Delineating the expanding phenotype associated with *SCAPER* gene mutation

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*To the Editor*:

A potential role for the cyclin A2–cyclin-dependent kinase 2 complex (CCNA2–CDK2) regulator SCAPER (S phase cyclin A–associated protein residing in the ER) in human diseasewas first suggested by Najmabadi *et al*, who identified a candidate homozygous frameshift *SCAPER* variant as the cause of non-syndromic intellectual disability (ID) in a small Iranian family (Najmabadi *et al*., 2011). We subsequently reported a single patient with biallelic loss of function (LOF) *SCAPER* variants associated with retinal disease (Carss *et al*., 2017). Biallelic LOF variants have since been associated with ID with or without retinitis pigmentosa (RP) in 7 individuals from 5 families from Spain, Israel and Iran (Hu *et al*., 2018; Tatour *et al*., 2017); in one individual from a Jordanian Arab family, a homozygous *SCAPER* gene variant was identified as the cause of non-syndromic RP (Jauregui *et al*., 2019). More recently, Wormser *et al* described a *SCAPER* gene variant associated with a Bardet-Biedl syndrome-like presentation comprising of ID, RP, short stature, obesity and brachydactyly in 8 individuals from 2 consanguineous Bedouin families belonging to the same tribe in southern Israel, alongside preliminary functional studies suggesting a possible role for SCAPER in ciliary dynamics and disassembly (Wormser *et al*., 2019). In the current study, we describe clinical and genetic findings, including 7 novel *SCAPER* variants, in 6 individuals of Amish, Caucasian and South Asian descent. Together with our molecular data, our comprehensive phenotypic assessments enable a more detailed clinical comparison to be drawn between the patient cohort described here (including previously published individual G001284; Patient 3 in this study, (Carss *et al*., 2017) with the 17 individuals in whom *SCAPER* variants were recently defined (Hu *et al*., 2018; Jauregui *et al*., 2019; Najmabadi *et al*., 2011; Tatour *et al*., 2017; Wormser *et al*., 2019), permitting a more precise definition of the clinical phenotype arising from pathogenic *SCAPER* variation.

Samples were taken with informed consent (study approved by the Ethics Committee of Akron Children’s Hospital, Moorfields Eye Hospital and Baylor College of Medicine, in compliance with the Declaration of Helsinki) for DNA extraction. SNP genotyping was performed (Patients 1 and 2) using the HumanCytoSNP-12 v2.1 beadchip array (Illumina). In Patients 1, 3 - 5, whole exome and whole genome sequencing (WES and WGS), variant alignment, calling, filtering and prioritisation was performed as previously described (Carss *et al*., 2017; Rawlins *et al*., 2019; Xu *et al*., 2015). Allele specific primers were designed using Primer3 web software to evaluate segregation of the candidate *SCAPER* gene variants identified via dideoxy sequencing. Patient 6 underwent WES at GeneDx and was identified via GeneMatcher (Sobreira, Schiettecatte, Valle, & Hamosh, 2015) as part of the Matchmaker Exchange Repositories (Philippakis *et al*., 2015). All variants identified in the study have been submitted to ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>).

Patients 1 and 2 are Ohio Amish siblings. Candidate variants identified through WES of DNA from Patient 1 were cross-referenced with regions of autozygosity common to both affected siblings, identified through whole genome SNP genotyping. This identified only a single plausible candidate variant, located within the largest (18Mb) shared region of autozygosity on chromosome 15 (rs1509805 - rs4243078; chr15(GRCh38):g. 60281446-78374545), a novel homozygous duplication in exon 18 of the *SCAPER* gene, predicted to result in a frameshift (NM\_020843.2: c.2236dupA, p.(Ile746Asnfs\*6) Chr15(GRCh38):g.76705914dupT; Figure 1). Dideoxy sequencing confirmed the presence and co-segregation of this variant in both siblings. This variant was detected in heterozygous form in five unrelated individuals in a database of 116 regional Amish controls, corresponding to an estimated allele frequency of ~0.04, not uncommon for founder mutations within this population. WES/WGS performed in Patients 3-6, identified compound heterozygous *SCAPER* variants; c.1116delT, p.(Val373Serfs\*21) (Chr15(GRCh38):g.76771874delA) and c.2179C>T, p.(Arg727\*) (Chr15(GRCh38):g. 76705971G>A) in Patient 3, c.1495+1G>A (Chr15(GRCh38):g.76765562C>T) and c.3224delC, p.(Pro1075Glnfs\*11) (Chr15(GRCh38):g.76434165delG) in Patient 4, c.829C>T, p.(Arg277\*) (Chr15(GRCh38):g. 76775061G>A) and c.3707\_3708delCT, p.(Ser1236Tyrfs\*28) (Chr15(GRCh38):g.76376309\_ 76376310delAG) in Patient 5, and c.2377C>T, p.(Gln793\*) (Chr15(GRCh38):g.76702873G>A) and c.2166-3C>G (Chr15(GRCh38):g.76705987G>C) in Patient 6. The *SCAPER* variants in each of these patients were confirmed to be biallelic by familial segregation analysis using dideoxy sequencing. None of these variants are present in the genome aggregation (gnomAD) or 1000 Genomes databases and those in Patients 1, 2, 4 – 6 are novel.

Table 1 summarizes the core phenotypical features of individuals not previously reported, aged between 18 months and 31 years (Patients 1, 2, 4 - 6 ), provides additional clinical details for Patient 3 (Carss *et al*., 2017), and compares these to the clinical features of all SCAPER syndrome patients described to date. ID and developmental delay was present in all 6 affected individuals, and 4 patients also exhibited hyperactivity and attention deficit hyperactivity disorder (ADHD). Autism and dyspraxia were each noted in one individual. Neuroimaging performed in Patients 1, 3, 5 and 6 revealed no abnormalities. Additional dysmorphic features noted in both Amish siblings (Patients 1 and 2) included inverted nipples, brachydactyly, camptodactyly, proximally placed thumbs (Figure 1) and a characteristic facial appearance with frontal bossing and almond-shaped eyes; growth parameters were all normal. Patients 1, 3, 4 - 6 all presented between the ages of 10-23 with a reduction in night vision and visual field deficits; Patient 2 (18 months) described no visual symptoms at the time of presentation. Fundus examination in Patients 3 - 6 revealed findings typical of RP including optic disc pallor, attenuated retinal vessels and intraretinal mid-peripheral bone-spicule pigmentation and loss of photoreceptor outer segments with retained central macular structure on Optical Coherence Tomography (OCT) imaging (Figure 1; Table S1). Additional variable ocular features described in some patients with SCAPER syndrome include cataracts (in 2 individuals) and myopia and keratoconus in one individual each.

Our clinical and genetic studies in 6 affected individuals, including additional new clinical details for Patient 3 (Carss *et al*., 2017) takes the total number of SCAPER syndrome patients described to date to 23. Although the extent for which clinical data is available for the previously reported patients is variable, our detailed clinical phenotyping allows a more comprehensive clinical comparison to be made with the previously reported cases, confirming the presence of a variable pattern of dysmorphic features associated with SCAPER syndrome. It is now clear that the cardinal clinical features of the disorder include mild/moderate ID and developmental delay particularly affecting speech and language and motor milestones. Hyperactivity appears to be a common feature, with some affected individuals receiving a formal diagnosis of ADHD. Early adult onset RP is also a key clinical finding, and the retinal phenotype appears remarkably consistent. In all individuals for whom we have data, progressive loss of night vision begins in first or second decade of life. Together with studies in mice demonstrating expression of SCAPER in multiple retinal layers, particularly in the retinal pigment epithelium and photoreceptor inner and outer segments, this supports a role for SCAPER in photoreceptor function and/or maintenance (Tatour *et al*., 2017).

Tapering fingers, brachydactyly and proximally placed thumbs, described in eight individuals from two consanguineous Bedouin families of the same tribe in southern Israel, were also identified as a consistent feature in the two Amish siblings, confirming the association of this feature with the SCAPER syndrome. Short stature and obesity were also a common feature amongst the affected Bedouin patients, and this constellation of clinical features including RP, obesity, short stature, intellectual disability, developmental delay and brachydactyly has consequently led to a suggested diagnosis of Bardet-Biedl syndrome (BBS) in these individuals. Although there is some overlap between the clinical features characteristic of ciliopathies and those seen in SCAPER syndrome, the Amish siblings (who are of normal height and weight for age) demonstrate that the digital, retinal and cognitive abnormalities may occur independently of short stature and obesity. The other common primary features of BBS, including renal anomalies, post-axial polydactyly, hypogonadism (males) and genital abnormalities (females) have not been reported in association with SCAPER mutation (Forsythe & Beales, 2013). The dysmorphic facial features and inverted nipples, noted on examination of both Amish siblings, have not been previously noted in other individuals with *SCAPER* variants.

Recently, a single individual homozygous for a c.2023-2A>G *SCAPER* variant presenting with non-syndromic RP and no evidence of intellectual disability, was reported in this journal (Jauregui *et al*., 2019). The same c.2023-2A>G *SCAPER* gene variant has also been reported previously in association with RP, ADHD and mild ID (Tatour *et al*., 2017) indicating the variability in the presence and severity of the extraocular features associated with the SCAPER syndrome (Table 1). However, this may also be accounted for by the difficulties in conclusively defining milder developmental delay in some situations, when more subtle clinical findings may not be identified if not specifically assessed. Conversely, associated ocular pathology may remain undetected or unrecognised in individuals with intellectual disability, as such individuals often have difficulty recognising or articulating their visual symptoms. This highlights the importance of visual screening and ophthalmological assessment in these patients. Other common ocular features include cataracts (in particular posterior subcapsular cataracts, which are commonly associated with RP; (Pruett, 1983) and strabismus, with nystagmus and keratoconus noted in a single patient. The high incidence of cataracts, a potentially treatable cause of sight loss, again supports the case for screening in early childhood.

The allele frequency (~0.04) of the Ohio Amish *SCAPER* founder mutation suggests that, despite no previous reports, this disorder represents an under-recognised cause of RP and mild ID within this community. This further highlights the importance of careful clinical evaluation in children and adults with ID and enables targeted genetic testing for this *SCAPER* variant for Amish individuals with this clinical presentation. Together with our clinical review of all previously published patients, this study expands the molecular spectrum of disease-causing *SCAPER* variants and enables a clearer delineation of the core (and variable) phenotypical features of SCAPER syndrome to be characterised. Our findings also highlight the importance of prompt visual screening and ophthalmic assessment in all individuals with SCAPER-associated disease. Despite the increasing numbers of individuals identified with SCAPER syndrome, the precise functions of SCAPER in human growth and development are not fully understood. Further studies to elucidate the precise molecular and developmental roles of this molecule in human growth and skeletal, retinal and brain development and function, will yield important insights into the clinical heterogeneity increasingly observed in SCAPER-associated disease.

### Figure legend

**Figure 1: (a)** Simplifiedpedigree of the Amish family investigated, with electropherograms showing the *SCAPER* c.2236dupT sequence variant in all affected and unaffected individuals in generations VI and VII ( black arrow identifies the duplicated nucleotide). **(b)** Pictorial representation of the SNP genotypes across the ~ 18.1Mb chromosome 15q21-22 region identified in this family. **(c-j)** Clinical features of SCAPER syndrome patients. (**c-d**) Brachydactyly, camptodactyly and proximally placed thumbs identified on examination of Patient 1. **(e-f)** Ocular imaging and investigations from Patient 3 illustrating features of RP (**e**: right eye, **f**: left eye) Fundus photograph (Optos California) showing optic disc pallor, attenuated retinal vessels and mid-peripheral bone spicule pigmentation (**g**: right eye, **h:** left eye) Fundus autofluorescence (FAF) imaging showing mid-peripheral hypoautofluorescence with a central ring of hyperautofluorescence demarcating the surviving outer retinal structures. (**i**: right eye, **j**: left eye) optical coherence tomography (Spectralis-OCT) of the central retina demonstrating loss of photoreceptor outer segments with retained central macular structure corresponding to FAF findings.

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