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CORRESPONDENCE

Awareness of olfactory impairment in a cohort of patients with *CNGB1*-associated retinitis pigmentosa

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To the Editor:

The *CNGB1* gene encodes a protein involved in both photoreceptor and olfactory signal transduction. Patients with retinitis pigmentosa (RP) due to bi-allelic variants in this gene were previously reported to describe no olfactory problems [1, 2]. A subsequent quantitative study found objectively reduced olfactory function in eight of nine patients tested (89%), with three patients (33%) aware of their olfactory impairment [3]. Variants can occur in the N-terminal glutamic acid-rich protein (GARP) domain or in the channel domain. The GARP domain is important in rod photoreceptors, but its role in olfactory neurons is less clear; an alternatively spliced variant (CNGB1b), lacking this domain, is expressed in olfactory neurons in rats [4]. We investigated awareness of olfactory problems in our molecularly characterised cohort, and explored in which domain variants occurred.

The electronic inherited retinal disease database of Moorfields Eye Hospital was searched for patients with a molecularly confirmed diagnosis of *CNGB1*-associated RP. Patients were asked (by telephone or during clinic visits) whether they were aware of problems with their sense of smell. Disease-causing variants were classified by occurrence within the GARP or channel domain of the protein. It was hypothesised that patients with both variants in the channel domain might be more likely to be aware of olfactory impairment (as a GARP domain change would not affect translation of a splice variant that lacked this domain).

Nineteen affected patients (mean (SD) age 60 (11) years; 11 females) from 18 families were identified. Fifteen patients (79%) were successfully contacted (mean (SD) age 61 (11) years; nine females). Of these, six (40%) reported reduced or absent sense of smell; the remainder reported no problems. Mean age and sex distribution did not differ between those with or without awareness of olfactory impairment. Table 1 summarises patient characteristics, including causative variants, and their responses. The majority of variants have been previously reported [3, 5]. The novel variants all had a frequency in the gnomAD database of <0.0002 and were predicted to be disease-causing.

Seven out of the fifteen patients had both disease-causing variants occurring in the channel domain. Of these, five reported reduced or absent sense of smell. Of the eight remaining patients (who had at least one disease-causing variant in the GARP domain), only one was aware of a reduced sense of smell. The difference in proportions was significant ($p = 0.04$, Fisher exact test, two-tailed). If combined with the subjective reports of olfactory impairment in the previous study of nine patients (only one of whom had a variant in the GARP domain) [3], the difference in proportions remained significant ($p = 0.03$).

Our findings confirm that a substantial proportion of patients with *CNGB1*-associated RP report reduced or absent sense of smell when specifically questioned. In our cohort, patients with at least one variant in the GARP domain were less likely to report olfactory impairment, suggesting that this domain might be less important in olfaction than in photoreceptor function. Limitations of our study include reliance on subjective awareness of olfactory impairment; it is possible that objective quantitative assessment of olfaction would reveal more individuals with hyposmia. RP has hundreds of associated genes; awareness of specific non-ocular features associated with certain genotypes can assist in guiding gene testing or its interpretation.

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Table 1 Demographics, molecular changes and subjective perceived impairment in sense of smell for the patients included in the present study

Patient number	Age (years)	Sex	Variant 1		Variant 2		Both variants in channel domain?	Subjective sense of smell
			Base change	Effect	Base change	Effect		
1	50	M	c.2777-?_2958+? del (Exon 28-29 deletion)	p.?	c.2777-?_2958+? del (Exon 28-29 deletion)	p.?	Yes	Absent
2	45	F	c.2957A>T	p.(Asn986Ile)	c.2957A>T	p.(Asn986Ile)	Yes	Normal
3	68	M	c.2285G>A	p.(Arg762His)	c.2285G>A	p.(Arg762His)	Yes	Normal
4	53	F	c.2544dupG	p.(Leu849Alafs*3)	c.2544dupG	p.(Leu849Alafs*3)	Yes	Reduced
5	64	F	c.2957A>T	p.(Asn986Ile)	c.2544dupG	p.(Leu849Alafs*3)	Yes	Reduced
6	56	M	c.1729delG	p.(Glu577Serfs*6)	c.1729delG	p.(Glu577Serfs*6)	Yes	Reduced
7	71	F	c.2676C>A	p.(Tyr892*)	c.2980G>T	p.(Glu994*)	Yes	Reduced
8	68	F	c.2957A>T	p.(Asn986Ile)	c.534+1G>A	Splice defect	No	Normal
9	42	M	c.2544dupG	p.(Leu849Alafs*3)	c.262C>T	p.(Gln88*)	No	Normal
10	82	M	c.2540G>A	p.(Gly847Glu)	c.346C>T	p.(Gln116*)	No	Normal
11	59	F	c.262C>T	p.(Gln88*)	c.664C>T	p.(Gln222*)	No	Normal
12	67	F	c.2258T>A	p.(Leu753*)	c.807G>C	p.(Gln269His)	No	Normal
13	63	F	c.413-1G>A	Splice defect	c.413-1G>A	Splice defect	No	Absent
14	69	F	c.952C>T	p.(Gln318*)	c.2957A>T	p.(Asn986Ile)	No	Normal
15	64	M	c.952C>T	p.(Gln318*)	c.2957A>T	p.(Asn986Ile)	No	Normal

Patients 14 and 15 are siblings. The transcript ID for variant annotation is NM_001297.4. The following variants have not been previously reported in the context of *CNGB1*-associated retinitis pigmentosa (frequency in the gnomAD database, https://gnomad.broadinstitute.org, accessed 6 May 2019, of each allele is also given): p.(Gln116*), 4.02×10^{-6}; p(.Glu577Serfs*6), not found in gnomAD; p.(Arg762His), 1.61×10^{-5}; p.(Gly847Glu), 8.01×10^{-6}; p.(Tyr892*), not found in gnomAD; p.(Glu994*), not found in gnomAD. All were predicted to be disease-causing (http://www.mutationtaster.org/, accessed 6 May 2019). c.534 + 1G>A affects a splice donor site, and has a frequency in gnomAD of 3.63×10^{-5}. Exon 28–29 deletion is not found in gnomAD

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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