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Condensin Dysfunction Associated Microcephaly

Shikha Laloraya*

Department of Biochemistry, Indian Institute of Science, India, 560012

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***Corresponding author:** Shikha Laloraya, Department of Biochemistry, Indian Institute of Science, C. V. Raman Avenue, Bangalore, Karnataka, India, Tel: 91-80-23608122, 91-80-22933052; Fax: 91-80-23600814; Email: slaloraya@iisc.ac.in

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Abbreviations: SMC: Structural Maintenance of Chromosomes; WES: Whole Exome Sequencing; UFB: Ultra-Fine DNA Bridges

Mini Review

Chromatin organization within the cell is complex and highly regulated. In cells, DNA associates with histone protein octamers and a linker histone to form nucleosomal arrays that are further folded and organized with the help of non-histone proteins. Chromatin organization is also dynamic and undergoes dramatic changes as cells transit from interphase to mitosis. The organization of chromatin in interphase is altered when cells enter mitosis by further condensation of the chromatin to form discrete rod like chromosomes. This structural reorganization facilitates chromosome segregation and partitioning. Structural maintenance of chromosomes (SMC) proteins are a conserved family of proteins that are crucial for higher order chromatin organization [1].

The basic configuration of SMC proteins consists of an ATP binding head domain that includes amino and carboxy terminal regions that come together by folding of the SMC molecule at the hinge region, and coiled coil regions connecting the hinge with the head domain. In eukaryotic cells, SMC proteins associate at their hinge regions to form heterodimers that in combination with a few non-SMC subunits form and SMC complex. Cohesin, Condensin and the SMC 5/6 complex are well studied examples of SMC protein complexes in eukaryotes. SMC complexes can bind DNA and bring together different regions on the same or two different DNA molecules forming loops to facilitate condensation or chromosome pairing respectively.

Condensin is a key architect of mitotic chromosomes [2]. Not only is it crucial for mitotic chromosome condensation, a process involving folding of chromosomes by formation and further condensation of large loops resulting in shortening of the DNA molecule along its long axis, and also lateral compaction, but it is also required for organization of chromatin within the interphase nucleus [3,4]. Condensin is composed of an SMC2 and SMC4 heterodimer associated with the Kleisin subunit CAP-H, along with CAP-D and CAP-G subunits having HEAT repeats. A distinguishing feature of condensin relative to other SMC complexes is the close apposition of the coiled coil regions of SMC2 and SMC4 resulting in a more rod like architecture of the condensin complex. The ends of the Kleisin subunit bridge the head domains of SMC2 and SMC4 in an asymmetric fashion while the central part binds the HEAT repeat containing subunits. Condensin has also been reported to be required for sister chromatid cohesion, DNA repair and dosage compensation.

Human cells have two distinct condensin complexes, condensin I and condensin II [2,3]. The two complexes share the same SMC2 and SMC4 subunits but have different non-SMC subunits (NCAP-H, NCAP-D2 and NCAP-G in case of condensin I, and NCAP-H2, NCAP-D3 and NCAP-G2 in case of condensin II). Condensin II is localized in the nucleus in interphase and is thought to be important for axial shortening of chromosomes while condensin I is cytoplasmic at this stage and only comes in proximity with chromosomes upon nuclear envelop breakdown during mitosis when it aids lateral chromosome compaction.

Primary microcephaly is an autosomal recessive condition in which the brain (and also the cranium) is disproportionately smaller relative to the body indicative of defects in neurogenesis and brain growth. Microcephaly is often associated with mutations in genes encoding proteins important for cell cycle progression e.g. centrosomal proteins whose malfunction affects spindle formation and perturbs the cleavage plane orientation of neural progenitors [5]. In a recent search for new microcephaly genes, Martin et al. examined disease associated mutations in a patient cohort exhibiting severe microcephaly by whole exome

sequencing (WES) [6]. In four cases out of a group of nearly 200 patients displaying a range of microcephaly phenotypes, mutations were found in genes encoding the non-SMC components of both condensin I and condensin II.

The pattern of inheritance within the affected family was consistent with a rare recessive disorder in which the defective phenotypes were only observed in the homozygous state in the patient but not in the heterozygous parents. Two patients exhibiting severe microcephaly had mutations disrupting splicing or introducing a frame-shift in the open reading frame. One patient (P1) was homozygous for a splice site mutation in NCAPD2 (encoding a non-SMC subunit of condensin I), while another (P2) was a compound heterozygote for a frame-shift mutation and a base substitution that generated a new splice donor site within intron 3 of NCAPD3 (encoding a non-SMC subunit of condensin II). A third patient exhibiting milder microcephaly (P3) had a missense mutation in NCAPH, the gene encoding the Kleisin component of condensin I, resulting in a deleterious substitution (p.Pro243Leu) in a highly conserved residue. In addition, another patient exhibiting mild microcephaly (P4), was homozygous for a missense mutation in NCAPD3 resulting in an amino acid substitution (p.Glu153Ala) in a highly conserved residue. The patients bearing the more drastic mutations (frame shift and splice site mutations) exhibited more severe symptoms including microcephaly accompanied by reduced stature and intellectual disability while the patients having the missense substitutions showed less prominent symptoms such as mild microcephaly but no distinctive facial features or malformations and some intellectual disability.

Since both condensin I and II are required for chromosome compaction, chromatin organization in patient derived primary fibroblast lines was examined. In all four cases the chromatin was more disorganized when its structure was evaluated by a qualitative assay for chromosome structural organization. Interestingly, a hypomorphic Ncaph2 condensin II mouse mutant [7] having a missense mutation (p.Ile15Asn) displayed reduced brain and body weight, and reduced cortical surface area [6], establishing it as a suitable mouse model for condensin dysregulation associated microcephaly. Unlike other microcephaly syndromes that show perturbation of the mitotic spindle orientation in apical neural progenitors [8-10], the mitotic spindle position of apical progenitors in the Ncaph2I15N/I15N mouse was unaltered relative to controls, indicating an alternate mechanism may underlie the defects seen in condensin associated microcephaly. Interestingly, an enhanced frequency of chromatin bridges was observed in Ncaph2I15N/I15N neural apical progenitors during anaphase that may result in chromosome mis-segregation and cell death and thus contribute to microcephaly in this case. Consistent with this, fibroblasts from the severely affected patients P1 and P2 also showed enhanced ultra-fine DNA bridges (UFB), chromatin bridges that may result from a failure to decatenate DNA in the mutants, and lagging chromosomes. Increased frequency of micronuclei and aneuploidy was also observed in the patients' fibroblasts.

Intriguingly, the previously identified primary microcephaly gene MCPH1 [11], encodes a protein that inhibits condensin II [12,13]. Premature chromosome condensation is observed in MCPH1 associated microcephaly patient cells [11]. Interestingly, a severe case of microcephaly and mental deficiency has been reported having combined mutations in NCAPG2 and MCPH1 [14]. In addition to MCPH1, it is possible that mutation in other associated condensation regulatory factors e.g. SET1 [15] may contribute to the development of microcephaly; such a case is yet to be discovered. Another interesting candidate for microcephaly may be the human homolog of the CFDP1 protein that is involved in craniofacial development and osteogenesis in vertebrates that is known to be required for condensin recruitment and chromatin organization in human cells [16].

Conclusion

In conclusion, deficiency of either condensin I or condensin II results in microcephaly in humans, perhaps through a mechanism distinct from previously characterized similar syndromes. In case of condensin associated microcephaly, the observed defects may result from chromosome mis-segregation, aneuploidy and associated cell death resulting from persistence of chromatin bridges in anaphase cells, particularly the apical neural progenitor cells, rather than spindle mis-orientation unlike other previously characterized microcephalies. It is possible that future searches for microcephaly associated causative mutations may identify not only additional subunits of the human condensin complexes but also their regulators and other members of the condensin interaction network.

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