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Review article

Pangenomics: A new era in the field of neurodegenerative diseases

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ABSTRACT

A pangenome is composed of all the genetic variability of a group of individuals, and its application to the study of neurodegenerative diseases may provide valuable insights into the underlying aspects of genetic heterogenetiy for these complex ailments, including gene expression, epigenetics, and translation mechanisms. Furthermore, a reference pangenome allows for the identification of previously undetected structural commonalities and differences among individuals, which may help in the diagnosis of a disease, support the prediction of what will happen over time (prognosis) and aid in developing novel treatments in the perspective of personalized medicine. Therefore, in the present review, the application of the pangenome concept to the study of neurodegenerative diseases will be discussed and analyzed for its potential to enable an improvement in diagnosis and prognosis for these illnesses, leading to the development of tailored treatments for individual patients from the knowledge of the genomic composition of a whole population.

1. Introduction

The pangenome, a collection of the total genetic variability of a species based on the representative specimens that are collected (Fig. 1), has been the subject of increasing research since its development for the study of the bacterial genome (Bobay, 2020; Brockhurst et al., 2019; McInerney et al., 2020; Medini et al., 2020), as it has been extensively used for the delineation of genetic characteristics in plants and animals, particularly those of economic, commercial, and industrial value (Aggarwal et al., 2022; Golicz et al., 2020; N. Li et al., 2023). Specifically in humans, the concept has already been applied to the elucidation of the genetics of cancer (Apicella et al., 2023; López-Carrasco et al., 2021; Neou et al., 2020; Stenman et al., 2021b, 2021a; Yu et al., 2022), and it has the promising potential to be studied in relation to the genetic roots of a variety of other diseases, including neurodegeneration and related dementias. These conditions, which involve the progressive loss of nerve cells, affect millions of people around the world and are an increasingly important public health concern: by understanding the genetic factors associated with these disorders, it may be possible to develop novel and more effective treatments and therapies (GBD, Collaborators, 2019, 2021; GBD 2019 Dementia Forecasting Collaborators, 2022; Logroscino et al., 2022).

In further detail, a human pangenome (Fig. 1) is composed of all the genetic variability of the group of individuals used to build it, as it includes single nucleotide polymorphisms (SNPs, also known as "point mutations" as they involve a single base pair along a DNA sequence), copy number variations (CNVs, a type of structural variation that involves the duplication or deletion of larger genetic segments, such as whole genes), as well as other structural rearrangements (mobile elements, inversions, translocations), and the concept can be similarly be applied to epigenetic modifications (pan-epigenome (Chen et al., 2020)), gene expression (pan-transcriptome (Cui et al., 2021)), and translation (pan-proteome (Broadbent et al., 2016)) among other disciplines investigating the totality of a set of objects in an organism (i.e., the so-called "-omics"). Each genetic modification may contribute to a neurodegenerative disease in different ways, making it difficult to identify the exact cause of such complex disorders (Lashuel, 2021; Logroscino et al., 2022; Perrone et al., 2021; Young et al., 2018). Despite

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this intricacy, it is already possible to successfully pinpoint with statistical significance and reasonable certainty some of the genetic signatures associated with neurodegeneration and related dementias (Abondio et al., 2021; Bruno et al., 2021; Rossi et al., 2004). Other studies may look at the effects of genetic modifiers in brain degeneration, finding out that certain elements may change the risk and timing of developing a condition caused by already known mutations (Barbier et al., 2021; Rossi et al., 2022). Despite these promising results at the single genome level, however, the understanding of the human pangenome and its contribution to the analysis of neurodegeneration and related dementia is still in its very early stages, as a draft of the pangenome has just been published very recently (Z. Gao et al., 2023; Y. Gao et al., 2023; Liao et al., 2023; Miga and Wang, 2021; Singh et al., 2022; Wang et al., 2022). Further research is warranted to better understand the complexities of the pangenome and how it may interact with environmental factors to cause (or protect against) a disease. In addition, it is important to consider how genetic variants may interact with each other and with lifestyle factors, such as diet and physical activity, to further influence the development of neurodegenerative conditions and their phenotypic manifestations through dementia. However, the prospect of a human genomic reference that would encompass the totality of variation within a population offers hope that more appropriate treatments and therapies may one day be developed to improve the lives of those affected.

Here, the application of the pangenome concept to the study of neurodegenerative diseases will be discussed and analyzed for its potential to enable an improvement in diagnosis and prognosis of these illnesses, leading to the development of tailored treatments to individual patients from the knowledge of the genomic composition of a whole population (Fig. 2).

2. Confirming and discovering genetic risk factors

The genetic basis of any given neurodegenerative disorder is constantly being elucidated through cohort studies and target gene analysis (Abondio et al., 2022a; Barbier et al., 2021; Bruno et al., 2021; Rossi et al., 2022), which are designed pragmatically to include only individuals with a full medical diagnosis and only a limited set of genes is usually investigated. However, the use of the pangenome may provide a way to identify previously unknown genetic components that may be contributing to the phenotypic variability of the disease. Indeed, the application of the pangenome to the study of human diseases has been a relatively recent development (e.g. in cancer research), and its potential in the study of neurodegenerative disorders is an increasingly interesting perspective (Sherman and Salzberg, 2020). The idea behind the use of the pangenome in ailments such as Alzheimer's disease (AD) is to capture the maximum amount of genetic diversity accessible, by characterizing not only known variants associated with the disease, but also previously undescribed mutations (Ebler et al., 2022; Gong et al., 2023; Hurgobin and Edwards, 2017; Liao et al., 2023; Mun et al., 2023). This approach has the advantage of allowing the examination of both known and unknown genetic factors contributing to the disease, and can potentially provide insight into the relationship between genotype and phenotype, for example through pangenome-wide association studies (pan-GWAS) (Gupta, 2021; Jin et al., 2023; Li et al., 2021; N. Li et al., 2023; Narumi, 2023; Walsh et al., 2023; Zhao et al., 2022). At the same time, it is important to acknowledge that the concept of the human pangenome is still in its infancy, and there are a number of potential hurdles to be overcome before a meaningful application of the pangenome to the study of neurodegenerative diseases can be achieved. Firstly, there is the issue of data availability: the pangenome is only as useful as the amount of genetic information used to create it, especially with the perspective of performing association studies with disease phenotypes (Eisenstein, 2023; Moore et al., 2019; Nishino et al., 2018; Politi et al., 2023). For this reason, there is the need to produce huge datasets of completely sequenced human genomes from diverse populations in order to identify the full range of possible human genetic variants. This is a significant challenge, as such datasets can often be difficult to build and, given their clinical relevance, only limited data access may be provided to the public (Borry et al., 2018; Rehm et al., 2021; Scollen et al., 2017). Furthermore, the use of the pangenome brings with it the potential for the confirmation of known genetic factors which have so far gone undemonstrated. For example, although a number of genes have been linked to AD, their mutations have not necessarily been confirmed as being causative genetic factors (e.g. mutation A713T in the *APP* gene clearly shows a strong association to familial dominant AD, however is still considered a variant of uncertain significance (Abondio et al., 2021; Rossi et al., 2004)). In such cases, the pangenome can potentially be used to provide conclusive evidence for one or more of these genetic variants by correlating its genotype with the symptomatic phenotype across populations. A possible technical limitation, however, lies in the handling and interpretation of such a huge amount of data, which requires extensive skills in using sophisticated bioinformatics approaches (Baaijens et al., 2022; Fagorzi and Checcucci, 2021). Additionally, the tremendous complexity of the neurodegenerative pathology itself, as well as the interactions between potential comorbidities sometimes mediated by the same mutated gene (i.e. pleiotropy), means that the genetic components of the disease are more arduous to analyze (Angelopoulou et al., 2021, 2023; Bruno et al., 2022,

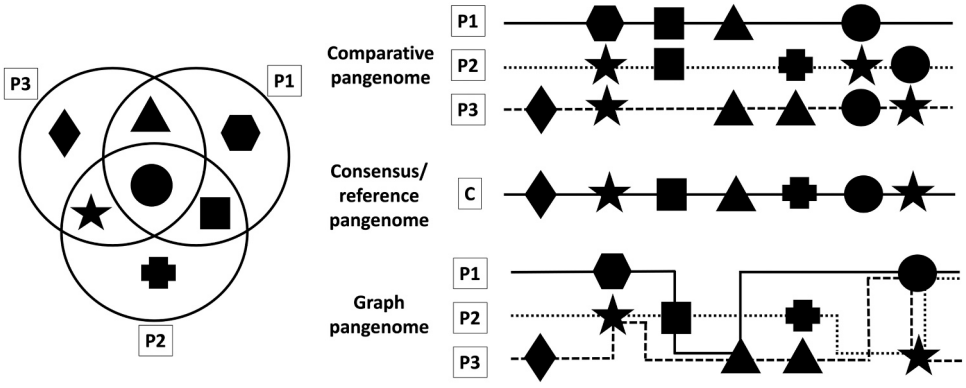

Fig. 1. Example of a pangenome based on three sequenced patients (P1, P2, P3). The Venn diagram on the left is descriptive of genetic elements shared across all three genomes (black circle), two genomes at a time (star, triangle or square) or unique for an individual (hexagon, rhombus or cross). On the right: the schematics for a linear comparative pangenome is presented on top; a consensus or reference pangenomic sequence (C) is given at the center; a graph-like reconstruction of the pangenome is provided at the bottom. Patient P3 presents a duplication of the triangular element shared with P1; patient P2 shows an inversion of the terminal segment, where the star and circle are reversed with respect to the consensus/reference.
Figure adapted by the original author from Abondio et al. (2023b).

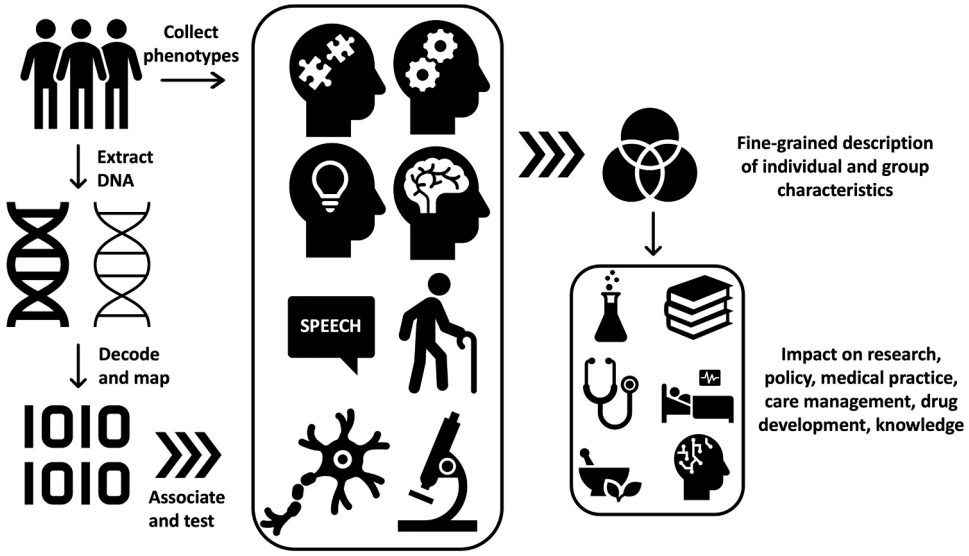

Fig. 2. Stylized framework for the relevance of the pangenomic approach in neurodegeneration.

2023b; Kerstens et al., 2023; J. S. Kim et al., 2023; Rudnicka-Drożak et al., 2023; Shen et al., 2019, 2023). Furthermore, this type of studies is limited to genetic material, making difficult to integrate information about behavior, environmental exposure, lifestyle and other non-genomic factors which can have a significant influence on the disorder's onset and progression (Ayeni et al., 2022; Bruno et al., 2023a; Madore et al., 2020; Nabi and Tabassum, 2022; Popa-Wagner et al., 2020; Schymanski et al., 2019).

3. Application of pangenomics to behavioral and psychological symptoms of dementia

As pointed out previously, pangenomics provides great prospects to gain insight into the genetics of a variety of neurological conditions, diseases, and complex traits. Furthermore, the application of pangenomics to the study of dementia as a manifestation of an underlying genetic neurodegenerative disorder has the potential to provide a new and comprehensive approach to the diagnosis and treatment of this condition. However, the specific nature of behavioral and psychological symptoms of dementia (BPSD, a heterogeneous group of co-occurring non-cognitive manifestations including apathy, aggression, depression, agitation and anxiety, to name a few) poses unique challenges and there may be contradictions regarding the efficacy of this approach: BPSD are highly complex and individualized, and much remains unknown about their underlying genetic aetiologies (Altomari et al., 2022; Laganà et al., 2022; Lozano-Tovar et al., 2023). This complexity is compounded by the fact that BPSD can present a marked inter-individual variability in different patient populations and environmental factors can play a major role (Halverson and Alagiakrishnan, 2020; Talebzadeh et al., 2023; van der Velde-van Buuringen et al., 2023; Wan et al., 2021). As a result, pangenomic approaches may be limited in their ability to provide a comprehensive and nuanced understanding of this condition. Furthermore, pangenomic studies depend on the generation of a robust, uniform, and accurately annotated dataset; however, existing collections of behavioral and psychological data for dementia patients are often incomplete or of questionable quality, which limits the ability of researchers to produce meaningful results by integrating different sources (Bechard et al., 2022; Kutschar et al., 2019; Sunderland et al., 2019; Waite et al., 2019; Westervelt et al., 2017). In addition, pangenomic studies rely on population-based rather than individual-level data, meaning they may fail to capture the unique experiences of each patient: this could limit the potential to identify interventions and preventative measures that are tailored to an individual's needs. Moreover, BPSD may be impacted by proteomic (as related to protein function) and epigenetic (as related to stable, heritable non-DNA-sequence based characteristics) changes, such as DNA methylation or histone modification, which cannot be detected through routine sequencing methods; therefore, approaches that account for these features may be more effective at elucidating the complexities of the disorder (Mao et al., 2020; Vasilopoulou et al., 2022). Ultimately, for pangenomic approaches to be effective in informing clinical research around a variety of diseases and conditions, it is important for the researchers themselves to consider the limitations of such studies when evaluating the efficacy of applying these strategies to correlate genetic information with behavioral and psychological parameters. By recognizing the potential restrictions of population-level pangenomic studies and utilizing complementary methods that focus on the individual level, deeper insights into the molecular mechanisms underlying BPSD may be more easily gained.

4. Translational research: biomarkers, drug response and illness evolution

The concept of pangenome has been already implemented to the study of cancer genetics (Stenman et al., 2021b, 2021a; Yu et al., 2022), however its potential application in translational research, particularly in the field of neurodegeneration, is just beginning to be theorized. The pangenomic approach allows to expand the study of genetic variability within a population to mutations, gene presence/absence and structural variation across individuals by looking beyond the current reference human genomes (Carvalho and Lupski, 2016; Collins et al., 2020; Quan et al., 2022). This structure provides a more comprehensive view of the genomic landscape of a population, which can be particularly useful as the complexity of these diseases often requires the analysis of multiple genetic factors simultaneously (Bern et al., 2019; Terhune et al., 2021; van Rheenen et al., 2019). In particular, pangenomics can be leveraged to identify genetic networks associated with specific neurological traits and characteristics, as well as to elucidate novel pathways which may be related to the development of neurodegeneration, dementia and other neuropsychiatric ailments (Fang et al., 2022; Yu et al., 2023). By analysing the shared genetic components across a population, this approach can help to reveal genetic markers which may indicate an increased risk of developing particular neurological diseases, as well as potential targets for therapeutic interventions. In addition, it can also be used to identify novel genetic elements which may be associated with disease progression and/or the emergence of neurological symptoms (Modenini et al., 2023). By analysing the genetic profiles of individuals of different

ages and stages of neurological progression, researchers can gain a better understanding of the underlying molecular mechanisms of the disease and the genetic changes that accompany its evolution (Macciardi et al., 2022). Overall, the pangenomic perspective provides a powerful tool to gain a more comprehensive insight into the genetic basis of neurodegeneration and related-dementias. Therapeutic interventions may be better tailored to a single individual if the probable cause of the disease is associated to a unique characteristic of the subject, while a more general approach can be applied for those mutations that are found across the entire cohort of afflicted patients. This approach can help to facilitate the development of new and more efficient bench-to-bedside strategies through the contextualization of the genetic characteristics of a patient in the background of the whole human pangenome, and ultimately help to improve the quality of life for individuals affected by these diseases by producing meaningful, applicable results that directly benefit human health. Indeed, the potential of the pangenome to discover genetic targets in neurodegeneration and dementia has been made possible by the recent advances in genomics (namely, telomere-to-telomere sequencing (Aganezov et al., 2022; Kille et al., 2022; D. S. Kim et al., 2023; Mao and Zhang, 2022; Nurk et al., 2022)) and the associated bioinformatic tools that allow the management and analysis of such huge amounts of data in a purposeful way (Baaijens et al., 2022; Eisenstein, 2023; Fagorzi and Checcucci, 2021). In this context, an extension towards pan-omic analyses can be used to uncover genetic markers that may be associated with the pathology. For example, gene expression profiling of human post-mortem brain samples through pan-transcriptomics may be employed to identify clusters of similarly regulated genes significantly associated with AD and other forms of dementia (Manzoni et al., 2018; Pinu et al., 2019). This analytical lens can be used to detect novel pathways and possible drug targets that may be promising candidates for therapeutic interventions. Additionally, the identification of gene clusters associated with particular neurodegenerative disorders can also be used to better characterize the biological pathways and mechanisms underlying the disease, which may in turn provide insight into the fundamental causes of the disorder (de la Fuente et al., 2023; Gravandi et al., 2023). On top of its potential in uncovering genetic targets in neurodegeneration and dementia, the pangenomic approach can also be used to directly identify potential biomarkers for disease progression and prognosis. For example, a temporal transcriptomic analysis of samples from patients with mild cognitive impairment (MCI) and AD can be exploited to identify gene clusters associated with the early stages of the disease, as well as those possibly linked to more advanced stages of the disorder (Guo et al., 2021; Macciardi et al., 2022). By better understanding the molecular pathways associated with AD progression and prognosis, researchers can develop targeted treatment strategies that may be more effective at slowing the progression of the disorder. The pangenomic approach also has potential applications in the realm of ancestry-informed precision and personalized medicine. By analysing the genetic variation across populations of different ancestries, it may be possible to identify gene mutations and clusters associated with a particular disorder in a particular group of patients, which may be used to inform treatments properly tailored to that individual's unique genetic profile (Abondio et al., 2023a, 2022a).

5. The genetics of brain architecture, cognition and mental health

The human brain is a highly intricate organ in the human body: with a complex network of connected neurons, each with thousands of synapses, understanding the many different links and pathways that make the brain function in the ways it does is a demanding task (Zhao et al., 2022). Two of the major challenges in research into neurodegenerative diseases and dementia manifestations is that distinct brain areas are affected differently, as corroborated by non-invasive multimodal imaging techniques (Aberathne et al., 2023; Cogswell and Fan, 2023; Shimizu et al., 2018), and that multifactorial interactions of genetic, environmental, social and behavioral risk factors modulate phenotypic expression in a nuanced manner (Barati et al., 2022; Dunn et al., 2019; Hamrah et al., 2023; Ribeiro et al., 2023; Wiese et al., 2023). Research driven by human pangenomic methods may open the possibility of looking at the genetic interactions between different brain areas in extreme detail, to better understand how diseases progress and how potential therapies could be developed. Broadly speaking, human pangenomics can also be interpreted as a way to identify shared genetic patterns across different areas of the brain, allowing us to better understand the complex interplay between different functional brain regions and decipher the relationship between the genetics and physiology of neurological diseases. By studying the entire genome of patients and its structural variations, researchers can indeed gain valuable insights into which interacting pathways may be involved in different areas of the brain, and this could lead to the development of more effective treatments (Agnati et al., 2023; Cragnolini et al., 2020; St-Pierre et al., 2022). Furthermore, human pan-omic methods can also be used to observe changes in neuronal cell types in different brain regions of patients with dementia. For example, researchers can observe how changes in total gene expression in different areas of the brain can lead to changes in cell type, morphology, and function in patients with neurodegenerative diseases, when compared among each other and with healthy subjects (Cragnolini et al., 2020; St-Pierre et al., 2022). Ultimately, this understanding of the genetic basis of expression patterns in the brain could lead to the development of new targeted therapies to tackle the relevant pathways and specific cell types involved in the disease, by distinguishing them on the basis of their expression profile, for example as it is already done at single-cell level with immune cells (Abondio et al., 2022b; Pace, 2021; Pace et al., 2018; Pace and Amigorena, 2020).

Interestingly, pangenomics may be also associated to the analysis and the genetics of the brain connectome (https://www.humanconnectome.org, last accessed 12 June 2023) (Axer and Amunts, 2022; Elam et al., 2021). The brain connectome encodes the intricate pattern of connections among neurons in the brain that allow for the integration of sensory information, motor control, and memory formation (Bazinet et al., 2023). Disruptions in these networks can lead to different neurodegenerative diseases and other brain disorders (Filippi et al., 2023; Y. Gao et al., 2023; Z. Gao et al., 2023). Using human pangenomic methods, researchers can now examine the complete set of genetic variants in an individual's genome in order to determine which ones are related to the risk of developing a specific type of neurodegenerative disease or other psychiatric disorder. These methods can also be used to investigate the genetic basis of variations in brain wiring, which can result from mutations (Fox, 2018; Yu et al., 2021). For example, researchers have identified genes associated with early-onset forms of AD, that are associated with specific anatomical features (such as reduced cortical thickness and connectome variability in localized brain regions) and that change expression levels through the lifespan (Cai et al., 2021; Vidal-Pineiro et al., 2020). By leveraging the genetic variability in the brain connectome, scientists may be able to develop targeted therapeutic interventions to hopefully prevent the progression of neurodegenerative diseases. Moreover, pangenomics can help us better understand how individual differences in genes contribute to dissimilarities in cognition (Farsi and Sheng, 2023; Reas et al., 2023). Pangenomic methods may also being used to explore the decision-making processes in the human brain: for example, by studying the genetic basis of stress responses in individuals, researchers have already been able to identify gene variants associated with the risk of developing depression or anxiety (Baba et al., 2022; Choi, 2022; Dalvie et al., 2021; Fang et al., 2022). By anchoring to a pangenomic interpretation these variants, as well as yet unknown structural variants, could potentially be used to help predict an individual's likelihood for developing these disorders so that interventions and treatments can be tailored to each individual. Finally, pangenomic methods may reveal stronger links between genes and the environment in terms of how the brain processes information

through its extended connections (Giddaluru et al., 2016). By studying both an individual's genetic makeup and the environmental exposures and contextual parameters they have experienced, researchers can begin to determine how these factors interact to influence cognitive processes and mental health. In summary, human pangenomic methods are offering scientists a powerful new tool to study the genetic underpinnings of the brain connectome and its associated diseases. With it, researchers can gain a better understanding of the complex systems that underlie brain development, behavior, and mental health. At the same time, these methods may allow scientists to develop novel therapeutic interventions for a variety of psychiatric disorders and to gain insights into the role of genetics and environment in the development of mental health.

6. Genetic and molecular details of the disease at a single-cell level

The association of single-cell sequencing technologies with a pan-omic methodology can also provide new ways into the detailed study of neurodegenerative disorders. This approach to understanding the mechanisms behind disease progression may focus on a combined examination of the collective expression profile, or pan-transcriptome (Cui et al., 2021), and the synthesized proteins, or pan-proteome (Broadbent et al., 2016), of a group of cells from a single tissue, by considering them as a population (Apicella et al., 2023; Neou et al., 2020). By incorporating this approach into traditional single-cell sequencing technologies (Fig. 3), researchers may be able to uncover novel nuanced differences among cell types constituting the brain regardless of whether these differences exist on the gene level, in coding regions or elsewhere (Abondio et al., 2022b; Sreenivasan et al., 2022; Vodovotz, 2023). The information emerging from this kind of approach may help to refine the understanding of the importance of local variation in disease risk profiles, and potentially opens up strategies to drive drug development and targeted treatments for specific cell types (Sreenivasan et al., 2022; Vodovotz, 2023). Furthermore, telomere-to-telomere single-cell sequencing (if this will ever be possible) may identify cells carrying particular mutations, therefore providing insight into how such variants may affect cellular behavior and gene regulation processes (Z. Li et al., 2023; Luquette et al., 2022). In combination with gene expression profiling, this may enable the characterization of cellular responses to different environmental signals, which lends insight into how diseases develop. Single-cell sequencing has indeed the potential to advance the goal of designing personalized medicine approaches for treating neurodegenerative disorders by widening the view of the scientific community into the unknown and applying the insights gained to individual patients (Z. Li et al., 2023; Luquette et al., 2022). Such information is invaluable for designing treatment strategies for patients who would previously have necessitated generic, one-size-fits-all approaches. The field of medical research stands to benefit significantly from the combined application of single-cell sequencing and pan-omics to the study of neurodegenerative disorders. By pushing the boundaries of traditional methods, studying the minutia of single-cell genetics in association with the collective genome of the group, these technologies may revolutionize the field of molecular medicine: not only can individual genetic variants be identified across genomes, but links between particular genetic variants and particular responses to disease at a single tissue level can be established.

7. Ethical, legal and medical aspects

As discussed above, the concept of the human brain pangenome, which involves scanning and mining the genetic information of numerous individual subjects and combining it into a single map, is of great interest in neurodegenerative and dementia research. In theory, a pangenome could provide a clearer picture of all the genetic factors

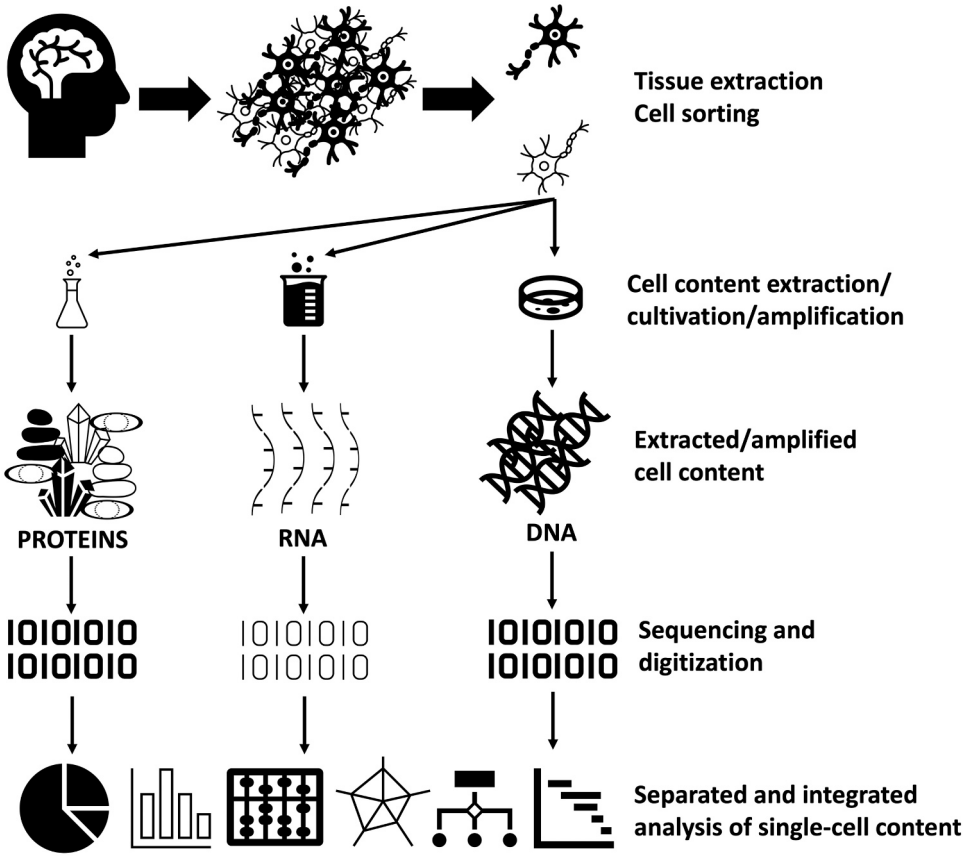

Fig. 3. Stylized framework for an integrated multi-omic approach to single-cell sequencing from brain tissue.

associated with such diseases. Its application, however, also raises ethical questions regarding how to properly respect the autonomy and rights of the individuals whose genetic information is being used, specifically considering cohorts of patients affected by an condition such as a neurodegenerative disease (Bhardwaj and Santulli, 2023; Diaz-Gil et al., 2023; Poth et al., 2023). Indeed, there may be clear concerns around the possibility for individuals with brain degeneration and dementia to legally consent to participation in scientific research, as it is generally expected not only that the subject is in its full mental capacity when consenting to treatment, but also that the subject itself must maintain at any moment the possibility to recede from further therapeutic courses of action. This condition may not be in place if a person agrees to participate in a clinical study and then develops such an advanced state of dementia that they cannot acknowledge their own wellbeing anymore. While it is a consolidated practice to involve a proxy, such as a legally authorised family member (most often the subject's spouse) or tutor (in cases of guardianship), in healthcare decisions via power of attorney, it is also true that these people may not necessarily act in accordance with the patient's original wishes (Barzun, 2023); moreover, individuals without any living family or in a domestic partnership may pose a further ethical dilemma. A speedy, althgough not definitive, solution could be the drafting of an advance research (and healthcare) directive, a legal document that determines the subject's will to procede in case they become no longer able to take autonomous decisions because of illness or incapacity (Bravo et al., 2018).

Another core ethical consideration involves the question of informed consent (Horton and Lucassen, 2019; Koplin et al., 2022a; Rego et al., 2020): individuals must be asked to volunteer their genetic information for use in a pangenome before it can be collected, consulted and scrutinized; researchers must be sure that potential participants understand exactly what the project involves and that their rights are respected; explanations should also be provided regarding the potentially sensitive nature of the information that will be collected and processed (Falvo et al., 2021; Kim, 2011; Poppe et al., 2020; Thorogood et al., 2018). Privacy and confidentiality issues must also be taken into account, as information collected under the auspices of a pangenome project must be properly safeguarded and stored in a secure environment (Ochang et al., 2022; Rehm et al., 2021; Shen et al., 2022; Wan et al., 2022; Wong-Lin et al., 2020). Furthermore, the individuals who have agreed to participate in the project should be informed as to how their data and the results of the project will be disseminated: from a regulatory perspective, transparency and truthful communication of results requires that the vast majority of data discovered as part of a study must be made available publicly, to ensure full data access, research repeatability and result reproducibility (Ienca et al., 2018). Additionally, it is important to point out that researchers may be allowed to share data with industry partners for the purposes of patenting and commercialisation (Koplin et al., 2022b; Liddicoat et al., 2019; Nicol et al., 2019), particularly for drug discovery and the development of novel treatments for complex genetic diseases (Martins et al., 2022; Schaper and Schicktanz, 2018). It is, however, a personal choice of the participant to allow the use of their own genetic material in a specific way and this, once again, has to be based on full disclosure and intransgressable consent. Furthermore, while a pangenome may lead to advances in preventive care, a potential risk of genetic discrimination must also be kept in mind: patients should not be unfairly denied access to medical care or insurance due to factors such as their genetic background (Chapman et al., 2020; Clayton et al., 2019; Joly et al., 2021, 2020; Joly and Dalpe, 2022; Kim et al., 2021), and the same standard should be applied when utilizing collective data contained in a pangenome project, although it may provide an extended form of anonymity, as it does not represent the genetic makeup of a single individual (Abondio et al., 2023a). On the contrary, an additional ethical imperative exists to ensure access to the benefits arising from a pangenome project: results obtained from such study should be made publicly available without discrimination based on financial considerations. Furthermore, especially in the case of neurodegenerative and dementia studies, those individuals who volunteered to have their genetic information included in the project should be given access to any new treatments or therapies that the project may uncover (Byrd et al., 2020; Chapman et al., 2020; Clayton et al., 2019; Dos Santos Rocha et al., 2023; Lindemann and Häberlein, 2023). By focusing on rigorous informed consent, privacy and data confidentiality, as well as access to the benefits of the project, we can ensure that the whole process of research is conducted in a manner that respects the autonomy and rights of the individuals who donated their genetic information to form the basis of the pangenome.

8. Concluding remarks

As a strongly emerging field with years of application in microbiology and its expansion towards plant, animal and human population genomics, there is no doubt that pangenomics is here to stay. The application of the concept of pangenome to neurodegenerative diseases is promising as it may provide several advantages in the analysis of these ailments on a population-wide scale, by expanding the array of possible variables.

The draft human pangenome based on 47 phased, diploid assemblies from a cohort of genetically diverse individuals allowed to add 119 million bases pairs of euchromatic polymorphic sequences and 1115 gene duplications relative to the existing reference GRCh38. These results represents the tip of the iceberg as the ultimate goal of the Human Pangenome Reference Consortium project will continue into 2024, when the researchers plan to release a final pangenome with genomic information from 350 individuals (Liao et al., 2023). Thanks to this, the potential for cutting-edge translational research is ever-growing: leveraging long read sequencing and new bioinformatic tools that support the comparison of many complete human genomes, it was already possible to exploit the draft human pangenome to shed light on recombination mechanisms involving the acrocentric chromosomes, providing unexpected insight into infertility and congenital conditions (Guarracino et al., 2023).

It is therefore not difficult to hypothesize that the human pangenome will also allow a more detailed and comprehensive analysis of the genetic variability in neurological disorders, as the pangenome approach may more accurately capture the range of genetic diversity present in the population of patients afflicted by a particular neurodegenerative disease, as well as the differences among populations of different ancestries (Abondio et al., 2023a, 2022a). For example, a pangenome analysis may be able to identify genes that are not present in all individuals but may be expressed in a subset of the population, thereby helping to identify those genetic variants that may be associated with a particular subclass of a specific disease (as it can be seen today with the ever-advancing research on non-canonical biomarkers to differentiate stages or subtypes of neurodegenerative and psychiatric disorders (Macciardi et al., 2022; Modenini et al., 2023)). This could allow access to the nuances of genetic interaction and polygenic contribution to the phenotypic manifestations of the disease. Furthermore, a reference pangenome allows for the identification of genetic differences in individual genomes by direct comparison, which can provide valuable insights into the underlying mechanisms of disease and lead to the development of new personalized treatments on the basis of previously established pangenomic discoveries (Anderson and Bisanz, 2023; Hyun et al., 2022). Novel therapeutic targets may be revealed in terms of still undetermined structural variations and genomic rearrangements that are expressed in a subset of the population. Indeed, the application of the pangenome concept to the study of neurodegenerative diseases holds a great potential to benefit medical research: the study of these complex multifactorial illnesses in a population-based pangenome may provide a more accurate diagnosis and a more precise prognosis to illnesses such as Alzheimer's, Parkinson and Huntington disease on the basis of their molecular makeup. This can be particularly useful in the context of personalized medicine, as it can enable the development of treatments

tailored to an individual patient but starting from the fundamental knowledge around the complete aggregated genomic complexity of an entire population.

Finally, the adoption of a human pangenome in the near term not only requires the characteristics of representativeness and inclusiveness, but also a robust definition of accurate variant calling pipelines and relevant graphical representations. These represent the fundamental steps for a successful implementation of a pangenomic analysis for mapping human genetic variations and to facilitate the traslation of the relevant findings in the clinical practice.

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Data Availability

No data was used for the research described in the article.

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