Polygenic risk scores of several subtypes of epilepsies in a founder population

**Objective** Polygenic risk scores (PRSs) are used to quantify the cumulative effects of a number of genetic variants, which may individually have a very small effect on susceptibility to a disease; we used PRSs to better understand the genetic contribution to common epilepsy and its subtypes.

**Methods** We first replicated previous single associations using 373 unrelated patients. We then calculated PRSs in the same French Canadian patients with epilepsy divided into 7 epilepsy subtypes and population-based controls. We fitted a logistic mixed model to calculate the variance explained by the PRS using pseudo-R² statistics.

**Results** We show that the PRS explains more of the variance in idiopathic generalized epilepsy than in patients with nonacquired focal epilepsy. We also demonstrate that the variance explained is different within each epilepsy subtype.

**Conclusion** Globally, we support the notion that PRSs provide a reliable measure to rightfully estimate the contribution of genetic factors to the pathophysiologic mechanism of epilepsies, but further studies are needed on PRSs before they can be used clinically.

Neuraxial dysraphism in EPAS1-associated syndrome due to improper mesenchymal transition

**Objective** To investigate the effect of somatic, postzygotic, gain-of-function mutation of Endothelial Per-Arnt-Sim (PAS) domain protein 1 (EPAS1) encoding hypoxia-inducible factor-2α (HIF-2α) on posterior fossa development and spinal dysraphism in EPAS1 gain-of-function syndrome, which consists of multiple paragangliomas, somatostatinoma, and polycythemia.

**Methods** Patients referred to our institution for evaluation of new, recurrent, and/or metastatic paragangliomas/pheochromocytoma were confirmed for EPAS1 gain-of-function syndrome by identification of the EPAS1 gain-of-function mutation in resected tumors and/or circulating leukocytes. The posterior fossa, its contents, and the spine were evaluated retrospectively on available MRI and CT images of the head and neck performed for tumor staging and restaging. The transgenic mouse model underwent Microfil vascular perfusion and subsequent intact ex vivo 14T MRI and micro-CT as well as gross dissection, histology, and immunohistochemistry to assess the role of EPAS1 in identified malformations.

**Results** All 8 patients with EPAS1 gain-of-function syndrome demonstrated incidental posterior fossa malformations—one Dandy-Walker variant and 7 Chiari malformations without syringomyelia. These findings were not associated with a small posterior fossa; rather, the posterior fossa volume exceeded that of its neural contents. Seven of 8 patients demonstrated spinal dysraphism; 4 of 8 demonstrated abnormal vertebral segmentation. The mouse model similarly demonstrated features of neuraxial dysraphism, including cervical myelomeningocele and spinal dysraphism, and cerebellar tonsil displacement through the foramen magnum. Histology and immunohistochemistry demonstrated incomplete mesenchymal transition in the mutant but not the control mouse.

**Conclusion** This study characterized posterior fossa and spinal malformations seen in EPAS1 gain-of-function syndrome and suggests that gain-of-function mutation in HIF-2α results in improper mesenchymal transition.