

## Two genes of interest from comparative longevity genomics: *FAM126B* and *OBSCN*

David Bahry\*<sup>1</sup>

<sup>1</sup> Department of Biology, Carleton University, 1125 Colonel By Dr, Ottawa, ON K1S 5B6, Canada

\* email: [davidbahry@cmail.carleton.ca](mailto:davidbahry@cmail.carleton.ca)

**Abstract.** This note highlights two genes of interest from two comparative genomic studies: *FAM126B*, coding for a protein related to hyccin, from a study of mammals; and *OBSCN*, coding via alternate RNA splicing for giant and small obscurins, from a study of rockfish. Existing knowledge and disease associations are summarized, and implications for the evolution of longevity across species discussed.

Much biogerontological research focuses on the evolutionarily conserved metabolic regulatory pathways involved in certain modest longevity interventions known from model organisms; such interventions as caloric restriction (CR) in many species, *age-1* and *daf-2* mutations in nematodes, and drugs such as rapamycin have drawn much attention to such pathways as IGF-1, mTOR, sirtuins, and AMPK (Pan & Finkel, 2017). However, these longevity interventions pale next to what evolution regularly achieves (Bahry, 2022): among mammals, while a mutant dwarf mouse might live up to almost 5 years instead of up to almost 4, a naked mole-rat lives up to 31; a human 122; and a bowhead whale over 200 (AnAge database: Tacutu et al., 2018). Thus comparative biogerontology is a vital field (Finch, 1990; Austad, 2022), though research on the genetics of species differences is young, having become feasible only with genome sequencing of non-traditional model species such as bats, mole-rats and whales (Ma & Gladyshev, 2017; cf. Seluanov et al., 2018).

This note highlights two genes of interest, from two recent comparative genomic studies: *FAM126B*, from a study of mammals (Li & de Magalhães, 2013); and *OBSCN* from a study of rockfish (Kolora et al., 2021) (Figure 1; Table 1).

Li and de Magalhães (2013), in a study of mammals, compared nine pairs of closely-related species in which one had evolved increased maximum lifespan since their common ancestor, to look for proteins showing signatures of positive selection in lineages that evolved longevity. They used three selectivity thresholds, for different possible patterns of selection strength (e.g. weak selection in branches where longevity evolves, vs. selection in all branches but stronger in branches where longevity evolves); under each threshold, they assigned each protein a longevity-specific selectivity (LSS) score. Their discussion section emphasized three candidate pathways as likely involved in longevity evolution: lipid metabolism; DNA repair; and the ubiquitin-proteasome system for selective protein degradation. Their results, however, noted only one protein with a high LSS under all three thresholds (p. 306): “an unstudied protein,” *FAM126B*.

Kolora et al. (2021) sequenced and compared the genomes of 88 species of rockfish (*Sebastes*) and related outgroups, with maximum lifespans ranging from 11 to over 200 years. Among their methods, they looked for protein-coding genes showing signatures of positive selection in short- and long-lived species, as well as protein-coding genes whose relative evolutionary rates (RERs) were correlated, either positively or negatively, either with lifespan, or with residual lifespan independent of body size and swimming depth. My intuition is that the most interesting genes are those that are positively selected as longevity evolves. Although Kolora et al. did not emphasize it, one gene in their data stands out as showing both positive selection in more than one long-lived species, and an RER positively correlated with both lifespan and residual lifespan: *OBSCN*.

*FAM126B* (family with sequence similarity 126 member B) codes for a barely-studied protein in the hyccin family. The first protein of this family found, hyccin (*FAM126A*), is a membrane protein involved in nervous system myelination, deficiency of which causes the white matter disorder hypomyelination and congenital cataract (HCC) (Zara et al., 2006); hyccin forms part of the PI4KIII $\alpha$  lipid kinase complex (Lees et al., 2017), regulating the synthesis of PtdIns(4)P, a determinant of plasma membrane identity (Baskin et al., 2015). Baskin et al. also found that *FAM126B* can partially compensate reduced hyccin in fibroblasts, as well as that in the brain, *FAM126B* is expressed more, and can better compensate reduced hyccin, in neurons than in oligodendrocytes (pp. 135–136), and Zhang et al. (2022) found that *FAM126B* can compensate hyccin reduction in glia cells in the visual system; it is tempting to wonder in this connection if *FAM126B* might play a role in or against nervous system aging (cf. Arking, 2006, pp. 169–184). However, *FAM126B* has also given small glimpses of other roles. Chauhan et al. (2015) found that *FAM126B* polymorphisms are predictive in vitro of chemosensitivity to Triptolide, a compound found in the traditional Chinese medicinal herb Thunder God



Table 1. Summary of *FAM126B* and *OBSCN*.

	<i>FAM126B</i>	<i>OBSCN</i>
	Family with sequence similarity 126 member B	Obscurin(s)
<b>NCBI Gene ID:</b>	285172	84033
<b>Protein family discovered:</b>	Zara et al. (2006).	Young et al. (2001)
<b>Summary</b>	A barely-studied protein; related to hyccin, which is involved in plasma membrane identity and nervous system myelination.	Giant sarcomeric proteins obscurin-A and obscurin-B in striated heart and skeletal muscle, as well as other giant and small isoforms in various tissues.
<b>Comparative genomics of longevity</b>	<b>Mammals:</b> <i>FAM126B</i> was the only gene with a high longevity-specific selectivity score under all three selectivity thresholds (Li and de Magalhães, 2013).	<b>Rockfish:</b> <i>OBSCN</i> was the only gene with both signatures of positive selection in plural long-lived species, and a relative evolutionary rate positively correlated with both lifespan and residual lifespan independent of size and depth (Kolora et al., 2021, supplementary materials).
<b>Disease associations</b>	<p>Little known. However, <i>FAM126B</i> polymorphism is associated with in vitro sensitivity to Triptolide, a compound found in Thunder God Vine, with anti-proliferative, apoptotic and autophagic properties (Chauhan et al., 2015; Noel et al., 2019), and whose derivatives are being studied as cancer treatments.</p> <p>Deficiency of its homolog hyccin (<i>FAM126A</i>) causes the white matter disorder, hypomyelination and congenital cataract (HCC) (Zara et al., 2006).</p>	<p>Mutations in obscurin, and in obscurin-binding regions of titin, are associated with heart and skeletal muscle disease (Grogan and Kontrogianni-Konstantopoulos, 2019; Grogan et al., 2020a). Mutations in obscurin are associated with cancer, including colorectal and breast cancer (Sjöblom et al., 2006); obscurins have been studied in a number of cancers, but especially as tumor suppressors in breast epithelium (Guardia et al., 2021).</p>
<b>Further connections to biogerontology</b>	<p>Little known. However, <i>FAM126B</i> polymorphism is associated with mast cell degranulation in mice exposed to silver nanoparticles (Johnson et al., 2018); it is also part of an RNA-interaction network distinguishing the inflammatory gum conditions periimplantitis and periodontitis (Zhou et al., 2020), as well as part of a protein and miRNA interaction network involved in the brain cancer glioblastoma multiform (Alshabi et al., 2019).</p>	<p><i>OBSCN</i>-knockout mice show age- and sex-related cardiac remodeling and arrhythmia (Grogan et al., 2020a), and age-related decreased performance in intensive exercise to exhaustion (Randazzo et al., 2017b). Obscurins regulate ubiquitin-dependent selective protein degradation (Wang et al., 2018); loss of proteostasis is a hallmark of aging (López-Otín et al., 2013), and the ubiquitin-proteasome system is associated with mammal longevity evolution (Li and de Magalhães, 2013).</p>
<b>Recommended further reading</b>	Zara et al. (2006); Li and de Magalhães (2013); Baskin et al. (2016); Chauhan et al. (2015); Noel et al. (2019).	Perry et al. (2013); Randazzo et al. (2017a); Wang et al. (2018); Grogan and Kontrogianni-Konstantopoulos (2019); Guardia et al. (2021); Kolora et al. (2021).

be especially fruitful for such giant modular genes with many isoforms as obscurin: which exons show signatures of selection in long-lived species may hint at which domains and isoforms matter most.

In motivating their unbiased-genome scan approach, Li and Magalhães noted that “Proteins related to longevity in model organisms appear to be well conserved and might even tend to be better conserved than expected by chance, suggesting that the genetic mechanisms for longevity regulation within species are not the same that determine species differences in longevity” (2013, p. 308). Notably, at the time of this writing neither *FAM126B* nor *OBSCN* are included in the GenAge Ageing Gene Database (Tacutu et al., 2018), suggesting that Li and de Magalhães may be right. Under this hypothesis we might think of CR and molecules such as IGF-1, mTOR, sirtuins, and AMPK as being like the “fine-adjustment” dial on a microscope, with between-species differences controlled by a largely distinct “coarse-adjustment” dial; alternatively, we might hypothesize that those fine-adjustment proteins are high-level control genes whose life-extending effects are implemented by adjusting numerous downstream proteins, with species differences evolving via more direct adjustment to those downstream proteins. However, it is also possible that *FAM126B* and obscurins simply haven’t been noticed due to their being only recently discovered and relatively little-studied. Also notably, *OBSCN* was not among the genes reported for mammals by Li and de Magalhães, while *FAM126B* was not among the genes reported for rockfish by Kolora et al. This might suggest that these genes are not involved in longevity evolution after all; on the other hand, it may suggest that longevity evolves by partly different mechanisms in different taxa. The latter possibility would be good news: humans, as long-lived mammals, may already be using the usual mammalian longevity tricks, while rockfish longevity tricks may be new opportunities (cf. Seluanov, 2018).

Such genes, first noticed as associations in comparative genomics, can also then be studied experimentally in model organisms, just as can genes first noticed in mutational screens (cf. Kenyon, 2011). Gene-editing tools such as CRISPR, and non-traditional vertebrate model organisms such as short-lived African turquoise killifish (Harel et al., 2016), along with old vertebrate and invertebrate standbys like nematodes and mice, make this an exciting time for such research.

## References

- Ackermann, M. A. et al. (2014). Obscurins: Goliaths and Davids take over non-muscle tissues. *PLoS One*, *9*, e88162. [doi.org/10.1371/journal.pone.0088162](https://doi.org/10.1371/journal.pone.0088162)
- Alshabi, A. M. et al. (2019). Identification of crucial candidate genes and pathways in Glioblastoma Multiform by bioinformatics analysis. *Biomolecules*, *9*, 201. <https://doi.org/10.3390/biom9050201>
- Arking, R. (2006). *The Biology of Aging: Observations and Principles* (3<sup>rd</sup> ed.). Oxford University Press.
- Baer, C., Claus, R., & Plass, C. (2013). Genome-wide epigenetic regulation of miRNAs in cancer. *Cancer Res.*, *73*, 473–477. <https://doi.org/10.1158/0008-5472.CAN-12-3731>
- Bahry, D. (2022). Book review: *Methuselah’s Zoo* by Steven N. Austad. *BioEssays*, 2200144. [doi.org/10.1002/bies.202200144](https://doi.org/10.1002/bies.202200144)
- Bartel, D. P. (2018). Metazoan microRNAs. *Cell*, *173*, 20–51. <https://doi.org/10.1016/j.cell.2018.03.006>
- Baskin, J. M. et al. (2016). The leukodystrophy protein FAM126A/Hyccin regulates PI4P synthesis at the plasma membrane. *Nat. Cell Biol.*, *18*, 132–138. [doi.org/10.1038/ncb3271](https://doi.org/10.1038/ncb3271)
- Chauhan, L. et al. (2015). Genome-wide association analysis identified splicing single nucleotide polymorphism in CFLAR predictive of triptolide chemo-sensitivity. *BMC Genomics*, *16*, 483. <https://doi.org/10.1186/s12864-015-1614-1>
- Finch, C. E. (1990). *Longevity, Senescence, and the Genome*. The University of Chicago Press.
- Grogan, A. & Kontrogianni-Konstantopoulos, A. (2019). Unraveling obscurins in heart disease. *Pflugers Arch.*, *471*, 735–743. [doi.org/10.1007/s00424-018-2191-3](https://doi.org/10.1007/s00424-018-2191-3)
- Grogan, A., Tsakiroglou, P., & Kontrogianni-Konstantopoulos, A. (2020a). Double the trouble: giant proteins with dual kinase activity in the heart. *Biophys. Rev.*, *12*, 1019–1029. [doi.org/10.1007/s12551-020-00715-3](https://doi.org/10.1007/s12551-020-00715-3)
- Grogan, A. et al. (2020b). Deletion of obscurin immunoglobulin domains Ig58/59 leads to age-dependent cardiac remodeling and arrhythmia. *Basic Res. Cardiol.*, *115*, 60. [doi.org/10.1007/s00395-020-00818-8](https://doi.org/10.1007/s00395-020-00818-8)
- Guardia, T., Eason, M., & Kontrogianni-Konstantopoulos, A. (2021). Obscurin: A multitasking giant in the fight against cancer. *Biochim. Biophys. Acta Rev. Cancer*, *1876*, 188567. [doi.org/10.1016/j.bbcan.2021.188567](https://doi.org/10.1016/j.bbcan.2021.188567)
- Harel, I., Valenzano, D. R., & Brunet, A. (2016). Efficient genome engineering approaches for the short-lived African turquoise killifish. *Nat. Protoc.*, *11*, 2010–2028. [doi.org/10.1038/nprot.2016.103](https://doi.org/10.1038/nprot.2016.103)

- Johnson, M. et al. (2018). Genomic and transcriptomic comparison of allergen and silver nanoparticle-induced mast cell degranulation reveals novel non-immunoglobulin E mediated mechanisms. *PLoS One*, 13, e0193499. <https://doi.org/10.1371/journal.pone.0193499>
- Kenyon, C. (2011). The first long-lived mutants: discovery of the insulin/IGF-1 pathway for ageing. *Philos. T. R. Soc. B.*, 366, 9–16. [doi.org/10.1098/rstb.2010.0276](https://doi.org/10.1098/rstb.2010.0276)
- Kolora, S. R. R. et al. (2021). Origins and evolution of extreme life span in Pacific Ocean rockfishes. *Science*, 374, 842–847. [doi.org/10.1126/science.abg5332](https://doi.org/10.1126/science.abg5332)
- Lees, J. A. et al. (2017). Architecture of the human PI4KIII $\alpha$  lipid kinase complex. *Proc. Natl. Acad. Sci. U.S.A.*, 114, 13720–13725. [doi.org/10.1073/pnas.1718471115](https://doi.org/10.1073/pnas.1718471115)
- Li, Y. & de Magalhães, J. P. (2013). Accelerated protein evolution analysis reveals genes and pathways associated with the evolution of mammalian longevity. *Age (Dordr)*, 35, 301–314. [doi.org/10.1007/s11357-011-9361-y](https://doi.org/10.1007/s11357-011-9361-y)
- López-Otín, C. et al. (2013). The hallmarks of aging. *Cell*, 153, P1194–1217. [doi.org/10.1016/j.cell.2013.05.039](https://doi.org/10.1016/j.cell.2013.05.039)
- Ma, S. and Gladyshev, V. (2017). Molecular signatures of longevity: Insights from cross-species comparative studies. *Semin. Cell Dev. Biol.*, 70, 190–203. [doi.org/10.1016/j.semcdb.2017.08.007](https://doi.org/10.1016/j.semcdb.2017.08.007)
- Noel, P. et al. (2019). Triptolide and its derivatives as cancer therapies. *Trends Pharmacol. Sci.*, 40, 327–341. <https://doi.org/10.1016/j.tips.2019.03.002>
- Pan, H. and Finkel, T. (2017). Key proteins and pathways that regulate lifespan. *J. Biol. Chem.*, 292, 6452–6460. [doi.org/10.1074/jbc.r116.771915](https://doi.org/10.1074/jbc.r116.771915)
- Perry, N. A. et al. (2013). Obscurins: Unassuming giants enter the spotlight. *IUBMB Life*, 65, 479–486. [doi.org/10.1002/iub.1157](https://doi.org/10.1002/iub.1157)
- Randazzo, D. et al. (2017a). The potential of obscurin as a therapeutic target in muscle disorders. *Expert Opin. Ther. Targets*, 21, 897–910. [doi.org/10.1080/14728222.2017.1361931](https://doi.org/10.1080/14728222.2017.1361931)
- Randazzo, D. et al. (2017b). Exercise-induced alterations and loss of sarcomeric M-line organization in the diaphragm muscle of obscurin knockout mice. *Am. J. Physiol. Cell Physiol.*, 312, C16–C28. [doi.org/10.1152/ajpcell.00098.2016](https://doi.org/10.1152/ajpcell.00098.2016)
- Salmena, L. et al. (2011). A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? *Cell*, 146, 353–358. <https://doi.org/10.1016/j.cell.2011.07.014>
- Seluanov, A. et al. (2018). Mechanisms of cancer resistance in long-lived mammals. *Nat. Rev. Cancer*, 18, 433–441. [doi.org/10.1038/s41568-018-0004-9](https://doi.org/10.1038/s41568-018-0004-9)
- Tacutu, R. et al. (2018). Human ageing genomic resources: new and updated databases. *Nucleic Acids Res.*, 46, D1083–D1090. [doi.org/10.1093/nar/gkx1042](https://doi.org/10.1093/nar/gkx1042)
- Wang, L. et al. (2018). Thick filament protein network, functions, and disease association. *Compr. Physiol.*, 8, 631–709. [doi.org/10.1002/cphy.c170023](https://doi.org/10.1002/cphy.c170023)
- Young, P., Ehler, E., and Gautel, M. (2001). Obscurin, a giant sarcomeric Rho guanine nucleotide exchange factor protein involved in sarcomere assembly. *J. Cell Biol.*, 154, 123–136. [doi.org/10.1083/jcb.200102110](https://doi.org/10.1083/jcb.200102110)
- Zara, F. et al. (2006). Deficiency of hyccin, a newly identified membrane protein, causes hypomyelination and congenital cataract. *Nat. Genet.*, 38, 1111–1113. [doi.org/10.1038/ng1870](https://doi.org/10.1038/ng1870)
- Zhang, Q. et al. (2022). Hyccin/FAM126A deficiency reduces glial enrichment and axonal sheath, which are rescued by overexpression of a plasma membrane-targeting PI4KIII $\alpha$  in *Drosophila*. *Biochem. Biophys. Res. Commun.*, 598, 71–77. <https://doi.org/10.1016/j.bbrc.2021.11.106>
- Zhou, H. et al. (2020). LncRNA-mediated ceRNA network was identified as a crucial determinant of differential effects in periodontitis and periimplantitis by high-throughput sequencing. *Clin. Implant. Dent. Relat. Res.*, 22, 424–450. <https://doi.org/10.1111/cid.12911>