proteinspotlight
> ONE MONTH, ONE PROTEIN <

Issue 91, February 2008
www.proteinspotlight.org

The hands to say it

Vivienne Baillie Gerritsen

When I was a little girl, I thought that my left-handed classmates were special. I envied their difference. And I used to marvel at the way they crouched over their desk, embracing something invisible as they did their best to avoid smudging ink all over their sheet of paper. Left-handedness *is* special. But so is right-handedness. Humans are not the only animals to make use of their hands – or claws, or paws, or hooves - but they are the only ones who show a marked preference for either the left one, or the right one. If this is so, there must be a reason for it. And not only must there be a reason but it must translate a certain structure of our brain: an asymmetry somewhere. Indeed, our brain is divided into two hemispheres which are dedicated to processing different activities. One side looks after our dreams, while the other is far more down to earth. LRRTM1 is the first protein to have been discovered which seems to be directly involved in this brain asymmetry. Consequently, it influences the handedness of a human-being and, more astonishingly, may also predispose individuals to psychotic troubles such as schizophrenia.

Two men engaged in conversation

Source unknown

Humans are particularly clever with their hands. One of the very first special events in our evolution was to get onto our hind limbs and free our hands for collecting food and making tools. A subsequent good move was to take away the burden of communication on our hands by developing our vocal instruments. Indeed speech, and its fine-tuned elaboration that only humans have managed to master so far, has given our hands great freedom which we have put to use in a multitude of ways. But none of this can explain why we are – for the great majority (90%) – right-handed. Hosts of other species also use their appendages for collecting food, eating or grooming but they don't have a distinct preference for one hand over the other.

The passing of roles from hand to mind expresses a particular brain structure. In turn, the progressive use of speech has continued to mould our brain into a shape peculiar to the human species. But why would that make us right-handed? For speech to evolve, one part of our brain had to evolve differently too, and in so doing it made most humans right-handers. This is what is known as the 'right-shift factor'. Consequently, our right-handedness is not the result of nature selecting right-handers over left-handers but rather of nature nudging our brain into a shape which encourages the act of speaking. As a result, over the millions of years, the human brain has been divided into two hemispheres. The right hemisphere is dedicated to the world of emotions and imagination, whilst the left hemisphere deals with talking and logical processes.

LRRTM1, or leucine-rich repeat transmembrane neuronal protein 1, is a protein involved in brain development. It has a set of repetitive domains in its sequence which are known to be involved in protein-protein interactions, a vital activity in the light of brain structure and development. LRRTM1 may be one of the factors which bestow upon the brain its asymmetry. It is expressed very early in the development of forebrain structures and may function in neuronal differentiation and connectivity. It is

also thought that it could have a role in intracellular trafficking in axons. Left-handedness, which is handed down by the father, may well be due to LRRTM1 dysfunction causing the original asymmetry to be flipped around, or reduced. However, it has been pointed out that chimpanzee LRRTM1 is 100% identical to human LRRTM1, yet no one has found a left-handed chimp, or an articulate one for that matter. Handedness and subtle brain asymmetry, as found in humans, are the result of much more than just one protein – and environmental factors are undoubtedly of great influence too.

With a role in brain development and possible neuronal connectivity, it is hardly surprising that LRRTM1 has been linked to neuronal diseases such as schizophrenia, autism and language impairment. Likewise, a logical step was to wonder whether left-handedness could not be taken as an indication to a predisposition for neuropsychiatric disorders. It so happens that in one study carried out on schizophrenic individuals many were left-handed. This kind of result has to be taken with caution though. It does not mean that every left-handed individual is prone to some form of psychosis. Many right-handers suffer from psychiatric impairment too. However, it does suggest that genetic components involved in the structure of our brain may be indicative of a predisposition to a neuronal illness, given the environment. Surprisingly, other studies have shown that left-handers are more prone to accidents than right-handers. No clear explanation has yet been given but it may just be because our society is really built for right-handers.

LRRTM1 is predicted to link to another protein – or proteins – where the bond would supposedly trigger off a reaction. With this in mind, if it can be shown that LRRTM1 does have a role in the development of neuropsychiatric diseases, it may well prove to be precious in the design of novel therapies to lessen such disorders. Once again though, no protein acts on its own. There are genes upstream and downstream of LRRTM1 involved in its expression. Furthermore, an individual's environment is hugely important in triggering off a psychiatric disorder: drugs, alcohol, abuse, violence, stress etc. And, besides psychiatric disorders, what to think of someone who writes with their left hand and throws with their right? What is their brain structure? Is LRRTM1 also part of semi left-handedness? It is all very mysterious. But the fascinating part of the story is to realise that were it not for our words, we would not be able to carry out nearly as much as we do with our hands.

Cross-references to Swiss-Prot

LRRTM1, *Homo sapiens* (Human) : Q96DN1

References

1. Francks C., Maegawa S., Lauren J., Abrahams B.S., Velayos-Baeza A., Medland S.E., Colella S., Groszer M., McAuley E.Z., Caffrey T.M., Timmusk T., Pruunsild P., Koppel I., Lind P.A., Matsumoto-Itaba N., Nicod J., Xiong L., Joober R., Enard W., Krinsky B., Nanba E., Richardson A.J., Riley B.P., Martin N.G., Strittmatter S.M., Moeller H.-J., Rujescu D., St Clair D., Muglia P., Roos J.L., Fisher S.E., Wade-Martins R., Rouleau G.A., Stein J.F., Karayiorgou M., Geschwind D.H., Ragoussis J., Kendler K.S., Airaksinen M.S., Oshimura M., De Lisi L.E., Monaco A.P.
   LRRTM1 on chromosome 2p12 is a maternally suppressed gene that is associated paternally with handedness and schizophrenia
   Molecular Psychiatry 12:1129-1139(2007)
   PMID: 17667961

2. Harrison R.M., Nystrom P.
   Handedness in captive bonobos (*Pan paniscus*)
   Folia Primatologica 79:253-268(2008)
   PMID: 18212503

3. Wolman D.
   The secrets of human handedness
   The New Scientist Magazine, Issue 2524, November 5th 2005