Genomics Proteomics Bioinformatics xxx (2016) xxx–xxx

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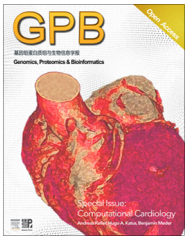

REVIEW

Toward Personalized Intervention for Alzheimer's Disease

Xing Peng [1,2,a], Peiqi Xing [1,2,b], Xiuhui Li [1,2,c], Ying Qian [1,2,d], Fuhai Song [1,2,e], Zhouxian Bai [1,2,f], Guangchun Han [1,g], Hongxing Lei [1,2,3,*,h]

[1] *CAS Key Laboratory of Genome Sciences and Information, Beijing Institute of Genomics, Chinese Academy of Sciences, Beijing 100101, China*
[2] *Cunji Medical School, University of Chinese Academy of Sciences, Beijing 100049, China*
[3] *Center of Alzheimer's Disease, Beijing Institute for Brain Disorders, Beijing 100053, China*

Received 18 December 2015; revised 14 January 2016; accepted 31 January 2016
Available online xxxx

Handled by Ge Gao

KEYWORDS

Alzheimer's disease;
Demographic information;
Genome;
Peripheral biomarkers;
iPSC technology

Abstract **Alzheimer's disease** (AD) remains to be a grand challenge for the international community despite over a century of exploration. A key factor likely accounting for such a situation is the vast heterogeneity in the disease etiology, which involves very complex and divergent pathways. Therefore, intervention strategies shall be tailored for subgroups of AD patients. Both demographic and in-depth information is needed for patient stratification. The **demographic information** includes primarily *APOE* genotype, age, gender, education, environmental exposure, life style, and medical history, whereas in-depth information stems from **genome** sequencing, brain imaging, **peripheral biomarkers**, and even functional assays on neurons derived from patient-specific induced pluripotent cells (iPSCs). Comprehensive information collection, better understanding of the disease mechanisms, and diversified strategies of drug development would help with more effective intervention in the foreseeable future.

Introduction

Alzheimer's disease (AD) is one of the leading causes of death in senior people. Caring for AD patients with deteriorating cognitive and daily functions poses a great economic and psychological burden for the families as well as society. Initially discovered in 1906, the pathological hallmarks of AD, namely amyloid plaques and neurofibrillary tangles, have been well documented over a century. However, little had been known about the disease mechanisms at molecular level until the identification of the gene encoding amyloid precursor protein

* Corresponding author.
E-mail: leihx@big.ac.cn (Lei H).
[a] ORCID: 0000-0002-3645-8115.
[b] ORCID: 0000-0002-5675-1036.
[c] ORCID: 0000-0002-9808-1173.
[d] ORCID: 0000-0002-4622-1904.
[e] ORCID: 0000-0003-0848-8349.
[f] ORCID: 0000-0001-7071-666X.
[g] ORCID: 0000-0001-9277-2507.
[h] ORCID: 0000-0003-0496-0386.

Peer review under responsibility of Beijing Institute of Genomics, Chinese Academy of Sciences and Genetics Society of China.

http://dx.doi.org/10.1016/j.gpb.2016.01.006

Please cite this article in press as: Peng X et al, Toward Personalized Intervention for Alzheimer's Disease. Genomics Proteomics Bioinformatics (2016), http://dx.doi.org/10.1016/j.gpb.2016.01.006

(*APP*) and the genetic mutations causing familial AD [1,2]. Nonetheless, familial AD only constitutes ~2% of AD patients [3], while the vast majority of AD cases are not caused by the genetic mutations affecting the coding or processing of *APP*. For sporadic AD, the molecular pathogenesis seems to be far from understood as yet.

Up till now, only four drugs have been approved for AD treatment by the Food and Drug Administration (FDA) in USA and its counterparts in Europe [4]. These drugs target neural transmission and are all used for symptom relief, sometimes even with unbearable side effects. They are unable to modify the disease trajectory, not even slowing down the disease progression. Therefore, the "neural transmission" hypothesis for AD has not been well supported by the human trials, and deficiency in neural transmission may merely be a downstream and symptomatic problem in AD. In the past couple of decades, most of the efforts on drug development have been devoted to the clearance of amyloid or the aggregating oligomers, which is believed to be a major causal factor according to the "amyloid cascade hypothesis" [5]. Although recent studies targeting amyloid showed marginal progress in the early stage AD [6,7], most of the clinical trials along this line have been very disappointing. Beyond amyloid clearance, other prevention or treatment strategies have also been initiated with no conclusive evidence of success so far [8].

To achieve more positive outcome, better patient stratification shall be adopted in the future based on comprehensive collection of patient information. The details will be discussed in the following sections (**Figure 1**).

Demographic information for AD

Currently, the well-recognized demographic information about AD includes *APOE* genotype, age, gender, education, environmental exposure, life style, and medical history.

APOE genotype

APOE ε4 allele is the major genetic risk of sporadic AD, which confers risks 3–4 folds higher for people carrying one ε4 allele and ~10 folds higher for peoples carrying two ε4 alleles compared to non-carriers [2]. Although mainly viewed as a gene involved in the lipid metabolism pathway, *APOE* seems to be associated with many AD-related processes. Most notably, *APOE* is involved in amyloid β (Aβ) metabolism and amyloid clearance [9]. *APOE* may also be involved in brain development. For example, infants carrying *APOE* ε4 allele have different brain structure compared to non-carriers [10]. The altered brain structures at early developmental stage may confer susceptibility for AD at the old age. *APOE* ε4 genotype is also associated with reduced glucose metabolism in the brain independent of amyloid aggregation [11]. Since deficiency in energy metabolism is considered as one of the major upstream factors in AD pathogenesis, this study suggests that *APOE* genotype itself can be a causal factor for AD. Thus, AD patients with 0, 1, or 2 ε4 alleles may follow different paths to the disease stage and therefore shall be treated differently. Due to the critical roles of *APOE* in the development of

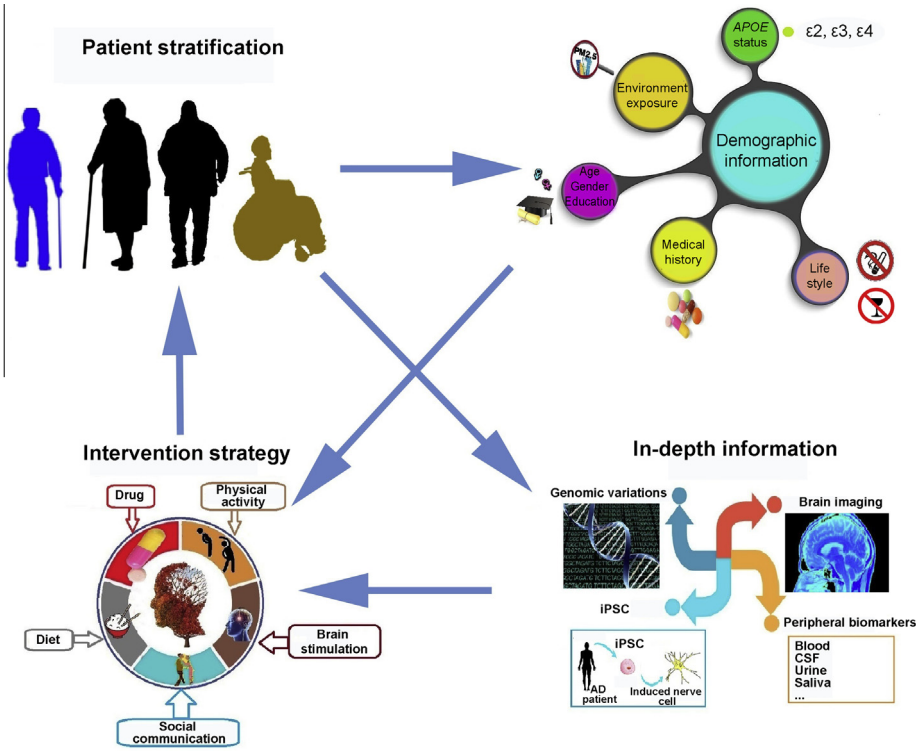

Figure 1 Path from patient stratification to personalized intervention for AD

Collection of demographic information is the basis for patient stratification. Incorporation of in-depth information will greatly facilitate the design of personalized intervention. AD, Alzheimer's disease; iPSC, induced pluripotent stem cell; CSF, cerebrospinal fluid; PM 2.5, particulate matter (⩽2.5 μm).

Please cite this article in press as: Peng X et al, Toward Personalized Intervention for Alzheimer's Disease. Genomics Proteomics Bioinformatics (2016), http://dx.doi.org/10.1016/j.gpb.2016.01.006