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

David Bahry*[1]

[1] Department of Biology, Carleton University, 1125 Colonel By Dr, Ottawa, ON K1S 5B6, Canada
* email: 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 PI4KIIIα 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

Vine, and whose derivatives including the more water-soluble Minnelide are being investigated as cancer treatments due to Triptolide's anti-proliferative, apoptotic and autophagic properties (Noel et al., 2019). Johnson et al. (2018) found that FAM126B polymorphisms were associated in mouse strains with susceptibility to mast cell degranulation, an immune response better known for its role in allergy, upon exposure to silver nanoparticles. Zhou et al. (2020) found that FAM126B was central to a network of miRNAs, lncRNAs, and mRNAs whose expression distinguishes the inflammatory gum conditions periimplantitis and periodontitis; note however that they framed their analysis in terms of the "competing endogenous RNA" (ceRNA) hypothesis, which has been questioned (cf. Salmena et al., 2011; Bartel, 2018, p. 35); Zhou et al. also cited the finding on silver nanoparticles, discussing a role in periimplantitis of responses to metal ions more generally. Returning to nervous tissue, Alshabi et al. (2019) found that FAM126B is part of a protein-protein interaction network involved in glioblastoma multiform, a brain cancer, and interacts with 289 miRNAs, of interest since miRNAs may drive cancer progression (Baer et al., 2013).

OBSCN codes via alternative RNA splicing for the giant obscurins, exhibiting a modular design of signaling and protein-binding domains, as well as for smaller isoforms (Perry et al., 2013; Randazzo et al., 2017a; Wang et al., 2018). Also discovered recently (Young et al., 2001), obscurins' best-known isoforms are the giants obscurin-A and obscurin-B, found in the sarcomeres of striated heart and skeletal muscle, together with the other sarcomeric giant proteins titin and nebulin and the "sliding filament" proteins myosin and actin (Wang et al., 2018). Obscurin-A's COOH-terminus contains ankyrin-binding domains, while obscurin-B's COOH-terminus instead contains two kinases; their structure is otherwise identical, including an NH_2-terminus with a titin-binding domain (Figure 1). Obscurin-A, by binding titin and small ankyrin 1, likely tethers the sarcoplasmic reticulum, a specialized endoplasmic reticulum responsible for calcium transport to trigger muscle contraction, to the myofibril; obscurins also play further incompletely-understood structural and regulatory roles in sarcomere genesis and integrity. It is intuitive that mutations in obscurin and in obscurin-binding domains of titin have been linked to heart and skeletal muscle disorders (Grogan & Kontrogianni-Konstantopoulos, 2019; Grogan et al., 2020*a*), and tempting to wonder if obscurins play a role in or against heart and skeletal muscle aging (Arking, 2006, pp. 151–162). Interestingly, in this connection, in mice, deletion of the titin-binding Ig58/Ig59 obscurin domains causes age-dependent cardiac remodeling and arrhythmia (Grogan et al., 2020*b*), and *OBSCN*-knockout mice perform worse than controls at intensive exercise, in an age-dependant manner (Randazzo et al., 2017b); *OBSCN* also regulates ubiquitin-dependent protein degradation in striated muscle (Wang et al., 2018), of interest since loss of proteostasis is a hallmark of aging (López-Otín et al., 2013) and since the ubiquitin-proteasome system was also linked to mammal longevity evolution (Li and de Magalhães, 2013). Obscurins have also been found in non-muscle tissues (Ackermann, 2014), however, and have also been linked to cancer: for instance, in one study *OBSCN* and *TP53* were the only two mutations found as common in both breast and colorectal cancer (Sjöblom et al., 2006); obscurins have been studied in a number of cancer types, but especially as tumor-suppressors in breast epithelium (Guardia et al., 2021). Returning to rockfish longevity, finer-grained molecular evolutionary analysis may

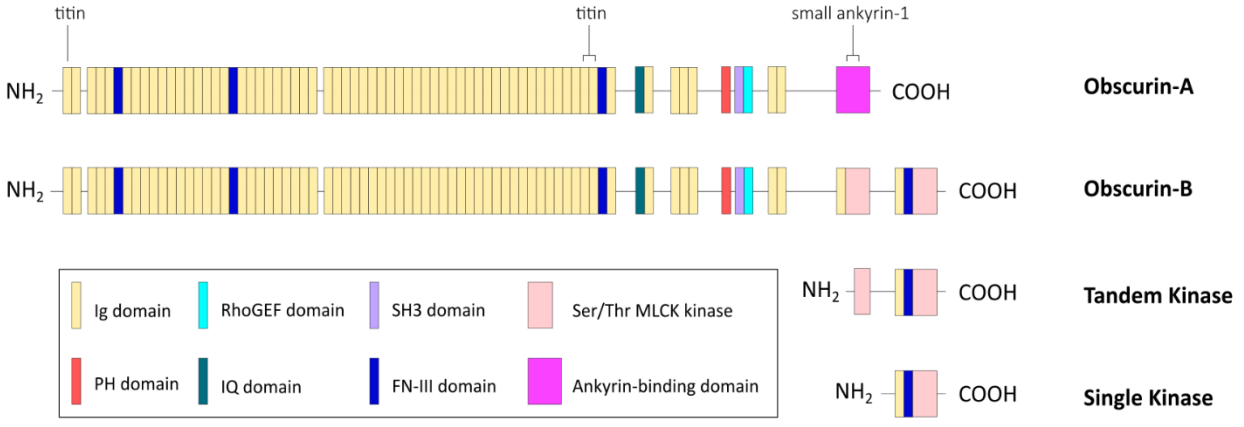

Figure 1. Four obscurin isoforms in striated heart and skeletal muscle. Adapted from (Wang et al., 2018).

Table 1. Summary of FAM126B and OBSCN.

	FAM126B	*OBSCN*
	Family with sequence similarity 126 member B	Obscurin(s)
NCBI Gene ID:	285172	84033
Protein family discovered:	Zara et al. (2006).	Young et al. (2001)
Summary	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.
Comparative genomics of longevity	**Mammals:** *FAM126B* was the only gene with a high longevity-specific selectivity score under all three selectivity thresholds (Li and de Magalhães, 2013).	**Rockfish:** *OBSCN* 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).
Disease associations	Little known. However, *FAM126B* 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. Deficiency of its homolog hyccin (FAM126A) causes the white matter disorder, hypomyelination and congenital cataract (HCC) (Zara et al., 2006).	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., 2020*a*). 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).
Further connections to biogerontology	Little known. However, *FAM126B* 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).	*OBSCN*-knockout mice show age- and sex-related cardiac remodeling and arrhythmia (Grogan et al., 2020*a*), and age-related decreased performance in intensive exercise to exhaustion (Randazzo et al., 2017*b*). 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).
Recommended further reading	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.

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