The Conserved Functional Role of non-CpG Methylation in Mammalian and Avian Brain

Kyle M. Schachtschneider[1,2], Martijn F.L. Derks[2,3,4], Ole Madsen[2], Veronika N. Laine[3], Lawrence B. Schook[1], Martien A.M. Groenen[2], Koen J.F. Verhoeven[5], Kees van Oers[3]

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Abstract

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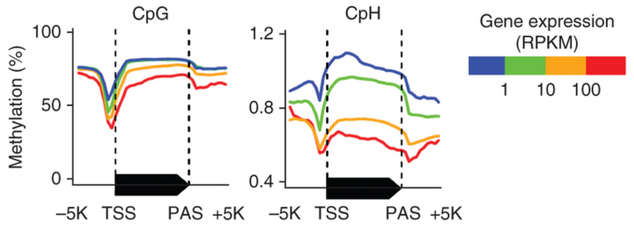

(Guo et al., 2014)

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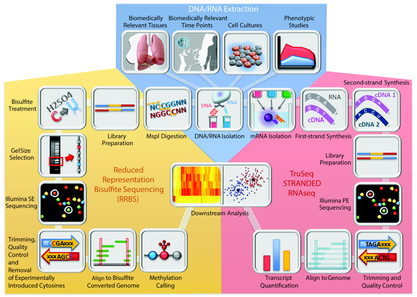

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DNA methylation is an epigenetic regulator of gene expression that plays a role in many cellular processes affecting a variety of traits. In this study DNA methylation was assessed in neuronal tissue from three pigs (frontal lobe) and one great tit (whole brain) using reduced representation and whole genome bisulfite sequencing, respectively. In addition, gene transcription patterns were profiled using RNA-seq. In total over 1.5 and 10.2 million CpG, and 5.5 and 167.4 million non-CpG sites were covered in the porcine and great tit samples, respectively. The observed genome-wide DNA methylation patterns in both species were consistent with previous mammalian findings, including low but significant non-CpG methylation that occurred predominantly at CpA dinucleotides. Both CpG and non-CpG methylation were negatively correlated with gene expression in porcine (Spearman's rho < -0.053, $P < 1x10^{-15}$) and great tit brain (Spearman's rho < -0.22, P < 0.0001). In addition, increased CpG and decreased non-CpG methylation was found within transposable elements (TEs) compared to surrounding regions in the great tit brain. TE activity was negatively correlated with non-CpG methylation both within TEs (Spearman's rho -0.12, $P < 1x10^{-15}$) and the surrounding 2 kb regions (Spearman's rho < -0.19, $P < 1x10^{-15}$). These findings provide the first evidence for conservation of non-CpG methylation in mammalian and avian neuronal tissue, and suggest a functional role for non-CpG methylation in avian neuronal tissue. These results raise interesting questions regarding the universal role of non-CpG methylation in neuronal epigenetic regulation and its potential role in learning and memory.

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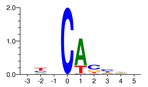

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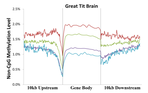

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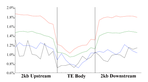

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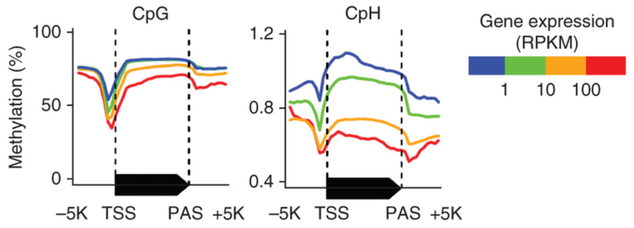

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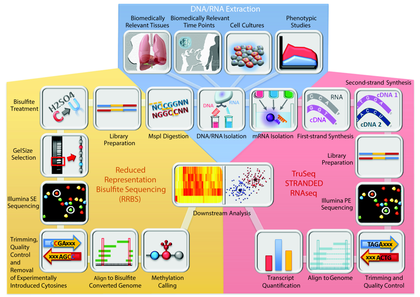

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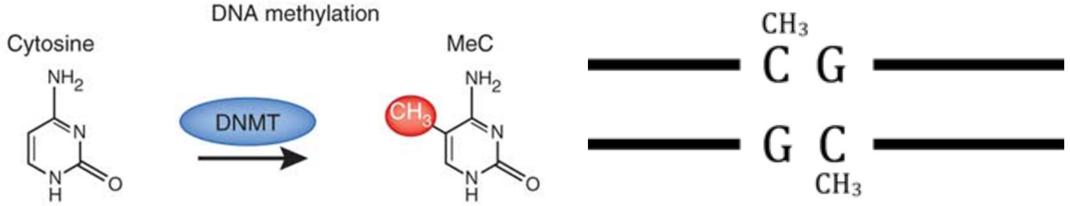
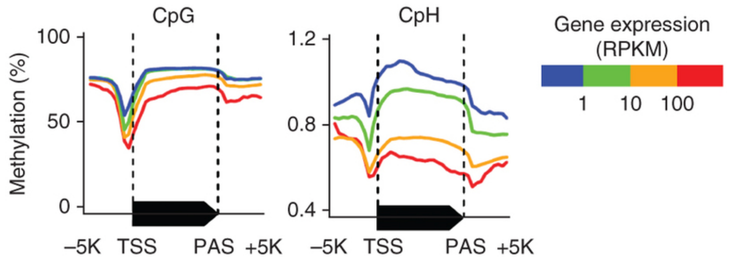
- DNA methylation is an epigenetic regulator of gene expression that plays a role in many cellular processes affecting a variety of traits.
- DNA methylation mainly occurs at CpG sites in animals.



- Non-CpG methylation is observed in embryonic stem cells, oocytes, and neurons of humans and mice.
- Both CpG and non-CpG methylation are negatively correlated with gene expression at transcription start sites (TSS) and gene bodies in human and mouse neurons.



- DNA methylation also suppresses transposable element (TE) activity, and TEs are highly active in neuronal tissue.
- Little is known about the regulatory role of non-CpG methylation in porcine and avian neurons.

(Day et al., 2010; Guo et al., 2014)

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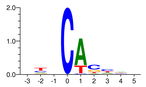

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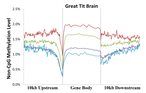

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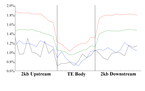

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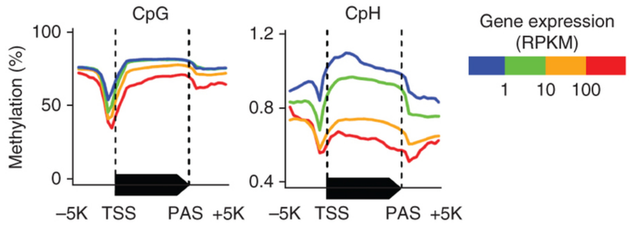

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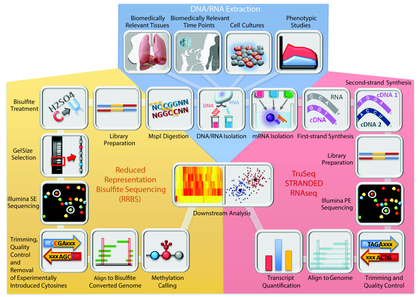

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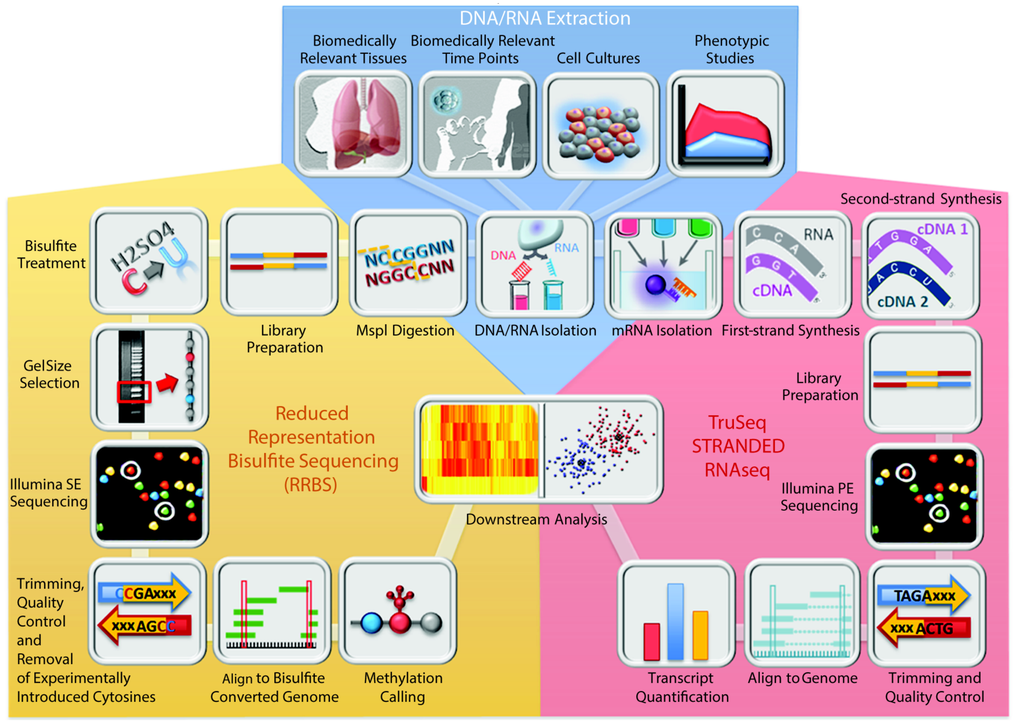

- Frontal lobe DNA methylation patterns were assessed in three pigs using reduced representation bisulfite sequencing (RRBS)
  - Alignment and methylation calling using BSseeker2
- Whole brain DNA methylation patterns were assessed in one great tit using whole genome bisulfite sequencing (WGBS)
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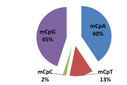
- Gene and TE transcription patterns were profiled using RNA-seq
  - Alignments performed using Tophat2
  - Expression quantification performed using Cufflinks

Results



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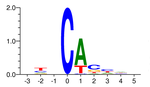

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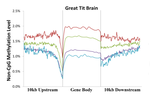

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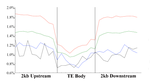

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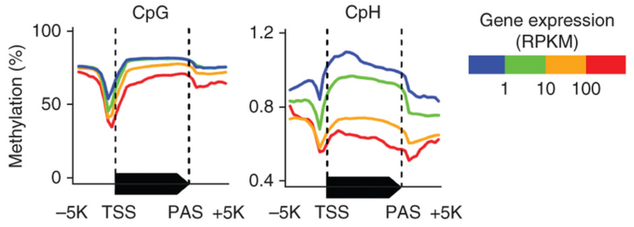

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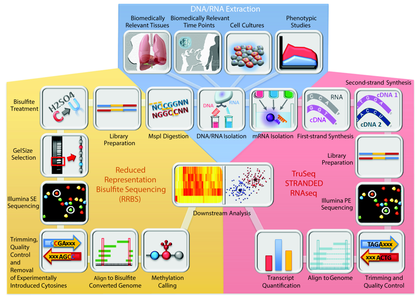

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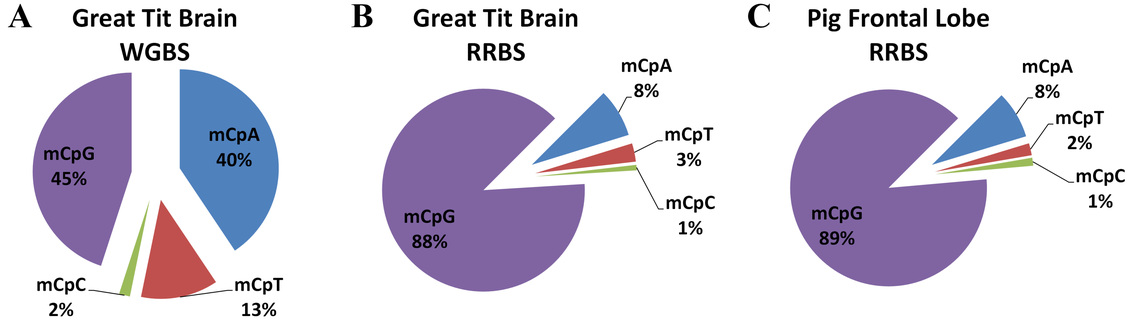

Distribution of methylated (>10%) cytosines in (a) great tit brain and (c) pig frontal lobe. Differences between (a) great tit and (c) pig neuronal patterns are due to differences between (a) WGBS and (b) RRBS techniques.

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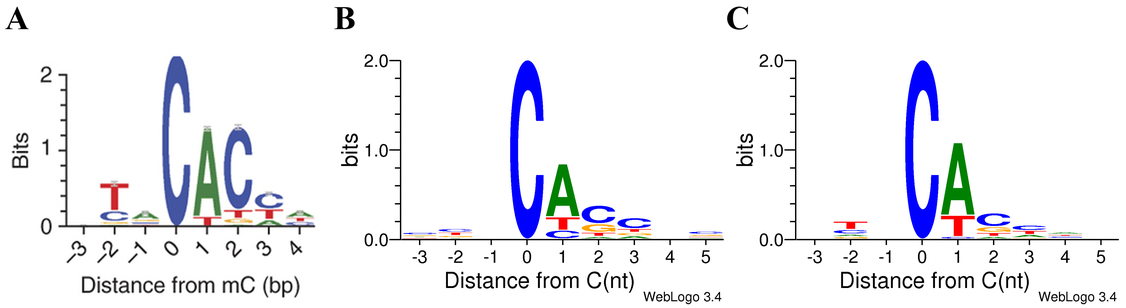

Occurrence of nucleotides are given relative to the distance from the methylated (>10%) C nucleotide for (a) mouse (Guo et al., 2014), (b) pig, and (c) great tit brain.

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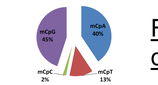

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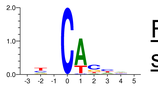

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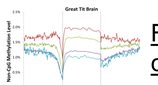

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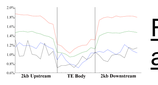

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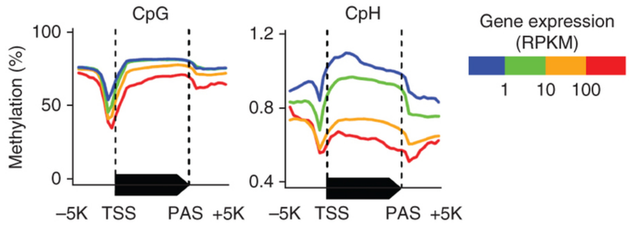

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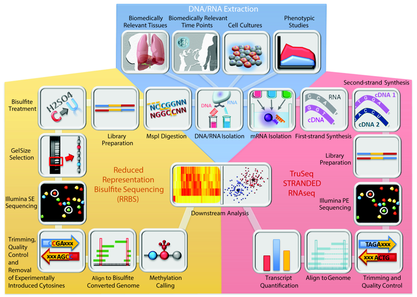

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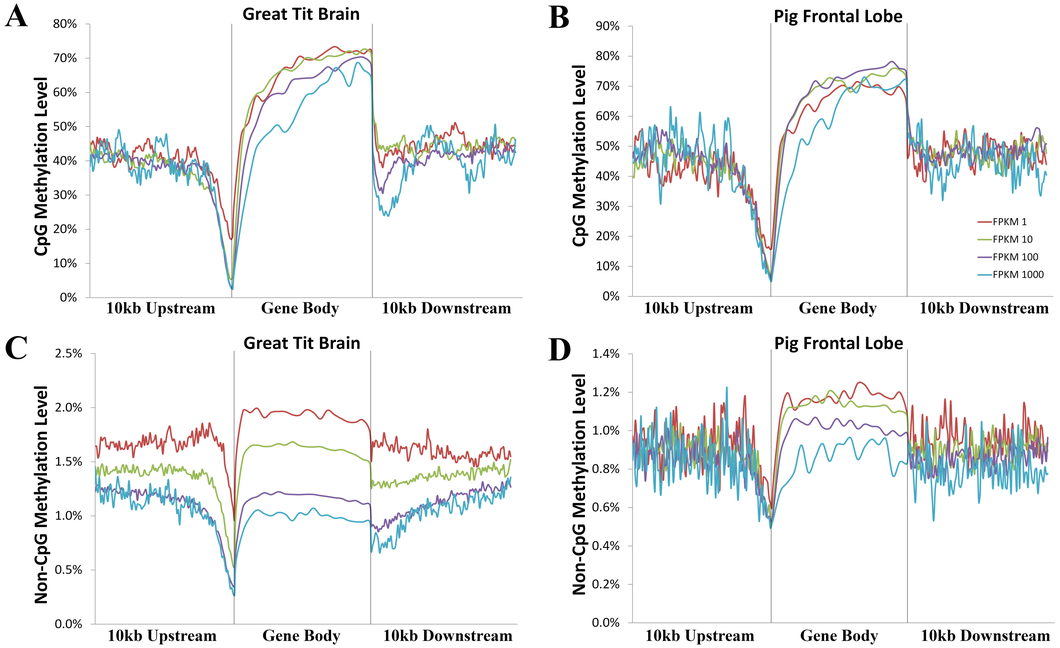

(a) Great tit brain and (b) pig frontal lobe CpG methylation is negatively correlated with gene expression at TSS (Spearman's Rho = -0.30 and -0.16, respectively, P < 1x10-15) and gene bodies (Spearman's Rho = -0.32 and -0.08, respectively, P < 1x10-15). (c) Great tit brain and (d) pig frontal lobe non-CpG methylation is negatively correlated with gene expression at TSS (Spearman's Rho = -0.24 and -0.05, respectively, P < 1x10-14) and gene bodies (Spearman's Rho = -0.46 and -0.11, respectively, P < 1x10-15).

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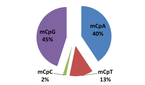

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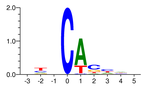

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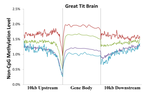

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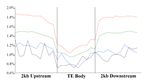

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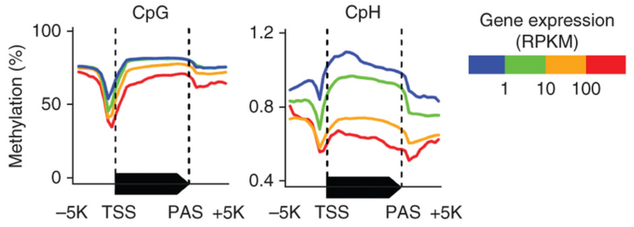
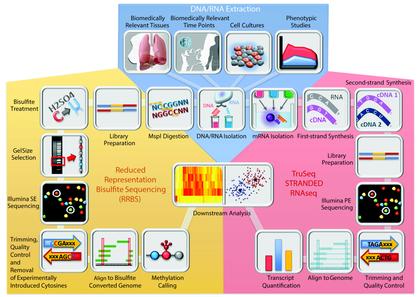
Introduction



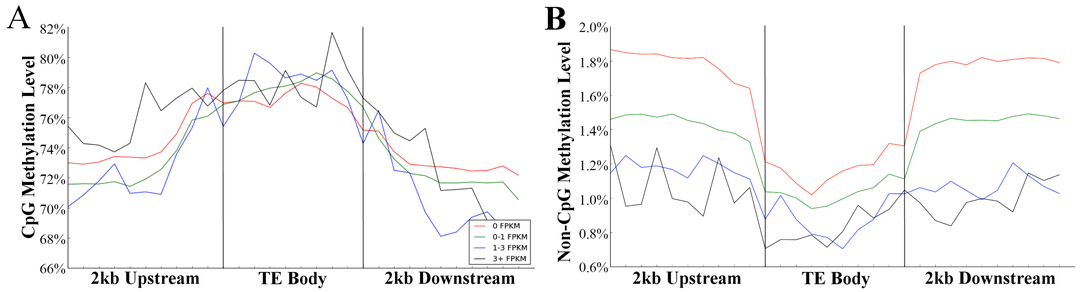
(Guo et al., 2014)

Methods



Results

Figure 4: Non-CpG methylation is associated with TE activity in great tit brain



(a) TE CpG methylation is not correlated with TE activity in great tit brain (Spearman's Rho TE body = 0.033, upstream = -0.006, downstream = -0.002). (b) TE non-CpG methylation is negatively correlated with TE activity in great tit brain (Spearman's Rho TE body = -0.11, upstream = -0.20, downstream = -0.19, P < 1x10-15).

Conclusions

- Both CpG and non-CpG methylation are negatively correlated with gene expression in great tit and pig neurons.
- Non-CpG methyation is negatively correlated with TE activity in great tit neurons.
- These findings provide the first evidence for conservation of non-CpG methylation between mammalian and avian neurons, and suggest a functional role for non-CpG methylation in avian neurons.

Results

Figure 1: Neuronal DNA methylation distribution amongst dinucleotides

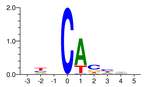


Figure 2: Dominant non-CpG methylation sequence motif

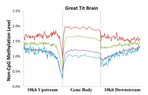


Figure 3: DNA methylation is negatively correlated with gene expression

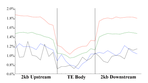


Figure 4: Non-CpG methylation is associated with TE activity in great tit brain

Conclusions

These findings provide the first evidence for conservation of non-CpG methylation between mammalian and avian neurons, and suggest a functional role for non-CpG methylation in avian neurons.

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