Isolated and syndromic retinal degeneration associated with POC5 variants.

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Purpose:

Biallelic gene defect in *POC5* have been recently reported in association with syndromic rod-cone degeneration in one patient. Systemic findings included low weight, short stature, microcephaly and recurrent glomerulonephritis [1]. The purpose of this study was to report a detailed phenotypic description of French patients harboring *POC5* pathogenic variants.

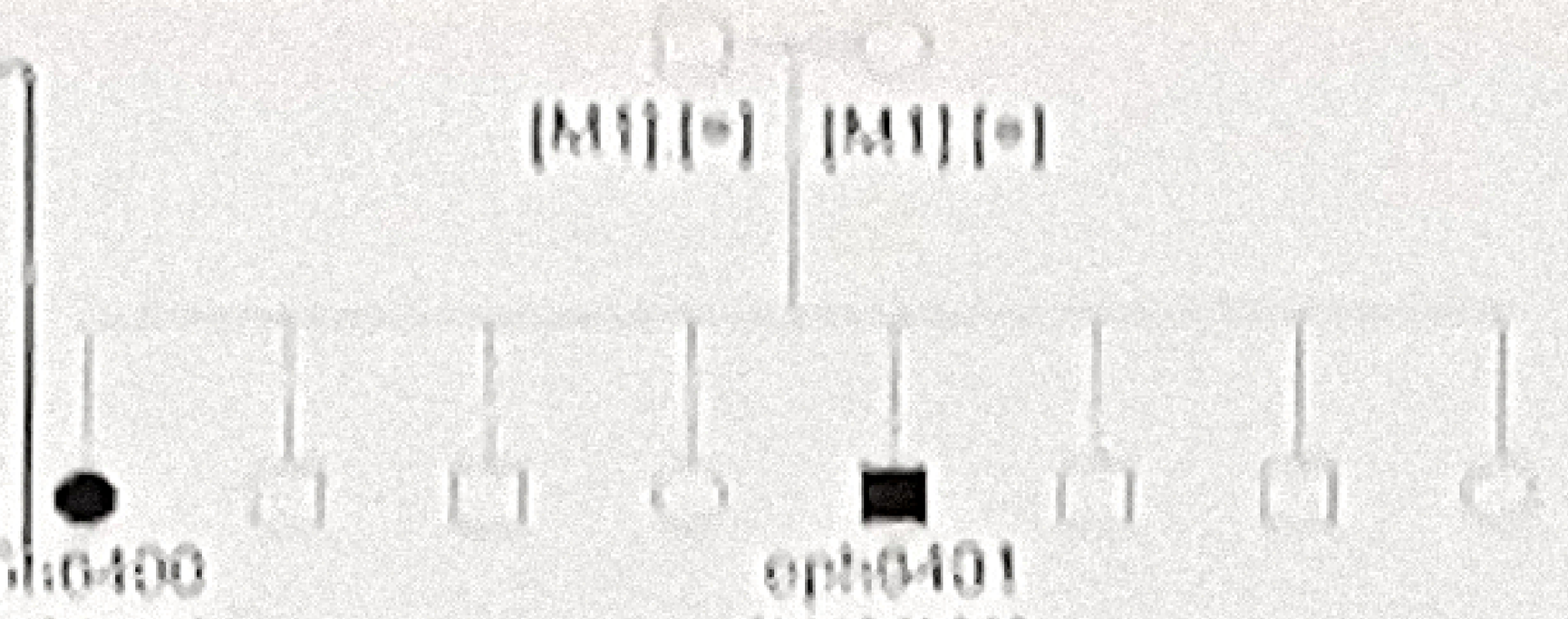
Methods:

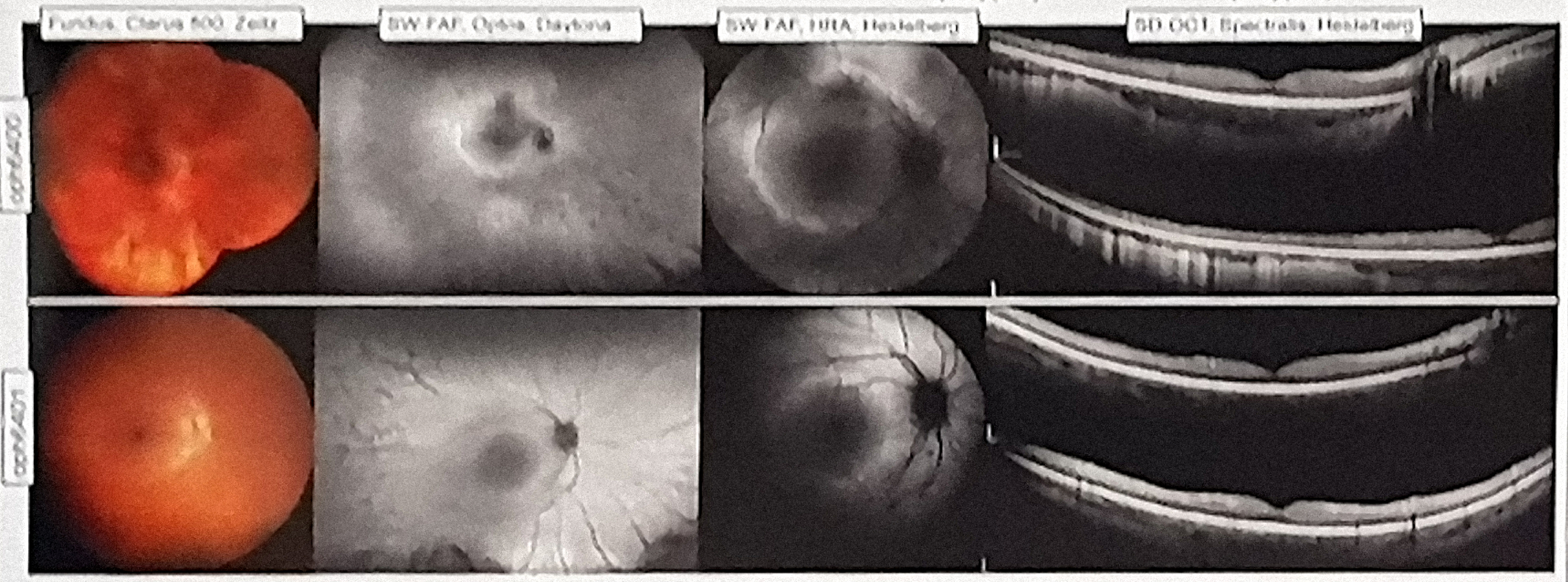
Patients harboring biallelic gene defects in *POC5* were selected from cohorts of Inherited Retinal Degeneration (IRD) patients followed at the Exploration de la Vision et Neuro-Ophtalmologie, CHU de Lille and at the National Reference Center for rare ocular diseases, REFERET, of Quinze-Vingts hospital, Paris. Best corrected visual acuity (BCVA), slit-lamp examination, static and kinetic perimetry, full field electroretinography (ffERG) and multimodal imaging including color photos, infrared reflectance (IRR), short-wave autofluorescence(SWAF) and optical coherence tomography (OCT) were done for all patients. Past medical history was also collected. *POC5* variants were identified applying customized IRD multigene NGS panels. Variant confirmation and familial segregation, when possible was performed by direct Sanger sequencing.

oph6400, 17 y.o.: night blindness and progressive visual loss

	RE	LE
BCVA, Snellen	20/200	20/200
Refraction, D		
Anterior segment	Posterior subcapsular cataract	

M1:
POC5
c.568 C>T
p. (Arg190*)
ACMG: pathogenic (PVS1, PP1.S, PM2)



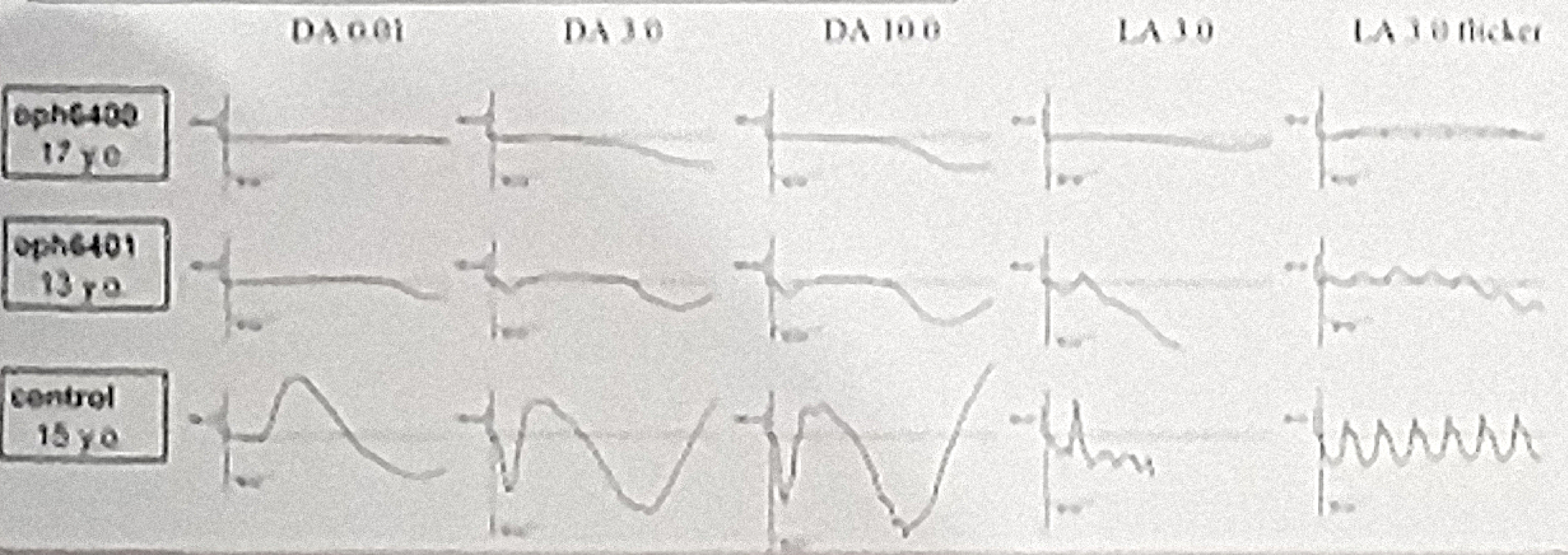


oph6401, 13 y.o.: convergent squint LE, no visual complaints

	RE	LE
BCVA, Snellen	20/125	20/125
Refraction, D	+8(-1.50)20°	+8.50(-1.50)170°
Anterior segment	Normal	

- No systemic involvement
- Low weight (-2DS both)
- Normal PC
- Normal kidney and liver function
- Regular schooling

Full-field ERG, Mon Color, Metrovision®

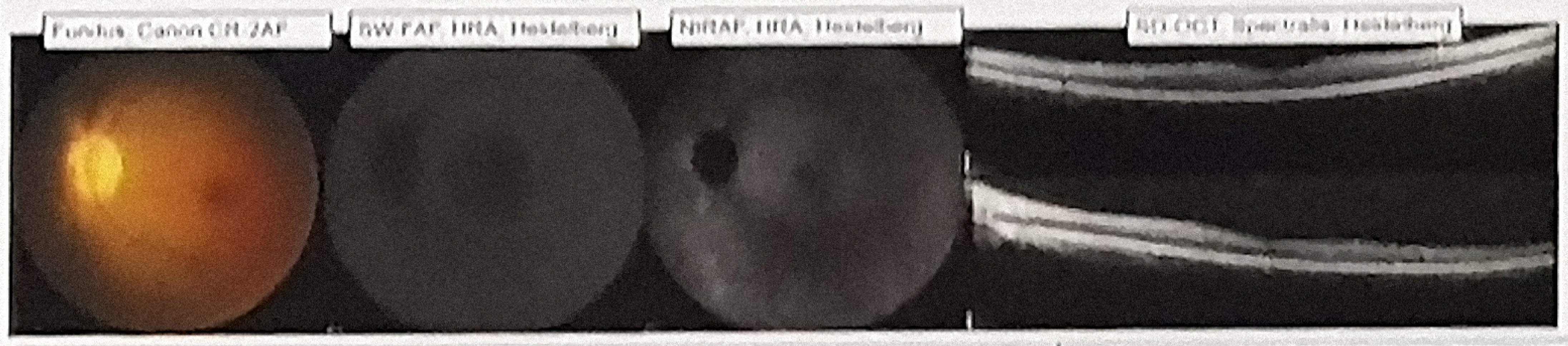


oph6400: undetectable
oph6401: rod-cone dystrophy, cone-dominated ERG under dark-adapted conditions

F5404 CIC09410, 27 y.o. infantile nystagmus, low visual acuity since childhood, light sensitivity

	RE	LE
BCVA, Snellen	20/320	20/400
Refraction, D	-1.0	2(-1)170°
Anterior segment	Normal	

M2:
POC5
c.616C>T
p.(Gln206*)
ACMG: likely pathogenic (PVS1, PM2)

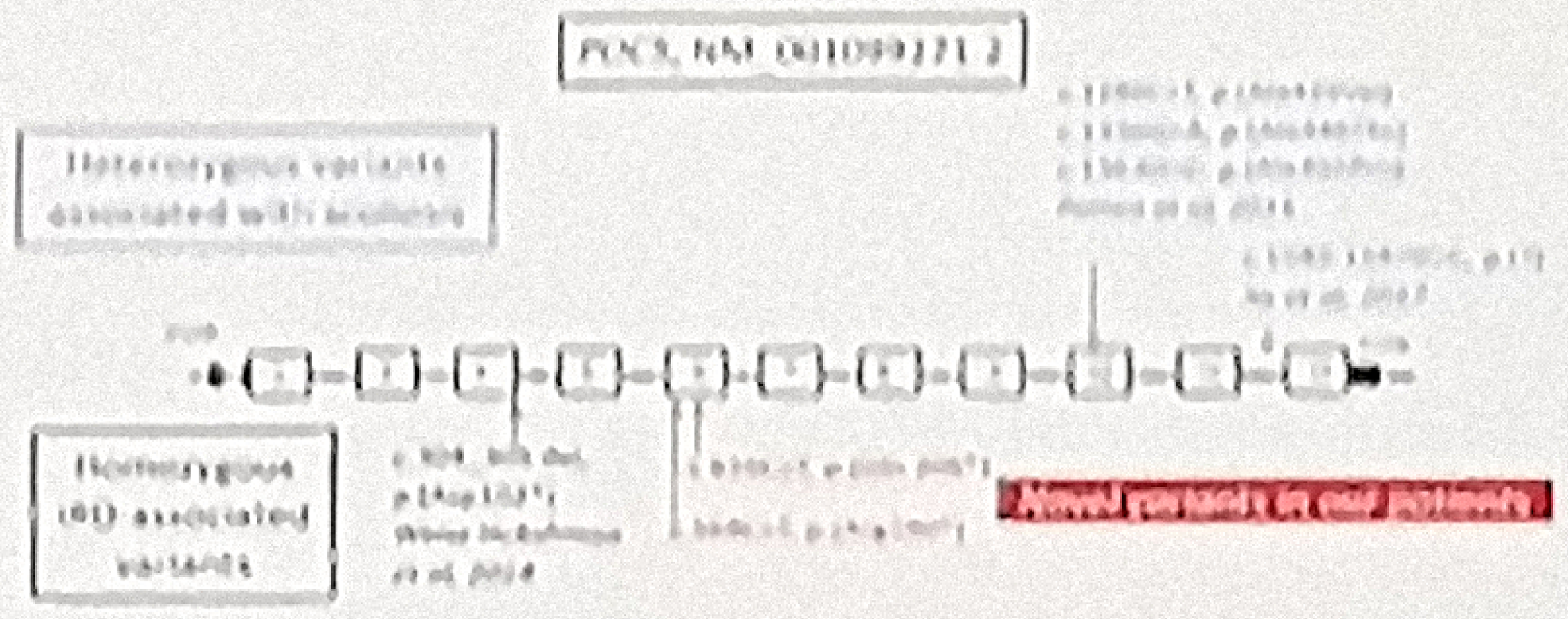


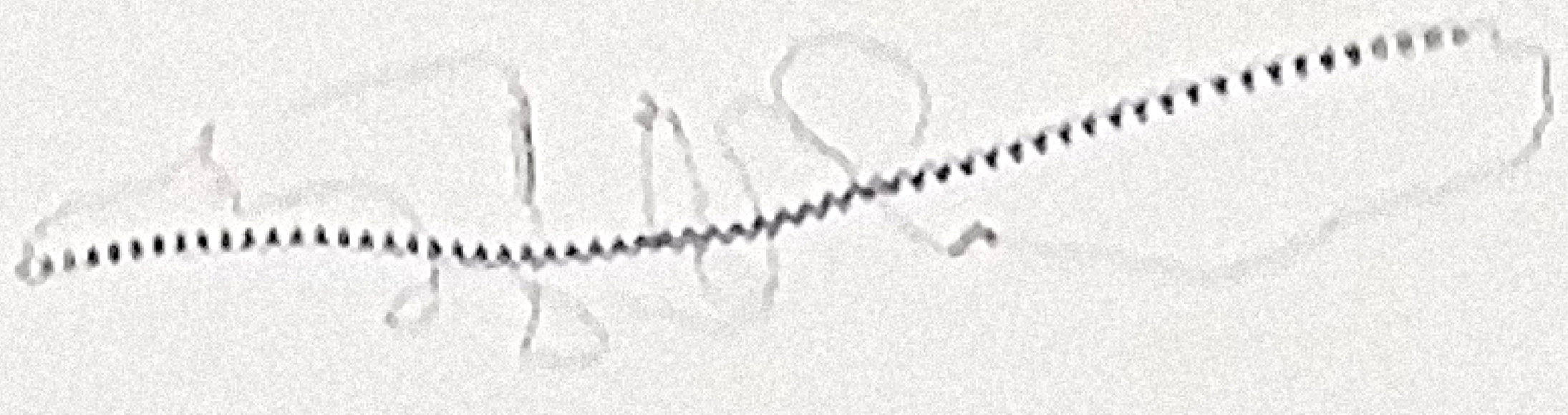
Full-field ERG: undetectable dark- and light-adapted responses

Systemic features:

- Short stature (1m55) and low weight (46 kg), BMI 19
- Non-autoimmune insulin-requiring diabetes since 13 y.o., high insulino-resistance
- Chronic glomerulonephritis with persistent non-selective massive proteinuria (1,3 g/l) since 18 y.o.
- Cirrhosis (Child A5) with steatosis, hepato- and splenomegaly, mild portal hypertension
- Arterial hypertension
- Oligomenorrhea, polycystic ovary syndrome
- Psoriasis and acanthosis nigricans

Genotype/phenotype correlations





Prediction of POC5 3D structure,
https://alphafold.ebi.ac.uk/

POC5 (C5ORF37)

- Ubiquitously expressed, but higher levels in retina, brain and reproductive tissues
- Protein associated with distal part of centrioles, required for centriole elongation and cell cycle progression [1]
- POC5 depleted morphant cells are stacked in S-phase and undergoes p53-mediated cell death [1]
- In photoreceptors, POC5 is localized in the basal bodies of connecting cilium [2]
- In zebrafish POC5 morphants outer photoreceptor segments were defective (decreased length) and the retinal function abnormal [2]
- Heterozygous missense variants have been reported in association with scoliosis, but data are still unclear as the Minor Allele Frequency of these variants is high [3]
- Patient reported by Weisz Hubshman et al. presented a syndromic phenotype including a rod-cone retinal degeneration, chronic glomerular nephropathy, short stature and microcephaly, recurrent episodes of rhabdomyolysis
- In our patients oph6400 and oph6401 the phenotype was retina-restricted at the age of assessment
- In an older patient CIC09410 the clinical picture was in keeping with previously reported case (syndromic ciliopathy including growth, renal, liver, ovarian abnormalities and rod-cone retinal degeneration)
- These data expand the clinical spectrum of *POC5*-related ciliopathy

References:

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Conclusions:

The clinical phenotype of patients harboring biallelic *POC5* defects could be both syndromic and retina restricted. Identification of *POC5* pathogenic variants in patients with inherited retinal degeneration should trigger the systemic work-up for morphological abnormalities, kidney and liver disease, endocrine dysfunction. Careful follow-up is mandatory, as the phenotype might broaden with time.