VIEWPOINT

Intellectual disability, oncogenes and tumour suppressor genes: the way forward?

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Intellectual disability (ID) affects 1–3% of the population and is characterized by limitation in intellectual function and adaptive behaviour, with onset in childhood. In most of these patients the etiology remains unknown. Frequent identifiable causes of severe intellectual disability originate from chromosomal imbalances. High-throughput technologies for genomewide analysis such as comparative genomic hybridization (array-CGH) have been recently demonstrated to improve the diagnostic detection rate of genetic abnormalities.

Based on the genomewide array-CGH, studies investigating patients with ID with or without dysmorphic features suggested a diagnostic yield of 10–25%, of which *de novo* findings count for approximately 10% (Thuresson *et al*. 2007). High-resolution array-CGH assays performed in clinical diagnostic settings generate large amounts of data. Identifying pathogenic copy number variations (CNV) involved in genomic disorders is now challenging (Lee *et al*. 2007). Among factors influencing the assessment of CNV's pathogenicity in the diagnosis of patients with intellectual disability, the presence of CNV including gene expressed in the brain or with specific brain function is a strong argument. In contrast, CNV affecting only genes involved in oncogenesis are mostly ignored. However, links between some oncogenes or tumour suppressor genes and intellectual disability deserve attention.

This is exemplified by the role of a large HECT, UBA, and WWE domain-containing protein 1 (HUWE1), an E3 ubiquitin ligase, in both tumour processes and intellectual disability. Indeed, Myc oncoprotein and tumour suppressor P53 are major HUWE1 substrates. HUWE1 overexpression has been associated with colorectal carcinomas, leading to increased P53 ubiquitination and, subsequently, to its proteasomal degradation (Bernassola *et al*. 2008). *HUWE1* gene is also highly expressed in a significant proportion of lung and breast carcinomas (Bernassola *et al*. 2008). Recently, germ line *HUWE1* gene duplication was found in patients presenting a nonsyndromic X-linked mental retardation (Froyen *et al*. 2008). Intellectual disability is explained by the deregulated expression of P53 or N-Myc conferred by the overexpression of HUWE1 at an earlier developmental stage. P53 would maintain the balance between the generation and elimination of neuroblasts (Medrano and Scrable 2005) and thus reduced levels of P53 could affect normal brain development (Froyen *et al*. 2008). As well, the N-Myc oncoprotein has an essential role in the developing nervous system for the correct timing of cell-cycle exit, differentiation and organization of the cerebellar architecture (Zhao *et al*. 2008; D'Arca *et al*. 2010). Further, other tumour suppressor genes have been reported in intellectual disability. In the 17p13.1 microdeletion syndrome associated with intellectual disability and multiple congenital abnormalities several tumour suppressor genes are potential candidate genes to explain the observed phenotype (Krepischi-Santos *et al*. 2009). Among them, *KTCD11*, a suppressor of Hedgehog signalling, plays a critical role in brain morphogenesis by regulating the ventral patterning of the neural tube. Initially, *KCTD11* displays allelic deletion as well as significantly reduced expression in medulloblastoma (Di Marcotullio *et al*. 2004). Duplication of the *VHL* gene has also been reported in a patient with ID, multiple congenital anomalies but no tumour (Chabchoub *et al*. 2010). *VHL* gene is a tumour suppressor gene and germ line *VHL* gene deletions were initially associated with Van-Hippel Lindau syndrome, an inherited neoplastic disorder with retinal and central nervous haemangioblastomas and high risk of renal cancers (Maher *et al*.

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2011). In this case it is interesting to note that depending on the nature of the CNV, the phenotypic consequences are radically different.

Together these observations suggest that the impact of CNV, i.e. the deregulated expression of tumour suppressor genes or oncogenes, may have different consequences depending on the nature of the variation and whether the genetic change occurs in the somatic or germ line cells. Constitutional chromosome abnormalities, encompassing genome regions containing tumour suppressor genes or oncogenes, in patients with mental impairment or congenital abnormalities may represent an important mechanism linking abnormal phenotypes. An increasing number of observations in the literature support this theory between oncogenes and intellectual disability syndromes. For example, germ line abnormalities of oncogene *H-RAS* involved in the Ras/MAPK pathway are reported in Costello syndrome (Gripp and Lin 2012). As well, mutations of tumour suppressor genes *TUSC3* or *ST*5 link intellectual disability (Garshasbi *et al*. 2008; Göhring *et al*. 2010).

Although higher tumour frequency has not been observed in all patients with constitutional CNVs affecting oncogenes, it would be appropriate to consider the highest risk of cancer in these patients and to organize regularly a clinical follow-up. Interestingly, brain tumours are sometimes associated with these constitutional disorders (Rauen 2007). In addition, genes reported here like *KTCD11* or *VHL* are also involved in brain tumour oncogenesis. Therefore, genes described initially in brain tumours would deserve a particular attention as potential candidates in intellectual disability.

These observations also highlight the interest of considering *de novo* germ line CNV including well known oncogenes, and particularly those involved in the development of brain tumours, as potential pathogenic candidates to explain some cases of intellectual disability. Indeed, these genes may be critical in many developmental processes through their transversal function in cell differentiation, proliferation or apoptosis. This concept must be integrated into the medical practice of intellectual disability investigation.

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