0,629	<0.078	2,225	0,632	5,29	<0.049
II-2	146,8	<0.078	1,86	0,081	0,223	<0.078	0,083	<0.078	n.d.	<0.049
I-1	86,3	<0.078	1,53	0,245	0,397	<0.078	3,152	0,682	1,58	<0.049
I-2	71,5	<0.078	0,84	0,084	0,208	<0.078	0,124	0,117	1,85	<0.049
I-3	79,2	<0.078	1,23	0,203	0,324	<0.078	4,160	0,665	0,82	0,051
I-4	102,7	<0.078	1,85	0,103	0,259	<0.078	0,159	0,187	1,87	<0.049

Figure 1

No mutations were identified in the CBG gene coding-regions. We identified only five SNPs: rs3748320 (T126T), rs2228542 (S246S), rs2228541 (S246A), rs1042394 (L312L) and rs2228543 (D337D). Linkage analysis identified a likely paternal transmission of the CBG alleles (*Figure 2*).

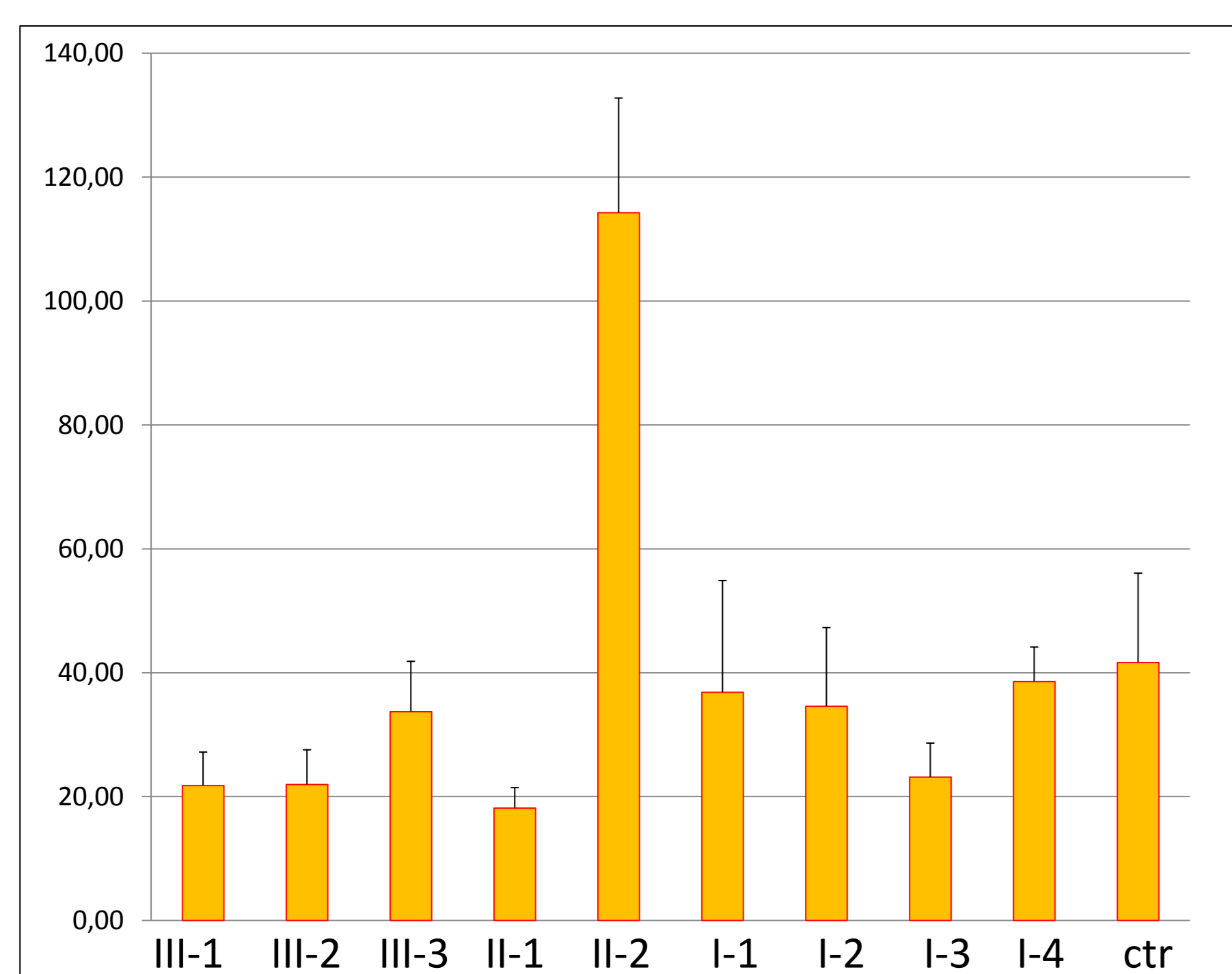


Figure 3

The maternal grandfather, the father and the two male children presented low plasmatic CBG levels (normal range 28-52 µg/ml). A surprising high level of plasmatic CBG was instead observed in the mother. As expected, all control healthy subjects had a plasmatic CBG protein concentration in the normal range (*Figure 3*).

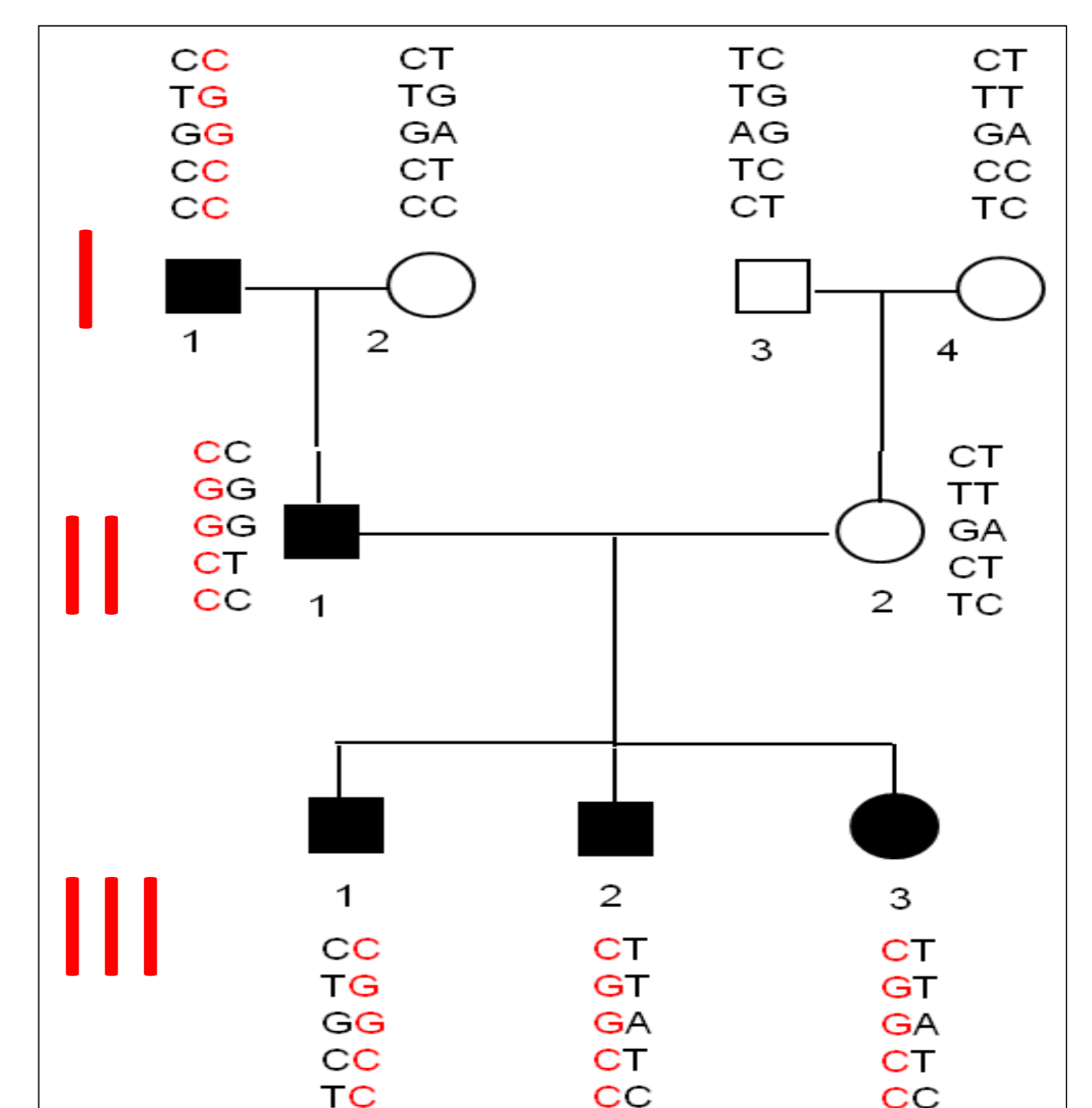


Figure 2

Conclusions: With the hypothesis that our family is affected by inherited CBG deficiency, molecular analysis of non-coding regions and functional studies of CBG gene will be performed. In addition, the involvement of supplementary gene-disease will be demonstrated by CGH array and exome sequencing analysis.