Neurobiology of Disease 144 (2020) 105021

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

Somatic mutations in neurodegeneration: An update

Christos Proukakis

Department of Clinical and Movement Neurosciences, Queen Square Institute of Neurology, University College London, London, UK

ARTICLE INFO

Keywords:
Somatic mutation
Mosaicism
Neurodegeneration
Single cell sequencing
Synucleinopathy
Huntington's disease
DNA damage
Parkinson's disease
Multiple system atrophy
Alzheimer's disease
ALS

ABSTRACT

Mosaicism, the presence of genomic differences between cells due to post-zygotic somatic mutations, is widespread in the human body, including within the brain. A role for this in neurodegenerative diseases has long been hypothesised, and technical developments are now allowing the question to be addressed in detail. The rapidly accumulating evidence is discussed in this review, with a focus on recent developments. Somatic mutations of numerous types may occur, including single nucleotide variants (SNVs), copy number variants (CNVs), and retrotransposon insertions. They could act as initiators or risk factors, especially if they arise in development, although they could also result from the disease process, potentially contributing to progression. In common sporadic neurodegenerative disorders, relevant mutations have been reported in synucleinopathies, comprising somatic gains of *SNCA* in Parkinson's disease and multiple system atrophy, and in Alzheimer's disease, where a novel recombination mechanism leading to somatic variants of *APP*, as well as an excess of somatic SNVs affecting tau phosphorylation, have been reported. In Mendelian repeat expansion disorders, mosaicism due to somatic instability, first detected 25 years ago, has come to the forefront. Brain somatic SNVs occur in DNA repair disorders, and there is evidence for a role of several ALS genes in DNA repair. While numerous challenges, and need for further validation, remain, this new, or perhaps rediscovered, area of research has the potential to transform our understanding of neurodegeneration.

1. Introduction

Somatic mutations occur post-zygotically, in development or ageing, and lead to mosaicism, the presence of cells with different genomes in an individual. Although their link to cancer is well established, the traditional assumption that the nuclear genome is otherwise invariant throughout the lifespan has been challenged in recent years (Forsberg et al., 2016). Indeed, genomic mosaicism in normal brain may be important for function, as in the immune system, and not necessarily detrimental (Rohrback et al., 2018b). The term "mutation" is quite broad, and in this review refers to any type of change affecting the DNA sequence. Mutation types therefore include single nucleotide variants (SNVs, "point mutations") and copy number variants (CNVs), but also repeat expansions, insertions of transposable elements such as LINE-1, other types of structural variants (SVs), and whole chromosome changes (aneusomies) leading to aneuploidy, with mechanisms responsible for each of these likely to be quite different (Supek and Lehner, 2019). The first evidence of brain genomic mosaicism, predating recent genetic technologies, came from studies demonstrating aneuploidy (Rehen et al., 2005, Rehen et al., 2001; Yurov et al., 2005), which may function as a substrate for selection in the developing brain (Peterson et al., 2012). Selection of neuronal nuclei by sorting (Rehen et al., 2005) was subsequently used in studies showing DNA content variation in individual neurons (Westra et al., 2010), and more recently numerous studies of single neuronal sequencing, which demonstrated mosaicism in healthy brain (reviewed by (McConnell et al., 2017; Rohrback et al., 2018b)). A role for somatic mutations in a wide range of neurodevelopmental disorders is now well established (D'Gama and Walsh, 2018), and the first studies in neurodegeneration have been previously reviewed (Leija-Salazar et al., 2018; Lodato and Walsh,

Abbreviations: AD, Alzheimer's disease; A-T, ataxia-telangiectasia; ALS, amyotrophic lateral sclerosis; CNV, copy number variant; CS, Cockayne syndrome; DLB, dementia with Lewy bodies; DPR, dipeptide-repeat proteins; DDR, DNA damage response; ddPCR, droplet digital PCR; DSB, double-strand break; EC, entorhinal cortex; FISH, fluorescent in situ hybridisation; GCI, glial cytoplasmic inclusions; FTLD, frontotemporal lobar degeneration; GTEx, genotype-tissue expression; HD, Huntington's disease; Hip, hippocampus; HR, homologous recombination; ILBD, incidental Lewy body disease; LCM, laser-capture microdissection; LINE-1, long interspersed nuclear element-1; MMR, mismatch repair; MSA, multiple system atrophy; NER, nucleotide excision repair; NHEJ, non-homologous end joining; OB, olfactory bulb; PD, Parkinson's disease; PFF, pre-formed fibrils; SCA, spinocerebellar ataxia; SN, substantia nigra; SNV, single nucleotide variant; SSB, single-strand break; SV, structural variant; TC, temporal cortex; UMI, unique molecular identifier; UTR, untranslated region; WGS, whole genome sequencing; XP, xeroderma pigmentosum

E-mail address: c.proukakis@ucl.ac.uk.

https://doi.org/10.1016/j.nbd.2020.105021
Received 10 March 2020; Received in revised form 12 June 2020; Accepted 13 July 2020
Available online 24 July 2020
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2019; Nicolas and Veltman, 2019; Verheijen et al., 2018).

In this review, I focus on recent developments in somatic mutations of, and damage to, the nuclear genome in neurodegeneration. In Section 2, the mutation prevalence in normal brain is discussed, in order to help put the disease findings in context. Theoretical considerations of the roles of mutations, which could be a cause and/or result of the disease process, and strategies and technical issues in their detection, are also reviewed. In Section 3, the current knowledge in specific neurodegenerative diseases is reviewed, including the common, usually sporadic ones, but also inherited disorders where somatic instability of the germline mutation, or downstream effects of a germline mutation affecting DNA repair, play a role. In the final section, the question of the relationship between protein aggregation and mutations is discussed, followed by some comments specific to retrotransposons, and a summary. The complex case of mitochondrial DNA in neurodegeneration will not be discussed here, but it has been reviewed elsewhere (Nissanka and Moraes, 2018), and updated for Parkinson's disease (PD) in particular (Alegre-Abarrategui et al., 2019).

2. Somatic mutations in the nervous system, and possible relevance to neurodegeneration

2.1. How do neurons acquire somatic mutations?

Broadly speaking, mutations can be divided as arising in mitosis, or post-mitotically. The former would give rise to clonal patterns, with the same mutation found in a significant proportion of cells in one or multiple tissues, while the latter would be limited to the single cell in which they occurred. SNVs, CNVs, LINE-1 insertions and aneuploidy can all arise in mammalian neurogenesis (Bae et al., 2017; Faulkner and Billon, 2018; Rohrback et al., 2018a). As neurons cannot, in general, be renewed, they are likely to accumulate more DNA damage than replicating cells during an individual's lifetime. If the damage is not enough to lead to cell death, then a dysfunctional neuron with private somatic mutations may survive for a considerable period, and this may vary with neuronal type (Rutten et al., 2007). Mutations in general can be seen as being determined by both the damage to the DNA, and the response to it (Volkova et al., 2019), although variations in DNA repair may be more important in determining differential somatic mutation rates (Supek and Lehner, 2019). DNA damage leads to the "DNA damage response" (DDR), and has been long associated with neurological disorders (Coon and Benarroch, 2018; Iyama and Wilson, 2013; McKinnon, 2017).

DNA damage types can be divided into those that do not result from a primary "break" to the DNA phosphodiester backbone, and those that do, affecting a single strand, or both strands (Tiwari and Wilson, 2019) (Table 1). Double-strand breaks (DSBs) are probably the most harmful type, and their occurrence in neurons is well documented (Alt and Schwer, 2018). DSB and can be repaired by homologous recombination (HR), and non-homologous end-joining (NHEJ), which is more error-prone (Moynahan and Jasin, 2010), and they also allow the capture of sequences at breakpoints (Lin and Waldman, 2001). NHEJ directly rejoins chromosome ends, without requiring a nucleic acid template, and is thus available to all cells, including neurons, although it frequently leads to deletions. Traditional HR requires DNA synthesis, and therefore may not be possible in post-mitotic cells, unless there is aberrant cell cycle re-entry. RNA templates can also be used, however, for HR (Keskin et al., 2014), including in post-mitotic neurons (Welty et al., 2018). DSBs may, paradoxically, also have a physiological function, aligning with the view of genomic mosaicism as part of normal brain biology (Rohrback et al., 2018b; Weissman and Gage, 2016). This was first suspected in neurogenesis, after the demonstration that DNA end-joining proteins are required (Gao et al., 1998). This led to the suggestion that developing neurons may be susceptible at a particular period, with genomic rearrangements after DSB allowing selection during apoptotic programmed cell death (Chun and Schatz, 1999). DSBs have now been conclusively demonstrated in mouse neurodevelopment, notably affecting neuronal genes (Schwer et al., 2016), and indeed the time of their occurrence parallels the generation of mouse neuronal CNVs (Rohrback et al., 2018a). DSBs also arise post-mitotically, induced by activity, with a likely role in learning and memory (Madabhushi et al., 2015). Direct demonstration of large CNVs arising in neurons after DSBs has been recently provided by deletion of Topoisomerase 1, which maintains genomic integrity during transcription, leading to a doubling of the neurons containing them (Fragola et al., 2020). Several other types of DNA damage can lead to SNVs (discussed in next section) or other small-scale mutations (Table 1). Bulky lesions which distort the helix are repaired by nucleotide excision repair (NER). Base modifications, caused by a number of processes, with oxidative stress particularly relevant, are dealt with by base-excision repair (BER). Mismatch repair (MMR) deals with mismatched complementary bases. Primary single strand breaks (SSB) are repaired by a similar pathway to BER, but are best considered separately, as germline defects lead to neurological disease (Section 3.4) without malignancy, while malignancies also arise in BER disorders (Tiwari and Wilson, 2019).

2.2. What is the mutation prevalence and relation to age in normal brain?

An understanding of recent developments in the "normal", or background, mutation pattern in brain leading to genomic mosaicism, and comparison to other tissues, will help set the framework for the interpretation of somatic mutations detected in neurodegenerative diseases. If mutations are established in embryogenesis, and neutral, then their frequency should remain unchanged with age in post-mitotic neurons. If neurons with developmental mutations are less robust to the challenges of ageing, they would be lost preferentially. Conversely, an increase with age would suggest a post-mitotic origin for at least a subset of mutations.

Table 1
DNA damage and repair in neurodegeneration. The types of DNA damage and repair are shown, together with the likely resulting mutations types if they are not repaired correctly (Helleday et al., 2014; Weckselblatt and Rudd, 2015), assuming the cell does not die, and that the same principles as in somatic tissues apply. Examples of disorders which include neurodegeneration arising from germline mutations in known DNA repair genes are shown, with recently reported possible associations, or modifier roles, in brackets (see Section 3.3).

Primary DNA break?	DNA lesion	Repair type	Possible relevant resulting mutation	Neurodegenerative diseases related to germline mutations/variants in pathway
No	Mismatch	MMR	Further repeat expansion	(Repeat expansion disorders)
	Bulky adduct	NER	SNV	CS, XP
	Base damage	BER	SNV	
Yes	SSB	SSBR	SNV	AOA1, SCAN1, AOA4, AOA5
	DSB	NHEJ	CNV/SV, LINE-1 or gencDNA insertion	A-T, ATLD (familial ALS: *FUS*, *TDP-43*, *C9orf72*, *NEK1*) (AOA2) (PD: *possible* GWAS associations)
		HR	CNV/V	

2.2.1. Overall SNV generation in development and ageing, and comparison with other tissues

Individual neurons may have over a thousand somatic SNVs (Lodato et al., 2015), at least some of which arise in neurogenesis (Bae et al., 2017). The somatic SNV generation rate in development, based on sequencing clonally-expanded human fetal brain neuronal precursors, was calculated as 1.3 per cell division pre-gastrulation, rising to 8.6 per cell division in neurogenesis (Bae et al., 2017), indicating that neurogenesis is susceptible to somatic SNV generation, as well as CNV generation which was discussed in the previous section. Conversely, the relationship of somatic SNVs to age has been studied in single neuronal WGS from the prefrontal cortex and hippocampus of 15 neurologically normal individuals, in a study specifically designed to detect post-mitotic mutations (Lodato et al., 2018), and through expressed SNV detection in the transcriptomes of multiple tissues available through the GTEx consortium (García-Nieto et al., 2019). There was an increase in mutations with age in the brain in both studies to some extent. In the GTEx study, the correlation of mutations with age in the brain was highest overall in the putamen, hypothalamus and nucleus accumbens. Single neurons showed increasing prevalence of SNVs with age overall, leading to the term "genosenium" to describe the apparent ageing of the nuclear genome (Lodato et al., 2018). The GTEx dataset also allowed comparisons between the total somatic SNV burden in brain and other tissues. All brain regions except pituitary had relatively low mutation prevalence overall, with whole blood in the other extreme. This is likely to reflect the number of cell divisions, rather than lower mutability, as the rate of new SNVs per cell division was actually lower in normal haematopoiesis (1.14)(Werner et al., 2020). The GTEx data clearly are derived from a mix of glia and neurons, and the author is not aware of any studies of SNVs in glial cells specifically.

2.2.2. Patterns of brain somatic SNVs

Considering individual mutations, or "mutation signatures", can provide further insights into their origin. GTEx data revealed T > C to be the commonest SNV in the brain, followed by C > T (~38% and 29 respectively across all regions excluding pituitary)(García-Nieto et al., 2019), while C > T mutations were the commonest in single neuron studies (Lodato et al., 2015), in exomes derived mostly from cerebellar DNA (Wei et al., 2019), and in targeted analysis of genes involved in neurodegeneration (Keogh et al., 2018). Interestingly, there was a highly significant negative correlation in the GTEx data between expression of NER genes and C > T mutations in most brain regions, including the hippocampus, but not the frontal cortex. In fact, the negative correlation with NER gene expression was seen in the hippocampus and nucleus accumbens for all SNVs. The concept of "mutation signatures", used widely in the cancer field, which are determined by the relative mutability of trinucleotides, helps identify the likely biochemical process leading to the observed mutation pattern(s) (Alexandrov et al., 2013). In the single neuron studies, three such signatures were seen. "Signature A" comprised predominantly C > T and T > C, and showed the clearest increase with age. It was reminiscent of "signature 5" reported in cancer and normal tissues. This likely to reflect a universal genomic ageing mechanism (Blokzijl et al., 2016). More recent data from breast cancer show that signature 5 is not related to cell cycle gene expression, but is related to oxidation, and may reflect continuous exposure to an unspecified mutagen (Y.-A. Kim et al., 2019b). It appears therefore that this "genome ageing" clock also applies to post-mitotic neurons (Lodato and Walsh, 2019). C > T mutations on their own comprised "signature B", which was more common in the hippocampus than prefrontal cortex. "Signature C" included C > A mutations, which may arise from oxidative damage, and showed modest correlation with age ($p = 0.04$). These may well arise as a result of oxidative damage in the ageing or diseased brain, but it is worth emphasising that they are also frequent in the late stages of neurogenesis (Bae et al., 2017). In the GTEx study, C > T and T > C mutation prevalence in the frontal cortex did not increase with age, although there was some increase in the hippocampus, and C > A mutations were correlated with age in the putamen and caudate, but not in the cortex, but firm comparisons cannot be made without formal determination of mutation signatures (García-Nieto et al., 2019). These results all need cautious interpretation, but they do suggest subtle differences in the mutation patterns for SNVs in different brain regions, which could be linked to disease susceptibility. SNVs do seem to accumulate with age in some regions at least. SNVs due to oxidative damage may arise in the putamen and caudate predominantly, with no data from the substantia nigra (SN) so far, and errors in NER may be the main driving force of SNVs in the hippocampus.

2.2.3. CNVs in ageing and brain cell types

In the largest single-cell study of CNVs in 15 healthy brains (Chronister et al., 2019), the proportion of cortical neurons with large CNVs was ~12%. It declined with age (from > 25% to < 10%), raising the interesting possibility that they are formed early, as discussed in Section 2.1, and shown in mouse neurogenesis (Rohrback et al., 2018a), and may affect long-term survival of neurons carrying them. In the three control brains with single cell CNV data from both neurons and non-neurons, the proportion of neurons with CNVs was higher (13% v 7%), although no specific glial types were identified (Chronister et al., 2019).

2.3. Are somatic mutations cause, effect, or both?

These possibilities are clearly non-mutually-exclusive, and there may well be a complex relationship, as will be discussed (Fig. 1). They could thus be seen as "initiators" or "executioners", borrowing terminology from the caspase field.

1) Cause (contributor), or initiator:

A somatic mutation leads to dysfunction and contributes to disease, in the same way that a germline variant in the same gene/pathway conveys disease risk. A mutation with a high penetrance when inherited could substantially increase disease risk if occurring somatically, while a mutation which is only a modest risk factor when inherited would convey minimal risk as somatic. In both of these cases, *risk = "intrinsic" pathogenicity of somatic mutation x mosaicism level* (the % of cells of relevant type carrying it), and there may indeed be a continuum of risk (Frank, 2010). The (relevant) mosaicism level will depend on the embryological origin, and any selection for or against it. It should be noted that a large burden of unique single cell mutations could have similar adverse effects as a single clonal mutation, if similar levels are reached (Leija-Salazar et al., 2018). The risk may be magnified if there is spread in relevant pathways of the protein product (Leija-Salazar et al., 2018).

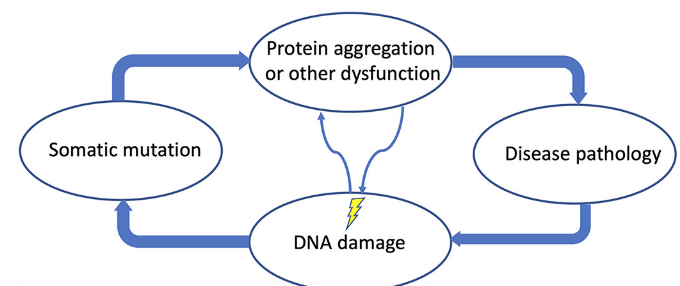

Fig. 1. Scheme of possible role of somatic mutations in neurodegeneration. In the simplest "causal" scenario, the somatic mutation, possibly arising in neurodevelopment, leads to aggregation of the relevant protein (or other dysfunction), and to disease if a critical threshold is reached. In the opposing situation, mutations arise due to the disease process, but may contribute to progression, and a "feedback loop" is possible. The possibility of protein aggregation leading to DNA damage, and vice versa, is discussed in later sections.

Table 2
Summary of sequencing studies targeting somatic SNVs in multiple AD cases. The name of the first author is shown. The studies are listed in the order in which they are discussed. Deep seq is targeted sequencing of very high coverage. TC = temporal cortex. EC = entorhinal cortex. OB = olfactory bulb. Hip = hippocampus. LCM = laser capture microdissection. ND = neurodegeneration. CVD = cerebrovascular disease. DLB = dementia with Lewy bodies. AF = allele frequency (% of the entire DNA in the sample) of mutations reported.

Study	AD patients	Other patients	Controls	DNA source	Technique	Number of genes	Somatic SNVs	AF
Frigerio et al., 2015	72	-	58	brain (EC)	deep seq	4	1 in AD, 2 in controls	~1%
Keogh et al., 2018	20	20 PD/DLB	14	brain (up to 5 regions ± blood)	deep seq (capture + UMI)	102 (56 ND, 46 cancer)	39 (most in cancer genes)	0.47–1.56%
Helgadottir et al., 2019	8	-	8	brain (TC) and blood	deep seq + ddPCR for one	28	11 in AD brain only	0.7–2.6%
Nicolas et al., 2018	445	-	-	brain in 98, blood in rest	deep seq + UMI	11	2 in brain, 7 in blood	0.2–10.8%
Ivashko-Pachima et al., 2019	20	-	20	brain (OB, Hip)	ddPCR (+ RNAseq)	1 (2 SNVs)	1 (+ RNAseq)	< 0.06%
Parcerisas et al., 2014	17	2 CVD	2	brain (hip) + cerebellum in 3	low coverage	exome	~575 per Hip (+ controls)	?
Wei et al., 2019	244	1217 other ND	362	brain (cerebellum in most)	low coverage	exome	> 1% of all brains	> 10%
Park et al., 2019	52	-	11	brain (LCM Hip) and blood	high coverage (+ deep seq)	exome	? pathogenic in 27%	0.52–15.3%

2) Effector, or executioner:

In this scenario, exogenous factors such as oxidative stress lead to accumulation of somatic mutations determined by the affected pathway, which impair cellular function and, ultimately, viability. Importantly, *germline* variation in DNA repair genes may contribute to the accumulation of *somatic* mutations resulting from dysfunction of the relevant repair pathway(s). In this case, they may also act as a modifier, with the phenotype determined partly by variability in the cell/region-specific accumulation pattern.

2.4. Where and how should we look for relevant somatic mutations?

Sporadic, and even inherited, neurodegenerative disorders have highly heterogeneous clinical and pathological features. Different levels of mosaicism across brain regions and cell types may underlie this variability, if they lead to direct adverse effects in the cells carrying them. It would accordingly make sense to analyse the most affected region, for example the SN in PD, and the hippocampus or entorhinal cortex (EC) in AD, but the following considerations are important.

(1) If somatic mutations, whatever their time of origin or type, lead to cell death, it may be impossible by definition to detect them in end-stage disease. It may be paradoxically easier to detect them in less susceptible cell types or brain regions, assuming an embryological origin and shared lineage (Leija-Salazar et al., 2018). A suitable brain region would be one demonstrating some pathology but limited cell death, such as the cingulate gyrus in synucleinopathies (Perez-Rodriguez et al., 2019). Even easily accessible non-ectodermal tissue, such as blood, could be used to detect mutations arising before gastrulation by high coverage sequencing, as mutations present in > 5–10% of brain cells may be found in all germ layers (Lodato et al., 2015). This strategy was used successfully to detect somatic mutations in cerebral cortical malformations (Jamuar et al., 2014). If DNA from dying neurons is detectable in the CSF, this could be analysed for mutations of interest. Analysis of cell-free DNA from "liquid biopsies" is having a major impact in oncology, and cell-free DNA in the CSF allowed tracking of mutations in glioma (Miller et al., 2019). DNA from dead neurons, detected by its methylation pattern, has been detected in CSF (Chatterton et al., 2019), and, remarkably, in blood (Lehmann-Werman et al., 2016).
(2) As protein aggregation pathology may spread through the CNS, the mosaicism level that matters may not even be in the region seen as most affected, and looking for mosaicism in directly connected regions, or in the earliest ones to be affected, may be more relevant. This requires a good understanding of disease pathophysiology. Target regions could even be outside the CNS, eg in the gastrointestinal tract for PD, if there is indeed a "gut-first" PD (Borghammer and Van Den Berge, 2019).

Detecting somatic mutations in a given tissue requires methods to detect them at low levels, and the various types of mutation may require different laboratory or bioinformatic analyses. Broadly speaking, the main choice is between sequencing "bulk" DNA, possibly with enrichment of desired cell type, or single cells, with each approach having relative strengths and weaknesses (D'Gama and Walsh, 2018). It is important to note that studies analysing DNA (directly, or indirectly through the transcriptome) extracted from "bulk" tissue include data from glia, and indeed almost certainly blood. Furthermore, microglia have a mesodermal origin, from the early hematopoietic system, and constant turnover (Réu et al., 2017), while oligodendrocyte precursor cells (OPCs) can also divide, and indeed proliferate in MSA (Ahmed et al., 2013). An increase of mutations with age or disease progress in "bulk" rather than pure neuronal data could therefore still be derived from mitosis. While single cell genomic analysis has revolutionised this

field, there are still significant technical and analytical challenges (Lähnemann et al., 2020; Rohrback et al., 2018b), some of which are mentioned below. Sampling is a critical issue, with straightforward calculations able to determine the numbers of cells needed depending on the expected mosaicism (Davis et al., 2019), but most studies have examined a small number of cells from a few brains. "Whole genome" amplification (WGA) does not recover the whole genome, with locus and allele dropouts, and results are heavily influenced by the technology used. False positives can include single base changes and chimeric structural variants, and by definition it is impossible to orthogonally validate a variant present in a single cell. Furthermore, bioinformatic pipelines are not standardised, and may lead to differences in results from the same dataset, as indeed shown for early control neuronal datasets (Garvin et al., 2015).

3. Somatic mutations and neurodegenerative disorders

3.1. Somatic mutations in Alzheimer's disease

Several studies have addressed this question in AD, focusing on SNVs (Table 2), and on *APP* structural variants. In an atypical family where dementia was not the main feature, a patient with predominant parkinsonism at age 42 had a somatic *PSEN1* SNV with allele frequency (AF) 14% in the cortex, and had transmitted it to her daughter, who was affected at an earlier age with a severe predominantly cerebellar syndrome (Beck et al., 2004). More recently, since the first targeted deep sequencing study in AD brain (Frigerio et al., 2015), several studies have aimed to detect low level SNVs in AD by high coverage sequencing, either of specific genes, or the whole exome, which can provide broad unbiased detection, not limited to known target genes, but validation by another technique is important, especially for somatic mutations. Targeted sequencing studies used very high coverage (frequently > 1,000x, and even higher for validation), combined in some cases with "unique molecular identifiers" (UMI). These "tag" an individual DNA molecule, and significantly reduce, but do not eliminate, the risk of PCR and other false positives; this principle has been reviewed in detail (Kinde et al., 2011; Sala Frigerio et al., 2017). Validation has also been performed selectively using targeted droplet digital PCR (ddPCR), an exquisitely sensitive method for low level SNV validation (Abyzov et al., 2017), which requires careful optimisation and controls.

3.1.1. Targeted detection of somatic SNVs in AD

A combination of different methods for targeting, and very stringent bioinformatic analysis, was used in one study (Keogh et al., 2018), which included synucleinopathies, discussed in the next section. In 20 AD cases, the mean age of death was 80 (onset age not given), and three brain regions were available for 18 of these (cerebellum, and entorhinal and frontal cortex), with matched blood in one. No mutations in AD genes were detected, although one had a synonymous coding mutation in *VPS35* in the entorhinal cortex only. This is a known PD gene, but has also been associated with AD (Rovelet-Lecrux et al., 2015). Intriguingly, a synonymous mutation in another PD gene, *LRRK2*, was found in one AD case also in the EC only. Overall, mutations were found in similar proportions in cases and controls, although the authors calculated that much larger numbers would be needed to find significant differences. Another study with careful design and analysis used matched brain and blood, targeted capture, and further data for some SNVs by ddPCR, but had an even smaller sample size, with half the patients having onset ~50 (Helgadottir et al., 2019). A total of 11 somatic SNVs was found in AD temporal cortex (TC), being absent in blood, while there were no such variants in control brains. One variant in a patient with onset at age 70 was validated by ddPCR with AF 0.4%. This is in candidate regulatory region of *CD55*, which inhibits the complement pathway, and when overexpressed in a recent landmark study prevented microglia-induced synaptic elimination, and ensuing memory loss (Wang et al., 2020). Further investigation of this gene is clearly warranted. One large study of young onset (all < 66 years), based mostly on blood samples, with brain DNA from 98 patients, did not report any definitely relevant findings in the brain (Nicolas et al., 2018). The nine somatic SNV reported in AD included two very low AF variants in *APP* (< 0.3%), one in blood and one in brain, predicted as deleterious by three algorithms, but likely benign because of their location. Two variants in *SORL1*, one in brain, were possibly deleterious. Finally, one study focused on the *ADNP* gene, in which de novo mutations are associated with autism (Ivashko-Pachima et al., 2019), using only ddPCR. One mutation was frequently detected in the olfactory bulb (OB) and/or hippocampus, but without significant differences between disease and controls overall. Furthermore, the AF was very low (< 0.07%), and almost all negative cases also had droplets positive for the mutation, raising the possibility of contamination, or non-specific binding of the mutant probe to the wild type sequence, and RNA sequencing showed no evidence of this mutation.

3.1.2. Exome studies in AD brain

The first exome study focused on AD compared blood and hippocampal DNA (Parcerisas et al., 2014). All patients had a large number of loci (~575) with SNVs in the hippocampus only, and some SNV-bearing genes shared were between many patients. No mutations were in known AD genes. Caution is required for several reasons. The mean coverage was only 60.8, even bases with coverage > 25 were considered, ~95% of the "hippocampal-only" SNVs were known SNPs even at the time of the study, and the number of "hippocampal-only" SNVs was similar in non-AD samples. Finally, designation of a SNV as somatic was based on comparison of allelic imbalance, with no correction for multiple testing. Allelic imbalance has been subsequently reported to be more prevalent using targeted capture in brain rather than blood (Helgadottir et al., 2019). Re-analysis of that data with algorithms validated for somatic mutations would be of interest. A later comprehensive exome analysis of 1461 brains with a combination of neurodegenerative disorders (including 244 AD, 277 FTD/ALS, 228 CJD, 97 PD/DLB) and 362 controls also used modest coverage (51.9x), but robust bioinformatics (Wei et al., 2019). Somatic SNVs were detected in > 1%, with no excess in disease, but this was a heterogenous group, and the DNA used was mostly cerebellar.

A very elegant recent study used deep exome sequencing for DNA from laser-capture microdissected (LCM) regions of the hippocampus, with matched blood (coverage brain 565x, blood 599x), and very high coverage targeted sequencing to validate a subset of calls (Park et al., 2019). As in other studies, the overall somatic mutation burden did not differ between disease and controls in brain or blood. Mutations were, however, 5-fold more common in AD blood than brain (~59 v 12 SNVs per sample; $p < 0.0001$), and the mutation signatures differed. Although the "clock-like" signature discussed earlier was the commonest in both, a signature related to oxidative DNA damage was prominent only in brain. Unbiased gene-set enrichment analysis demonstrated that SNVs in AD brain only were associated with biological pathways which modulate tau activity, with 28 genes harbouring mutations apparently involved in tau phosphorylation. More than half mutations were C > A, suggesting oxidative damage. As discussed earlier, however, such mutations can arise in neurogenesis, and should not be assumed to have arisen with ageing. The authors report that overall SNVs in AD increased significantly with ageing, particularly in blood (2.55 per year, v 0.53 in brain). It should be noted, however, that, while the correlation in the blood was very clear ($p < 0.0001$), in line with abundant recent data on age-related clonal haematopoiesis, the correlation in brain was modest ($p = 0.02$), and driven by four older cases with unusually high number of mutations (see supplementary Fig. 1a-b in paper). Furthermore, the median AF recorded in brain (AD 1.85%, control 1.6%) is high enough to indicate clonality, and it appears unlikely that a mutation affecting an individual post-mitotic neuron, arising from disease or age-related oxidative stress, would occur independently in enough

cells to reach such significant levels in the tissue. On balance, therefore, most mutations detected may have arisen in neurogenesis, suggesting the interesting possibility that early mutations affecting tau phosphorylation contribute to AD. Even if they did arise as post-mitotic events, they could still contribute to disease onset and/or progression.

3.1.3. Further analysis of the APP gene

As inherited gains of *APP* lead to familial AD, somatic CNVs in this gene are an obvious candidate. A de novo *APP* duplication has been described in one AD trio study (Rovelet-Lecrux et al., 2015). Although de novo mutations could be somatic events leading to mosaicism, rather than arising in the germline (Nicolas and Veltman, 2019), there was no support for this. In the brains of sporadic cases, intriguing early data showed gains in AD frontal cortex of at least some *APP* exons (Bushman et al., 2015). Further detailed investigation using prefrontal cortex from seven AD and six control brains demonstrated a novel mechanism for acquired genetic variability of *APP*, termed "gencDNA" (genomic complementary DNA), arising from somatic recombination (Lee et al., 2018). GencDNA's are intron-less, comprising either the entire *APP* coding sequence, the coding sequence of known neuronal splice variants, or a wide range of smaller recombinants indicating different junctions between exons (45 in total in AD), with frequent superimposed SNVs and indels. Several techniques were used to confirm these, including non-PCR based methods, with in situ hybridisation showing up to 13 spatially distinct gencDNA in individual AD neuronal nuclei. GencDNA not corresponding to known splice variants, and containing SNVs, were more prevalent in AD than controls. In AD, 11 SNVs known to be pathogenic in familial cases were seen within gencDNA of sporadic cases. Importantly, gencDNA affecting *APP* were subsequently independently demonstrated in the hippocampus from four AD cases using the high coverage exome data discussed above (Park et al., 2019). One of the approaches used in the Lee et al study, targeted capture, included reads caused by plasmid vector contamination (J. Kim et al., 2019a), but further capture using different kits also revealed gencDNA, in data verified to be free of vector contaminants, and some reads with inter-exonic junctions including sequence from the *APP* UTR (M.-H. Lee et al., 2019b). Several interesting questions arise in relation to gencDNA (Box 1).

3.2. Somatic mutations in synucleinopathies

The rationale for a role of somatic mutations in these was discussed before (Proukakis et al., 2013). Synucleinopathies can be familial, but clearly have a major non-heritable component, particularly MSA, which has a heritability of < 7% (Federoff et al., 2016), with PD latest estimates 22% based on GWAS (Nalls et al., 2019), and up to 31% based on twins (Goldman et al., 2019), while DLB appears the most heritable at 60% (Guerreiro et al., 2019). Studies have focused either on SNVs, or CNVs.

3.2.1. Somatic SNV detection in synucleinopathies

A study of brain DNA for somatic SNV detection by targeted high coverage sequencing which included synucleinopathies was partly discussed in the AD section (Keogh et al., 2018). The synucleinopathy cases were 17 DLB, some with co-existing AD, and 3 PD. The cerebellum and EC were analysed for all, medulla for 17, cingulate for 5, and blood for 3. No mutations in PD genes were found, but the SN was not studied. Intriguingly, ~90% of mutations found in multiple brain regions in this study overall were in genes known to be associated with myeloproliferative disorders, and the AF was higher in matched blood where available ($n = 4$; mean 7.9x). These are therefore derived from the hematopoietic system. As this includes microglia, it is interesting to observe that the levels of mutations in genes involved in myeloproliferative disorders in different regions of the same brain, are significantly different ($p = 0.0004$), being highest in the medulla (3.7%), intermediate in the cortex (1.8% in entorhinal) and lowest in the cerebellum (0.2%), and this variation may be partly due to the % of microglia in each region (Mittelbronn et al., 2001)(supplementary Fig. S1). This is an important reminder of the fact that DNA extracted from "bulk" tissue will not all be from the neuroectoderm. Furthermore, the apparent excess of these mutations in synucleinopathy compared to control brains (present in 40% v 7%, nominal $p = 0.05$) is tantalising, and cannot be due to simple age-related factors, as the ages of death were 79.9 for cases and 81.6 for controls.

We have also aimed to detect somatic SNVs in synucleinopathy brains, focusing mainly on PD, including DNA from the SN, which have been negative. In early studies restricted to *SNCA* coding exons, with a detection limit of ~5–10% AF, over 400 brains were studied, including 25 SN samples (Proukakis et al., 2014, Proukakis et al., 2013). A recent study using very high coverage targeted sequencing with UMI's of coding regions of *SNCA* and other PD genes, which could detect AF as low as 0.33%, included the SN, up to two other brain regions, and blood from three cases, from 26 PD cases (including 7 previously analysed), three MSA, and one incidental Lewy body disease (ILBD) (Leija-Salazar et al., 2020). There is therefore no evidence to date of somatic SNVs in synucleinopathies, but the use of "bulk" DNA in these studies may have impeded detection of any low level SNVs specific to dopaminergic (DA) neurons, as they constitute a small fraction of the total cell number, particularly in end-stage disease, so their existence cannot be excluded.

3.2.2. Somatic CNV detection in synucleinopathies

The author's lab has investigated *SNCA* CNVs in synucleinopathies, focusing on PD and MSA, mostly in the SN and cingulate cortex (Mokretar et al., 2018; Perez-Rodriguez et al., 2019). Fluorescent in-situ hybridisation (FISH) was used to detect of very low levels of mosaicism for *SNCA* gains, as array-based methods were inconclusive, partly due to GC-related biases in DNA extraction (Nacheva et al., 2017). As FISH was performed using sections, it was possible to differentiate DA neurons by their neuromelanin content, and cortical neurons were identified using NeuN and nuclear size. The use of sections, however, precludes reliable detection of losses, as a nucleus with an apparent loss may simply be due to sectioning of part of it. *SNCA* CNVs (gains) were present in almost all disease cases, in both brain regions. The proportion of cells of each type with gains was always low, with the highest individual values in cases of MSA with predominant striatonigral degeneration (MSA-SND): just under 7% in DA neurons and cingulate neurons, and ~6% for other cells in the SN. Gains were less frequent in controls, and tended to be less frequent in non-neurons, at least in the cingulate. Across all cells counted in the cingulate, gains were seen in 2.8% of all neurons from 14 MSA cases, 2.18% from 26 PD cases, and 1.12% of controls, with the respective numbers in non-neurons being 1.5%, 0.97%, and 0.79%. Interestingly, the differences in neurons are significant for each disease when compared to controls, but for non-neurons, which are more relevant to MSA, the difference is significant only in MSA.

Importantly, the cells designated as non-neurons were not further characterised in most cases, and it remains possible that higher mosaicism in oligodendrocytes is obscured by other non-neuronal cell types. Indeed, in the SN of three MSA-SND cases, where FISH was combined with immunohistochemistry for Olig2, an oligodendroglial lineage marker, Olig2-positive cells had the highest mosaicism levels observed (~8.6%), almost four times higher than cells from the same samples which were negative for both neuromelanin and Olig2. No clear correlation with pathological PD stage, or load of glial cytoplasmic inclusions in MSA, was found. However, neither study was powered to detect this, early-stage PD had not been included, and the FISH (on sections from flash-frozen brain) and histological analysis (on sections from fixed brain) were performed on different sides of the brain. The detection of CNVs in some controls suggests that they are not adequate to trigger disease, although further blinded analysis by the brain bank provided an interesting finding: Out of 5 "controls" which had gains in > 1.2% of nigral DA neurons, the one with the highest

Box 1
Questions arising from the report of *APP* gencDNA.

1) Do gencDNAs integrate in the genome, and if so, where?

GencDNA may integrate in the genome, although this has not been demonstrated at the time of writing. Extrachromosomal circular DNA is, however, increasingly recognised, and has been shown in embryonic mouse brain (Shibata, 2012). Intriguingly, a human study found *APP*-derived species in muscle, but not blood (Møller et al., 2018).

2) Are they relevant to normal brain function?

A role in genomic plasticity, by providing a "recording" and "playback" mechanism, was suggested (Lee et al., 2018).

3) Are they directly involved in AD pathogenesis as "initiators" or "executioners", and do they relate to disease progression?

They were shown to accumulate with age in neurons in a mouse AD model (Lee et al., 2018), but no comparison between early and late AD is available yet.

4) Do they exert their adverse effects through production a toxic protein?

Transfection of human embryonic kidney cells demonstrated synthesis of the protein from three with preserved reading frame, but not from one without. Two of these were toxic when transfected into neuroblastoma cells (Lee et al., 2018).

5) Is another toxic mechanism, such as generalised genome damage, more likely?

Production of gencDNA is likely to require transcription, reverse transcription, and DSB breaks to allow integration. In hamster ovarian cells, induction of DSB was required to observe gencDNA, and they were abolished by reverse transcriptase inhibition (Lee et al., 2018). Integration in sites of DSB, resulting in genome damage and generalised dysfunction, appears plausible, particularly if there are increased DSB in AD (see 4.2).

6) How does recombination occur within gencDNA, and why do SNVs arise?

Microhomologies appears to underlie the former, and the low fidelity of reverse transcriptase was proposed to explain the latter (Lee et al., 2018).

7) Is APP the only gene subject to this phenomenon?

Another gene tested, *PSEN1*, was negative (Lee et al., 2018), but more work is needed.

8) Does this phenomenon also occur outside neurons?

GencDNA were not detected by PCR in non-neuronal cells from AD brain, lung fibroblasts, or a kidney cell line, although low levels were apparent by hybridisation for a specific gencDNA in the mouse model used (where they did not change with age), and in two AD blood exomes (M.-H. Lee et al., 2019b). Insertion of several DNA species has been previously reported in the mouse zygote during repair of DSB generated by CRISPR/Cas9 (Ono et al., 2015). These included retrotranscribed mRNAs, and overall 20% of inserted sequences were exonic, suggesting that this mechanism may be widespread.

level was re-designated as ILBD (Mokretar et al., 2018), and another two demonstrated some α-synuclein immunopositivity in the SN.

If the CNVs are established early and have a role in disease initiation, a higher load may correlate with more severe disease, and/or younger onset (Frank, 2010; Proukakis et al., 2013). We demonstrated a correlation between mosaicism level and young onset in the SN, limited to DA neurons in PD ($r = -0.39$, $p = 0.013$) (Mokretar et al., 2018), and other cells in MSA-SND, where it was nominally significant if one case (of 10) with unusually late onset at 75 was excluded ($r = -0.78$, $p = 0.018$) (Perez-Rodriguez et al., 2019). The only significant correlation noted in the cingulate cortex was in PD, between neuronal mosaicism level and death at a younger age ($r = -0.47$, $p = 0.019$). As PD is a very variable disorder, we also wondered whether the mosaicism in the SN of the 40 cases studied was correlated with clinical features, and noted that the presence of mosaicism was significantly less likely in cases with tremor at presentation ($p = 0.035$) (Mokretar et al., 2018). Indeed, all cases presenting without tremor or asymmetry had evidence of gains, while asymmetric cases sometimes did not. Further work related to these observations should obviously include larger sample sizes, with precise definition of non-neuronal cell types, and a systematic comparison of affected and unaffected regions in each subtype of PD and MSA.

It is important to determine whether CNV mosaicism in synucleinopathies is specific to *SNCA*, or there are gains throughout the genome. As a continuation of the FISH analysis, we performed the first single cell WGS study in a synucleinopathy, analysing 169 cells from two MSA cases. These were derived from the SN of both, and the pons and putamen of one, and revealed CNVs (> 1 Mb) throughout the genome in ~30% of cells (Perez-Rodriguez et al., 2019). These were a mix of gains and losses in neurons, and almost exclusively gains in non-neurons, including some Olig2-positive cells. Nuclear isolation was combined with immunohistochemistry for alpha-synuclein, allowing cells with neuronal nuclear inclusions, and some with extra-nuclear ones retained during the process, to be identified. One pontine neuron without an obvious inclusions had multiple gains, including a 10 Mb one which included *SNCA*, and one with a small nuclear inclusion had a 1.4 Mb gain in the *GRID2* gene, a very long gene near *SNCA* which is a putative somatic CNV hotspot (Chronister et al., 2019). The enrichment of CNV breakpoints for segmental duplications, and possible clonality of some, suggest a mitotic origin at least for these. Two genes with roles

Box 2
Questions related to a possible central role of somatic expansions in repeat disorders.

1) Does the selective vulnerability depend on the cell-type specific somatic instability?

Studies in humans and mouse models, including single cell analysis, indicate instability is higher in neurons than glia, and in striatum rather than cortex of early HD (Shelbourne et al., 2007). Furthermore, in young mouse striatum, the expansion is more unstable in medium spiny neurons, than in relatively spared neighbouring interneurons. If this applies universally, other disorders, such as the SCAs, should have instability patterns corresponding to their neuropathology. This was not, however, detected in several early studies (Cancel et al., 1998; Hashida et al., 1997; Kraus-Perrotta and Lagalwar, 2016; Muñoz et al., 2002), but it would be worth repeating with single cell, or specific cell sub-type, methods.

2) Could treatments for all repeat expansion disorders be directed specifically at somatic instability (Kaplan et al., 2007)?

A small molecule inducing contractions of germline and somatically expanded alleles in HD has indeed just been reported (Nakamori et al., 2020).

3) Are repeats below the pathogenic range also unstable in the nervous system?

It is plausible that intermediate repeats (27–35), rarely found in HD (Oosterloo et al., 2015), could lead to disease if they expand in striatal medium spiny neurons (Leija-Salazar et al., 2018). This question is particularly relevant to ALS, which is usually sporadic. There is still no evidence that a normal *C9orf72* allele could expand somatically and lead to sporadic ALS. One recent study detected no such events in 19 patients, but only the ventral spinal cord was studied, and the lowest AF detectable was 5% (Ross et al., 2019). Perhaps intermediate-size repeats could act as "pre-mutations", prone to further expansion.

4) Could instability in culture could be a major confounder in iPSC-based studies?

Indeed, extra repeats were seen after reprogramming in almost all *TAF1* cases (Westenberger et al., 2019), and HD cases (Goold et al., 2019). There was also variability in the size of *TAF1* repeats in fibroblasts, which included contractions in one of the two cases with the largest repeat size. This may be a result of both instability in passaging, and pre-existing mosaicism in fibroblasts, as reported for CNVs (Abyzov et al., 2017). It should therefore be mandatory to perform initial and repeat evaluation of the repeat size.

in neurodegeneration, *MAPT* and *TLR4*, were in the breakpoint regions of possibly clonal gains, although precise breakpoint definition is not yet possible in single cell WGS. No firm conclusions, however, can be drawn about the significance of any CNVs other than *SNCA*, and about the higher proportion of cells with CNVs than that reported in control frontal neurons and non-neurons (Chronister et al., 2019), without fully matched control data sets. Indeed, analysis of pathways based on genes affected by CNVs across all neurons revealed similar results with control cortical neuronal CNVs, suggesting that these are intrinsic neuronal properties, rather than disease-specific. Pathways affected by CNVs in the SN, however, differed between neurons and non-neurons, with MHC genes over-represented in neurons, although it is not known if this is a disease-specific finding (Perez-Rodriguez et al., 2019).

3.3. The role of germline variants predisposing to DNA damage and/or somatic mutations

DNA repair is important both in rapidly dividing precursors in neurogenesis, and in post-mitotic neurons, which cannot generally be renewed throughout the lifespan, and various insults to DNA are possible, with potentially highly detrimental DSBs occurring in both (Section 2.1, Table 1). This section will discuss the evidence for inherited variation in genome maintenance contributing to neurodegenerative diseases.

3.3.1. Somatic instability in repeat expansion disorders

Several neurodegenerative conditions are due to expanded repeats, with full penetrance once the threshold is crossed, although "intermediate" low penetrance alleles are recognised. There is therefore no obvious need to invoke somatic mutations, but it has recently become clear that the phenotype, and possibly the penetrance in a given case, is influenced by further somatic expansion. Mosaicism for expansion size was actually demonstrated soon after gene discovery in Huntington's disease (HD) (Telenius et al., 1994) and spinocerebellar ataxia type 1 (SCA1) (Chong et al., 1995), and it was predicted for repeat disorders in general that increasing contiguous CAG length raises the susceptibility to further somatic expansion (Kaplan et al., 2007). This topic has come back to attention recently after GWAS of age-of-onset variability, which is not fully determined by the repeat length, demonstrated a clear influence of DNA repair genes in HD (J.-M. Lee et al., 2019a) and other CAG diseases (Bettencourt et al., 2016), suggesting that somatic expansion is indeed the factor which modulates age of onset. In HD, variants interrupting the CAG tract were recently studied, and it is the length of consecutive CAG repeats, rather than the total polyglutamine number, which is the inherited determinant of onset age (J.-M. Lee et al., 2019a; Wright et al., 2019).

Validation in HD was provided in recent functional studies of two candidate genes. *MSH3* encodes a DNA MMR protein (Flower et al., 2019). The short, probably ancestral, allele of a complex 9bp repeat is associated with reduced CAG repeat somatic expansion in HD and delayed onset, possibly mediated through reduced expression. Increased expression of *MSH3* is associated with earlier HD onset (Lee et al., 2015), and deletion of the gene in mice protects against repeat instability (Dragileva et al., 2009). The apparent paradox of a DNA repair gene expression level being inversely correlated with repeat stability may be due to a non-canonical role of the complex comprising MSH3, distinct from its role in DNA repair (McKinney et al., 2020). This results from an interaction with Z-DNA, a "zig-zag" left handed helix, which may also arise from CAG repeat expansions (Khan et al., 2015). An additional gene at a risk locus is *FAN1*, the product of which binds the CAG expansion and protects from further expansion, possibly by preventing error-prone DNA repair, or by facilitating correct repair (Goold et al., 2019).

Somatic instability has been shown in other repeat disorders. In myotonic dystrophy, *MSH3* also affects somatic instability and disease severity (Flower et al., 2019). In Friedreich's ataxia, somatic instability in the CNS is well recognised, but it appears even more pronounced in other affected tissues, the heart and the pancreas (Long et al., 2017). The wide variability of *C9orfF72*-related phenotypes could be determined by regional somatic expansion patterns (Cooper-Knock et al.,

2014). There is accumulating evidence for aberrant DNA conformations of expanded *C9orf72* repeats (Šket et al., 2015; Zhang et al., 2018), and it will be interesting to determine whether, and how, these contribute to somatic instability. The recently described hexanucleotide repeats in *TAF1* are unstable in the brain, with repeat sizes in the striatum potentially exceeding these found in blood (Westenberger et al., 2019). Further studies are needed to determine if MSH3, or other DNA repair genes, modulate somatic instability and phenotype in other repeat expansions disorders. A recent study detect no evidence of *MSH3* acting as a modifier in Friedreich's ataxia or SCA3 (Yau et al., 2020), but this may have been due to lack of power (Flower et al., 2020). Somatic expansions of repeats may be crucial to the pathogenesis of all these disorders, and this raises several crucial questions, which cannot be fully addressed here (Box 2).

3.3.2. Neurodegenerative disorders resulting from germline mutations in DNA repair genes

Several inherited disorders linked to known DNA repair genes lead to neurodegeneration, especially these involved in DNA strand break repair (Madabhushi et al., 2014; McKinnon, 2017; Tiwari and Wilson, 2019). Somatic mutations may therefore result from germline mutations in genes affecting DNA repair directly, or genomic stability indirectly. Mutations affecting SSB repair lead to almost exclusively neurological disease, and are likely to lead to post-mitotic neuronal DNA damage, while those affecting DSB repair also affect mitotic cells, and hence can also have a developmental component (Tiwari and Wilson, 2019). While it is difficult to conclusively prove that such mutations are the only cause of neurodegeneration in these cases, it appears likely that, at the very least, they contribute. Ataxia-telangiectasia (A-T) is caused by loss of function mutations of the ATM kinase, which is crucial in the response to DSB, by preventing deleterious NHEJ (Balmus et al., 2019). Loss of function increases LINE-1 retrotransposition (Coufal et al., 2011), and LINE-1 insertions are more frequent in A-T patient brains (Coufal et al., 2011; Jacob-Hirsch et al., 2018). ATM knockout mice develop α-synuclein inclusions, as well as nigrostriatal degeneration, suggesting the possibility that DNA damage can lead to α-synuclein aggregation (Fig. 1). Mutations in senataxin, which can lead to ataxia with oculomotor apraxia (AOA2) or a form of motor neuron disease (ALS4), led to increased DSB in iPS cell lines (Becherel et al., 2015), and it may function in repair of neuronal DSBs arising during transcription (Cohen et al., 2018).

NER may be particularly important in relation to brain somatic SNVs (Section 2.2), and inherited NER disorders such as Cockayne syndrome (CS) and xeroderma pigmentosum (XP), lead to neurodegeneration as part of their complex phenotype. These were studied by single cell WGS in tandem with healthy neurons, and showed a clear excess of somatic SNVs (Lodato et al., 2018). Mutational patterns were, however, different between these two conditions, with "signature B" (C > T mutations), likely including early developmental events, enriched only in CS, suggesting that XP does not predispose to developmental neuronal mutations (Lodato and Walsh, 2019). Despite the rarity of these conditions, there are several autopsy reports with interesting neuropathology. Extensive neurofibrillary tangles were seen in one CS case, including the SN (Takada and Becker, 1986), and neuronal loss in the SN, other brainstem regions, and cortex, has been reported (Röyttä and Anttinen, 1986), although it is most pronounced in the cerebellar cortex (Itoh et al., 1999; Soffer et al., 1979), with no features PD or AD (Weidenheim et al., 2009). In XP, marked neuronal atrophy in the SN and other regions is documented (Röyttä and Anttinen, 1986).

Disorders related defects in the repair of DNA SSBs have predominant cerebellar degeneration, often with associated peripheral neuropathy and oculomotor apraxia (Yoon and Caldecott, 2018). Notably, there is no excess of cancer. This may imply that they are not mutagenic, and the inability to repair SSBs in post-mitotic cells could lead to neuronal death (Tiwari and Wilson, 2019). These include spinocerebellar ataxia with axonal neuropathy 1 (SCAN1), and several types of ataxia with oculomotor apraxia (AOA1, 4, and 5). The genes involved in these disorders are also implicated in DSB repair, except for *XRCC1*, underlying AOA5. This suggests that the defect underlying cerebellar degeneration is indeed in SSB repair, and indeed recent evidence in AOA4 fibroblasts demonstrates reduced SSB repair as the relevant defect (Kalasova et al., 2020).

3.3.3. DNA damage resulting from several familial ALS mutations

Evidence for a role of DNA damage in several monogenic forms of ALS has accumulated very recently. *FUS* is an ALS gene which functions in neuronal DNA damage response and repair. DNA damage was observed in patients with *FUS* mutations, with the protein recruited early to DSBs, and disease-linked mutants having a partial loss of function (Wang et al., 2013). The precise deficit was later reported to be in repair of SSB due to oxidative DNA damage, and function was restored by correcting the mutation in iPSC-derived motor neurons (Wang et al., 2018). Another ALS gene, *TDP-43*, functions in repair of DSB by NHEJ (Mitra et al., 2019). Additionally, its loss leads to increased LINE-1 retrotransposition, with higher copy numbers in human disease neuronal nuclei without TDP-43, and increased retrotransposition in cell lines (Liu et al., 2019). The commonest inherited cause of ALS, the *C9orf72* expansion, leads to the production of dipeptide-repeat proteins (DPR) through aberrant translation, and several studies now indicate that they can lead to DNA damage. They disrupt DNA repair mediated by ATM (Walker et al., 2017), with poly-GA sequestering ATM and preventing it from reaching DNA damage sites (Nihei et al., 2020), and may impair DSB repair in several different ways (Andrade et al., 2020). Increased DSB were found in spinal cord from patients with C9orf72 expansions (Walker et al., 2017). A more recently described ALS gene, *NEK1*, has a role in DNA repair, and iPSC-derived motor neurons show increased DNA damage and impaired DDR (Higelin et al., 2018). The first ALS gene described, *SOD1*, does not appear to act via DNA damage, as iPSC-derived neurons from two SOD1 patients with different mutations had normal DNA repair capacity (Kim et al., 2020). DNA damage is not, however, limited to inherited cases, as it was also reported in the motor cortex and LCM-acquired spinal motor neurons from sporadic ALS cases (Kim et al., 2020). The above suggest that in familial ALS, excluding *SOD1*-linked ALS, and possibly in sporadic, DNA repair may be an initiator or contributor pathogenesis, although DNA damage may also arise as a downstream result of the disease process, acting as an effector or "executioner".

3.3.4. Are sporadic patients with neurodegeneration particularly prone to somatic mutations, or DNA damage?

Although none of the Mendelian PD and AD genes have a known role in DNA repair, peripheral cells from PD and AD patients may be prone to DNA damage (reviewed in Leija-Salazar et al., 2018) raising the question of whether there is some inherited impairment of DNA repair in these disorders. NER was impaired in fibroblasts in PD, especially in cases with *LRRK*2 mutations (two each with G2019S and R1441G), but not AD (Sepe et al., 2016). Disease-relevant inherited variation in DNA repair could be detected by GWAS results. In PD, no enrichment of DNA repair pathways was reported in the recent meta-analysis (Nalls et al., 2019), but two of the risk loci merit discussion. A very common risk locus designated PARK16 has been linked to *RAB29* (also known as *RAB7L1*) (Blauwendraat et al., 2019), an endosomal pathway protein, but there may be multiple independent signals, and the strongest association is with *NUCKS1* (Nalls et al., 2019). This gene is important for DNA repair by HR, and DNA stability (Parplys et al., 2015). Another PD risk locus contains two genes involved in the DDR, *SCAF11* (Boeing et al., 2016), and *ARID2* which regulates DNA repair by HR after DSB (De Castro et al., 2017). Although DNA repair genes have not been associated with AD, a recent GWAS analysis using imputation detected an association with ZNF423, a likely DNA repair gene (Baker et al., 2019). In ALS, one GWAS hit, *C21orf2*, may have a role in

DNA repair (Van Rheenen et al., 2016). Furthermore, a recent analysis of neurological disorders GWAS data combined with long-range genomic interactions provided evidence for an involvement of DNA damage/repair pathway genes in PD, AD, and ALS, although the exact pathways were not specified (Sey et al., 2020). This was also seen in neurodevelopmental disorders, but not in multiple sclerosis. There are clearly several genetic pathways with clear association to the risk of PD and AD. Overall, while inherited variation in DNA repair is only one of many pathways genetically identified in PD, AD, and ALS, the evidence above suggests that aberrations in DNA repair pathways may be associated with the most common neurodegenerative disorders.

3.3.5. A possible connection of MAPT mutations to mosaic aneuploidy

A separate class of somatic mutations, aneuploidy likely due to mitotic non-disjunction, was previously discussed as a possible result of mutations in *MAPT*, which underlies some frontotemporal lobar degeneration (FTLD) cases (Leija-Salazar et al., 2018). The first study of four human brains with three different mutations reported increased aneuploidy in cortical neurons and glia for both chromosomes studied by FISH of nuclear suspensions, and reported apoptosis preferentially in aneuploid cells (Caneus et al., 2018). Furthermore, an excess of aneuploidy was seen in a karyotypically normal human epithelial cell line transfected with two forms of mutant *MAPT* compared to vector transfections, but a similar pattern was seen with wt *MAPT*. If germline *MAPT* mutations lead to aneuploidy arising in neurodevelopment, it would be reasonable to also expect this to occur in neurons differentiated from iPS cells of patient with MAPT mutations, but karyotyping in several such studies did not reveal chromosomal abnormalities (Karch et al., 2019; Nakamura et al., 2019; Sohn et al., 2019; Sposito et al., 2015; Verheyen et al., 2018). Single cell sequencing of human tauopathy brain will be important for further investigation of the FISH findings.

4. Further analysis and outlook

4.1. Are somatic mutations and pathology found in the same cells?

If pathogenic somatic mutations are functional, and lead to synthesis of the relevant mRNA and protein, they should lead to pathology in the cells carrying them. This may of course also develop in cells without mutations, due to spread of abnormal proteins, and/or other cellular dysfunction. Single cell “multi-omics”, where several biological propertied can be measured simultaneously in the same cell, is an expanding but technically challenging field (Macaulay et al., 2017). Ultimately, changes in the protein levels and/or conformations, rather than the RNA, are the likely determinants of cell dysfunction. The comparison of the genomes of cells with and without relevant protein pathology would therefore be of great interest.

In synucleinopathies, the combination of FISH for *SNCA* CNVs and immunohistochemistry for α-synuclein inclusions in the SN suggests a very interesting disease-specific relationship (Perez-Rodriguez et al., 2019). In five cases with Lewy body disease (one DLB, four ILBD), inclusions were detected six times more frequently in DA neurons with CNVs, than without. In seven MSA-SND cases analysed, a similar relationship was seen only in non-DA cells, which were four times more likely to have inclusions if they had CNVs. It should be noted, however, that most cells with CNVs did not have detectable inclusions, though these may have been degraded by the pepsin used in the FISH protocol. In MSA, there has been debate about the source of the aggregating oligodendrocyte α-synuclein, with the latest data suggesting that exogenous neuronal α-synuclein can act as a template for endogenous oligodendrocyte aggregation (Kaji et al., 2018; Mavroeidi et al., 2019). This would be consistent with the finding of neuronal mosaicism in MSA, where it may even be higher than in PD (Mokretar et al., 2018; Perez-Rodriguez et al., 2019), with *SNCA* gains in different cell types, if functional, acting in concert to generate pathology (Fig. 2).

The best way to address the question of co-localisation of somatic mutations with cytoplasmic inclusions or other pathology may be by LCM and DNA sequencing, ideally at the single cell level. LCM was, in fact, used to analyse small pools of neurons from AD hippocampus for a somatic variant predicted to be highly pathogenic in *PIN1*, which has a crucial role in tau phosphorylation (Park et al., 2019). The AF of the mutation was five times higher in neurons with hyperphosphorylated tau, than those without. These studies therefore provide preliminary support for a direct role of somatic mutations in synucleinopathies and AD leading to pathology in the same cell, which may act as the focus of spread. Reverse causation remains possible, if the pathology were to lead to the specific mutations observed.

4.2. Do protein aggregates lead to somatic mutations or DNA damage?

Could misfolded, or aggregated, proteins lead to DNA damage and post-mitotic somatic mutations in neurons, or mitotic events in dividing glial cells? The limited evidence for this tantalising idea did not allow detailed discussion before (Leija-Salazar et al., 2018), but the picture in synucleinopathies and AD has evolved. Although the cytoplasmic role of α-synuclein is usually considered foremost, it has long also been found in the nucleus, and indeed its name stems from this (Maroteaux et al., 1988). Neuronal nuclear inclusions containing α-synuclein are often seen in MSA (Cykowski et al., 2015; Perez-Rodriguez et al., 2019), and recently also demonstrated in DLB (Pinho et al., 2019), while oligomers were seen in sorted nuclei from PD frontal cortex (Garcia-Esparcia et al., 2015). Several studies have presented evidence of direct DNA binding (Pinho et al., 2019; Schaser et al., 2019; Vasquez et al., 2017). α-Synuclein pre-formed fibrils (PFF) and viral overexpression in mouse led to DNA damage in DA neurons, with the authors concluding that a wide range of DNA lesions can result from aggregated α-synuclein (Milanese et al., 2018). Independently, addition of PFF to cultured cortical neurons and DA neurons led to nitric oxide synthase activation, DNA damage, and eventual neuronal death (Kam et al., 2018). This was mediated through the action of Poly(ADP-ribose) (PAR) polymerase-1 (PARP-1), a DNA damage sensor. This also resulted in a more toxic α-synuclein strain, suggesting that the relationship between DNA damage and protein aggregation may be bidirectional (Fig. 1). Furthermore, in a study which demonstrated DSB in the amygdala of DLB patients as well as two mouse models, mouse cortical neurons with inclusions in mice had evidence of increased DSB, and a tentative similar correlation (but not at single cell level) was reported in patients (Schaser et al., 2019). It may not be a coincidence, therefore, that a putaminal neuron with a rare prominent nuclear inclusion in MSA had multiple DNA losses, which intriguingly also included *SNCA* (Perez-Rodriguez et al., 2019). Interestingly, *SNCA* knockout mice showed increased DSB which were rescued by α-synuclein (Schaser et al., 2019). A role of α-synuclein in DNA repair was therefore proposed, with the authors suggesting that cytoplasmic aggregation leads to a reduction of the functional protein available in the nucleus, and resulting DNA damage, but further evidence is required before concluding that α-synuclein participates in DNA repair.

In AD, DNA repair by NHEJ is reduced (Shackelford, 2006), oxidative DNA damage occurs early (Lovell and Markesbery, 2007), and DSB have now been reported in neurons and astrocytes from hippocampus and frontal cortex, including early stage patients (Shanbhag et al., 2019). These could allow integration of gencDNA (see earlier). Oligomeric $A\beta_{42}$ species impair DNA repair by RNA-templated HR, thus representing a plausible molecular mechanism for increased DSB secondary to protein pathology (Welty et al., 2018). Impaired DSB repair ability in AD would exacerbate the situation, and reduced levels of key proteins involved in DSB repair were previously reported in AD (Jacobsen et al., 2004; Shen et al., 2016; Suberbielle et al., 2015), but no such changes were detected in analysis of unbiased proteomic (Li et al., 2019) or single cell RNA data (Mathys et al., 2019).

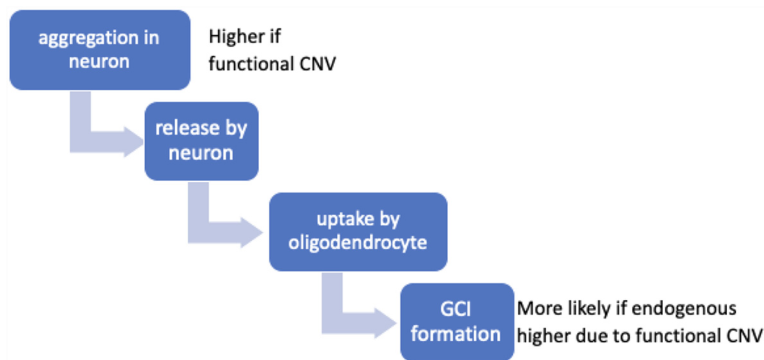

Fig. 2. Scheme of possible role of somatic *SNCA* CNVs leading to increased α-synuclein in neurons and non-neurons in the pathogenesis of MSA. If the *SNCA* gains lead to increased mRNA, a gain in a neuron may lead to increased α-synuclein secretion, and a gain in a neighbouring oligodendrocyte may enhance templating of more abundant endogenous α-synuclein. GCI = glial cytoplasmic inclusion.

4.3. A note on transposons and reverse transcription in the nervous system

LINE-1 retrotransposons comprise one-sixth of our genome. A specific pattern of LINE-1 reactivation in the direct reprogramming of mouse embryonic fibroblasts into DA neurons suggested a role in differentiation (Della Valle et al., 2020). Insertions were demonstrated in lineage-specific active genes, and blocking reverse transcriptase inhibited trans-differentiation. This may indicate that somatic mutations, at least LINE-1 insertions, are crucial to the cell identity specification, supporting the old hypothesis that a shared pattern of somatic mutations determines neuronal sub-type identity (Dreyer et al., 1967). LINE-1 induced mosaicism may even be modifiable, if a report of maternal influence on LINE-1 retrotransposition in mouse neuronal genomes is confirmed (Song and Gleeson, 2018). There are several studies consistent with LINE-1 insertions in neuronal precursors, but they can also occur in post-mitotic neurons (Macia et al., 2017), although this phenomenon requires further study to determine the prevalence beyond the engineered system used. In this context, however, it is notable that NHEJ, the main DSB repair mechanism in neurons, may also allow insertions of retrotranscribed LINE-1 elements (Suzuki et al., 2009). The consequences of insertions would presumably depend on the integration sites, and whether they are functional, but a direct role of LINE-1 in DA neuronal death was suggested by the demonstration that their overexpression triggers oxidative-stress induced DNA DSBs (Blaudin de Thé et al., 2018).

It should be clear that there are many uncertainties, as the technical challenges in confirming retrotransposition in single neurons are considerable, and the frequency and precise nature of these events remains unclear. It is also possible that increased LINE-1 DNA copy numbers reported do not indicate actual insertions, with accumulation of molecules which are not integrated into the genome possible (Faulkner and Billon, 2018), or indeed that the toxic effects of transposons are mediated through mechanisms unrelated to DNA damage (Tam et al., 2019), such as inflammation (De Cecco et al., 2019). Nevertheless, the possibility that LINE-1 activation plays a major role in modulating the neuronal genome (Singer et al., 2010), as recently shown for cancers (Rodriguez-Martin et al., 2020), influencing differentiation and potentially predisposing to dysfunction and neurodegeneration, is worthy of further consideration. The emerging data on retrotransposons, and the discovery of somatic *APP* gencDNA, suggest that neuronal reverse transcriptase activity in neurons may be harmful, at least in the ageing brain. This would suggest that trials of reverse transcriptase inhibitors, already in wide use in HIV should be considered (Lee et al., 2018), particularly since these compounds can protect DA neurons against oxidative stress (Blaudin de Thé et al., 2018), and reduce tau-induced death mediated through transposable element mobilisation in a Drosophila model (Sun et al., 2018).

4.4. Conclusions

It will be crucial to define the balance of mitotic v post-mitotic mutations in brain, and to understand specific patterns, in order to understand the mechanism by which they arise, and their timing, and consider any possible future interventions. Are particular brain regions, and/or cell types, prone to particular mutation types or "signatures"- for example, is an oligodendrocyte in the SN more likely to share mutations with other cell types in the SN, or with oligodendrocytes outside the SN? Furthermore, how do any common patterns arise? A shared mutagenic environment will affect cells in close proximity, eg oxidative stress in the SN would lead to an oxidative damage mutation signature in all cell types in that region. Conversely, cell-type specific patterns could arise from shared embryological lineage, with the AF and distribution of clonal mutations dependent on when and where they arose. Similarities could, however, also be the result of DNA damage induced by the biological properties and the intracellular milieu of a given cell type, whether arising during development or ageing.

Despite the challenges, there is rapidly emerging evidence for a role of somatic mutations in neurodegeneration. Rare inherited disorders of DNA repair have yielded crucial insights, and should be studied further. The importance of somatic instability in repeat expansion diseases is now unquestionable. DNA damage is a common theme in several disorders, notably in ALS. In terms of specific somatic mutations, the findings of *SNCA* gains in synucleinopathies, and SNVs in genes related to tau, as well as *APP* gencDNA, sometimes containing pathogenic SNVs, in AD, suggest a role for these in the pathogenesis of the two most common classes of sporadic neurodegenerative disease. Further validation is however needed, and disentangling cause and effect is not straightforward. The technical challenges of detecting diverse and possibly unusual or complex mutations present in a low fraction of cells remain considerable, but constant improvements in single cell sequencing are likely to allow bold steps forward.

Acknowledgements

I am grateful to the Michael J Fox Foundation for Parkinson's research for funding to investigate somatic mutations in synucleinopathies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2020.105021.

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