

**Project Title:** From normative to poor readers: looking for genetic associations underlying reading abilities in adults.

**Supervisor:** Alexandra Reis (CBMR) and Natércia da Conceição (CCMAR).

**Institution:** University of Algarve

**Webpage:** The CBMR group (<http://cbmr.ualg.pt/>; <http://gnc.cbmr.ualg.pt/>); The CCMAR group (BioSkel, [bioskel.ccmr.ualg.pt/](http://bioskel.ccmr.ualg.pt/)).

**Contact: email:** [aireis@ualg.pt](mailto:aireis@ualg.pt)

**Location of research lab/research center:** The research centers involved (CBMR and CCMAR) are highly suitable for the implementation of this project.

### **Summary: (1000 characters)**

Dyslexia is a neurologically-based developmental learning specific deficit affecting word recognition, reading and writing, with a prevalence around 5-10% in school-aged children across different populations. An individual diagnosed with dyslexia in childhood typically remains diagnosed as dyslexic throughout life. Problems in learning to read and write constitute a major constraint for educational and vocational training in modern knowledge-based societies and are associated with academic underachievement, incomplete high school/college studies, and underemployment as well as all consequent psychological-behavioral problems. According to Pennington (2006), a substantial amount of the variance in reading ability is explained by inherited factors: genetic variance explains about 20-80% of the total variance in reading skills. Although many studies associate certain genes variants with reading and their disorders, so far this association remains inconclusive because many results have not been consistently replicated. The lack of consistency could be partially explained by the age and educational stage at which the diagnosis of dyslexia affection status and the quantitative trait measurement took place (Carrion-Castillo et al., 2017).

One way of overcoming these age-varying effects is to genotype a sample of adults with dyslexia and normative readers. A critical open question is how some adults, called compensated dyslexics, attain age-appropriate reading skills and succeed in their academic career despite a history of reading difficulties (compensated) while others do not (non-compensated dyslexics). Therefore, genetic analysis is an open window to understand the both the heterogeneity of reading difficulties and the fact that some of dyslexics compensate and succeed.

We plan to (1) identify the correlation between the observed reading phenotypes in adult readers (assessed with an extensive cognitive battery) and their genotype and (2) to understand the role of the identified genetic variations in compensated vs. non-compensated dyslexics. An add value of this proposal is to develop a close collaboration between research in human genetics and cognitive neurosciences by identifying human gene mutations affecting cognitive profile responsible for reading disorders in adults. This will serve as an important stepping stone in the pursuit of a deeper causal understanding of developmental reading difficulties, including dyslexia and other impaired attainments of reading expertise.

### **Bibliographic references**

Bates, T.C., Lind, P.A., Luciano, M., Montgomery, G.W., Martin, N.G., & Wright, M.J. (2010). Dyslexia and DYX1C1: deficits in reading and spelling associated with a missense mutation. *Molecular Psychiatry*, 15, 1190-1196.

- Becker, J., Czamara, D., Scerri, T.S., et al. (2014). Genetic analysis of dyslexia candidate genes in the European cross-linguistic NeuroDys cohort. *European Journal of Human Genetics*, 22, 675-680.
- Carrion-Castillo, A., Franke, B., & Fisher, S. E. (2013). Molecular Genetic of Dyslexia: An Overview. *Dyslexia*, 19, 2014-2140.
- Carrion-Castillo, A., Maassen, B., Franke, B., Heister, A., Naber, M., Van der Leij, A., Francks, C., & Fisher, S. E. (2017). Association analysis of dyslexia candidate genes in a Dutch longitudinal sample. *European Journal of Human Genetics*, 25(4), 452-460.
- Cope, N., Harold, D., Hill, G., et al (2005). Strong evidence that KIAA0319 on chromosome 6p is a susceptibility gene for developmental dyslexia. *American Journal of Human Genetics*, 76, 581-591.
- Dahdouh, F., Anthoni, H., Tapia-Paez, I., et al. (2009). Further evidence for DYX1C1 as a susceptibility factor for dyslexia. *Psychiatric Genetics*, 19, 59-63.
- Deacon, S.H., Cook, K., & Parrila, R. (2012). Identifying high-functioning dyslexics: is self-report of early reading problems enough? *Annals of Dyslexia*, 62, 120-134.
- Deffenbacher, K.E., Kenyon, J.B., Hoover, D.M., Olson, R.K., Pennington, B.F., DeFries, J.C., & Smith, S.D. (2004). Refinement of the 6p21.3 quantitative trait locus influencing dyslexia: linkage and association analyses. *Human Genetics*, 115(2), 128-138.
- Francks, C., Paracchini, S., Smith, S.D., Richardson, A.J., Scerri, T.S., Cardon, L.R., Marlow, A.J., MacPhie, I.L., Walter, J., Pennington, B.F., Fisher, S.E., Olson, R.K., DeFries, J.C., Stein, J.F., Monaco, A.P. (2004). A 77-kilobase region of chromosome 6p22.2 is associated with dyslexia in families from the United Kingdom and from the United States. *American Journal of Human Genetics*, 75, 1046-1058.
- Gayán, J., Smith, S.D., Cherny, S.S., Cardon, L.R., & Fulker, D.W. (1999). Quantitative-Trait Locus for Specific Language and Reading Deficits on Chromosome 6p. *The American Journal of Human Genetics*, 64, 157-164.
- Giraud, A.L., & Ramus, F. (2013). Neurogenetics and auditory processing in developmental dyslexia. *Current Opinion in Neurobiology*, 23, 37-42.
- Harold, D., Paracchini, S., Scerri, T., et al. (2006): Further evidence that the KIAA0319 gene confers susceptibility to developmental dyslexia. *Molecular Psychiatry*, 11, 1085-1091.
- Lasky-Su, J., Lyon, N.H., Emilsson, V. et al. (2008). On the Replication of Genetic Associations: Timing Can Be Everything!. *The American Journal of Human Genetics*, 82 (4), 849-858.
- Lyon, G., Shaywitz, S., & Shaywitz, B. (2003). A definition of dyslexia. *Annals of Dyslexia*, 53, 1-14.
- Livingstone, M. S., Rosen, G. D., Drislane, F. W., & Galaburda, A. M. (1991). Physiological and anatomical evidence for a magnocellular defect in developmental dyslexia. *Proceedings of the National Academy of Sciences*, 88(18), 7943-7947.
- Meng, H., Smith, S.D., Hager, K., et al. (2005). DCDC2 is associated with reading disability and modulates neuronal development in the brain. *Proceedures of National Academy of Science USA*, 102, 17053-17058.
- Michou, L., Conceição, N., Morissette, J., Gagnon, E., Miltenberger-Miltenyi, G., Siris, E.S., Brown, J.P., Cancela, M.L., 2012. Genetic association study of UCMA/GRP and OPTN genes (PDB6 locus) with Paget's disease of bone. *Bone*, 51, 720-728.
- Newbury, D.F., Winchester, L., Addis, L., et al. (2009). CMIP and ATP2C2 modulate phonological short-term memory in language impairment. *American Journal of Human Genetics*, 85, 264-272.
- Parrila, R., Georgiou, G., & Corkett, J. (2007). University Students with a Significant History of Reading Difficulties: What Is and Is Not Compensated? *Exceptionality Education Canada*, 17 (2), 195-220.
- Pennington, B.F. (2006). From single to multiple deficits models of developmental disorders. *Cognition*, 101, 385-413.
- Poelmans, G., Engelen, J.J., Van Lent-Albrechts, J., Smeets, H.J., Schoenmakers, E., Franke, B., Buitelaar, J.K., Wuisman-Frerker, M., Erens, W., Steyaert, J., Schrandt-Stumpel, C. (2008). Identification of novel dyslexia candidate genes through the analysis of a chromosomal deletion. *American Journal of Medical Genetics (Part B) Neuropsychiatric Genetics*, 150B(1), 140-7.
- Ramus, F., Altarelli, I., Jednoróg, K., Zhao, J. & Covella, L. S. (2017-published online). Neuroanatomy of developmental dyslexia: pitfalls and promise. *Neuroscience and Behavioral Reviews*, pii: S0149-7634(16) 30746-1.
- Schumacher, J., Anthoni, H., Dahdouh, F. et al. (2006). Strong genetic evidence of DCDC2 as a susceptibility gene for dyslexia. *The American Journal of Human Genetics*, 78, 52-62.
- Scerri, T.S., Fisher, S.E., Francks, C. et al. (2004). Putative functional alleles of DYX1C1 are not associated with dyslexia susceptibility in a large sample of sibling pairs from the UK. *Journal of Medical Genetics*, 41, 853-857.
- Scerri, T.S., Morris, A.P., Buckingham, L., Newbury, D.F., Miller, L.L., Monaco, A. P., et al. (2011) DCDC2, KIAA0319 and CMIP Are Associated with Reading-Related Traits. *Biological Psychiatry*, 70, 237-245.
- Stein, J., & Walsh, V. (1997). To see but not to read; the magnocellular theory of dyslexia. *Trends in Neurosciences*, 20(4), 147-152.
- Stoodley, C.J., & Stein, J. F. (2011). The cerebellum and dyslexia. *Cortex*, 47(1), 101-116.
- Taipale, M., Kaminen, N., Nopola-Hemmi, J., et al. (2003). A candidate gene for developmental dyslexia encodes a nuclear tetratricopeptide repeat domain protein dynamically regulated in brain. *Proceedures of National Academy of Science USA*, 100, 11553-11558.
- Vaessen, A., Bertrand, D., Toth, D., Csépe, V., Faisca, L., Reis, A., & Blomert, L. (2010). Cognitive development of fluent word reading does not qualitatively differ between transparent and opaque orthographies. *Journal of Educational Psychology*, 102 (4), 827-842.
- Vale, A.P., Sucena, S., & Leopoldina, V.F. (2011). Prevalência da dislexia entre crianças do 1.º Ciclo do Ensino Básico falantes do português europeu. *Revista Lusófona de Educação*, 18, 45-56.
- Vellutino, F.R., Fletcher, J.M., Snowling, M.J., & Scanlon, D.M. (2004). Specific reading disability (dyslexia): what have we learned in the past four decades?. *Journal of Child Psychology and Psychiatry*, 45(1), 2-40.
- Vernes, S.C., Newbury, D.F., Abrahams, B.S., et al. (2008). A functional genetic link between distinct developmental language disorders. *New England Journal of Medicine*, 359, 2337-2345.
- Vidyaagar, T., & Pammer, K. (2010). Dyslexia, a deficit in visuo-spatial attention, not in phonological processing. *Trends in Cognitive Sciences*, 14(2), 57-63.
- Ziegler, J.C., Bertrand, D., Tóth, D., Csépe, V., Reis, A., Faisca, L., et al. (2010). Orthographic depth and its impact on universal predictors of reading. *Psychological Science*, 21, 551-559.

Zhang, Y., Li, J., Song, S., Tardif, T., Burmeister, M., Villafuerte, S.M., Su, M., McBride, C., & Shu, H. (2016). Association of DCDC2 Polymorphisms with Normal Variations in Reading Abilities in a Chinese Population. *PLoS One*, 21, 11(4):e0153603.