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Commentary

The Chromosomal Conformation Signature: A New Kid on the Block in ALS Biomarker Research?

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Salter and colleagues introduce the concept of a chromosomal conformation signature (or CCS) as a candidate biomarker in ALS [1]. Such a signature is achieved by employing a high resolution technology that detects structural epigenetic changes throughout the genomic architecture. Epigenetic changes include among others DNA methylation and histone post-translational modifications, resulting in chromatin remodeling (an open chromatin structure (euchromatin) versus a compact chromatin structure (heterochromatin)) possibly leading to a higher or lower accessibility to the genome [2].

Salter and colleagues now evaluated the CCS in patients with ALS. An individual potential chromosomal confirmation can be absent or present in a cell, and if present, the abundancy of this phenotype can be quantified in a biological sample. An microarray was now designed to pick up the presence of 13,880 potential chromosome confirmations across 308 selected loci, primarily related to ALS's immune-footprint. 153 biomarkers were selected out of this array, based on the ability to distinguish between ALS and healthy controls, and translated into PCR based-detection probes for this CCS-biomarker set. These probes were then employed to evaluate the CCS-biomarker profile between patients with ALS and healthy controls. A distinct CCS profile, containing 8 genomic loci, was observed in blood of patients with ALS, discriminating these patients from healthy controls with a sensitivity and specificity of 83 to 88% and 75 to 77%, respectively.

The field of ALS would greatly benefit from a biomarker that could speed up the diagnosis of ALS. Clinical diagnostic guidelines combined with electromyography enable to eventually diagnose ALS [3]. However, the median diagnostic delay in ALS, indicating the time span between onset of symptoms and the final diagnosis, is 10 months or so, which is on average about one third to one fifth of the survival time after onset [4]. For clinical trials, an earlier diagnosis would facilitate the inclusion of patients in the early stage of the disease, which is hypothesized to yield a higher therapeutic efficacy than if patients are included in the more advanced stage of the disease.

It is of interest to further evaluate the diagnostic performance of the CCS-biomarker set. For this matter, retrospective and prospective biomarker studies into the early phase of ALS should be designed, including also proper control cohorts. Furthermore, the added diagnostic value of CCS-biomarkers to current, yet novel, biomarkers for ALS, including the phosphorylated neurofilament heavy chains, should be addressed [4–6]. It is yet to be understood if CCS profiles in blood are specifically related to motor neuron degeneration, or are bystanders of disease. Furthermore, it is important to rule out if any epigenetic changes are primarily driven by known and prevalent genetic causes of ALS.

Epigenetic mechanisms have been reported to underlie several human neurological disorders including epilepsy, Alzheimer's disease (AD), Huntington's disease (HD) and ALS [7]. In aging and HD, for example, reduced levels of histone modifications are noticed usually associated with open chromatin structure [7]. In AD, the alterations appear to be distinct with global losses of heterochromatin marks, which is the compact form of chromatin resistant to the binding of various proteins of the transcriptional machinery, as well as locus-specific losses and gains of activating marks [7]. Evidence is emerging that histone modifications, altered chromatin regulation and distinct DNA methylation might be involved in the pathophysiology of ALS [7–10]. Many observed defects in ALS remained largely unexplained, offering an opportunity to the field of epigenetics in ALS. Although the current study was not designed to reflect strong epigenetic changes at the CCS level genome-wide, it encourages the identification of novel epigenetic changes to be linked to pathophysiological changes in ALS via e.g. an unbiased Next-Generation Sequencing approach. Indeed, the heterogeneity of ALS, reflected by a varying age of onset, site of onset, disease progression rate and survival is yet to be understood. Therefore, it is of interest to explore if CCS profiles in ALS are related to these parameters. It is exciting to see if these CCS profiles in blood withstand as a reflection of a central neurodegenerative process.

Finally, epigenetics could further nourish the link between ALS and frontotemporal lobar degeneration (FTLD). Recent insights suggest that genes with a specific DNA-methylation pattern are involved in pathways common to ALS and FTLD [9,10]. It is to be expected if deep epigenetic screening offers additional hits that link ALS to FTLD, possibly contributing to further understand the underlying mechanisms of behavioral variants in ALS.

Altogether, Salter and colleagues offer an attractive tool to detect structural related epigenetic changes in ALS, which opens a new research avenue to better understand the clinical heterogeneity in ALS.

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Disclosure

KP has employed in a previous publication an immunoassay for pNfH provided by Euroimmun AG (Lübeck, Germany).

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