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Review

COPA syndrome, 5 years after: Where are we?

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ABSTRACT

Heterozygous missense mutations in *COPA*, encoding coatomer protein subunit alpha (COPA), cause an interferonopathy mainly associating lung, joint and kidney involvement. This rare autoinflammatory disease is characterised by variable expression and a remarkably high frequency of clinical non-penetrance. Lung features, predominantly chronic diffuse alveolar haemorrhage (DAH), are observed in almost patients and can result in end-stage respiratory insufficiency. The initially described phenotype was broadened to include isolated DAH or lupus nephritis. Rare manifestations reminiscent of other monogenic interferonopathies occur. This indicates the need for careful clinical evaluation in patients with suspicion or diagnosis of COPA syndrome. Considering the dominant inheritance model and the highly variable phenotype, ranging from severe multi-organic disorder to non-penetrance, a careful family screening is recommended. New insights in disease pathogenesis have linked COPA mutations to STING-mediated interferon signalling. Beside a variable efficacy of 'classical' immunosuppressive drugs, Janus kinase (JAK) inhibitors constitute a promising treatment in COPA syndrome, and further targeted therapies are awaited.

1. Introduction

Autoinflammation is a rapidly evolving field, as evidenced by the identification of more than 50 new monogenic autoinflammatory diseases (AIDs) in the last 10 years [1,2]. The concept of autoinflammation is now part of a pathophysiological continuum between immunodeficiency, autoimmunity and autoinflammation, and AIDs are currently classified as primary immune deficiencies. The phenotypic spectrum of AIDs has progressively expanded from predominantly mono-organic diseases to systemic multi-organic disorders. AIDs onset is mainly reported to occur in childhood however adult forms have been also described [3,4].

Heterozygous mutations in *COPA*, encoding coatomer protein subunit alpha, were described in 2015 to cause a hereditary inflammatory syndrome predominantly associating lung, kidney and joint involvement [5]. This disease is rare, most commonly beginning in childhood, but is possibly under-diagnosed in adult onset, asymptomatic or mono-organic forms. COPA is part of a complex involved in intracellular trafficking of cargo proteins, and underlying pathophysiology of COPA syndrome has gained insights in the last years and was recently linked to interferon (IFN) signalling.

Here, we provide an overview of COPA syndrome, and describe new insights in disease pathogenesis, various phenotypic presentations, key investigations for diagnosis process and therapeutic perspectives.

2. Genetics

Heterozygous mutations in *COPA* are inherited as an autosomal dominant trait. *COPA* (NC_000001.11) is located on chromosome 1q23.2 and counts 33 exons (54 kb). To date, 10 missense substitutions have been reported to be associated with COPA syndrome in a total of 17 families worldwide (Fig. 1 and Table 1). All of them are located in the WD40 domain of the protein (mostly in the WD5 and WD6 domains) involved in COPA ability to bind cargo proteins (see Section 4). One mutation, c.698G > A p.Arg233His accounts for 41% of the reported cases (Fig. 1). Of note, a high clinical non-penetrance–around 25% – is observed in COPA syndrome as asymptomatic adult carriers have been described (Table 2). Although this is not uncommon in autosomal dominant inherited disorders and is observed in other monogenic IFN-related AID (e.g. due to gain-of-function mutations in *IFIH1* encoding MDA5 [6]), this suggests that additional environmental and/or genetic or

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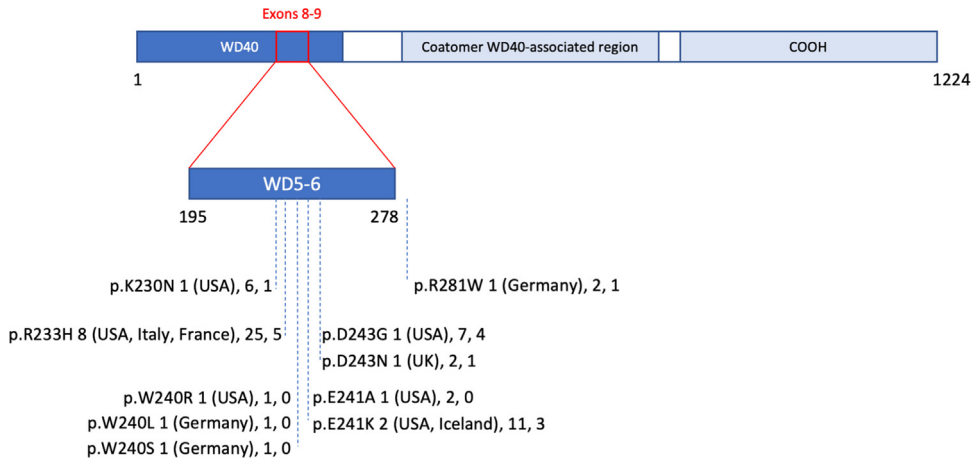

Fig. 1. Schematic representation of COPA protein highlighting the WD40 repeat domain, the coatomer WD40-associated region, and the coatomer C-terminal region. *COPA* exons 8-9 encode the WD5 and WD6 repeat domains where are located most of the mutations. The reported mutations are listed with respectively the number of identified families (country), reported individuals carrying the mutation, and asymptomatic carriers.

Table 1
Summary of the reported *COPA* (NM 001098398) substitutions.

Exon	Mutation name (cDNA)	Mutation name (protein)	Mutation abbreviated name	References
Exon 8	c.690G > T	p.Lys230Asn	p.K230 N	Watkin et al., 2015
	c.698G > A	p.Arg233His	p.R233H	Watkin et al., 2015 Volpi et al., 2017 Boulisfane-El Khalifi et al., 2019 Taveira-DaSilva et al., 2019 Krutske et al., 2019 Frémond et al., 2020 Lepelley et al., 2020
Exon 9	c.718T > C*	p.Trp240Arg	p.W240R	Noorelahi et al., 2018
	c.719G > T	p.Trp240Leu	p.W240L	Prenzel et al., 2020
	c.719G > C	p.Trp240Ser	p.W240S	Prenzel et al., 2020
	c.721G > A	p.Glu241Lys	p.E241 K	Watkin et al., 2015 Jensson et al., 2017
	c.722A > C	p.Glu241Ala	p.E241A	Patwardhan and Spencer 2019
	c.727G > A	p.Asp243Asn	p.D243 N	Lepelley et al., 2020
	c.728A > G	p.Asp243Gly	p.D243G	Taveira-DaSilva et al., 2019
	c.841C > T	p.Arg281Trp	p.R281 W	Prenzel et al., 2020

*This cDNA mutation name is a deduction from the protein mutation name reported in Noorelahi et al., 2018.

epigenetic factors are necessary for clinical disease to manifest [7]. COPA-associated substitutions are described to act as dominant-negative mutations [5,8].

3. Phenotype

COPA syndrome is a rare disease (less than 60 patients reported so far) and is characterized by variable expression and possible non-penetrance [5,8–15]. Although the reported age at presentation is usually before 5 years [5,9–13], adult onset has been documented in a few patients.

Following clinical pictures are the most seen:

- recurrent diffuse alveolar haemorrhage (DAH);
- DAH and/or interstitial lung disease (ILD) associated with arthritis and positive antibodies such as rheumatoid factor (RF) or antineutrophil cytoplasmic antibody (ANCA);
- apparently isolated lupus-like nephropathy;
- apparently isolated polyarticular juvenile idiopathic arthritis (JIA) with antibodies–in particular with early onset and/or uncommon severity and/or response to treatment.

A summary of the characteristics of COPA patients described in the literature is provided in Table 2.

3.1. Lung phenotype

Almost all symptomatic individuals present with lung features, predominantly chronic DAH. ILD with no DAH can also be observed, both presentations eventually resulting in pulmonary fibrosis and end-stage respiratory insufficiency in some cases. At diagnosis, COPA lung disease is usually associated with extra-pulmonary manifestations, joint involvement being the second most observed phenotype. However, a severe lung restricted form of COPA syndrome has also been reported [16]. Clinical presentation usually associates chronic cough, tachypnoea on exertion or at rest. As recurrent fever and cough are observed concomitantly, and haemoptysis is rare in children, patients are commonly misdiagnosed since recurrent pneumonias diagnosis is evocated before DAH. Poor weigh gain or failure to thrive is also a common sign to all causes of chronic respiratory insufficiency. Lung examination may highlight retractions, crackles, and signs of hypoxia such as cyanosis or clubbing. Rarely, thoracic deformation including pectus excavatum [15] has been reported and may be incidentally present but can also be related to chronic retractions.

Radiological pattern, documented by chest high resolution CT-scan can highlight DAH signs such as predominant patchy ground glass opacities and focal alveolar condensations. Signs of chronic ILD with more diffuse ground glass opacities, septal thickening, reticulations as well as sub-pleural or parenchymal traction cysts,

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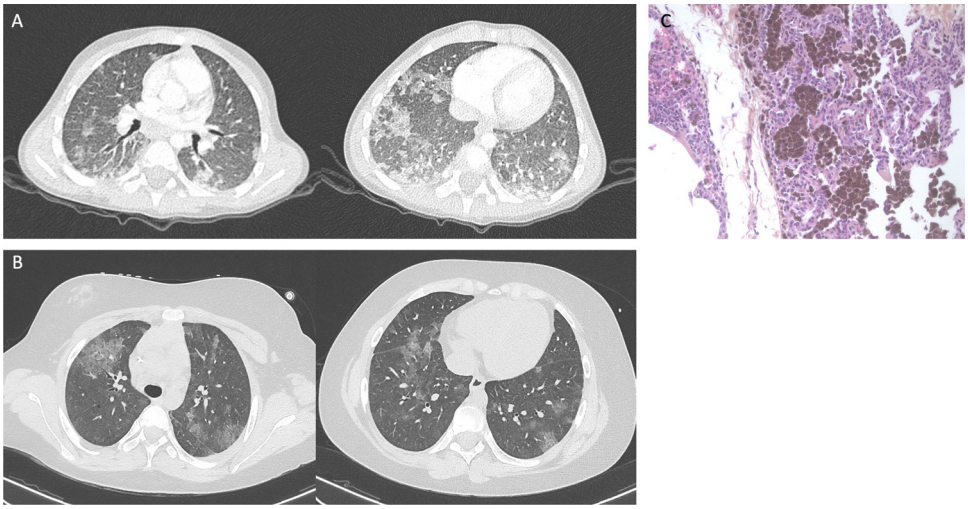

Fig. 2. High resolution chest CT-scan and lung biopsy of a patient carrying the COPA p.D233H mutation. High resolution chest CT-scan at age 4: Patchy diffuse abnormalities (ground glass opacifications and alveolar opacities). There is no predominant localisation with central and peripheral lesions in the whole lungs. The aspect is consistent with an alveolar haemorrhage. (B) Same patient at age 12: Patchy diffuse dense ground glass opacities consistent with an alveolar bleeding recurrence. Appearance of infracentimetric intraparenchymal cysts in the upper lungs and reticulations in favor of a fibrosis evolution. (C) Surgical lung biopsy at age 4. Hematoxylin & eosin staining shows a heterogeneous repartition of the lesions with haemosiderin-laden macrophages (siderophages) filling the alveolar spaces and no sign of lung fibrosis.

honeycombing lesions and alveolar distortion indicating a lung fibrosis evolution (Fig. 2A&B). In some cases, chest CT-scan can remain normal in asymptomatic patients and/or between DAH flares.

Blood gas and overnight oxygen record can highlight hypoxia at rest, especially if the patients are anaemic due to alveolar bleeding. Pulmonary function tests are non-specific and usually display a restrictive pattern with gas diffusion impairment.

Bronchoalveolar lavage can confirm the DAH while documenting a light pink to bloody sample related to haemoglobin-laden macrophages–called siderophages. Apart from DAH, bronchoalveolar lavage can also reveal an alveolitis, usually with elevated lymphocytes ratio, or either be normal, especially if realised in a preserved area of the lung.

The lung histopathological features so far documented in COPA syndrome comprise non-specific features of DAH, and/or fibrosing ILD. DAH lesions are constituted by siderophages – that appear to be blue after Pearls staining – filling the alveoli. The lesions are usually heterogeneous with preserved areas of lung parenchyma (Fig. 2C). Interstitial lesions are also unspecific (thickening of the alveolar walls, alveolar distortion, alveolitis, fibrosis). Some lesions are more specific of COPA syndrome such as lymphoid follicles with germinal-centre organisation, infiltrating T-cells and capillaritis with neutrophils within the alveolar septa. Of note, because of the heterogeneity of the lesions, a very small lung sample can appear to be normal.

3.2. Joint involvement

Joint involvement is frequent in COPA syndrome, observed in almost 75% of patients. Arthritis mainly occurs in the early teen years but earlier onset even before the age of 5 years is also recorded [9,11,17]. Arthritis affects predominantly the knees and the interphalangeal joints of the hands, being mostly polyarticular, and is usually associated with autoantibodies (antinuclear and ANCA, and RF). In children, arthritis resembles polyarticular JIA and can be severe as reported by Volpi et al. with an involvement of the cervical spine responsible for vertebrae fusion [11]. Other patients suffer from disabling joint pain. Positivity for RF was recorded in almost two thirds of COPA patients tested, most of them presenting with arthritis (Table 2). This suggests that RF could be a useful diagnostic marker of COPA syndrome, especially in childhood, during which RF+ polyarticular JIA rarely occurs [18]. Of interest, rheumatoid nodules have been described in one child with RF+ polyarticular JIA [17], a phenotype reminiscent of adult rheumatoid arthritis [18]. Of note, four COPA patients with arthritis [5,10,17] displayed high or middle levels of anti-cyclic citrullinated peptide (CPP) antibodies that have been previously associated with joint destruction [19]. Osteonecrosis and severe erosive bone lesions have been documented in several patients [5,11,13].

3.3. Renal involvement

A glomerular pathology has been recorded in almost half of COPA patients [9]. The renal pattern observed in patients varies in type but can be severe, as emphasised by the requirement for a kidney transplant in two COPA patients [5,20]. Lupus-like nephritis and IgA nephropathy have been reported [5,20]. Of importance, one clinically asymptomatic individual – screened for familial living donor kidney transplantation – suffered from chronic proteinuria related to a membranous glomerulonephrititis [20]. This indicates the need for careful renal investigation in patients with suspicion or diagnosis of COPA syndrome (see Section 5.1). Histological findings documented focal segmental glomerulosclerosis, membranous glomerulonephritis, crescentic glomerulonephritis, immune complex deposits (IgA, IgM, IgG, C1q, C3, C4).

Non-immune-related kidney involvement has been described in one family [13] with nephrolithiasis and renal carcinoma in a patient and her father, respectively.

3.4. Others organ involvement

Along with the description of new cases, the recognised phenotype of COPA syndrome has subsequently broadened to include (Table 2): autoimmune thyroiditis [5]; hepatitis [8]; skin features: vitiligo [8], unspecific polymorphic rash [10]; neurological features: paroxysmal exertional dyskinesia [5], neuromyelitis optica [13], disruptive behaviour disorder [15]; macrophagic activation syndrome [8]; GERD [8]; cardiac hypertrophy [8]. It is possible that such organ involvement may be more common signs of COPA syndrome,

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Table 2
Characteristics of the 59[a] COPA patients reported in the literature.

General characteristics	
Last status, *n* (%)	Alive: 58 (98)
Sex-ratio	
All patients	26:33 (0.8)
Asymptomatic carriers	7:5 (1.4)
Clinical characteristics of the 45 (76%) symptomatic individuals	
Median clinical onset[b], y (range)	7 (0.5-56)[c]
Onset before 5 y, *n* (%)	26/41 (65)[d]
Thoracic involvement, *n* (%)	43 (96)
ILD	28/33 (85)
Acute haemorrhage	15/33*(45)
Lung fibrosis	Reported in few patients extensively described/explored
Pectus excavatum	1 (NA)
Joint involvement, *n* (%)	
Arthritis	30 (67)
Arthralgia without arthritis	3 (7)
Systemic involvement, *n* (%)	
Recurrent Fevers	2 (NA)
Systemic inflammation	12/24 (50)
Kidney involvement, *n* (%)	9/19 (47)
Immune-related GN	7/19 (37)
Non-immune kidney involvement (nephrolithiasis, renal carcinoma)	2/19 (11)
Skin involvement, *n*	
Vitiligo	1
Skin rash (suspicion of erythema multiforme)	1
Nervous system involvement, *n*	
Paroxysmal exertional dyskinesia	2
Neuromyelitis optica	1
Disruptive behaviour disorder	1
Other symptoms	
MAS, hepatitis, cardiac hypertrophy, severe GERD, delayed puberty, autoimmune thyroiditis	NA
Autoantibodies	
ANA	28/40
Anti-DNA	0/23
ANCA[e]	23/36
RF	20/33
Treatments and procedures	
Steroids	31/41
DMARDs	21/24
Biologics[f]	9/24
Response to conventional IS	Inconstant
JAK1/2, JAK1/3 inhibitors	4/42
Kidney transplantation	2/42
Lung transplantation	4/42

Abbreviations: ANA: antinuclear antibodies; ANCA: antineutrophil cytoplasmic antibodies; anti-DNA: anti-double-stranded DNA antibodies; DMARD: disease-modifying antirheumatic drugs; GERD: gastro-esophageal reflux disease; GN: glomerulonephritis; IgA: immunoglobulin A; ILD: Interstitial lung disease; IS: immunosuppression; JAK: Janus kinase; MAS: macrophage activation syndrome; NA: not assessed; *n*: number; RF: rheumatoid factor; y: year. *Diffuse alveolar haemorrhage diagnosed by a large number of hemosiderin-laden macrophages in bronchoalveolar lavage, at least in two patients.

[a] [5,8–17,20,31,42]. The patients diagnosed through screening of chILD cohorts and for whom detailed clinical pictures are not available are not included in the present literature of patients [43].

[b] The age at onset was assessed only for symptomatic carriers.

[c] Not recorded for seven patients.

[d] Not recorded for four patients.

[e] With specificity against MPO in four patients and against MPO and PR3 in one individual.

[f] Including anti-CD20, anti-TNF, anti-CTLA4, and anti-IL6 receptor monoclonal antibodies.

together with the description of new features. This also indicates the need for careful clinical evaluation in the case of suspicion or diagnosis of COPA syndrome, including skin and neurological examination. Of interest, some of these rare manifestations overlap with well-described monogenic interferonopathies [21].

4. Pathophysiology

Coat protein subunit alpha is part of the coatomer protein complex I (COPI) that is described to play a role in retrograde transport of proteins between the Golgi and the endoplasmic reticulum (ER) [22,23]. Of interest, all of the substitutions reported so far in *COPA* are located in the WD40 domain that is described to ensure the recognition of the cargo proteins through their dilysine motif [22,24]. However, the pathophysiological mechanisms underlying the mutant COPA-associated phenotype were not properly understood until recent insights in IFN induction due to mutations in COPA.

4.1. ER stress and Th17 response

Evidence of ER stress and priming of a T helper 17 (Th17) response were reported in the context of mutant COPA protein and in patient-derived cells [5], so that COPA syndrome was considered as an autoimmune disorder. A murine model of COPA (see also Section 4.3) highlighted a defect in thymic selection of T cells leading to increased autoreactive T cells and decreased regulatory T cells, both of which mediated autoimmunity [25]. Of note, high titres of autoantibodies are frequently–albeit not necessarily–recorded when tested in patients (Table 2). Of further interest, none patient presented double-stranded DNA (dsDNA) antibodies, a hallmark of systemic erythematosus lupus.

4.2. Interferon pathway activation

In 2017, Volpi et al. described an increased transcription of interferon (IFN) stimulated genes (ISGs) in blood circulating cells of five COPA patients [11], further confirmed by a second report from our team [16]. There is an obvious clinical overlap between COPA syndrome and a recognised IFN-mediated AID (belonging to the group of type I interferonopathies) due to gain-of-function in *STING1* encoding STING, a key adaptor of the cytoplasmic DNA signalling. This disease referred to SAVI (STING-associated vasculopathy with onset in infancy) can also associate ILD, joint involvement and haemorrhagic alveolitis [26]. Of interest then, STING is an ER-resident protein and its signalling implies trafficking from the ER to the Golgi to induce IFN production. A recent published work has provided important evidence further implicating enhanced IFN signalling in COPA syndrome pathogenesis [8]. The authors demonstrated that mutations in COPA induced STING-dependent signalling and an enhanced trafficking of STING to the Golgi, and detected an indirect interaction between STING and COPA. This was further confirmed by the data of three groups [27–30]–in particular, indicating a possible binding adaptor protein between STING and COPA. Taken together, these data indicate that COPA syndrome represents a monogenic interferonopathy, in light of the continuum between autoimmunity and autoinflammation in AIDs.

4.3. Mouse model

A murine model of COPA syndrome has been generated and studied in two works from the same group [28,25]. The germline knock-in mutant mice carry a missense mutation previously reported in COPA patients, i.e. p.E241 K [5]. These mice had no clinical or histological features of inflammatory arthritis. In contrast, they presented with lung pathological lesions consistent with ILD and more specifically with the findings in lung sections from COPA patients. Indeed, cellular bronchiolitis with germinal centre formation was observed in *Copa*$^{E241K/+}$ lung biopsies, with a predominance of CD4+ T cells in the mononuclear infiltrates and lymphoid aggregates comprised of B cells, reminiscent of the lung pathology seen in COPA patients [5,31]. Interestingly, none mouse

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showed evidence of alveolar haemorrhage. However, one animal had an inflammation in a pulmonary artery, suggestive of vasculitis. This model further showed spontaneous activation of cytokine-secreting T cells, besides a defect in thymic selection of T cells, leading to T cell-related lung disease. Moreover, thymic epithelial cells and splenocytes isolated from *Copa*$^{E241K/+}$ mice showed an increased expression of ISGs that was abrogated when crossing the mice with a STING knockout background [28]. The loss of STING also rescued the disturbance of peripheral T cells populations [28]. Of interest, homozygous *Copa*$^{E241K/E241K}$ mice were embryonically lethal, but rescued by loss of STING, further implicating STING in COPA syndrome pathogenesis [28].

5. Diagnostic process

When suggestive clinical signs of COPA syndrome are associated, routine laboratory tests–if not performed previously–and an assessment of type IFN pathway should be proposed. It has to be reminded that lung disease may appear as the sole expression of COPA syndrome so that this diagnosis should be evocated in case of unexplained DAH and ILD.

5.1. Routine laboratory tests

Even non-specific of COPA syndrome, routine laboratory tests are of major importance to collect evidences in favour of autoinflammation and autoimmunity, and to help deciphering the involved organs. Of note, an inflammatory syndrome is inconstant and discordant CRP and ESR can be observed. In COPA patients with inflammatory arthritis and/or kidney disease, DAH can present with few or no symptoms and be revealed by non-specific biology results mimicking haemolytic anaemia i.e. low level of haemoglobin together with high counts of reticulocytes and low iron blood level. Lupus nephritis was described to be pauci-symptomatic in one patient, warranting investigation of the kidney. Moreover, routine laboratory tests will serve as references values for follow-up evaluation of disease severity and treatment efficacy. They include, non-exhaustively, inflammatory markers (hemogram, ESR, CRP), evidences for chronic bleeding (reticulocytes, iron), autoantibodies (ANA, ANCA, anti-CCP, rheumatoid factor), immune markers (IgA, IgM, IgG, C1q, C3, C4), immunophenotyping (Th17 cells), and organ-specific markers (TSH, proteinuria, urine creatine, serum creatine, liver enzymes).

5.2. IFN pathway assessment [21]

Direct assessment of IFN has been challenging since the 1950s when it was first described. In order to evaluate IFN pathway activation, indirect methods have been subsequently developed to include:

- IFN activity assay [32];
- IFN signature i.e. the expression of several ISGs using RT-qPCR [33–36] or NanoString technology [37].

IFN activity assay relies on the indirect cytopathic effect of a patient's liquid (serum, cerebrospinal fluid) in an *in vitro* model of viral infection [32], and requires fresh blood samples (or frozen aliquots of serum/cerebrospinal fluid sent in dry ice). In contrast, IFN signature is more convenient to screen patients, in particular from more distant clinical units, since the blood tube required (PAXgene tube) is stable at room temperature for 72 hours.

In 2016, a direct quantification of IFN alpha protein *per se* was described using an ultra-sensitive Simoa digital ELISA assay [38] and highly specific anti-pan-IFN alpha antibodies [39]. To our knowledge, this ground-breaking technology is so far not available routinely and only performed in research laboratories.

In the presence of suggestive features of COPA syndrome, the identification of an induction of the IFN pathway confirmed at least on two separate occasions, in the absence of recent viral infection, is a further point in favour of genetic investigation [21]. Of note, in asymptomatic individuals (clinical non-penetrance) the induction of the IFN pathway is absent or milder [8]. This is not the case in asymptomatic individuals with gain-of-function mutations in *IFIH1* encoding MDA5 [6,40], further emphasising the role of additional environmental and/or genetic or epigenetic factors in disease pathogenesis [7].

5.3. Genetic testing

Genetic testing is usually performed as a second-intention test, when clinical and biological evidences for a COPA syndrome are convincing. They are realised in expert centres. Depending on the centres available technics, a mutation in *COPA* can be identified by several ways that include:

- targeted Sanger sequencing of the exons and the flanking intronic junctions of *COPA* or restricted to the exons 8 and 9 spanning the hot-spot of mutations in *COPA*;
- next-generation sequencing by targeted-sequencing (e.g. 'AIDs panel', 'chILD panel');
- whole exome or whole genome sequencing.

Considering the targeted sequencing, it is important to note that one substitution has been described at position 281 [15], farer than the initial 'hot spot' indicating the possibility of an extended cluster of mutations and warranting a non-restricted sequencing.

6. Family screening and genetic council

Considering the dominant inheritance model and the highly variable phenotype, ranging from severe multi-organic disorder to non-penetrance, a careful family screening is recommended. A genetic council has to be offered to the family, and based on the medical history and the local genetic screening policies, a genetic screening is recommended for both parents of the probands, for all symptomatic relatives, and, in most countries, for the requesting asymptomatic adults–even in the absence of the strong induction of the IFN pathway [8].

Prenatal and pre-implantation diagnosis are subsequent important issue that have to be discussed in the frame of multidisciplinary team meetings, with a case by case evaluation of the requests in each family [41].

7. Therapeutic perspectives

7.1. Medical treatments

Most reported COPA patients were treated with steroids, and one or various lines of immunosuppressive drugs, encompassing disease-modifying antirheumatic drugs (DMARDs) and biologics (Table 2). Although response to treatments is not detailed in all cases, there is a certain efficacy reported of conventional immunosuppressors. The recent finding of a link between COPA syndrome and IFN pathway activation led to the attempt of the use of JAK inhibition–i.e. blocking the IFN receptor (IFNAR) downstream signalling–in several patients [16,17]. Promising effects of the JAK1/2 (ruxolitinib) and JAK1/3 (tofacitinib) inhibitors were described, although questions of sustained efficacy require

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longer-term evaluation in particular for the lung disease. Regarding the latter case, a patient with severe AH ameliorated with ruxolitinib [16], but experienced recurrence of AH associated with a progression to lung fibrosis on chest CT-scan, requiring the association with anti-IL1-receptor antibodies and the switch to another JAK1/2 inhibitor (baricitinib) (data not published).

7.2. Lung and kidney transplantation

COPA-related pulmonary disease can lead to severe fibrosis and end-stage respiratory failure so that lung transplantation has been attempted in four adult patients. In three cases, information on post-transplant survival is not reported [10] or only very briefly [9] ('near standard post-transplant survival'). The fourth patient, aged 25, is alive and doing well 15 months post-transplant [14]. Considering the involvement of the haematological compartment in COPA syndrome pathogenesis, a longer-term follow up is required to evaluate the risk of relapse on transplanted lungs.

Kidney transplantation has been described in two patients [5,20], further indicating the need for careful renal screening. Post-transplant follow-up is not available besides the information of a satisfactory renal function 3 months after transplantation in one adult [20].

8. Conclusion

Five years after its first description, COPA syndrome is now considered as an IFN-related AID i.e. monogenic interferonopathy–with autoinflammatory and/or autoimmune features. The initially described phenotype has been subsequently broadened to include isolated lung or kidney disease, and rare manifestations reminiscent of other monogenic interferonopathies. The onset of symptoms is usually before age 5, however, recently reported adult patients and the high clinical non-penetrance warrant clinical and biological investigations and careful genetic counselling. Novel insights in disease pathogenesis provided targeted therapies and promised new specific therapeutic approaches that may also be useful to more frequent autoimmune/autoinflammatory disorders where a key pathogenic role of IFN has been described.

Disclosure of interest

The authors declare that they have no competing interest.

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References

[1] Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, et al. Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol 2020;40:24–64, http://dx.doi.org/10.1007/s10875-019-00737-x.
[2] Aksentijevich I, Soriano A, Hernández-Rodríguez J. Editorial: autoinflammatory diseases: from genes to bedside. Front Immunol 2020;11:1177, http://dx.doi.org/10.3389/fimmu.2020.01177.
[3] Martorana D, Bonatti F, Mozzoni P, Vaglio A, Percesepe A. Monogenic Autoinflammatory Diseases with Mendelian Inheritance: Genes, Mutations, and Genotype/Phenotype Correlations. Front Immunol 2017;8:344, http://dx.doi.org/10.3389/fimmu.2017.00344.
[4] Georgin-Lavialle S, Ducharme-Benard S, Sarrabay G, Savey L, Grateau G, Hentgen V. Systemic autoinflammatory diseases: Clinical state of the art. Best Pract Res Clin Rheumatol 2020:101529, http://dx.doi.org/10.1016/j.berh.2020.101529.
[5] Watkin LB, Jessen B, Wiszniewski W, Vece TJ, Jan M, Sha Y, et al. COPA mutations impair ER-Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis. Nat Genet 2015;47:654–60, http://dx.doi.org/10.1038/ng.3279.
[6] Rice GI, Del Toro Duany Y, Jenkinson EM, Forte GM, Anderson BH, Ariaudo G, et al. Gain-of-function mutations in IFIH1 cause a spectrum of human disease phenotypes associated with upregulated type I interferon signaling. Nat Genet 2014;46:503–9, http://dx.doi.org/10.1038/ng.2933.
[7] Kumrah R, Mathew B, Vignesh P, Singh S, Rawat A. Genetics of COPA syndrome. Appl Clin Genet 2019;12:11–8, http://dx.doi.org/10.2147/TACG.S153600.
[8] Lepelley A, Martin-Niclós MJ, Le Bihan M, Marsh JA, Uggenti C, Rice GI, et al. Mutations in COPA lead to abnormal trafficking of STING to the Golgi and interferon signaling. Journal of Experimental Medicine 2020:217, http://dx.doi.org/10.1084/jem.20200600.
[9] Vece TJ, Watkin LB, Nicholas S, Canter D, Braun MC, Guillerman RP, et al. Copa syndrome: a novel autosomal dominant immune dysregulatory disease. J Clin Immunol 2016;36:377–87, http://dx.doi.org/10.1007/s10875-016-0271-8.
[10] Jensson BO, Hansdottir S, Arnadottir GA, Sulem G, Kristjansson RP, Oddsson A, et al. COPA syndrome in an Icelandic family caused by a recurrent missense mutation in COPA. BMC Med Genet 2017;18:129, http://dx.doi.org/10.1186/s12881-017-0490-8.
[11] Volpi S, Tsui J, Mariani M, Pastorino C, Caorsi R, Sacco O, et al. Type I interferon pathway activation in COPA syndrome. Clin Immunol 2018;187:33–6, http://dx.doi.org/10.1016/j.clim.2017.10.001.
[12] Noorelahi R, Perez G, Otero HJ. Imaging findings of Copa syndrome in a 12-year-old boy. Pediatr Radiol 2018;48:279–82, http://dx.doi.org/10.1007/s00247-017-3961-3.
[13] Taveira-DaSilva AM, Markello TC, Kleiner DE, Jones AM, Groden C, Macnamara E, et al. Expanding the phenotype of COPA syndrome: a kindred with typical and atypical features. J Med Genet 2019;56:778–82, http://dx.doi.org/10.1136/jmedgenet-2018-105560.
[14] Mallea JM, Kornafeld A, Khoor A, Erasmus DB. Lung Transplantation in a Patient with COPA Syndrome. Case Rep Transplant 2020;2020:1–2, http://dx.doi.org/10.1155/2020/3624795.
[15] Prenzel F, Harfst J, Schwerk N, Ahrens F, Rietschel E, Schmitt-Grohé S, et al. Lymphocytic interstitial pneumonia and follicular bronchiolitis in children: A registry-based case series. Pediatr Pulmonol 2020;55:909–17, http://dx.doi.org/10.1002/ppul.24680.
[16] Frémond M-L, Legendre M, Fayon M, Clement A, Filhol-Blin E, Richard N, et al. Use of ruxolitinib in COPA syndrome manifesting as life-threatening alveolar haemorrhage. Thorax 2020;75:92–5, http://dx.doi.org/10.1136/thoraxjnl-2019-213892.
[17] Krutzke S, Rietschel C, Horneff G. Baricitinib in therapy of COPA syndrome in a 15-year-old girl. Eur J Rheumatol 2019:1–4, http://dx.doi.org/10.5152/eurjrheum.2019.18177.
[18] Hinks A, Marion MC, Cobb J, Comeau ME, Sudman M, Ainsworth HC, et al. Brief Report: The Genetic Profile of Rheumatoid Factor-Positive Polyarticular Juvenile Idiopathic Arthritis Resembles That of Adult Rheumatoid Arthritis. Arthritis Rheumatol 2018;70:957–62, http://dx.doi.org/10.1002/art.40443.
[19] Hamamoto Y, Ito H, Furu M, Hashimoto M, Fujii T, Ishikawa M, et al. Serological and Progression Differences of Joint Destruction in the Wrist and the Feet in Rheumatoid Arthritis - A Cross-Sectional Cohort Study. PLoS One 2015;10:e0136611, http://dx.doi.org/10.1371/journal.pone.0136611.
[20] Boulisfane-El Khalifi S, Viel S, Lahoche A, Frémond M-L, Lopez J, Lombard C, et al. COPA syndrome as a cause of lupus nephritis. Kidney Int Rep 2019;4:1187–9, http://dx.doi.org/10.1016/j.ekir.2019.04.014.
[21] Melki I, Frémond M-L, Type I. Interferonopathies: from a Novel Concept to Targeted Therapeutics. Curr Rheumatol Rep 2020;22:32, http://dx.doi.org/10.1007/s11926-020-00909-4.
[22] Brandizzi F, Barlowe C. Organization of the ER-Golgi interface for membrane traffic control. Nat Rev Mol Cell Biol 2013;14:382–92, http://dx.doi.org/10.1038/nrm3588.
[23] Arakel EC, Schwappach B. Formation of COPI-coated vesicles at a glance. J Cell Sci 2018;131:jcs209890, http://dx.doi.org/10.1242/jcs.209890.
[24] Ma W, Goldberg J. Rules for the recognition of dilysine retrieval motifs by coatomer. EMBO J 2013;32:926–37, http://dx.doi.org/10.1038/emboj.2013.41.
[25] Deng Z, Law CS, Ho FO, Wang KM, Jones KD, Shin J-S, et al. A Defect in Thymic Tolerance Causes T Cell-Mediated Autoimmunity in

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a Murine Model of COPA Syndrome. J Immunol 2020;204:2360–73, http://dx.doi.org/10.4049/jimmunol.2000028.
[26] Tang X, Xu H, Zhou C, Peng Y, Liu H, Liu J, et al. STING-Associated Vasculopathy with Onset in Infancy in Three Children with New Clinical Aspect and Unsatisfactory Therapeutic Responses to Tofacitinib. J Clin Immunol 2019, http://dx.doi.org/10.1007/s10875-019-00690-9.
[27] Deng Z, Chong Z, Law CS, Mukai K, Ho FO, Martinu T, et al. A defect in COPI-mediated transport of STING causes immune dysregulation in COPA syndrome. Journal of Experimental Medicine 2020:217, http://dx.doi.org/10.1084/jem.20201045.
[28] Deng Z, Chong Z, Law CS, Mukai K, Ho FO, Martinu T, et al. A defect in COPI-mediated transport of STING causes immune dysregulation in COPA syndrome. BioRxiv 2020, http://dx.doi.org/10.1101/2020.05.20.106500.
[29] Mukai K, Ogawa E, Uematsu R, Kuchitsu Y, Uemura T, Waguri S, et al. Homeostatic regulation of STING by Golgi-to-ER membrane traffic. BioRxiv 2020, http://dx.doi.org/10.1101/2020.05.20.107664.
[30] Steiner A, Hrovat Schaale K, Prigione I, De Nardo D, Dagley LF, Yu C-H, et al. Activation of STING due to COPI-deficiency. BioRxiv 2020, http://dx.doi.org/10.1101/2020.07.09.194399.
[31] Tsui JL, Estrada OA, Deng Z, Wang KM, Law CS, Elicker BM, et al. Analysis of pulmonary features and treatment approaches in the COPA syndrome. ERJ Open Research 2018:4, http://dx.doi.org/10.1183/23120541.00017-2018.
[32] Lebon P, Ponsot G, Aicardi J, Goutières F, Arthuis M. Early intrathecal synthesis of interferon in herpes encephalitis. Biomedicine 1979;31:267–71.
[33] Baechler EC, Batliwalla FM, Karypis G, Gaffney PM, Ortmann WA, Espe KJ, et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc Natl Acad Sci USA 2003;100:2610–5, http://dx.doi.org/10.1073/pnas.0337679100.
[34] Bennett L, Palucka AK, Arce E, Cantrell V, Borvak J, Banchereau J, et al. Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. J Exp Med 2003;197:711–23, http://dx.doi.org/10.1084/jem.20021553.
[35] Rice GI, Forte GMA, Szynkiewicz M, Chase DS, Aeby A, Abdel-Hamid MS, et al. Assessment of interferon-related biomarkers in Aicardi-Goutières syndrome associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2 C, SAMHD1, and ADAR: a case-control study. Lancet Neurol 2013;12:1159–69, http://dx.doi.org/10.1016/S1474-4422(13)70258-8.
[36] Rice GI, Melki I, Frémond M-L, Briggs TA, Rodero MP, Kitabayashi N, et al. Assessment of type I interferon signaling in pediatric inflammatory disease. J Clin Immunol 2017;37:123–32, http://dx.doi.org/10.1007/s10875-016-0359-1.
[37] Kim H, de Jesus AA, Brooks SR, Liu Y, Huang Y, VanTries R, et al. Development of a validated interferon score using nanostring technology. J Interferon Cytokine Res 2018;38:171–85, http://dx.doi.org/10.1089/jir.2017.0127.
[38] Rodero MP, Decalf J, Bondet V, Hunt D, Rice GI, Werneke S, et al. Detection of interferon alpha protein reveals differential levels and cellular sources in disease. J Exp Med 2017;214:1547–55, http://dx.doi.org/10.1084/jem.20161451.
[39] Meyer S, Woodward M, Hertel C, Vlaicu P, Haque Y, Kärner J, et al. AIRE-Deficient Patients Harbor Unique High-Affinity Disease-Ameliorating Autoantibodies. Cell 2016;166:582–95, http://dx.doi.org/10.1016/j.cell.2016.06.024.
[40] Rice GI, Park S, Gavazzi F, Adang LA, Ayuk LA, Van Eyck L, et al. Genetic and phenotypic spectrum associated with IFIH1 gain-of-function. Hum Mutat 2020;41:837–49, http://dx.doi.org/10.1002/humu.23975.
[41] Borie R, Kannengiesser C, Gouya L, Dupin C, Amselem S, Ba I, et al. Pilot experience of multidisciplinary team discussion dedicated to inherited pulmonary fibrosis. Orphanet J Rare Dis 2019;14:280, http://dx.doi.org/10.1186/s13023-019-1256-5.
[42] Patwardhan A, Spencer CH. An unprecedented COPA gene mutation in two patients in the same family: comparative clinical analysis of newly reported patients with other known COPA gene mutations. Pediatr Rheumatol Online J 2019;17:59, http://dx.doi.org/10.1186/s12969-019-0359-9.
[43] Tang X, Li H, Liu H, Xu H, Yang H, Liu J, et al. Etiologic spectrum of interstitial lung diseases in Chinese children older than 2 years of age. Orphanet J Rare Dis 2020;15:25, http://dx.doi.org/10.1186/s13023-019-1270-7.

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