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Postzygotic brain mosaicism as a consequence of partial reversion of prezygotic aneuploidy

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Strap-line (two sentences):

Brain somatic mosaicism is linked to several neurological disorders, thought to arise post-zygotically. The recent study by Miller et al. suggests prezygotic aneuploidy followed by postzygotic partial reversion leads to a recurrent form of brain mosaicism-related epilepsy.

Not all cells within a human individual are genetically identical. Differences in genomic sequences of cells within an organism are referred to as mosaicism, creating a patchwork-like quilt of genetic clones in the body. Brain somatic mosaicism can cause neurological disorders, such as focal epilepsy and brain tumors, and likely contributes to more common conditions like autism spectrum disorders, schizophrenia, and Alzheimer's disease. While mosaicism is thought to arise in the post-zygote stage, Miller et al. report in the current issue of Nature Genetics, a potentially prezygotic origin in humans that undergoes partial postzygotic reversion, leading to brain mosaicism and focal epilepsy[1].

The authors report a 1q copy number gain in six patients detected in brain malformations resected for severe epilepsy. They demonstrate the additional 1q copy arises from the presumably non-transmitted maternal chromosome. The clue was that the mosaic brain variants were part of a haplotype that could only have arisen in a parental prezygotic aneuploid cell. Of note, the 1q gain was observed exclusively in patient brain cells, predominantly in astrocytes, not observed in buccal or blood cells. Single-cell transcriptomics revealed unique patterns of gene expression in the astrocytes carrying the 1q gain. Authors suggest that zygotic aneuploidy reverts to diploidy in most or all other tissues but is retained in focal brain regions, through yet unknown mechanisms.

One fascinating finding from this study is the origin of the 1q gain, which they traced back to the maternal germ cell. The researchers propose three potential scenarios for how aneuploidy occurred, involving either meiotic or mitotic errors. The primary scenario they emphasize involves two rare sequential 1q events: nondisjunction during meiosis I

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followed by centric mis-division during meiosis II. The second scenario involves prezygotic nondisjunction in meiosis II followed by postzygotic isochromosome formation during mitosis. The third scenario proposes a mitotic 1q expansion in maternal germ cells, without additional meiotic errors. Each scenario possesses its own strengths and weaknesses, so further exploration will be required.

Another fascinating finding of this study is that the 1q gain cells were only observed in the brain and only there in certain cell types, suggesting early embryonic somatic 'repair' mechanisms might revert non-brain cells to euploidy as a condition of cell survival (Fig. 1). Somatic elimination of deleterious aneuploidies has been reported as early as the blastocyst stage in the form of 'DNA shedding'[2]. The human placenta demonstrates a higher tolerance for aneuploidy than the embryo itself, even potentially absorbing trisomic cells from somatic tissues for reversion[3]. The current paper suggests similar mechanisms may occur in the embryo, where brain cells demonstrate a higher tolerance of aneuploidy than somatic tissues. This means that mutations that are harmful to most cells could be "weeded out" under negative selection. Authors show both a subset of astrocytes and microglia, derived from two different germ layers, carry the 1q copy gain, presumably surviving this selection. While it is still unclear how certain cells tolerate aneuploidy, this could be due to selective pressure being lower, or that certain cells cannot be replaced by healthier cells.

Notably, the brain malformations described in this study are not the only example where genomic DNA is repaired under severe selective pressures. Recombination-induced somatic correction of germline mutations (i.e. revert mutational correction) in ichthyosis with confetti and loricrin keratoderma had been described previously[4]. In this example, mitotic recombination leads to islands of non-mutant cells surrounded by mutant cells. Another example is SMAD9-related phenotypes, driven by toxic gain-of-function point mutations, rescued through a variety of mechanisms including monosomy and uniparental disomy[5]. These mutations are associated with blood cancer and neurodegeneration as a result of the reversion. These examples demonstrate that revertant mutation correction can occur in somatic tissues under selective pressure. None of those mechanisms were reported in the current study, suggesting a cell division-related rather than a recombination-induced mechanism. Thus, in addition to the clinical implications, the current study opens questions about mechanisms of embryonic genome integrity.

Early human embryos, especially the first cell divisions, bear a higher mutation burden than later stages, likely a result of dynamic chromatin changes required for cell division and specification[6]. These changes could introduce both vulnerabilities as well as dynamic reversion mechanisms, also seen in conditions like clonal hematopoiesis which can bias stem cell pools and gradually reshape cell populations during aging[7]. The current study begs for models to explore mechanisms of both aneuploidy tolerance and reversion. In this case, only the strong and healthy clones manage to make it through the selection process. Miller et al. not only demonstrate the distinct clinical phenotype from 1q gain but also open new mutational mechanisms potentially important to improve our understanding of human development and aging.

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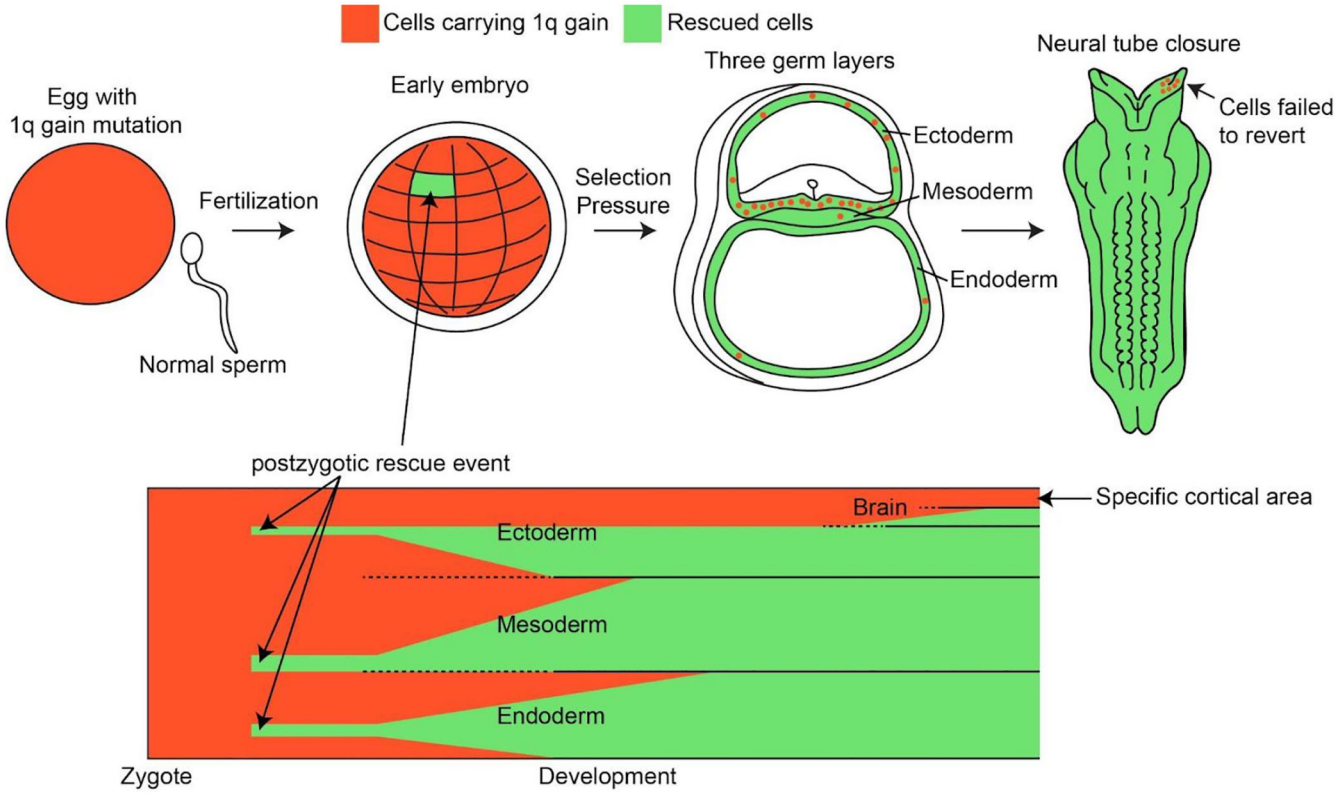

Fig. 1.

Focal brain dysplasia originates from a prezygotic 1q gain, subsequently mitigated by postzygotic rescue in one or more cells. Although most mutant cells are eventually eliminated, presumably through negative selection, a select few manage to persist, possibly through greater tolerance to the mutation or inability to be replaced by non-mutant cells, ultimately leading to focal brain dysplasia.