FKBP5 Gene Expression Predicts Antidepressant Treatment Outcome in Depression

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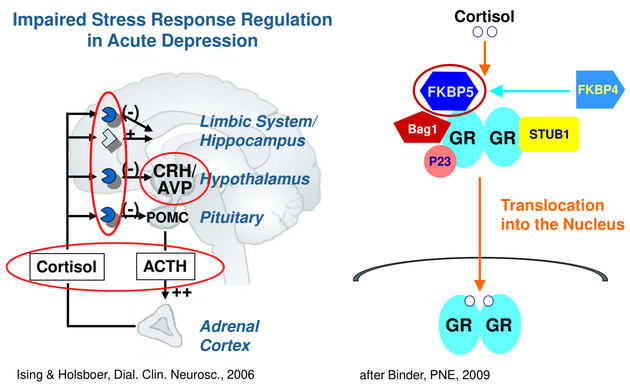
1 Background

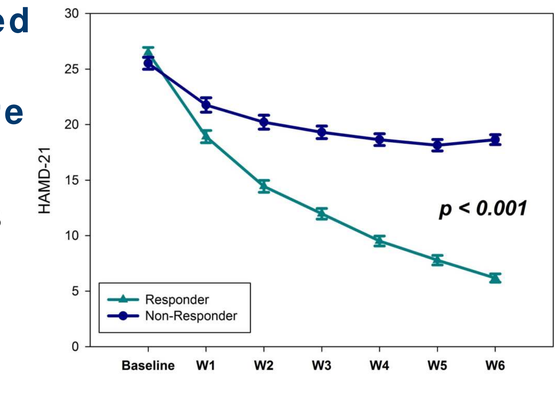
- ***FKBP5*** and its expression product **FKBP51** functionally attenuate the sensitivity of the glucocorticoid receptor (GR), and thus, are **important modulators** of the **stress response**.



- Consistent genetic findings point to an **important role** of the **minor T** allele of the ***FKBP5*** SNP **rs1360780** for stress response regulation, **depression risk** and **antidepressant treatment** outcome. The minor T allele …
  - …is associated with **increased** and **prolonged stress response** in healthy subjects.
  - …is associated with **increased depression risk** in **traumatized healthy subjects**.
  - …is associated with **recurrence risk** in depression and with **antidepressant treatment outcome**.

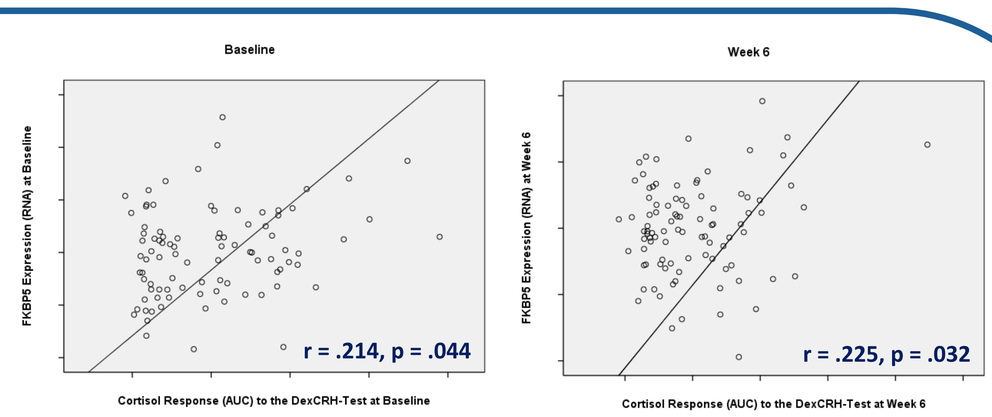
2 Materials and Methods

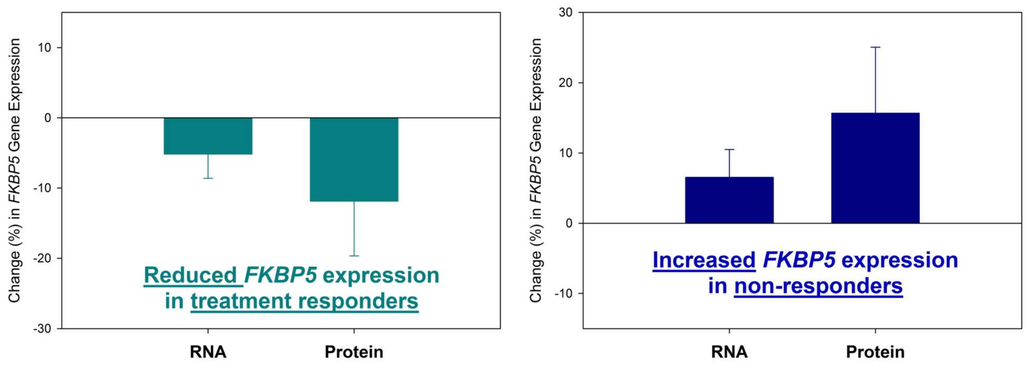
- This study included **297 inpatients**, who participated in the **Munich Antidepressant Response Signature (MARS)** project and were treated for acute depression.
- **Changes in blood FKBP51 expression** during antidepressant treatment were analyzed using RT-PCR and ZeptoMARK™ reverse phase protein microarray.
- **Stress response regulation** was evaluated in a subgroup of patients using the combined dexamethasone (dex)/corticotropin releasing hormone (CRH) test.
- 173 patients = **58% responded** after six weeks of treatment, while 124 patients = **42% were non-responders**.
- Responders vs. non-responders **did not differ** in sex, age, diagnosis, baseline depression severity or FKBP51 expression.



3 Results

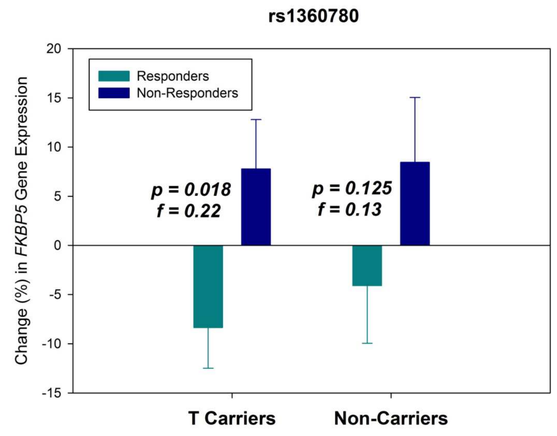
- **Increased FKBP51 expression** is associated with an **impaired stress response regulation** at baseline and after six weeks of treatment indicated by a **positive association** between **FKBP51 RNA levels** and the **cortisol response** to the combined dex/CRH test.





- **Patients responding to antidepressant treatment** after six weeks had a **pronounced reduction of *FKBP5* gene and FKBP51 protein expression**, while **non-responders showed increasing expression levels**. This effect was small to medium for change in RNA expression (f = .14, p = .018) and reached the border of a large effect for change in protein expression (f = .36, p = .038).

- This effect of FKBP5 RNA expression on treatment outcome was additionally **moderated by the *FKBP5* genotype rs1360780**, with **carriers of the minor T allele showing the most pronounced association** (f = .22 > f = .13).



4 Summary and Conclusion

- **Successful antidepressant treatment** is accompanied by a **reduction of *FKBP5* gene and FKBP51 protein expression**, particularly, in those patients, who are carrying the ***FKBP5* rs1360780 risk allele**.
- Our findings demonstrate that ***FKBP5*** and, specifically, its expression product **FKBP51** are **important modulators of antidepressant treatment outcome**, pointing to a new, **promising target** for future **antidepressant drug development**.

Reference: Ising et al. Int.J.Mol.Sci. 2019; 20(3), 485.

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