# Chapter 6

Future Perspectives

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Currently molecular analysis of *SLC6A8* is performed by direct DNA sequencing. Although this method is very robust and trustworthy, new techniques will emerge which will replace this current gold standard, with next generation sequencing being the most probable candidate. With this technique, not only will larger groups of patients be sequenced simultaneously, but the spectrum of disorders sequenced will also be widened. At present patients are being selected based upon biochemical findings. After suspicion of ID, firstly the urine is analysed biochemically, followed by enzymatic analysis. If the pattern is consistent with SLC6A8 deficiency, the patients' DNA is sequenced. In the future this order will be reversed. One (will) start(s) with whole exome or even whole genome sequencing, of for instance patients suffering from epilepsy, followed by biochemical analysis in case of unclassified variants in *SLC6A8*. This approach has two collateral effects. First, awareness of SLC6A8 deficiency will increase, as the number of correctly diagnosed patients will rise. Second, new variants, both inside and outside of the ORF as well as intronic, will be detected. This will result in better understanding of the correct functioning of SLC6A8 as a protein, the function of each transmembrane domain, the intronic regions, the regulatory regions and the promoter. In its turn, this will result in faster and more accurate diagnosis of this disorder.

With this in mind, the introduction of *SLC6A8* sequencing in newborns is also within reach. Although this disorder does not meet the criterion of being treatable, its detection does have significant consequences for genetic counselling. Also, this might have an even bigger impact once a treatment becomes available in the future.

The proper strategy of treating SLC6A8 deficiency still has to be elucidated. Initially patients were treated with creatine monohydrate and creatine precursors in order to restore cerebral creatine levels, which did not yield the desired results. Lipophilic creatine analogs have now moved to the spotlight. Although creatine-benzyl-ester, phosphocreatine-Mg-complex acetate, creatine-ethyl-ester and dodecyl-creatine-ester did not have any effect in clinical pilots [1-6], cyclocreatine did show it could be transported to the brain in brain-specific *Slc6a8* knockout mice[7]. This even led to improved cognitive functioning. It remains the question if a

similar effect will be perceived in a model more comparable to human SLC6A8 deficient patients, the ubiquitous Slc6a8 knockout mouse model.

Recently, the function of the monocarboxylate transporter 12 (MCT12), encoded by the *SLC16A12* gene was elucidated. Apparently this protein, which is highly expressed in human kidney, retina, lung and testis, also transports creatine[8]. Unlike SLC6A8, which transports creatine in a $Na^+$ and $Cl^-$ dependent manner, MCT12 performs facilitated transport of creatine. Additional research might reveal the function and role of MCT12 and especially how its cooperation with SLC6A8 in the transport of creatine.

**References**


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