Trends in Biomedical Research

Review Article ISSN: 2632-0509

Understanding of "-omics" of Parkinson's disease

Sha Zheng[1]*, Xue Wen[2]*, Jian Feng[2]*, Fangfang Liu[3], Greg Mirt[4] and Fan Xu[2]

[1]Pharmacy School, Chengdu Medical College, Sichuan, China

[2]Department of Public Health, Chengdu medical college, Sichuan, China

[3]Art College, Southwest Minzu University, Sichuan, China

[4]Neuro Occupational Activity Centre Novo mesto, Slovenia

Abstract

Parkinson's Disease (PD), as one neurodegenerative disease, reduce the life quality of our patients extensively. Since the identification and validation of role of alpha-synuclein in PD, several impactful hypotheses pointed out the direction of our research, while the bioinformatic studies initialized to focus on the generation, formation, transportation and aberrant clearance of alpha-synuclein. The pioneer studies of Braak provided a comprehensive classification between alpha-synuclein and the severity of PD. Currently our understanding of bioinformatic on PD are increasing sharply as well from genomic, proteomic and metabolomic. To our best knowledge, here we provide a comprehensive picture of this disease from genomic to metabolomic.

Introduction

Parkinson's Disease (PD) is a serious neurodegenerative disease of the central nervous system. The prevalence of population over 65 years old arrived at 1.7% and the global incidence rate is 1.5% [1]. In 2016, there were 6.1 million people suffered from PD, including 2.9 million women and 3.2 million men. It caused 211,296 deaths [2], unfortunately incidence increased with age [3]. According to epidemiological statistics prediction, there will be more than 14 million patients of PD in 2040.

The treatment on PD requires robust financial support. Obviously, it is a huge economic burden not only for patients and his/her families, but also on the society. According to the global epidemiological statistics, the sum of direct and indirect costs of treatment on PD in Europe reached 7.7 billion Euros in 2010. While in United States, the total cost of medical and non-medical treatment for every PD patient has increased by a total of $22,800 [4]. As for China, the annual direct medical expenses for patients with PD per year in Shanghai, amount to 4,305 yuan, and the non-medical expenses are about 3,301 yuan [5].

Date back to 2003, Braak, *et al.* proposed the PD stage according to the specific pattern of α-syn diffusion, which describing the relationship between α-synuclein and disease severity [6]. These six stages clarified the severity of PD accordingly to deficit from sensory to sport zone in the brain. The key pathological traits of PD is the damage or deficit of dopaminergic neurons in the dense part of the substantia nigra. This can be leading to a decrease in the secretion of dopaminergic neurons [7]. The loss of dopaminergic neurons reaches 50%, and the corresponding clinical manifestations appears [8]. The clinical features are mainly static. Sport symptoms such as tremors, bradykinesia, muscle rigidity, and unstable posture are also associated with non-motor symptoms, including constipation, sensory disturbances, depression, autonomic disorders, and sleep disorders [9] (Figure 1). Non-motor symptoms of PD are earlier with exercise needle symptoms [10].

Accumulation of α-synuclein is the main cause of Parkinson's disease [11], but recent studies have shown that dopamine metabolites can increase neuronal deformation, dopamine is oxidized to produce reactive sputum substances, hydrogen peroxide and other reactive oxygen species. These metabolites have an accelerating effect on PD [12].

The mainstream hypotheses on PD

Oxidative stress is a stress injury caused by intracellular oxidation and anti-oxidation imbalance [13]. Reactive oxygen species (ROS) is produced during oxidative stress, leading to mitochondrial disorders and ultimately neuronal death. Under physiological conditions, reactive oxygen is an important redox form that regulates various signaling pathways. It plays an important role in regulating different cellular metabolism, post-transcriptional modification, antioxidant defense mechanisms, and excessive reactive oxygen destroy cellular lipids. Studies disclosed that dopamine neurons in the brain damaged via the path of oxidative stress and mitochondrial dysfunction, due to the reduced dopamine secretion [14].

The accumulation of unfolded or misfolded proteins caused by glucose starvation, hypoxia, calcium homeostasis or oxidative stress is known as endoplasmic reticulum stress [15]. Folding false or unfolded proteins inhibit synaptic function and interfere with signal transduction pathways, these are key factors leading to ubiquitin proteasome system-mediated protein degradation dysfunction, thereby altering the normal physiological morphology of cells, disrupting protein homeostasis, triggering protein accumulation, and causing the neuron degeneration [11].

Correspondence to: Fan Xu, Department of Public Health, Chengdu Medical College, Chengdu, Sichuan Province, China, Tel: +86 28 6273 9397; E-mail: xufan@cmc.edu.cn

Key words: *parkinson's disease, bioinformatics, genomics, proteomisc, metabolomics.*

Received: November 01, 2019; **Accepted:** November 14, 2019; **Published:** November 18, 2019

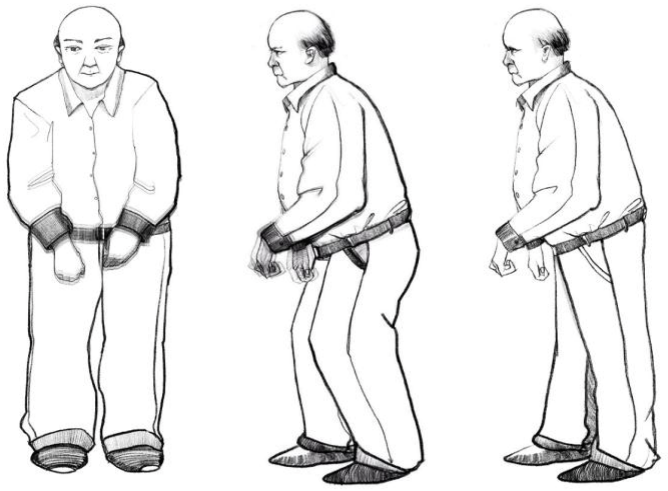

Figure 1. Dominant manifestation Trembling of Parkinson's Disease

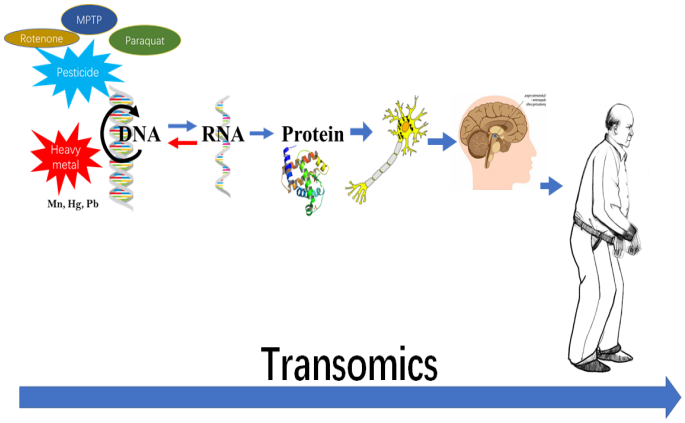

Figure 2. The concept of data flow of reasoning in PD

Neuroinflammatory response is considered to be one of the major pathogenic factors of neurodegenerative disease [16]. Activation of astrocytes and microglia releases harmful reactive oxygen species and pro-inflammatory factors, while over-activated microglia also increase oxidative stress and cause neuronal cell deformation [17]. Intestinal flora and its metabolites increase intestinal permeability and bacterial translocation, stimulate local and systemic inflammation of the intestine, resulting in the production of lewy bodies in the intestine, and the metabolic products (lipopolysaccharides, etc.) [18]. Ring blood-brain barrier, promoting inflammation and the damage of the substantia nigra.

Accompanied with our increased knowledge several interest gene *SNCA* (PARK1; encoding α-synuclein) [19], *LRRK2* (PARK8; encoding dakarin) [20], *VPS35* (encoding vacuolar protein sorting 35) [21], *PINK1* (PARK6; PTEN-induced kinase 1) [22], *DJ-1* (PARK7) [23], *Parkin* (PARK2) [22], *ATP13A2* (PARK9) [24] and *FBXO7* [25] lead to autosomal recessive PD and/or Parkinson's disease, have been validated that they associated with development of PD [18].

Environment selection role is playing dominant role in gene function performing. Several pollutants, such as water, air pollution and food pollution, can be induced the onset of PD. Currently, the use of pesticides is very popular. Especially in rural areas, it caused concerns for the general public. The James Ka study in 2015 showed that the presence of pesticides in groundwater can cause Parkinson's disease [26]. The pollutants in the air, including PM, ozone, diesel exhaust and fierce, can be leading to increased cytokine expression and oxidative stress in the brain. Activating microglia may affect the neurodegenerative pathway [27]. In 2017, Lee H, *et al.* reported that short-term exposure to air pollution may increase the risk of PD exacerbation [28]. Chen CY, *et al.* in 2017 established that long-term exposure to PM10 has a positive effect on subsequent PD development, and the presence of any combined disease increases the likelihood of PD [29].

Di, *et al.* so contributes as risk factor in the development of PD. In 2019, Anna Sauerbier, *et al.* reported a correlation existed between diet and Parkinson's disease [30]. Andre Rodrigues Vasconcelos, *et al.* demonstrated that dietary energy restriction (DER) may induces activation of the transcription factor Nrff2, which activates the expression of phase 2 detoxification enzymes, thereby increasing neuronal resistance against oxidative stress and death, and reducing PD risk [31]. At the same time, X. Gao, *et al.* disclosed that the intake of some flavonoids may reduce the risk of PD. Oxidative stress has a negative impact on flavonoids such as apoptosis and the formation of α-synuclein fibers. Also it inhibits the use of dopamine neurons [32].

Genomic understanding of PD

The pathology of PD is caused by the imbalance of alpha-synuclein generation and clearance [33]. In 1998, Polymeropoulos, *et al.* investigated the beta-synuclein gene was extremely high expressed in brain, this gene showed the inhabitation phospholipase D2 selectively [34]. In 2007, Gasser T, *et al.* studied the gene function of SNCA, causing the alpha-synuclein gene to develop sporadic PD [35]. Wade-Martins, *et al.* investigated the function of Leucine gene rich with repeat kinase 2 (*LRRK2*) in PD. The data disclosed this gene is involved in endosomal-autophagic pathway and the recruitment of specific membrane microdomains under the physiological human gene expression [36]. In 2010, Papapetropoulos S, *et al.* tested the function of RNA splicing gene SRRM2 (or SRm300), sereine/arginine repetitive matrix 2. It is playing the crucial role in RNA splicing in PD [37]. In 2011, Das F, *et al.* discovered that oncogene *DJ-1* prevents oxidative damage and apoptosis of dopaminergic neurons in animal models of Parkinson's disease [38]. In 2012 Maraganore DM, *et al.* performed the first genome-wide association study (GWAS), identified a series of candidate gene including, C8orf4 participate in inflammation process. CACNB4 has a calcium channel function. *TRPM3* inhibit AKT protein kinase and *ITPK 2* encode the ER function [39]. In 2014, Screaton RA, *et al.* reported upon mitochondrial damage such as PINK1is stabilized on the outer mitochondrial membrane where it phosphorylates ubiquitin, generates a signal for the recruitment and activation of Parkin [40].

Similar research interest, LRRK attracts numerous attentions as well. Saniz J found *LRRK2-G2019S* participated in Akt signaling, glucose metabolism and immunity in 2014 [41] and cell adhension molecular, complement, coagulation cascade in 2016 [42]; Sealfon SC reported *LRRK2-G2019S* may increase kinase activity to antagonize specific microRNAs [43]. Moreover, the gene PARKs also draws great research interest. Hoffman-Zacharska D, *et al.* found it predominantly involved in rearrangement processes in genomic region in 2015 [44]; while Alonso I, *et al.* validated its similar functions mediate the deletion in homogeneous population in 2016 [45]. More interestingly, Bosch E, *et al.* discovered correlation between stop codon and PARK in 2017 [46] (Table 1).

Table 1. Genomic understanding of PD

Author	Year	Interested Gene	Function
Polymeropoulos MH	1998	beta-synuclein gene	Inhibit phosphatase D2 selectively
Gasser T	2007	SNCA	alpha-synuclein
Wade-Martins R	2009	LRRK2-R1441C	Abnormal autophagy balance, abnormal MVB formation
Papapetropoulos S	2010	SRRM2	mRNA expression, signal transduction
Das F_	2011	DJ-1	Anti-apoptosis
Maraganore DM	2012	C8orf4	Inflammation
		CACNB4	Calcium channel complex protein
		TRPM3	Inhibition of AKT protein kinase
		ITPK2	Calcium channel encoding ER
Screaton RA	2014	PINK1	Phospho-ubiquitin method on the outer membrane of mitochondria, recruitment and activation to generate signals
Sainz J	2014	LRRK2-G2019S	Akt signaling, glucose metabolism or immunity
Sealfon SC	2015	LRRK2-G2019s	Increases kinase activity to antagonize specific microRNAs
Hoffman-Zacharska D	2015	PARK2	rearrangement processes
Orr-Urtreger A	2015	GBA	Peripheral blood leukocyte-associated gene down-regulation
Lou Z	2015	Parkin	mitotic defects, genomic instability, tumorigenesis
Alonso I	2016	PARK2	rearrangement processes
Sainz J	2016	LRRK2-G2019s	Cell adhesion molecule, complement, coagulation cascade
Bosch E	2016	PARK2	Premature stop codon
Kim J	2017	GBA-GBAP1	Pseudogene rearrangement, gene conversion
		LK2GS	gene expression in the intestinal cells.

Proteomic understanding of PD

To our best knowledge, the imbalance between generation and clearance of alpha-synuclein is playing dominant role in PD [47]. The CSF is produced by the brain and participates in the internal circulation of the brain. Therefore, it is the best indicator to reflecting the structural characteristics of the pathophysiology of the brain [48]. The pathological marker of PD is the formation of Lewy bodies, while α-synuclein (α-syn) is the main component. alpha-synuclein may resist damage through aggregation. So when the damage occurs, alpha-synuclein will be aggregate continuously, resulting in mitochondrial damage caused by oxidative stress, beyond the ability of the cell to withstand, and cannot clear abnormal proteins, thereby producing toxic effects on cells and accelerating cell deaths [49].

Studies also uncovered that the level of alpha-synuclein in CSF of patients with PD gradually decreases with the progression of the disease. Decrease in the total α-syn entering the systemic circulation after α-syn fibrosis in the brain tissue may result in total alpha CSF [50]. With respects to the function of alpha-synuclein, Nussbaum RL, *et al.* found that the alpha-synuclein may bind to the membrane of oligomers, lipid droplet and affected triglyceride metabolism [51]. In 2018, Yen SH demonstrated that it may participate in cell viability [52]. Maguire-Zeiss KA, *et al.* found that it was involve in oxidative stress and inflammation [53], while Lindquist S, *et al.* demonstrated that it inhibit the vesical transport [54].

Regarding to other researches interest proteins, Singh MP, *et al.* reported that the albumin precursor, serum albumin chain-A, PRR14 and serum transferrin N-terminal lobe can be reduce the neuronal dysfunction in 2009 [55]. Yang P, *et al.* summarized that apolipoprotein A-I is involve in lipid metabolism and deposition process of proteins in 2015 [56]. Burkhard PR, *et al.* disclosed that cytosolic non-specific dipeptidase 2 (CNDP2) participate in oxidative stress, protein aggregation and inflammation [57]. Robinson PA, *et al.* validated that protein Parkin participate in the regulating mitochondrial activity [58].

In 2018, Ketterman AJ validated that the human glutathione transferase omega 1 modulating stress response [59]. Arenas E, *et al.* reported that leucine-rich repeat kinase 2 accelerate the maturation of substantia nigra dopaminergic neurons [60]. While, Rubinsztein DC, *et al.* revealed that Leucine-rich repeat kinase 2, LRRK2, may impair the activity of ubiquitin proteasome pathway [61]. Harvey, *et al.* demonstrated that LRRK2 participate in protein translation and trafficking [62]. Mann M, *et al.* figured out that LRRK2 involve in vesicle transport [63].

Moreover, Cookson MR, *et al.* disclosed that the DJ-1 may protect the neurons against death [64]. Zhang Y, *et al.* reported that the mitochondrial heat shock protein 75 (MTHSP75), phosphoglycerate dehydrogenase (PHGDH), laminin binding protein (LBP), tyrosine 3/tryptophan 5-monooxygenase activation protein (14-3-3ε) and YWHAZ protein (14-3-3ζ) are involved in mitochondrial dysfunction, serine synthesis, amyloid clearance, apoptosis process and neuroprotection [65] (Table 2).

Metabolism understanding of PD

Kaddurah-Daouk R, *et al.* disclosed that uric acid may reduce the antioxidative damage in 2009 [66]; Jones DP, *et al.* found that the polyamine regulate cell growth and its size value in 2013 [67]; Pamplona R, *et al.* reported that glutathione participate in buffering oxidative stress [68]; Kong L, *et al.* found that creatine may protect neurons from oxidative stress in 2014 [69]; Rango M, *et al.* reported in 2015 that HEP involved in oxidative phosphorylation, mitochondrial damage and lactic acid may reduce mitochondrial damage [70]; Powers R, *et al.* reported that sorbitol sugar can cause the mitochondrial dysfunction, oxidative stress. Pyruvate is involved in Tricarboxylic acid cycle. This is known since 2015 [71]; Liu H, *et al.* reported that serotonin participate in metabolic pathways including antioxidant activities and citrate cycle [72]. Cai H, *et al.* found that guanosine participate in neurodegeneration to prevent 1-methyl-4-phenylpyridinium (MPP+)-induced PC12 cell, and carnosine protect brains mainly through antioxidant, and antiglycative properties in 2015 [73]. Gao H, *et al.* found that Glu, Gln, GABA inhibit neurotransmitter GABA and lactate may increase the lactate level in the striatum of 6-OHDA-induced PD ratsin 2015 [74].

Madine J, *et al.* found that taurine may stabilise cell membranes because assisting in ion transport to antioxidant and increase cognitive

function; Dimethylamine may produce NO which can induce oxidative/nitrative stress conditions and in turn damage mitochondrial complex I, complex II and mitochondrial aconitase [75]; Cai Z, *et al.* established that Tryptophan influent CNS inflammation and amino acid play a notable role in signal exchange between neurons [76] (Table 3.1).

Roy R, *et al.* found that branched-chain amino acids regulate the mitochondrial respiration and participate in the synthesis of neurotransmitters, while histidine helps in scavenging ROS [77]; Lamberts JT, *et al.* found in 2019 that urate involved in antioxidant and reactive oxygen species (ROS) scavenger, meanwhile, adenosine play anti-inflammatory effects [78]; Eggers C, *et al.* found that mannose regulate the immune signal and mediate inflammatory response [79]; Le W, *et al.* found that cerebrospinal fluid metabolome involved in antioxidative stress responses and metabolic pathways of sphingolipid, glycerophospholipid and amino acid. Consistently, urate participate in against oxidative stress in 2019 [80]. Hattori N, *et al.* discovered that benzoate-related metabolites may altered in gut microbiota and caffeine and its metabolites affect the malabsorption [81]. Xu F, *et al.* reported that adenosine may attenuating oxidative stress, excitotoxicity and neuroinflammation, promoting sleep, improving cognitive function and exerting anti-depressive effects in 2019 [82] (Table 3.2).

Table 2. Proteins Discovered in PD

Author	Date	Key protein	Biological function (Annotation)
Nussbaum RL	2005	Alpha-synuclein	Preferentially binds to oligomers of the membrane, binds to lipid droplets and affects triglyceride metabolism
Singh MP	2009	albumin precursor, serum albumin chain-A, PRR14 and serum transferrin N-terminal lobe	Neuronal dysfunction
Fasano M	2014	alpha-synuclein	reduces nuclear factor kappa B activation
Yang P	2015	apolipoprotein A-I	lipid metabolism, deposition process of proteins
Burkhard PR	2016	CNDP2	oxidative stress, protein aggregation inflammation.
Iseri P	2016	E3-protein ubiquitin ligase	cell metabolism
Robinson PA	2017	Parkin	regulating mitochondrial activity within cells
Mandell JW	2018	caspases	synapse loss
Ketterman AJ	2018	Human glutathione transferase omega 1	modulating stress response
Arenas E	2018	Leucine-rich repeat kinase 2	Maturation of substantia nigra dopaminergic neurons
Yen SH	2018	alpha-synuclein	compromise cell viability.
Maguire-Zeiss KA	2018	Alpha-synuclein	Oxidative stress, inflammation
Rubinsztein DC	2018	lrrk2	impairs the activity of the ubiquitin-proteasome pathway,
Lindquist S	2018	Alpha-synuclein	Inhibition of vesicle transport
Cookson MR	2018	DJ-1	Protected neurons against death
Harvey K	2019	lrrk2	protein translation and trafficking
Zhang Y	2019	(MTHSP75), (PHGDH), (LBP), (14-3-3epsilon) and YWHAZ protein(14-3-3zeta)	mitochondrial dysfunction, serine synthesis, amyloidclearance, apoptosis process and neuroprotection
Mann M	2019	lrrk2	Vesicle transport

Table 3. Metabolism of PD understanding from 2009-2017

Author	Date	Metabolites	Pathway
Kaddurah-Daouk R	2009	uric acid	Antioxidative damage
Jones DP	2013	Polyamine	Regulate cell growth and increase value
Pamplona R	2014	Glutathione	Buffering oxidative stress
Kong L	2014	Creatine	Protect neurons from oxidative stress
Rango M	2015	HEP	Oxidative phosphorylation, mitochondrial damage
		Lactic acid	Mitochondrial damage
Powers R	2015	Sorbitol sugar	Mitochondrial dysfunction, oxidative stress
		Pyruvate	Tricarboxylic acid cycle
Liu H	2015	Serotonin	metabolic pathways, antioxidant activities, citrate cycle
Cai H	2015	Guanosine	neurodegeneration, prevent 1-methyl-4-phenylpyridinium (MPP+)-induced PC12 cell
		α-synuclein	the first genetic causal factor linked to PD
		Carnosine	protect brains mainly through antioxidant, metal chelating, and antiglycative properties
Gao H	2015	Glu, Gln, GABA	inhibitory neurotransmitter GABA
		lactate	Increased the lactate level in the striatum of 6-OHDA-induced PD rats relative to normal rats
Jolicoeur M	2017	ATP	Energy metabolism, oxidative stress
Madine J	2017	Taurine	stabilise cell, membranes assisting in ion transport and is suggested to have antioxidant properties and to increase cognitive function
		Creatinine	anti-oxidant
		Dimethylamine	produce NO which can induce oxidative/nitrative stress conditions and in turn damage to mitochondrial complex I, complex II, and mitochondrial aconitase
Cai Z	2017	Tryptophan	influence CNS inflammation
		fatty acids	They play roles in metabolic and inflammatory disorders
		Tauroursodeoxycholic acid	neuro protective agent
		Amino acid neurotransmitters	play a notable role in signal exchange between neurons

Table 3.2. Metabolism of PD understanding from 2018-2019

Author	Date	Metabolites	Pathway
Roy R	2018	branched-chain amino acids	mitochondrial respiration, participate in the synthesis of neurotransmitters
		histidine	an antioxidant, helps in scavenging ROS
Lamberts JT	2019	Urate	antioxidant and reactive oxygen species (ROS) scavenger
		Adenosine	anti-inflammatory effects
Eggers C	2019	fatty acids	fatty acid oxidation
		mannose	immune signal, mediate inflammatory response
Le W	2019	Cerebrospinal fluid metabolome	involved in antioxidative stress responses, and metabolic pathways of sphingolipid, glycerophospholipid and amino acid
		Urate	against oxidative stress
Hattori N	2019	fatty acid	lipid metabolism
		benzoate-related metabolites	alteration in gut microbiota.
		caffeine and its metabolites	malabsorption
Xu F	2019	Adenosine	attenuating oxidative stress, excitotoxicity and neuroinflammation, promoting sleep, improving cognitive function and exerting anti-depressive effects

Philosophy on computational

Thanks to the knowledge of central dogma, it disclosed the basic life rules from replication, transcription, reverse transcription and translation of DNA. It maintains the general life process and responses the modification from inner and outer of body [83]. Several databases, such as GEO, GenBank etc., which collected the data from all over the world. This is not only an opportunity, but also a risk. Due to ununified samples and different design principles, the data we see may only one tip of iceberg.

Robust algorithm and powerful online platform

Due to numerous customized packaged developed and test in R, including sequencing [84], mapping [85], comparing [86], identifying [87], finding [25] and predicting [88]. More particular, the package named as "Bioconductor", so far there are 1714 packages. They can be classified into assay domain, biological question, annotation data, experiment data and workflow, which almost cover full aspects of bioinformatics. While many online platform developed to disclose the cellular pathway [89], including over-representation analysis tool, geneset enrichment analysis, network module-based pathway analysis. Furthermore, aim to get a comprehensive picture of changes, molecular network alteration became another emerging hot topic. For example, the network perturbation analysis, causal reasoning analysis, were developed as valuable complementary tools to conventional pathway analyses.

It is worth noting that no matter the robust code or powerful online platform, it is only handling the unique dataset. Because the experiment or trial on Parkinson's patient was customized, including the inclusive and exclusive criteria, specific intervention, biological sampling, samples processing method. Any kind of different middle term may introduce the variation. It furtherly strength the difficult in data merge. Therefor the current data only reflect one perspective, not comprehensive and globe view of the object. The reason behind may explain as the below cartoon, every investigator may report one fact based on his/her dataset. But another challenge remains, that is how to merge the data orderly

Big data need big idea

An obvious tendency accompanied with the big data is that the mainstream data are overload with much noise, and the discovery of the truths that underly big data poses various challenges. Here are some challenges remaining, such as the sample uniformity in different bioinformatic databases including DNA, RNA and metabolism. The biggest challenge is heterogeneity, the bioinformatic data were generated by different methods from different biological samples at different periods. Therefore, it is obvious that the principle of current data merge is not suitable or reliable. Even though comprehensive data were being introduced more and more under the surroundings of big data era, however, the error fact or noise were also being introduced.

Big data needs big idea. Traditional data analysis explain the modifications under a certain period with specific purpose. As for the Parkinson's Disease, the pathological changes occurred in time sequence. For example, with unknown etiologic reason, several toxins from environment such as rotenone, MPTP, paraquat, pesticide and heavy metal may induced the damage on structure of DNA, consequently, the balance between clearance and generation of alpha-synuclein was broken. The abnormal deposition of alpha-synuclein among neurons may reduce the depletion of dopamine. Consequently, the movement disorder may be presented from the early stage of PD, (Figure 2). Therefore, the concept of transomic is emerged. The integral data need to be drawn from different databases with unified samples, while the data flow needs to be merged or combined according to the time-series

Conclusion

Thanks to huge development of "-omic" studies, our understanding of PD grows rapidly as well. From the genomic perspective, to identifying and validating the key driver gene become a critical issue. Because more and more genes may be triggered and to modified the pattern of translation and transcription due to increased entropy, while it may be reported due to a single research. However, the general picture may missing. That is of importance to discover the key driver gene. While the treatment effect and adverse event of deep brain stimulation on PD receive great satisfactory from both patients and doctors. It has been serviced in front clinic for two decades. Numerous evidence validated the modification of electric field on micro-environment among neurons can be rearrange the dopamine distribution. Therefore, to rearrange and generate the neuron transmitters may become the new strategy to against the Parkinson's Disease. We place great expectations on these technologies to personalize treatment for patients with Parkinson's Disease.

Acknowledgements

We thank the Dr Huang Kun from Chengdu TME Co.,Ltd for providing a robust and valuable big data analysis. This work was supported by the Chengdu Medical College Natural Science Foundation

(CYZ18-08, CYZ18-20, CYZ18-33), the Sichuan Provincial Education Department (17ZA0134), the Sichuan Medical Association (S18023), and Sichuan undergraduate innovation and startup program funding support (S201913705080, S201913705130, S201913705059)

Conflict interest

The authors declare no potential conflict of interest with respect to research, authorship and/or publication of this manuscript.

Copyright and permission statement

To the best of our knowledge, the materials included in this chapter do not violate copyright laws. All original sources have been appropriately acknowledged and/or referenced. Where relevant, appropriate permissions have been obtained from the original copyright holder(s).

References

1. Benito-Leon J (2018) Epidemiology of Parkinson's disease in Spain and its contextualisation in the world. *Rev Neurol* 66: 125-134.
2. Dorsey ER, Elbaz A, Nichols E, Abd-Allah F, Abdelalim A, et al. (2018) Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 17: 939-953.
3. Pringsheim T, Jette N, Frolkis A, Steeves TD (2014) The prevalence of Parkinson's disease: A systematic review and meta-analysis. *Mov Disord* 29: 1583-1590.
4. Afentou N, Jarl J, Gerdtham UG, Saha S (2019) Economic Evaluation of Interventions in Parkinson's Disease: A Systematic Literature Review. *Mov Disord Clin Pract* 6: 282-290.
5. Wang G, Cheng Q, Zheng R, Tan YY, Sun XK, et al. (2006) Economic burden of Parkinson's disease in a developing country: a retrospective cost analysis in Shanghai, China. *Mov Disord: Movement Disorder Society* 21: 1439-1443.
6. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, et al. (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 24: 197-211.
7. Forno LS (1996) Neuropathology of Parkinson's disease. *J Neuropathol Exp Neurol* 55: 259-272.
8. Gaenslen A, Swid I, Liepelt-Scarfone I, Godau J, Berg D (2011) The patients' perception of prodromal symptoms before the initial diagnosis of Parkinson's disease. *Mov Disord: Movement Disorder Society* 26: 653-658.
9. Bridi JC, Hirth F (2018) Mechanisms of alpha-Synuclein Induced Synaptopathy in Parkinson's Disease. *Front Neurosci* 12: 80.
10. Lee HM, Koh SB (2015) Many Faces of Parkinson's Disease: Non-Motor Symptoms of Parkinson's Disease. *J Mov Disord* 8: 92-97.
11. Cabral-Miranda F, Hetz C (2018) ER Stress and Neurodegenerative Disease: A Cause or Effect Relationship? *Curr Top Microbiol Immunol* 414: 131-157.
12. Li SQ, Li WB, Zhang M, Wu YZ, Hu YY (2013) The role of neuroglobin in the neuroprotection of limb ischemic preconditioning in rats. *Mol Neurobiol* 47: 197-208.
13. Hemmati-Dinarvand M, Saedi S, Valilo M, Kalantary-Charvadeh A, Alizadeh Sani M, et al. (2019) Oxidative stress and Parkinson's disease: conflict of oxidant-antioxidant systems. *Neurosci Lett* 709: 134296.
14. Crotty GF, Ascherio A, Schwarzschild MA (2017) Targeting urate to reduce oxidative stress in Parkinson disease. *Exp Neurol* 298: 210-224.
15. Segura-Aguilar J (2019) On the Role of Aminochrome in Mitochondrial Dysfunction and Endoplasmic Reticulum Stress in Parkinson's Disease. *Front Neurosci* 13: 271.
16. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH (2010) Mechanisms underlying inflammation in neurodegeneration. *Cell* 140: 918-934.
17. Kalia LV, Lang AE (2015) Parkinson's disease. *Lancet* (London, England) 386: 896-912.
18. Hernandez DG, Reed X, Singleton AB (2016) Genetics in Parkinson disease: Mendelian versus non-Mendelian inheritance. *J Neurochem* 139: 59-74.
19. Konno T, Ross OA, Puschmann A, Dickson DW, Wszolek ZK (2016) Autosomal dominant Parkinson's disease caused by SNCA duplications. *Parkinsonism Relat Disord* 22: S1-S6.
20. Healy DG, Falchi M, O'Sullivan SS, Bonifati V, Durr A, et al. (2008) Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. *Lancet Neurol* 7: 583-590.
21. Rahman AA, Morrison BE (2019) Contributions of VPS35 Mutations to Parkinson's Disease. *Neuroscience* 401: 1-10.
22. Bonello F, Hassoun SM, Mouton-Liger F, Shin YS, Muscat A, et al. (2019) LRRK2 impairs PINK1/Parkin-dependent mitophagy via its kinase activity: pathologic insights into Parkinson's disease. *Human molecular genetics* 28: 1645-1660.
23. Bonifati V, Rizzu P, Squitieri F, Krieger E, Vanacore N, et al. (2003) DJ-1(PARK7), a novel gene for autosomal recessive, early onset parkinsonism. *Neurol Sci* 24: 159-160.
24. Bento CF, Ashkenazi A, Jimenez-Sanchez M, Rubinsztein DC (2016) The Parkinson's disease-associated genes ATP13A2 and SYT11 regulate autophagy via a common pathway. *Nat Commun* 7: 11803.
25. Chen R, Peng Y, Choi B, Xu J, Hu H (2014) A private DNA motif finding algorithm. *J biomed infor* 50: 122-132.
26. James KA, Hall DA (2015) Groundwater pesticide levels and the association with Parkinson disease. *Int J Toxicol* 34: 266-273.
27. Block ML, Elder A, Auten RL, Bilbo SD, Chen H, et al. (2012) The outdoor air pollution and brain health workshop. *Neurotoxicology* 33: 972-984.
28. Sarfo FS, Ovbiagele B (2017) Mobile health for stroke: a promising concept for research and practice. *m Health* 3: 4.
29. Chen CY, Hung HJ, Chang KH, Hsu CY, Muo CH, et al. (2017) Long-term exposure to air pollution and the incidence of Parkinson's disease: A nested case-control study. *PloS one* 12: e0182834.
30. Sauerbier A, Schrag A, Martinez-Martin P, Hall LJ, Parry M, et al. (2018) Dietary Variations in a Multiethnic Parkinson's Disease Cohort and Possible Influences on Nonmotor Aspects: A Cross-Sectional Multicentre Study. *Parkinson's disease* 2018: 7274085.
31. Vasconcelos AR, Dos Santos NB, Scavone C, Munhoz CD (2019) Nrf2/ARE Pathway Modulation by Dietary Energy Regulation in Neurological Disorders. *Front Pharmacol* 10: 33.
32. Gao X, Cassidy A, Schwarzschild MA, Rimm EB, Ascherio A (2012) Habitual intake of dietary flavonoids and risk of Parkinson disease. *Neurology* 78: 1138-1145.
33. Jan A, Jansonius B, Delaidelli A, Bhanshali F, An YA, et al. (2018) Activity of translation regulator eukaryotic elongation factor-2 kinase is increased in Parkinson disease brain and its inhibition reduces alpha synuclein toxicity. *Acta Neuropathol Commun* 6: 54.
34. Lavedan C, Leroy E, Torres R, Dehejia A, Dutra A, et al. (1998) Genomic organization and expression of the human beta-synuclein gene (SNCB). *Genomics* 54: 173-175.
35. Fuchs J, Tichopad A, Golub Y, Munz M, Schweitzer KJ, et al. (2008) Genetic variability in the SNCA gene influences alpha-synuclein levels in the blood and brain. *FASEB journal* 22: 1327-1334.
36. Alegre-Abarrategui J, Christian H, Lufino MM, Mutihac R, Venda LL, et al. (2009) LRRK2 regulates autophagic activity and localizes to specific membrane microdomains in a novel human genomic reporter cellular model. *Human molecular genetics* 18: 4022-4034.
37. Shehadeh LA, Yu K, Wang L, Guevara A, Singer C, et al. (2010) SRRM2, a potential blood biomarker revealing high alternative splicing in Parkinson's disease. *PloS one* 5: e9104.
38. Das F, Dey N, Venkatesan B, Kasinath BS, Ghosh-Choudhury N, et al. (2011) High glucose upregulation of early-onset Parkinson's disease protein DJ-1 integrates the PRAS40/TORC1 axis to mesangial cell hypertrophy. *Cell Signal* 23: 1311-1319.
39. Chung SJ, Armasu SM, Biernacka JM, Anderson KJ, Lesnick TG, et al. (2012) Genomic determinants of motor and cognitive outcomes in Parkinson's disease. *Parkinsonism Relat Disord* 18: 881-886.
40. Ng AC, Baird SD, Screaton RA (2014) High-content functional genomic screening to identify novel regulators of the PINK1-Parkin pathway. *Methods Enzymol* 547: 1-20.
41. Infante J, Prieto C, Sierra M, Sanchez-Juan P, Gonzalez-Aramburu I, et al. (2015) Identification of candidate genes for Parkinson's disease through blood transcriptome analysis in LRRK2-G2019S carriers, idiopathic cases, and controls. *Neurobiol Aging* 36: 1105-1109.
42. Infante J, Prieto C, Sierra M, Sanchez-Juan P, Gonzalez-Aramburu I, et al. (2016) Comparative blood transcriptome analysis in idiopathic and LRRK2 G2019S-associated Parkinson's disease. *Neurobiol Aging* 38: 214.e1-.e5.

43. Chikina MD, Gerald CP, Li X, Ge Y, Pincas H, et al. (2015) Low-variance RNAs identify Parkinson's disease molecular signature in blood. *Mov Disord : Movement Disorder Society* 30: 813-821.

44. Ambroziak W, Koziorowski D, Duszyc K, Gorka-Skoczylas P, Potulska-Chromik A, et al. (2015) Genomic instability in the PARK2 locus is associated with Parkinson's disease. *J Appl Genet* 56: 451-461.

45. Morais S, Bastos-Ferreira R, Sequeiros J, Alonso I (2016) Genomic mechanisms underlying PARK2 large deletions identified in a cohort of patients with PD. *Neurology Genetics* 2: e73.

46. Spataro N, Roca-Umbert A, Cervera-Carles L, Valles M, Anglada R, et al. (2017) Detection of genomic rearrangements from targeted resequencing data in Parkinson's disease patients. Mov Disord: *Movement Disorder Society* 32: 165-169.

47. Sevlever D, Jiang P, Yen SH (2008) Cathepsin D is the main lysosomal enzyme involved in the degradation of alpha-synuclein and generation of its carboxy-terminally truncated species. *Biochemistry* 47: 9678-9687.

48. Marques TM, van Rumund A, Bruinsma IB, Wessels H, Gloerich J, et al. (2018) Cerebrospinal Fluid Galectin-1 Levels Discriminate Patients with Parkinsonism from Controls. *Mol Neurobiol*.

49. Poschmann G, Seyfarth K, Besong Agbo D, Klafki HW, Rozman J, et al. (2014) High-fat diet induced isoform changes of the Parkinson's disease protein DJ-1. *J Proteome Res* 13: 2339-2351.

50. Majbour NK, Vaikath NN, van Dijk KD, Ardah MT, Varghese S, et al. (2016) Oligomeric and phosphorylated alpha-synuclein as potential CSF biomarkers for Parkinson's disease. *Mol Neurodegener* 11: 7.

51. Cole NB, Murphy DD, Grider T, Rueter S, Brasaemle D, (2002) Lipid droplet binding and oligomerization properties of the Parkinson's disease protein alpha-synuclein. *J Biol Chem* 277: 6344-6352.

52. Kulathingal J, Ko LW, Cusack B, Yen SH (2009) Proteomic profiling of phosphoproteins and glycoproteins responsive to wild-type alpha-synuclein accumulation and aggregation. *Biochim Biophys Acta* 1794: 211-224.

53. Beraud D, Hathaway HA, Trecki J, Chasovskikh S, Johnson DA, et al. (2013) Microglial activation and antioxidant responses induced by the Parkinson's disease protein alpha-synuclein. *J Neuroimmune Pharmacol* 8: 94-117.

54. Gitler AD, Bevis BJ, Shorter J, Strathearn KE, Hamamichi S, et al. (2008) The Parkinson's disease protein alpha-synuclein disrupts cellular Rab homeostasis. *Proc Natl Acad Sci USA* 105: 145-150.

55. Sinha A, Srivastava N, Singh S, Singh AK, Bhushan S, et al. (2009) Identification of differentially displayed proteins in cerebrospinal fluid of Parkinson's disease patients: a proteomic approach. *Clin Chim Acta* 400: 14-20.

56. Zhang X, Yin X, Yu H, Liu X, Yang F, et al. (2012) Quantitative proteomic analysis of serum proteins in patients with Parkinson's disease using an isobaric tag for relative and absolute quantification labeling, two-dimensional liquid chromatography, and tandem mass spectrometry. *The Analyst* 137: 490-495.

57. Licker V, Cote M, Lobrinus JA, Rodrigo N, Kovari E, et al. (2012) Proteomic profiling of the substantia nigra demonstrates CNDP2 overexpression in Parkinson's disease. *J Proteomics* 75: 4656-4667.

58. Davison EJ, Pennington K, Hung CC, Peng J, Rafiq R, et al. (2009) Proteomic analysis of increased Parkin expression and its interactants provides evidence for a role in modulation of mitochondrial function. *Proteomics* 9: 4284-4297.

59. Wongtrakul J, Saisawang C, Kumrapich B, Wipasa J, Roytrakul S, et al., (2018) Proteomic analysis of human glutathione transferase omega (hGSTO1) stable transfection in a 6-hydroxydopamine-induced neuronal cells. *Gen Physiol Biophys* 37: 141-152.

60. Salasova A, Yokota C, Potesil D, Zdrahal Z, Bryja V, et al. (2017) A proteomic analysis of LRRK2 binding partners reveals interactions with multiple signaling components of the WNT/PCP pathway. *Mol Neurodegener* 12: 54.

61. Lichtenberg M, Mansilla A, Zecchini VR, Fleming A, Rubinsztein DC (2011) The Parkinson's disease protein LRRK2 impairs proteasome substrate clearance without affecting proteasome catalytic activity. *Cell death & disease* 2: e196.

62. Pellegrini L, Hauser DN, Li Y, Mamais A, Beilina A, et al. (2018) Proteomic analysis reveals co-ordinated alterations in protein synthesis and degradation pathways in LRRK2 knockout mice. *Human molecular genetics* 27: 3257-3271.

63. Steger M, Diez F, Dhekne HS, Lis P, Nirujogi RS, et al. (2017) Systematic proteomic analysis of LRRK2-mediated Rab GTPase phosphorylation establishes a connection to ciliogenesis. *eLife* 6.

64. Canet-Aviles RM, Wilson MA, Miller DW, Ahmad R, McLendon C, et al. (2004) The Parkinson's disease protein DJ-1 is neuroprotective due to cysteine-sulfinic acid-driven mitochondrial localization. *Proc Natl Acad Sci USA* 101: 9103-9108.

65. Jiang H, Yu Y, Liu S, Zhu M, Dong X, et al. (2019) Proteomic Study of a Parkinson's Disease Model of Undifferentiated SH-SY5Y Cells Induced by a Proteasome Inhibitor. *Int J Med Sci* 16: 84-92.

66. Quinones MP, Kaddurah-Daouk R (2009) Metabolomics tools for identifying biomarkers for neuropsychiatric diseases. *Neurobiol Dis* 35: 165-176.

67. Roede JR, Uppal K, Park Y, Lee K, Tran V, et al. (2013) Serum metabolomics of slow vs. rapid motor progression Parkinson's disease: a pilot study. *PloS one* 8: e77629.

68. Jove M, Portero-Otin M, Naudi A, Ferrer I, Pamplona R (2014) Metabolomics of human brain aging and age-related neurodegenerative diseases. *J Neuropathol Exp Neurol* 73: 640-657.

69. Lu Z, Wang J, Li M, Liu Q, Wei D, et al. (2014) (1)H NMR-based metabolomics study on a goldfish model of Parkinson's disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *Chem Biol Interact* 223: 18-26.

70. Rango M (2015) Parkinson's disease: in vivo brain metabolomics by MRS. *Int Rev Neurobiol* 122: 81-94.

71. Lei S, Powers R (2013) NMR Metabolomics Analysis of Parkinson's Disease. *Current Metabolomics* 1: 191-209.

72. Weng R, Shen S, Tian Y, Burton C, Xu X, et al. (2015) Metabolomics Approach Reveals Integrated Metabolic Network Associated with Serotonin Deficiency. *Sci Rep* 5: 11864.

73. Chen X, Xie C, Sun L, Ding J, Cai H (2015) Longitudinal Metabolomics Profiling of Parkinson's Disease-Related alpha-Synuclein A53T Transgenic Mice. *PloS one* 10: e0136612.

74. Zheng H, Zhao L, Xia H, Xu C, Wang D, et al. (2016) NMR-Based Metabolomics Reveal a Recovery from Metabolic Changes in the Striatum of 6-OHDA-Induced Rats Treated with Basic Fibroblast Growth Factor. *Mol Neurobiol* 53: 6690-6697.

75. Phelan MM, Caamano-Gutierrez E, Gant MS, Grosman RX, Madine J (2017) Using an NMR metabolomics approach to investigate the pathogenicity of amyloid-beta and alpha-synuclein. *Metabolomics* 13: 151.

76. Luan H, Wang X, Cai Z (2019) Mass spectrometry-based metabolomics: Targeting the crosstalk between gut microbiota and brain in neurodegenerative disorders. *Mass Spectrom Rev* 38: 22-33.

77. Nagesh Babu G, Gupta M, Paliwal VK, Singh S, Chatterji T, et al. (2018) Serum metabolomics study in a group of Parkinson's disease patients from northern India. *Clin Chim Acta* 480: 214-219.

78. Nybo SE, Lamberts JT (2019) Integrated use of LC/MS/MS and LC/Q-TOF/MS targeted metabolomics with automated label-free microscopy for quantification of purine metabolites in cultured mammalian cells. *Purinergic Signal* 15: 17-25.

79. Glaab E, Trezzi JP, Greuel A, Jager C, Hodak Z, et al. (2019) Integrative analysis of blood metabolomics and PET brain neuroimaging data for Parkinson's disease. *Neurobiol Dis* 124: 555-562.

80. Shao Y, Le W (2019) Recent advances and perspectives of metabolomics-based investigations in Parkinson's disease. *Mol Neurodegener* 14: 3.

81. Okuzumi A, Hatano T, Ueno SI, Ogawa T, Saiki S, et al. (2019) Metabolomics-based identification of metabolic alterations in PARK2. *Ann Clin Transl Neurol* 6: 525-536.

82. Huang W, Xu Y, Zhang Y, Zhang P, Zhang Q, et al. (2019) Metabolomics-driven identification of adenosine deaminase as therapeutic target in a mouse model of Parkinson's disease. *J Neurochem*.

83. Liu CC, Jewett MC, Chin JW, Voigt CA (2018) Toward an orthogonal central dogma. *Nat Chem Biol* 14: 103-106.

84. Krall A, Brunn J, Kankanala S, Peters MH (2014) A simple contact mapping algorithm for identifying potential peptide mimetics in protein-protein interaction partners. *Proteins* 82: 2253-2262.

85. Flower R, Roulis E, Hyland C (2018) Whole-genome sequencing algorithm for blood-group typing. *Lancet Haematol* 5: e233-e234.

86. Swerdel JN, Hripcsak G, Ryan PB (2019) FPheValuator: Development and Evaluation of a Phenotype Algorithm Evaluator. *J Biomed Inform* 2019: 103258.

87. Naor Z, Yeshurun Y, Myslobodsky M (1996) Bilateral comparison of occipital lobe sulci: a sulcus identifying algorithm. *Neuropsychol Rev* 6: 95-105.

88. Wang L, Sha L, Lakin JR, Bynum J, Bates DW, et al. (2019) Development and Validation of a Deep Learning Algorithm for Mortality Prediction in Selecting Patients with Dementia for Earlier Palliative Care Interventions. *JAMA Netw Open* 2: e196972.

89. Glaab E (2018) Computational systems biology approaches for Parkinson's disease. *Cell Tissue Res* 373: 91-109.