An updated SYSCILIA gold standard (SCGSv2) of known ciliary genes, revealing the vast progress that has been made in the cilia research field

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Running Head. Provide a running head fewer than 40 characters.

Abbreviations. List only nonstandard abbreviations that are used three or more times in the text.

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Brief report 20,000 characters exc spaces max excluding materials and methods and references

18,810 characters

Abstract (200 words or less) 173 words
Cilia are microtubule-based organelles with important functions in motility and sensation. They contribute to a broad spectrum of developmental disorders called ciliopathies, and have recently been linked to common conditions such as cancers and congenital heart disease. There has been increasing interest in the biology of cilia and their contribution to disease over the past two decades. As a result, in 2013 we published a 'Gold Standard' list of genes confirmed to be associated with cilia. This was published as part of the SYSCILIA consortium systems biology study dissecting the contribution of cilia to human health and disease, and was named the Syscilia Gold Standard (SCGS). Since this publication, interest in cilia and understanding of their functions has continued to grow, and we now present an updated SCGS version 2. This includes an additional 383 genes, more than doubling the size of SCGSv1. We use this dataset to conduct a review of advances in understanding of cilia biology 2013-2021, and perspectives on the future of cilia research. We hope that this continues to be a useful resource for the cilia community.

Introduction
Cilia are microtubule-based cell surface organelles with important functions in motility and sensation. There are three subclasses of cilia defined by their microtubule ultrastructure. Firstly, motile cilia are found in large numbers on the epithelial cells of the reproductive tracts, brain ventricles and respiratory tract. As a result, cells with motile cilia are often called multiciliated cells (MCCs). These cilia have a backbone (axoneme) of a ring of 9 microtubule doublets, with a central pair of microtubules, and dynein arms allowing the cilia to beat in a coordinated motion to facilitate fluid flow over their surface (Legendre *et al.*, 2021). Secondly, nodal cilia are a population of cilia which exist transiently in embryonic development at the embryonic node. They lack the central pair of microtubules but retain motility, and function in directional fluid flow at the node to establish left-right asymmetry in the embryo (Nonaka *et al.*, 1998). Finally, primary cilia are single non-motile organelles found on the surface of all other epithelial cells in the body, and some other cell types such as fibroblasts. They lack the central pair of microtubules and dynein arms. They do not beat and their primary functions are in chemosensation, mechanosensation and, in the retina, photosensation (Wheway *et al.*, 2018). The outer segment of the photoreceptor cell of the retinal is a huge and highly specialised primary cilium (Bujakowska *et al.*, 2017).

Until several decades ago primary cilia were believed to be vestigial organelles with no significant function. They were assumed to have lost their motility and been rendered redundant. This view was challenged in the early 2000s when it was demonstrated that primary cilia are required for normal kidney function, with the discovery that IFT88, mutated in a mouse model of polycystic kidney disease, is required for cilium assembly (Pazour *et al.*, 2000). This led to molecular investigations which identified the primary cilium as a sensory organelle, with mechanosensory roles in the kidney mediated by polycystins in the cilium membrane (Yoder *et al.*, 2002; Nauli *et al.*, 2003). This was an important discovery as it uncovered the role of the primary cilium in autosomal dominant polycystic kidney disease, one of the most common human genetic diseases (Ong and Wheatley, 2003). Primary cilia have subsequently been shown to be a central signalling organelle, with roles signal transduction in the Hedgehog (Huangfu *et al.*, 2003), Wnt and PDGFRα signalling pathways (Schneider *et al.*, 2005; Simons *et al.*, 2005). They play important roles throughout development, from very early embryogenesis. The clinical consequences of the aberrant development or function of primary cilia extend beyond polycystic kidney disease to encompass a spectrum of severe inherited human disorders known collectively as the ciliopathies (Oud *et al.*, 2017).

Much of our understanding of the basic structure and function of cilia has derived from the study of ciliated model organisms including the single-celled eukaryotes *Chlamydomonas reinhardtii*, *Paramecium tetraurelia*, *Tetrahymena thermophila* and *Trypanosoma brucei* (Vincensini et al., 2011). Study of these organisms provided us with the first proteomes of the cilium (Pazour *et al.*, 2005; Smith *et al.*, 2005; Broadhead *et al.*, 2006; Arnaiz *et al.*, 2009) and basal body (Kilburn *et al.*, 2007), constructed using approaches such as high-throughput proteomics and comparative genomics. *Caenorhabditis elegans* and *Drosophila melanogaster* were useful models for early characterisation of genes encoding ciliary proteins, through genome-wide identification of promoters containing an X-box, and study of genes under control of ciliary transcription factors (Blacque *et al.*, 2005; Efimenko *et al.*, 2005; Laurençon *et al.*, 2007). These simple model organisms show some striking conservation with humans and have been useful for identifying and characterising orthologs of human ciliopathy genes (Keller *et al.*, 2005; Chen *et al.*, 2006), further developed through studies of vertebrate models such as *Xenopus tropicalis* and *laevis* and zebrafish (Song *et al.*, 2016; Rao and Kulkarni, 2021). Rat and mouse have been important mammalian models for understanding and modelling the role of cilia in human health and disease (Norris and Grimes, 2012). Collectively, many high-throughput genomic, proteomic and gene expression studies in model organisms and humans have contributed to ciliary databases such as Cildb (Arnaiz *et al.*, 2009; Arnaiz *et al.*, 2014), the ciliary proteome (Gherman *et al.*, 2006) and ciliome (Inglis *et al.*, 2006). These databases comprise lists of genes and proteins identified in high-throughput ciliary studies in different ciliated model organisms and humans but are generally assembled using computational methods and not curated by human experts (with perhaps the exception of (Nogales-Cadenas *et al.*, 2009).

To address this, in 2013 we published version 1 of the SYSCILIA gold standard (SCGSv1) (van Dam *et al.*), a manually curated list of known ciliary components compiled with expert review of each entry (van Dam *et al.*, 2013). This was borne out of a need for a robust positive control set of high confidence ciliary genes to aid interpretation of the multiple large datasets being produced by hypothesis-neutral screening approaches implemented in the collaborative European research programme 'SYSCILIA' http://www.syscilia.org/index.shtml. This positive control set proved instrumental in quantifying the enrichment of known ciliary genes in these screening results, allowing us to evaluate the success of such screening strategies and confidence in our novel findings (Slaats *et al.*, 2015; Wheway *et al.*, 2015; Boldt *et al.*, 2016; Lambacher *et al.*, 2016). This original list was focused on primary cilia genes, with less consideration for motile cilia genes.

In the eight years since this resource was published, the paper has been a useful resource for other groups analysing screening data (Gupta *et al.*, 2015; Roosing *et al.*, 2015; Shim *et al.*, 2016; Pusapati *et al.*, 2018; Gheiratmand *et al.*, 2019), for evolutionary genetics studies (Nevers *et al.*, 2017; Shulman and Tsou, 2017) and in prioritisation of candidate genes from exome and genome sequencing of ciliopathy patients (Shaheen *et al.*, 2016). The field of ciliary biology has advanced rapidly since the publication of SCGSv1, and in response we now provide an updated SCGS, including updated annotation of all genes, achieved through systematic literature searching and candidate gene analysis. The result is the SCGSv2 listing 686 genes, a major increase from SCGSv1 which contained 303 genes. We advance the utility of this dataset by grouping entries into two main categories; first order and second order cilia genes, elaborating a concept first put forward by Jeremy Reiter and Michel Leroux (2017)(Reiter and Leroux, 2017). Profs Reiter and Leroux propose ciliopathies fall into two categories; first order ciliopathies which are diseases caused by aberrations in genes encoding proteins localised to the cilium and; second order ciliopathies which arise as a result of defects in genes which do not encode proteins localising to the cilium but have a role in cilium formation or function. Similarly, we annotate genes as first order if they encode proteins which localise to the cilium or basal body, and second order if they encode proteins which do not localise to the cilium or basal body but otherwise have roles in cilium structure or function. SCGSv1 was focussed on primary cilia genes, and in SCGSv2 we expand this further to more comprehensively include motile cilia genes also. We review the new entries to give a perspective on recent advances in understanding of cilium structure, function and their role in development and disease.

Results and discussion

383 additional gold standard cilia genes were identified, producing the SCGSv2 of 686 genes, a major increase from SCGSv1 which contained 303 genes. 539 of these 686 (78.6%) are first order cilia genes, and 133 are second order (19.4%). 14 have not had their protein localisation reported, and so are not designated first order or second order. A retrospective analysis of SCGSv1 shows that 273/303 genes were first order cilia genes (90.1%) and 25/303 were second order cilia genes (8.3%). This may suggest that since the publication of SCGSv1 an increasing awareness of cilia outside of the cilia community has led to more study of the cilium functions of proteins. Alternatively or additionally, it may suggest that the discovery of first order cilium genes is becoming saturated, and so a proportional increase in second order cilia gene discovery is seen more recently.

57 of the new 383 genes (14.9%) were originally qualified as predicted in SCGSv1 paper. These 57 genes appeared in experimental and bioinformatics screens without in-depth validation of their function or localisation and were provided as an appendix to the SCGSv1. 187 of the new 383 genes (48.8%) were predicted in CiliaCarta (van Dam *et al.*, 2019), demonstrating the validity of this Bayesian-based approach to predict ciliary function from genomic, proteomic, transcriptomic and evolutionary data.

Of the novel cilium genes identified there are clear trends in the biological pathways that these genes are associated with. An enrichment analysis of Gene Ontology terms (Ashburner *et al.*, 2000; Carbon *et al.*, 2009; The Gene Ontology Consortium, 2019) describing Biological Processes (GO BP terms) in the list of new cilia genes compared to SCGSv1 shows that the new list of genes is particularly enriched for genes involved in cell stress responses, (de)ubiquitination, autophagy, ageing, DNA repair, chromatin remodelling, multiple signalling pathways and regulation of cardiac growth.

In the new list of cilia genes, one of the most enriched types of genes are those with GO BP terms relating to cellular response to external/environmental stimulus (GO:0071496/GO:0104004, fold enrichment 14.75/6.47, p=1.20E-13 /2.54E-10). There is particularly enrichment of genes with roles

in response to stress (GO:0006950, 2.46 fold enrichment, p= 1.74E-10), cellular response to nutrient nutrient levels/starvation (GO:0031669/GO:0042594, fold enrichment 10.87/10.09 p= 5.90E-08/ 6.66E-07), response to decreased oxygen levels (GO:0036293, 6.21 fold enrichment, p=7.73E-06), cellular response to radiation (GO:0071478, 6.21 fold enrichment, p=7.73E-06), including DNA repair (GO:0006281, 8.54 fold enrichment, p=6.37E-05). This suggests a recent increase in understanding of the role of cilium in sensation of cell environment and orchestrating the response to cell stress. In many cases of shock or stress, literature suggests that rapid responses such as ciliogenesis or cilium resorption are executed via rapid protein degradation via the ubiquitin-proteasome system (UPS). For example, it has been shown that MIB1, which represses ciliogenesis by ubiquitinating CEP131 and PCM1 at centriolar satellites, is abruptly inactivated in response to cell stress, leading to loss of CEP131 and PCM1 ubiquitination and stimulation of ciliogenesis, even in proliferating cells (Villumsen *et al.*, 2013).

Indeed, in addition to MIB1 E3 ligase, many other genes involved in ubiquitination and even more involved in protein deubiquitination (GO:0016579) are found in SCGSv2 than SCGS1 (10.87 fold enrichment, p=5.90E-08). MIB1-mediated ubiquitination and degradation of PCM1 during serum-starvation induced ciliogenesis is antagonised by deubiquitinating enzyme USP9X (Wang *et al.*, 2019). USP9X further contributes to cell cycle dependent ciliogenesis; in the G0/G1/S phase, USP9X is recruited to the centrosome by NPHP5 where it protects NPHP5 from ubiquitination, promoting cilia assembly. In the G2/M phase, USP9X dissociates from the centrosome allowing BBS11/TRIM32 (E3 ligase) to K63 ubiquitinate NPHP5, triggering protein delocalization and loss of cilia. USP14 has been shown to control ciliogenesis, cilia length and localisation of mediators of Hedgehog (Hh) signalling in cilia through deubiquitination and stabilisation of KIF7 (Massa *et al.*, 2019). USP8 deubiquitinates HIF1a to control ciliogenesis in normoxia (Troilo *et al.*, 2014), and antagonises Smo ubiquitination (Ma *et al.*, 2016). SUMOylation has also been implicated in the trafficking of Smo into cilia (Ma *et al.*, 2016), further broadening our understanding of how protein degradation pathways control cilium structure and function. The increase in understanding of the protein modifications involved in protein metabolism relevant to ciliogenesis and cilium function is reflected in the enrichment of terms in SCGSv2 related to positive regulation of phosphorylation (GO:0042327, 3.98 fold enrichment, p=7.59E-11), positive regulation of kinase activity (GO:0033674, 4.97 fold enrichment, 1.46E-10), protein modification by small protein removal (GO:0070646, 11.64 fold enrichment, p=4.87E-09) and positive regulation of protein modification process (GO:0031401, 2.98 fold enrichment, 4.33E-08).

In the years since the publication of SCGSv1 it has also become apparent that autophagy plays a role in this rapid ciliogenesis/cilium resorption process. Indeed, genes with GO BP terms relating to regulation of autophagy (GO:0010506) are enriched in the new additions to SCGSv2 (3.3 fold enrichment, p=1.45E-02). This includes ATG3 and ATG5 which are required for rapid degradation of OFD1 at centriolar satellites in response to serum starvation (Tang *et al.*, 2013). This landmark publication in Nature led to a suite of papers in recent years describing autophagic processes removing 'cilia roadblocks' to promote ciliogenesis, control cilium length and control cell volume (Jang *et al.*, 2016; Orhon *et al.*, 2016; Hsiao *et al.*, 2018; Liu *et al.*, 2018; Struchtrup *et al.*, 2018; Boukhalfa *et al.*, 2020). The interest in autophagy of cilia components has even led to the suggestion of a specific term for this process; 'ciliophagy' (Cloonan *et al.*, 2014). It has long been observed that serum starvation can induce ciliogenesis in cell culture, and this recent work studying the UPS, SUMOylation pathway and autophagy has provided insights into the mechanisms and dynamics of this process.

Whilst cilia have been recognised as signalling hubs for a number of years now, the extent to which the cilium plays a role in almost every signalling pathway in the cell was perhaps unprecedented. Since the publication of SCGSv1 the cilium has been reported as playing a role in IGF signalling (Yeh

et al., 2013), FGF signalling (Kunova Bosakova *et al.*, 2019), , Hippo/YAP/TAZ signalling (Kim *et al.*, 2015), prostaglandin signalling (Jin *et al.*, 2014), notch signalling (Boskovski *et al.*, 2013), mTOR signalling (Zhong *et al.*, 2016; Park *et al.*, 2018) and TGFbeta signalling (Clement *et al.*, 2013). TGFbeta signalling through the cilium was shown to be important for cardiomyogenesis (Clement *et al.*, 2013), and GO BP terms relating to cardiac muscle growth (GO:0055021, 6.99 fold enrichment, p=4.77E-03) are also enriched in the new cilia genes of SCGSv2. Whilst one of the earliest discoveries in 9+0 cilia biology was the role of nodal cilia in establishing leftward nodal fluid flow, breaking left-right symmetry for proper heart looping (Nonaka *et al.*, 1998) more recently there have been advances in understanding of the role of primary cilia in later heart development and function, and the contribution of cilia defects to congenital heart disease (Li *et al.*, 2015; Scott *et al.*, 2017; Toomer *et al.*, 2019). Overall, however, there is a significant underrepresentation of genes involved in developmental processes such as brain development, limb morphogenesis, heart looping and left/right asymmetry the new cilia gene list compared to SCGS1, suggesting that in recent years smaller gains have been made in understanding of the role of cilia in early developmental processes.

Enrichment of genes with GO BP terms chromatin organization (GO:0006325, 11.64 fold enrichment, p=4.87E-09), histone modification (GO:0016570) and covalent chromatin modification (GO:0016569) (both 9.32-fold enriched, p-6.97E-06) in SCGSv2 represents an increase in understanding of transcriptional regulation of ciliogenesis, and also of the dual roles of histone modifying enzymes in histone modification and other roles in the cilium. This includes KDM5C which is involved in regulating ciliogenesis by regulating actin gene expression, and also through directly binding to the actin cytoskeleton, creating a responsive "actin gate" that involves ARP2/3 activity and IFT (Yeyati *et al.*, 2017) and TRRAP, an essential component of multiple histone acetyltransferase complexes, which regulates multiciliated cell formation (Wang *et al.*, 2018). There has also been an increase in understanding of how various transcription factors regulate ciliogenesis, such as MCM2 which binds to transcription start sites of cilia inhibiting genes to control ciliogenesis in postmitotic cells (Casar Tena *et al.*, 2019) and MYB transcription factor which plays a role in multiciliogenesis, as progenitors exit the cell cycle and amplify their centrioles (Tan *et al.*, 2013). Furthermore, transcription factor ATOH1 controls ciliogenesis in neuron progenitors (Chang *et al.*, 2019) and transcription factor SREBF1 activates expression of PLA2G3 to repress cilium formation in cancer cells (Gijs *et al.*, 2015). Recent studies have also expanded understanding of the role of RFX transcription factors RFX2 and 7 in regulating coordinated ciliogenesis (Chung *et al.*, 2014; Manojlovic *et al.*, 2014). Furthermore, it has been shown that some transcription factors have secondary functions in cilia, such as SALL1 transcription factor which Interacts with factors related to cilia function, including the negative regulators of ciliogenesis CCP110 and CEP97 (Bozal-Basterra *et al.*, 2018). Additionally, post-trancriptional regulation of cilia genes is beginning to be understood with the discovery that pre-mRNA splicing factors regulate splicing of cilia genes (Wheway *et al.*, 2015; Buskin *et al.*, 2018), and NUDT16L1 (SDOS) post-transcriptionally regulates cilia genes by binding and regulating translation of cilia mRNAs (Avolio *et al.*, 2018).

Finally, it is an interesting observation that the new genes in SCGSv2 are enriched for GO BP term aging (GO:0007568, 9.32 fold enrichment, p=6.97E-06). Whilst there are few publications directly linking cilia to ageing (Carroll and Korolchuk, 2018) it is well known that the cilium plays a central role in nutrient sensing, and reduced responsiveness of nutrient sensing pathways is associated with ageing. The nutrient-sensing role of cilia in ageing may become more apparent in future research. Furthermore, recent research has linked cilia defects to induction of cell senescence (Jeffries *et al.*, 2019) and conversely that depolarization of senescent cell plasma membrane leads to primary cilia defects and a resultant failure to inhibit growth factor signaling (Carroll *et al.*, 2017). Senescence has been described as a feature of some ciliopathies such as nephronophthsis type 7 (Lu *et al.*, 2016). This is significant, because cilia are classically associated with developmental

disorders, yet may also play a role in ageing and associated disease, which are some of the most costly burdens to our society today, both economically and socially.

The aim of this study was to produce a high confidence list of cilia genes annotated by cilia experts. The approach prioritised the exclusion of false positives over the exclusion of false negatives, and as a result the list is highly stringent and not a completely comprehensive list of all cilia and basal body genes. Absence of a gene from this list does not necessarily mean that gene does not play a role in ciliogenesis, cilium structure or function but inclusion of a gene in this list means that it is highly confidently associated with these processes in humans. The literature search did not include grey literature or literature in pre-print servers prior to peer review and as a result, the most recently identified and characterised genes will not be included. The literature search focussed on human genes (with 'human' included as search term) and the titles of search results were reviewed for mention of genes in humans or vertebrate models such that cilia genes which are have been described in model organisms but for which the ortholog has not been well characterised in humans/human cell lines will be omitted. The resulting list is a stringent, high-confidence list of genes involved in ciliogenesis, cilium structure and function with a focus on human cilia and ciliopathy genes. For more comprehensive lists of genes which include candidate genes, likely false positives, and genes which have no ortholog in humans, we direct the reader to CiliaCarta (van Dam *et al.*, 2019) or cildb (Arnaiz *et al.*, 2014).

Materials and Methods

On 1st January 2021 a systematic review of Medline was conducted using the following MESH terms:

((((((((((((((((cili*[Title/Abstract]) NOT ciliary body[Title/Abstract]) AND ("2013/05/01"[Date - Publication] : "3000"[Date - Publication])) AND English[Language]) AND Humans[Mesh])) NOT ciliate[Title/Abstract]) AND Humans[Mesh])) NOT ciliary muscle[Title/Abstract]) AND Humans[Mesh])) NOT Ciliary Neurotrophic Factor Receptor[Title/Abstract]) AND Humans[Mesh])) NOT cilioretinal[Title/Abstract]) AND Humans[Mesh])) NOT ciliochoroidal[Title/Abstract]

This returned 4,548 results. Each title was assessed for mention of gene names, or for the word 'screen'. Where novel genes or screen results were reported in vertebrates, human cells or human cell lines, abstracts and figures were studied to identify nature of protein function and immunofluorescence or immunogold electron microscopy images showing the localisation of the protein. Official gene symbol, Ensembl gene ID, any associated OMIM ID, curators note, relevant PubMed IDs and localisation were recorded in a spreadsheet.

In addition to the systematic literature search, the 286 genes predicted to be cilia genes in the CiliaCarta(van Dam *et al.*, 2019) study were specifically included in a Medline search using MESH terms cili*[Title/Abstract]) AND [gene name 1] OR [gene name 2]… OR [gene name n]. Every paper from this search was studied in depth to identify any reported protein functions in cilia and localisation.

Once all genes were extracted from this systematic review into a results table, every entry was independently reviewed by a second cilia expert, who entered additional data and annotated the 'curators note' column on this table.

If the protein localisation was reported as cilium, axoneme, basal body or part thereof, this gene was scored as a first order cilium gene. If a protein's localisation was reported as any other cell location,

including centriole, centrosome, centriolar satellite but not explicitly basal body, the gene was scored as a second order cilium gene.

Once finally compiled, Ensembl gene IDs were filtered to identify which we predicted in the SCGSv1 paper, and which were predicted in the CiliaCarta paper.

Gene Ontology enrichment analysis of SCGSv2 was conducted using amiGO (Carbon *et al.*, 2009) Enrichment of gene ontology terms relating to biological processes in SCGSv2 compared to SCGSv1 was conducted using a binomial test, with Bonferroni correction of the p value to account for multiple testing. Ensembl gene IDs were used as input in amiGO.com which accesses the Panther database.

Table legend

Table showing all entries in SYSCILIA Gold Standard Version 2 (SCGSv2) with Ensembl gene ID, description of gene, official gene name, any associated OMIM number(s), curators note, associated PubMed ID(s), localisation of the protein product of the gene, whether this is first order (at the cilium or basal body) or second order (elsewhere), whether it was in SCGSv1 or predicted in SCGSv1 or CiliaCarta.

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