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Chapter 13

Anderson's Disease/Chylomicron Retention Disease and Mutations in the *SAR1B* Gene

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Additional information is available at the end of the chapter

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1. Introduction

Anderson's Disease (AD)/Chylomicron Retention Disease (CMRD) (OMIM #607689) is a rare autosomal recessively inherited lipid malabsorption syndrome characterized by hypocholesterolemia associated with failure to thrive, diarrhea, steatorrhea and abdominal distension that presents most frequently in young infants. Charlotte Anderson first published a description of the disorder in 1961 [1] based upon observations of a young girl of seven months of age who manifested a characteristic macroscopic and microscopic appearance of the intestinal mucosa which was filled with fat. Forty two years later, in 2003, Jones and colleagues [2], in 8 families, identified mutations in the *SAR1B* gene, which encodes for the intracellular trafficking protein SAR1b, and proposed that this was the molecular defect in the disorder. The disease is very rare. From the first clinical description of the disease up to the identification of the causal gene, only 39 patients from 24 families were described in the literature [3-21]. From 2003 to the present, 23 new patients from 14 additional families have been identified. In all, 16 different mutations in the *SAR1B* gene now have been described in 34 patients from 21 families [2, 22-27]. Here, we provide an overview of this disease, including the description of 4 new patients from 3 new families (one new mutation), and we describe the predicted molecular impact on the SAR1b protein of novel or previously-described mutations in the *SAR1B* gene.

2. Clinical features

The first symptoms of AD/CMRD, which most frequently occurr within a few months after birth, consist of failure to thrive, diarrhea with steatorrhea and abdominal distension. Of the 62 patients described in the literature, only 4 were diagnosed as adults; two sisters presented with diarrhea that was found to have begun in infancy [21, 23], the third adult had severe neurological signs in infancy [6] and the past medical history of the last adult revealed some

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clumsiness in walking and running and very loose bowel movements in infancy [7]. These patients may have spontaneously avoided the fat in their diets to minimize symptoms. Non specific malabsorptive diarrhea is present in almost all cases with steatorrhea, even when a low fat diet is observed [28]. The diagnosis is sometimes delayed (often for several years) because the symptoms are non-specific and are attributed to chronic diarrhea (cystic fibrosis or coeliac disease). Thus, 39/45 patients exhibited the first symptoms before one year of age, whereas only 21/52 received the proper diagnosis without undue delay. As consequence of diarrhea, failure to thrive (-1 to -4DS for height and/or weight) is also frequent (45/51 patients) and persists if a low fat diet is not instituted. Other digestive symptoms, such as vomiting or a grossly distended abdomen are commonly observed. Usually, if a low fat diet supplemented with lipid soluble vitamins is instituted, the growth starts again; however, some patients with a delayed diagnosis do not attain a normal height and weight [29]. Tolerance to fat in the diet has been reported in a few cases [14, 16, 22, 24, 27]; however, in most instances, diarrhea begins again when fat is reintroduced in the diet [29].

Hepatic and neurological abnormalities, although sometimes reported in young patients, generally are tardive manifestations, particularly when the diagnosis and the implementation of dietary vitamin supplements are delayed. Several cases of transient hepatomegaly have been described [6, 9, 11, 16, 17, 22] and one or both amino-transaminases (ASAT and ALAT) are frequently reported to be increased (13/15 patients of Charcosset [22]) but confirmed hepatic steatosis are infrequent (three cases described) [11, 25]. However, no instance of cirrhosis has been reported. In young adults or older patients, neurological abnormalities consist mainly of areflexia [11, 12, 14, 22]. In some cases, more severe neurological degeneration consisting of ataxia, sensory neuropathy and/or tremor has been reported [6, 7, 11, 19]. Mild defects in color vision and retinal function also have been observed [11, 14, 28] but no retinis pigmentosa has been reported. Acanthocytosis is very rare and usually transient [6, 12, 17, 27].

Mild muscular abnormalities have been described in several patients and consist mainly of muscular pain and cramps; one patient was described with myopathy [6]. Creatine kinase (CK) levels are often found to be elevated (1,5-2,5 times normal) [23, 27]. Jones et al (2003) have shown that high levels of SAR1B mRNA expression occurs in tissues other than intestine [2] and, therefore, extra-intestinal clinical manifestations might occurr in AD/CMRD. Silvain et al have described a cardiomyopathy in an adult and documented the accumulation of lipids in some muscle fibers [23]. Consequently, clinical evaluation and follow-up of these patients should include CK levels and cardiac examination.

Poor mineralization and delayed bone maturation may be present and vitamin D levels may be normal or decreased [5, 12, 18, 21, 23, 28]. Several patients also have exhibited associated infectious diseases [14, 16].

AD/CMRD patients exhibit a particular recessive hypocholesterolemia which differs from other familial hypocholesterolemias. The hypocholesterolemia manifests itself by a decrease of plasma LDL (LDLc) and HDL (HDLc) cholesterol (both by approximately 50%) associated with a normal level of triglycerides (Table 1). The severe decrease of HDLc (the mean level

in patients is 0,49mM) associated with a normal triglyceride level is pathognomonic of AD, if all the secondary causes of malabsorption such as celiac disease, exocrine pancreatic insufficiency (cystic fibrosis or Shwachman-Diamond syndrome), and the Mc Kusick syndrome (small height and malabsorption with exactly the same lipid profile as AD) have been ruled out. Further, other causes of familial hypocholesterolemias must be carefully ruled out; for example, some patients with AD/CMRD have low levels of triglycerides and high levels of HDLc that are similar to those found in atypical abetalipoproteinemia [30, 31] or homozygous hypobetalipoproteinemia (data not shown). Plasma levels of vitamin E, measured before supplementation in patients diagnosed during the last decade, are usually low or very low (but detectable, from 0,5 to 6,8 μM, 3 of 19 patients had undetectable levels). In patients described previously, the undetectable levels were probably due to technical limitations (reported values range from 0, 23 to 11,3 μM, and 13 of 28 patients had undetectable levels). Mild decreases of vitamin A have also been found [5, 6, 11, 12, 18, 21, 24, 27] but there are normal levels of other fat soluble vitamins in most of the AD/CMRD patients.

Patients data	All published cases	Published cases with mutations
N	62	34
age at onset	56% < 3 mths, 87% < 1 year	53% < 3 mths, 84% < 1 year
age at diagnosis	60% > 1 year, 23% > 10 years	50% > 1 year, 23% > 10 years
major clinical data	90% diarrhea, 88% failure to thrive	90% diarrhea, 57% failure to thrive
TC mM	n=54 M=1,75 (0,86-3,38)	n=34 M=1,81 (1,11-2,82)
TG mM	n=48 M=0,87 (0,36-2,06)	n=33 M=0,92 (0,36-1,98)
HDLc mM	n=26 M=0,49 (0,32-0,83)	n=23 M=0,50 (0,32-0,83)
LDLc mM	n=26 M=0,87 (0,26-1,61)	n=23 M=0,88 (0,31-1,61)
apoB g/l	n=37 M=0,44 (0,20-0,82)	n=21 M=0,49 (0,20-0,82)
apoA1 g/l	n=31 M=0,52 (0,26-0,90)	n=18 M=0,52 (0,38-0,90)
Vitamin E μM	n=43 M=2,74 (0 – 11,3)	n=23 M=2,81 (0 – 7,6)

(TC: total cholesterol, TG: triglycerides, HDLc: HDL cholesterol, LDLc: LDL cholesterol)

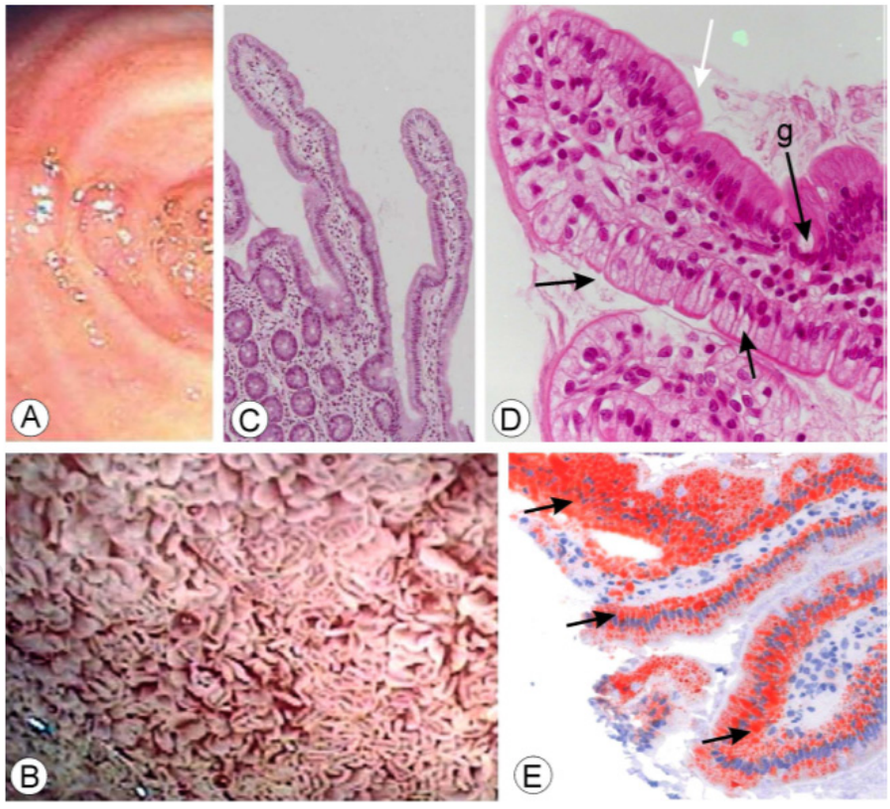
Table 1. Mean data for all the published cases

In most cases, an essential fatty acid (FA) deficiency has been not investigated, nevertheless, a decrease of linoleic acid (C18:2 n-6) and normal levels of n-3 FA have been found in two files of patients [10, 28]. For all the patients, the lipid profiles of the heterozygous parents were normal.

Four new cases of AD/CMRD in 3 families have recently been discovered (Table 2, 3). All the individuals presented with diarrhea and failure to thrive (4/4 patients). Interestingly, one of the patients presented with tremor at diagnosis (Table 2). The plasma lipids and vitamin E exhibit a wide range of levels and, in particular, the triglycerides and total and LDL cholesterol values which is an other characteristic of AD.

The inability of the enterocytes to secrete chylomicrons and apoB 48 after a fat load is a common clinical feature of AD/CMRD, ABL (abetalipoproteinemia) and, generally,

homozygous FHBL (familial hypobetalipoproteinemia). When observed with video-endoscopy, the intestine of AD/CMRD patients shows a white mucosa ("*gelée blanche*"). This typical white stippling, like hoar frosting, covers the mucosal surface of the small intestine (Fig 1A, B) even in the fasted state in contrast to healthy individuals. When intestinal biopsies from patients who have fasted are observed by light microscopy, they appear to have a normal number of *villi* of appropriate length. However, the enterocytes are overloaded with birefringent droplets in the cytoplasm (Fig 1 C, D) [1, 5, 6, 8, 9, 11, 12, 14, 16-18, 20, 25, 27]. These droplets are present, mainly, in the upper one-third of the *villus* of the enterocyte and they stain positively with oil red O indicating that they are fat droplets (mainly triglyceride) (Fig 1D, E). In some cases, the droplets are seen to be present preferentially on one side of the *villus* as opposed to both sides, whereas, in other cases (or sometimes in the same case), they may be present on both sides [32]. When the biopsies are examined by electron microscopy, two types of lipid-containing structures, in fact, are observed in the cytoplasm which alter the normal architecture of the cells.Very large lipid droplets (1025 nm average diameter), not in a membrane-bound compartment, are present along with smaller lipoprotein–sized particles (305 nm average diameter) which are present in membrane-bound structures (Fig 2 A, B) [32]. This is in contrast to enterocytes in biopsies



Intestinal endoscopy after a 12-hour fast. In contrast to what is observed in a normal subject (A), video-endoscopy of the duodenum (D) of patient AD2 (B), shows the typical « white hoary frosting » on the small intestinal mucosa. In contrast with a normal subject(C), light microscopy of the duodenal biopsy from AD2 (D) shows the typical vacuolated enterocytes (black arrows) that stain positively with oil red O (E, black arrows). Note the typical heterogeneous aspect of the villi either fat loaded (black arrows) or without lipid droplets (white arrows).
Goblet cells are normal (D, arrow g). (C ×100; D ×400; E ×200).

Figure 1. Intestinal endocopy after a 12-hour fast (A, B, C, D, E) (from A. Georges [27])

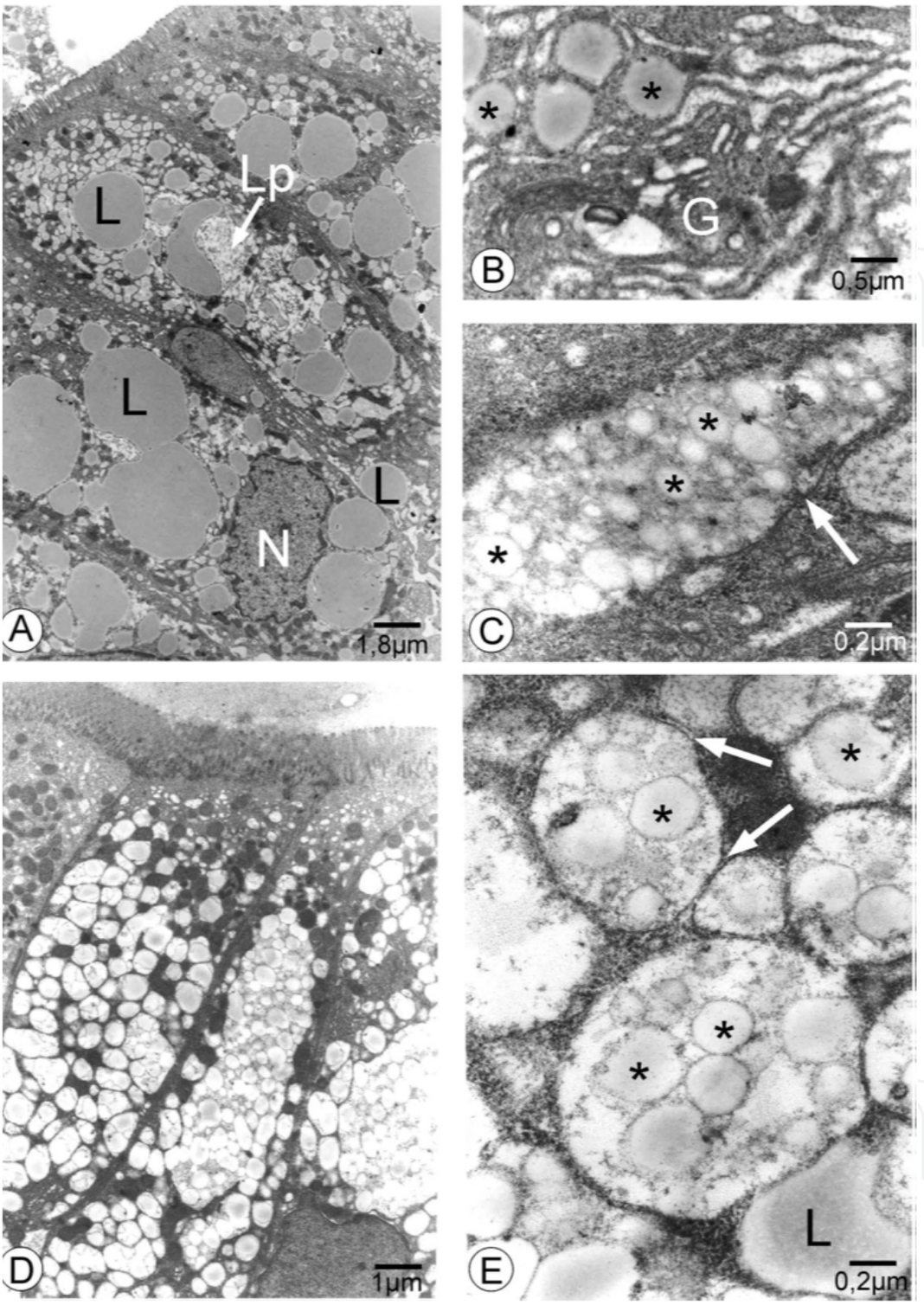
from patients with ABL which exhibit only (or predominantly) the very large lipid droplets whereas the smaller lipoprotein-sized particles, in membrane bound structures, are absent. In the enterocytes of both AD/CMRD and ABL patients, the Golgi apparatus is often distended but it is, generally, empty and free of lipoprotein-like particles. Further, in AD/CMRD, lipoprotein-like particles are observed, although in only a few cases, in the intercellular spaces between the enterocytes in contrast to ABL where they are never observed in intercellular spaces.

In addition to the lipid profiles of the patient and the parents, the diagnosis is supported by the absence of secretion of chylomicrons after a fat load, the presence of white duodenal mucosa upon endoscopy, the presence of cytosolic lipid droplets and lipoprotein-sized particles in the enterocytes of the intestinal biopsy and, finally, the discovery of a mutation in *SAR1B* gene. It should be noted, however, that the AD/CMRD phenotype has been observed in patients for which there is no mutation in the coding sequence of the *SAR1B* gene ([33] and unpublished data).

3. Functions of the SAR1B protein

SAR1 is a well-known GTPase (guanine tri-phosphatase) which belongs to the ARF (ADP-ribosylation factor) family of small GTPases [34, 35]. SAR1 initiates the assembly of COPII (coat protein complex II) in the endoplasmic reticulum (ER) by binding to SEC12. Then, SAR1-GDP is converted into SAR1-GTP which undergoes a large conformational change in the two switch regions. The residue Threonine 56, in switch 1, forms bonds to the y phosphate and Mg2+ and the residue Glycine 78, in switch 2, binds to the y phosphate. The movements expose the amino terminal, amphipatic α1 helix (« the membrane anchor ») which then inserts into the ER membrane [36]. Mg2+ has an important regulatory role in this conformational change, mostly related to switch 1 [37]. The membrane-bound SAR1 recruits SEC23-SEC24 and triggers the formation of the pre-budding complex which then recruits SEC13-SEC31 to form the COPII vesicle [36, 38]. SEC24 interacts with specific cargo proteins and concentrates them into the COPII vesicle [39]. SAR1 GTP hydrolysis is stimulated by SEC23 and SEC31 and permits vesicle fission, allowing transport to the Golgi, and eventual disassembly of the coat for recycling of the components [40-42]. SED4p, a protein with 45% homology to SEC12p, accelerates the dissociation of SEC23-24 from the membrane if no cargo is transported with COPII vesicles and it has been proposed that this restricted disassembly might play a role in concentrating cargoes into COPII vesicles [43].

The typical size of the COPII vesicles ranges from 60 to 70 nm in diameter, which would appear to prohibit these vesicles from carrying chylomicrons (250 nm average diameter) from the ER to the Golgi apparatus [44]. Another vesicle (350-500 nm in diameter), the pre-chylomicron transport vesicle (PCTV), has been shown to be able to transport chylomicrons [45]. The PCTV is composed of several proteins: VAMP7 (vesicle-associated membrane protein 7) which is the v-SNARE (vesicle-associated soluble N-ethylmaleimide-sensitive factor attachment protein receptor), apoprotein B48 (a cargo), FABP1 (also called liver fatty acid- binding protein, LFABP) (budding initiator), the fatty acid transporter CD36 (a fatty



Electron microscopy of duodenal biopsies of patients with AD. As shown for AD3 (A, B, C) and AD2 (D, E), two types of particles are apparent in the enterocytes in these patients (A, D): large lipid droplets, free in the cytoplasm (L), and smaller, lipoprotein-sized like particles (Lp), surrounded by a membrane. A higher magnification shows in (B) some individual lipoprotein-sized particles surrounded by a membrane (*)near a Golgi apparatus (G) which appears distended but devoid of particles and in (C, E) numerous lipoprotein-sized particles accumulated in membrane bound compartment (membrane, white arrow). The intercellular spaces are empty. The cell nucleus is labelled N.

Figure 2. Electron microscopy of duodenal biopsies of patients with AD (from A. Georges ref 27)

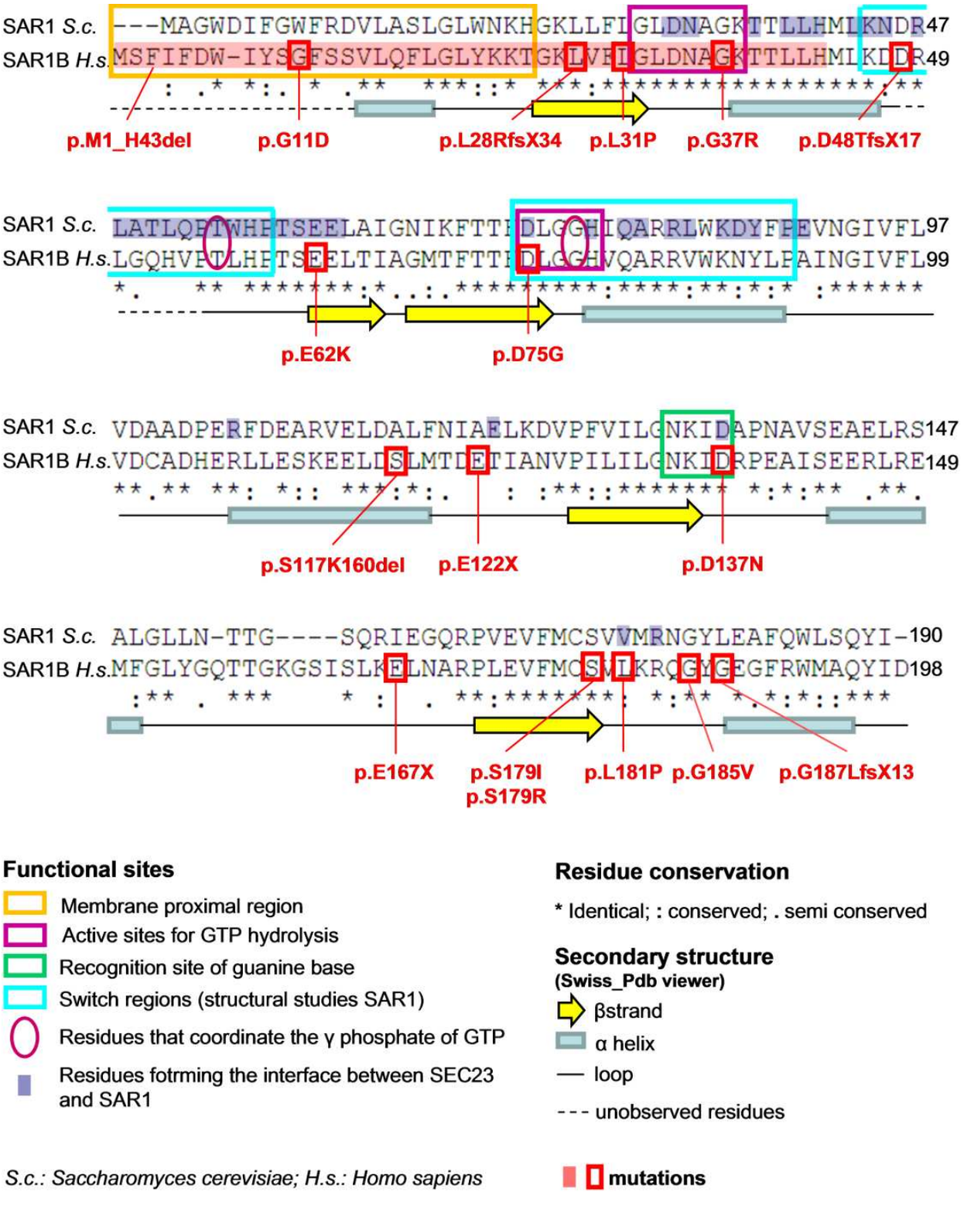


Figure 3. Sequence alignment of SAR1B protein with functional regions

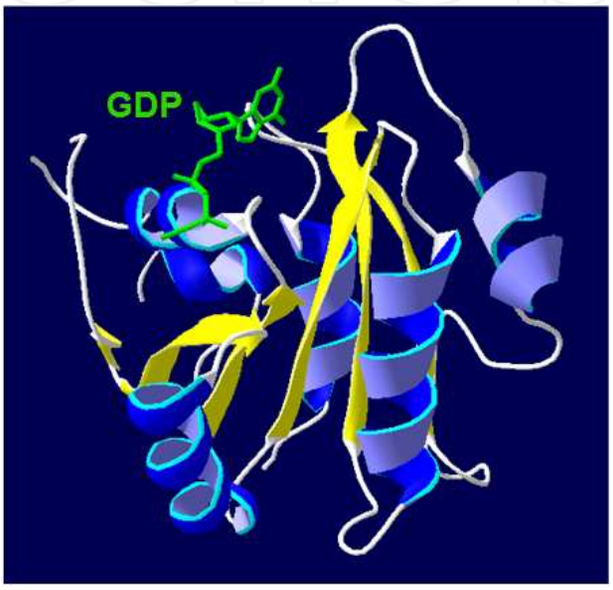
acid translocase) and the COPII proteins [46]. PCTV budding does not require GTP (and, consequently, SAR1) but rather ATP [44]. Further, VAMP7 is necessary for the fusion of the PCTV with the Golgi [44, 47]. The role of Sar1 in the budding of PCTV has been clarified, recently, in an elegant study by Siddiqi and Mansbach (2012) [47]. They showed that the binding of FABP1 to intestinal ER generates PCTV. A cytosolic multi-protein complex (composed of SAR1b, SEC13, SVIP (Small VPC/p97- Interactive Protein) binds all the FABP1 which is subsequently liberated by the phosphorylation of SAR1b by PKCζ (Protein Kinase C Zeta).

These findings raise a number of questions as to the mechanism by which *SAR1B* gene mutations could affect PCTV transport to produce AD/CMRD. In particular, it is not clear how mutations that are located in regions involved in the binding and hydrolysis of GDP/GTP (and for which the effect on COPII mediated transport is evident) would affect PCTV transport (see below: Predicted impact of the mutations). Since SAR1b plays a role in both vesicle budding and vesicle fusion to the Golgi apparatus, further studies will be necessary to completely understand the apparently multiple roles that SAR1b plays in PCTV transport. Recently, L Jin and coll showed that the ubiquitylation by CUL3-KLHL2 allow the formation of COPII vesicle of a size sufficient to transport collagen (300-400 nm) [48]. It is of interest to know whether this mechanism also could permit the transport of chylomicrons. These recent data provide novel insights into the possible mechanisms for the transport of chylomicrons (either by PCTVs or COPII vesicles) and are very interesting because impaired COPII function results not only in AD/CMRD but also in collagen deposition defects [49] and lenticulo-structural dysplasia (SEC23A mutation). However, given the ubiquitous expression and essential roles of COPII components such as SAR1 and SEC23 as well as other proteins involved in trafficking between ER and Golgi, it is still not entirely clear as to how mutations in these proteins produce diseases with such marked tissue specific effects and low incidence.

4. Structure of the SAR1b protein

Although the SAR1 protein is included in the GTPase superfamily (and, in particular, the RAS superfamily) members of which are present in most living cells, from bacteria to vertebrates, it is only slightly related to other RAS or ARF proteins and is distant from the RAB/YPT1/SEC4 subclass [50, 51]. SAR1 is conserved from an evolutionary standpoint and appears to present in all eukaryotes. However, whereas yeast and insects have a single SAR1 protein, higher organisms express two forms, SAR1b and SAR1a (both with 198 amino acids), which differ by 20 amino-acid residues [52].The function of SAR1a has not been elucidated yet and, to date, no variant in the *SAR1A* gene has been described. The sequence alignment of SAR1b as compared to SAR1p (Figure 3) illustrates the different regions that are highly conserved across species and shows the different functional motifs in SAR1b that participate in vesicle budding, in GDP/GTP binding and hydrolysis and in interactions with other COP proteins.

Five X-ray crystallographic-derived structures for SAR1b bound to GDP or GTP, alone or complexed with other COPII components, have been deposited in the Protein Data Bank. Three of these structures are derived from *S. cerevisiae* (yeast) recombinant protein and two from *Cricetulus griseus* (hamster) recombinant protein. These structures provide insights into the structural changes that SAR1b may undergo upon GDP/GTP binding as well as demonstrating which parts of the protein constitute interfaces with other COPII components. No X-ray derived structures of SAR1b complexed with components of the PCTV are available to our knowledge. There is also one X-ray derived structure for SAR1a using human recombinant protein.



Using the 1F6B model Cricetulus griseus SAR1b [53]
(which lacks the first twelve AA)
and Swiss pdb Viewer:
two residues were modified (I80V, V163I)
in order to produce a structural module
having a sequence identical to that of human SAR1b.
In yellow: **β strands**
In blue: ***α* helixes**
In white: **loops**
In green**: GDP**

Figure 4. Three dimensional structure of SAR1B protein

The X-ray structures show that SAR1b has six central β strands (5 parallel, β2 antiparallel) that are sandwiched between three *α* helixes on each side (Figure 4). In SAR1-GDP (the inactive form), the *α*1helix is retracted into a pocket formed by the β2- β3 hairpin. The β strands 1-2-3 are approximately parallel to the membrane allowing their juxtaposition with the membrane (the N and C terminus and β2- β3 hairpin would participate in this membrane interaction) [36]. The Mg2+ ion is coordinated by an oxygen atom of the phosphate of the GDP and the hydroxyl oxygen of Threonine residue 39 (in SAR1-GDP) [37]. Many H bonds stabilize the structure and could be altered by mutations (see discussion below), for example Ser 179 with Asp 137 and Leu 181 [2].

The X-ray data also provide insights into the roles played by the different parts of the structure in SAR1b functions (see the protein alignment Figure 3). The amino- (N) terminal part of SAR1b contains the STAR (SAR1 NH2 Terminal Activation Recruitment) motif, a hydrophobic sequence of amino acids (AA) (1-9), a structure different from other ARF superfamily GTPases, which recruits SEC12, and the α1 amphipathic helix (AA 15-19, residues VLNFL). The role of the α1 amphipathic helix is fundamental as demonstrated by the loss of all export activity of SAR1B following the substitution of the 4 hydrophobic AA by 4 Alanine [53]. Between the STAR motif and the α1 helix, a short domain (AA 9-14, YSGFS) participates in deforming the ER membrane [38]. Three other regions contact the membrane, one each in the N- (AA 1-25) and carboxyl- (C) (AA 195-198) terminii and a central motif in the β2- β3 strand (AA 65-70) [36, 38]. There is one motif that recognizes the guanine base (AA 134-137, NKXD) and two active sites for GTP hydrolysis (AA 32-38, motif GXXXXGK and AA 75-78, motif DXXG) [54]. Close to the GTP hydrolysis site, Threonine 39 is a highly conserved residue and the substitution T39N inhibits SAR1 function by interfering with activation by SEC12 [53].

The two switch regions (AA 48-59 and AA 78-94) contain two very important residues, the Threonine at position 56 and the Glycine at position 78, respectively [53]. A second unique structural region of SAR1, not observed in the ARF GTPases, is a long surface-exposed loop (AA 156-171) which connects the α4 helix and the β6 strand and which regulates the function of SAR1b. The substitution Thr158Ala abolishes the activity of SAR1 [53]. A specific C-terminal motif (AA 171-181, PXEVFMC/VSV/L), present in the β6 strand, targets SAR1b to the ER [55].

The three-dimensional structure was obtained by crystallography [36, 53] and then by a computational approach. By crystallography (without the nine first and the 48-55 residues), SAR1-GDP appeared as a dimer [37, 53]. Nothing is available about an in vivo GTPase activity with this dimer structure. Moreover, Long and coll (2010) showed that SAR1b may function as a monomer [56], so we will only consider the monomer form.

5. Predicted impact of the mutations in the *SAR1B* gene on the structure and function of the protein

Currently, including the 4 new cases belonging to 3 new families reported here (one new missense mutation), mutations in the *SAR1B* gene have been established for 43 individuals with AD/CMRD (belonging to 24 families). There are only 17 unique mutations. The majority of individuals are homozygous for their mutation (38/43) and 5 individuals from 4 families are compound heterozygous. There are a total of 7 nonsense and 10 missense mutations (Table 2). Since structural information concerning SAR1b in PCTV vesicles is not available, the discussion of the possible effects of *SAR1B* gene mutations upon protein function will be limited to the COPII vesicle transport system.

Recently we identified the same mutation (del exon2) as the Algerian family (n°2) in 3 patients from 2 Tunisian families (to be published).

SAR1B	DNA variant	protein mutation	ethnic origin	Family number	sex	status	age dg	references
exon 2	c.32 G>A	p.G11D	thaï	1	M	comp Hz	11m	24
(1-58 bp)	c.-4482_58 +1406 del	p.M1_H43del	algerian	2	F	Ho	6y	22
	5946 ins 15bp (*named* del exon 2)	p.M1_H43del	algerian	2	M	Ho	8y	22
exon 3	c.83_84 delTG	p.L28R fsX34	french canad	3	F	comp Hz	?	2, 11
(59-178bp)	c.83_84 delTG	p.L28R fsX34	morrocan	4	F	Ho	7m	25
	c.83_84 delTG	p.L28R fsX34	morrocan	5	F	Ho	8m	27
	c.92 T>C	p.L31P	morrocan	6	M	Ho	3m	*this article*
	c.92 T>C	p.L31P	morrocan	6	M	Ho	15y	*this article*
	c.109 G>A	p.G37R	algerian	7	F	Ho	3,5y	2, 13
	c.109 G>A	p.G37R	algerian	7	M	Ho	3m	2, 13
	c.109 G>A	p.G37R	morrocan	8	M	Ho	3y	2, 12
	c.142 delG	p.D48T fsX17	turkish	9	M	Ho	10m	27
	c.142 delG	p.D48T fsX17	turkish	9	F	Ho	1m	27
exon 4	c.184 G>A	p.E62K	tunisian	10	F	Ho	7y	26
(179-244bp)	c.224 A>G	p.D75G	thaï	1	M	comp.Hz *(see family 1 exon 2)*		
exon 6	c.349-1 G>C	p.S117K160del	italian	11	M	Ho	12y	2, 19
(349-480bp)	c.349-1 G>C	p.S117K160del	italian	11	M	Ho	19y	2, 19
	c.364 G>T	p.E122X	turkish	12	M	Ho	3m	22
	c.364 G>T	p.E122X	turkish	12	F	Ho	6y	22
	c.364 G>T	p.E122X	turkish	12	F	Ho	8y	22
	c.364 G>T	p.E122X	turkish	12	M	Ho	11y	22
	c.409 G>A	p.D137N	french canad	13	M	Ho	?	2, 11
	c.409 G>A	p.D137N	french canad	13	F	Ho	?	2, 11
	c.409 G>A	p.D137N	french canad	3	F	comp.Hz *(see family 3 exon 3)*		
	c.409 G>A	p.D137N	french canad	14	M	Ho	3m	22
	c.409 G>A	p.D137N	french canad	14	M	Ho	2m	22
	c.409 G>A	p.D137N	french canad	15	M	Ho	3m	22
	c.409 G>A	p.D137N	french canad	16	F	comp Hz	2w	22
	c.409 G>A	p.D137N	french canad	16	M	comp Hz	3,5m	22
	c.409 G>A	p.D137N	french canad	17	F	Ho	50y	*this article*
	c.409 G>A	p.D137N	caucasian	18	M	Ho	8m	*this article*
exon 7	c.499 G>T	p.E167X	caucasian	19	F	Ho	34y	21, 23
(481-597bp)	c.499 G>T	p.E167X	caucasian	19	F	Ho	38y	23
	c.536 G>T	p.S179I	pakistan	20	F	comp Hz	6m	2
	c.537 T>A	p.S179R	french canad	16	F	comp.Hz *(see family 16 exon 6)*		
	c.537 T>A	p.S179R	french canad	18	M	comp.Hz *(see family 16 exon 6)*		
	c.537 T>A	p.S179R	french canad	21	F	Ho	10y	22
	c.537 T>A	p.S179R	french canad	21	M	Ho	2m	22
	c.537 T>A	p.S179R	french canad	22	F	Ho	5m	22
	c.542 T>C	p.L181P	pakistan	20	F	comp.Hz *(see family 20 exon 7)*		
	c.554 G>T	p.G185V	portuguese	23	F	Ho	2y	22
	c.555-557 dupTTAC	p.G187LfsX13	turkish	24	F	Ho	1y	2, 16
	c.555-557 dupTTAC	p.G187LfsX13	turkish	24	M	Ho	1y	2, 16

(Ho: homozygous, comp Hz: compound heterozygous, age dg: age at diagnosis, m months, y years, w weeks)

Table 2. All published mutations in *SAR1B* gene

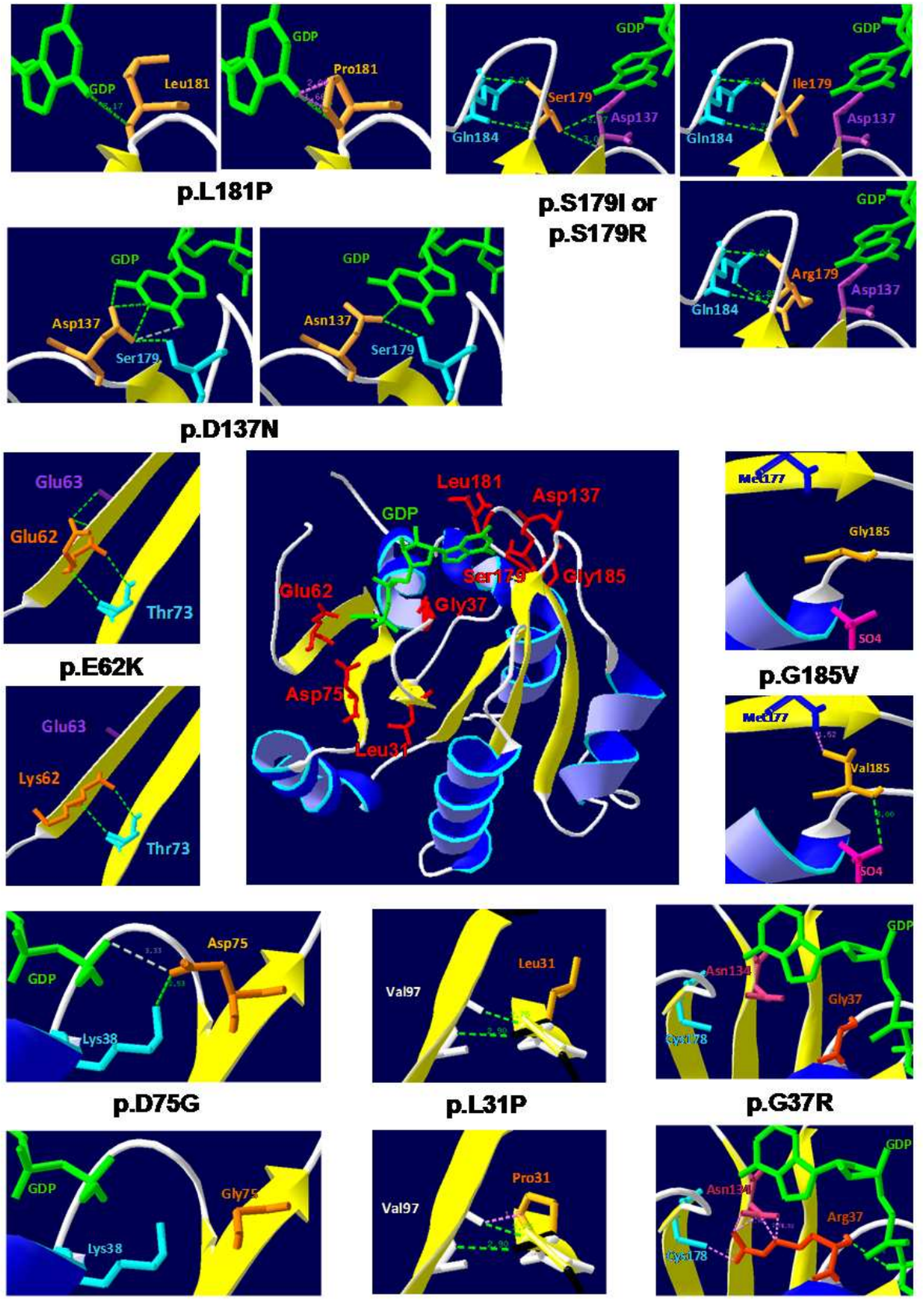
5.1. Nonsense mutations

Among the seven non-sense mutations, one deletes exon 2 (p.1-4482_58+1406 del 5946 ins 15bp, named "del exon 2") and one eliminates exon 6 (p.S117K160del), two are stop codons (p.E122X, p.E167X) which lead to truncated proteins, and two deletions and an insertion produce frameshifts followed by stop codons (p.L28RfsX34, p.D48TfsX17, p.G187LfsX13) leading to truncated proteins and modified C-terminal sequences. The major deletion (5943bp) of exon 2 (family 2 and new Tunisian patients) potentially leads to 4 different proteins [22] each of which lacks part of the N-terminus. The largest fragment lacks the first 43 residues, including the STAR motif, the α1 helix, the active site for GTP hydrolysis and Threonine 39. The deletion of exon 6 eliminates the recognition site for the guanine base (AA 134-137) thus abolishing the function of SAR1b. The five other nonsense mutations (resulting in stop codons) produce truncated proteins lacking the C-terminus. The shortest fragment is predicted to have about 33 AA and the longest contains 187/198 AA but, interestingly, all are predicted to abolish the function of the protein in the same manner. This suggests that the C terminal part of the protein plays a major role in the function of SAR1.

5.2. Missense mutations

The Swiss-pdb Viewer 3.1 program ([57], available on http://www.expasy.org/spdbv/) was used to calculate atomic resolution structural models for SAR1b having missense mutations (Table 3). First, using the 1F6B model [53] and PDB for *Cricetulus griseus* SAR1b (which lacks the first twelve AA and the 48-55 residues), two residues were modified (I80V, V163I) in order to produce a structural module having a sequence identical to that of human SAR1b. The effects of the missense mutations of AD/CMRD on this "humanized" structure were then modelled.

All the missense mutations are located on the exterior of the three dimensional structure, in strategic places near the recognition, binding and hydrolysis sites for the guanine base (in the N- and C-terminii) and/or affect a highly conserved residue in SAR1/Arf proteins. From the N- to the C- terminus the predicted effects may be summarized as the following (Figure 3). The p.G11D mutation is located in the membrane interacting site (anchorage of the N-terminal part of the molecule) and probably prevents binding to SEC12 and fixation to the ER membrane. The substitution G11P, associated with Y9F and S14F, has been described as being deleterious for vesicle release [38], however no model is available for this mutation (since the coordinates of the first 12 residues of the protein could not be established by the X-ray study leading to the 1F6B structure). The new mutation p.L31P affects the AA just before the active site of GTP and could decrease the GTP hydrolysis. The substitution of a linear (leucine) by a cyclic (proline) residue could lead to steric hindrance (Figure 5). The p.G37R and the p.D75G mutations are located in two different GDP hydrolysis sites. Replacement of glycine 37 by arginine creates steric hindrances with C178 and N134 and the replacement of the aspartic acid 75 by glycine abolishes the H bond with L38. All four of these mutations reduce or eliminate the affinity of SAR1b for GDP/GTP and are expected to



Using the 1F6B model Cricetulus griseus SAR1b [53] and Swiss Pdb Viewer

Figure 5. Localization of missense mutations in the three-dimensional structure of SAR1B

	Energy kJ/mol [a]	Grantham distance [b]	Consequence of mutation on prot. (concerned residue) [a]	Residue conservation [c]				PolyPhen prediction (Score) [d]	SIFT prediction (Score)[e]
				Sar1b prot.	Sar1 prot.	Sar1/ Arf family prot.	Small GTP binding prot.		
wild type	-9 749								
G11D	no modelisation	94	no modelisation	?	0	0	0	possibly damaging (0,927)	affect protein (0,03)
L31P	-6560	98	steric hindrance (Val97)	+	c	c	c	probably damaging (1,0)	affect protein (0,02)
G37R	75988	125	steric hindrances (Asn134, Cys178)	+	+	+	+	probably damaging (1,0)	affect protein (0,00)
E62K	-7777	56	loss of one H-(Glu63)	+	c	+	0	possibly damaging (0,955)	affect protein (0,00)
D75G	-9406	94	loss of one H-(Lys38)	+	+	+	+	probably damaging (0,99)	affect protein (0,00)
D137N	-10 086	23	loss of one H-bond (GDP)	+	+	+	+	probably damaging (1,0)	affect protein (0,00)
S179I	-8867	142	loss of : one weak H-bond (GDP) and one H-bond (Asp137)	+	+	s	0	probably damaging (1,0)	affect protein (0,00)
S179R	-7550	110	loss of : one weak H-bond (GDP) and one H-bond (Asp137)		+	s	0	probably damaging (1,0)	affect protein (0,00)
L181P	-9023	98	steric hindrances with GDP	c	0	0	0	beningn (0,281)	affect protein (0,00)
G185V	127 288	109	Steric hindrance (Met177)	+	+	+	0	probably damaging (1,0)	affect protein (0,00)

a Swiss Pdb Viewer 3.7 based upon the template 1F6b lacking the first 12 residues of SAR1b *C.g.* (resolution: 1,70Å, R value: 0,220, homolgy 98,9%) modified (p.I80V and p.V163I: homology 100%)
b Grantham distance (Alamut)
c http://www.ebi.ac.uk/clustalw/
residue conservation: +, identical; c, conserved substitution; s, semi conserved substitution
d PolyPhen-2 v2.2.2r395 http://genetics.bwh.harvard.edu/pph/
e Sorting Intolerant From Tolerant: http://blocks.fhcrc.org/sift/SIFT.html

Table 3. Molecular impact of missense mutations

affect the stability of the protein. The substitution p.E62K affecting a well-conserved AA belongs to some residues forming the interface with SEC23 [36], abolishes the H-bond with Glu63 and is predicted to be deleterious by "in silico" analysis (Polyphen, available on http://genetics.bwh.harvard.edu/pph2/ [58] and SIFT available on http://sift.jcvi.org/ [59-63]). A H-bond with the guanine in the guanine recognition site is abolished by the p.D137N mutation (Figure 5). Similarly the p.S179I and p.S179R mutations abolish the H-bonds with Asp 137 and with the guanine base. The substitution of a leucine for a proline (L181P) leads to steric hindrance with the guanine base and p.G185V modifies a highly conserved residue in the Arf/Sar1 family and is predicted to be deleterious by "*in silico*" analysis (Polyphen, SIFT). The last four mutations modify the α helix and β strands in the C-terminus and could affect the stability as well as the conformation of the protein.

6. Possible founder effects:

Founder effects are likely in the North African and French Canadian families (Table 2); it is likely that the same founder effect is responsible for the mutations of the North African patients (del exon 2, c.109 G>A). However, it is more uncertain for the c.409G>A and c.83_84delTG mutations, since the pedigrees of these families are not available. Perhaps there are hot spots, or different founder effects at the same place in the gene.

7. The biological and clinical impact of SAR1b mutations:

Table 4 provides the lipid profiles of the patients for which mutations in *SAR1B* have been established. As is typical for individuals affected with AD/CMRD, the mean values of total and HDL-cholesterol, apoAI and apoB are decreased, LDL-cholesterol is mildly decreased and triglycerides are in the normal range, however there is a large range of values for each of these parameters. As previously discussed, some patients present with low triglycerides or apoB levels and could be confused with atypical abetalipoproteinemia (familes 7, 12), and those with normal HDL cholesterol (family 10) could be confused with heterozygous FHBL. In homozygous patients, missense mutations are more frequent (12 families) than nonsense (8) and are as severe as nonsense mutations, except for the patient in family 10 (p.E62K) who has a normal HDL cholesterol level. The clinical data are not different among patients with different mutations. Several patients have been diagnosed later (adult or teenager) probably because of a mild intestinal syndrome and false diagnoses. Nevertheless, among the late diagnoses (10 patients after 10 years of age), only 3 have a missense mutation.

It has been suggested previously [22] that there is no apparent correlation between the genotype and the phenotype in AD/CMRD patients. For example, patients (from different families) with the same homozygous *SAR1B* mutation (for example the D137N mutation) exhibit different lipid profiles and vitamin E levels as do patients from the same families with the same mutations (the E122X and the S179R mutations). It is possible that modifier genes could be a cause of the different phenotypes. For example, a decrease in the transcriptional factor SREBP (Sterol Regulatory Element Binding Protein) has been shown to block the incorporation of SCAP (SREBP chaperone) in COPII vesicles and an acute depletion of

cellular cholesterol concentration has been shown to decrease COPII transport [64, 65]. Other genes that modulate cholesterol homeostasis could interfere such as *MTTP* (microsomal triglycerides transfert protein), *APOB*, *ABCG5/G8* (ATP Binding Cassette G5/G8).

mutation	ethnic origin	family	sex	status	TC	TG	HDLC	LDLC	apoB	apoA1	vitE	references
p.G11D	thaï	1	M	comp Hz	1,81	1,29			0,54	0,43	1,5	24
p.M1_H43del	algerian	2	F	Ho	2,01	1,44	0,32	1,04	0,5	0,42	3,3	22
p.M1_H43del	algerian	2	M	Ho	2,32	0,78	0,4	1,57	0,55	0,45	2,6	22
p.L28R fsX34	french canad	3	F	comp Hz	2,2	0,73					1,4	2, 11
p.L28R fsX34	morrocan	4	F	Ho	1,45	0,77	0,36	0,73	0,39	0,4	1,2	25
p.L28R fsX34	morrocan	5	F	Ho	2,31	1,36	0,7	1	0,82	0,5	2,4	27
p.L31P	morrocan	6	M	Ho	1,96	0,89	0,77	0,79	0,37	0,91	1,34	*this article*
p.L31P	morrocan	6	M	Ho	2,09	0,93	0,59	1,31			3,75	*this article*
p.G37R	algerian	7	F	Ho	1,26	0,67			0,2	0,39	7,6	2, 13
p.G37R	algerian	7	M	Ho	1,79	1,44			0,33	0,38		2, 13
p.G37R	morrocan	8	M	Ho	1,55	0,59			0,36	0,64	2,9	2, 12
p.D48T fsX17	turkish	9	M	Ho	2,61	1,24	0,57	1,48	0,56	0,7	4,4	27
p.D48T fsX17	turkish	9	F	Ho	2,72	1,36	0,83	1,28	0,43	0,9	6,8	27
p.E62K	tunisian	10	F	Ho	2,59		1,3	1,14	0,4			26
p.D75G	thaï	1	M	comp Hz								24
p.S117K160del	italian	11	M	Ho	2,07	0,94	0,52	0,78			1	2, 19
p.S117K160del	italian	11	M	Ho	2,43	1,28	0,7	1,22			5	2, 19
p.E122X	turkish	12	M	Ho	1,99	0,43	0,57	1,23	0,36		4,71	22
p.E122X	turkish	12	F	Ho	1,26	0,5	0,53	0,51	0,38	0,43	0,88	22
p.E122X	turkish	12	F	Ho	1,37	0,72	0,39	0,66	0,33	0,51	1,44	22
p.E122X	turkish	12	M	Ho	1,36	0,45	0,45	0,71	0,35	0,59	1,42	22
p.D137N	french canad	13	M	Ho	1,85	0,94					0	2, 11
p.D137N	french canad	13	F	Ho	2,08	0,59					1,6	2, 11
p.D137N	french canad	2	F	comp Hz								2, 11
p.D137N	french canad	14	M	Ho	1,3	0,45	0,49	0,61				22
p.D137N	french canad	14	M	Ho	0,86	0,37	0,38	0,31				22
p.D137N	french canad	15	M	Ho	1,24	0,82	0,41	0,46				22
p.D137N	french canad	16	F	comp Hz	1,39	0,91	0,36	0,62				22
p.D137N	french canad	16	M	comp Hz	1,11	0,54	0,45	0,42				22
p.D137N	french canad	17	F	Ho	2,52	1,35	0,53	1,38				*this article*
p.D137N	caucasian	18	M	Ho	1,41	0,85	0,35	0,68	0,24	0,57	2,5	*this article*
p.E167X	caucasian	19	F	Ho	1,86	0,43			0,44	0,57	<1	21, 23
p.E167X	caucasian	19	F	Ho	2,15	0,36			0,55	0,62	<1	23
p.S179I	pakistan	20	F	comp Hz	1,4	0,79	0,44	0,6	0,59			2
p.S179R	french canad	16	F	comp Hz								22
p.S179R	french canad	16	M	comp Hz								22
p.S179R	french canad	21	F	Ho	2,82	1,36	0,59	1,61				22
p.S179R	french canad	21	M	Ho	1,5	0,78	0,56	0,59				22
p.S179R	french canad	22	F	Ho	1,78	1,28	0,56					22
p.L181P	pakistan	20	F	comp Hz								2
p.G185V	portuguese	23	F	Ho	2,36	1,98	0,49	0,98	0,61	0,46	2,5	22
p.G187L fsX13	turkish	24	F	Ho	2	1,6			0,7	0,5	6,6	2, 16
p.G187L fsX13	turkish	24	M	Ho	1,5	1,5			0,5	0,5	3,6	2, 16

(TC total cholesterol, TG triglycerides, LDLc LDL cholesterol, HDLc HDL cholesterol : mM; apoB, apoA1: g/l; vitE vitamin E: μM)

Table 4. Biological data in described cases with mutations

Recently a polymorphism of *PCSK9* (proprotein convertase subtilisin/kexin type 9), p.L15_16insL, has been reported in an AD patient [27]. This polymorphism is frequent (25% heterozygous in normal individuals and 34% in cases of HBL) and weakly hypocholesterolemic (-14%) [66]. Further, mutations or polymorphisms in other COPII and PCTV genes could contribute to the different phenotypes by modifying the network of all their corresponding proteins. However, none of these mutations have been described in cases of AD/CMRD. The search for polymorphisms in multiple proteins is very time-consuming but could be facility by the new sequencing methods. Rare polymorphisms in the coding regions of the *SAR1B* and *SAR1A* genes have been described but none of these has been observed in the *SAR1A* gene in any of our patients and only one polymorphism (heterozygous) has been found in the *SAR1B* gene (L45L) in our patients. This polymorphism is found with the same frequency in the patients as in normal individuals (0,18 versus 0,19, respectively). The impact of this polymorphism has not been studied.

8. Management of AD/CMRD (for details, see the guidelines of Peretti, 2010 [29])

Treatment consists primarily of a low fat diet, with the appropriate amounts of n-6 and n-3 fatty acids, supplemented with fat soluble vitamins. The failure to thrive of the children is the most important clinical feature and catch-up growth is not observed systematically [29]. The neurological and ophtamological complications may be less severe than in other familial hypocholesterolemias and may depend upon the levels of the fat soluble vitamins and when vitamin supplementation is instituted. Myolysis and cardiac abnormalities have been observed in some AD/CMRD patients [23] and consequently, measurement of the serum CK level should be included in the evaluation and follow-up of the patients. A moderate degree of fat liver is common, but until now no case of cirrhosis has been published.

9. Conclusions and future prospects

Significant advances in the diagnosis of AD/CMRD and in the understanding of lipoprotein secretion have occurred over the last decade. However, many questions remain to be answered. SAR1b is a ubiquitous protein, essential for the trafficking of proteins between the ER and the Golgi. Why do the mutations in *SAR1B*, that have been reported to date, apparently affect only the intestine and the transport of chylomicrons in the enterocyte? Although an increase of *SAR1A* mRNA was measured in enterocytes containing mutated *SAR1B* [27], the AD/CMRD phenotype was still manifested by a lack of chylomicron secretion. Under what conditions, if any, could SAR1a replace SAR1b? Is SAR1a the veritable GTPase for COPII vesicles? Do some mutations or polymorphisms in other regulator genes explain the lack of correlation between genotype and phenotype in AD/CMRD? There are some CMRD patients without mutations of *SAR1B, SAR1A, VAMP7, MTTP* genes (unpublished data). What gene mutations could explain the AD/CMRD phenotype in these patients? Novel technologies (such as whole exome and whole genome sequencing) may provide a better understanding of this disease and open novel diagnostic approaches.

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