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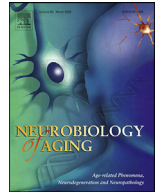
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Brief communication

CSF sTREM2 is elevated in a subset in GRN-related frontotemporal dementia

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ABSTRACT

Excessive microglial activation might be a central pathological process in GRN-related frontotemporal dementia (FTD-GRN). We measured soluble triggering receptor expressed on myeloid cells 2 (sTREM2), which is shed from disease-associated microglia following cleavage of TREM2, in cerebrospinal fluid of 34 presymptomatic and 35 symptomatic GRN mutation carriers, 6 presymptomatic and 32 symptomatic C9orf72 mutation carriers and 67 healthy noncarriers by ELISA. Although no group differences in sTREM2 levels were observed (GRN: symptomatic (median 5.2 ng/mL, interquartile range [3.9–9.2]) vs. presymptomatic (4.3 ng/mL [2.6–6.1]) vs. noncarriers (4.2 ng/mL [2.6–5.5]); $p = 0.059$; C9orf72: symptomatic (4.3 [2.9–7.0]) vs. presymptomatic (3.2 [2.2–4.2]) vs. noncarriers: $p = 0.294$), high levels were seen in a subset of GRN, but not C9orf72, mutation carriers, which might reflect differential TREM2-related microglial activation. Interestingly, 2 presymptomatic carriers with low sTREM2 levels developed symptoms after 1 year, whereas 2 with high levels became symptomatic after >5 years. While sTREM2 is not a promising diagnostic biomarker for FTD-GRN or FTD-C9orf72, further research might elucidate its potential to monitor microglial activity and predict disease progression.

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1. Introduction

Frontotemporal dementia (FTD) is frequently caused by autosomal dominant genetic mutations in granulin (GRN).

Although the exact mechanisms by which GRN mutations lead to FTD are poorly understood, accumulating evidence suggests a role for dysregulation of microglial homeostasis (Bright et al., 2019; Chitramuthu et al., 2017). GRN^{-/-} mice display excessive microglial activation with subsequent release of proinflammatory factors and neuronal loss (Lui et al., 2016; Martens et al., 2012; Tanaka et al., 2013), and suppression of genes characteristic for homeostatic microglia

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(Götzl et al., 2019), whereas *GRN* overexpression reduces microglial recruitment following nerve injury (Altmann et al., 2016). Biomarkers that accurately reflect microglial activity *in vivo* are currently lacking and might provide more insight into disease pathogenesis, as well as measure treatment effect in clinical trials aiming to restore immune dysregulation.

Triggering receptor expressed on myeloid cells 2 (TREM2) is a membrane-bound receptor expressed by microglia which regulates the transition from homeostatic to disease-associated microglia (Keren-Shaul et al., 2017; Kleinberger et al., 2014; Schlepckow et al., 2017). Cleavage of its extracellular domain produces a soluble fragment, sTREM2, which is measurable in cerebrospinal fluid (CSF) (Piccio et al., 2008). CSF sTREM2 levels likely reflect cerebral TREM2 expression and TREM2-triggered microglial activity (Ewers et al., 2020; Ewers et al., 2019; Keren-Shaul et al., 2017; Suárez-Calvet et al., 2019). Elevated sTREM2 levels have been observed mainly in the prodromal stages of Alzheimer's disease (AD) (Liu et al., 2018; Ma et al., 2020; Suárez-Calvet et al., 2019). Reports of sTREM2 levels in FTD are inconsistent (Heslegrave et al., 2016; Kleinberger et al., 2014; Piccio et al., 2016), but high levels have been reported in a few FTD-*GRN* cases (Woollacott et al., 2018).

In the present study, we measured CSF sTREM2 in an international cohort of presymptomatic and symptomatic *GRN* mutation carriers and noncarriers to determine its value as a biomarker in FTD-*GRN*. To study potential gene-specificity, we additionally measured sTREM2 in carriers of a *C9orf72* repeat expansion, the most common genetic cause of FTD.

2. Methods

Subjects were recruited from 8 research centers in Europe and the USA through familial FTD studies. We included 34 presymptomatic and 35 symptomatic *GRN* mutation carriers, 6 presymptomatic and 32 symptomatic *C9orf72* mutation carriers, and 67 healthy noncarriers from *GRN* or *C9orf72* mutation families. Subjects were classified as symptomatic if they met international consensus criteria for behavioral variant FTD, primary progressive aphasia or amyotrophic lateral sclerosis (ALS) (Brooks et al., 2000; Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Symptom onset and disease duration were based on caregivers' estimations of the emergence of first symptoms. Subjects had no known neurological or immunological co-morbidities. Global cognitive functioning was scored using the Mini Mental State Examination (MMSE).

CSF was collected in polypropylene tubes, centrifuged and stored at -80°C within 2 hours after withdrawal. sTREM2 levels were measured using an ELISA as previously described (Kleinberger et al., 2014). Samples were randomly distributed across plates and measured in duplicate; the median coefficient of variation (CV) of duplicate samples was 3.6%. One sample with a duplicate CV $> 15\%$ was excluded. Samples were measured in 2 batches (median between-batch CV 4%) in the German Center for Neurodegenerative Diseases (DZNE), Munich, Germany. Laboratory technicians were blinded to all clinical and genetic information.

Statistical analyses were performed in IBM SPSS Statistics 24 applying a significance level of 0.05 (2-sided). Demographic variables were compared using Kruskal-Wallis tests for numerical variables and χ^2 tests for categorical variables. Group comparisons of sTREM2 levels were performed by Mann Whitney U tests or Kruskal-Wallis tests as the data were not normally distributed. After log-transformation, sTREM2 levels were normally distributed, as confirmed by the Shapiro-Wilk test, and group comparisons were additionally performed by ANCOVA with correction for age, gender and assay batch. Spearman's rho was used for correlative

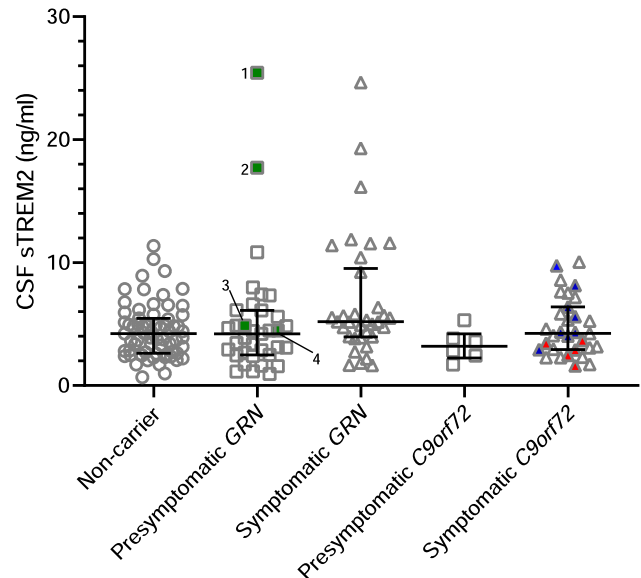


Fig. 1. sTREM2 levels in presymptomatic and symptomatic mutation carriers and noncarriers. Error bars represent median \pm interquartile range. Red and blue triangles indicate subjects with isolated or concomitant amyotrophic lateral sclerosis, respectively. Green squares indicate subjects who developed symptoms after CSF collection; subject 1 developed FTD with corticobasal syndrome after 7 years; subject 2 suffered cognitive decline after 5 years; subject 3 developed memory-predominant FTD after 1.2 years; subject 4 developed behavioral variant FTD after 1 year. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

analyses. Bonferroni correction for multiple testing was applied where appropriate.

3. Results

3.1. Demographics

Subject characteristics are shown in Table 1. In both genetic groups (*GRN* and *C9orf72*), symptomatic mutation carriers were older at CSF collection than presymptomatic carriers and noncarriers ($p < 0.001$). sTREM2 levels were positively correlated with age across the entire cohort ($r_s = 0.271$, $p < 0.001$) and in non-carriers alone ($r_s = 0.247$, $p = 0.044$) but not in symptomatic *GRN* or *C9orf72* mutation carriers (*GRN*: $r_s = 0.020$, $p = 0.911$; *C9orf72*: $r_s = 0.206$, $p = 0.258$) (supplementary Fig. 1). No differences were found in sTREM2 levels between males and females ($p = 0.470$).

3.2. sTREM2 levels in *GRN* mutation carriers

No significant differences in sTREM2 levels were seen in symptomatic *GRN* mutation carriers (median 5.2 ng/mL, interquartile range [3.9–9.2]) compared to presymptomatic carriers (4.3 ng/mL [2.6–6.1]) and noncarriers (4.2 ng/mL [2.6–5.5]) ($p = 0.059$ by Kruskal-Wallis test; $p = 0.513$ by ANCOVA) (Fig. 1). sTREM2 levels did not correlate with disease duration ($r_s = 0.210$, $p = 0.226$) or MMSE score ($r_s = -0.364$, $p = 0.057$, $n = 28$) among symptomatic carriers. Furthermore, no significant differences in sTREM2 levels were seen between the various FTD phenotypes ($p = 0.830$) (Table 1).

Three presymptomatic *GRN* mutation carriers developed FTD respectively 1 year, 1.2 years, and 7 years after CSF collection (Fig. 1). In addition, one presymptomatic *GRN* carrier developed mild behavioral abnormalities and cognitive deficits 5 years after CSF col-

Table 1

Subject characteristics. All continuous variables are reported as medians (interquartile range).

N	GRN mutation carriers		C9orf72 mutation carriers		Noncarriers	p
	Symptomatic ^a	Presymptomatic	Symptomatic ^b	Presymptomatic		
	35	34	32	6	67	-
Gender, male (%)	16 (46%)	15 (44%)	18 (56%)	0 (0%)	27 (40%)	0.132 ^c
Age at CSF collection, years	61 (57–65)	51 (41–59)	62 (54–67)	34 (26–43)	54 (42–59)	<0.001 ^d
Disease duration, years	2.0 (1.5–3.1)	-	1.9 (0.7–5.1)	-	-	0.672
MMSE	23 (18–27)	29 (29–30)	26 (22–28)	29 (29–30)	30 (29–30)	<0.001 ^d
sTREM2 (ng/mL)	5.2 (3.9–9.2)	4.3 (2.6–6.1)	4.3 (2.9–7.0)	3.2 (2.2–4.2)	4.2 (2.6–5.5)	0.090 ^e

Abbreviations: CSF, cerebrospinal fluid; MMSE, mini mental state examination.

^a Phenotypes: behavioral variant FTD (bvFTD) ($n = 20$), primary progressive aphasia (PPA) ($n = 8$), dementia not otherwise specified ($n = 4$), memory-predominant FTD ($n = 2$), and FTD with corticobasal syndrome (CBS) ($n = 1$).^b Phenotypes: bvFTD ($n = 13$), PPA ($n = 3$), FTD with amyotrophic lateral sclerosis (ALS) ($n = 9$), ALS ($n = 5$), memory-predominant FTD ($n = 1$), and FTD with CBS ($n = 1$).^c By χ^2 test.^d In both genetic groups, symptomatic mutation carriers were older and had lower MMSE scores than presymptomatic carriers and noncarriers (all comparisons $p < 0.001$). There were no significant differences in age or MMSE between symptomatic GRN and C9orf72 carriers (by Mann-Whitney U tests).^e By Kruskal-Wallis test across all groups.

lection, although clinical diagnostic criteria for FTD were not fulfilled.

Visual inspection of Fig. 1 revealed high sTREM2 levels in 8 symptomatic GRN mutation carriers (>10 ng/mL). We did not identify any association with specific clinical or genetic features in these subjects (i.e., disease severity or duration, phenotype, age at symptom onset, genetic mutation) (supplementary Table 1).

3.3. sTREM2 levels in C9orf72 mutation carriers

No significant differences in sTREM2 levels were seen between symptomatic (median 4.3 ng/mL [2.9–7.0]) and presymptomatic (3.2 ng/mL [2.2–4.2]) C9orf72 mutation carriers or noncarriers ($p = 0.294$ by Kruskal-Wallis test; $p = 0.433$ by ANCOVA) (Fig. 1). Results were unchanged after exclusion of subjects with isolated ALS ($n = 4$) or FTD with ALS ($n = 9$). sTREM2 levels did not correlate with disease duration ($r_s = 0.199$, $p = 0.275$) or MMSE score ($r_s = -0.037$, $p = 0.856$, $n = 27$) among symptomatic carriers.

3.4. Comparison between GRN and C9orf72 mutation carriers

sTREM2 levels did not differ between symptomatic GRN and C9orf72 mutation carriers ($p = 0.196$) or between presymptomatic GRN and C9orf72 mutation carriers ($p = 0.288$) (both by Mann-Whitney U tests).

4. Discussion

The present study revealed no significant differences in CSF sTREM2 levels between presymptomatic and symptomatic GRN or C9orf72 mutation carriers and noncarriers. Although the lack of group differences and overlap in sTREM2 levels between groups preclude its value as a diagnostic biomarker, a remarkable degree of variability in sTREM2 levels was observed among GRN mutation carriers, which warrants further study.

Several GRN mutation carriers had very high sTREM2 levels, whereas sTREM2 levels among C9orf72 carriers and noncarriers appeared to be more consistent, which is in line with previous findings (Woollacott et al., 2018). These high levels are unlikely to be measurement errors given the favorable assay characteristics (Kleinberger et al., 2014) and low inter-plate and duplicate CVs. Elevated CSF sTREM2 levels are thought to reflect increased TREM2-dependent microglial activation, a hypothesis that is supported by more convincingly elevated levels in typical neuroinflammatory diseases such as multiple sclerosis (Piccio et al., 2008) and by a

correlation between brain sTREM2 levels and microglial activity on TSPO-PET imaging in mouse models (Brendel et al., 2017). Our findings might therefore reflect a variable degree of microglial involvement specifically among GRN mutation carriers. The identification of subsets of carriers with more or less microglial activation would be highly valuable for patient stratification in inflammation-directed clinical trials. Interestingly, much variability has also been observed for the microglia-derived proteins YKL-40 and chitotriosidase (CHIT-1) in FTD (Abu-Rumeileh et al., 2019; Oeckl et al., 2019; Woollacott et al., 2020) and future studies that elucidate the relationship between these proteins in FTD-GRN would be of interest.

Three presymptomatic GRN mutation carriers developed FTD after CSF collection, and cognitive decline was reported in one. Interestingly, 2 of these subjects with very high sTREM2 levels only developed symptoms several years after CSF collection, while 2 subjects with low sTREM2 levels declined within 2 years. It is tempting to speculate that increased microglial activity and accordingly, high sTREM2 levels, in the late-presymptomatic stage might delay disease onset. In mild cognitive impairment and AD, higher CSF sTREM2 levels have been associated with reduced rates of clinical decline and attenuated amyloid- β accumulation on amyloid PET imaging, suggesting that TREM2-related processes might play a protective role (Ewers et al., 2020; Ewers et al., 2019; Franzmeier et al., 2020). In line with these findings, increased microglial activation on TSPO-PET imaging predicted slower disease progression in (prodromal) AD (Hamelin et al., 2018). Such associations require further study in a much larger cohort of FTD-GRN patients, and could be highly relevant for clinical trial design as they could potentially confound outcome measures, i.e., slow progression rates could falsely be attributed to the study drug.

The positive correlation between sTREM2 levels and age is in line with previous studies (Ma et al., 2020; Piccio et al., 2016; Suárez-Calvet et al., 2016; Suárez-Calvet et al., 2019; Woollacott et al., 2018) and is thought to reflect physiological age-related microglial activity (Heneka et al., 2014; Kleinberger et al., 2017). Although we cannot rule out that co-existence of other (asymptomatic) neurodegenerative diseases such as AD might have affected sTREM2 levels in our cohort, several studies have found no correlation between sTREM2 levels and CSF amyloid- β (Piccio et al., 2016; Suárez-Calvet et al., 2016; Suárez-Calvet et al., 2019); therefore, the effect of concomitant amyloid pathology on sTREM2 levels in the present study is probably limited.

Neuroinflammation is thought to be the result of a highly complex and dynamic interaction between many factors (Bright et al., 2019). Different disease stages might be characterized by variable

degrees of microglial activation and subsequent sTREM2 shedding, making group comparisons difficult to interpret. This is exemplified by findings of elevated sTREM2 levels in preclinical and early-stage AD, followed by slightly attenuated levels in later disease stages (Liu et al., 2018; Ma et al., 2020; Suárez-Calvet et al., 2019). Longitudinal measurements of sTREM2 in FTD-GRN might provide insights into its dynamics over the course of disease as well as determine its value as a disease monitoring marker.

A major strength of this study is the inclusion of presymptomatic and symptomatic carriers of GRN and C9orf72 mutations, as opposed to clinically diagnosed FTD patients, enabling investigation of well-defined, pathologically homogeneous cohorts. Limitations include the relatively small sample size, which may have affected statistical power to detect group differences. Furthermore, the MMSE score might not be an optimal measure of disease severity in FTD, however it is a highly standardized instrument which we feel provides a suitable cognitive screening for this multicenter study. Finally, we cannot rule out that some subjects may have carried rare genetic variants in TREM2, which are known to affect sTREM2 levels (Kleinberger et al., 2014; Suárez-Calvet et al., 2019).

In conclusion, while sTREM2 is of limited diagnostic utility in FTD-GRN, its further study might help to elucidate the role of neuroinflammation in FTD pathogenesis. It would be interesting to further characterize the small number of GRN mutation carriers with very high sTREM2 levels and to investigate sTREM2 dynamics over the course of disease through longitudinal measurements.

Disclosure statement

C.H. collaborates with Denali Therapeutics, participated in one advisory board meeting of Biogen and received a speaker honorarium from Novartis and Roche. C.H. is chief advisor of ISAR Bioscience. The remaining authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2021.02.024.

References

Abu-Rumeileh, S., Steinacker, P., Polisch, B., Mammana, A., Bartoletti-Stella, A., Oeckl, P., Baiardi, S., Zenesini, C., Huss, A., Cortelli, P., Capellari, S., Otto, M., Pardi, P., 2019. CSF biomarkers of neuroinflammation in distinct forms and subtypes of neurodegenerative dementia. *Alzheimers Res Ther* 12 (1), 2.

Altmann, C., Vasic, V., Hardt, S., Heidler, J., Häussler, A., Wittig, I., Schmidt, M.H.H., Tegeer, I., 2016. Progranulin promotes peripheral nerve regeneration and reinnervation: role of notch signaling. *Mol Neurodegener* 11 (1), 69.

Brendel, M., Kleinberger, G., Probst, F., Jaworska, A., Overhoff, F., Blume, T., Albert, N.L., Carlsen, J., Lindner, S., Gildehaus, F.J., Ozmen, L., Suárez-Calvet, M., Bartenstein, P., Baumann, K., Ewers, M., Herms, J., Haass, C., Rominger, A., 2017. Increase of TREM2 during aging of an Alzheimer's disease mouse model is paralleled by microglial activation and amyloidosis. *Front Aging Neurosci* 9, 8.

Bright, E., Werry, E.L., Dobson-Stone, C., Piguat, O., Ittner, L.M., Halliday, G.M., Hodges, J.R., Kiernan, M.C., Loy, C.T., Kassioti, M., Kril, J.J., 2019. Neuroinflammation in frontotemporal dementia. *Nat Rev Neurol* 15 (9), 540–555.

Brooks, B.R., Miller, R.G., Swash, M., Mansat, T.L. World Federation of Neurology Research Group on Motor Neuron, D., 2000. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 1 (5), 293–299.

Chitramuthu, B.P., Bennett, H.P.J., Bateman, A., 2017. Progranulin: a new avenue towards the understanding and treatment of neurodegenerative disease. *Brain* 140 (12), 3081–3104.

Ewers, M., Biechele, G., Suárez-Calvet, M., Sacher, C., Blume, T., Morenas-Rodríguez, E., Deming, Y., Piccio, L., Cruchaga, C., Kleinberger, G., Shaw, L., Trojanowski, J.Q., Herms, J., Dichgans, M., Alzheimer's Disease Neuroimaging, 2020. Higher CSF sTREM2 and microglia activation are associated with slower rates of beta-amyloid accumulation. *EMBO Mol Med* 12 (9), e12308.

Ewers, M., Franzmeier, N., Suárez-Calvet, M., Morenas-Rodríguez, E., Caballero, M.A.A., Kleinberger, G., Piccio, L., Cruchaga, C., Deming, Y., Dichgans, M., Trojanowski, J.Q., Shaw, L.M., Weiner, M.W., Haass, C., Alzheimer's Disease Neuroimaging, I., 2019. Increased soluble TREM2 in cerebrospinal fluid is associated with reduced cognitive and clinical decline in Alzheimer's disease. *Sci Transl Med* 11 (507).

Franzmeier, N., Suárez-Calvet, M., Frontzkowski, L., Moore, A., Hohman, T.J., Morenas-Rodríguez, E., Nuscher, B., Shaw, L., Trojanowski, J.Q., Dichgans, M., Kleinberger, G., Haass, C., Ewers, M., Alzheimer's Disease Neuroimaging, I., 2020. Higher CSF sTREM2 attenuates ApoE4-related risk for cognitive decline and neurodegeneration. *Mol Neurodegener* 15 (1), 57.

Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S.F., Ogar, J.M., Rohrer, J.D., Black, S., Boeve, B.F., Manes, F., Dronkers, N.F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B.L., Knopman, D.S., Hodges, J.R., Mesulam, M.M., Grossman, M., 2011. Classification of primary progressive aphasia and its variants. *Neurology* 76 (11), 1006–1014.

Götzl, J.K., Brendel, M., Werner, G., Parhizkar, S., Sebastian Monasor, L., Kleinberger, G., Colombo, A.V., Deussing, M., Wagner, M., Winkelmann, J., Diehl-Schmid, J., Levin, J., Fellerer, K., Reifschneider, A., Bultmann, S., Bartenstein, P., Rominger, A., Tahirovic, S., Smith, S.T., Madore, C., Butovsky, O., Capell, A., Haass, C., 2019. Opposite microglial activation stages upon loss of PGRN or TREM2 result in reduced cerebral glucose metabolism. *EMBO Mol Med* 11 (6), e9711. doi:10.15252/emmm.201809711.

Hamelin, L., Lagarde, J., Dorothée, G., Potier, M.C., Corlier, F., Kuhnast, B., Caillé, F., Dubois, B., Fillon, L., Chupin, M., Bottlaender, M., Sarazin, M., 2018. Distinct dynamic profiles of microglial activation are associated with progression of Alzheimer's disease. *Brain* 141 (6), 1855–1870.

Heneka, M.T., Kummer, M.P., Latz, E., 2014. Innate immune activation in neurodegenerative disease. *Nat Rev Immunol* 14 (7), 463–477.

Heslegrave, A., Heywood, W., Paterson, R., Magdalinou, N., Svensson, J., Johansson, P., Ohrfelt, A., Blennow, K., Hardy, J., Schott, J., Mills, K., Zetterberg, H., 2016. Increased cerebrospinal fluid soluble TREM2 concentration in Alzheimer's disease. *Mol Neurodegener* 11, 3.

Keren-Shaul, H., Spinrad, A., Weiner, A., Matcovitch-Natan, O., Dvir-Szternfeld, R., Ulland, T.K., David, E., Baruch, K., Lara-Astaiso, D., Toth, B., Itzkovitz, S., Colonna, M., Schwartz, M., Amit, I., 2017. A unique microglia type associated with restricting development of Alzheimer's disease. *Cell* 169 (7), 1276–1290 e17.

Kleinberger, G., Brendel, M., Mrcsko, E., Wefers, B., Groeneweg, L., Xiang, X., Focke, C., Deusing, M., Suárez-Calvet, M., Mazaheri, F., Parhizkar, S., Pettkus, N., Wurst, W., Feederle, R., Bartenstein, P., Mueggler, T., Arzberger, T., Knuesel, I., Rominger, A., Haass, C., 2017. The FTD-like syndrome causing TREM2 T66M mutation impairs microglia function, brain perfusion, and glucose metabolism. *Embo J* 36 (13), 1837–1853.

Kleinberger, G., Yamanishi, Y., Suarez-Calvet, M., Czirz, E., Lohmann, E., Cuyvers, E., Struyfs, H., Pettkus, N., Weninger-Weinzierl, A., Mazaheri, F., Tahirovic, S., Lleo, A., Alcolea, D., Fortea, J., Willem, M., Lammich, S., Molinuevo, J.L., Sanchez-Valle, R., Antonell, A., Ramirez, A., Heneka, M.T., Sleegers, K., van der Zee, J., Martin, J.J., Engelborghs, S., Demirtas-Tatlidede, A., Zetterberg, H., Van Broeckhoven, C., Gurvitz, H., Wyss-Coray, T., Hardy, J., Colonna, M., Haass, C., 2014. TREM2 mutations implicated in neurodegeneration impair cell surface transport and phagocytosis. *Sci Transl Med* 6 (243) 243ra86.

Liu, D., Cao, B., Zhao, Y., Huang, H., McIntyre, R.S., Rosenblatt, J.D., Zhou, H., 2018. Soluble TREM2 changes during the clinical course of Alzheimer's disease: a meta-analysis. *Neurosci Lett* 686, 10–16.

Lui, H., Zhang, J., Makinson, S.R., Cahill, M.K., Kelley, K.W., Huang, H.Y., Shang, Y., Oldham, M.C., Martens, L.H., Gao, F., Coppola, G., Sloan, S.A., Hsieh, C.L., Kim, C.C., Bigio, E.H., Weintraub, S., Mesulam, M.M., Rademakers, R., Mackenzie, I.R., Seeley, W.W., Karydas, A., Miller, B.L., Borroni, B., Ghidoni, R., Farese Jr., R.V., Paz, J.T., Barres, B.A., Huang, E.J., 2016. Progranulin deficiency promotes circuit-specific synaptic pruning by microglia via complement activation. *Cell* 165 (4), 921–935.

- Ma, L.Z., Tan, L., Bi, Y.L., Shen, X.N., Xu, W., Ma, Y.H., Li, H.Q., Dong, Q., Yu, J.T., 2020. Dynamic changes of CSF sTREM2 in preclinical Alzheimer's disease: the CABLE study. *Mol Neurodegener* 15 (1), 25.
- Martens, L.H., Zhang, J., Barmada, S.J., Zhou, P., Kamiya, S., Sun, B., Min, S.W., Gan, L., Finkbeiner, S., Huang, E.J., Farese Jr., R.V., 2012. Progranulin deficiency promotes neuroinflammation and neuron loss following toxin-induced injury. *J Clin Invest* 122 (11), 3955–3959.
- Oeckl, P., Weydt, P., Steinacker, P., Anderl-Straub, S., Nordin, F., Volk, A.E., Diehl-Schmid, J., Andersen, P.M., Kornhuber, J., Danek, A., Fassbender, K., Fliessbach, K., German Consortium for Frontotemporal Lobar, D., Jahn, H., Lauer, M., Muller, K., Knehr, A., Prudlo, J., Schneider, A., Thal, D.R., Yilmazer-Hanke, D., Weishaupt, J.H., Ludolph, A.C., Otto, M., 2019. Different neuroinflammatory profile in amyotrophic lateral sclerosis and frontotemporal dementia is linked to the clinical phase. *J Neurol Neurosurg Psychiatry* 90 (1), 4–10.
- Piccio, L., Buonsanti, C., Cella, M., Tassi, I., Schmidt, R.E., Fenoglio, C., Rinker 2nd, J., Naismith, R.T., Panina-Bordignon, P., Passini, N., Galimberti, D., Scarpini, E., Colonna, M., Cross, A.H., 2008. Identification of soluble TREM-2 in the cerebrospinal fluid and its association with multiple sclerosis and CNS inflammation. *Brain* 131 (Pt 11), 3081–3091.
- Piccio, L., Deming, Y., Del-Aguila, J.L., Ghezzi, L., Holtzman, D.M., Fagan, A.M., Fenoglio, C., Galimberti, D., Borroni, B., Cruchaga, C., 2016. Cerebrospinal fluid soluble TREM2 is higher in Alzheimer disease and associated with mutation status. *Acta Neuropathol* 131 (6), 925–933.
- Rascovsky, K., Hodges, J.R., Knopman, D., Mendez, M.F., Kramer, J.H., Neuhaus, J., van Swieten, J.C., Seelaar, H., Dopper, E.G., Onyike, C.U., Hillis, A.E., Josephs, K.A., Boeve, B.F., Kertesz, A., Seeley, W.W., Rankin, K.P., Johnson, J.K., Gorno-Tempini, M.L., Rosen, H., Prileau-Latham, C.E., Lee, A., Kipps, C.M., Lillo, P., Piguet, O., Rohrer, J.D., Rossor, M.N., Warren, J.D., Fox, N.C., Galasko, D., Salmon, D.P., Black, S.E., Mesulam, M., Weintraub, S., Dickerson, B.C., Diehl-Schmid, J., Pasquier, F., Deramecourt, V., Lebert, F., Pijnenburg, Y., Chow, T.W., Manes, F., Grafman, J., Cappa, S.F., Freedman, M., Grossman, M., Miller, B.L., 2011. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 134 (Pt 9), 2456–2477.
- Schlepckow, K., Kleinberger, G., Fukumori, A., Feederle, R., Lichtenthaler, S.F., Steiner, H., Haass, C., 2017. An Alzheimer-associated TREM2 variant occurs at the ADAM cleavage site and affects shedding and phagocytic function. *EMBO Mol Med* 9 (10), 1356–1365.
- Suárez-Calvet, M., Kleinberger, G., Araque Caballero, M., Brendel, M., Rominger, A., Alcolea, D., Fortea, J., Lleó, A., Blesa, R., Gispert, J.D., Sánchez-Valle, R., Antonell, A., Rami, L., Molinuevo, J.L., Brosseron, F., Träschütz, A., Heneka, M.T., Struyfs, H., Engelborghs, S., Sleegers, K., Van Broeckhoven, C., Zetterberg, H., Nellgård, B., Blennow, K., Crispin, A., Ewers, M., Haass, C., 2016. sTREM2 cerebrospinal fluid levels are a potential biomarker for microglia activity in early-stage Alzheimer's disease and associate with neuronal injury markers. *EMBO Mol Med* 8 (5), 466–476.
- Suárez-Calvet, M., Morenas-Rodríguez, E., Kleinberger, G., Schlepckow, K., Araque Caballero, M., Franzmeier, N., Capell, A., Fellerer, K., Nuscher, B., Eren, E., Levin, J., Deming, Y., Piccio, L., Karch, C.M., Cruchaga, C., Shaw, L.M., Trojanowski, J.Q., Weiner, M., Ewers, M., Haass, C., Alzheimer's Disease Neuroimaging, I., 2019. Early increase of CSF sTREM2 in Alzheimer's disease is associated with tau related-neurodegeneration but not with amyloid- β pathology. *Mol Neurodegener* 14 (1), 1.
- Tanaka, Y., Matsuwaki, T., Yamanouchi, K., Nishihara, M., 2013. Exacerbated inflammatory responses related to activated microglia after traumatic brain injury in progranulin-deficient mice. *Neuroscience* 231, 49–60.
- Woollacott, I.O.C., Nicholas, J.M., Heller, C., Foiani, M.S., Moore, K.M., Russell, L.L., Paterson, R.W., Keshavan, A., Schott, J.M., Warren, J.D., Heslegrave, A., Zetterberg, H., Rohrer, J.D., 2020. Cerebrospinal fluid YKL-40 and chitotriosidase levels in frontotemporal dementia vary by clinical, genetic and pathological subtype. *Dement Geriatr Cogn Disord* 49 (1), 56–76.
- Woollacott, I.O.C., Nicholas, J.M., Heslegrave, A., Heller, C., Foiani, M.S., Dick, K.M., Russell, L.L., Paterson, R.W., Keshavan, A., Fox, N.C., Warren, J.D., Schott, J.M., Zetterberg, H., Rohrer, J.D., 2018. Cerebrospinal fluid soluble TREM2 levels in frontotemporal dementia differ by genetic and pathological subgroup. *Alzheimers Res Ther* 10 (1), 79.